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Prognostic and Predictive Markers in Early Detection of Different Types of Cancers for Selected Organ Sites

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Abstract: ***Background****: Tumor markers are substances that are produced by cancer or by other cells of the body in response to cancer or certain benign (noncancerous) conditions. Tumor markers are used to help detect, diagnose, and manage some types of cancer. Although an elevated level of a tumor marker may suggest the presence of cancer.* ***Aim:*** *The aim of this review is to compare and analyze the present and newer oncogenic markers which help in diagnosis of different types of cancers.* ***Material & Methods:*** *An extensive literature survey was done aiming to compare and compile cancer tests makers required in diagnosis of diseases.* ***Results:*** *Cytoplasmic Proteins, Cell Surface Antigens, Oncofetal Antigens, Receptors, Oncogenes and their metabolic products, Acute-Phase Proteins, Enzymes, Hormones or Tumor associated antigens such as Carcino-Embryonic Antigen (CEA) and Alpha Feto Protein (AFP) are makers for routine analysis whereas several studies have confirmed and consolidated the usefulness of markers such as AFP: Alfa fetoprotein; β-hCG: Beta human chorionic;gonadotropin; CA: Carbohydrate antigen; CEA: Carcinoembryonic antigen; ER: Estrogen receptor; HIAA: Hydroxy indole acetic acid; LDH: Lactate dehydrogenase; PLAP: Placental alkaline phosphatase; PR: Progesterone receptor; PSA: Prostate-specific antigen.* ***Conclusion:*** *There is no "universal" tumor marker that can detect any type of cancer. Further investigation is necessary to define these biomarkers in terms of usefulness in assessing diagnosing various types of cancers.*
Keywords*: Monitoring; Recurrence; Screening; Prognosis; Diagnosis; Response to therapy.*

Tumor markers are substances that can often be detected in higher than normal amounts in the blood, urine, or body tissues of some patients with certain types of cancer. These substances can be proteins, enzymes, biochemicals, or antigens. Tumor markers may be produced directly by a tumor or by other tissues in response to a tumor, they can be metabolic products, acute-phase proteins, enzymes, hormones or tumor associated antigens such as Carcino-Embryonic Antigen (CEA) and Alpha Feto Protein (AFP).In general, tumor marker levels are lower in early stage disease (but still higher than normal) and higher with advanced disease. Furthermore, their levels decrease in response to treatment and increase when the cancer progresses. Tumor markers are very useful in monitoring the course of a diagnosed malignant tumor, for example pre-treatment and subsequent serial values are essential for the evaluation of the response to the treatment modality with time. When used in combination with x-rays and other tests the detection of tumour markers in the blood can be extremely useful in the detection and diagnosis of cancer.
Tumor markers are often used to:

- ***Monitor response to treatment****—some tests show whether the cancer is responding to treatment*
- ***Monitor for progression****—in general, an increase in some tumor markers indicates disease progression*
- ***Detect recurrence****—regular monitoring of some tumor markers during a remission may help detect recurrence*
- ***Detect metastasis****—metastasis is the spread of cancer from its site of origin to another distant location in the body*
- ***Screen at-risk individuals****—Prostate specific antigen is an example of a tumor marker that is specific enough for one condition—prostate cancer—to function as a screening test for asymptomatic, at-risk men, which generally refers to men over 50 years of age with at least a 10-year life expectancy.*
- ***Identify specific cancer subtype****—some cancers are divided into subtypes that are more or less aggressive; some tumor marker tests make it possible to distinguish between cancer types*
- ***Predict prognosis****—test results may indicate the chance of a negative or positive outcome, based on outcomes of other patients with similar results.*

An elaborate explanation of the currently available tumor markers for different cancer types based on the organ site are discussed here under

I. Bladder Cancer

Carcinoma of the urinary bladder, the fourth most common cancer in men and the ninth most common cancer in women, results in significant morbidity and mortality[1]. Most patients with bladder cancer receive the

diagnosis after they present with gross or microscopic hematuria. At initial diagnosis, approximately 70% of patients have bladder cancers that are confined to the epithelium or subepithelial connective tissue. These cancers can be managed with endoscopic resection and intravesical therapy. The recurrence rate for these tumors ranges from 50% to 70%, and 10% to 15% of cases progress to muscle invasion over a 5-year period [2,3]. Recurrence may be seen locally and rarely in the upper urinary tract even after several years, necessitating lifelong surveillance. The remaining 30% of patients have muscle-invasive cancer at initial diagnosis. Of this population, 50% have distant metastasis within 2 years, and 60% die within 5 years despite treatment[4]. Common tumor markers of bladder cancer are

A. **Bladder tumor antigen (BTA):** BTA is found in the urine of many patients with bladder cancer [5]. It may be a sign of some non-cancerous conditions, too, such as kidney stones or urinary tract infections. The results of the test are reported as either positive (BTA is present) or negative (BTA is not present). It's sometimes used along with NMP22 [6] to test patients for the return (recurrence) of bladder cancer.

This test is not used often. It's not as good as cystoscopy (looking into the bladder through a thin, lighted tube) for finding bladder cancer, but it may be helpful in allowing cystoscopy to be done less often during bladder cancer follow-up. At this time, most experts still consider cystoscopy the best way to diagnose and follow-up bladder cancer [7].

B. **Nuclear matrix protein (NMP22):** NMP22 is a part of the structural framework of the nucleus.This protein is produced during cell division and is associated with transitional epithelial cancer[8].It has been shown to be more sensitive and specific for low grade bladder cancers than urine cytology alone. It has a concentration in urothelial carcinomas of 25x than in normal urothelial cells. However, NMP22 levels are raised in patients with urinary tract infections, concurrent urolithiasis, history of bladder interposition, other malignancies, intravesical therapies and even cystoscopy. These conditions should be evaluated clinically to avoid false positivity of results [9].

II. Bone Cancer

A **bone tumor**, (also spelled **bone tumour**), is a neoplastic growth of tissue in bone. Abnormal growths found in the bone can be either benign (noncancerous) or malignant (cancerous). Bone tumors may be classified as "primary tumors", which originate in bone or from bone-derived cells and tissues, and "secondary tumors" which originate in other sites and spread (metastasize) to the skeleton. Carcinomas of the prostate, breasts, lungs, thyroid, and kidneys are the carcinomas that most commonly metastasize to bone. Secondary malignant bone tumors are estimated to be 50 to 100 times as common as primary bone cancers. Markers of bone tumor diagnosis are as follows

A. **Specific Alkaline Phosphatase (BSAP):** Measuring blood levels of these substances, called biological markers, can be useful for diagnosing cancer involving the bones. Higher levels can indicate that a cancer has progressed [10]. Though most biological markers are not routinely used for the diagnosis of bone cancers at this time, some are very useful, while others show promise for the future.

Bone specific alkaline phosphatase (BSAP) is an enzyme that is present in the cells that participate in bone formation, called osteoblasts. BSAP has been used for many years to detect increases in bone formation activity. Blood levels of BSAP are increased in patients with bone cancer and other conditions that result in increased bone remodeling [11]. Increases in BSAP have been detected in patients with bone metastasis caused by prostate cancer, and to a lesser degree, in bone metastases from breast cancer. Unfortunately, BSAP is not completely specific for cancer because alkaline phosphatases are also produced by other organs and can be elevated by other conditions. Nonetheless, BSAP can be monitored in patients who are known to be at risk of bone metastases.

