# Tumor markers currently utilized in cancer care

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**Abstract**
A review of tumor markers that are currently used in cancer care.

## Introduction

Tumor markers are products that may derive from malignant cells and/or other cells of the organism in response to the onset of cancer [1-5]. Their production may also be induced by noncancerous benign tumors [1-5]. Some tumor markers can be detected in malignant tissues obtained from biopsies [6-19], whereas others can be analyzed in the blood, bone marrow, urine, or other body fluids [20-25]. Sometimes, tumor markers may also be observed in cancer-free subjects, but in much lower doses than oncological patients. In addition, relatively high levels of a certain tumor marker might develop from various non-malignant pathological conditions, such as liver diseases, inflammations, kidney-related dysfunctions, infections and hematological disorders. On these grounds, high levels of a certain tumor marker in the blood, or in other body fluids might indicate the presence of a malignancy. However, per se, this finding is not sufficient to substantiate the diagnosis of a cancer. For this reason, the analysis of tumor markers in the blood, or other fluids must be combined with the analysis of biopsies, or other tests in order to confirm the diagnosis. The detection of tumor markers can be used for a wide variety of malignancies and for a number of applications, which may comprise diagnosis, follow-up the clinical course of the disease, optimize the efficacy of the treatment, assess the response to therapy and monitor the recurrence of the disease [1-5]. The National Academy of Clinical Biochemistry and The American Society of Clinical Oncology (ASCO) provide the guidelines for the proper utilization of tumor markers in cancer care, which must be approved by the Food and Drug Administration (FDA), in order to be used in the clinical setting of the United States of America (U.S.A.). This article describes the methods that are adopted for the detection of tumor markers that are currently used in cancer care, along with new strategies that aim at developing personalized medicine programs for the treatment of malignancies.

| Tumor marker | Type of tumor/tumors | Application |
|---|---|---|
| 21-Gene signature (Oncotype DX). | Breast cancer. | Assess risk of tumor recurrence. |
| 70-Gene signature (Mammaprint). | Breast cancer. | Assess risk of tumor recurrence. |
| Anaplastic lymphoma kinase (ALK) (mutations). | Non-small cell lung cancer and anaplastic large cell lymphoma. | Diagnosis and determine type of treatment. |
| BRAF (mutations). | Melanoma, colorectal cancer and thyroid cancer. | Diagnosis and determine type of treatment in patients with melanoma. |

| | | |
|---|---|---|
| Epidermal growth factor receptor (EGFR), or HER1 | Cancers of the breast, head and neck, non-small cell lung, pancreas and colon. | Predict outcomes and determine type of treatment. |
| HER2, or HER2/neu, erbB-2, EGFR2 | Breast cancer, stomach cancer and esophageal cancer. | Predict outcomes and determine type of treatment. |
| Hormone receptor (estrogen and progesterone) | Breast cancer and gynecologic malignancies, such as endometrial stromal sarcomas and endometrial cancers. | Predict outcomes and determine type of treatment. |
| KIT | Gastrointestinal stromal tumor and mucosal melanoma. | Diagnosis and determine type of treatment. |
| KRAS (mutations) | Advanced colorectal cancer and lung cancer. | Determine type of treatment. |
| S-100 | Melanoma. | Diagnosis. Blood tests allow for the follow-up of the clinical course of the disease. |
| Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor (PAI-1). | Breast cancer. | To assess the aggressiveness of the malignancy and determine the type of treatment. |

**Table 1**. List of tumor markers that are detected in malignant tissues, other than the blood.

**Tumor markers detected in malignant tissues**

The detection of these tumor markers requires the removal of a biopsy from the patient [6-19]. In certain cases, biopsy-derived tumor markers are utilized just once, in order to confirm a diagnosis. The list of tumor markers that are analyzed in malignant tissues is summarized in Table 1.

**21-Gene signature (Oncotype DX)**

This set of markers is utilized to assess the risk of the reappearance of the tumor in patients with breast cancer [9,26-28]. The 21-gene signature comprises genes that are related to the estrogen receptor (ESR1, PGR, BCL2, SCUBE2), HER2 (HER2 and GRB7), cell proliferation (Ki67, STK15, survivin, cyclin B1, MYBL2), cellular invasion (stromelysin3, cathepsin L2), macrophage marker CD68, anti-apoptotic genes (BAG1 and GSTM1) and five housekeeping genes that are used as reference (β-actin, GAPDH, RPLPO, GUS and TFRC) [9, 26-28]. Oncotype DX is a gene-expression profiling that requires RNA samples derived from paraffin-embedded tumor biopsies and was introduced for the first time in the U.S.A. market in 2004 (Genomic Health Inc., Redwood City, CA) [29].

**70-Gene signature (MammaPrint)**

This set of markers is utilized to assess the risk of the recurrence of the tumor in patients with breast cancer (for a review see references 31-35). In contrast to the 21-Gene signature (Oncotype DX), this assay needs a preparation of fresh tissues in a solution designed to preserve the integrity of RNA molecules [31]. The MammaPrint 70-gene signature test is provided by Agendia Inc. (Irvine, CA).

