SEOM-GETTHI clinical guideline for the practical management of molecular platforms (2021)

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Abstract
The improvement of molecular alterations in cancer as well as the development of technology has allowed us to bring closer to clinical practice the determination of molecular alterations in the diagnosis and treatment of cancer. The use of multi-determination platforms is spreading in most Spanish hospitals. The objective of these clinical practice guides is to review their usefulness, and establish usage guidelines that guide their incorporation into clinical practice.

Keywords Molecular platforms · Precision medicine · Next-generation sequencing · Biomarkers

Selecting biomarkers for a molecular platform

In 2011, the Spanish Society of Medical Oncology (SEOM) and the Spanish Society of Pathology launched a joint project to establish guidelines on biomarker testing in patients with advanced NSCLC that have been updated, last time in 2020 as a paradigm, getting the challenge for precision medicine [1].

In 2018 the European Society of Medical Oncology (ESMO) defined a scale for clinical actionability of molecular targets in cancer (ESCAT), with the aim of offering a common language to classify genomic alterations based on clinical evidence-based criteria (Fig. 1) [2]. The first

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recommendation for the use of NGS considering ESCAT was published by ESMO last year. They propose routine use of NGS for advanced non-squamous non-small-cell lung cancer (NSCLC), prostate cancers, ovarian cancers, cholangiocarcinoma and as an alternative to PCR for colorectal (CCR) cancer [3]. In addition, based on the Keynote-158 trial, the tumor mutational burden (TMB) test is also recommended for some tumours: cervical cancers, well and moderately differentiated neuroendocrine tumours, salivary cancers, thyroid cancers, and vulvar cancers [4]. They also encourage clinical research centers to perform it in the context of molecular screening programs to increase the access to innovative drugs and to speed up clinical research.

ASCO guidelines do not include a specific document on recommendations for cancer biomarkers yet. However, they have created the non-free access NCCN Biomarker Compendium® to support decision-making around the use of biomarker tests in cancer patients [5].

We summarize the most relevant biomarkers to develop a personalized and useful NGS platform in oncology practice based on the few recommendations that have been published by scientific societies [6, 7] (Table 1).

Others a site-agnostic biomarkers must be included:

**Neurotrophic receptor tyrosine kinase receptor (NTRK)1–3** incidence is higher in carcinoma of salivary glands (42–100%), secretory breast cancers (90–100%), papillary thyroid carcinoma (2–15%); while they are infrequent, <1%, in more common adults’ tumours. ESMO recommends using NGS to detect these aberrations only in cancers where this technology is otherwise recommended [8].

SEOM with other societies as Spanish Society of Pathological Anatomy and the Spanish Society of Pediatric Hematology and Oncology has developed a consensus document that includes guidelines on the diagnostic, clinical, and therapeutic aspects of NTRK-fusion tumours proposing NGS for tumours with a high frequency of alterations or in which alterations in NTRK must be known to make a diagnosis [9]. In this scenario, as immunohistochemistry (IHC) is the detection method of choice in most cases, it is necessary to confirm the fusion of the NTRK genes by NGS before initiating NTRK inhibitors, which has shown promising activity in early phase pan-tumor trials [10, 11].

**PD1 and PD-L1 status**, assessed by IHC staining, has been identified as a biomarker associated with a higher chance of tumor response in patients treated with anti-PD-L1 antibodies and a better OS in multiple tumor types [12].

**TMB high** have been correlated with overall survival benefits following treatment with ipilimumab in melanoma, pembrolizumab in NSCLC and atezolizumab in bladder cancers. It is currently believed that a high TMB yields numerous immunogenic cancer cell neo-epitopes that may be recognized by T cells upon presentation by MHC molecules. However, TMB seems to be a prognostic marker independent of the intratumorally inflammatory gene expression profile [12].

**Mismatch repair status.** Tumours with DNA mismatch repair deficiency (dMMR) have shown great sensitivity to anti-PD-L1 therapies. It is currently believed that tumours harboring an erroneous MMR system will accumulate DNA mutations, which can lead to the presence of high levels of mutation-associated neoantigens (MSI-H), most recognized by immune cells. dMMR/MSI-H status is an approved biomarker for pembrolizumab [12].