Other biochemical markers are under investigation, but at this time, none have been approved for use in the clinical setting.

III. Brain cancer

Brain tumor begins when normal cells in the brain change and grow uncontrollably, forming a mass. A brain tumor can be low grade (generally not cancerous and slower growing) or high grade (more likely to grow and spread quickly). In general, primary brain tumors, meaning those that start in the brain, do not spread outside of the CNS. Different markers that aid in early detection are:

A.EGFR abnormalities: Gliomas are the most common primary tumor of the central nervous system and one of the most common molecular defects in these tumors is overexpression/mutation of the epidermal growth factor receptor[12].

B. EphA2 protein: In case of Glioblastoma multiforme, inactive form of EphA2 protein in the brain cells were responsible for spread of cancer cells [13]. EphA2 protein, which is found in cell membranes, allows normal cells to communicate with their environment and each other. In its normal active state, the protein seems to inhibit abnormal cell growth and division. It is found that the inactive form of EphA2 aids in the survival and spread of cancer cells.

C. Huntingtin interacting protein 1 (HIP1): It is a multidomain oncoprotein whose expression correlates with increased epidermal growth factor receptor (EGFR) levels in certain tumors. HIP1 is overexpressed with high frequency in brain cancers and that this overexpression correlates with EGFR and platelet-derived growth factor β receptor expression[14]. Furthermore, serum samples from patients with brain cancer contained anti-HIP1 antibodies more frequently than age-matched brain cancer–free controls.

IV. Breast Cancer

Breast cancer is a kind of cancer that develops from breast cells. Breast cancer usually starts off in the inner lining of milk ducts or the lobules that supply them with milk. A malignant tumor can spread to other parts of the body. A breast cancer that started off in the lobules is known as *lobular carcinoma*, while one that developed from the ducts is called *ductal carcinoma*. Routine breast cancer screening involves the diagnosis of the markers mentioned hereunder

A. CA 15-3: CA 15-3 is mainly used to watch patients with breast cancer [15,16]. Elevated blood levels are found in less than 10% of patients with early disease and in about 70% of patients with advanced disease. Levels usually drop if treatment is working, but they may go up in the first few weeks after treatment is started. (This rise is caused when dying cancer cells spill their contents into the bloodstream.) Levels of this marker can also be higher in other cancers, like lung, colon, pancreas, and ovarian, and in some non-cancerous conditions, like benign breast conditions, ovarian disease, endometriosis, and hepatitis.

B. CA 27.29: This is another marker that can be used to follow patients with breast cancer during or after treatment [16,17]. This test measures the same marker as the CA 15-3 test, but in a different way. Although it is a newer test than CA 15-3, it's not any better in detecting either early or advanced disease. And it's not elevated in all people with breast cancer.The normal level is usually less than 40 U/mL (units/milliliter), depending on the testing lab. This marker can be elevated in other cancers, too, such as cancers in the colon, stomach, kidney, lung, ovary, pancreas, uterus, and liver. It may also be higher than normal in some non-cancerous conditions, for instance, in women in the first trimester of pregnancy; and in people with endometriosis, ovarian cysts, non-cancerous breast disease, kidney stones, and liver disease.

C. Carcino-embryonic antigen(CEA): CEA[18] is one of the first tumor markers to be identified and characterized [19]. Since its discovery, CEA has been evaluated in a wide range of malignancies, including breast cancer, and, historically, has been considered the standard to which new serum markers are compared. Several studies have reported that positive serum CEA levels at the time of primary breast cancer diagnosis may represent a negative prognostic parameter [20] and correlate with the stage of disease [21] . Several authors have shown that an increase or a decrease in the CEA levels may reflect the status of disease progression or regression [22].

V. Cervical Cancer

Cervical cancer is the second most common cancer in women worldwide and remains a major cause of morbidity and mortality. Since the Pap test was introduced in the 1940s, there has been an approximately 70% reduction in the incidence of squamous cell cervical cancers in many developed countries by the application of organized and opportunistic screening programs.

A. Ki-67: Ki-67 is a nuclear and nucleolar protein expressed during the G1, S, G2, and M phase of the cell cycle, while not being present in resting cells (G0 phase), and can, therefore, provide an index of the cell growth fraction. While the function of the Ki-67 protein remains unclear, its expression appears to be an absolute requirement for progression through the cell-division cycle [23, 24]. Since HPV infection leads to increased epithelial cell proliferation in infected tissues, increased Ki-67 staining can be an indicator of HPV infection. In normal human cervical squamous mucosa, expression of Ki-67 is limited to the proliferating basal and parabasal cells. In dysplasia and carcinoma, however, expression extends above the basal one third of the epithelium.

B. **p16INK4a**: The protein p16INK4a is a cell-cycle regulator, with its expression tightly controlled in normal cells. This tumor suppressor protein inhibits cycle-dependant kinases 4 and 6, which phosphorylate the retinoblastoma (Rb) protein [25, 26]. It is widely accepted that p16INK4a is a sensitive and specific marker of dysplastic cells of the cervix and is a useful biomarker in cervical cancer lesion diagnosis and cervical screening [27–29].

C. BD ProEx C: BD ProEx C is a protein-based biomarker reagent (BD Diagnostics, Burlington, NC, USA) containing antibodies to the nuclear proteins minichromosome maintenance protein 2 (MCM 2) and

topoisomerase II alpha (TOP2A), proteins that have been shown to accumulate in HPV-transformed cells. BD ProEx C staining is limited to the basal proliferating layer of normal cervical epithelium and is absent in differentiated and quiescent cells. In contrast, in cervical glandular and squamous dysplasia, BD ProEx C expression is dramatically increased[30-33].

VI. Colorectal Cancer

It is also known as **colon cancer**, **rectal cancer**, or **bowel cancer**, is a cancer from uncontrolled cell growth in the colon or rectum (parts of the large intestine), or in the appendix. Genetic analysis shows that essentially colon and rectal tumours are genetically the same cancer. Colorectal Cancer diagnostic markers are

A. Carcino-embryonic antigen(CEA): It is a type of protein molecule that can be found in many different cells of the body, but is typically associated with certain tumors and the developing fetus. CEA is one of the most widely used tumor markers worldwide and certainly the most frequently used marker in colorectal cancer. Both the concentration and proportion of patients with increased CEA values tend to increase with increasing disease stage. Several studies have shown that well-differentiated colorectal cancers produce more CEA per gram of total protein than poorly differentiated specimens [34-36].

B. CA 19-9: The CA 19-9 test was first developed to detect colorectal cancer [37], but it's most often used in people with pancreatic cancer. In very early disease the level is often normal, so it's not good as a screening test. Still, it's the best tumor marker for following patients who have cancer of the pancreas. Normal blood levels of CA 19-9 are below 37 U/mL (units/milliliter). A high CA 19-9 level in a newly diagnosed patient usually means the disease is advanced. CA 19-9 can be used to watch bladder cancer and see how aggressive it is. It may also be used to watch colorectal cancer, but the CEA test is preferred for this type of cancer..

