Perspective

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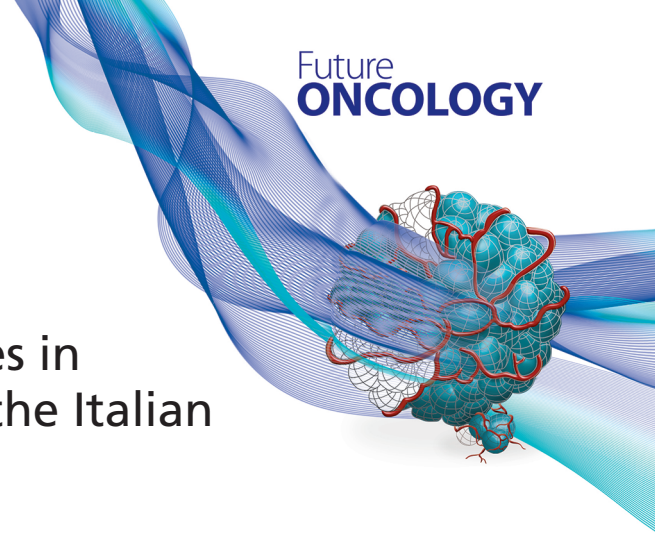

Molecular tests and target therapies in oncology: recommendations from the Italian workshop

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Next-generation sequencing (NGS) and liquid biopsy are new technologies that can allow overall tumor profiling in a single analysis and play an important role in the implementation of precision oncology. However, the lack of guidelines in this setting has limited the development of precision oncology in Italy. This article summarizes recommendations for the appropriate use of NGS in tumor gene profiling, as well as access to tests and target drugs, that were prepared by a group of key opinion leaders and relevant stakeholders. In particular, the need to create laboratory networks capable of carrying out NGS tests in Italy is highlighted. It also appears necessary to establish an adequate reimbursement system for NGS tests. However, the expert panel recommends that the use of NGS tests in clinical practice should be limited to specific tumor types, based on the number and complexity of biomarkers and the availability of treatments.

Lay abstract: The increasingly precise and extensive characterization of tumors through gene profiling allows a greater understanding of the molecular mechanisms underlying tumor growth, thus permitting better, more personalized therapeutic options. In the past two decades, tests to individually profile genes (molecular alterations) of different tumors – including lung, stomach, colorectal, breast, ovarian cancer and melanoma – into clinical practice have been introduced, allowing patients who carry specific genomic alterations greater access to more effective therapies. The first phase of the era of genomic profiling was limited to the identification of molecular alterations, each detectable with a specific test, aiming to define the sensitivity/resistance to a single drug and for a specific cancer site. The second phase of precision medicine determined several molecular alterations tested for single cancer types, often with different techniques. We have now reached a third phase, characterized by important technological developments and, in particular, by the introduction of next-generation sequencing (NGS) and liquid biopsy (using patients' blood). These techniques allow a comprehensive genomic profile of the tumor in a single analysis using the same biological sample. These new techniques have led to the selection of increasingly precise patient candidates for target therapy and then to the monitoring of their treatment, together with identification of resistant tumor clones. However, the lack of guidelines in this setting has limited the development of precision medicine in Italy. This article reports a summary of recommendations for appropriate indications in tumor gene profiling, as well as for access to tests and target drugs, that were prepared by a group of key opinion leaders and relevant stakeholders.

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Gene profiling, one of the most important innovations in the understanding and treatment of cancer, has assumed fundamental importance in the management of cancer patients from the perspective of precision medicine. After the initial phase, which was limited to the analysis of single biomarkers, and the second phase, in which multigene panels were adopted, we are now entering a third phase in which large gene panels can allow comprehensive genomic profiling (CGP) in a single analyses. However, there are still open issues on clinical, technological and organizational aspects that need to be determined. In Italy, the development of genomic-driven oncology is still limited due to problems related to the nonuniform diffusion of analysis centers throughout the country, differences in the reimbursement of biomolecular tests between regions and the difficulty of accessing nonregistered drugs (Box 1). To produce a reference document for the Italian oncology community and health authorities, the Istituto Superiore di Sanità (ISS) and the Federation of Italian Cooperative Oncology Groups (FICOG) promoted the workshop 'Molecular Tests and Target Therapies in Oncology,' which developed and defined possible approaches in three main areas for public health: evidence and state of the art, technologies and platforms and clinical applications and organizational models. This document therefore presents the synthesis of the work of the Italian Workshop held on 4 and 17 November 2020. The recommendations for implementation of precision oncology in Italy are summarized in Table 1.