**Some mutations can be germline and or somatic.** Germline alterations require confirmation in matched normal samples from the tumor-bearing host and after confirming is also necessary to perform cascade testing on family members. Table 2 [13].
Table 1  Genetics Biomarkers for precision cancer therapies by tumor type [3–5]

| Tumor Type         | ESCAT I                               | ESCAT II                              | ESCAT III                          |
|--------------------|---------------------------------------|---------------------------------------|-------------------------------------|
| NSCLC              | EGFR 15% del 19, L858R                | 3% MET focal amplifications           | 1.2% BRCA 1/2                       |
|                    | 60% EGFR mutant: acquired             | 12% KRASG12C                          | 1.2–7% PI3K                        |
|                    | T790M exon 20                         | 2–5% ERBB2                            | 1.7% NRG1                          |
|                    | 2–10% uncommon EGFR mutations         |                                       |                                    |
|                    | (exon 18,20,21)                       |                                       |                                    |
|                    | 5% ALK                                |                                       |                                    |
|                    | 3% MET ex skipping                    |                                       |                                    |
|                    | 2% BRAFV600E                          |                                       |                                    |
|                    | 1–2% ROS1                             |                                       |                                    |
|                    | 0.2–3% NTRK fusions                   |                                       |                                    |
|                    | 1–2% RET fusions                      |                                       |                                    |
| NSCLC              | EGFR 15% del 19, L858R                | 3% MET focal amplifications           | 1.2% BRCA 1/2                       |
|                    | 60% EGFR mutant: acquired             | 12% KRASG12C                          | 1.2–7% PI3K                        |
|                    | T790M exon 20                         | 2–5% ERBB2                            | 1.7% NRG1                          |
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|                    | (exon 18,20,21)                       |                                       |                                    |
|                    | 5% ALK                                |                                       |                                    |
|                    | 3% MET ex skipping                    |                                       |                                    |
|                    | 2% BRAFV600E                          |                                       |                                    |
|                    | 1–2% ROS1                             |                                       |                                    |
| CRC                | 44% KRAS                              | 2% ERBB2                              | 17% PI3K hotspot mutations          |
|                    | 4% NRAS                               |                                       | 5% ATM mutations                    |
|                    | 8.5% BRAFV600E                        |                                       | 1.7% MET amplifications             |
|                    | 4–5% MSI-H                            |                                       | 1% AKT1E17K                        |
|                    | 0.5% NKTR1                            |                                       | 1% TMB-High in MSS                  |
|                    |                                       |                                       | 0.3% RET fusions                    |
|                    |                                       |                                       | 0.2% ALK fusions                    |
| BREAST CANCER      | 15–20% ERBB2 amplification            | 4% ERBB2 hotspot mutation             | 6% NF1??                           |
|                    | ER, PR                                | 3% BRCA 1/2 somatic mutation          | 1% MDM2                            |
|                    | 30–40% PI3K                           | 10% ESR1 (mutation mechanism resistance) | 2% ERBB3                           |
|                    | 1% MSI-H                              |                                       |                                    |
|                    | 1% NTRK fusions                       |                                       |                                    |
|                    | 4% BRACA 1/2 germine mutations/       | 7% PTEN                               |                                    |
|                    | deletions                             | 5% AKT1E17K                           |                                    |
|                    | androgen receptor and                 |                                       |                                    |
|                    | PDL-1 (Triple negative BC)            |                                       |                                    |
| PROSTATE CANCER    | 9% BRCA1/2 somatic mutations/ deletions | 40% PTEN                             | 3% PI3K                            |
|                    | 1% MSI-H                              | 5% ATM                                | 1% AKT1E17K                        |
| ENDOMETRIAL CANCER*| 2–5% MSI-H, PMS2                      | ESR1                                  | POLE-aberrant                      |
|                    |                                       |                                       | BRAF                                |
|                    |                                       |                                       | KRAS                                |
|                    |                                       |                                       | PIK3CA                              |
|                    |                                       |                                       | PTEN?                               |
| OVARIAN*           | BRCA 1/2 germline, somatic            |                                       | ATM, BRIP1, CHEK2, PALB2, RAD51C, RAD 51B |
| CHOLANGIOCARCINOMA | 20% IDH1 mutations                    | 5% BRAFV600E mutations                | 10% ERBB Amplifications             |
|                    | 15% FGFR2 mutations                   |                                       | 2% ERBB2 mutations                  |
|                    | 2% MSI-H                              |                                       | 7% PI3CA hotspot mutations          |
|                    | 2% NKTR fusions                       |                                       | 3% BRCA1/2 mutations                |
|                    |                                       |                                       | 2% MET amplifications               |
| CENTRAL NERVOUS SYSTEM* | 1p19q co-deletions                |                                       |                                    |
| SARCOMAS*          |                                       |                                       |                                    |
|                    |                                       |                                       |                                    |
|                    |                                       |                                       |                                    |
| GIST               |                                       |                                       |                                    |
| PANCREATIC CANCER  | 1–4% BRCA1/2 germine mutation         | 3% BRCA 1/2 somatic mutations         |                                    |
|                    | 1–3% MSI-H                            | 90% KRAS mutations                    |                                    |
|                    | <1% NTRK                              | 3% PI3CA                              |                                    |
|                    |                                       | 3% BRAFV600E                         |                                    |
|                    |                                       | 2% MDM2 amplifications               |                                    |
|                    |                                       | 1–2% ERBB2 amplifications/ mutations |                                    |
|                    |                                       | 1% NRG1 fusions                      |                                    |
|                    |                                       | <1% ALK fusions                      |                                    |
|                    |                                       | <1% RET fusions                      |                                    |
|                    |                                       | <1% ROS1 fusions                     |                                    |
Genetics platforms for hereditary cancer syndromes