VII. Esophageal cancer

Esophageal carcinoma still has a poor prognosis due to late diagnosis, rapid growth and spread, and high rate of recurrence. Most patients present with advanced disease at the time of diagnosis (Katlic et al.,1990*)*. In comparison to other malignancies of the gastrointestinal tract, there are no suitable biomarkers for esophageal carcinoma. SCC-antigen and CEA have been used as tumor markers for esophageal carcinoma, but their sensitivity has not proven satisfactory[38,39].

1.SCC-Antigen: Squamous cell carcinoma antigens (SCCA) are members of the serpin family of endogenous serine proteinase inhibitors. The first variant of SCCA, SCCA1, was originally identified in squamous cell carcinoma (SCC) of the uterine cervix [40]. Further studies found that SCCA1 and its isoform, SCCA2, are produced by two tandemly arranged genes located on chromosome 18q21 [41]. SCCA1 and SCCA2 are approximately 98% and 92% homologous at their nucleotide and amino acid levels, respectively. Although SCCA1 and SCCA2 inhibit different classes of proteases, dictated by differences in amino acids located in the reactive site loop (RSL), both isoforms are expressed in stratified squamous epithelia and have been found to be produced in SCCs [42,43]. High levels of SCCA are often associated with poorly differentiated and advanced metastatic SCCs.

2.CEA: In patients with gastric or esophageal carcinoma, for example, an elevated CEA level during serial follow-up after preoperative chemotherapy has been shown to be predictive of relapse, and has demonstrated the potential for diagnosis of recurrent disease in advance of its clinical presentation [44].

VIII. Gastric Cancer

Gastric cancer is a major health problem worldwide, remaining the second most common digestive tract cancer, despite decreasing incidence. Gastric cancer is often not diagnosed until it is in the advanced stages. Even when surgical resection is possible, long-term survival is observed in only a minority of patients, with overall five-year survival of patients following gastrectomy less than 30% [45].

A.CEA: Although serum CEA has not proved satisfactory as an indicator of early gastric cancer [46], elevated CEA levels have been detected in the majority of patients with advanced carcinoma of the stomach [47,48].

B.CA19.9: The CA 19-9 antibody has been obtained by immunizing mice with human colorectal cell line [49]. The tumor marker CA 19-9 is a sensitive marker for pancreatic and hepatobiliary malignacies [50]. The highest frequency of elevated serum CA 19-9 level is found in patients with pancreatic cancer. Occasionally reported in other primary neoplasms, it is most often associated with the gastrointestinal tract [51]. Patient with an extremely high serum CA 19-9 level resulting from a gastric adenocarcinoma has also been reported previously[52].

C. CA72.4: Elevated CA 72-4 levels in serum and plasma have been reported in various malignant diseases including carcinomas of pancreas, stomach, gallbladder, colon, ovaries, cervix and endometrium. The highest diagnostic sensitivities, according to current studies, are found for carcinomas of the gastrointestinal tract and

ovaries. Although some benign diseases such as rheumatic diseases or ovary cysts may also result in elevated levels of CA 72-4, clinical studies demonstrated diagnostic specificities of more than 95% for gastrointestinal and ovarian malignancies. There is a good correlation between CA 72-4 levels and tumor stage and size[53].

CA 72-4 is the marker of choice for the therapeutic monitoring and follow-up care of gastrointestinal cancer patients. Suitable second markers are CA 19-9 or CEA [54]. It has been used as an independent marker for the therapeutic monitoring and follow-up care of ovarian cancer patients, in particular in CA 125 negative patients.

E. Cytokeratins (cyfra 21.1, TPA, TPS): CYFRA21-1 is unique in that it's epitope is from a polypeptide which is most likely released following cell death [55].CYFRA21-1,which recognizes soluble cytokeratin 19fragments [56] has been introduced as the most sensitive tumour marker for lung carcinomas, except for small-cell lung cancer[55].Aside from lungcancer, CYFRA21-1 has been reported in uterine carcinomas [57] and head and neck carcinomas [58]. The association between serumCYFRA21-1evel and the clinicopathological features and prognosis in Patients with gastric cancer was studied. Further, the clinical usefulness ofCYFRA21-1 as a tumour marker in gastric cancer was established [59].

F. β subunit of HCG : Beta Human Chorionic Gonadotropin (βHCG), a marker of the trophoblastic neoplasm, is also secreted by non-trophoblastic neoplasms including gastric carcinomas. A large proportion of gastrointestinal carcinomas have been shown to secrete HCG [60]. Few studies have reported Beta Human Chorionic Gonadotropin (βHCG) positivity in gastric carcinomas by immunohistochemical techniques [61,62]. However, its role in disease progression is not clear, with some studies showing a definite association of βHCG positive tumors with poor prognosis, [61] and some showing no such association [62].

G. CA 50: CA 50 is also not organ-specific and its elevated levels in serum can be observed in a variety of malignancies, especially gastrointestinal cancers

IX. Head and Neck Cancer

Despite the obvious advantage to earlier diagnosis of head and neck malignancies, no strategy has proven to effectively detect these tumors at early stages. Most head and neck neoplasms are detected when the patient has become symptomatic from the effects of the primary disease or when lymphatic metastases are palpable. These tumors are infrequently found incidentally on physical exam, and in these cases are often discovered at an earlier stage. Stage of disease at time of diagnosis is the primary metric used for determination of therapy and prognostication of life expectancy.

A.EGFR: Epidermal growth factor receptor (EGFR) is a member of the ErbB family of receptors. Its stimulation by endogenous ligands, EGF or transforming growth factor-alpha (TGF-α) results in activation of intracellular tyrosine kinase, therefore, cell cycle progression. High levels of EGFR expression are correlated with poor prognosis and resistance to radiation therapy in a variety of cancers, mostly in squamous-cell carcinoma of the head and neck (SCCHN). EGFR is a prime target for new anticancer therapy in SCCHN.
B. Free β-hCG : HCG (also known as beta-HCG or β-HCG) blood levels are elevated in patients with some types of testicular and ovarian cancers (germ cell tumors) and in gestational trophoblastic disease, mainly choriocarcinoma. They are also higher in some people with mediastinal germ cell tumors — cancers in the middle of the chest (the mediastinum) that start in the same cells as germ cell tumors of the testicles and ovaries. Levels of HCG can be used to help diagnose these conditions and can be watched over time to see how well treatment is working. They can also be used to look for cancer that has come back after treatment has ended (recurrence).

An elevated blood level of HCG will also raise suspicions of cancer in certain situations. For example, in a woman who still has a large uterus after pregnancy has ended, a high blood level of this marker might be a sign of a cancer. This is also true of men with an enlarged testicle or anyone with a tumor in their chest. It's hard to define the HCG normal level because there are different ways to test for this marker and each has its own normal value.

C. IGF-I and IGFBP-3: This gene is a member of the insulin-like growth factor binding protein (IGFBP) family and encodes a protein with an IGFBP domain and a thyroglobulin type-I domain. The protein forms a ternary complex with insulin-like growth factor acid-labile subunit (IGFALS) and either insulin-like growth factor (IGF) I or II. In this form, it circulates in the plasma, prolonging the half-life of IGFs and altering their

interaction with cell surface receptors. Alternate transcriptional splice variants, encoding different isoforms, have been characterized.