Evidence & state of art

Evidence

Molecularly targeted therapies in oncology are a rapidly expanding therapeutic strategy that is accompanied by the need to develop diagnostic tests to determine the presence of molecular biomarkers for the selection of the most appropriate therapy [1–5]. In 2019, all new oncology drugs approved by the EMA were molecularly targeted, and five were associated with a predictive biomarker. The availability of new sequencing technologies, which can simultaneously assess the presence of high numbers of molecular alterations, offers the possibility of searching for a wide range of alterations [6–8]. Current drug evaluation methods may pose difficulties when applied to the scenarios that lie ahead. Some mutations potentially predictive of response to molecularly targeted drugs may be so infrequent that robust phase III studies cannot be performed. At the same time, studies that cross-validate drugs targeting a specific molecular genetic alteration face the problem of requiring control cohorts with a large heterogeneity of comparison therapies. Many clinical trials evaluating CGP approaches for the purpose of combining molecularly targeted therapies have ended without successful results, probably for several reasons, including the advanced cancer stage of the patients, the choice of biomarkers and the low efficacy of some drugs. The decision on whether to submit an individual patient to extensive profiling, the type of sample to be used and the identification of the mutation(s) determining the success of the therapeutic approach require a multidisciplinary panel of specialists. In this regard, the Molecular Tumor Board (MTB) plays a fundamental role in this phase of development of precision medicine both to ensure the prescriptive appropriateness of the CGP tests and to warrant the correct interpretation of the test results and their clinical application. In fact, many clinicians have limited confidence in the interpretation of multigene next-generation sequencing (NGS) tests [9,10].

Critical issues

The difficulty of carrying out traditional studies leads to the identification of alternative sources of evidence, such as data collection on common platforms that ensure homogeneity and quality of the collected data, to make them potentially usable for regulatory purposes. The majority of Italian oncologists currently base their decisions on the Tumor-Node-Metastasis (TNM) classification and find it difficult to access platforms for tumor gene profiling. Consideration should be given to using evidence from clinical practice, but this approach requires action to make the data collected reliable. The central authority needs to qualify the platforms where the data are to be collected and define the criteria to be met, as well as plan the distribution and quality control of the labs performing the diagnostic tests. The criteria for the establishment and operation of MTBs must also be defined uniformly throughout the country.

Box 1. Italian Health System.

The National Health System in Italy (INHS) provides coverage for authorized health services to all Italian citizens and to foreigners who are recognized as residents of the country. Decisions related to the services provided by the INHS are taken at a central and national level and at a local, 19 regions and two autonomous provinces, level. The national parliament every year, after discussion on a document prepared by the government, determines the provisional budget for the health expenditures and the part of this dedicated to the procurement of drugs. The Italian Medicine Agency (AIFA/Agenzia Italiana del Farmaco) decides on the reimbursement of drugs and negotiates the price with the holder of the marketing authorization. Diagnostic tests are reimbursed to the public or recognized private laboratories or hospitals if included in lists defined both at the national or regional level.

Table 1. Recommendations for implementation of precision oncology in Italy.

• Create a laboratory network capable of carrying out next-generation sequencing (NGS) testing of tissue and liquid biopsy, in the context of the regional oncological networks
• Organize a quality control system of the laboratories that carry out NGS tests
• Use NGS technologies in cancers selected on the basis of the number and type of genomic alterations and the availability of approved drugs
• Establish an appropriate system of reimbursement of the costs of NGS tests
• Create molecular tumor boards at the national level to ensure the appropriateness of the prescription of NGS tests and the correctness of their interpretation for clinical purposes

The use of gene profiling technologies and molecularly targeted drugs are inevitably associated with costs for the health system. Diagnostic tests are, in most cases, not included in the 'guaranteed levels of care,' and access can be very different at regional and even subregional levels. The complete separation between the authorization and reimbursement pathways for drugs and diagnostics in the universal coverage offered by Italian health system is a further obstacle to the dissemination of molecular targeted therapies. To facilitate rapid and uniform access to molecular-targeted therapies on a national level through the recognition of innovativeness, it could be appropriate to reexamine the criteria for its allocation as defined by the Italian Medicine Agency (Agenzia Italiana del Farmaco, AIFA) in March 2017.

