Cancerworld

Precision testing – moving into the limelight

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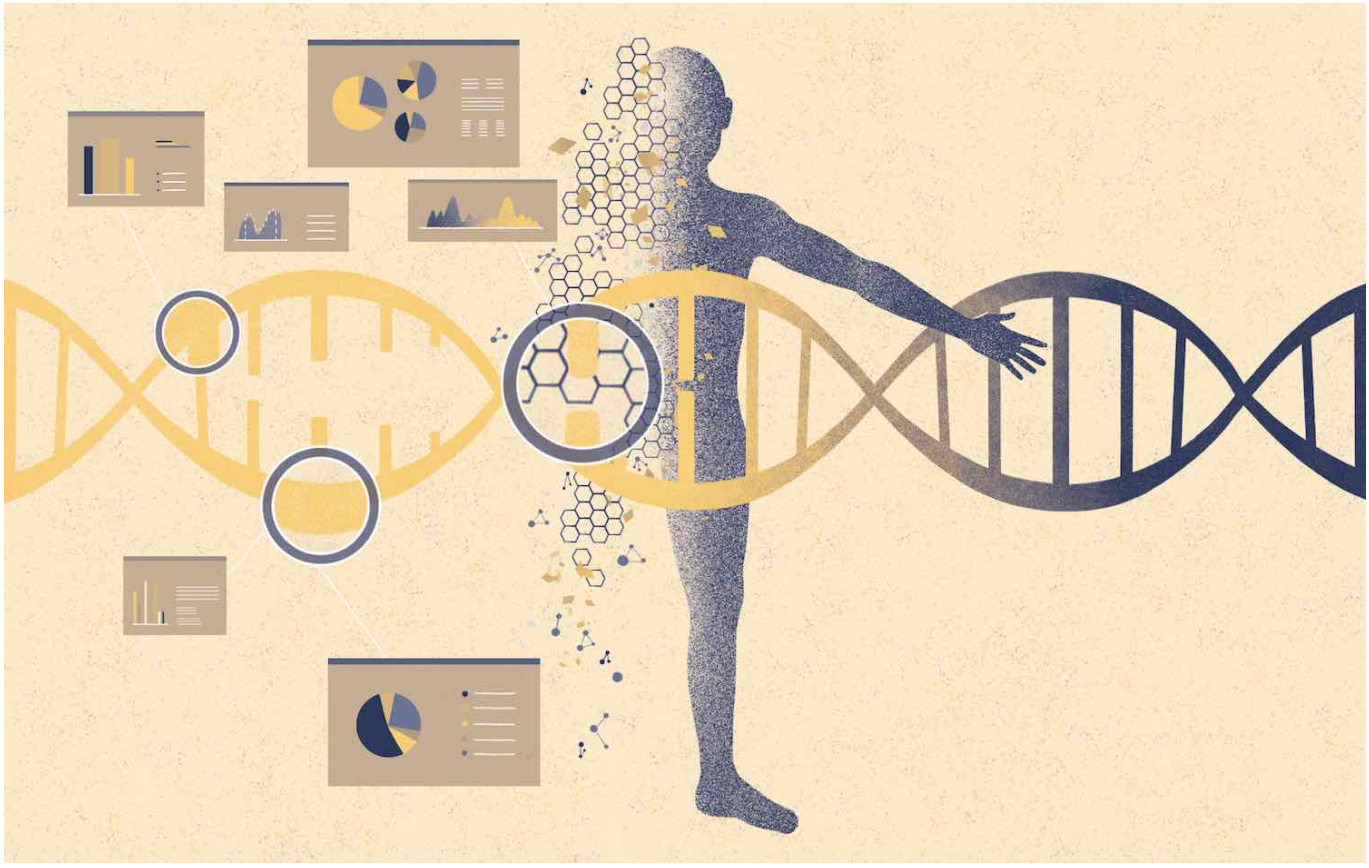

