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# Laboratory Evaluation of Tumor Biomarkers: An Updated Review

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## Abstract

*Tumor biomarkers are biochemical substances produced by cancer cells or other body cells in response to malignancies, released into circulation. They play a critical role in cancer diagnosis, treatment monitoring, and recurrence detection. Despite their clinical utility, tumor biomarkers have limitations, including limited specificity and sensitivity, necessitating their integration with other diagnostic modalities for accurate oncological assessment.This review aims to provide an updated overview of tumor biomarkers, their clinical applications, laboratory evaluation methods, and the challenges associated with their use in cancer management.The review discusses various laboratory techniques for tumor biomarker detection, including enzyme assays, immunoassays, high-performance liquid chromatography (HPLC), immunohistochemistry (IHC), fluorescent in situ hybridization (FISH), polymerase chain reaction (PCR), and microarray analysis. It also covers specimen requirements, preanalytical guidelines, and factors influencing biomarker levels, such as biological variability and analytical interferences.Tumor biomarkers, such as alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and prostate-specific antigen (PSA), are widely used in clinical practice. However, their diagnostic and prognostic value is optimized when combined with imaging and histopathological findings. Advances in proteomics and genomics have enhanced the identification and quantification of genetic and molecular biomarkers, improving cancer diagnosis and personalized treatment strategies.Tumor biomarkers are invaluable tools in oncology but are not standalone diagnostic modalities. Their clinical utility is maximized when integrated with other diagnostic approaches. Ongoing advancements in laboratory techniques and biomarker discovery hold promise for improving cancer detection, monitoring, and treatment outcomes.*

**Keywords:** *Tumor Biomarkers, Cancer Diagnostics, Immunoassays, Molecular Genetics, Proteomics, Clinical Oncology.*

## Introduction

Tumor biomarkers are biochemical entities generated by neoplastic cells or other bodily cells in response to malignancies and subsequently released into circulation [1]. These biomarkers exhibit diverse structural characteristics, ranging from simple molecules such as catecholamines to well-defined proteins, including hormones, enzymes, and gene products. Additionally, some tumor biomarkers encompass heterogeneous glycoproteins or mucins, such as carbohydrate antigen 125 (CA 125), which can be quantitatively assessed through antibody-based assays. Key tumor biomarkers, including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and human chorionic gonadotropin (hCG), belong to the category of oncofetal antigens. These biomarkers are typically expressed at minimal levels in normal fetal development and healthy tissues but may be overexpressed in various malignancies [2]. The assessment of tumor biomarkers plays a crucial role in multiple clinical applications and constitutes an integral component of oncological diagnostics and management strategies. Using diverse analytical techniques, these biomarkers can be detected in specific bodily fluids such as blood, urine, and pleural or peritoneal effusions. Tumor biomarker assays contribute to early cancer detection, facilitate diagnostic evaluations, guide therapeutic

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decision-making, monitor treatment efficacy, assess disease progression, and enable the detection of cancer recurrence [3].

Despite their clinical relevance, tumor biomarker assays have inherent limitations, rendering them unsuitable as exclusive diagnostic modalities [4]. Their diagnostic and prognostic value is optimized when interpreted in conjunction with clinical findings, imaging modalities, and histopathological examination to ensure an accurate and comprehensive oncological assessment. The ideal tumor biomarker would exhibit intrinsic molecular stability, coupled with high specificity, sensitivity, accuracy, and reproducibility. Additionally, it should provide cost-effective utility in cancer screening, diagnosis, and prognostic evaluation. However, no single biomarker currently employed in clinical practice possesses all these attributes. The specificity, sensitivity, and clinical applicability of most tumor biomarkers remain constrained, necessitating their integration with other diagnostic methodologies for comprehensive oncological evaluation and patient management [1][3][5].