The use of multigene tests could reveal genetic alterations for which approved drugs are available but with a different indication. This phenomenon could lead to the use of drugs outside the authorized and reimbursed indications. It is clear that this phenomenon requires appropriate regulation to ensure that patients have access to a potentially active therapy within a regulatory framework that also allows for the generation of knowledge. In this respect, the current authorization mechanisms may not be adequate to respond in a timely manner to the need for treatment.

Finally, the Italian public health system provides free assistance to all cancer patients. However, an impact of the disease has been observed on cancer patients in terms of financial toxicity [11]. Research on this topic is very active in Italy [12,13]. Therefore, it will be important to monitor the effects of precision medicine on the financial toxicity of Italian cancer patients.

Interventions

On the basis of the foregoing, the following priority actions are identified:

- The definition of platforms to collect data on the use of molecularly targeted therapies and the outcomes of these therapies
- The possibility of access to the National Observatory on Clinical Trials to enable patients to be referred to clinical trials of molecularly targeted drugs
- The definition at central level of diagnostic pathways, distribution and quality requirements of molecular diagnostics laboratories and criteria for the composition and functioning of MTBs
- The definition of diagnostic pathways that guarantee the quality, appropriateness and cost coverage of molecular tests at national level
- The implementation of a negotiation strategy with pharmaceutical companies to make a significant contribution to evidence-building and compensation for diagnostic costs through authorizations and reimbursements of a defined duration

- The regulatory definition of mechanisms to make medicines available in a timely manner
- Revision of the criteria for awarding innovation by AIFA
- Monitoring the effects of precision medicine on the financial toxicity of Italian cancer patients

Technologies & platforms

General aspects

The number of biomarkers to be assessed in clinical practice for molecularly targeted treatments is steadily increasing [2]. This evolution of precision medicine requires a careful choice of technologies to ensure that they are performed appropriately, within the timeframe of clinical needs and with the often limited amounts of biological material available. The introduction of massively parallel sequencing technologies in molecular diagnostics, better known as NGS, represents an important technological contribution to address these new clinical needs.

NGS can be performed with panels of various sizes, capable of analyzing from a few dozen to hundreds of genes. In clinical research centers, the availability of drug-targeted studies increasingly imposes the need for comprehensive genomic profiling (CGP) in selected patient populations. CGP is likely to play an important role in customizing therapies in the future, but it is not a viable approach in current clinical practice.

The choice of analysis technology: NGS versus standard techniques

NGS techniques in clinical practice should be applied in selected advanced-stage neoplasms, depending on the number of molecular targets to be detected, their complexity and the percentage of patients with biomarkers approved by regulatory bodies and national and international guidelines. In this respect, an NGS test performed for the identification of biomarkers approved in clinical practice is part of normal diagnostic procedures [14]. According to current knowledge, adenocarcinoma of the lung, cholangiocarcinoma, prostate and ovarian carcinomas are examples of tumors that should be subjected to NGS analysis. In these tumors, the use of NGS technology allows the optimization of tissue sample utilization and/or the detection of recently characterized changes that could not be detected by other methods of analysis.

The list of malignancies in which NGS technology is recommended is, however, subject to continuous updating based on new knowledge. The NGS panels to be used should cover all molecular genetic alterations for which there is a clinical indication – point mutations, insertions/deletions (indels), gene copy number variations (CNVs) and structural rearrangements, such as fusions, where required. For fusions, RNA sequencing ensures better diagnostic reliability. NGS panels of different sizes are commercially available. In clinical practice, panels limited to the few dozen biomarkers approved in clinical practice are adequate. The use of large panels for CGP, covering hundreds genes, should be allowed in the context of clinical research protocols, whereas whole exome sequencing (WES) is not yet ready for clinical purposes.

The choice of sample: tissue versus liquid biopsy

At the onset of disease, tumor tissue is preferred to liquid biopsy (i.e., circulating free DNA [cfDNA]), for the identification of molecular targets. cfDNA analysis is an alternative when tissue is unavailable or inadequate or the patient has comorbidities that exclude an invasive diagnostic approach. At relapse, in patients undergoing treatment with target drugs, liquid biopsy has the advantage of better representing tissue heterogeneity and allows the identification of mechanisms of acquired resistance, where there is a clinical indication for the use of this information.

