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TOPIC HIGHLIGHT

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Perspectives on new biomarkers in gastric cancer: Diagnostic and prognostic applications

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Abstract

Gastric cancer is considered one of the most deadly tumors worldwide. Even with the decline in its incidence, the mortality rate of this disease has remained high, mainly due to its late diagnosis and to the lack of precise prognostic markers. The main purpose of this review is to present genetic, epigenetic and proteomic molecular markers that may be used in a diagnostic and prognostic manner and to discuss the pros and cons of each type of marker for improving clinical practice. In this sense, we observed that the use of genetic markers, especially mutations and polymorphisms, should be carefully considered, as they are strongly affected by ethnicity. Proteomic-based markers show promise, but the higher costs of the associated techniques continue to make this approach expensive for routine use. Alternatively, epigenetic markers appear to be very promising, as they can be detected in bodily fluids as well as tissues. However, such markers must be used carefully because epigenetic changes may occur due to environmental factors and aging. Despite the advances in technology and its access, to date, there are few defined biomarkers of prognostic and diagnostic use for gastric tumors. Therefore, the use of a panel of several approaches (genetic, epigenetic and proteomic) should be considered the best alternative for clinical practice.

Key words: Molecular markers; Epigenetic; Genetic; Proteomic; Diagnosis; Prognosis; Gastric tumors

Core tip: Despite the advances in technology and its access, to date, there are few defined biomarkers of prognostic and diagnostic use for gastric tumors. Therefore, a combination of several approaches (genetic, epigenetic and proteomic) should be considered the best alternative for clinical practice. Considering this point of view, this review aims to discuss the most studied biomarkers, discussing the pros and cons of each type of marker and their use in the clinical practice.

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INTRODUCTION

Despite the decline in its incidence since World War Ⅱ,

gastric cancer remains the fourth most common type of cancer worldwide and is tied with lung cancer as the second leading cause of death from cancer[1,2]. The global incidence of gastric cancer for 2008 was estimated to be 989000 new cases and 738000 related deaths[3].

It is known that gastric cancer is a multifactorial disease involving environmental factors, such as *Helicobacter pylori* infection, and genetic susceptibility[4,5]. Histologically, gastric cancer is classified according to Làuren[6] into two types, diffuse (or undifferentiated) and intestinal (or differentiated), with the majority of cases being of the intestinal type[7].

Despite improvements in medical technology, such as the development of new diagnostic imaging methods, gastric cancer remains a silent disease that is frequently diagnosed in advanced stages, which is responsible for its elevated mortality[8]. Additionally, the presence of metastasis in the lymph nodes is a frequent event in this type of neoplasia and is considered an important prognostic marker because it may contribute to the high rates of recurrence and/or gastric cancer mortality[9].

Considering the increasing level of understanding of the molecular basis of tumor biology, several biomarkers have been identified for many types of tumors[10]. These biomarkers or molecular markers are molecular entities (DNA, RNA or protein) that can be isolated from biological materials and are useful in the five main areas of cancer study and medicine: cancer screening, diagnosis, tumor classification, prognosis and prediction of a therapeutic response[11]. Despite its importance in translational medicine, some important factors determining the efficiency of a molecular marker assay are the levels of sensitivity and specificity[12], which currently limit their use in clinical practice.

Due to the above-mentioned factors, it is very important to establish molecular markers that can help health professionals in the diagnosis and prognosis of gastric cancer, including those that can be used in a non-invasive way. In this sense, this review aims to present the biomarkers of diagnostic and prognostic use with a broad spectrum of biological samples and detection methods, including genetic, epigenetic and proteomic approaches.

GENETIC MARKERS

Genomic instability

Genomic instability is considered one of the hallmarks of cancer[13]. It can be classified into chromosome instability (CIN) and microsatellite instability (MSI), with the latter being a major pathway involved in gastric carcinogenesis and occurring in at least 20% of all gastric cancer (GC) patients. Several studies have assessed the MSI status of GC patients around the world; however, to date, there are no conclusive studies regarding its significance in the diagnosis and/or prognosis of sporadic or familial gastric cancer[14,15].

MSI usually results from alterations in the genes responsible for DNA repair, such as *MLH1* and *MSH2*, both of which are associated with the development of Lynch syndrome and gastric carcinogenesis[16,17].