*Etiology and Epidemiology*

Cancer encompasses a heterogeneous group of diseases characterized by unregulated cellular proliferation. Malignant neoplasms possess the capacity to infiltrate, invade, and compromise adjacent tissues [6]. The etiology of cancer is primarily attributed to genetic mutations, which may be inherited or acquired due to environmental carcinogen exposure [7]. Established carcinogenic agents include tobacco smoke, asbestos, ionizing and ultraviolet radiation, and pathogenic infections, all of which contribute to oncogenesis [8]. Cancer remains a predominant global health burden, responsible for approximately 10 million deaths annually [9]. The lifetime risk of developing cancer before the age of 75 is estimated at 22.6% in women and 18.6% in men [10]. Hematological malignancies are more frequently diagnosed in younger individuals, whereas the incidence of breast, prostate, lung, and colorectal cancers is higher among older populations. Collectively, these four malignancies account for over half of cancer diagnoses worldwide. The increasing prevalence of cancer is driven by population aging, lifestyle modifications, and escalating environmental pollution. The first tumor biomarker identified in medical literature was Bence Jones protein [11]. Since its discovery, numerous protein- and hormone-based tumor biomarkers have been characterized and incorporated into clinical practice. Advances in proteomics and genomics have further enabled the identification and quantification of genetic and molecular tumor biomarkers through microarray-based analytical techniques.

*Specimen Requirements*

Specimen Requirements and Procedure The National Academy of Clinical Biochemistry (NCAB) has established preanalytical quality guidelines for tumor biomarkers.[12] Serum assays should be collected using red-top containers, while other body fluids must be placed in fluid-specific containers.[13] For chromosomal assessment of bone marrow, 2 to 3 mL should be extracted from the first pull of the repositioned needle during marrow collection.[14] Whole blood samples are necessary for microarray analyses.[15] Immunohistochemistry staining requires approximately 1 mL of tissue, which must be deparaffinized and rehydrated before processing.[16] Samples should ideally be analyzed immediately. Tissue and bone marrow specimens intended for chromosomal assessment, fluorescent in situ hybridization, or microarray analysis should not be frozen. Salivary contamination may lead to falsely elevated CEA and carbohydrate antigen 19-9 concentrations.[17] Specimens can be collected at any time since no diurnal variation has been identified. However, collection should occur before invasive procedures, as tissue trauma may temporarily elevate tumor marker levels. For instance, PSA levels rise after urinary catheterization and prostate biopsy, while CEA levels increase following a colonoscopy. Tumor biomarker assays should ideally be repeated after 2 to 3 weeks for confirmation.[18] Most commonly assessed tumor markers demonstrate stability. However, serum or plasma should be separated from the clot and stored at 4 °C for short-term preservation or at -30 °C as soon as possible following established guidelines. Long-term storage requires freezing at -70 °C.[19] Heat treatments should be avoided, as they can degrade certain biomarkers. Specifically, PSA and hCG may dissociate into their free α- and β-subunits at elevated temperatures, impacting assay accuracy.[20]

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*Diagnostic Tests*

Various malignancies have specific tumor biomarkers that play a crucial role in diagnosis, treatment monitoring, and recurrence detection. These biomarkers, detected through laboratory assays, assist in determining the presence and progression of cancer. Table 1 presents malignancies along with their associated tumor biomarkers.

- Bronchogenic Carcinoma: Bronchogenic carcinoma includes small cell carcinoma, adenocarcinoma, and squamous cell carcinoma. Small cell carcinoma is commonly associated with neuron-specific enolase (NSE) and pro-gastrin–releasing peptide (pro-GRP) as biomarkers. Adenocarcinoma of the lung is linked to carcinoembryonic antigen (CEA), while squamous cell carcinoma expresses squamous cell carcinoma antigen (SCC) and cytokeratin 19 fragment as its biomarkers [1].

- Ovarian Cancer: Ovarian malignancies include epithelial, mucinous, and nonepithelial subtypes. Epithelial ovarian cancer is identified by elevated carbohydrate antigen 125 (CA 125), whereas mucinous ovarian carcinoma can express CEA. Nonepithelial ovarian tumors, particularly granulosa cell tumors, often produce inhibin A and B [2].

- Colorectal Adenocarcinoma: CEA is a widely used biomarker for colorectal cancer, with carbohydrate antigen 19-9 (CA 19-9) and tissue plasminogen activator (TPA) also serving as supportive indicators for disease presence and progression [3].

