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The role of genetic testing in the prognosis and management of solid tumors. A literature review

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ABSTRACT

Introduction: Cancer is the leading cause of death and an important impediment to increasing life expectancy in every country of the world. During the process of oncogenesis, genetic and epigenetic changes lead to abnormal expression of genes associated with cellular pathways that coordinate extremely important functions such as cell multiplication, cell differentiation, cell death, and cell cycle.

Methods: There are over 200 approved biomarker-driven drugs for various types of cancer. Valuable biomarkers are analyzed to establish their importance in specific therapies. Precision medicine for oncological patients has been recognized as a valuable approach to solid tumors.

Results: Various genes and their mutations either have a direct pathogenic effect or can give hints to a certain prognosis regarding the oncological pathology. A comprehensive genetic test for a broad molecular profile and complete characterization of tumor genetic heterogenicity should contain genes that are aligned with professional practice, guidelines and clinical trials, full coding region coverage for each gene and targeting of unique emerging and actionable markers. It is useful to use such a comprehensive test when a broad genomic profile identifies treatment options including immunotherapies and targeted drugs for patient enrollment or when relapse or disease progression has occurred after prior therapies.

Conclusions: For patients with solid tumors, personalized medicine has been recognized as a successful strategy treatment, but it is not sufficient to seize cancer growth and progression up to a single molecular alteration due to specific hallmarks such as tumor heterogeneity, clonal evolution, and independent resistance mechanisms. Earlier studies have evaluated the effectiveness of using multigene panel screening methods for personalized cancer therapy, with controversial results. Future research in the field of circulating tumor DNA analysis might be the key to overcoming some of these limitations. The liquid biopsy could enable dynamic molecular profiling of all patients diagnosed with solid tumors enhancing accuracy, prognosis, and management

Keywords: literature review, oncogenetics, personalized therapies, molecular marker, cancer classification

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INTRODUCTION

Due to demographic changes and the spread of associated risk factors in developed countries, mortality from cancer overtook mortality due to cardiovascular diseases.

Across all sexes and all age groups, lung cancer continues to have the greatest cancer mortality rate (18%), followed by blood cancer (13.6%), colorectal (9%), stomach (8.7%), and prostate (7,7%). (according to the International Agency for Research on Cancer, Globocan 2020)

Most cancers (particularly lung cancer) are discovered in surgically advanced stages because the disease frequently evolves without specific signs and symptoms, and when symptoms do appear, they are too late for curative treatment [1-4].

Our capability to fight cancer has increased as well. Technological and scientific advances have provided us with multiple tools to diagnose and treat cancer at multiple stages. Genetic testing for multiple cancer such as ovarian, breast, lung, colorectal, pancreatic cancer, gliomas, and sarcomas is now a reality and a keystone of the oncologic approach. A wide range of markers can be identified by various techniques such as fluorescence in situ hybridization (FISH), real-time polymerase chain reaction (RT-PCR), Sanger sequencing and Next Generation Sequencing (NGS) [5-13].

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Relevant medical articles were found through a comprehensive PubMed search for papers in the English medical literature and through a manual review of the references of identified reports. Recent articles were included in this review. We excluded papers written in foreign languages.

METHODS

Solid tumors can occur in many types of tissues and are grouped into three major categories based on their origin [14]:

Carcinoma: represents the most frequent type of cancer and originates from epithelial cancer;

Sarcoma: rare tumor which usually affects children and young individuals and originates in the connective tissue;

Melanoma: associated with sun exposure and originates from pigmentation cells of the epidermis.

Genes implicated in cellular processes that regulate extremely important functions like cell differentiation, cell proliferation, cell apoptosis and cell cycle, suffer genetic and epigenetic changes that are at the base of carcinogenesis. Some of these alterations are responsible for the tumor's clinical characteristics such as pathogenic risk, TNM (tumor, node and metastasis)-staging, clinical outcome, diagnosis, treatment efficacy and survival [14].

Despite the numerous discoveries in chemotherapeutic therapies in oncology, there are various types of very aggressive and invasive cancers that acquire drug resistance against conventional drugs, which still plague the management of oncologic patients [14-16]. Nowadays there are numerous studies about abnormalities implicating DNA methylation that have provided us with further insight regarding the role of DNA epigenetics in tumor genesis.

