NATIONAL LABORATORY HANDBOOK

Laboratory Testing for Tumour Markers

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Person-centred, co-ordinated care

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ROYAL COLLEGE OF PHYSICIANS OF IRELAND

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Background

A tumour marker is defined as a substance produced either by a tumour or in response to a tumour that aids cancer detection and/or monitoring[1].
The clinical use of tumour marker assays is dependent on their specificity, sensitivity, positive predictive value, and the availability of an established tumour staging system.
For most tumour markers, clinical utility is limited by their poor specificity for malignancy. Many current markers can be synthesised by normal tissues, may be elevated in benign disease and are not organ specific. There is a lack of sensitivity, as markers may not be elevated when malignancy is in the early stages or when it is confined to the primary site. Also, markers are generally elevated only in a proportion of patients with a particular tumour type, even in advanced disease. The term “tumour marker” is not particularly helpful and should be regarded as a misnomer.
The following tumour markers have been selected for this Guideline because they are frequently requested and can be easily measured using automated immunoassay technology in routine clinical laboratories. The main target user group would be hospital inpatient and outpatient services. The use of tumour markers in primary care is directed by separate guidelines (PSA and CA-125) and is otherwise usually restricted to monitoring of known cases of malignancy.

AFP (Alpha-Fetoprotein)

AFP is normally formed during gestation in the yolk-sac and foetal liver and gastro-intestinal tract (GI) tract. Levels are increased in the first year of life and may also be found during pregnancy. There are several benign liver diseases with elevated AFP levels, including acute viral hepatitis, biliary tract obstruction and alcohol mediated cirrhosis.[1]

Malignancies with elevated levels of AFP include testicular non-seminomatous germ cell tumours (NSGCTs), hepatocellular carcinoma (HCC), hepatoblastoma and advanced adenocarcinomas.

The use of AFP (with hCG) is recommended for the diagnosis, staging and surveillance of patients with NSGCTs. Post-orchidectomy, rising levels may provide sufficient evidence to initiate further treatment.[2] AFP may also be used as a screening test to aid detection of HCC in high risk populations (chronic hepatitis, cirrhosis, areas of very high prevalence).[3]

hCG (Human Chorionic Gonadotropin)

Intact hCG is a glycoprotein which consists of 2 subunits, α and β, however it exists in many different forms in serum including free α and β chains and various degradation products. National Academy of Clinical Biochemistry (NACB) guidelines emphasise that both intact hCG and its free β subunit should be measured by assays used in oncology. hCG is

produced by the placenta during pregnancy and mildly increased levels may be seen post-menopause due to pituitary hCG secretion.

Increased levels in non-pregnant patients may occur in a number of tumours including germ cell, ovarian and bladder cancers. The main clinical indications for measurement include the diagnosis, staging and surveillance of patients with testicular cancer (with AFP) and management of patients with Gestational Trophoblastic Disease. (GTD) [2, 4]

CEA (Carcinoembryonic Antigen)

CEA is found mainly in the foetal GI tract and serum. Its formation is repressed after birth and serum CEA is hardly measurable in healthy adults. Small quantities exist in hepatic, pancreatic and intestinal tissue.

Levels may be elevated in many benign diseases of the intestine, liver and lungs and there may be a slight increase in cigarette smokers.[1]

CEA levels may be elevated with many advanced adenocarcinomas but its clinical use is limited to patients with colo-rectal carcinoma (CRC). CEA should not be used as a screening test for CRC. Levels may be useful in determining prognosis preoperatively in patients with diagnosed CRC. In combination with radiology it is the marker of choice for post resection non-invasive detection of recurrent disease. It also has a role in monitoring patients with advanced/metastatic CRC.[2, 5, 6, 7]

CA 19-9

CA 19-9 may be found in low concentrations in adult liver, lung and pancreatic tissues. Levels may be increased in benign conditions such as pancreatitis, cirrhosis, cholangitis, cystic fibrosis and inflammatory bowel disease. As it is excreted exclusively by the liver, cholestasis can lead to elevated levels.[7]

CA 19-9 may be elevated in patients with pancreatic, gastric, colorectal and cholangiocarcinoma.[8]

The main clinical application of CA 19-9 is in the differential diagnosis and monitoring of patients with pancreatic adenocarcinoma. In both of these settings levels of CA 19-9 should be interpreted in conjunction with clinical findings and results of other modalities. Levels may be elevated in up to 67% of patients with hepatobiliary carcinoma. It is potentially useful in patients with CEA negative colorectal carcinoma.

CA 15-3

CA 15-3 is a transmembrane glycoprotein found in the luminal secretion of glandular cells and does not normally circulate in the blood. When cells become malignant their basal membranes become permeable and CA 15-3 may be detectable in serum. Levels may be increased in benign liver and possibly benign breast disease.

Malignant conditions with elevated levels include breast and other advanced/metastatic adenocarcinomas.

CA 15-3 is rarely elevated in early breast cancer or when disease is localised. It is not currently recommended by any group for screening, diagnosis or staging of breast cancer. ASCO (American Society of Clinical Oncology) and NACB guidelines support its use in conjunction with imaging and clinical findings when monitoring treatment in patients with metastatic disease. It is of limited use in routine postoperative surveillance. [9, 10]

Scope

The aim of this guideline is to provide guidance on appropriate requesting of serum tumour markers for use by clinicians and clinical laboratories, including circumstances where testing is not recommended. These guidelines apply to adult non-pregnant patients.