- Hepatocellular Carcinoma: Alpha-fetoprotein (AFP) is the primary biomarker for hepatocellular carcinoma, commonly utilized for both screening and monitoring treatment response [4].

- Pancreatic Adenocarcinoma: CA 19-9 is the most relevant biomarker for pancreatic adenocarcinoma. CEA may also be elevated in pancreatic cancer cases, providing additional diagnostic support [5].

- Prostate Adenocarcinoma: Prostate-specific antigen (PSA) is the key biomarker for prostate cancer diagnosis and monitoring. Prostatic acid phosphatase (PAP) has also been used historically but has lower sensitivity compared to PSA [6].

- Germ Cell Tumors: Germ cell malignancies, including testicular and ovarian germ cell tumors, are associated with human chorionic gonadotropin (HCG), AFP, lactate dehydrogenase (LDH), and placental alkaline phosphatase. These biomarkers aid in classification and treatment assessment [7].

- Breast Cancer: Carbohydrate antigen 15-3 (CA 15-3) and carbohydrate antigen 27.29 (CA 27.29) are the most commonly used tumor biomarkers for breast cancer monitoring. Hormonal receptors, such as estrogen receptor (ER) and progesterone receptor (PR), play a critical role in treatment planning. Additionally, human epidermal growth factor receptor 2 (Her2) status determines eligibility for targeted therapies. Urokinase plasminogen activator and plasminogen activator inhibitor also serve as prognostic markers [8].

*Testing Procedures*

Various laboratory assays are used to evaluate tumor biomarkers, each with distinct methodologies and applications. These procedures aid in cancer diagnosis, prognosis, and treatment selection. The primary techniques employed include enzyme assays, immunoassays, chromatography, immunohistochemistry, molecular genetics methods, and microarray analysis.

- Enzyme Assays: Enzyme activity assays quantify most enzymatic tumor biomarkers, with the exception of PSA, by measuring their catalytic activity within a sample. The process involves

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introducing an excess of substrate and necessary cofactors to the prepared specimen, observing their transformation into the final product. Kinetic enzyme assays offer an alternative approach by measuring substrate conversion rates at specified intervals. These assays provide insights into biomarker concentration based on enzymatic reactions [1].

- Immunoassays: Immunoassays detect tumor biomarkers through antigen-antibody interactions, where the biomarker acts as the antigen, and antibodies designed to recognize it facilitate measurement. Several immunoassay techniques are widely used, including enzyme-linked immunosorbent assay (ELISA), electrochemiluminescence immunoassay, and immunohistochemistry. These methods are commonly applied to quantify biomarkers such as AFP, CEA, hCG, prolactin, calcitonin, and various carbohydrate antigens [21].

- High-Performance Liquid Chromatography (HPLC): HPLC is primarily utilized for detecting catecholamines and their metabolites in plasma and urine. This technique separates analytes based on their chemical and physical properties by passing them through a chromatographic column. The high specificity of HPLC makes it a valuable tool for analyzing tumor biomarkers related to neuroendocrine tumors and other malignancies [22].

- Immunohistochemistry: Immunohistochemistry (IHC) is an immunoassay technique specifically used for the detection of tumor biomarkers in solid tissue specimens collected through biopsy. The procedure involves placing a thin tissue section onto a slide, followed by the application of antibodies targeting specific antigens. The use of colorimetric secondary antibodies enables visualization of antigen-antibody interactions. IHC is frequently employed to assess estrogen and progesterone receptors and Her2 expression, playing a crucial role in determining breast cancer treatment options [23].

- Fluorescent In Situ Hybridization (FISH): FISH is a molecular cytogenetic technique designed to detect specific genetic alterations in tumor cells. Fluorescently labeled DNA probes hybridize to target genetic sequences within cells, making them visible under a fluorescence microscope. This method is particularly useful for identifying mutations in genes such as adenomatous polyposis coli (APC) and ras, as well as for assessing Her2 overexpression. FISH plays a key role in diagnosing and selecting targeted therapies for various cancers [24, 25].