Fluorescence in Situ Hybridization (FISH)

FISH is a cytogenetic-molecular technique introduced in the 1980s. The purpose of FISH is to highlight certain DNA target sequences in the nuclei of the neoplastic cells in solid tumors (formalin-fixed paraffin-embedded tissue). FISH has contributed to the clinical integration of molecular cytogenetics and cytology techniques [17-19].

The pre-analytical steps are crucial for the result's relevance. The percentage of tumor cells in the sample is essential because a low percentage may result in an inconclusive FISH score [17, 19-22].

Real-time PCR

Genomic heterogeneity and complex mutations require varied methods of molecular diagnosis and description. A proper classification of tumors, based on gene expression, requires adequate preservation of RNA and more reliable markers such as DNA and proteins [23, 24]. Quantitative real-time PCR can identify gene deletions or duplications [24]. Furthermore, melting curve analysis performed following PCR can locate small mutations, down to single base changes. These techniques are gaining popularity because they are faster, simple to use, and can be multiplexed. Real-time PCR methods are an appropriate choice for analyzing cancer markers [23, 24].

NGS Sequencing

The development of personalized medicine principles has naturally drawn the need to identify and apply some diagnostic tests that simultaneously identify several mutations / genomic variants important for treatment and prognosis in current practice. The new generation sequencing analyzes several genes simultaneously (in a single assay), reducing execution time, costs, and the amount of biopsied tissue required. However, NGS results can be difficult to interpret at times and cannot be used to personalize the therapeutic plan [25, 26].

The increased accessibility, affordability, and reliability of DNA and RNA capacity in sequencing platforms and bioinformatic database capabilities enable clinicians to provide a customized management plan for every patient, referred to as precision oncology [27].

Cancer therapy decisions are strongly based on the genomic pattern of tumors, and there are nowadays wide numbers of genomic tests feasible to medical oncology. Single gene and multigene tumor panels are examples of genomic analyses that have been tailored to help with treatment management decisions. Cancer therapy decisions are strongly based on genetic information, and currently, a wide range of genomic tests are available in medical oncology. Genetic tests are customized and narrow down decisions regarding treatment management, including those that identify abnormalities in single genes and multigene tumor panels [25, 27]. Multimarker panels contain targeted gene-expression profiling tests which are used to assess the risk of recurrence regarding the pathology and to anticipate the prognosis [28].

There are over 200 approved biomarker-driven drugs for various types of cancer [29-32]. Ongoing studies are assessing the efficiency of their customized therapies. Some of these are tissue-specific biomarkers, whereas others are systemic biomarkers (liquid biopsy) [33]. In addition to the approved biomarkers for non-small cell lung cancer (NSCLC) (EGFR, ALK, ROS1, BRAF, PD-L1), RET rearrangements and MET exon 14 mutations are valuable markers of interest [34].

Most biomarkers used and approved for clinical use are DNA-based variants like point mutations or translocations. Mutation analysis provides qualitative results, i.e. the presence or absence of mutations, and is simpler to be deciphered than quantitative tests in which particular cut-offs and calibration curves must be set and standardized and whose results must be evaluated objectively [32, 34, 35].

These characteristics decrease variability and biases among genetic laboratories, facilitating the standardization of protocols and guidelines.

The detection of biomarkers has been the main piece for the comprehensive characterization of solid tumors, with essential roles in screening, risk evaluation, differential diagnosis, prognosis assessment, prediction of treatment response, and monitoring of disorder progression. They are routinely carried out using various biological materials, including blood, urine, tissue samples, and others. There is a wide variability of biomarkers that can include nucleic acids, proteins, antibodies, and peptides for the detection of which laboratory methods are used.

Immunohistochemistry (IHC), which identifies cellular markers and phenotypes particular to certain diseases by staining with highly specific antibodies, is one of the most frequently used detection technique in clinical laboratories [30, 36].

RESULTS

Cancer-associated genes and therapeutic consequences (Table 1)

DISCUSSION

Non-small cell Lung Cancer (NSCLC)

Targeted drugs guided by genomic diagnostics are considered the gold standard for treating particular lung cancer patients. The presence of genetic driver abnormalities in the cancer cells leads to tumor growth and allows the selection of a specific treatment regime for lung cancer patients [47-51, 65, 66-68]. Targeted therapies have long been recommended for the personalized management of NSCLC.