**Anaplastic lymphoma kinase (ALK)**

The ALK gene is analyzed for the presence of mutations [33-35]. This tumor marker may provide useful information both for the prognosis and to determine the type of treatment for non-small cell lung cancer (NSCLC) and anaplastic large cell lymphoma (ALCL) [33-35]. If mutations are

present, the patient can be treated with crizotinib (or Xalkori), which is a protein kinase inhibitor that targets the aberrant ALK kinase [33, 35]. However, crizotinib interferes also with some other protein kinases [36, 37]. ALK mutation assay analyzes tissues by means of various techniques, such as fluorescent in situ hybridization (FISH), immunohistochemistry (IHC) and polymerase chain reaction (PCR) [35]. FDA approved in 2011 the ALK Break Apart FISH Probe Kit (Abbot Vysis, Schaumburg, IL). This procedure requires unstained tissues, which are hybridized overnight with the probe and then analyzed by fluorescence microscopy [35]. IHC-based techiniques work well for the ALK detection in ALCL, However, IHC-based ALK detection is not efficient in NSCLC biopsies, because of lower levels of ALK protein. IHC detection of ALK in ALCL utilizes the following antibodies: ZAL4 (Invitrogen, Carlsbad, CA), 5A4 (Novocastra, Newcastle, UK) and D5F3 (Cell Signaling Technology, Denvers, MA). Lastly, PCR-derived techniques are able to detect the presence of ALK in NSCLC with various protocols, which comprise reverse-transcriptase multiplexed PCR and RT-PCR [35].

**BRAF**

Mutations of the BRAF gene may be present in melanoma [11, 38, 39], colorectal cancer [40, 41] and thyroid cancer [42, 43]. This tumor marker is used for the diagnosis and to determine the type of treatment in patients with melanoma [11, 38, 39]. The so-called BRAF V600E mutation may be detected in approximately 50% of cases of melanoma [44]. Patients with advanced melanoma can be treated with vemurafenib (or Zelboraf), if mutations in the BRAF gene are found [45, 46]. Vemurafenib has the ability to target the abnormal BRAF protein [45-47]. Various assays are currently available for the detection of the BRAF V600E mutation in formalin-fixed paraffin-embedded (FFPE) tumor tissues, which may also be mounted on slides. Such assays comprise techniques based on pyrosequencing (Laboratory Corporation of America, Burlington, NC), dideoxy sequencing (Quest Diagnostics Inc., Madison, NJ; Vanderbilt Pathology Laboratory Service, Nashville, TN) and PCR either with or without fluorescence monitoring (ARUP Laboratories, Salt Lake City, UT; Mayo Medical Laboratories, Rochester, MN; UNC Health Care McLendon Clinical Laboratories, Chapel Hill, NC).

**Epidermal growth factor receptor (EGFR)**

EGFR is also termed HER1 [48, 49]. The overexpression of this cell surface receptor may be indicative of poor clinical outcomes, as cancerous tissues growth fast, malignant cells spread rapidly and the tumor tends to be more resilient to the treatment [48-52]. EGFR may be used to predict outcomes and to determine the type of treatment for cancers of the breast [53-56], head and neck [57-59], non-small cell lung [34, 51, 60, 61], pancreas [62, 63] and colon [64-66]. Tumor tissues must be prepared in formalin-fixed paraffin-embedded (FFPE) samples. A real-time PCR test analyses mutations in exons 18, 19, 20 and 21 of the EGFR gene, which may be present in DNA obtained from FFPE human non-small cell lung cancer (NSCLC) tumor tissues (Roche Diagnostics, cobas® EGFR Mutation Test, Indianapolis, IN). Another PCR-based method utilizes the therascreen® EGFR RGQ PCR Kit - P120022 kit (Qiagen Manchester Ltd, Manchester, U.K.) for the analysis of FFPE human NSCLC tumor tissue-derived DNA. A qualitative IHC-based system utilizes the EGFR pharmDxTM kit to monitor EGFR expression levels in normal and malignant tissues of the colon and of head and neck squamous carcinoma, which must be fixed for histological analysis (Dako North America, Inc., Carpinteria, CA). A chromogenic in situ hybridization CISH protocol was developed for the analysis of FFPE breast cancer tissues (Zymed Laboratories, Inc., New York. NY). FFPE breast cancer tissue may also be analyzed by IHC, utilizing a monoclonal antibody to EGFR (Clone 31G7, Zymed Laboratories, Inc., New York. NY).