- Polymerase Chain Reaction (PCR): PCR is a molecular technique used to amplify and detect specific DNA sequences. This method involves repeated cycles of denaturation, primer annealing, and DNA strand extension using a thermostable DNA polymerase. PCR is widely applied in oncology, particularly for identifying the bcr-abl1 fusion gene associated with chronic myeloid leukemia. It is also instrumental in detecting microsatellite instability and mutations in oncogenes such as K-ras, N-ras, and BRAF, which have prognostic and therapeutic implications in colorectal cancer. Furthermore, PCR is employed to determine HER2 gene amplification, aiding in the selection of patients who may benefit from HER2-targeted therapies [26].

- Microarrays: Microarray technology enables the simultaneous analysis of multiple genetic alterations by utilizing a solid-phase support, such as a silicon chip, embedded with thousands of gene sequences. Fluorescent-labeled complementary DNA from tumor samples binds to corresponding sequences on the chip, and the resulting signal is quantified. This high-throughput technique has various oncological applications, including genetic profiling of ovarian and colorectal cancers, classification of leukemias, and identifying the tissue of origin in metastatic cancers [27].

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*Interfering Factors and Disadvantages of Tumor Biomarkers*

*Interfering Factors:*

Variability in sample collection, processing, storage, and assay methodologies can impact tumor biomarker profiles. Standardizing preanalytical and analytical procedures helps reduce these inconsistencies. Early-stage tumors often present low biomarker concentrations, necessitating highly sensitive assays to ensure detection [28].

*Disadvantages of Tumor Biomarkers*

- Limited Specificity: Some tumor biomarkers are produced by both normal and cancerous cells and may be elevated in noncancerous conditions, leading to false-positive results and unnecessary diagnostic procedures or treatments [2].

- Insufficient Sensitivity: Not all cancers exhibit elevated biomarker levels, especially in early stages, potentially causing false-negative results. This can delay diagnosis and reduce early treatment opportunities [29].

- Biological Variability: Factors such as age, gender, genetics, and comorbidities influence biomarker levels, complicating the establishment of universal reference values [30].

- Analytical Variability: Differences in assay platforms, reagents, and laboratory techniques can result in inconsistent measurements, making cross-laboratory comparisons difficult [31].

- Limited Diagnostic Value: Tumor biomarker assays should not be used as standalone diagnostic tools but rather in combination with imaging, biopsies, and clinical evaluations for accurate cancer diagnosis [2].

*Common Interferences*

- High-Dose Hook Effect: Extremely high biomarker concentrations can lead to falsely low readings, particularly during initial assays. This can be mitigated by using high-binding capacity antibodies, conducting assays at multiple dilutions, and ensuring proper wash steps [32].

- Specimen Carryover: High-concentration markers can contaminate subsequent samples, affecting assay accuracy.

- Heterophilic or Human Anti-Mouse Antibodies: Patients receiving monoclonal antibody therapy or with circulating anti-animal antibodies may have falsely high or low biomarker values. Suspected interference can be evaluated by testing at different dilutions, using a blocking agent, adding nonimmune mouse serum, or employing an alternative assay method from another manufacturer [33, 34].

- Pharmaceutical Interference: Anticoagulants such as ethylenediaminetetraacetic acid (EDTA) may interfere with certain biomarker assays, impacting test reliability [35].

*Results, Reporting, and Critical Findings*

Reported findings should include method-specific reference intervals derived from a relevant healthy population [36]. When presenting results, the assay technique should be specified if possible. If there has been a shift in methodology, laboratories should indicate any potential impact on trend interpretation. A clear protocol should be in place for method changes, and the anticipated effects should be communicated to clinical users in advance [3]. Managing such changes may require reanalyzing the previous specimen using

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the new method or obtaining a fresh specimen to reestablish the baseline or validate the trend in biomarker levels [37]. Rather than focusing on a single value, assessing biomarker concentration trends over multiple testing intervals provides a more accurate reflection of disease progression. Graphical representation of data can facilitate a clearer interpretation of biomarker trends over time [1]. Including concise clinical details alongside laboratory results enhances interpretation. Reports should also provide guidance on confirmatory specimen requirements and the recommended intervals for future testing.