One of the well-established molecules in this respect is Erlotinib, indicated as a first line of therapy (NICE, SMC) for metastatic NSCLC (NICE, NCCN, ASCO, FDA, BNF, SMC) with EGFR sensitivity mutations (e.g. exon 19 deletion, the L858R mutation - FDA, NCCN, ASCO; EGFR G719A, EGFR G719C, EGFR G719S, EGFR L861Q, EGFR S768I - NCCN). Erlotinib can be recommended as a single treatment or in combination with other drugs (Ramucirumab – FDA, NCCN; Bevacizumab – NCCN, non-squamous only) [69].

The presence of EGFR resistance mutations, such as the T790M mutation, EGFR Exon 20 Insertion and A763_Y764insFQEA mutations, ROS1 fusion/rearrangements, MET amplifications, KRAS resistance mutations of ALK fusions (NCCN) predicts a drug resistance condition [69].

Breast and Ovarian Cancers

Development of hereditary ovarian and breast cancer (HBOC) is increased by pathogenic germline variants in the genes BRCA1 and BRCA2 in carriers [52, 69, 70]. The overall ovarian cancer risk at age 80 is 44% for BRCA1, whilst only 17% for BRCA2 variant carriers [69-71].

Women with no known family history of any type of epithelial ovarian cancer have been identified with germline variants of BRCA1/BRCA2 in 14% of the patients. Regarding high-grade serous ovarian cancer (HGSOC), women with no known family history have been identified with germline variants of BRCA1/BRCA2 in ~17% of the cases [72]. Moreover, somatic mutations were noticed in BRCA genes in another 3% of HGSOC. In total, up to 50% of high-grade serous ovarian cancers have homologous recombination deficiency linked to pathogenic variants of BRCA1 or BRCA2 or other homologous recombination (HR) pathway genes [69, 72-74].

Poly(ADP-ribose) polymerase (PARP) is a protein involved in base repair by excision and represents a very important DNA repair path in case of single-strand breaks. Pathogenic loss of function variants in BRCA1 or BRCA2 triggers chromosomal instability and cell cycle arrest, ending in apoptosis. It has been assumed that the inhibition due to PARP allows the persistence of DNA injury which is physiologically repaired by homologous recombination [75-79].

Molecular testing in patients with breast and ovarian cancers is essential for the following reasons:

- Hereditary risk assessment is useful in taking preventive measures upon a physician appointment.
- Early detection improves the survival rate for breast and ovarian oncology patients.
- Prognosis and staging of the detected cancer.
- Prescribing the best available treatment e.g. PARP inhibitors, which improve overall survival and inhibit tumor progression.

Endometrial cancer (EC) classification

In 2013, EC molecular classification has been elaborated, which states:

1. POLE – ultramutated,
2. Microsatellite instability (MSI) – hypermutated,

Table 1. Genes involved in the targeted therapy for different types of cancer

Gene	OMIM	Structure. Function	Clinical implications
BRAF	164757	The BRAF gene is found on chromosome 7 (7q34) and belongs to the RAF family of protein kinases. The BRAF protein acts in the MAP Kinase / ERK signaling pathway, being implicated in the regulation of the cell cycle, cell differentiation, and intracellular signaling. Pathogenic variants in the BRAF gene have been linked to a poor prognosis for a variety of neoplasms. Cells with mutated BRAF variants are found in 40% of human skin melanomas [37]. There are 3 types of BRAF mutations with oncogenic potential, each class of mutations being associated with a particular response to specific inhibitors [38, 39].	Pathogenic BRAF gene variants are classified into three subclasses based on kinase activity: CLASS 1 with high kinase activity and a favorable response to RAF inhibitors CLASS 2 with high intermediate kinase activity exhibits confirmed vemurafenib resistance mutations, although there is a possibility that it will respond to newer RAF inhibitors or MEK inhibitors. CLASS 3 with no kinase activity; the only available therapeutic option for this class is MEK inhibitors [38-41].
KRAS	190070	The KRAS gene is located on chromosome 12, it is part of the gene family that codes for multiple GTPases.The K-Ras protein acts in the Ras/MAPK signaling pathway, being implicated in cell cycle regulation and cell differentiation [42].	The regulation of cell division is impacted by activating variants in the KRAS gene, the most frequent of which is a single amino acid substitution. This results in the appearance of chemotherapy resistance in various cancer types, including lung, pancreatic, colorectal, etc. [42, 43].
NRAS	164790	It is located on chromosome 1 (cytogenetic position 1p13.2), codes for a protein that is found at the level of the cell membrane and is taking part in the regulation of cell division, in signal transduction [43].	Pathogenic mutations or variants in the NRAS gene confer oncogenic activity through the ZDHHC9/GOLGA7 cellular signaling complex and are found in a variety of cancers, including colon, melanoma, thyroid, autoimmune lymphoproliferative syndromes, and juvenile myelomonocytic leukemia. Although studies on targeted treatment have not delivered satisfactory results, determining the mutational status of the NRAS gene is important for prognosis. Whyte DB et al and Brock EJ et al: "K and N-RAS are geranylgeranylated in..." and "how to target activated RAS protein" [43-45].
PIK3CA	171834	It is located on chromosome 3 (3q26.32) and codes for a p110 alpha protein, which is part of the PI3K enzyme complex. It is involved in the phosphorylation of various substrates, thereby being involved in cellular regulation processes such as cell growth and division, cell migration, cell transport, etc. [46].	Pathogenic PIK3CA gene variations, which induce uncontrolled cell proliferation, are more frequent in a variety of malignancies, including breast, bladder, skin, and cholangiocarcinomas. So far, clinical trials using PIK3CA inhibitors have had limited favorable outcomes. Alpelinib is presently approved by the FDA for patients with HER2-negative and HR-positive breast cancers, as well as PIK3CA gene mutations [46].
EGFR	131550	It is located on chromosome 7 (7p11.2) and encodes a polypeptide that functions as an epidermal growth factor receptor and has tyrosine kinase activity, acting in the EGF/EGFR signaling pathway [47].	Activating pathogenic variants in the EGFR gene results in cellular overexpression of the EGFR protein, which has oncogenic potential. EGFR pathogenic variants are associated with various forms of cancer, found in approximately 7.61% of solid tumors, mostly non-small cell lung carcinoma, but also in glioblastoma, colorectal adenocarcinoma and lung adenocarcinoma. Tyrosine-kinase inhibitors are effective in solid tumors that express activating variants in the EGFR gene, thus having important therapeutic consequences [48]. There are mutations in EGFR-coding genes that induce resistance to treatment (the best known being T790M which confers resistance to generation I tyrosine kinase inhibitors and G719X or S768I which leads to generation II tyrosine kinase inhibitors resistance) [47-50]. The newest generations of tyrosine kinase inhibitors appear to be effective in managing tumors with the aforementioned resistance mutations [47-50].
ALK	105590	The ALK (anaplastic lymphoma kinase) gene is located on chromosome 2 (2p23.2) and encodes a tyrosine kinase receptor involved in the Wnt/beta-catenin signaling pathway [51].	In different forms of cancer, the gene is frequently mutated, amplified, or involved in chromosomal rearrangements. The most common rearrangements are ALK (chr.2)/EML4 (chr.2), ALK/RANBP2 (Chr.2), ALK/ATIC (Chr.2), ALK/TFG (Chr.3), ALK/NPM1 (Chr.5), ALK/SQSTM1 (Chr.5), ALK/KIF5B (Chr.10), ALK/CLTC (Chr.17), ALK/TPM4 (Chr.19) and ALK/MSN (Chr. X) [51].