D. IL-6: Cytokines such as IL-6 have been cited as key molecular factors that link inflammation to epigenetic and genetic changes in tissue [63]. IL-6 is a pleiotropic cytokine, meaning that it has multiple influences on different tissues, although it is generally viewed as a pro-inflammatory cytokine. Genetic variants in the *IL6* gene also have been related to levels of circulating C-reactive protein (CRP) [64]and with plasma IL-6 response to immunization [65].

E. Prolactin: Prolactin (PRL), the peptide hormone secreted by the anterior pituitary gland, has, for long, remained restricted to the field of lactation and infertility. Prolactin is a pleiotropic hormone with an established role in the molecular carcinogenesis of breast cancer and other malignancies. Prolactin (PRL) is a hormone with multiple biological actions, synthesized by the anterior pituitary gland [66] and is best known for its roles in the mammary gland. The connection between prolactin and cancer has been suspected for many years, but never conclusively proven. The similarity of prolactin with growth hormone and its actions through the growth-promoting JAK/STAT pathway suggest its tumor-promoting effects. Recent research has underlined the role of PRL and PRL receptor (PRLR) most importantly in breast and prostate cancers, but also in a variety of other cancers. This review article has been designed to present an overview of the recent understanding regarding role of PRL in cancer and new modalities of cancer therapy based on the PRL pathway. However, it is now revealed that PRL is able to exert its effects on additional cells and tissues (decidual cells of the placenta, bone, brain, lymphocytes and breast epithelial cells) [67, 68]. PRL is secreted not only by lactotrophic cells of the pituitary gland but also by a variety of other normal tissues and human tumours [69] including malignant tumours of the lung[70], kidney[71], uterine[72], ovary [73], and breast[74].

F.SCC Ag: Squamous cell carcinoma antigen (SCC) is a sub-fraction of TA-4, a tumor-associated antigen first described by Kato et al. in 1977 [75]. SCC belongs to the family of serine protease inhibitors [76]. In most studies, it is total SCC that is measured and used to determine clinical utility.

Molecular cloning of the SCC genomic region has revealed the presence of two genes, SCC1 and SCC2, which are both located on chromosome 18q21.3 and arrayed in tandem. SCC1 codes for the neutral isoform of SCC and SCC2 codes for the acidic isoform [77]. The neutral isoform is detected in both normal epithelial cells and malignant tissues, whereas the acidic isoform is found in tumor cells, especially those located at the periphery of the tumor, and in the sera of cancer patients with well-differentiated squamous cell carcinomas [78]. It has been suggested that SCC1 and SCC2 are capable of regulating proteolytic events involved in both normal (e.g. tissue remodeling, protein processing) and pathologic processes (e.g. tumor progression) [79]. SCC1 and SCC2 are almost identical, differing only in their reactive site loops. There is evidence that SCC1 and SCC2 have different biological functions [77, 79, 80].

G. VEGF : Angiogenesis is a fundamental process in tumor growth and metastasis, and its significance and that of vascular endothelial growth factor (VEGF) expression as prognostic indicators have been documented for various types of human tumors. VEGF is a heparin-binding glycoprotein that occurs in least four molecular forms; these consist of 121, 165, 189, or 206 amino acids from the same gene by alternative mRNA splicing

X. Leukemia

Leukemia is cancer of the blood cells. It starts in the bone marrow. AML(Acute Myeloid Leukaemia) is a condition where the bone marrow makes large numbers of abnormal immature white blood cells which are derived from a myeloid stem cell. The abnormal immature cells are called blasts. Identification markers for leukemia are

A. Core Binding Factor (CBF): Leukemias affecting CBF are characterized by rearrangements of genes that code for components of the heterodimeric transcription factor CBF, which plays an essential role in haematopoiesis [81]. These include AML1 (RUNX1) rearrangements, AML1 mutations, CBFb-MYH11, CEBPA.

B. PML-RARα: Acute promyelocytic leukemia is a distinct subtype of AML (AML-M3) according to the FAB classification. AML-M3 is characterized by t(15;17) that involves the retinoic acid receptor a (RARα) gene on chromosome 17 and the promyelocytic leukemia gene (PML) on chromosome 15. At the molecular level, t(15;17) results in a hybrid PML/ RAR α gene, which is easily identified by reverse transcriptase-polymerase chain reaction (RT-PCR). This test provides a rapid and refined diagnosis. The usefulness of minimal residual disease monitoring during follow up [82] has been well established.

C. DEK-CAN : AML defined by t(6;9) is a relatively rare disease, associated with specific clinical and morphological features [83].Especially in young adults, the leukemic phase can be preceded by dysplastic features, conferring a bad prognosis.

D. NPM1: NPM1 gene is located in 5q35 and encodes a phosphoprotein, nucleophosmin, which moves between the nucleus and the cytoplasm. The gene product is thought to be involved in several processes including regulation of the ARF/p53 pathway. Mutations in exon 12 in this gene are associated with AML with normal karyotype (50%) and especially correlate with monocytic leukemias. Patients with NPM1 mutations have a significantly higher rate of complete remissions (CRs) after standard induction chemotherapy except for cases associated with internal tandem duplications mutations of FLT3[85,86].

E.c-KIT: KIT is a proto-oncogene located on chromosome band 4q11-12 and encodes a 145-kDa transmembrane glycoprotein member of the type III receptor tyrosine kinase family. Ligand independent activation of KIT results from mutations in the extracellular portion of the receptor (exon 8), transmembrane and juxtamembrane domains (exons 10 and 11, respectively), and activation loop of the tyrosine kinase domain (exon 17).
F. FLT3: Flt3 is a member of the class III tyrosine kinase receptor family that includes the c-kit, c-fms, and PDGF receptors. The Flt3 receptor is preferentially expressed on hematopoietic stem cells and mediates stem cell differentiation and proliferation.

G. EVI1 overexpression :The ectopic viral integration site 1 (EVI1), located in chromosome 3q26, has been recognized in the last years as one of the most aggressive oncogenes associated to human leukemia [87].

H.BAALC AND MN1 :The Brain and Acute Leukemia Cytoplasmic (BAALC), human gene located on chromosome 8q22.3, has also been found to be an important adverse prognostic factor if overexpressed in normal karyotype AML, suggesting a role for BAALC overexpression in acute leukemia.

I. WT1 -The Wilms' tumor locus: This gene is located on chromosome 11p13 and encodes a zinc-finger transcription factor influencing the expression of several growth factors and their corresponding receptors. It is also known to be involved in the early stage of hematological cell differentiation. Aberrant expression may be one mechanism by which the normal function of WT1 is disrupted. However, the exact role of WT1 in hematopoiesis and leukemogenesis still remains unclear. The abundant overexpression of WT1 in leukemia creates a very attractive target for quantitative MRD studies in AML, especially in those samples with no specific fusion gene available.

J. MLL rearrangement and MLL-PTD: The MLL (mixed lineage leukemia) gene located at 11q23, is fused to a variety of partner genes through chromosomal translocations in acute leukemias. Up to now, more than 40 different MLL partner genes have been identified. MLL gene contains 100 kb of DNA, but nearly all breakpoints are clustered within a 8.3 kb region. Molecular analysis shows that fusion of the amino terminus of MLL to the carboxy terminus of partner genes generates the critical leukemogenic fusion proteins. Abnormalities of the mixed-lineage leukemia (MLL) gene can be detected in de novo acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) as well as in therapy-related AML.

