TALKING IMAGES
VOICES FROM THE OPEN FRONTIER OF IMAGING

PRECISION MEDICINE: PAST, PRESENT AND FUTURE.

Luisa Poggi
Precision Imaging is profoundly changing the diagnostic process of the healthcare world.

It is an ongoing, complex and yet unstoppable process

Precision Imaging is already a reality and will shortly become a standard of care.

For this reason, with Talking Images, the podcast that deals with how the current issues of our society are intertwined with diagnostic medicine, we have decided to dedicate an episode to precision medicine and to confront ourselves with:

Gabriel Krestin, radiologist and Emeritus professor of radiology at Erasmus Medical Centre in Rotterdam. For the past 25 years, he was Chair of the department of radiology in Rotterdam.
Lucy Costantino, Head of the Department of Molecular Genetic of the Centro Diagnostico Italiano.
Francesco Blasi, Global Research & Development, Bracco Imaging S.p.A.

I am **Luisa Poggi**, research and Development Program Manager at Bracco Imaging, and I will be your host in this journey.

Luisa Poggi
Medicine is evolving on a day-by-day basis and, thanks to precision medicine, it's becoming personalized, unique, individual.

Precision medicine is both personalized therapy and personalized diagnostics, also called precision imaging.

That's the objective of the emerging approach of precision imaging, that considers individual variabilities such as genes, environment, and lifestyle as fundamental for diagnostic and prevention.

To fully understand what we want to talk about, it is important to start from the beginning. Before even giving a definition, let's start with the name. Professor Krestin, who has been dealing with the subject for a few decades tells us about the genesis of precision imaging.

Gabriel Krestin
I have been confronting with this topic quite some time ago, at that time we were talking about personalized medicine, that was the first definition. And I have been involved in an exercise that was conducted by the European Science Foundation with a big panel of people, many people participated there to make a definition of how we see the evolution of healthcare and medicine and healthcare in general towards personalized medicine at that time.

With science this all evolved and it moved towards a wave from this concept of personalized or individualized medicine towards more precision medicine were we are not talking about each and every individual but about a selection of a group of individuals that have similar, not identical, but similar trades, similar characteristics from different point of view. So, if I may give a very simplistic definition, it is taking into account individual variabilities between individual of patients.

The term precision healthcare also came out because we realized that there is even more than the biologic characteristics and the phenotype of each individual, there are also other factors that influence the probability that somebody has a surgent disease and a probability whether the patient will respond to a certain treatment and these can be external factors, factors that are link to the environment, to the lifestyle of the individual, to the social environment and so on and so forth.

Luisa Poggi
It is easy to see how these findings are important, both for prevention and therapy.

But like all great changes or innovations, there are positive elements that speed up the process and negative elements that hinder it.

Professor Krestin tells us about the role of AI and big data:

Gabriel Krestin
So that's about precision healthcare, the only way to go into this direction is gathering as much information as possible, information about the biological characteristics, about describing the phenotype of a certain individual and describing all this factors from outside the patient. And that is an unbelievable task because the data that you can gather is infinite, I would say even if we think that we know a lot we still have a lot more to know and we can gather even more. That's where this data science comes into play because handling all that sheer amount of information and combining it and seeing the interactions between different pieces of information with each other, is almost impossible to do for a human brain: a human brain is extremely good in detecting different shaping, some specific characteristic for instance, in images a human brain is still much better than a computer to detect something that's in different shaping, something that we called normal from abnormal, but a computer has difficulties with that.

On the other hand, computer is extremely good in integrating infinite amount of data and extracting without any prejudice. Out of this data valuable information and knowledge that can

be then used to precisely determine there is factors that there is for a patient the risk to develop something and to choose the right approach and the right treatments. So, this integration of different layers of information the genetic, the metabolic, the proteomic, the microbiomic, the exposomic and the imagiomic information and integrating that all together gives us the possibilities to make a very precise diagnosis and choose a very precise treatment.

And for that we need the computers and yes, AI is a way to go for.

Luisa Poggi
As a matter of fact, COVID-19 has accelerated a change in the way of working and the centralization of information, data and processes.

One may wonder what kind of data needs to be collected and analysed in a precision medicine approach. Indeed, precision therapy relies on the ability to fully characterize the pathology of an individual patient.

We need to perform personalized diagnosis, and hence changes are coming also in precision Diagnostic, how Francesco Blasi told us.