Introduction

Over the last years, interest in precision testing in oncology has increased dramatically. Precision testing allows the tailoring of medical treatment or drug administration to the individual molecular characteristics of a given patient's tumour. As such, it is part of a concept often referred to as personalised medicine. The management of cancer has clearly shifted from a now obsolete one-size-fits-all approach to one where the ability to make detailed biomarker assessments allows for better appreciation of an individual patient's disease status and likely evolution. However, the term « personalised medicine » is somewhat misleading insofar as the identification of biomarkers actually aims at stratification of patients into subpopulations with regard to likely responsiveness to specific drugs. Crucially, as well as being able to identify patients who will benefit from particular therapies, precision testing is also used to avoid therapies that will not work but which will deliver all the negative side-effects nonetheless.

Tumour types and techniques

To date, there is uneven uptake of precision testing on different cancer types. Many tumours are still conventionally treated by chemotherapy and radiotherapy. The number of biomarkers usefully recognized for testing is variable depending on the tumour type and traditional histological analysis is still prevalent. What is changing is that the list of actionable genomic alterations is expanding at a rapid rate, as are the number of drugs available for treatment, albeit with issues of timelags for approval.

Precision testing uses numerous techniques now available to test for molecular alterations, such as:

MSI – Microsatellite Instability
dMMR – defective DNA Mismatch Repair
IHC – Immunohistochemistry
FISH – Fluorescence in situ hybridisation
PCR – Polymerase Chain Reaction
TMB – Tumour Mutational Burden
NGS – Next Generation Sequencing
ctDNA – Circulating Tumour DNA
WGS – Whole Genome Sequencing
CGP – Comprehensive Genomic Profiling

Standard techniques targeting genomic biomarkers assess a single biomarker per analysis, whereas Next Generation Sequencing (NGS) for example assesses genomic alterations in multiple genes in a single analysis and is therefore revolutionising the scope and applicability of precision testing.

There are advantages and disadvantages for each of the various techniques depending on tumour type, tumour heterogeneity and temporal heterogeneity – the magic is in the mix! The aim here is not to give a detailed account of the best testing tools for different tumour types, nor to provide a listing of biomarkers used. Instead, consideration will be given to the factors that need to be addressed in order to maximise the benefits that precision testing can bring. With these new and complex methods, a re-think of current practices and structures is necessary.

Multidisciplinarity and new organisational structures

Because of the paradigm shift that precision testing is bringing to the diagnostics, prognostics and treatment therapies for cancer, it has become clearly apparent that a multi-disciplinary approach is essential to realize the benefits of precision testing methodologies. Professions are changing and the lines delimiting the different professions are shifting. New organisational structures must be envisaged which break down silos of knowledge and enable sharing of expertise. The role of the pathologist is expanding. The classical methods which investigate tumours based on tumour size, morphology and histological type are now being complemented by detailed molecular profiling and tumour agnostic techniques, as well as the use of cell-free DNA technologies and liquid biopsies. The resulting medical pathology report is necessarily more complex and precise. In precision medicine, the results of molecular pathology can ideally help individualize patient treatment, selecting different therapies and tailoring treatment to the unique molecular profile of an individual patient’s cancer. Significant benefits are that treatment is more effective and often less costly since carefully targeted. Whilst pathologists have been traditionally involved in the early detection of disease, they are now involved in the early detection of treatment targets. This is a new field, shaping a new generation of pathologists. Similarly, there is a need for next-generation medical oncologists with modified skill sets.

In the sub-sections below, an attempt will be made to put forward the context within which precision testing is evolving, and the topics where change is needed in order to gain the true benefits of using the new techniques and methodologies.

Next Generation Sequencing (NGS)

Many pathology departments are now moving towards working far more with NGS, as conventional molecular testing approaches are no longer sufficient due to the ever increasing number of identified biomarkers and therapies available. NGS has completely changed the approach for genomic medicine, especially in oncology. Targeted panel sequencing is used for the capture of oncogenes which are known to be associated with treatment selection. Testing can go even further, with WES (whole exome sequencing) or WGS (whole genome sequencing), but the data analysis and interpretation is very time-sensitive and is not carried out in routine clinical practice.