Reporting significant increases in tumor biomarker levels, while considering analytical performance, biological variations, and individualized reference intervals, aids in the early detection of relapse. Laboratories should define the percentage change that represents a significant shift, considering both analytical and biological variations. Additionally, expected rates of change in benign and malignant conditions should be detailed, along with the time between sample collections [38]. Biological variation among tumor biomarkers contributes to differences in these percentages [39]. The tumor biomarker's half-life must be accounted for in result interpretation. Before surgical treatment, the known biomarker half-life helps estimate the duration required for its level to return to a normal or undetectable state [40]. If the decline in biomarker levels is used to assess the likelihood of complete tumor removal, testing should not be conducted until at least two weeks post-surgery, with four weeks being ideal [1]. Various factors, including renal or hepatic dysfunction, can influence the biomarker decline rate [41]. For instance, serum CEA may remain elevated in patients with hepatic dysfunction due to impaired biomarker metabolism [42]. Similarly, persistently high serum β-2 microglobulin levels are common in patients with acute or chronic kidney disease, as the damaged glomerular system struggles to filter the small-sized β-2 microglobulin molecule efficiently [43]. When applicable to a specific malignancy, clinicians should consider ordering a panel of tumor biomarkers to enhance diagnostic accuracy. Many cancers exhibit heterogeneous cellular compositions and express multiple biomarkers, making the measurement of multiple biomarkers essential to achieving a detection sensitivity exceeding 90% [1,13].

*Clinical Significance*

Tumor biomarkers demonstrate varying degrees of clinical applicability and are associated with specific malignancies. While certain tumor biomarkers are expressed in normal cells or tissues, their circulating levels can also be influenced by benign conditions. Evaluating the sensitivity and specificity of biomarker assays must be performed within the clinical context of each patient [30]. Several national and international organizations have issued guidelines on the selection and application of tumor biomarkers. Institutions such as the National Academy of Clinical Biochemistry, the European Group on Tumor Markers, the American Cancer Society, the National Comprehensive Cancer Network, and the National Institute for Health and Care Excellence have formulated recommendations based on the strength of available evidence.

*The Clinical Significance of Commonly Utilized Tumor Biomarkers is Outlined Below*

- Alpha-fetoprotein (AFP) is an oncofetal antigen glycoprotein synthesized by the yolk sac and embryonic liver. It is used for diagnosing and monitoring hepatocellular carcinoma, hepatoblastoma, and germ cell tumors, while also serving as a prognostic indicator for germ cell tumors [3]. However, AFP levels may be elevated in pregnancy, neonates, benign liver conditions, and gastrointestinal diseases [44].

- Carcinoembryonic antigen (CEA) is an oncofetal antigen glycoprotein derived from fetal gastrointestinal tissue. It is primarily utilized for monitoring colorectal adenocarcinoma response to treatment and recurrence [45]. However, its specificity is limited as serum levels may be low in early-stage or poorly differentiated cancers and elevated in benign renal, hepatic, and pulmonary conditions [45].

- Alkaline phosphatase (ALP) is an enzyme present in bone, placenta, small bowel, and the biliary tract. Isoenzymes improve specificity, and ALP elevation is observed in osteosarcoma, cholangiocarcinoma, and metastatic bone malignancies [46]. However, elevated ALP levels may

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also be observed during normal pregnancy and in benign conditions affecting the bone, small bowel, and hepatobiliary system [47].

- Lactate dehydrogenase (LDH) is an enzyme found in nearly all body cells, catalyzing the interconversion of pyruvate and lactate. Due to its ubiquitous presence, LDH levels are frequently elevated in malignancies [48]. However, elevations can also occur in various anemias and conditions associated with cellular destruction.

- Prostatic acid phosphatase (PAP) is a glycoprotein dimer used for monitoring prostate adenocarcinoma therapy response and relapse [49]. Elevated PAP levels can also be found in lysosomal storage disorders and benign prostate diseases.

- Neuron-specific enolase (NSE) is an enzyme synthesized by neuroendocrine cells. Its levels are increased in neuroblastoma, small cell lung cancer, and pancreatic adenocarcinoma. Proper handling of samples is critical to avoid assay delays [50].