**HER2**

HER2 is also known as HER2/neu, erbB-2, or EGFR2 [67]. This cellular receptor may contribute to the growth and/or dissemination of certain types of tumors [14, 67, 68]. HER2 overexpression is found in 20% of patients with breast cancer [13, 69, 71]. High HER2 expression levels may also be observed in tumors of the stomach [72-74] and esophageal cancers [75, 76]. The analysis

of HER2 expression can be utilized to predict outcomes and to define a line of treatment for breast cancer [13, 14, 69] and advanced stomach cancer [77, 78]. FFPE tumor tissues can be tested for HER2 status either via IHC, or FISH analysis, which utilizes probes contained in the following kits: PathVision (Abbott France SAS, Rungis, France) pharmDx (Dako France SAS, Trappes, France) INFORM (Ventana Medical Systems SA, Ilkirch, France). IHC assays can be carried out either with anti-human HER2 polyclonal antibodies A0485 (Dako France SAS, Trappes, France), or with the HerceoTest kit (Dako France SAS, Trappes, France).

**Hormone receptors**

All biopsies from patients with breast cancer are tested for estrogen and progesterone receptors [69]. These hormones have the ability to stimulate the proliferation of breast cancer cells [69]. Estrogen receptor expressing breast cancer cells are termed ER-positive, whereas progesterone receptor expressing breast cancer cells are termed PR-positive [69]. Approximately two thirds of breast cancers result positive for at least one of these two hormone receptors [69]. The analysis of hormone receptors in breast cancer cells and in some gynecologic cancers may be utilized for the diagnosis and to determine whether hormone therapy is suitable or not for the treatment of the malignancy [69, 79-84]. A typical example of hormone therapy is based on tamoxifen [69]. The gynecologic cancers that can be tested for hormone receptors comprise endometrial stromal sarcomas [85, 86] and endometrial cancers [87-89]. Typically, the ER expression levels in breast cancer tisues can be detected by IHC, with monoclonal antibody ID5 (Dako Cytomation Carpinteria, CA). Another possibile system for monitoring estrogen receptor expression levels is based on PET scan. 18F-fluoroestradiol (18F-FES) is used as a tracer for the PET imaging of ER molecules in breast cancer patients. 18F is generated with a cyclotron (Siemens Eclipse Cyclotron, Siemens Healthcare, Erlangen, Germany; Scanditronix MC-50, Uppsala, Sweden) [85]. 18F-FES synthesis can be conducted as described [85]. Typically, patients receive injections of 222 MBq radiopharmaceutical in 20 ml of isotonic phosphate-buffered saline that contains less than 15% ethanol by volume. The molecular mass and radiochemical and chemical purity of 18F-FES must be evaluated after each synthesis with high-performance liquid chromatography–mass spectrometry analysis (Waters 2690 HPLC, Waters Corporation, Milford, MA; MicroMass ZMD (ES2), Waters Corporation, Milford, MA). Radiochemical purity must be in the range of 98%, whereas the specific activity must be greater than 37 x 1012 Bq/mmol at the time of injection. Patients are positioned supine and imaged with a GE Healthcare Advance PET scanner (Little Chalfont, U.K.).

PR expression levels in breast cancer cancer can be assessed by IHC, with monoclonal antibody 636 (Dako Cytomation, Carpinteria, CA).

**KIT**

The proto-oncogene KIT is a transmembrane protein, which is also termed CD117 [90-96]. This proto-oncogene is associated with gastrointestinal stromal tumor [90-92] and mucosal melanoma [93-96]. The analysis of this marker is utilized for the diagnosis of the illness and to determine the type of therapeutic intervention in oncological patients with these two types of malignancies [90-96]. KIT can be detected by IHC in gastrointestinal stromal tumor and mucosal melanoma FFPE tissue sections, by using a rabbit polyclonal antibody against human KIT (Code number A-4502, dilution 1:100; Dako Cytomation, Carpinteria, CA).

**KRAS**

Mutations in the KRAS gene may enhance chemo-resistance in advanced colorectal cancer [97, 98] and in certain lung tumors [99-101]. For instance, cetuximab (or Erbitux) and panitumumab (or Vectibix) are used for the targeting of EGFR in patients with advanced colorectal cancer [102-104]. However, both cetuximab and panitumumab become essentially useless in patients who carry the mutated KRAS gene and, therefore, these two drugs cannot be administered in therapy. Similarly, KRAS mutations may render some lung cancers more resistant to erlotinib (or Tarceva) and gefitinib (or Iressa) [105-108]. On these grounds, the analysis of KRAS mutations may provide useful information on the type of treatment that has to

be adopted for the treatment of advanced colorectal cancer and certain forms of lung tumors [97-108]. KRAS gene mutations can be detected with a real-time PCR kit provided by Entrogen, Inc. (Woodland Hills, CA).

**S-100**

S-100 is present in the majority of melanoma cells and may be utilized for the diagnosis of melanoma, following the removal of a biopsy from the patient [17, 18, 109]. This marker can also be detected with blood tests, which allow for the monitoring of the spreading of melanoma before and/or in response to the treatment [110]. S-100 can be detected in FFPE tissue sections with antibodies provided by Dako Cytomation (Carpinteria, CA).

**Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor (PAI-1)**

These two markers are analyzed to assess the aggressiveness of the malignancy and to determine the type of treatment in patients with breast cancer [8, 111, 112]. An ELISA kit is currently available for the detection of uPA (American Diagnostics, Greenwich, CT). For this protocol, breast tumor biopsies are initially frozen at -70oC. Subsequently, tutmor tissues are homogeneized in 50 mM Tris HCl pH = 7.4, supplemented with 1 mM monothioglycerol (1:7; w/v). The homogenate is then centrifugated at 2,000 g for 10 minutes and the supernatant is extracted with 1% Triton X-100. Another centrifugation step is carried out at 10,000 g for 20 minutes. After this centrifugation, uPA can be detected with the aforementioned ELISA kit. The same protocol for the extraction of uPA can be utilized for PAI-1, which is then detected with another ELISA kit (Monozyme, Horsholm, Denmark).

| Tumor marker | Type of tumor/tumors | Tissue and/or fluid tested | Application | Possible cross-reaction with noncancerous conditions |
|---|---|---|---|---|
| 5-Protein signature (Ova1). | Ovarian cancer. | Blood. | Assess malignancy of pelvic mass for suspected ovarian cancer prior to surgery. | - |
| Alpha-fetoprotein (AFP) | Liver cancer (hepatocellular carcinoma); germ cell tumors. | Blood. | Diagnose liver cancer and follow response to therapy. Evaluate stage, prognosis and response to therapy of germ cell tumors. | Acute and chronic hepatitis |
| BCR-ABL | Chronic myeloid leukemia (CML) | Blood, bone marrow. | Diagnose chronic myeloid leukemia | - |

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| | | | (CML) and follow response to therapy. | |
| Beta-2-microglobulin (B2M) | Chronic lymphocytic leukemia (CLL); multiple myeloma; a number of lymphomas, comprising Waldenstrom macroglobulinemia. | Blood, urine, cerebrospinal fluid. | Prognosis and response to therapy. | Hepatitis and kidney disease. |
| Bladder tumor antigen (BTA) | Bladder cancer. | Urine. | Diagnosis and follow-up clinical course of the disease. This test is less efficient than cystoscopy. | Urinary tract infections and kidney stones. |
| CA 15-3 | Breast cancer. This marker can also be found in tumors of the ovaries, lung, pancreas and colon. | Blood. | Diagnosis and follow-up clinical course of the disease. | Benign breast tumors, hepatitis; ovarian disease and endometriosis. |
| CA 19-9 | Colorectal cancer; pancreatic cancer; bladder cancer. High levels can also be found in other tumors of the digestive tract, such as bile ducts and stomach. | Blood. | Diagnosis and follow-up clinical course of the disease. | Rheumatoid arthritis, thyroid disease, pancreatitis and inflammatory bowel disease. |
| CA 27-29 | Breast cancer. High levels of this marker are also associated with cancers of the uterus, ovary, kidney, liver, pancreas, stomach, colon and lung. | Blood. | Diagnosis and follow-up clinical course of the disease. | Women in the first trimester of pregnancy; ovarian cysts; endometriosis; non-cancerous breast disease; kidney stones; liver disease. |
| CA 125 | Epithelial ovarian cancer; primary peritoneal cancer; fallopian tube cancer; uterine cancer. High | Blood. | Follow up response to therapy. | Endometriosis; uterine fibroids. |

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| | levels of this marker can also be found in women and men with cancer of the liver, lung, colon, breast and pancreas. | | | |
| Calcitonin | Medullary thyroid carcinoma (MTC). High kevels of this marker can also be found in leukemias and lung cancers. | Blood. | Diagnosis. | - |
| Carcinoembryonic antigen (CEA) | Colorectal cancer; breast cancer; lung cancer. High levels of this marker can also be found in other malignancies, such as leukemia, melanoma and cancer of the liver, pancreas, thyroid, stomach, prostate, kidney, cervix, ovary and bladder. | Blood. | Diagnosis and screening. | Hepatitis; rheumatoid arthritis, chronic obstructive pulmonary disease, pancreatitis, colitis and smokers without cancer. td> |
| CD20 | Non-Hodgkin lymphoma. | Blood. | Determine efficacy of therapy/ | - |
| Chromogranin A (CgA) | Neuroendocrine tumors, such as neuroblastoma, carcinoid tumors; small cell lung cancer. High levels of this marker can also be found in advanced prostate cancer. | Blood. | Diagnosis. | - |
| Chromosomes 3, 7, 17 aneuploidy and loss of 9p21 locus. | Bladder cancer. | Urine. | Monitor relapse of the disease. | - |
| Cytokeratin fragments 21-1. | Lung cancer. | Blood. | Monitor relapse of the disease. | - |
| Fibrin/fibrinogen. | Bladder cancer. | Urine. | Follow-up clinical course of the | - |