Genetic diagnosis of hereditary cancer syndromes offers the opportunity to establish more effective predictive and preventive measures for the patient and their families. Next Generation Sequencing (NGS) technologies have transformed hereditary cancer syndromes testing process. Several multigene panels (MP) offers an important improvement in the efficiency of genetic diagnosis, but there is a debate about what genes should and should not be tested because of lack of actionability. Multi-gene testing may be most useful when more than one gene can explain an inherited cancer syndrome [14]. Although clinical criteria for genetic testing continue to be largely based on personal and family history with around a 10% detection rate, broader criteria are being applied with a lower threshold for detecting mutations when there are therapeutic implications for patients [15]. Assess for germline BRCA1/2 mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy biomarkers for platinum therapy [16] and PARP inhibitors [17]. Another therapeutically actionable germline variants are in CHEK2, ATM, mismatch repair genes (MLH1, MSH2, MSH6, PMS2, and EPCAM), and

Table 1 (continued)

| Cancer Type                      | ESCAT I                      | ESCAT II                     | ESCAT III                     |
|----------------------------------|------------------------------|------------------------------|------------------------------|
| GASTROESOPHAGEAL ADENOCARCINOMA  | 16% ERBB2 amplifications    | 6% EGFR amplifications      | 3% ERBB2 hotspots mutations  |
|                                  | 8% MSI-H                     | 3% MET amplifications       | 1.3% MET Mutations           |
|                                  | 2% NTRK fusions              | 7% PI3KCA hotspot mutations | 4% FGFR2 amplifications      |
|                                  |                              | 3% ATM mutations            | 3% ATM mutations             |
|                                  |                              | 1–5% BRCA 1/2 mutations     | <1% ROS 1 fusions            |
|                                  |                              |                              | <1% RET fusions              |
|                                  |                              |                              | 3% ERBB3 hotspot mutations   |
| MELANOMAS                        |                              |                              |                              |
|                                  | 50% BRAF<sup>V600E</sup>    |                              |                              |
| HEPATOCELLULAR CARCINOMA         | 1% NTRK fusions              |                              | 4% PI3CA hotspot mutations   |
|                                  | 1% MSI-H                     |                              | 4% MET amplifications        |
|                                  |                              |                              | 2% RAS mutations             |

*Non-specific ESCAT available, the classification is proposed regarding SEOM specific tumor type guidelines

Table 2  Somatic mutations that should be referred to genetic counseling [15]