Francesco Blasi
Diagnostic imaging is the pillar of precision medicine. Together with genomic and proteomic analyses, imaging can contribute to fulfil the ultimate goal of precision medicine, which is to administer the precise treatment to the right patient at the right time. Imaging has some unique features that fit perfectly the needs of precision medicine.

It is mainly non-invasive, it carries minimal risk for the patient, it can be repeated several times, resolving the temporal heterogeneity of some diseases like cancer, it can provide with high spatial resolution anatomical, physiological, and molecular information which are impossible to derive using other technologies. With diagnostic Imaging we can look into the human body with unparallel precision and retrieve information extremely relevant for the medical decision-making process. In other words, using the motto of Bracco, imaging is life from inside.

Luisa Poggi
Diagnostic Imaging refers to the techniques and processes used to create images of the human body for clinical purposes, and encompasses all medical procedures seeking to reveal, diagnose, or examine disease. Francesco Blasi will drive us through these techniques.

Francesco Blasi
It is well-established that about 70% of medical decisions are based on laboratory results, and if we add on top of that the contribution of in vivo diagnostics it is clear how relevant is the value of diagnostics for precision medicine. Traditional medical imaging, either radiology or

nuclear medicine, already support greatly precision medicine, providing crucial information from early screening to staging and re-staging and to late-stage response monitoring to treatment.

In addition, due to the inherent digital nature of modern medical images, the application of machine-learning and artificial intelligence algorithms may allow to extract additional values and information from the images; for instance, the process of data mining from information-rich medical images called radiomics, may improve diagnosis, prognostication, and clinical decision support, further enabling precision medicine.

Luisa Poggi
Most of the diagnostic imaging techniques are well established procedures that physicians rely upon on a day-by-day basis.
These techniques were here decades ago, way before we started talking about precision medicine. How diagnostic imaging is evolving in the clinical onset of precision medicine?

Francesco Blasi
Medical imaging is evolving to fulfil the needs of precision medicine, adding to the well-established information on anatomy and physiology or metabolism, also molecular features, what we call molecular imaging. Molecular imaging, defined as “visualization, characterization, and measurement of biological processes at the molecular and cellular levels in living systems”, is an invaluable tool in the era of precision medicine.

By enabling disease imaging at cellular level, molecular imaging may help to identify disease at early stages, classify which group of patients may benefit from a particular targeted therapy, and assess treatment response. For example, we can non-invasively assess the expression of a protein antigen that is specific for a given disease and monitor its variation over time in the whole body. This is probably not in vivo immunohistochemistry yet, but we are getting close.

Luisa Poggi
One may wonder, in a precision medicine approach, if synergies between diagnosis and therapy can be further fostered and optimized. Are there specific evolutions of precision imaging in this respect?

Francesco Blasi
The evolution of molecular imaging is called theranostics, which is the combination of the words diagnostics and therapeutics, because some drugs may be exploited not only for imaging applications but also to treat a disease, particularly an oncology. The concept of theranostics really means that if you can see a disease, you probably can also treat it.

Platforms originally designed for diagnostic imaging can be adjusted to serve also therapeutic purposes and the future will bring us new potential indications to explore using cutting-edge technologies.

Lusia Poggi
So far, we have extensively discussed about in vivo diagnosis. However, for early detection, screening and for the molecular characterization of disease that will allow to drive personalized therapy, in vitro diagnostics plays a crucial role.

In vitro and vivo diagnosis operate in two different onsets, with different requirements and different technological challenges.
Lucy Costantino will explain to us the importance of in vitro precision diagnosis.

Lucy Costantino
To apply early detection in vitro is critical to perform tests with high sensitivity, the new technological approaches have help us to perform precision in medicine never applied before. Evidence-based laboratory medicine assists clinical management of patients by integrating into clinical decision making the best available research evidence for the use of laboratory investigations with the clinical expertise of the physician and the needs, expectations and concerns of the patients, in order to improve the care and outcomes of individual patients and the effective use of healthcare resources.

But Laboratory tests offer value only if they are: clinically valid, they provide highly accurate diagnostic or prognostic information for clinical decision making; they contribute to improve patient-centered outcomes; they contribute to reduce health care costs. In brief, laboratory tests have value if they provide benefit to patients at acceptable costs.

Luisa Poggi
For centuries in Europe, medicine has been marked by a “curative” approach, in the 21st century healthcare system entered in the era of “4P” medicine characterized by: **personalized** and targeted interventions, **prediction** and **prevention** of diseases, more precise diagnoses and a more **participatory** role for patients.