In general, the occurrence of MSI in GC is associated with any change (genetic or epigenetic) in DNA repair genes[18]. To define the MSI status of an individual, researchers must assess a panel defined by the National Cancer Institute (BAT25, BAT26, D2S123, D5S346 and D17S250). In this sense, MSI can be considered a prognostic marker, as GC patients who are positive for microsatellite instability (MSI+) have certain features and prognosis, such as tumors located in the antrum and an intestinal phenotype with an expansive growth pattern, especially when associated with *MLH1* methylation[19]. Direct invasion of adjacent organs and extensive nodal metastasis have both been reported, along with a lack of distant metastasis and chemoresistance to fluorouracil treatment[20-22], but with a better prognosis[23], especially in cases of the intestinal type[24,25].

The presence of MSI consequently influences the emergence of mutations in other genes that are important for the maintenance of cellular homeostasis. To date, this association has been reported in genes involved in cell cycle regulation and apoptosis (*TGFβRII, IGFIIR*, *TCF4*, *RIZ*, *BAX*, *CASPASE 5*, *FAS*, *BCL10* and *APAF1*) and in the maintenance of the genomic integrity (*MSH6*, *MSH3*, *MED1*, *RAD50*, *BLM, ATR* and *MRE11*). Consequently, changes in these genes lead to the accumulation of mutations that can result in the development of a malignant phenotype[15,26].

In addition to MSI, another well-studied phenomenon is the CIN phenotype, the most common type of genomic instability observed in solid tumors and a major source of genomic instability in GC. This phenotype is characterized by gross chromosomal abnormalities, such as the gain or loss of entire chromosomes (*i.e.*, aneuploidy) and/or fractions of chromosomes (*i.e.*, loss of heterozygosity, amplifications and translocations)[27-30].

In contrast to MSI, for which the same markers are analyzed in any population, CIN analyzes the entire genome of the individual tumor. In this sense, a common characteristic observed is that several markers may be influenced by the patient's ethnicity. One example is the description of a loss of chromosome 11q observed in diffuse-type GC, which is unique to the population of North Brazil[31].

However, in a broader sense, the results of CIN suggest that several altered chromosome regions are shared independent of the studied population. Therefore, we can observe that losses of chromosome 4q, 9p, 18q, 21q and 22q and gains of chromosomes 5p, 8p, 8q, 17q, 20p and 20q are frequent events in GC and are related to the patient's clinical outcome, as this depends on the amount of DNA copy number alterations[30-33].

It is worth noting that the rearranged chromosomes are always involved with important genes, such those controlling the cell cycle machinery. This was explored by the work of Fan *et al*[32], who used array Comparative Genome Hybridization and found several events of losses

Table 1 Main genetic and epigenetic alterations in gastric cancer tissues and their clinical application as biomarkers

Alteration	Type of alteration	Clinical application	Ref.
HER-2 amplification	Genetic	Prognostic and therapeutic	[34-40]
MYC amplification	Genetic	Progression and metastasis	[52]
TP53 Arg72Pro	Genetic	Risk predictor, prognostic	[63-67,69-72]
CDH1 -160 C>A	Genetic	Risk predictor	[76-78]
CDH1 hypermethylation	Epigenetic	Prognostic, metastasis	[167,170,171]
p16 hypermethylation	Epigenetic	Diagnostic, prognostic and therapeutic	[156-160]

and gains of entire chromosomes and amplifications and deletions of parts of the genome. All of these alterations involved or harbored regions of 321 known or candidate oncogenes (*e.g.*, *MYC*, *HER2*, *TGFB1*), frequently showing copy number gains, and 12 tumor suppressor genes (*e.g.*, *p16*, *SMAD4*, *SMAD7*), showing frequent copy number losses.

Another common feature of gastric tumors is the presence of gene amplification. It is known that the increased production and amplification of *HER2* can be observed in various types of cancer. Several clinical studies have been able to identify HER2 protein overexpression or *HER2* gene amplification in gastric cancer, with great variation in the number of patients with HER2-positive tumors[34]. Although the prognostic value of this biological marker remains questionable for resected gastric cancer[35-37], it is well documented that this amplification event is more frequent in intestinal-type GC[38-40] and is significantly associated with a poor prognosis[34-40]. Furthermore, this gene amplification is considered an important biological marker for guiding clinical decisions regarding adjuvant chemotherapy with trastuzumab, especially in patients with lymph node metastasis, as it predicts sensitivity to this chemotherapeutic agent[34,36,38,41-45].