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|---|---|---|---|---|
| | | | disease and response to therapy. | |
| HE4 | Ovarian cancer. | Blood. | Follow-up clinical course of the disease and monitor for relapse of the illness. | - |
| Human chorionic gonadotropin (HCG) | Some types of germ cell tumors; ovarian cancer; testicular cancer; choriocarcinoma. | Blood. | Diagnosis, follow-up response to therapy and monitor relapse of the disease. | - |
| Immunoglobulins (monoclonal gammopathy) | Excessive levels of immunoglobulin M (IgM) are associated with Waldenstrom macroglobulinemia; in multiple myeloma high levels of IgG are frequently observed, followed by IgA and IgM. | Blood. | Diagnose and follow-up response to therapy. | - |
| Free light chains of immunoglobulins, or Bence Jones protein if found in the urine. | Multiple myeloma. | Blood; urine. | Diagnosis and to guide treatment. | - |
| Inhibin | Ovarian stromal cancer. | Blood. | Diagnosis and monitor for relapse of the disease. | - |
| Lactate dehydrogenase (LDH) | Testicular cancer; germ cell tumors; melanoma; neuroblastoma; lymphoma. | Blood. | Prognosis, follow-up response to therapy and monitor for relapse of the disease. | Liver disease, hematological illnesses, muscle injury, heart attack and stroke. |
| Neuron-specific enolase (NSE) | Neuroendocrine tumors, such as | Blood. | Follow-up response to | - |

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| | neuroblastoma, carcinoid tumors; small cell lung cancer. High levels of this marker are also found in melanoma, pancreatic endocrine tumors and medullary thyroid cancer. | | therapy. | |
| Nuclear Matrix protein 22 (NMP22) | Bladder cancer. | Urine. | Diagnosis. | This marker can be present in the urine of patients who had a recent chemotherapy intervention. |
| Prostate-specific antigen (PSA) | Prostate cancer. | Blood. | Diagnosis, follow-up response to therapy and monitor clinical course of the disease. | Benign prostatic hyperplasia (BPH), infection of the prostate and inflammation of the prostate. |
| Prostatic acid phosphatase (PAP) | Prostate cancer; multiple myeloma; lung cancer. | Blood. | Diagnosis. | - |
| S-100 | Melanoma. | Blood. | Diagnosis and monitor clinical course of the disease. | - |
| Soluble mesothelin-related peptides (SMRP) | Mesothelioma. | Blood. | Diagnosis and monitor relapse of the disease. | - |
| Thyroglobulin | Thyroid cancer. | Blood. | Diagnosis, follow-up response to therapy and monitor for relapse of the disease. | Noncancerous thyroid diseases. Some individuals may have immunoglobulin anti-thyroglobulin, which interfere with the analysis. |

**Table 2**. List of tumor markers that are detected in the blood and/or other body fluids.

**Tumor markers that are detected in the blood or fluids.**

The analysis of tumor markers that are present in the blood and/or body fluids is usually conducted routinely on patients diagnosed with various types of malignancies, in order to follow the clinical course of the disease and/or to assess the response to therapy and/or to monitor the reappearance of the tumor. In a number of cases, the detection of tumor markers in the blood and/or body fluid may be carried out in conjunction with other pathological tests to confirm a diagnosis [113-115].

**5-Protein signature (Ova1)**

Ova1 comprises five different proteins, such as CA 125, β-2-microglobulin (B2M), ApoA1, transthyretin (TT) and transferrin (TF) [20, 117-119]. This set of markers is detected in the blood of patients with ovarian cancer and is conducted prior to surgery in order to determine if a malignancy is present in a pelvic mass, which is usually indicative of ovarian cancer [20, 117-119]. Serological OVA1 tests are carried out by Vermillion, Inc. (Austin TX).

**Alpha-fetoprotein (AFP)**

AFP is tested in the blood. High levels of AFP might be associated either with hepatocellular carcinoma [21, 120,121, 123], or with germ cell tumors [123-126]. However, patients with acute and chronic hepatitis also exhibit high levels of AFP [21, 120, 121, 123]. As it stands, this marker can be used to diagnose liver cancer and to follow-up the response to therapy [21, 120, 121, 123]. In addition, AFP is utilized to evaluate the stage, prognosis and response to therapy of patients with germ cell tumors, which may comprise rare forms of ovarian cancer, such as yolk sac tumor, or mixed germ cell cancer, some testicular cancers and mediastinal germ cell tumors [124-127]. An ELISA kit is currently available for AFP serum detection (Catalog number: EK-310-09; Phoenix Pharmaceuticals, Inc.; Burlingame, CA).

**BCR-ABL**

This marker is present only in chronic myeloid leukemia (CML) cells and derives from a specific chromosomal translocation, which produces the so-called Philadelphia chromosome [128-134]. Such a translocation takes place between chromosome 9 and chromosome 22 and is termed t(9;22)(q34;q11). As a consequence, the Abl1 gene on chromosome 9 (region q34) is fused in frame with the BCR (breakpoint cluster region) gene on chromosome 22 (region q11). The resulting fusion gene is termed BCR-ABL, which is tested either in the blood, or in the bone marrow via polymerase chain reaction (PCR). In addition to the diagnosis of CML, BCR-ABL may be used to follow the response to therapy and can be analyzed with a real time PCR kit (QuantidexTM BCR-ABL IS CMR Kit; Asuragen, Austin, TX) [128-134].