- Human chorionic gonadotropin (hCG) is a glycoprotein hormone produced by placental syncytiotrophoblasts and is significant for diagnosing, prognosticating, and monitoring gestational trophoblastic tumors and germ cell tumors [3]. However, elevated levels are also detected in normal pregnancy [51].

- Prolactin is an anterior pituitary hormone implicated in pituitary adenocarcinoma. Its serum levels exhibit diurnal variation and may be increased due to benign pituitary prolactinomas or medication use [52].

- Calcitonin is a mucin glycoprotein secreted by thyroid parafollicular C cells and is crucial for diagnosing and monitoring medullary thyroid carcinoma. However, false elevations can occur in Zollinger-Ellison syndrome, pernicious anemia, and chronic renal disease [53].

- Catecholamines and metanephrines are biogenic amines synthesized by the adrenal gland and sympathetic nervous system, used in diagnosing and monitoring neuroblastoma, pheochromocytoma, and paragangliomas [54]. Serum levels may be influenced by medications and diurnal variations.

- Serotonin is a biogenic amine utilized in diagnosing and monitoring carcinoid tumors [55]. Dietary intake of certain meats and fruits can lead to elevated levels.

- Prostate-specific antigen (PSA) is a glycoprotein with serine protease activity, existing in free or protein-bound forms. It is used for prostate cancer screening, risk assessment, and monitoring [56]. However, PSA levels may be elevated due to benign prostate conditions or procedures affecting the lower genitourinary tract [57].

- Carbohydrate antigen 15-3 (CA 15-3) is a mucin glycoprotein used alongside CEA for monitoring breast cancer and evaluating treatment response. Its levels can also be elevated in benign and malignant breast, ovarian, and liver diseases [50].

- Carbohydrate antigen 19-9 (CA 19-9) is a Lewis blood group glycolipid associated with pancreatic and hepatobiliary cancers. It is utilized for pancreatic cancer monitoring post-resection. Contamination with saliva may yield falsely high values, and patients lacking the Lewis blood group may have absent or low levels [17].

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- Carbohydrate antigen 125 (CA 125) is a mucin glycoprotein used for ovarian epithelial carcinoma screening and monitoring. It can also be elevated in benign conditions affecting the pleurae, pericardium, and peritoneum [58].

- β-2 microglobulin is a major histocompatibility complex Class I component associated with chronic lymphocytic leukemia, multiple myeloma, and B-cell neoplasms [3]. Levels may be increased in renal diseases and active HIV infection.

- Thyroglobulin is a glycoprotein dimer essential for monitoring differentiated thyroid carcinoma [59]. Autoantibodies from thyroid disorders may cause falsely elevated levels.

- Human epidermal growth factor receptor 2 (Her2) is a tyrosine kinase receptor family glycoprotein involved in cell proliferation. Its overexpression is noted in breast, ovarian, and endometrial carcinomas [60]. Variability exists in tumor expression.

- Estrogen and progesterone receptors (ER, PR) function as nuclear transcription factors and steroid receptors, predicting breast cancer response to antihormonal therapies [60]. Biomarker expression may change over time.

- TP53 is a tumor suppressor gene frequently mutated in human cancers [3]. Its levels may increase in the presence of colon polyps.

- Retinoblastoma gene (RB) is a tumor suppressor gene mutated in nearly all human cancers [61].

- BRCA1 and BRCA2 are tumor suppressor genes associated with hereditary cancer susceptibility in both sexes [3].

- Adenomatous polyposis coli gene (APC) is a tumor suppressor gene linked to hereditary nonpolyposis colonic, breast, and esophageal adenocarcinomas [50]. It is elevated in colon polyps.

- ras is a proto-oncogene mutated in most human cancers [62]. Its mutations are widespread and complex.

- C-myc is a proto-oncogene involved in T-cell and B-cell lymphomas and small cell lung cancer, used to identify high-risk individuals [63]. Tumor-type variability in expression exists.

- bcl-2 is an oncogene that promotes cell survival, found in leukemia and lymphoma. Its presence indicates chemotherapy resistance [64].