XI. Liver Cancer

HCC is one of the most common cancers worldwide, and is frequently preceded by chronic viral hepatitis B or C or alcoholic liver disease. If treatment of these diseases is instituted early, the risk of HCC can be decreased or abolished. In patients who have already developed HCC, surgical resection or transplantation with curative intent requires early local detection of small lesions.
A. A -FETOPROTEIN : Alpha-fetoprotein (AFP) levels are often elevated in liver cancers (hepatocellular) and testicular cancers (non-seminomatous). Raised levels are also present during pregnancy or some gastrointestinal cancers.AFP is a 70-kD glycoprotein consisting of 591 amino acids and 4% carbohydrate residues, encoded by a gene on chromosome 4q11-q13 [for reviews see (59,60)]. Normally produced during gestation by the fetal liver and yolk sac, AFP is highly elevated in the circulation of newborns with concentrations decreasing during the next 12 months to 10-20 μg/L.

XII. Lung Cancer

Lung cancer is a disease characterized by uncontrolled cell growth in tissues of the lung. If left untreated, this growth can spread beyond the lung in a process called metastasis into nearby tissue or other parts

of the body. Most cancers that start in lung, known as primary lung cancers, are carcinomas that derive from epithelial cells. The main types of lung cancer are small-cell lung carcinoma (SCLC), also called oat cell cancer, and non-small-cell lung carcinoma (NSCLC).

A. Markers for NSCLC

i.Carcino-embryonic antigen (CEA): The carcinoembryonic antigen(CEA)level has been reported to be a prognostic factor and an indicator of recurrence after surgical resection for non-small cell lung Cancer (NSCLC). **Carcinoembryonic antigen** (CEA) is a glycoprotein involved in cell adhesion. It is normally produced in gastrointestinal tissue during fetal development, but the production of CEA stops before birth. Therefore, it is usually present only at very low levels in the blood of healthy adults, although levels are raised in heavy smokers. CEA is a glycosyl phosphatidyl inositol (GPI) cell surface anchored glycoprotein whose specialized sialofucosylated glycoforms serve as functional colon carcinoma L-selectin and E-selectin ligands, which may be critical to the metastatic dissemination of colon carcinoma cells.

B. Markers for SCLC

i. Neuron-specific enolase (NSE) :NSE is a glycolytic enzyme that catalyzes the conversion of phosphoglycerate to phosphoenol pyruvate. It is present in neurons, neuroendocrine cells, and amine precursor uptake and decarboxylation (APUD) cells. NSE levels are frequently increased in patients with SCLC and infrequently in patients with non-SCLC. NSE has therefore been used to monitor disease progression and management in SCLC. The tumour marker serum neuron-specific Enolase (S-NSE)has been found to be a potentially useful indicator of disease activity[88,89,90]. S-NSE is significantly related to extent of disease [88,91,92], to response duration[93] and to prognosis [94,95].

XIII. Lymphoma

Lymphoma is a general term for a group of blood cancers that start in the lymphatic system, , which is part of the body's immune system. The two main types of lymphoma are Hodgkin's lymphoma and non-Hodgkin's lymphoma.Non-Hodgkin lymphoma (NHL) is the term for a diverse group of blood cancers that share a single characteristic—they arise from an injury to the DNA of a lymphocyte progenitor. The damage to the DNA is acquired (occurs after birth) rather than inherited.

A. Lactic dehydrogenase (LDH): Lactic acid dehydrogenase (LDH) is an enzyme that helps produce energy. In humans serum lactate dehydrogenase (LDH) is used as a prognostic indicator in non hodgkins lymphoma. In particular elevated values of LDH [96] and increases of the isoenzymes LDH2 and LDH3[97] have been correlated with shortened survival times. In another , study , the same isoenzymes were elevated in patients affected by latent NHL [98]. It is present in almost all of the tissues in the body and becomes elevated in response to cell damage. Nevertheless active cancer activity can elevate them as it stresses and damages the surrounding body tissues. Although an LDH test isn't very useful for an initial diagnosis of lymphoma it is frequently used as monitoring test for those who already have lymphoma.

B. Beta-2-microglobulin (B2M): Among the most important serological markers Beta-2-microglobulin (β2m) reflects the tumour load.β2m is a low molecular weight polypeptide, non-covalently linked to the heavy chain of class 1- histocompatability antigens which are shed with cell turnover. It is plentiful on the surface of lymphocytes. Increased production or destruction of the cells causes β2m levels in the blood to increase.

C. Gamma globulin: Gamma globulin is a class of protein found in blood plasma. There are different types of gamma globulins, but the most important are immunoglobulins — also called antibodies

XIV. Melanoma Skin Cancer

Melanoma is a type of skin cancer. Melanoma skin cancer is a form of cancer that begins in the melanocytes of the skin.

A. TA 90: TA90 is a 90-kd tumor-associated antigen that is expressed by >70% of melanomas. After curative resection of malignant melanoma, patients with occult metastasis may exhibit elevated levels of a TA90-IgG immune complex (TA90-IC). Several reports have indicated that TA90-IC is a sensitive and specific marker of recurrence in patients with malignant melanoma and is associated with shortened survival [99; 100; 101]. Patients with TA90-IC detected early after curative resection of American Joint Committee on Cancer (AJCC) Stage I to III melanoma were found to have significantly lower 5-year overall survival (36% vs 84%, P <.001) and disease-free survival (24% vs 74%, P <.001) than TA90-IC-negative patients.

XV. Multiple Myeloma

Multiple myeloma is a cancer of the plasma cells. These are immune system cells that produce specialized molecules called antibodies to help fight infectious germs. Because most plasma cells live in bone marrow, multiple myeloma tumors are usually, but not always, found in bone. The bone marrow is where blood

cells are produced. Because multiple myeloma crowds out bone marrow, it can cause several kinds of blood deficiencies:

- Anemia, a shortage of red blood cells, which can lead to weakness and exhaustion
- Thrombocytopenia, a shortage of blood platelets called thrombocytes, which are necessary for forming blood clots. This condition therefore causes excessive bleeding or bruising.
- Leukopenia, a shortage of white blood cells that can lead to a weakening of the immune system

A. Bence Jones protein: The term "Bence-Jones protein" in fact designates a group of proteins often found in the urine of individuals with multiple myeloma and identified by the property of precipitating at 45-55" and redissolving upon boiling (1). Bence Jones proteins are considered the first tumor marker. Urine is the best specimen in which to look for Bence Jones proteins. Proteins are usually too large to move through a healthy kidney, from the blood into the urine. Bence Jones proteins are an exception. They are small enough to move quickly and easily through the kidney into the urine.

B. Myeloma protein(M-protein or M-spike): Myeloma Protein is usually a monoclonal antibody or immunoglobulin fragment that is produced by malignant myeloma cells, or plasma cells.Other terms for this protein is M-protein, spike protein, or paraprotein. This proliferation of the myeloma protein has several deleterious effects on the body, including impaired immune function, abnormally high viscosity ("thickness") of the blood, and kidney damage.

Immunoglobulins migrate to a unique place called the gamma region, and because they are all different (in normal patients), they migrate to slightly different places within that region, giving a gentle bell-shaped curve or smear. In myeloma, the immunoglobulin is monoclonal, so it all migrates to exactly the same spot on the gel, which gives a big spike This spike is called an M-spike (M for either monoclonal or myeloma), and the corresponding monoclonal protein that it represents is called an M protein.