HER2	164870	It is located on chromosome 17 (17q12-21.32) and codes for Human Epidermal Growth Factor Receptor 2; it has important functions in cell cycle regulation due to its tyrosine kinase activity [52].	In 10–20% of malignancies (particularly breast, gastric, gastro-oesophageal, ovarian, endometrial, colon, bladder, or lung), the HER2 gene is amplified or overexpressed, increasing HER2 receptor activity and uncontrolled cell proliferation. In comparison to HER2-negative tumors, tumor cells with HER2 amplification have a higher propensity to disseminate and recur following therapy. In addition to prognosis, determining the status of the HER2 receptor via FISH testing has implications for developing a targeted, personalized treatment for breast and gastro-esophageal cancers using tyrosine kinase inhibitors (Lapatinib, Neratinib), monoclonal antibodies (Trastuzumab, Pertuzumab) [52].
KIT	164920	The KIT gene is located on chromosome 4 and encodes a tyrosine-kinase receptor found on the surface of many cell types, having a role in cell division, differentiation and proliferation control [53].	Pathogenic KIT gene variants are found in different types of cancer (leukemia, gastrointestinal tumors, and melanoma), and their detection has therapeutic implications for tyrosine-kinase inhibitors [53-55].
PDGFRA	173490	The PDGFRA gene, which is found on chromosome 4 (4q12), encodes platelet-derived growth factor receptor alpha, which has tyrosine-kinase activity and is involved in signal transduction from the extracellular environment into the cell. The protein participates in several intracellular signaling pathways that promote cell growth and survival [56, 57].	Mutations in the PDGFRA gene can be involved in the etiopathogenesis of several types of solid tumors, such as gastrointestinal tumors (lung adenocarcinoma, colon adenocarcinoma) or hematological conditions (hypereosinophilic syndrome, lymphomas). The identification of pathogenic variants in the PDGFRA gene has therapeutic implications, as it is a predictive marker for the response to tyrosine-kinase inhibitors. Imatinib resistance is linked to the D842V mutation in exome 18 of the PDGFRA gene [56-58].
NTRK1	191315	The NTRK1 gene, which is found on chromosome 1, encodes a receptor protein from the NTRK family (neurotrophic tyrosine-kinase receptor), which is implicated in the MAPK signaling process. The protein has a variety of cell functions (especially important in neuronal development and survival)[59].	Pathogenic alterations of the NTRK1 gene have been documented in papillary thyroid carcinoma, glioblastoma, colorectal cancer, ovarian cancer, pulmonary cancer, breast cancer and endometrial cancer. The most frequent modifications on the NTRK1 gene imply rearrangements and gene fusion. Some of those associate the genes TPM3 and LMNA [59,60].
CDK4/ CDK6	123829/ 603368	The CDK4 gene is located on chromosome 12 (12q14.1) and is implicated in cell cycle regulation. The gene is part of the kinase-family Serine/ Threonine. The pathogenic variants of CDK4 associate uncontrolled cell division, which has been observed in pulmonary cancers (adenocarcinoma), glioblastoma and liposarcoma. The CDK6 gene is located on chromosome 12 (12q13.2) and as well as CDK4, is implicated in cell cycle regulation. Pathogenic variants of CDK6 can be identified in different types of cancer, among which include colon cancer (adenocarcinoma), pulmonary cancer, breast cancer, glioblastoma and endometrial cancers [61, 62].	The therapeutic indications have not been currently well outlined, yet a CDK-inhibitor (Palbociclib) has been utilized in several types of advanced breast cancer, in particular in patients that are HER2 Negative [61, 62].
ESR1 (ER)	133430	The gene ESR1 is located on chromosome 6 (6q25.1). This gene encodes an estrogen receptor and a ligand that activates the transcription factors. The gene has a role in the activation of expression in other genes which further regulate cell growth, cell metabolism and cell development [63].	Pathogenic variants of the ESR1 gene, appear frequently in breast and endometrial cancer. These variants confer resistance to endocrinological therapy. There are targeted treatments used to break down the ESR1 protein [63, 64].

3. Variations in the number of children decreased and increased.

All 3 types were characterized by few changes in the number of copies and a couple of mutations in the TP53 gene, yet often mutations in ARID1A, PTEN, CTNNB1, KRAS and ARID5B [80].

MSI hypermutation results from abnormalities in the repair system of mutations obtained by DNA mating errors (MMR). In The Cancer Genome Atlas (TCGA) study, most tumors in the MSI cluster presented a decrease in mRNA MLH1 expression, secondary to promoter methylation, evidence of loss of expression in somatic variants.

Common genomic variants in the MSI subgroup include PTEN mutations, ARID5B mutations, and mutations in the phosphatidylinositol-3-kinase family genes, as well as PIK3CA and PIK3R1.