| Syndrome                                         | Mutation| Main cancers involved                                                                 |
|--------------------------------------------------|---------|--------------------------------------------------------------------------------------|
| Li-Fraumeni                                      | TP53    | Sarcomas, breast, and brain                                                          |
| Lynch                                             | MSH2, MLH1, MSH6, PMS2 | Gastrointestinal tract, endometrium, ovary, brain, breast, renal pelvis            |
| Hereditary breast-ovarian cancer                 | BRCA1, BRCA2 | Breast, ovary, prostate, pancreas                                                  |
| Familial adenomatous polyposis                   | APC, MUTYH | CCR, small bowel, stomach, brain, bone, skin                                          |
| Hereditary diffuse gastric cancer                 | CDH1    | Stomach, breast                                                                      |
| Familial atypical multiple melanoma              | CDK4, CDKN2A | Melanoma, pancreatic cancer, astrocytoma                                          |
| Werner                                            | MEN1    | Pancreatic, pituitary gland tumors                                                   |
| Retinoblastoma                                    | RB1     | Eye, pineal gland, osteosarcoma, melanoma, soft tissue sarcoma                      |
| Multiple endocrine neplasia type 2               | RET     | Medullary thyroid cancer, pheochromocytoma                                           |
| Von Hippel-Lindau                                 | VHL     | Kidney                                                                                |
| Peutz-Jeghers                                    | STK11    | Breast, CCR, pancreas, stomach, hamartomas                                           |
| Familial paraganglioma                           | SDHD, SDHB, SDHC | Paragangliomas, pheochromocytomas                                                  |
| Bir-Hoge-Dube                                     | FLCN    | Chromophobe renal cell cancer                                                       |
| Tuberous sclerosis                               | TSC1/2  | Angiofibroma, angiomylipoma, giant cell astrocytoma                                 |
| Neurofibromatosis type 1                         | NF1     | Optic gliomas, neurofibromas                                                        |
| Neurofibromatosis type 2                         | NF2     | Schwannomas, meningiomas, gliomas, neurofibromas                                    |
| Gorlin                                           | PTCH1   | Childhood primitive neuroectodermal tumors, skin basal cell carcinomas               |
| Juvenile polyposis                               | BMPR1A, SMAD4 | Multiple non-cancerous growth in the colon                                     |
PALB2. Patients with microsatellite instability treatment with checkpoint inhibitors therapy can be considered when is available [18].

There are several issues to consider regarding multi-gene testing. Commercially available tests may differ significantly on a number of factors, such as number of genes analyzed among others. Therefore, the specific laboratory and multi-gene test should be chosen carefully [14] (syndrome-specific panel, cancer-specific panel, multi cancer panel, etc.). Genetic counselling by clinicians with specific training or expertise should always be offered before ordering germinal testing.

The presence of a BRCA1 or BRCA2 mutation accounts for the majority of hereditary breast and ovarian cancer syndromes. BRACAnalysis identifies patients with BRCA 1/2 mutation and allows therapy personalized. Genetic susceptibility to breast or ovarian cancer might also be associated with mutations in other high and moderate penetrance genes, some of which are associated with known hereditary cancer syndromes, such as p53, PTEN, NF1, CDH1, STK11, MLH1, MSH2, MSH6 and PMS2, BARD1, PALB2, CHEK2, ATM, RAD51C, RAD51D and BRIP1. Therefore, HBOC germline panels including these genes are recommended (II, A) [19, 20].

Germline mutations commonly found in pancreatic adenocarcinoma include BRCA1, BRCA2, CDKN2A, mismatch repair genes associated with Lynch syndrome, ATM, PALB2, STK11, and TP53 [21–23]. In addition, hereditary pancreatitis, which is associated with a significantly increased risk for pancreatic cancer, is associated with the genes PRSS1 and SPINK1 [24, 25].

Consider cancer predisposition next-generation sequencing (NGS) panel testing, which includes BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, and PMS2 in patients with prostate cancer who meets criteria [III, A] [26].

Genetic susceptibility to CRC includes well defined inherited syndromes such as Lynch syndrome, familial adenomatous polyposis (FAP), and MutY human homolog (MUTYH)-associated polyposis (MAP). Other entities include Muir-Torre, Turcot, Gardner, Cowden, Bannayan-Riley-Ruvalcaba, Peutz-Jeghers, juvenile polyposis, and serrated polyposis syndromes [27].

Syndrome specific testing of the panel of genes that cause Lynch syndrome (MLH1, MSH2, MSH6, PMS2, and EPCAM) may be considered for individuals who meet criteria for Lynch Syndrome [28].

Patients with multiple colorectal adenomas (>10) should be considered for panel germline genetic testing that includes APC, MUTYH, POLE, POLD1, GREM1 and NTHL1 genes [III, A] [29–31].

**Genetics platforms for unknown primary tumours**

At this time of medicine based on precision, one of the challenges of oncology is to diagnose the origin of the tumor to direct the treatment with greater precision and enhance the therapeutic results in tumours with low sensibility to the treatment with chemotherapy [32]. In 3–5% of malignant neoplasms, the primary origin is unknown, which is a challenge when it is time to select a treatment. The use of traditional diagnostic procedures makes it easier to identify the tissue of origin in 30%[33]. The predictive informed precisions are about 80–90% [34, 35] with the use of current molecular platforms.