The overexpression of the *MYC* gene, especially due to gene amplification, was described as a frequent event in GC, ranging from 15.6% to 100% in primary tumors, especially those of the intestinal type[46-51]. In a recent study, de Souza *et al*[52] demonstrated the overexpression of MYC in gastric tumors, linking it to tumor progression (deeper tumor extension and the presence of distant metastasis).

Mutations and polymorphisms

As genetic alterations have a clear influence on the development and outcome of cancer treatment, it is expected that gene-based markers have a significant impact on tumor control. Among the most prevalent and common genetic alterations in GC are mutations in the *TP53* and *CDH1* genes (Table 1). However, in terms of biomarkers of diagnosis and prognosis, there is some divergence in the results with respect to the occurrence of mutations and their relationship to the histological characteristics of the tumor or stage in GC[53-55].

In addition to mutations, other important genetic alterations influencing gastric tumorigenesis are single-nucleotide polymorphisms (SNPs), which are responsible for over 90% of the variation in the human genome[56]. It is known that infections and nutritional, environmental and genetic factors have a direct link with gastric carcinogenesis. However, individuals exposed to these factors that actually develop gastric cancer belong to a small group, suggesting that the genetic susceptibility, mainly SNPs, of the host must be taken into consideration[57-59].

The number of studies linking genetic polymorphisms and GC has increased exponentially over the past decades, in parallel with major advances in sequencing and genotyping, and polymorphisms may be useful indicators for assessing the risk of gastric cancer[60]. However, it is worth noting that the results derived from polymorphism studies still need to be carefully interpreted, as these biomarkers are generally population dependent, with a strong ethnic influence.

One well-studied polymorphism is *TP53* Arg72Pro, which remains controversial with regard to its potential as biomarker. Although no association with GC risk was observed in Turkish[61] and Korean[62] populations, several meta-analyses indicate its potential use as a risk predictor for Asian but not Caucasian populations[63-67]. According to Francisco *et al*[68], this difference must be related to ethnicity, as it may modulate the penetrance of Arg72Pro in cancer susceptibility.

In addition to its application as a risk predictor, this polymorphism has recently been used as a prognostic factor because it may be correlated with the clinical outcome of patients receiving chemotherapy, though with contradictory results. Wang *et al*[69] observed that the Arg allele is related to an unfavorable effect on patients treated with 5-fluorouracil (5-FU). However, different results were obtained by several other works in which the Pro allele was related to poor survival in patients using 5-FU[70], oxaliplatin[71] or a combination of paclitaxel and cisplatin[72]. Therefore, although promising, the use of the Arg72Pro polymorphism in this sense should be carefully analyzed.

Another studied polymorphism is -160C>A, which is located in the promoter region of *CDH1*, a gene that encodes a transmembrane glycoprotein responsible for mediating intercellular adhesion and cell polarity and plays an important role not only in the regulation of morphogenesis of normal and neoplastic tissues but also in tumor invasion and metastasis[73].

It has been described that the A allele of this polymorphism results in an approximately 68% reduction in transcriptional activity in comparison to the C allele[74,75] and has been associated a with the negative regulation of *CDH1*, which can lead to the loss of cell-to-cell adhesion

mediated by E-cadherin, resulting in increased susceptibility to tumor development and subsequent tumor invasion and metastasis[76]. Thus, the variant allele was suggested to be a likely genetic marker for an increased risk of GC[77,78].

A considerable number of studies have been conducted to investigate the association between this polymorphism and susceptibility to GC in humans, with conflicting results, which may also be explained by the ethnic composition of each population studied[55,60,79-84].

Although the AA genotype is related to an increased risk of GC in the Oman population[74] and Caucasians[73,76], several meta-analyses did not find any influence on the overall risk for the studied populations (Caucasians, Asians and mixed). However, when stratified by ethnicity, the results suggest a protective effect of the A allele in Asian populations[75,85,86].

Two other genotypes in *CDH1*, 347G>GA and +54T>C, were significantly associated with the risk of GC in a study conducted in China[87]. However, two studies in Japan[88] and Italy[89] did not confirm this relationship. According to Pan *et al*[90], to reach a definitive conclusion, further studies with better designs are needed to explore the association of *CDH1* gene polymorphisms with GC susceptibility.