The TCGA study also recognized two distinct molecular subgroups based on changes in the number of copies (CN): a subgroup with small variations in the number of copies and a CN subgroup with increased variations in the number of copies. The low CN group is also called "stable microsatellite" and includes above 50% of the low-grade endometrioid tumors. Copy Number Low (CNL) and Copy Number High (CNH) groups are defined by a different profile of CN aberrations (NAC). The CNH group has an increased incidence of TP53 changes.

It is well known that serous carcinomas present multiple chromosomal aneuploidies and high genomic instability. Generally, tumors classified as high CN have the most unfavorable outcome of the four molecular subgroups [81].

Melanoma

Changes in somatic variants in genes such as BRAF, NRAS, KIT, GNAQ/GNA11, MAP2K1/2 (MEK1/2), and PTEN are essential for melanoma pathogenesis. Deciphering these mechanisms in melanoma has opened the path to the development of targeted therapy [38-40].

Molecular markers involved in diagnosis and therapy have been more widely used to aid in the histopathological evaluation of these tumors. These genomic markers are helpful in properly diagnosing melanoma, but also in differentiating a precise subtype that would else be difficult to identify [40, 41].

Essential to the evolution of therapies directed against genetic alterations in melanoma is the reliable identification of these genetic abnormalities in tumor specimens, both fresh and formalin-fixed paraffin-embedded [82, 83]. Numerous targeted therapies have been included in the international guidelines and recommendations for the different types of cancer.

For example, Vemurafenib is indicated by NCCN, FDA, NICE, BNF and SMC in patients with metastatic melanoma and a BRAF V600 mutation (V600E - FDA, NCCN; V600K - NCCN; any BRAF V600 mutation - NICE, SMC, BNF) [84].

Vemurafenib can be used as a singular therapy or combined with other drugs (with Cobimetinib - BRAF/MEK inhibitor combination therapy) [85].

Colorectal cancer (CRC)

Colorectal carcinomas most often present alterations in the TP53, APC, KRAS, PIK3CA, and SMAD4 genes [84 – 87].

Testing for identifying the mutational status of EGFR is very important considering the therapeutic implications of the pathogenic variants observed in these genes, regarding the treatment by use of anti-EGFR monoclonal antibodies [88]. There are other variants in the EGFR signaling pathways genes which involve other exons of KRAS and in NRAS, BRAF, PIK3CA, and PTEN that may impact the response of CRC to anti-EGFR antibody treatment [84, 86, 89–93]. One example of targeted therapies recommended by the international forums for CRC is Cetuximab, a drug recommended (FDA, NCCN, ASCO, NICE, BNF, SMC) for colorectal cancer patients not carriers of BRAF V600, KRAS and NRAS pathogenic mutations to which the disease has been proven to be sensitive [94].

On the opposite, CRC is resistant to Cetuximab therapies in the presence of NRAS/KRAS Resistance variants [92].

Personalized therapies

The National Comprehensive Cancer Network (NCCN) Guidelines for Treatment of Cancer by Site provide clear directions regarding the use of particular tumor markers for each type of cancer and also make specific directions to enable the use of multi-gene panels in the evaluation of different types of cancer in order to identify rare driver mutations for which efficient drugs may already be market accessible or to adequately inform and enrol patients in available clinical trials [95].

A comprehensive genetic test for a broad molecular profile and complete characterization of tumor genetic heterogenicity should contain genes that are aligned with professional practice, guidelines and clinical trials, full coding region coverage for each gene and targeting of unique emerging and actionable markers [95].

It is useful to use such a comprehensive test when a broad genomic profile identifies treatment options including immunotherapies and targeted drugs for patient enrollment or when relapse or disease progression has occurred after prior therapies.

Table 2. Targeted therapies recommended for the different types of cancer (15, 16, 30, 43, 47-52, 78-86, 96-114)