When interpreting the results of liquid biopsy tests, the possibility of false negatives (no shedding tumors) and false positives (sequence artifacts, clonal hemopoiesis) must be taken into account. In addition, the detection of complex gene alterations by means of liquid biopsy poses additional problems of diagnostic sensitivity (fusions) and accuracy (CNVs).

There are no clear international recommendations on the most appropriate tissue (primary vs metastases) or the best timing (at diagnosis vs disease progression) for performing NGS tests. The expert panel believes that, if available, the NGS test should be performed on the most recent available tumor sample. In tumors with approved targeted drugs, the test should be performed before starting a first line of therapy. Given the remarkable plasticity of the tumor tissue, in case of progression after targeted therapy, the NGS test must be repeated. In these cases, liquid biopsy analysis can guarantee less invasiveness and a more adequate representation of tumor heterogeneity.

Organization of a laboratory performing NGS testing

The organizational criteria for a laboratory performing NGS tests should cover the following:

- Structural adequacy: availability of adequate areas for the various stages of data extraction, sequencing, analysis and storage
- Instrumental suitability: availability of the latest generation NGS instruments and technologies for orthogonal validation
- Adequacy of human resources: presence of adequately trained staff (pathologists, biologists, bioinformaticians)
- Sample, data and traceability management operating procedures (SOPs)
- Quality certification (at least ISO9001 and ideally ISO15189).

Validation & verification of NGS tests

Laboratory developed techniques and commercially available tests for research purposes must be validated with an adequate number of samples representative of the complexity found in clinical practice. Certified tests for use in clinical practice must still undergo a verification process similar to the validation process. All laboratories performing molecular pathology tests must also undergo the following:

- Internal quality controls, including periodic checks of test performance
- External quality controls.

Interpretation of NGS test results (integration of data in the clinical context)

The results of biomarker tests should be discussed in multidisciplinary groups. NGS panels for clinical practice could reveal the presence of actionable mutations for which there are drugs approved for a different indication or undergoing clinical trials. These cases should be referred to the MTBs, possibly assisted by artificial intelligence tools, the presence of which is still lacking in Italy. In fact, the information derived from CGP tests is often complex, with multiple genomic alterations detected in the same tumor. In addition, it will be more important in the future to analyze the correlation between the genotype and the clinical and pathological features of the tumor [15]. This will be possible only through the use of novel medical devices based on artificial intelligence. CGP tests should always be discussed within the MTB, whether they are carried out in-house or outsourced. The MTB report should be issued after collegial discussion of the molecular results and clinical data. Data on the effect of the proposed therapy and the occurrence of undesirable effects must also be recorded.

Management of identified possible germline mutations

NGS analyses for biomarkers used in clinical practice could reveal the presence of germline genetic alterations predisposing to cancer. This possibility is obviously more frequent when using the panels for the CGP. It is important to underline that mutations identified in the tumor tissue cannot be considered to be of a germinal nature in the absence of subsequent confirmation by tests carried out on nontumor tissue, usually peripheral blood. Given the important implications of germline mutations predisposing patients and their families to cancer, the patient with a suspected germline mutation should be referred to genetic counseling to schedule a possible germline DNA genetic test. This process provides for adequate patient information and informed consent.

Mutational report: structure & minimum information

An Italian Society of Pathologist (SIAPEC) Working Group is defining a reporting method for NGS tests. A structured NGS report should contain the following information:

- List of genes included in the panel used and coverage
- Panel sensitivity limits
- Pathological evaluation of sample adequacy
- Variant allele frequency
- Human Genome Variation Society nomenclature

A biological, pathological and clinical interpretation of the identified variants is also appropriate, using the American College of Medical Genetics) and Association for Molecular Pathology guidelines, available databases (OncoKb, ClinVar, etc.) and the European Society for Medical Oncology (ESMO) Scale for Clinical Actionability

of molecular Targets. Particular attention should be paid to variants of uncertain significance, the classification of which should be reassessed over time.