Different molecular diagnostic platforms evaluate the genomic expression, identify the tumor through a classifier of the type of cancer based on firms of DNA methylation microarrays or a RNA classifier based on tumor samples [35–37]. The molecular similarity of the tumor sample is quantified with a reference database with the tumors selected by the different platforms. There are different trading platforms (Table 3).

One of the main limits of molecular platforms is to have enough quality, quantity and percentage of tumor cells. The diagnostic use with immunohistochemistry through the use of antibodies directed to protein antigens is a standardized test that can exhaust the tumor tissue for its use in future diagnostic procedures, although it correlates well with the platforms. Diagnosis is sometimes difficult in orphan tumors and not very frequent or with unusual histopathology features because they are not included in the non-included features in the database of the platforms (Table 4).

Another limit of these platforms is that they are not subsidized by the National Health System. In the economic analysis, EPICUP showed profitable in breast, colon, pancreas, lung (NSCLC), hepatocellular and prostate cancers in
comparison with other available alternatives, increasing the amount of well-treated patients, directing the therapy and with a cost-effectiveness benefit [47].

The use of molecular diagnostic platforms helps to direct treatments in tumors with a low sensibility towards chemotherapy and also offers a very useful tool for the diagnosis of tumors with an unknown origin.

Predictive platforms

Molecular platforms may be useful tools to replace some clinically available IHQ, FISH and RT-PCR assays as the initial molecular diagnostic due to its cost effectiveness, and also, to be a tissue-saving option [48]. That said, we will proceed to review the currently approved molecular platforms that could be useful to predict response to target therapy for metastatic disease. No molecular platforms are approved yet for localized disease during daily clinical practice [49].

Colorectal cancer (CRC)

Praxis Extended RAS Panel is a NGS based in vitro diagnostic for evaluating 56 KRAS/NRAS mutations to determine patient’s eligibility for treatment with EGFR monoclonal antibodies (mAbs) [50]. Testing KRAS/BRAF is only recommended for stage IV CRC, and consequently, molecular platforms are not approved yet for other stages [51]. MMR or MSI testing is universally approved for all stages. Stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy. Also, they do benefit from anti PD-L1 treatment for advanced disease [52].

BRCA status to predict response to PARP inhibitors

Germline BRCA1 and BRCA2 status is a critical biomarker to help determine the appropriate therapy for patients with ovarian, prostate, pancreatic and breast tumors [53]. BRA-CAnalysis CDx detects germline mutations only, not somatic mutations from a patient’s blood sample [54]. FoundationFocusTM CDxBRCA and Myriad myChoice CDx are NGS based in vitro diagnostic device for qualitative detection of BRCA1 and BRCA2 alterations in formalin-fixed paraffin-embedded (FFPE) ovarian tumor tissue. These test does not provide information about susceptibility [55, 56]. Furthermore, Myriad myChoice CDx determinates Genomic Instability Score (GIS) using DNA isolated from FFPE tumor tissue specimens.

Non-small-cell lung cancer (NSCLC)

Molecular platforms can be extremely useful for non-squamous NSCLC, the solid tumor with the widest variety of potential therapeutic targets [57]. Oncomine Dx Target Test: Detects 46 cancer driver gene variants, including EGFR mutations (including L858R, T790M, and exon 19 deletions); BRAF, KRAS, ERBB2, and MET exon 14 skipping mutations; and ALK, ROS1, RET, and NTRK1/2/3 fusions [58].

Solid tumors

FoundationOne CDx was the first FDA-approved tissue-based broad companion diagnostic (CDx) that is clinically and analytically validated for all solid tumors. Test results include MSI, TMB and loss of heterozygosity (LOH) for ovarian cancer patients [59]. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) [60]. A hybridization capture-based NGS assay for targeted deep sequencing of all exons and selected introns of 341 key cancer genes in FFPE tumors. Omics Core and PGDx elio™ tissue complete use NGS of FFPE tumor tissue to detect both TMB and some information about point mutations and small insertions and deletions. PGDx also analyzes MSI status.