**Beta-2-microglobulin (B2M)**

B2M exhibits elevated levels of expression in the blood of patients with chronic lymphocytic leukemia (CLL) [25,135-138, 140], multiple myeloma [141-146] and a number of lymphomas [147-149], comprising Waldenstrom macroglobulinemia [151-154]. This marker can be detected in the blood, urine, or cerebrospinal fluid [25, 135-138,140-154]. B2M is useful for the prognosis and to monitor the response to therapy for the treatment of CLL. High levels of B2M may also be observed in subjects with hepatitis [155, 156] and kidney disease [157]. B2M expression levels in clinical samples can be assessed with a solid phase Elisa kit (R&D Systems, Inc.; Minneapolis, MN).

**Bladder tumor antigen (BTA)**

This marker is present in the urine of patients with bladder cancer and is utilized for the diagnosis and to follow-up the clinical course of the malady [158-161]. However, this test is less efficient than cystoscopy [158-161]. BTA may also be present in the urines of subjects with certain noncancerous conditions, such as infections of the urinary tract [162] and kidney stones [163]. BTA levels in the urine can be evaluated either qualitatively with the BTA stat® test, (Polymedco Inc., Cortlandt Manor, NY), or quantitatively with the BTA TRAK® test (Polymedco, Inc.; Cortlandt Manor, NY). The latter test requires trained personnel.

**CA 15-3**

CA 15-3 is the acronym of Carcinoma Antigen 15-3. This marker is detected in the blood and is associated with breast cancer [24, 164-166]. It may also be found in malignancies of the ovaries [167], lung [168], pancreas [169] and colon [170, 171]. CA 15-3 is used for the diagnosis and to monitor the clinical course of breast cancer. This marker may also be detected in benign breast tumors [172, 173], hepatitis [173], ovarian disease and endometriosis [174, 175]. An Elisa kit is commercially available for the detection of CA 15-5 in the serum (abcam; Cambridge, MA).

**CA 19-9**

CA 19-9 stands for Carbohydrate Antigen 19-9 [171, 176, 177]. Levels of CA 19-9 are detected in the blood of patients with colorectal cancer [171, 176, 177] and malignancies of the pancreas [178-180] and of the bladder [181-183]. High levels of CA 19-9 are also found in other tumors of the digestive tract, such as bile ducts and stomach [184-186]. Hematological levels of CA 19-9 may be utilized for the diagnosis and to monitor the clinical course of malignancies of the colorectal tract, pancreas and bladder [171, 176-183]. This marker may also be present in the blood of subjects who are affected by noncancerous illnesses, such as rheumatoid arthritis [187], thyroid disease [188], pancreatitis [189] and inflammatory bowel disease [190]. Expression levels of CA 19-9 in the blood can be measured with an Elisa kit (abcam; Cambridge, MA).

**CA 27-29**

CA 27-29, or Cancer Antigen 27-29, is detected in the blood of patients with breast cancer [24, 164, 166, 191]. High CA 27-29 levels may also be present in patients with cancers of the uterus, ovary, kidney, liver, pancreas, stomach, colon and lung [192]. CA 27-29 is an additional marker utilized for the diagnosis and follow-up the clinical course of breast cancer before and/or after the therapy. However, not all the patients with breast cancer exhibit high levels of CA 27-29 [162, 193-195]. In addition, considerable CA 27-29 levels may be present in subjects who do not have cancer, such as women in the first trimester of pregnancy [196], or with noncancerous breast disease [197]. CA 27-29 may also be associated with ovarian cysts [198], endometriosis [199], kidney stones [199] and liver disease [199]. CA 27-29 can be detected in the blood with an Elisa kit (MyBioSource, Inc.; San Diego, CA).

**CA 125**

CA 125 is the acronym of Cancer Antigen 125, Carcinoma Antigen 125, or Carbohydrate Antigen 125 [200, 201]. CA 125 may also be termed either mucin 16, or MUC16 [200, 201]. This marker is present in the blood of women affected with epithelial ovarian cancer [202-204], primary peritoneal cancer [205-209] and fallopian tube cancer [210-212]. High levels of CA 125 can also be present in the blood of patients with malignancies of the liver, lung, colon, breast and pancreas [166, 213, 214]. This marker is typically used for the follow-up of the response to therapy of patients with epithelial ovarian cancer, primary peritoneal cancer and fallopian tube cancer [202-212]. Considerable levels of CA 125 may be found in women with noncancerous conditions, such as endometriosis and uterine fibroids [212]. High CA 125 levels are also observed in patients with advanced heart failure [215, 216]. The detection of CA-125 in the blood of patients is based on an Elisa kit (abcam; Cambridge, MA).