Organization of a regional/national laboratory network for NGS testing

Given the need for adequate space and personnel and for continuous training of personnel and updating of technologies, together with the need to carry out constant quality control and the consideration that the costs of the tests are significantly reduced in relation to the volume of analyses, centralization of NGS tests is essential. To this end, the recognition of reference diagnostic centers should be encouraged. These centers should be able to invest in training and refresher courses for their staff and in the acquisition of appropriate technologies for carrying out complex biomolecular tests, with an adequate catchment area in relation to the population and geographic needs. These centers should be integrated into the regional oncology networks together with the MTBs.

Clinical applications & organisational models

Current & prospective clinical applications

Initially, genomic profiling was limited to the detection of a few detectable alterations with tests capable of identifying a single biomarker per analysis. This approach has long been sufficient to provide information on the sensitivity/resistance to a single drug and for a specific tumor site. Thanks to advances in knowledge and technology, numerous molecular targets and related drugs are now available for various cancers, thus expanding the possibility of personalized and precision therapy. However, traditional technologies for analyzing genetic alterations do not allow the determination of multiple biomarkers with the timeframe and amount of biological material available in clinical practice.

NGS techniques make it possible to obtain an overall molecular genetic profile of the tumor and thus to select patients who are sensitive to targeted therapy with increasing precision. It is now essential to guarantee equal access for cancer patients throughout the country to NGS tests for genomic profiling of tumors for which evidence and appropriateness is recognized. The use of these technologies must indeed comply with appropriateness criteria that relate to the type of tumor, the molecular targets and the drugs available, based on current knowledge and recommendations developed at the national and international levels.

The epidemiological impact, the possibility of identifying a subgroup defined on a molecular basis and the possibility of providing a target therapy must be considered with regard to the individual patient. Four different, variously interconnected scenarios may occur:

- A frequent tumor with a large epidemiological volume in which one or more subgroups selected on the basis of molecular alterations is identified and defined; an individual tumor may have one or more molecular alterations for target therapies
- A rare tumor that is characterized by molecular alterations
- Tumor with limited or unsatisfactory standard first-line therapy potential
- Tumor with limited or unsatisfactory standard treatment potential in patients with disease progression after first-line therapy.

In addition, different parameters have to be considered concerning the identification of genomic alterations as therapeutic targets:

- The number of molecular alterations to be tested for the individual tumor for the prescription of the drugs available in the disease setting
- The frequency of each molecular alteration that represents a therapeutic target in the tumor
- The relative frequency of the population setting requiring genomic profiling of the tumor
- The complexity of the genomic alterations to be identified and the limitations of the technologies available for their analysis.

The results obtained with extensive genomic profiling should be compared in consideration of the following potential advantages:

- Advantages related to the organization of the service in terms of the quality of the service provided, the response time, the training and specialization of operators, the technological resources available and the optimization of the staff and financial resources employed
- Benefits in terms of equity of access
- Advantages in terms of availability and optimization/savings of the biological sample used, which could represent, in particular for biopsies, a major limitation for determinations by single tests carried out at a later stage
- Clinical benefit in terms of efficacy, toxicity and impact on the patient's quality of life thanks to therapy matched to the molecular profiling

Given that the drug that can potentially be prescribed on the basis of the molecular target identified through genomic profiling, several elements must be considered:

- The level of expected potential benefit, taking into account the limited therapeutic alternatives currently available
- Known toxicity and impact on quality of life
- Access to the drug

On the basis of these evaluative elements and in consideration of the clinical evidence levels of molecular targets according to the ESCAT [16] and the ESMO Recommendations for the implementation of NGS for patients with metastatic cancers [14], nonsquamous non-small-cell carcinoma of the lung, prostate carcinoma, ovarian carcinoma and cholangiocarcinoma are identified for routine use of NGS on samples from patients with advanced neoplastic disease. In addition, the working group is aware of the relevance of using NGS technologies for sarcoma diagnostics. Patients should be able to understand information about molecular tests and their clinical implications in communication with their treatment providers.

Molecular biology centers & regional cancer networks

Technological innovation, together with the continuous growth of requests for molecular profiling of tumors as a function of therapeutic choices and the need to rationalize the use of all resources requires organizational models that provide for the centralization of molecular biology laboratories by volume of activity/population, with logistical planning for sample handling.