C. Beta-2-microglobulin (B2M): B2M blood levels are elevated in multiple myeloma, chronic lymphocytic leukemia (CLL), and some lymphomas (including Waldenstrom macroglobulinemia). Levels may also be higher in some non-cancerous conditions, such as kidney disease and hepatitis. Normal levels are usually below 2.5 mg/L (milligrams per liter). B2M is useful in helping predict the long-term outlook (prognosis) in some of these cancers. Patients with higher levels of B2M usually have poorer outcomes. B2M is also checked during treatment of multiple myeloma and Waldenstrom macroglobulinemia to see how well the treatment is working.

XVI. Ovarian Cancer

Ovarian cancer is any cancerous growth that may occur in different parts of the ovary. The majority of ovarian cancers arise from the epithelium (outer lining) of the ovary.

A. CA 125**(epithelial):** CA 125 is the standard tumor marker used to follow women during or after treatment for epithelial ovarian cancer (the most common type of ovarian cancer). Normal blood levels are usually less than 35 U/mL (units/milliliter). More than 90% of women with advanced ovarian cancer have high levels of CA 125. If the CA-125 level is increased at the time of diagnosis, changes in the CA-125 level can be used during treatment to get an idea of how well it's working.

Levels are also elevated in about half of women whose cancer has not spread outside of the ovary. Because of this, CA 125 has been studied as a screening test. But the trouble with using it as a screening test is that it would still miss many early cancers, and problems other than ovarian cancer can cause an elevated CA-125 level. For example, it's often higher in women with uterine fibroids or endometriosis. It may also be higher in men and women with lung, pancreatic, breast, liver, and colon cancer, and in people who have had cancer in the past. Because ovarian cancer is a rather rare disease, an increased CA-125 level is more likely to be caused by something other than ovarian cancer.

B. Alpha-fetoprotein (AFP): AFP can help diagnose and guide the treatment of liver cancer (hepatocellular carcinoma). Normal levels of AFP are usually less than 10 ng/mL (nanograms per milliliter). AFP levels are increased in most patients with liver cancer. AFP is also elevated in acute and chronic hepatitis, but it seldom gets above 100 ng/mL in these diseases. In someone with a liver tumor, an AFP level over a certain value can mean that the person has liver cancer. In people without liver problems, that value is 400 ng/mL. But a person with chronic hepatitis often has high AFP levels. For them, AFP levels over 4,000 ng/mL are a sign of liver cancer.

AFP is also useful in following the response to treatment for liver cancer. If the cancer is completely removed with surgery, the AFP level should go down to normal. If the level goes up again, it often means that the cancer has come back.AFP is also higher in certain germ cell tumors, such as some testicular cancers (those containing embryonal cell and endodermal sinus types), certain rare types of ovarian cancer (yolk sac tumor or mixed germ cell cancer), and germ cell tumors that start in the chest (mediastinal germ cell tumors). AFP is used to monitor the response to treatment, since high levels should go down when treatment works. If the cancer has

gone away with treatment, the level should go back to normal. After that, any increase can be a sign that the cancer has come back.

XVII. Pancreatic Cancer

Pancreatic cancer is a malignant neoplasm originating from transformed cells arising in tissues forming the pancreas. The most common type of pancreatic cancer, accounting for 95% of these tumors, is adenocarcinoma (tumors exhibiting glandular architecture on light microscopy) arising within the exocrine component of the pancreas. A minority arise from islet cells, and are classified as neuroendocrine tumors. The following is the most common identification and the only validated tumor marker

A.CA 19-9: The CA 19-9 test was first developed to detect colorectal cancer, but it's most often used in people with pancreatic cancer. In very early disease the level is often normal, so it's not good as a screening test. Still, it's the best tumor marker for following patients who have cancer of the pancreas[102]. Normal blood levels of CA 19-9 are below 37 U/mL (units/milliliter). A high CA 19-9 level in a newly diagnosed patient usually means the disease is advanced.

CA 19-9 can be used to watch bladder cancer and see how aggressive it is. It may also be used to watch colorectal cancer, but the CEA test is preferred for this type of cancer.CA 19-9 can be elevated in other forms of digestive tract cancer, especially cancers of the stomach and bile ducts, and in some non-cancerous conditions such as thyroid disease, rheumatoid arthritis, inflammatory bowel disease, and pancreatitis (inflammation of the pancreas).

XVIII. Prostate Cancer

Prostate cancer is a form of cancer that develops in the prostate, a gland in the male reproductive system. Most prostate cancers are slow growing; however, there are cases of aggressive prostate cancers. The cancer cells may metastasize (spread) from the prostate to other parts of the body, particularly the bones and lymph nodes.

A. Prostate specific antigen (PSA): PSA is a tumor marker for prostate cancer. PSA is a protein made by cells of the prostate gland, which is found only in men. It's the only marker used to screen for a common type of cancer, but most medical groups do not recommend using it routinely to screen all men [103]. The level of PSA in the blood can be elevated in prostate cancer, but PSA levels can be affected by other things, too. Men with benign prostatic hyperplasia (BPH), a non-cancerous growth of the prostate, often have higher levels. The PSA level also tends to be higher in older men and those with infected or inflamed prostates. It can also be elevated for a day or 2 after ejaculation.

PSA is measured in nanograms per milliliter (ng/mL). Most doctors feel that a blood PSA level below 4 ng/mL means cancer is unlikely. Levels higher than 10 ng/mL mean cancer is likely. The area between 4 and 10 is a gray zone. Men with PSA levels in this borderline range have about a 1 in 4 chance of having prostate cancer. A doctor may recommend a prostate biopsy (getting samples of prostate tissue to look for cancer) for a man with a PSA level above 4 ng/mL.

B. Prostatic acid phosphatase (PAP): PAP is another test for prostate cancer [104,105]. It was used before the PSA test was developed but is seldom used now because the PSA test is better. It may also be used to help diagnose multiple myeloma and lung cancer.

C. Prostate-specific membrane antigen (PSMA): Prostate specific membrane antigen (PSMA), is a unique membrane bound glycoprotein, which is overexpressed manifold on prostate cancer [106]as well as neovasculature of most of the solid tumors, but not in the vasculature of the normal tissues. This unique expression of PSMA makes it an important marker as well as a large extracellular target of imaging agents. PSMA can serve as target for delivery of therapeutic agents such as cytotoxins or radionuclides. PSMA has two unique enzymatic functions, folate hydrolase and NAALADase and found to be recycled like other membrane bound receptors through clathrin coated pits. The internalization property of PSMA leads one to consider the potential existence of a natural ligand for PSMA.

XIX. Renal Cancer

Renal cell carcinoma (RCC, also known as hypernephroma) is a kidney cancer that originates in the lining of the proximal convoluted tubule, the very small tubes in the kidney that transport GF (glomerular filtrate) from the glomerulus to the descending limb of the nephron. RCC is the most common type of kidney cancer in adults, responsible for approximately 80% of cases. It has been described as being among the most lethal of all the urological cancers. Markers for RCC are listed as

A. Von Hippel–Lindau pathway: The understanding of the role of the von Hippel–Lindau (VHL) tumor suppressor gene in RCC has been one of the landmarks for the considerations about angiogenic pathways. It is inactivated in almost all RCC in patients with VHL syndrome.