**Calcitonin**

This marker is present in the blood of patients with medullary thyroid carcinoma (MTC) and is utilized for the diagnosis of the disease [217-219]. High levels of calcitonin may also be observed in the blood of patients with leukemia [220, 221] and lung cancers [222, 223]. An Elisa kit can be utilized for the quantification of Calcitonin in human serum (ALPCO; Salem NH).

**Carcinoembryonic antigen (CEA)**

CEA is detected in the blood and is utilized for the diagnosis and screening of colorectal cancer [176, 224-228], breast cancer [165, 166, 229, 230] and lung cancer [166, 231, 232]. Considerable levels of CEA may also be observed in the blood of patients with leukemia [233], melanoma [234], and malignancies of the liver [234], pancreas [235], thyroid [236], stomach [237], prostate [238], kidney [239], cervix [240], ovary [241] and bladder [242]. However, CEA may also be found in blood samples of subjects with hepatitis, rheumatoid arthritis, chronic obstructive

pulmonary disease, pancreatitis, colitis and smokers without cancer [234]. CEA can be detected with an Elisa kit (abcam; Cambridge, MA).

**CD20**

This marker is detected in the blood of patients with non-Hodgkin lymphoma [243, 244]. CD20 is utilized to determine the efficacy of the therapeutic intervention [243, 244] and can be measured with an Elisa kit (MyBioSource, Inc.; San Diego, CA).

**Chromogranin A (CgA)**

This marker is detected in the blood and is used to diagnose neuroendocrine tumors, such as neuroblastoma, carcinoid tumors and small cell lung cancer [245-248]. High CgA levels can also be found in advanced prostate cancer [249]. CgA expression levels can be assessed with an Elisa kit (Epitope Diagnostic, Inc.; San Diego, CA).

**Chromosomes 3, 7, 17 aneuploidy and loss of 9p21 locus**

This chromosomal analysis is conducted with Fluorescence in situ Hybridization (FISH) of urologic cytology samples (PersonalizeDx, Rosetta GenomicsTM; Lake Forest, CA) [250, 251]. These chromosomal markers are utilized to monitor the recurrence of malignancies in the urinary tract [250, 251].

**Cytokeratin fragments 21-1**

Cytokeratin fragments 21-1 can also be termed Cyfra 21-1 [252-254]. This marker is detected in the blood of patients with lung cancer and is used to monitor the relapse of the disease [252-254]. Serum Cyfra 21-1 can be measured with solid-phase immunoradiometric assay (CIS Biointernational, Gif Yvette, France).

**Fibrin/fibrinogen**

This marker is found in the urine of patients with bladder cancer and is utilized to follow-up the clinical course of the disease and to monitor the response to therapy [255-257]. An Elisa kit is available for the detection of human fibrin/fibrinogen in the urines (abcam; Cambridge, MA).

**HE4**

HE4 is the acronym of Human Epididymis Protein 4 [258]. This marker is detected in the blood of patients with ovarian cancer and is used to follow-up the clinical course of the disease and to monitor the recurrence of the tumor [258-261]. Serum HE4 can be measured with an Elisa kit (MyBioSource, Inc.; San Diego, CA).

**Human chorionic gonadotropin (HCG)**

This marker is detected in the blood of patients with some types of germ cell tumors, such as ovarian cancer [262-264], testicular cancer [125, 265, 267] and choriocarcinoma [268-270]. HCG is utilized for the diagnosis, to follow-up the response to therapy and to monitor the relapse of the disease [125, 262-265, 267-270]. An Elisa kit is available to detect HCG in the serum (abcam; Cambridge, MA).

**Immunoglobulins (monoclonal gammopathy)**

Abnormal patterns of certain immunoglobulins expression may be detected in the blood of patients with some hematological malignancies [271, 272]. For instance, high levels of immunoglobulin M (IgM) are associated with Waldenstrom macroglobulinemia [152, 273], whereas in multiple myeloma high levels of IgG are frequently observed, which are followed by IgA and IgM [274-276]. Detection of abnormal patterns of immunoglobulin expression may be used for the diagnosis and to follow-up the response to the therapy [152, 271-276]. Monoclonal gammopathy can be analysed by serum proteinelectrophoresis (SPE) (Paragon SPE kit; Beckman Coulter, Inc.; Fullerton, CA), which allows for the electrophoretic separation of proteins. The protein migration pattern can be visualized, interpreted and quantitated at 600 nM with a Beckman APPRAISE densitometer (Beckman Coulter, Inc.; Fullerton, CA). This instrument calculates the relative percentage of each protein fraction.