PROTEOMICS

Proteomic-based techniques in cancer biology, such as 2-DE (two-dimensional electrophoresis), iTRAQ (isobaric tags for relative and absolute quantitation), ICAT (isotope-coded affinity tag), protein chip array and liquid chromatography, have been used to identify and quantify proteins that can be used as biomarkers in bodily fluids and tissues in GC[91].

Human serum contains a complex array of peptides. Some of these may function as biomarkers, with their presence/absence or relative abundance being correlated with health status and thus useful for prognosis or diagnosis[92]. To date, the most common fluid biomarkers available for GC include carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), carbohydrate antigen 72-4 (CA 72-4), Cytokeratins (CYFRA 21-1, TPA - tissue polypeptide antigen, TPS - tissue polypeptide-specific antigen), E-cadherin, pepsinogen, cytokines and the β-subunit of HCG. However, although some authors suggest that the sensitivity and specificity of these markers are not sufficient for the diagnosis of GC[93,94], their use in clinical practice is recommended by most authors because they are useful as prognostic, diagnostic and peritoneal recurrence markers[95-100]. The use of CEA and CA 19-9 as prognosis markers, for example, is recommended because their levels increase according to the tumor stage; these markers are especially useful when a cutoff ratio (divided in three stages: negative, low and high) is applied[94-96].

An expansive bibliography about new biomarkers in biological fluids of GC has accumulated over time[101-106]. These biomarkers include, for example, tubulin beta chain, thymosin beta-4-like protein 3, cytochrome b-c1 complex subunit 1, aromatic amino acids (tyrosine, phenylalanine, tryptophan), S100A9/AAT and S100A9/GIF, collagen type IV, hyaluronic acid, prostaglandin E2, EGF, TGFα, epidermal growth factor receptor (EGFR), proapolipoprotein A1 (proApoA1), apolipoprotein A1, transthyretin (TTR), D-dimer, vitronectin (VN), interleukin-6, a-2 macroglobulin, C-reactive protein and plasminogen activator inhibitor-1[107]. However, most of these biomarker candidates still need to be extensively validated in large clinical cohorts because they have been identified in many studies with different methods over time.

It is worth mentioning that other sources of proteins, such as tissue samples and cell lines, have been used in the discovery of new GC biomarkers. To date, tissue samples have not been widely used for this purpose due to poor reproducibility and the small overlap between studies as well as conflicting data. Moreover, in most of these studies, etiological differences between diffuse and intestinal tumor subtypes were ignored because finer sample classification was not possible with the limited patient materials[107]. Due to these difficulties, modern techniques in proteomic studies have enabled a much higher number of proteins in GC tissues to be described, including selenium-binding protein 1, ENO1, ADHIC, ETFB, VDAC, DMBT1, LTF, GRP78, GRP94, PPIA, PRDX1, PTEN, CRIP1, HNP-1, S100A6, S100A8, S100A9, α-defensin-1 and α-defensin-2[107-111]. Other proposed candidate biomarkers include CRIP1, HNP-1, and S100-A6[112] and human neutrophil peptides 1-3 (HNPs 1-3) and MIF[113]. In summary, the detection and verification of tissue biomarkers through the application of various proteomic methods can promote the more robust clinical evaluation of patients with gastric cancer.

As reported, the majority of tumor biomarkers in GC diagnosis are glycoproteins[114], with the most common being mucin-5AC (MUC5AC), IgG, mucin-1 (MUC1), IGHM, LRG1, haptoglobin (HP), albumin (ALB), TF, kininogen-1 (KNG1), alpha-1-acid glycoprotein (AGP), ceruloplasmin (CP), A1BG, vitamin D binding protein (GC), alpha-1-antitrypsin (SERPINA1), antithrombin (SERPINC1), angiotensin (AGT), CFB, serpin peptidase inhibitor, Clade A (SERPINA3), alpha-2-HS-glycoprotein (AHSG), Zn-alpha-2-glycoprotein (AZGP1), CLU, ITIH2, complement factor H (CFH), interalpha-trypsin inhibitor HCRP, SERPING1 and C4A variant protein (C4A)[115-118].