In line with the provisions of the institutional table coordinated by the National Agency for Health Services 'Revision of the Organisational Guidelines and Recommendations for the Oncology Network That Integrates Hospital Activity for Acute and Post-acute Cases with Territorial Activity' approved by Act 59/CSR of 17 April 2019 by the State-Regions Conference [17], a definition of molecular biology laboratories within the Regional Oncology Network is envisaged. For these purposes, the following are necessary:

- The creation of infrastructures for the implementation of a network laboratory system, which will involve
  - defining the process steps to enable the availability and transfer of samples between the diagnostic center and the molecular biology laboratory and
  - setting up a platform for managing this information and biobanks of biological samples.
- The identification of laboratories required by the network to ensure compliance with
  - average access time from participating sites,
  - volume of activities that ensures the appropriate use of technology and optimization of the required professional teams, and
  - ease and suitability of the concentration of human and technological resources.

The MTB

The aim of the MTB is to define the criteria for selecting cancer patients for whom there are no clear indications for target treatments and/or NGS molecular profiling to undergo CGP with the aim of assessing the significance and potential clinical indications derived from the identified molecular alterations.

A central element is the criteria for selecting patients for NGS analysis of tumor tissue (or even liquid biopsy), which corresponds to the potential availability and use of molecularly targeted drugs to indicate the optimal treatment for a patient. It is essential to define valid, recognized and reproducible criteria that will enable MTBs to make clinical recommendations for individual patients:

- High-volume or frequent tumors to rare or 'orphan' tumors
- Available treatment options and therefore assessment of therapeutic need
- Data available from cancer genome databases and therefore assessment of the frequency of actionable gene alterations for the specific cancer
- Targeted drugs available and accessible to the patient
- Efficacy assessment of the identified single-target drug in available clinical trials and at the different phases of trial development
- Evaluation of drug toxicity data and therefore cost–benefit analysis
- Evaluation of the possibility of a structured management and procedure related to the potential identification of germline alterations (even if rare) and thus of the subsequent hereditary implications
- Sustainability and appropriateness analysis of the entire pathway

The MTB for such purposes requires the active involvement of different professionals in a broad, multidisciplinary approach. In the MTB structure, a Core Team is required, together with noncore team members comprising professionals who can intervene for specific problems. The Core Team should include the medical oncologist, pathologist, molecular biologist, geneticist, clinical pharmacologist, hospital pharmacist, bioinformatician, clinical epidemiologist, bioethicist and the patient representative. Professionals on the noncore team are the radiotherapist, the surgeon and endoscopist for various specialities, the radiologist, intervention radiologist, nuclear doctor, organ specialists (pulmonologist, gastroenterologist, etc.) and psychologist. The MTBs must be identified and planned based on population volumes and health organization, in conjunction with the Diagnostic Therapeutic Treatment Pathways and the Multidisciplinary Pathology Groups within the Regional Oncology Network. Once the area of competence has been defined for large or regional areas, direct communication with the relevant ethics committees is indispensable. A national platform should allow for the registration of all profiled cases.

Rates

Access to gene profiling testing with NGS technology in oncology would allow both the use of the most effective therapy available for individual patients and a potential cost advantage for the national health service by avoiding the use of a less effective treatments and their associated costs. To avoid regional inequalities in tariffs, genomic profiling of patients by NGS should be included in the national Essential Levels of Assistance (LEAs) with the commission updating the LEAs themselves. Access to a genomic profiling tests for tumors using NGS requires adequate remuneration of the dedicated laboratories.

To date, there are no published cost estimates for cancer genomic profiling tests in Italy. These estimates represent a starting point for defining pricing for the tests, with the awareness that this may not exactly reflect the costs and that such pricing represents the real financing system of the services for the accredited private services and not for public ones. The estimate of the full profiling cost includes all inputs used, from personnel and consumables to equipment depreciation and indirect and common costs passed on to the specific profiling activity. The rapid evolution of technology, the greater extension of the panels used for NGS profiling and the change in the unit costs of some production factors require a systematic update of tariffs. Preliminary results of a study of two Italian hospitals on the use of NGS profiling for patients with non-small-cell lung cancer show a full cost per NGS test of 1150 euros in the current state of investigated mutations, compared with a cost of 1780 euros for standard methods. The full cost per NGS test, if the tumor mutational burden mapping were to be achieved, would be approximately 1850 euros.