B. Hypoxia-induced factor 1alpha: HIF-1a accumulates either in hypoxic cell conditions or when the pVHL is deficient. In a study by Wiesener et al, somatic mutations of the VHL gene were detected only in HIF-1 a overexpressing ccRCC. Consequently, an increased expression of HIF-1 a was found in 24 of 32 ccRCC tumors (75%), but only in three of eight non-ccRCC tumors. Moreover, none of the HIF-1a–negative ccRCCs displayed a VHL mutation.

C. Vascular endothelial growth factor: The idea of either the direct inhibition of VEGF or the blocking of its signaling cascade confounded the ‘‘therapeutic revolution’’ for metastatic RCC and is principle of most of today’s approved targeted therapies. Not surprisingly, VEGF has also been widely studied as an MM. VEGF production is significantly increased in RCC with VHL gene alterations and raised HIF-1 a protein expressions. Furthermore, it is associated with a more aggressive tumor phenotype [107]. Several groups could show that a raised VEGF expression is a significant predictor for outcome, and in some studies showed this correlation even using multivariate analyses together with stage and grade [108; 109; 110].

D. Grawitz 250 or carbonic anhydrase 9: As early as 1986 Oosterwijk et al described Grawitz 250 (G250) as an RCC-specific antibody [111]. It took several years to merge these findings with the parallel investigations on an RCC-related carbonic anhydrase 9 (CAIX) [112], later identified as identical targets. G250 and/or CAIX have been shown to be unique HIF-1 a target genes in ccRCC [113]. In contrast to normal kidney tissue, 95% of ccRCCs are CAIX and/or G250 positive [114].

E. Mammalian target of rapamycin pathway: The mammalian target of rapamycin (mTOR) pathway has been shown to be upregulated in many human cancers. As for RCC, it symbolizes the second major pathway of today’s targeted therapy options,with a proven efficiency of the mTOR inhibitors temsirolimus (PFS and OS, [115]) and everolimus (PFS only,[116]).

XX. Testicular Cancer

Testicular cancer is cancer that develops in the testicles, part of male reproductive system. The common diagnostic markers are

A. Human chorionic gonadotropin (HCG): HCG (also known as *beta-HCG* or *β-HCG*) blood levels are elevated in patients with some types of testicular and ovarian cancers (germ cell tumors) [117] and in gestational trophoblastic disease, mainly choriocarcinoma. They are also higher in some people with mediastinal germ cell tumors — cancers in the middle of the chest (the mediastinum) that start in the same cells as germ cell tumors of the testicles and ovaries. Levels of HCG can be used to help diagnose these conditions and can be watched over time to see how well treatment is working. They can also be used to look for cancer that has come back after treatment has ended (recurrence).An elevated blood level of HCG will also raise suspicions of cancer in certain situations .

B. Alpha-fetoprotein (AFP): AFP can help diagnose and guide the treatment of liver cancer (hepatocellular carcinoma). Normal levels of AFP are usually less than 10 ng/mL (nanograms per milliliter). AFP levels are increased in most patients with liver cancer. AFP is also elevated in acute and chronic hepatitis, but it seldom gets above 100 ng/mL in these diseases. In someone with a liver tumor, an AFP level over a certain value can mean that the person has liver cancer. In people without liver problems, that value is 400 ng/mL. But a person with chronic hepatitis often has high AFP levels. For them, AFP levels over 4,000 ng/mL are a sign of liver cancer.

AFP is also useful in following the response to treatment for liver cancer. If the cancer is completely removed with surgery, the AFP level should go down to normal. If the level goes up again, it often means that the cancer has come back. AFP is also higher in certain germ cell tumors, such as some testicular cancers [117,118] (those containing embryonal cell and endodermal sinus types), certain rare types of ovarian cancer (yolk sac tumor or mixed germ cell cancer), and germ cell tumors that start in the chest (mediastinal germ cell tumors). AFP is used to monitor the response to treatment, since high levels should go down when treatment works. If the cancer has gone away with treatment, the level should go back to normal. After that, any increase can be a sign that the cancer has come back.

XXI. Thyroid Cancer

Thyroid cancer is a malignant neoplasm originating from follicular or parafollicular thyroid cells. Thyroid cancer is usually found in a euthyroid patient, but symptoms of hyperthyroidism or hypothyroidism may be associated with a large or metastatic well-differentiated tumor. Thyroid nodules are of particular concern when they are found in those under the age of 20. The presentation of benign nodules at this age is less likely, and thus the potential for malignancy is far greater.

A. Calcitonin : Calcitonin is a hormone produced by cells called *parafollicular C cells* in the thyroid gland. It normally helps regulate blood calcium levels. Normal calcitonin levels are below 5 to 12 pg/ml (picograms per milliliter). In medullary thyroid carcinoma (MTC), a rare cancer that starts in the parafollicular C cells, blood levels of this hormone are often greater than 100 pg/ml. Other cancers, like lung cancers and leukemias, can also elevate calcitonin levels, but calcitonin blood tests are not usually used for detecting these cancers.

This is one of the rare tumor markers that can be used to help detect early cancer. Because MTC is often inherited, blood calcitonin can be measured to detect the cancer in its very earliest stages in family members known to be at risk.

B. Thyroglobulin :Thyroglobulin is a protein made by the thyroid gland. Normal blood levels depend on a person's age and gender. Thyroglobulin levels are elevated in many thyroid diseases, including some common forms of thyroid cancer [119].

Thyroglobulin levels in the blood should fall to undetectable levels after treatment for thyroid cancer. A rise in the thyroglobulin level after treatment can mean the cancer has come back (recurred). In people with thyroid cancer that has spread, thyroglobulin levels can be followed over time to watch the results of treatment. Some people's immune systems make antibodies against thyroglobulin, which can affect test results. Because of this, levels of anti-thyroglobulin antibodies are often measured at the same time.

XXII. Uterine Cancer

Also known as endometrial cancer is the most common gynecologic malignancy of women. And it is the 4th common cancer in women [120]. The incidence of endometrial cancer is arising whole over the world last 20 years [121]. Every year about 200,000 new endometrial cancer cases are diagnosed whole over the world and an estimated 50,000 women will die from this disease [122]. Endometrial cancer is diagnosed mostly in 6^{th} or 7^{th} decade and 70% of these cases are postmenopausal. The serum tumor markers in current use for endometrium cancer include.

A. CA 125: Also known as Cancer Antigen 125 or Carbohydrate Antigen 125, it is a mucin glycoprotein that was identified using monoclonal antibody OC 125, hence the name. CA 125 was originally identified by Bast et al. in the 1980s [123]. It is present in all humans and present in mesothelial cells of the pleura, pericardium, peritoneum and Mullerian epithelium derivatives such as tubal, endometrial, and endocervical cells. CA 125 is the most reliable serum marker for ovarian cancer. Elevation of serum CA 125 has been detected in a number of physiological and pathological conditions associated with endometrial proliferation, including menstrual cycle, pregnancy, endometriosis and endometrial carcinoma [124]. A single CA 125 determination provides no advance in the early detection of endometrial as well as ovarian carcinoma in asymptomatic postmenopausal women compared to transvaginal ultrasonography. The vast majority of women with an elevated CA 125 value have some reason other than an ovarian or endometrial malignancy for this finding [125].