Recently, Li *et al*[119] studied two multidrug-resistant cell lines and their parental drug-sensitive GC cell line to characterize the multiple drug resistance (MDR)-related cell surface glycoproteome. These authors successfully identified 56 cell membrane glycoproteins, 11 of which (Mesothelin, EGFR, Integrin alpha-3, CD59, Folate receptor alpha, Peptidyl-prolyl cis-trans isomerase FKBP9, Laminin subunit alpha-5, Dihydropyridine receptor alpha 2, Multidrug resistance protein 1, Prostaglandin F2 receptor negative regulator and Golgi apparatus protein 1) were

Table 2 miRNAs differently expressed in gastric cancer tissues and their clinical application

miRNA	Level of expression	Clinical application	Ref.
miR-301a	Up-regulated	Progression and prognostic	[127]
miR-29 family	Down-regulated	Prognostic and therapeutic	[128]
miR-146a	Down-regulated	Metastasis	[129]
miR-10b	Up-regulated	Progression and prognostic	[130]
miR-107	Up-regulated	Prognostic	[131]
miR-345 + miR-142	Up-regulated (miR-345) and Down-regulated (miR-142)	Recurrence and progression	[132]
let-7i	Down-regulated	Prognostic and therapeutic	[133]
miR-221	Up-regulated	Progression, prognostic and therapeutic	[125,134]
miR-148a	Down-regulated	Prognostic	[135]
miR-155	Down-regulated	Progression and metastasis	[136]
miR-129-2-3p	Down-regulated	Progression	[137]
miR-181b	Up-regulated	Prognostic	[138]
miR-21	Up-regulated	Prognostic	[138,139]

found to be differentially expressed with the same trend in both the drug-resistant and sensitive cell lines. This report was the first concerning the relationship between glycoprotein alterations and MDR in gastric tumors and was also helpful for better interpreting the sophisticated mechanisms of MDR in gastric cancer, which, of course, still require further investigation and verification.

Given the current multiplicity of proteomic studies in GC, due to the vast amounts of data generated, it is important to maintain an up-to-date and searchable index of the lists of biomarkers obtained in different studies. Finally, it is essential that future studies focus not only on identifying the disease-associated alterations in proteins but also on determining the cellular functions of the proteins identified as well as the mechanistic networks in which they participate. The biomarkers identified experimentally should serve as entry points for investigating the mechanisms of carcinogenesis and tumor progression.

EPIGENETICS

MicroRNA

MicroRNAs (miRNAs) are small (typically about 22 nt in size) regulatory RNA molecules that modulate the activity of specific mRNA targets and play important roles in a wide range of physiologic and pathologic process. miRNAs generally disrupt gene expression by inhibiting translation or through the cleavage of the target mRNA[120]. When associated with the tumor process, miRNAs are called oncomiRs; they may act as oncogenes or as tumor suppressor genes. As a result, oncomiRs can be used in the diagnosis and treatment of cancer, as the expression patterns of miRNAs in human cancer appear to be tissue specific[121]. In addition, genome-wide studies have shown that miRNA genes are frequently located within regions of heterozygosity loss and amplification and fragile sites, suggesting the vital role of miRNAs in tumorigenesis[122].

miRNAs have shown great potential as tissue-based markers for cancer definition. The presence of a miRNA signature in gastric cancer has been suggested by some authors, with specific genes being up- and down-regulated, which can be useful in the diagnostic process[123-125]. Moreover, due to their size, abundance, tissue specificity and relative stability in the circulation of biological fluids, these molecules can serve as accessible biomarkers to detect and monitor GC[126] (Tables 2 and 3).

Recently, miRNA studies have focused on the prediction of chemotherapeutic resistance, as some of those molecules, such as miR-19a/b and miR-106a, accelerate drug efflux, acting as a barrier to the success of GC chemotherapy[146,147].

Methylation and histone modifications

DNA methylation is an epigenetic modification in both prokaryotes and eukaryotes and occurs at carbon 5 of the cytosine ring within CpG dinucleotides, especially in the promoter region of several genes and in noncoding genomic regions[148,149]. Because DNA methylation has a tissue-specific pattern, is involved in a variety of cellular processes, such as gene expression regulation, genomic imprinting, transcriptional regulation and cellular differentiation, and can be modified during tumorigenesis, it is used as a molecular marker of the tumor-development process[150-152].

In GC patients, it is suggested that the methylation pattern of some genes is dependent on environmental factors, such as the presence of *H. pylori*[153-155], as well as on the patient's age[153]. Therefore, biomarkers should be carefully selected to avoid false results in a prognostic and diagnostic approach.