Access to drugs

The final element of this genomic profiling process is the return of information on clinical use and access to the drug. Several situations can be envisaged:

- The drug is reimbursed according to AIFA for the same tumor and indication
- The drug is reimbursed according to AIFA for different tumor and/or indication
- The drug is registered by EMA or by other international regulatory bodies for the same cancer and indication
- The drug is EMA/US FDA registered for a different tumor and/or indication
- The drug is not registered but available in an expanded access program

For situations in which the drug is not reimbursed by AIFA for the same tumor and indication, the MTB should take into account the following:

- The level of expected clinical benefit of the drug in relation to the target compared with the therapeutic standard for the specific disease setting
- The known toxicity of the target drug and the impact on quality of life

To date, the procedures and criteria for access to the drug have referred to Law 648/96, Law 326/2003 art. 48 (5% fund), Law 94/98 (off label use), DM 07/09/2017 (therapeutic use) and Class Cnn (Band C drugs, not negotiated). In fact, none of the methods described here has been designed to govern off-label use resulting from genomic profiling, and the urgency of access to the drug based on the decisions of MTBs is not compatible with these procedures in normal clinical practice. It is therefore desirable to consider a specific reference standard to regulate access to drugs and reimbursement by the national health service. To allow access to drugs, it might be desirable to grant conditional reimbursement and for manufacturers to share the risk, with periodic reviews based on the data recorded. As already mentioned, the registration of the drugs allocated on the basis of the identified targets and the clinical results of the treatment (efficacy, toxicity) must be carried out within the framework of a national platform to allow periodic reevaluations by AIFA.

Future perspective

The rapid evolution of precision medicine will require the determination of an increasing number of biomarkers for treatment decisions. This need will result in many diagnostic laboratories, especially in public health and academic institutions, to introduce NGS technologies into their clinical practice and research. In an era in which the molecular genetic profile of cancer will assume an increasingly important role in therapeutic decisions, access to NGS test networks will increasingly assume a strategic role for the realization of precision medicine in clinical practice. The increasing accumulation of clinical evidence together with the implementation of MTB and regulatory procedures for access to drugs will make it possible to ensure the adequacy of NGS tests and the accuracy of their interpretation for clinical purposes.

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Executive summary

Evidence & state of art

- Although molecular-targeted therapies represent an important innovation in oncology, the identification and validation of new therapeutic targets is limited by current approaches that are often inadequate for rare mutations or complex genomic frameworks.
- Alternative sources of evidence such as data collection on common platforms that ensure homogeneity and quality of the collected data can help to overcome the limits of classical experimentation.
- The complete separation between the authorisation and reimbursement pathways for drugs and diagnostics in the Italian health system is a further obstacle to the dissemination of molecular targeted therapies.
- A profound reorganization of the Italian health system appears necessary to ensure the implementation of precision oncology through the identification of paths and procedures suitable for producing, collecting and interpreting data of high scientific quality.

Technologies & platforms

- The use of next-generation sequencing (NGS) should be limited to tumors with high frequency of actionable mutations such as adenocarcinoma of the lung, cholangiocarcinoma, prostate and ovarian carcinomas.
- Comprehensive genomic profiling (CGP) should only be offered to selected patients within clinical research programs.
- At the onset of disease, tumour tissue should be preferred to circulating free DNA (cfDNA), whereas at relapse after treatment with targeted drugs, liquid biopsy has the advantage of better representing tissue heterogeneity and allows the identification of mechanisms of acquired resistance.
- Laboratory performing NGS testing should have an adequate level of organization, participate to external quality assessment schemes and validate their technologies prior to clinical use.

Clinical applications & organisational models

- It is considered necessary for the establishment of a national/regional laboratory network of centers with adequate equipment of technologies and personnel and expertise for the execution of complex genomic tests with NGS.
- The Molecular Tumor Boards (MTBs) must be identified and planned on the basis of population volumes and health organisation, within the Regional Oncology Network, with the aim to select patients undergoing CGP and provide treatment recommendations.
- Reimbursement rates for CGP need to be identified by the National Health System.
- New methods of drug reimbursement must be identified to allow the treatment of patients with actionable mutations with drugs not yet approved, in the context of a regulatory framework that favors the advancement of knowledge.

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