**Free light chains of immunoglobulins, or Bence Jones protein if found in the urine**

Free light immunoglobulin chains may be detected in the blood of patients with multiple myeloma [277-279]. This marker is termed Bence Jones protein, if it is found in the urine [280-

282]. Levels of free light immunoglobulin chains are monitored for the diagnosis of the disease and to determine the type of treatment for the patient [277-282]. The concentration of serum free light chains can be measured with a latex enhanced immunoassay (FreeliteTM Human Kappa Free Kit, The Binding Site GmbH, Schwetzingen, Germany), which is carried out on a Dade-Behring nephelometer (Siemens Healthcare GmbH, Erlangen, Germany). Free light chains in the urine and/or serum can be measured with a Hydragel Bence Jones kit (Sebia, Evry Cedex, France), which requires a Hydrasis instrument for the separation and characterizarion of free light chains (Sebia, Evry Cedex, France).

**Inhibin**

This marker is detected in the blood of patients with ovarian stromal cancer [283-285]. Inhibin is utilized to diagnose the malignancy and to monitor the reappearance of the tumor [283-285]. An Elisa kit is commercially available for the detection of serum inhibin (KAC1291 INHIBIN-EASIA; Biosource Europe S.A., Nivelles, Belgium).

**Lactate dehydrogenase (LDH)**

LDH is detected in the blood of patients with testicular cancer [261, 263, 286], other germ cell tumors [127], melanoma [110, 287, 288], neuroblastoma [289, 290] and lymphoma [291, 292]. This marker may be utilized for the prognosis, to follow-up the response to therapy and to monitor the recurrence of the tumor. However, high LDH levels may also be detected in noncancerous conditions, such as liver disease, hematological illnesses, muscle injury, heart attack and stroke [293]. For this reason LDH is less useful for the diagnosis of the aforementioned malignancies than the markers AFP and HCG [293]. An Elisa kit is available for the detection of LDH (abcam; Cambridge, MA).

**Neuron-specific enolase (NSE)**

NSE is detected in the blood of patients with neuroendocrine tumors, such as neuroblastoma [294-296], carcinoid tumors [296-299] and small cell lung cancer [292, 295]. This marker is utilized for the follow-up of the response to therapy. High levels of this marker are also present in melanoma [294], pancreatic endocrine tumors [300, 301] and medullary thyroid cancer [302, 303]. NSE can be readily detected with an Elisa kit (Alpha Diagnostic Intl., Inc.; San Antonio, TX).

**Nuclear Matrix protein 22 (NMP22)**

This marker is detected in the urine of patients with bladder cancer and is utilized for the diagnosis of the disease [304-306]. NMP22 may be present in the urine of patients who had a recent chemotherapeutic intervention, or underwent intravesical immunotherapy [307, 308]. An Elisa kit can be utilized for the detection of NMP22 (MyBioSource, Inc.; San Diego, CA).

**Prostate-specific antigen (PSA)**

PSA is detected in the blood of patients with prostate cancer and is utilized for the diagnosis, to follow-up the response to therapy and to monitor the clinical course of the disease [309-311]. This marker is also present in noncancerous conditions, such as benign prostatic hyperplasia (BPH), infection of the prostate and inflammation of the prostate [312]. Serum PSA can be measured with an Elisa kit (abcam; Cambridge, MA).

**Prostatic acid phosphatase (PAP)**

This marker is detected in the blood and is utilized for the diagnosis of prostate cancer [313-315], multiple myeloma [316] and lung cancer [317]. PAP can be detected in human serum with an Elisa kit (abcam; Cambridge, MA).

**S-100**

As anticipated, S-100 can be detected in tumor biopsies [17, 18, 109] and in the blood of patients with melanoma [110]. This marker may be utilized for the diagnosis of melanoma if found in biopsies [17, 18, 109] and to monitor the clinical course of the disease if detected in the blood [110]. Serum S-100 can be visualized with an Elisa kit (Genorise; Glen Mills, PA).

**Soluble mesothelin-related peptides (SMRP)**

This marker is detected in the blood of patients with mesothelioma and may be utilized for the diagnosis and to monitor the reappearance of the malignancy [318-320]. An Elisa kit is commercially available for the detection of human SMRP in the serum (Cusabio; Wuhan, China).

**Thyroglobulin**

This marker is detected in the blood of patients with thyroid cancer and may be used for the diagnosis, to follow-up the response to therapy and to monitor the recurrence of the tumor [321-323]. However, thyroglobulin may also be present in noncancerous thyroid diseases [324]. In addition, some individuals may have antibodies against thyroglobulin, which interfere with the blood test [325, 326]. Serum thyroglobulin can be measured with an Elisa kit (abcam; Cambridge, MA).

**Future directions**

Novel tumor markers based on multi-gene and/or circulating cancer stem cells signatures are currently under characterization [327-338]. In this respect, a particular emphasis has been placed on the characterization of micro-RNA (miRNA) molecules [337, 339-347]. The validation of these markers is still either at the early clinical trial stages, or preclinical phase [327-338]. The upcoming generation of tumor markers holds the potential of developing so-called personalized medicine in oncological programs, in which a combination of drugs can be selected to optimize the treatment of a specific patient [327-338].

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