Clinical oncology is now characterized by targeted therapies based on molecular subtypes and a pooling of knowledge and information in a multidisciplinary setting, with input and cross-discussion from oncologists, pathologists, geneticists, biologists, pharmacologists, bioinformaticians and other professional areas. These discussions evolve in the context of multidisciplinary tumour boards.

Molecular Tumour Board (MTB)

It is the evolution from tissue biopsy to molecular biology that has brought about the concept of the Molecular Tumour Board. MTBs are needed in order to obtain evidence-based translation of molecular alterations into clinical action. The real relevance of MTBs is for a highly diverse set of professionals to interact in order to make informed decisions on precision therapies directed at molecular targets, interpreting the biological and clinical relevance of genetic alterations. The use of molecular tumour boards is of great value due to the fact that precision testing is such a fast-moving field. Together, all the specialists can contribute their expertise to determine the best treatment for the patient. There are a growing number of approved drugs able to target specific genetic alterations, the novelty of precision testing being in the concept that a drug can now be used based on the target presence without a related specific tumour site. MTBs also provide a context where clinical trials can be evoked where patients could be included in order to have access to off-label drugs, and for these trials to then bring crucial new data for evaluation.

Artificial intelligence (AI) and big data

Due to the fact that the number of biomarkers identified has increased dramatically over the years, as has the number of available therapies, the need for using different NGS methods is essential. This requires the ability to analyze very large amounts of data. The use of AI and big data, where deep learning algorithms are applied to scanned images and other forms of data, is already making headway and is proving to be very useful in providing accurate molecular signature data in human malignancies. There is ample scope for integrating the precision diagnostics with electronic healthcare records to enrich diagnosis, treatment and monitoring. With better quality data sets, AI approaches should enable the identification of phenotypic subgroups in clinical data which in turn should help target and recruit patients to clinical experimental studies. The complexity of data will increase, requiring very advanced analytical tools.

Education

The MTB is a powerful educational forum. It is the ideal place for sharing complex genomic data and for medical oncologists' attention to be drawn to information of scientific relevance which they might otherwise not have known about. Using testing of various types, depending on tumour type

and temporal status (primary, metastatic etc.) provides results which are included in the medical pathology reports to which the actionable insights must be incorporated in a comprehensive way. There needs to be integration between laboratory medicine, cellular pathology and radiology, for example, which necessarily implies a sharing of skills and competencies which must be addressed through increased education.

Many oncologists lack sufficient knowledge of genomics and this has translated into only a small number of patients with actionable, or potentially actionable, alterations being enrolled in genotype matched trials. To counteract this knowledge gap, several publicly available resources (eg. My Cancer Genome, OncoKB) have been developed as decision-making tools.

In a multidisciplinary context it is crucial that healthcare professionals are able to communicate and interact with each other, as well as with patients and patient groups. The pathology report is a decision-making assistant, but the oncologists must be fully informed as to the interpretation as they have the direct link with the patients. Ultimately, it is the individual patient who is at the heart of the whole realm of cancer management. The next generation of oncologists will be using the detailed pathology report to help with drug prioritisation, in the knowledge that the best drug for one patient may not be right for another.

The need for education and transfer of knowledge has been mentioned but a whole other facet of education has to be considered with regard to all stakeholders within the sphere of precision testing. These include, but are not limited to, drug companies, patient groups, ministries of health and political powers. Education is crucial at all levels for the roll-out of precision testing. This concept should be deployed starting at an academic level with a reassessment of medical courses and training programs in universities and medical schools.