*Quality Control and Lab Safety*

The testing laboratory is responsible for implementing stringent quality control measures to ensure the accuracy and reliability of the test. Assays should be validated before clinical use to provide accurate and relevant reports. Recommended intra-assay and interassay variability are <5% and <10%, respectively. Some newer techniques may perform significantly better but may be less precise. Aspects of quality control, such as internal and proficiency testing (PT), should be implemented. The quality control specimen should mimic sera, and multiple levels can be used to cover the range of concentration, including the decision limits. It is important to include negative and low-positive controls. The number of internal quality control samples to be run for marker assay validation depends on the frequency of testing. The samples should be checked frequently for assay interferences. During tumor marker assay, calibration and daily maintenance should be conducted before running quality control (QC) samples.

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Immediate and appropriate action should be taken to avoid erroneous reporting when an assay run fails to meet objective criteria for assay acceptance. Criteria for acceptance should be predefined and based on logical criteria such as those of Westgard. The number of IQC specimens included per run should allow the identification of an unacceptable run with a given probability appropriate to the clinical application. Given the long-term monitoring of cancer care, assay stability should be ensured over prolonged periods. Laboratories should have procedures and acceptance criteria for assessing lot-to-lot variation that may adversely affect clinical outcomes. Quality control (QC) material not provided by the method manufacturer is preferable; kit controls may provide an overly optimistic impression of performance as they are unlikely to be commutable with patient serum. At least one authentic serum matrix control from an independent source should be included in addition to any QC materials provided by the method manufacturer. PT specimens should be commutable with patient specimens to ensure valid between-method comparisons. Concentrations should assess performance over the working range and should include an assessment of linearity on dilution, baseline security, and stability of results over time. The PT provider is responsible for ensuring that specimens are stable in transit. The target values, usually consensus means for heterogeneous analytes, should be accurate and stable, as demonstrated by assessing their accuracy, stability, and linearity on dilution. When performing tumor biomarker assays, adhere to standard laboratory safety practices, including personal protective equipment, proper handling and disposal of biohazardous materials, and maintaining a clean work environment. Follow equipment maintenance and calibration protocols, and ensure staff is trained in emergency procedures to promote a safe and efficient laboratory environment.

*Enhancing Healthcare Team Outcomes*

Tumor biomarker assay requires a multifaceted approach. Laboratory technicians with expertise in running tumor marker assays are essential to ensure accurate testing. Lab professionals' roles include selecting appropriate assays for specific cancer types, establishing appropriate cutoff values, and determining the significance of marker trends over time. Clinicians should have a strategy toward evidence-based practices and the clinical utility of tumor marker assays. Healthcare providers should uphold ethical principles while discussing test results, potential limitations, and implications for treatment choices. Patient safety is of paramount importance throughout the assay process. Adequate measures should be in place to prevent contamination, ensure specimen integrity, and safeguard patient information. Interprofessional communication and coordination are crucial for seamless care. Collaboration among physicians, pathologists, laboratory technicians, and other healthcare professionals ensures accurate sample collection, timely test results, and effective integration of tumor marker data into patient management plans. This collaborative effort enhances care coordination within a concise framework.

## Conclusion

Tumor biomarkers have revolutionized the field of oncology by providing critical insights into cancer diagnosis, treatment monitoring, and recurrence detection. These biochemical entities, produced by neoplastic cells or other bodily cells in response to malignancies, are detectable in various bodily fluids and tissues. Their clinical applications span early cancer detection, therapeutic decision-making, and post-treatment surveillance. However, the utility of tumor biomarkers is not without limitations. Issues such as limited specificity, sensitivity, and biological variability often necessitate their integration with other diagnostic modalities, including imaging and histopathological examinations, to ensure accurate oncological assessments. The review highlights the importance of standardized specimen collection, processing, and storage protocols to minimize preanalytical variability. Advances in laboratory techniques, such as immunoassays, high-performance liquid chromatography (HPLC), immunohistochemistry (IHC), and molecular genetic methods like PCR and microarray analysis, have significantly enhanced the detection and quantification of tumor biomarkers. These technologies enable the identification of genetic and molecular alterations associated with various cancers, facilitating personalized treatment strategies. Despite these advancements, challenges remain. Tumor biomarkers can be influenced by non-cancerous conditions, leading to false-positive or false-negative results. Analytical variability across different laboratory platforms further complicates the interpretation of biomarker levels. Therefore, it is crucial to establish method-specific reference intervals and consider biological variations when interpreting results. The integration of