Prognostic platforms

Predicting the risk of recurrence is critical to optimize adjuvant treatment. Diverse gene-based assays may be used to gain additional prognostic and/or predictive information to complement pathology assessment [61]. Breast and Colon cancer has the developed platforms:

For early breast cancer Oncotype, Mammprint, Nanostring are useful are useful for estimating the risk of recurrence and the benefit of adjuvant chemotherapy treatment in patients without metastatic axillary nodal involvement. Recently Oncotype has also shown usefulness for postmenopausal patients with nodal involvement [62–65]. The use of adjuvant CT in patients with stage II colorectal cancer (CRC) is controversial. Multigenic tests have
been developed to identify patients with higher risk of recurrence, who may benefit more from adjuvant CT. However, clinicians and patients may consider their use to complement clinicopathological information. Only Oncotype DX [66] and GeneFx Colon [67] have been validated in stage II CRC. Their use might be considered on intermediate-risk stage II scenarios: i.e. to treat T3 N0 classified as high risk by the signature, or for avoiding chemotherapy in T4 N0 classified as low risk by the signature. Immunoscore has been validated in patients with stage I-III CRC [68]. It could be considered to establish the prognosis of patients used in conjunction with the TNM scoring and thus support the CT decision-making process in stage II and even in low-risk stage III patients.

**Liquid biopsy**

The term liquid biopsy was first described by K. Pantel and C. Alix-Pambieres to study circulating tumor cells (CTCs) in the blood of cancer patient [69]. Currently it has been expanded to study circulating tumor nucleic acids (DNA and RNA) as well as other structures such as exosomes and platelets, extending to all biological fluids such as urine, cerebrospinal fluid, and others. The popularization of the liquid biopsy is due to the convenience and reproducibility to explore the alterations in the circulating free DNA. This approach is the current and future development field of oncology.

The initial concerns about the correlation with the tumoral biopsy has almost been overcome, the complementary or even principal information provided by liquid biopsy to the management of solid tumors seems superior, although it needs to demonstrate its clinical utility in most clinical situations like treatment selection, disease monitoring, minimal residual disease study and anticipating resistance, and finally early diagnosis [70].

In practice, there are two principal methods for studying ctDNA in plasma, based on PCR and by next generation sequencing (NGS). PCR-based detection of cfDNA, especially with the new digital PCR systems, is highly sensitive and easy to interpret with the limitation that can be studied only a few previously known mutations. The most promising development is with the NGS panels that study several genes at the same time or complete genome, but where the sensitivity is lower, although it is improving and requires complex equipment and a very high bio-informatics support. Intriguingly, the solitary publication of liquid biopsy and rare tumors is a clinical case of a hemangiopericytoma where try to characterize the CTCs [71].

Current evidence is that genotyping of cfDNA in plasma can be complementary to the tissue and vice versa, in patients with advanced disease to identify a biomarker for initiate targeted treatment [72]. Currently there are some tests to study ctDNA that are approved by FDA as companion diagnostics in some cancers and for some targeted treatments, although nonspecific for rare tumors that were underrepresented in the studies.

**Final considerations**

Currently, there are three major barriers for a wide implementation of precision oncology: restrictions in the access to molecular platforms, availability of targeted drugs for transversal indications and physicians skills in the interpretation of molecular results [73, 74]. Though universal testing should become a reality in the near future, doctors must decide what patients are more likely to benefit from a molecular platform, select the most appropriate tool and grant access to therapy in case of a “positive” finding [75].

The changing landscape of personalized medicine, where not only new drugs but also new platforms become available quickly, makes this decision particularly challenging. Additionally, cancer has shown a biological plasticity that leads to the appearance of new alterations along the course of the disease [76]. Thus, molecular testing should be repeated in cases where the understanding of the mechanism of resistance could lead to alternative therapeutic options (for instance EGFR mutations in lung cancer) [77].

As a result, oncologists do not only need to decide who must be tested but also how many times and when. A new and dynamic approach to this situation should replace the traditional model where guidelines or recommendations are fixed regularly.

Molecular Tumor Boards (MTB) have emerged as the best way to support clinicians struggling with precision medicine in daily practice. These committees should include genetic counselors and biologists able to interpret the results of molecular platforms, oncologists specialized in different areas (since drugs approved in one tumor could be interesting in a different indication) and personal from clinical trials units to ensure a wide access to targeted therapies [78].

Since many institutions cannot grant such multidisciplinary environment, initiatives like the GETTHI National Molecular Tumor Board, where any oncologist can submit a case for consideration (https://www.getthi.org/contenidos/investigacion/tumorBoard.aspx), could help to ensure that every patient gets the most updated management.

**Declarations**

**Conflict of interest** ACG reports Speaker and Grant from Takeda and Speaker from Angelini. MAVS reports Speaker from Pfizer and Pharmamam and Grant from Pfizer. JGDJ reports Consultant or Advisory

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Ethical approval and informed consent It is not necescary in this review paper.

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