Guidelines

Better harmonisation of molecular testing will be encouraged through EMA and FDA decisions as well as guidelines proferred by ESMO, ASCO, and various other authoritative bodies. Within Europe there need to be strict recommendations from ESMO on which tumour types to prioritise for precision testing – for example, indications for tumour mutational burden (TMB) or microsatellite instability (MSI) exist in some tumours but certainly not all. There are currently three existing scales for ranking molecular targets in classifying clinical actionability. The use of the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) is proving a very helpful framework for ranking genomic alterations. Also available are the Joint Consensus Recommendation (JCR) for reporting genetic variants in cancer, as well as the Oncology Knowledge Base (OncoKB). There is a clear need for a standardised scale in clinical practice and molecular tumour boards in order to have a common language governing genomic actionability.

Regarding best practices and standardisation, countries should be able to put in place a network of regional excellency centres dealing with biomarker testing. These must be governed by adequate guidelines which must imperatively be followed in order to obtain clinically useful analytics.

One stumbling block of note is the need to keep all key guidelines regularly updated to incorporate new understanding as it emerges, failing which they lose their relevance.

Costs

Costs, which are a major impediment to the availability of precision testing in many countries, must be brought to political agendas. A strong argument which can be made to encourage the development of precision testing is to consider the cost of not testing, where the financial burden of

patient care can be far higher in the long term. Precision oncology needs funding. Molecular tumour boards are structures which need funding to be able to function. Funding is needed for the development of new professions such as bioinformaticians, new-generation pathologists, oncologists, geneticists… Research and development requires strengthening. Studies are needed in order to evaluate cost-effectiveness. By far the most important costs in precision oncology are related to the drugs. By comparison the cost of testing is minimal (almost 10x less). Novel ways of distributing costs should be sought. An interesting model which has been suggested, for example, is for treatment costs to be covered by drug companies until beneficial results are proven, at which point the costs are then taken over by the medical insurance companies or public health system, depending on countries.

There is currently inadequate funding to ensure that availability, timeliness and reimbursability of precision testing is attained. Effective workflows need to be put in place and be operational. Due to the ever-expanding list of actionable genomic alterations, the new sets of professional skills needed, in biogenetics and bioinformatics for example, there is a need for a major system reform. However, the more players are added, the more the system becomes inherently lethargic and as a consequence workflow mechanisms and methodologies have to be clear, coherent and smooth.

Policies and Politics

It has now been clearly established that, for many cancers, identifying the specific molecular characterizations can vastly improve the choice of the most appropriate treatment – which may involve a combination of different drugs, but not only – and can lead to better outcomes. The use and applicability of precision testing is not equal within different tumour types or grades, certainly, but this aside, there are gaping inequalities across countries and within regions regarding access to such testing.

Skilled healthcare professionals, well-honed in the analysis of precision testing data, need to be available in excellency centres which can act as reference sites to smaller, less specialized centres. There is also the need for strong investment in state-of-the-art precision testing machinery, tools and expertise. High patient heterogeneity requires more integration of complex genomic data which implies having access to a large number of different competencies and expertise; hence the existence of such excellency centres is paramount. These centres need to have tight quality control mechanisms to ensure that the standards maintained are irreproachable, since as well as the expertise centres themselves, there need to be effective roll-out strategies. Excellency must permeate so that guidelines are followed and whether precision testing is carried out in regional or local centres, the results obtained are timely, accurate, and comparable.

Geography

Europe is very heterogenous and not all countries have well-developed cancer centre networks, or even access to MTBs, so paths must be found to counteract, at least to some extent, the discrepancies between national processes and policies. The culture of medicine is very different among countries. Academic centres, community oncology practices, medical centres, pharmaceutical companies and other key players are all very separate entities and yet information must flow between them in order to accelerate the process between stratification into patient sub-populations and patients being able to then receive the adequate treatment drugs. There are significant varitions in drug and test access, as well as significant delays between EMA or FDA approved drugs and what the results of biomarker testing point to. Multi-stakeholder discussions must take place to address these issues. Urgent discussions are needed also with, for example, national health insurances and health politicians with regard to reimbursement of costs and the use of drugs which are not yet approved or are used off-label.