An aberrant methylation pattern of several genes is currently associated with GC (Table 1). One of these genes is the classical tumor suppressor gene *p16*, which was identified as a diagnostic[156,157] and prognostic biomarker in several populations because it can be related to better survival in patients who received 5-fluoracil therapy[158], to metastasis and poor survival in patients without neoadjuvant therapy[159] and to tumor location[160].

Several other genes with altered methylation patterns were identified as potentially useful prognostic biomarkers, including *RKIP*[161], *ADAMTS9*[154], *XAF1*[162], *BCL6B*[163], miR34b and miR129-2[164] and *HOXD10*[165], but studies have only been performed in a few Asian

Table 3 miRNAs differently expressed in body fluids from gastric cancer patients and their clinical application

miRNA	Body fluid	Level of expression	Clinical application	Ref.
miR-200c	Blood	Up-regulated	Progression and survival	[140]
miR-421	Gastric Juice	Up-regulated	Screening	[141]
miR-21	Gastric Juice	Up-regulated	Screening	[142]
miR-106a	Gastric Juice	Up-regulated	Screening	[142]
miR-129-1-3p	Gastric Juice	Down-regulated	Screening	[137]
miR-129-2-3p	Gastric Juice	Down-regulated	Screening	[137]
miR-335	Blood	Up-regulated	Recurrence and prognostic	[143]
miR-221	Serum	Up-regulated	Screening	[144]
miR-744	Serum	Up-regulated	Screening	[144]
miR-376c	Serum	Up-regulated	Screening	[144]
miR-199a-3p	Plasma	Up-regulated	Progression, screening	[145]

populations.

Some of the markers analyzed to date have methylation patterns that are related to the patient's chemosensitivity, such as *MGMT*, *MLH1*, *BNIP3*, *DAPK* and *BMP4*[166-168]. As a result, these genes may be useful for predicting the best treatment for each patient.

One of the most interesting features of methylation markers is the fact that many of them may be used as non-invasive makers, as they can be detected in body fluids such as serum, plasma and peritoneal wash.

One of the most commonly used markers in body fluids is the *CDH1* gene methylation pattern, the main mechanism responsible for *CDH1* down-regulation[169]. The altered methylation pattern of this gene may be detected in peritoneal fluid and used as a marker of tumor recurrence, metastasis and tumor stage[167,170] or in serum, where it is used together with the *APC* methylation status as a marker of prognosis[171].

Some other markers may be detected in serum, such as *SFRP2*[172] and *SLC19A3*[173], or gastric washes, such as a combination of *MINT25*, *ADAM23* and *GDNF*[174]; these are useful as diagnostic markers.

Although studies associating the methylation status of a particular gene and tumorigenesis are frequent, those associating histone modifications, as well as the enzymes responsible, are still few. The majority of such studies are related to histone deacetylase enzymes, which are considered molecular markers of prognosis, with the expression of HDAC 1 and 2 being related to tumor aggressiveness[175,176].

Concluding remarks

Advances in technology have allowed the development of several methods to understand the mechanisms underlying gastric carcinogenesis, resulting in the identification of a large number of molecular targets that can be used as biomarkers with diagnostic and prognostic potential. Several of these (especially *HER-2* amplification, miR-19a/b, miR-160a and *p16* hypermethylation) can also be used for the prediction of therapeutic response, which is a tremendous help to clinicians. Despite this, many of these biomarkers, especially genetic markers, have been tested in only one or a few populations. We must consider that GC, as with other types of tumor, is influenced by ethnic and environmental factors, which can result in the following question: how universal can a prognostic/diagnostic genetic marker be? Thus far, there is unfortunately no answer to that question, and we believe that it will be a long time until this question may be conclusively answered. Therefore, the simplest approach at present is to validate the discovered markers in the target population and to use several biomarkers for each patient. One alternative could be the use of a proteomic approach, which only analyzes protein expression and is independent of the cause (genetic or epigenetic) of any altered pattern. However, there are some limitations to that approach, such as the availability of studies in only a few populations and the cost of the analysis, which remains very high.

Conversely, epigenetic markers appear to be much more tumor specific, as their pattern has been confirmed in all of the studied populations. Moreover, epigenetic markers are more prone to become target markers for therapeutics trials, as these types of alterations are reversible.

Therefore, one might carefully select molecular markers depending on their use. We must bear in mind that genetic markers are much more dependent on the ethnic component than epigenetic markers, making the latter a currently much more reliable option for clinicians.

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