In detail, raised CA 125 levels (>35 U/ml) have been reported in 11% - 33.9% of patients with endometrial cancer [126, 127, 128]. Ginath et al. found that 21.4% of 28 patients with endometrioid endometrial carcinoma had elevated serum CA 125, whereas the percentage of patients with positive tissue immunostaining for the antigen was 89.3%, which appeared to suggest the presence of mechanisms preventing the access of CA 125 into the circulation [129].

B. Other Tumor Markers: The serum markers CA 19.9, CA 15.3, CA 72.4 and CEA levels are raised in endometrial cancer patients in 22% - 24%, 24% - 32%, 22% - 32% and 14% - 22% of the cases, respectively. Scambia et al. found CA 15.3 levels > 30 U/ml in 47% of patients with occult stage III compared to 18% of those with surgical stages I and II disease. A significant relationship was detected between CA 15.3 positivity (>30 and >50 U/ml) and shorter[126]. Serial CA 15.3 levels showed a good correlation with the clinical behavior of disease. In the series of Cherchi et al., a statistically significant difference between intrauterine (96 cases) and extrauterine (16 cases) disease at surgical-pathological stage was noted for CA 15.3 (28.1% vs 56.2%), but not for CA 19.9 or CEA positivity. As for the concomitant determination of different markers, only the combination of CA 125 and CA 19.9 offered interesting results for post-treatment surveillance. In fact, the association of these markers had a high sensitivity (83.3%) for the detection of recurrence, with only 12.8% of false positive cases[128].

Hareyama et al. found elevated CA 72.4 levels in 31.9% of 72 patients with endometrial carcinoma. Multivariate analysis showed a significant correlation between serum antigen positivity and adnexal metastases. Seven patients had increased serum CA 72.4 and normal serum CA 125 and CA 19.9, and in four of them the disease had spread beyond the uterus [130].

C.YKL-40:It is another potential tumour marker for endometrial cancer and was found to be elevated in 76% of patients. Preoperative serum YKL-40 levels may lead to the identification of high risk subsets of patients with worse clinical outcomes [131]. Further investigation of this promising endometrial cancer marker in larger studies is warranted.

D. HE4: HE4 mentioned in the context of ovarian cancer, has also been shown to be elevated in early stage endometrial cancer and is more sensitive than CA 125, though one may debate the need for an early marker as most cases are present at early stage due to symptoms, it may benefit patients with Lynch II syndrome or those on tamoxifen. One study showed it to be the single most acurrate marker, regardless of stage as compared to CA 125, CA 72.4, soluble mesothelin-related peptide or alone [132]. However, its role in predicting recurrence and response to therapy need to be determined.
E. M-CSF :Raised serum macrophage colony-stimulating factor (M-CSF) levels were found about three fourths of patients with endometrial carcinoma, a significantly higher percentage of pathologic values than observed for either CA 125 or aminoterminal propeptide of type III collagen and also with stage I or stage II disease as often as with stage III or IV disease. As a result M-CSF may be useful in the early diagnosis of endometrial carcinoma. Also elevated levels of M-CSF at presentation appear to be predictive of an agressive clinical course [133].
F. OVX1: Beck et al. reported that the mean serum OVX1 levels measured with an enzyme-immunoassay were 2.00 (±1.32) U/ml in 192 patients with endometrial carcinoma compared to 1.34 (±0.74) U/ml in apparently healthy female. Applying a cut-off of 2.8 U/ml, serum OVX1 was elevated in 19.7% of patients with stage I disease, 29.4% of those with stage II, 22.7% of those with stage III, and 36.4% of those with stage IV disease [134].
G. serum sFas : Significantly elevated levels of serum sFas were demonstrated in endometrioid adenocarcinoma of the endometrium compared to that of healthy women [135]. Dobrzycka and et al. found significant correlation between clinical stage, histological grade, 5-year disease-free survival and vascular endothelial growth factor (VEGF) over expression [136].

Inference

Ideally, markers could be used as a screening tool for the general public. The goal of a screening test is to diagnose cancer early, when it is the most treatable and before it has had a chance to grow and spread. So far, the only tumor marker to gain wide acceptance as a screening tool is the Prostate Specific Antigen (PSA) for prostate cancer. Other markers are either not specific enough (too many false positives, leading to expensive and unnecessary follow-up testing), or they are not elevated early enough in the life of the cancer, and therefore the cancer cannot be detected any earlier than when symptoms begin to appear. Keep in mind that some substances used as markers are produced naturally in the body, and a "normal" level is not always zero.

Recent Breakthroughs in tumor marker research:

Most tumor markers are proteins. Since DNA is the code that determines which proteins will be produced by a cell, researchers are developing methods to detect DNA. Even in many early stage diseases, cancer cells may break away from the tissue where they originated and can be detected in the blood or other body substances. For example, researchers have detected abnormal DNA in the blood of people with breast, liver, lung, ovarian cancer, and melanoma, urine of individuals with bladder cancer, saliva of individuals with cancers of the oral cavity. This new approach to tumor marker testing can be thought of as measuring the cause (DNA) rather than the effect (protein), and may thus provide even more accurate and useful information for screening, early detection, monitoring, and planning treatment.

Another monumental study found that common genetic variation links all these cancers. Genetic markers are like spelling mistakes in a person's DNA that raise the risk of disease. This can be described as a genetic 'spelling mistake', where an A, G, C or T in the genetic code has been replaced with another. The spelling mistake is called Single Nucleotide Polymorphism (SNP). Cancer research has taken a huge leap forward with scientists now able to identify more than 80 genetic markers found to increase the risk of breast, ovarian and prostate cancer. The discovery of new genetic markers for common cancers will pave the way for tests that predict an individual's risk of disease and guide how they should be screened throughout their lives. But scientists hope to do far more with the findings. A major effort is under way to learn how the cancers develop in the first place. The genetic markers will hold many clues, and ultimately help scientists piece together how disruption to healthy biological pathways can lead to the uncontrolled cell division characteristic of cancer – and how drugs might stop the diseases.

Limitations: Tumor markers are not specific enough to be used alone for diagnosing cancer. Several reasons for this may be because tumor marker levels can be elevated even in people with benign (non-cancerous) disease. Tumor markers are not elevated in every person with cancer, particularly those with early stage disease. Most tumor markers are not totally specific for a single condition, meaning that many different cancers or diseases can result in a higher than normal level of a particular marker. For these reasons, tumor markers are not used in isolation; instead, results from tumor marker tests are evaluated in the context of a patient's history, symptoms, and other test results. Despite these limitations, researchers continue to study the markers mentioned above as

well as potential new markers to determine whether they may have a role in screening, early detection, and directing treatment.

Conclusion: Tumor markers can contribute usefully to patient management, but awareness of their limitations is essential. The main application of tumour markers is in monitoring. Serum tumor markers may aid cancer diagnosis, assess prognosis, guide choice of treatment, monitor progress during and after treatment, and/or be used as screening tests. Conservative estimates suggest that in the United Kingdom alone close to 15 million such measurements are made each year. If tumor markers are requested and interpreted correctly, they undoubtedly help clinical management.

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