Creative synergies must be found, with strong emphasis on communication – between countries and regions – and with ongoing discussions on the advancement of knowledge relating to tumour types within the realm of precision testing. There are currently significant variations in drug and test access as well as delays between EMA approved drugs and the needs identified by biomarker testing. There are still far too many discrepancies in national processes and policies with regard to NGS. Constant dialogue between health care professionals and political leadership with the ability to influence and carry decisions is key to mitigating this situation. To this end, CQA (Critical Quality Attributes) scheme participation and ISO accreditation should be mandatory in all European countries. All cancer patients eligible for biomarker-linked therapy should be able to undergo comprehensive, ongoing tumour testing throughout the course of their disease, regardless of their place of residence.

The European Commission

The EU oncology community is already working hard at addressing some of the issues mentioned above. The EU has several strong initiatives in place, such as the Cancer Mission and the Beating Cancer Plan, with different DGs (Directorate-General) of the European Commission in place studying diagnostics, treatments, reimbursement etc. Perhaps one of their most important activities is addressing the regulatory barriers that currently exist in the area of digital health data and cancer registries. The challenge is in pulling all the knowledge and conclusions together into an action-based plan, with the inclusion of resource assessment and corresponding budgets being allocated. This action at the European level is where the power and importance of networks can bear fruit. There are a number of very active organisations which feed into the EU efforts, such as the European Cancer Organisation, with its 40 member societies and Patient Advisory Committee, and the various National Cancer Institutes, amongst other expert organisations in the relevant fields. Patient Advocacy groups are also well represented and are a formidable source of lobbying in order to ensure that the management of cancer in all its forms is given the attention it requires and to make sure the subject is never allowed to slip out of focus.

Conclusion

In spite of advances, there are heavy limitations in access, availability and reimbursement of testing which explains why fewer than 25% of cancer patients currently benefit from precision oncology – a startling statistic. This is a reflection that precision testing is an area still in its infancy, but it is also a sign that countries have not yet been able to invest adequately in putting in place testing centres and infrastructures to enable all patients to have access to precision testing. Research and knowledge are advanced but implementation is where massive disparities exist. Perhaps the most pressing challenge today is persuading the policy-makers, decision-takers and politicians, who may well, in the lottery of life, already be patients or future patients, that to invest confidently in precision oncology is to maximise the possibility of longer lives with lesser negative impact and fewer side-effects from cancer treatments for all. This message should be high on political agendas.

In the light of the vast amount of new data on biomarkers and their relevance, as well as new insights into diagnostics and treatment therapies, a plethora of concurrent actions must be taken ranging from the establishment of competence centres, laboratory quality controls, investment in complex machinery and IT solutions, and in improving communication lines between all stakeholders.

The patient, for whom all the novel precision testing methodologies are ultimately developed, has a strong responsibility albeit not an immediately obvious one, in helping to determine cancer journey outcomes. In effect, because there are very few patients with the same molecular alterations, there are consequently many more what can be labelled «rare» cancers. Patients therefore have an

important role in allowing the medical body to collect and share their medical data, and indeed encouraging it to do so. Currently, it is near impossible to exchange patient data because of data protection issues. However, these need to be circumvented as it is through the blend of the use of big data, accessible electronic health records, machine learning and data sharing at least on a national level and better at a European or even wider level, that the true benefits of precision medicine can be increasingly realized.

Sources

Expert webinars on Precision Testing carried out by Sharing Progress in Cancer Care (SPCC):

- Best practices/state-of-the-art in precision testing in breast cancer
- Best practices/state-of-the-art in precision testing in lung cancer
- Best practices/state-of-the-art in precision testing in colorectal cancer
- New precision testing methodologies (NGS, CGP, Circulating Tumor Cells)
- Best practices in precision testing in selected cancers: which markers to test in order to ensure optimal treatment?
- Rules, collaborations and harmonization to improve access to precision testing

Material from the European Cancer Organisation (E.C.O.)