Cancer type	Molecular marker	Indication for testing	Associated treatments
Colorectal (metastatic, stage IV)	BRAF variants	Prognosis	N/A
Colorectal with metastases	KRAS NRAS	Pharmacogenomics	Cetuximab, panitumumab
Colorectal	EGFR	Pharmacogenomics	Cetuximab, panitumumab
Gastrointestinal stromal tumor (GIST)	BRAF sequencing SDHB	Diagnostic, Predictive	N/A
GIST	C-KIT mutation, expression	Pharmacogenomics	Imatinib, sunitinib, regorafenib
GIST	PDGFRA	Pharmacogenomics	Imatinib, sunitinib, olaratumab
Glioma (infiltrative)	NTRK1/2/3 (fusion)	Pharmacogenomics	Larotrectinib sulfate
Melanoma (metastatic)	BRAF variants	Pharmacogenomics	Vemurafenib, dabrafenib, trametinib/dabrafenib, vemurafenib/cobimetinib
Non-small cell lung	EGFR	Pharmacogenomics	Erlotinib, osimertinib (T790M), afatinib, dacomitinib, gefitinib
Non-small cell lung	ALK/NPM1 fusion	Pharmacogenomics	Crizotinib, ceritinib, alectinib
Uveal melanoma (metastatic and/ or unresectable)	NTRK1/2/3 (fusion)	Pharmacogenomics	Larotrectinib sulfate
Breast cancer	HER2 amplification, overexpression	Pharmacogenomics	Trastuzumab, pertuzumab, lapatinib, ado-trastuzumab emtansine, neratinib
Breast cancer	PI3K	Pharmacogenomics	Alpelisib
Breast cancer	CDK4/6 amplification	Pharmacogenomics	Palbociclib, ribociclib, abemaciclib
Breast cancer	ER expression	Pharmacogenomics	Tamoxifen, fulvestrant, anastrozole, letrozole, exemestane, everolimus, palbociclib, ribociclib, abemaciclib
Breast cancer	BRCA1/2*	Pharmacogenomics	Olaparib, niraparib, talazoparib, rucaparib
Ovarian cancer	BRCA1/2*	Pharmacogenomics	Olaparib, niraparib, talazoparib, rucaparib
Ovarian cancer	Homologous Recombination Deficiency (HRD)	Pharmacogenomics	Niraparib

CONCLUSIONS

For patients with solid tumors, personalized medicine has been recognized as a successful strategy treatment, but it is not enough to seize cancer development and progression up to a single molecular alteration due to specific features such as tumor heterogeneity, clonal evolution and specific resistance mechanisms. Previous research has assessed the efficiency of using multigene molecular screening to personalize cancer treatment therapy, with debatable findings.

A common type of cancer contains thousands of germline single-nucleotide variants that might affect protein function and a few dozen, up to several hundreds of somatic variants as well as numerous large-scale structural abnormalities in the genome. Clinical and biological interpretation of the effect of all such abnormalities remains a challenge.

The evolutionary relation to the metastatic lesions and the primary tumor can help recreate the metastatic process. Although it was suspected for a long time, advances in genomics have finally proven that metastatic alterations can give rise to new metastases.

Future research in the field of circulating tumor DNA analysis might be the key to overcoming some of these limitations. Liquid biopsy could allow dynamic molecular profiling of all patients diagnosed with solid tumors, improving accuracy, prognosis, and management.

Cancer is the leading cause of death worldwide and an important impediment to life expectancy and life quality.

ABBREVIATIONS

ASCO – American Society of Clinical Oncology

BNF – British National Formulary

CN – number of copies

CNH – Copy Number High

CNL – Copy Number Low

CRC – Colo-rectal Cancer

DNA – Deoxyribonucleic acid

FDA – Food and Drug Administration

FISH – fluorescence in situ hybridization

GIST – Gastrointestinal stromal tumor

HBOC – hereditary ovarian and breast

HGSOC – high-grade serous ovarian cancer

HR – homologous recombination

IHC – Immunohistochemistry

MMR – mismatch repair

MSI – Microsatellite instability

NCCN – test of quality The National Comprehensive Cancer Network

NICE – National Institute for Health and Care Excellence

NGS – Next Generation Sequencing

NSCLC – non-small cell lung cancer

PARP – Poly(ADP-ribose) polymerase

RNA – Ribonucleic acid

RT-PCR – real-time polymerase chain reaction

SMC – Scottish Medicines Consortium

TCGA – The Cancer Genome Atlas

TNM – tumor, node and metastasis

AUTHORS' CONTRIBUTION

VER – Writing draft, analysis, data visualization, data management

LGP – Writing draft, analysis, data visualization, data management

LCB – Writing draft, analysis, data visualization, data management

DS – Writing draft; analysis, data management

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MR – Writing draft, data visualization

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CONFLICT OF INTEREST

None to declare.

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