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multiple biomarkers and the use of trend analysis over single measurements can improve diagnostic accuracy and provide a more comprehensive understanding of disease progression. The clinical significance of tumor biomarkers is underscored by their role in guiding treatment decisions and monitoring therapeutic efficacy. National and international guidelines recommend their use in conjunction with other diagnostic tools to optimize patient outcomes. As research continues to uncover new biomarkers and refine existing ones, the potential for improved cancer screening, early detection, and targeted therapies grows. In conclusion, tumor biomarkers are indispensable tools in modern oncology, but their limitations must be acknowledged. A multidisciplinary approach, combining laboratory expertise, clinical judgment, and advanced diagnostic technologies, is essential for maximizing their clinical utility. Future research should focus on discovering more specific and sensitive biomarkers, standardizing assay methodologies, and integrating biomarker data with other diagnostic information to enhance cancer care and patient outcomes.

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# التقييم المخبري لمعظم دلالات الاورام: مراجعة محدثة

**الملخص:**

**الخلفية:** دلالات الاورام هي مواد بيوكيميائية تنتجها الخلايا السرطانية أو خلايا الجسم الأخرى استجابةً للأورام الخبيثة وتُفرز في الدورة الدموية. تلعب دورًا حاسمًا في تشخيص السرطان، ومراقبة العلاج، واكتشاف الانتكاس. رغم فائدتها السريرية، تعاني هذه دلالات من محدودية في الحساسية والنوعية، مما يستدعي دمجها مع وسائل تشخيصية أخرى لضمان تقييم دقيق للحالة السرطانية.

**الهدف:** تهدف هذه المراجعة إلى تقديم نظرة محدثة حول دلالات الاورام، وتطبيقاتها السريرية، وطرق تقييمها في المختبر، والتحديات المرتبطة باستخدامها في إدارة السرطان.

**الأساليب:** تناقش المراجعة مختلف التقنيات المخبرية للكشف عن دلالات الاورام، بما في ذلك معدلات الأنزيمية، ومعدلات المناعية، والكروماتوغرافيا السائلة عالية الأداء(HPLC) ، والتألق المناعي الكيميائي(IHC) ، والتهجين الموضعي الفلوري(FISH) ، وتفاعل البوليميراز المتسلسل(PCR) ، وتحليل المصفوفات الدقيقة. كما تغطي متطلبات العينة، والإرشادات قبل التحليل، والعوامل التي تؤثر على مستويات دلالات، مثل التباين البيولوجي والتداخلات التحليلية.

**النتائج:** تُستخدم واصمات ورمية مثل ألفا فيتوبروتين(AFP) ، والمستضد السرطاني المضغي(CEA) ، والمستضد البروستاتي النوعي (PSA) على نطاق واسع في الممارسة السريرية. ومع ذلك، يتم تحسين قيمتها التشخيصية والتنبؤية عند دمجها مع تقنيات التصوير والنتائج النسيجية المرضية. ساهمت التطورات في البروتيوميات والجينوميات في تحسين التعرف على دلالات الجينية والجزيئية وقياسها، مما أدى إلى تحسين تشخيص السرطان واستراتيجيات العلاج الشخصي.

**الاستنتاج:** تُعد دلالات الاورام أدوات لا غنى عنها في علم الأورام، لكنها ليست وسائل تشخيصية قائمة بذاتها. تتحقق أقصى فائدة سريرية عند دمجها مع طرق التشخيص الأخرى. تَعِد التطورات المستمرة في التقنيات المخبرية واكتشاف دلالات بتحسين اكتشاف السرطان، ومراقبته، ونتائج العلاج.

**الكلمات المفتاحية:** دلالات الاورام، تشخيص السرطان، المقايسات المناعية، الجينات الجزيئية، البروتيوميات، علم الأورام السريري.