Therefore, healthcare system is each day more and more committed in creating a patient-centered decision system. But what can be the impact of genetic testing and liquid biopsy on the future of personalized medicine?

Lucy Costantino
Advances in the field of human genetics over the past three decades have led to improvements in human health through development and availability of novel genetic testing approaches for diagnosis, prognosis, treatment therapy, safety, preventive screening and population-based risk assessment.

By combining and analysing information about our genome, with other clinical and diagnostic information, patterns can be identified that can help to determine our individual risk of developing disease; detect illness earlier and determine the most effective interventions to help improve our health; be they medicines, lifestyle choices, or even changes in diet.

Over the past decade, invasive techniques for diagnosing and monitoring cancers are slowly being replaced by non-invasive methods such as liquid biopsy.

Liquid biopsies have drastically revolutionized the field of clinical oncology, offering ease in tumor sampling, continuous monitoring by repeated sampling, devising personalized therapeutic regimens, and screening for therapeutic resistance.

Luisa Poggi
How the genomic approach could be synergic with diagnostic and therapeutic techniques in radiology?

Lucy Costantino
With the rapid development of new technologies, including artificial intelligence and genome sequencing, radio genomics has emerged as a state-of-the-art science in the field of personalized medicine. Radio genomics combines a large volume of quantitative data extracted from medical images with individual genomic phenotypes and constructs a prediction model through deep learning to stratify patients, guide therapeutic strategies, and evaluate clinical outcomes. Recent studies of various types of tumours demonstrate the predictive value of radio genomics.

Compared with conventional medical treatment, the concept of precision medicine follows a “one-size-fits-one” philosophy and sets out a tailored therapeutic plan according to the genotypic and phenotypic data of individual patients.

Luisa Poggi
Genotyping and phenotyping data for individual patients is the essential of precision diagnosis, and we have reached the point in which this is possible both in vivo and in vitro. While in vitro testing allows for early prevention and patient stratification to guide therapy, in vivo imaging allows for a precise visualization of the disease and for therapy monitoring, being also able to guide its eradication with imaging guided surgery approaches. In vivo and in vitro diagnosis have never been more complementary than in precision imaging. They are really two sides of the same coin.

How will the respective disciplines evolve in the future according to our guests? And, will we be able to predict the evolution of people's health and intervene appropriately?

Gabriel Krestin
We hope and we work in that direction, but prediction, you know, looking into a glass ball and predicting the future I wouldn’t say always but basically it remains something illusive because you will not be, maybe I’m saying too much, but ever I don’t know, maybe I’m too old to believe in that, ever be able to predict with a 100% precision what you do is you predict or you

determine a certain risk, and the risk can be increased based on the knowledge that you have now from the information that you gather now. And you say that this individual has a much higher risk to develop a certain condition than another individual, because it has a genetic predisposition because there are some environmental issues, there's lifestyle issue.

But, for the time being to say that you or I, given all this information that we have, will with certainty develop a disease it's impossible.

Lucy Costantino
I think that in the future tests based on non-invasive approaches such as LB will become the tool of choice with which not only to make early diagnoses before the disease sets in, but also to be able to evaluate the possible evolution of the damage and will allow us to have an advantage in terms of therapeutic treatment to preserve the state of well-being rather than cure the damage.

Francesco Blasi
Precision imaging is revolutionizing medical imaging; we have seen bench-to-bedside translation of novel technologies that are affecting medical decisions and improving patients' lives. So, it works, we can make such technologies happen. However, it still takes too long to take new drugs to the market, on average about 10 years or more. We need to work together with academic research scientists, industry associations, medical scientists, regulatory and funding agencies to reduce such long time. The COVID-19 pandemic has also shown us that there are ways to accelerate the process of bringing a new drug to the market, so we can do it, and we must do it to fulfil the goal of precision medicine and to fully exploit its benefits. Only in this way we can really make a difference and improve patients' lives, which is our ultimate goal at Bracco.

Luisa Poggi
Precision imaging may look as the future of medicine but it is, indeed, the present.

Years of research in this field have yield extraordinary results, with millions of patients that have already benefit from having received the right diagnosis and the right treatment at the right time.

We have come so far, but there's still a long road ahead of us and we need to constantly develop new drugs and new technologies to overcome limitations, to tackle unmet medical needs and to continue improving patients' lives, one life at a time.

This was Talking Images on the past, present and future of Precision Imaging.

I'm Luisa Poggi and I thank our guests for their invaluable contributions and all of you for having been part of this journey in the exciting world of Precision Imaging.