The tumour markers covered by this guideline are AFP, HCG, CEA, CA-19-9, and CA-15-3.

Testing for PSA and CA-125 are covered by separate Guidelines.

Key Recommendations

Laboratory testing for tumour markers is not useful to “screen” for the presence of cancer and should be reserved either to monitor patients with a known tumour or to test in circumstances where there is a pre-test probability of cancer or a high index of suspicion such as in certain pre-malignant conditions.

Epidemiology

The workload for tumour markers being sent for analysis to Irish laboratories suggests that there may be a problem with over-utilisation as a “screening test” for cancer given that many requests are being received on patients without malignancy or pre-malignant conditions.

Testing

All requests must be supported by adequate and relevant clinical details. Any request which does not fulfil the agreed criteria for tumour marker analysis will not be analysed. The samples will be separated and stored appropriately for up to 2 weeks for future analysis should the requester return with additional information which supports the agreed clinical indications.

Who to Test

Testing for Tumour Markers should generally be limited to the following clinical circumstances:

- In patients at high risk of malignancies, those with pre-malignant conditions and those who present with features compatible with specific cancers.
- A select number of tumour markers may also be useful in cases where malignancy is confirmed but the primary tumour is of unknown origin.
- Monitoring known cases of malignancy.

There are also specific clinical scenarios where tumour markers may be useful, see indications for measurement.

Indications for measurement

Tumour Marker	**Clinical Indications for Measurement**	**Other conditions associated with elevated levels**
AFP	Monitoring of NSGCTs (+hCG) Diagnostic aid in patients at high	Hepatitis Cirrhosis

	risk of HCC Aid to exclusion of NSGCT in investigation of cancers of unknown origin	Biliary tract obstruction Alcoholic liver disease Non-alcoholic fatty liver disease (NAFLD) Hepatoblastoma Advanced Adenocarcinoma
hCG	Monitoring of NSGCTs (+AFP) Choriocarcinoma Diagnosis and monitoring of GTD Aid to exclusion of NSGCT in investigation of cancers of unknown origin	Pituitary secretion (slight) Metastatic germ cell tumours (20%) Pancreatic adenocarcinoma GI malignancy
CEA	Surveillance post diagnosis and treatment of CRC	Hepatitis Cirrhosis Inflammatory Bowel Disease Pancreatitis Advanced Adenocarcinoma (breast, gastric, lung, oesophageal, pancreatic)
CA 19-9	Differential diagnosis and monitoring of pancreatic carcinoma	Pancreatitis Cirrhosis Cystic Fibrosis Hepatobiliary carcinoma CRC Gastro/oesophageal carcinoma
CA-15-3	Restricted to breast cancer clinics	Benign liver disease Benign breast disease

Sample Requirements and Stability

Serum samples are required. Samples should be sent to the laboratory as soon as possible after phlebotomy. Samples left unseparated overnight will be unsuitable for analysis.

Tumour markers should not be measured in body fluids other than serum.

Who to Re-Test

- Repeat tumour marker testing depends on the patient's condition, whether a malignancy or pre-malignant condition is being monitored.
- It is reasonable to perform repeat testing when requested by oncology or other specialist clinics.
- In certain cases it may be more appropriate to monitor the rate of change in tumour marker levels rather than the absolute value.

When Not to Test

Tumour Marker testing is **not recommended** in the following circumstances:

- Do not include in "Routine Bloods", health-screening requests, or other forms of screening.
- General screening of any patient groups, including new hospital admissions in the absence of solid indications as described above.

How to Test

Tumour markers should only be requested in those who meet the required criteria.

Patient preparation and sample collection should comply with local requirements stated in the Laboratory User Guide.

Ensure the sample is fully labelled and dispatched to the laboratory as soon as possible after venesection.

All samples must be accompanied by a laboratory test request form with adequate clinical details.

Information required on the referral form

The request form must include detailed patient and clinical information including:

- **Patient demographics**
  - Patient's Name
  - Patient's Date of Birth
  - Medical Record Number
  - Name of Referring Clinician
  - Name of Referring Hospital
  - Order number / external laboratory number (if applicable to external agencies only).
- **Request details**
  - Clinical indication for testing (see list above)
  - Details of any medications

- Relevant past medical and/or surgical treatment.

Requests received with no clinical details or with inadequate patient demographics will not be analysed.

Full clinical information should accompany all requests. In the event a request is received which does not have the required data (above) or does not have adequate clinical details the laboratory could:

- Issue a report to the requesting doctor, requesting additional clinical details and/or advise that the case is discussed with the local laboratory medicine consultant, and advising that the sample will be discarded after 2 weeks if there is no reply.
- Store the sample for up to 2 weeks awaiting further communication from the referring clinician.
- Samples can be discarded after 2 weeks if the referring clinician has not provided the required details or if it is determined that testing is not indicated.

Interpretation of tests

The laboratory report should include a reference range or clinical decision point and information on the kit/assay used for measurement.

It is important to note that reference ranges or clinical cut-off values for tumour markers provide guidance on levels that may be considered to be within the acceptable or normal range. Values below the upper range do not exclude the possibility of malignant disease while values above the range do not confirm malignancy.

There are many benign and malignant conditions associated with increased levels of tumour markers (see Quick Reference Card) and results should be interpreted in conjunction with clinical and other diagnostic findings.

Implications for ICT Systems

Computer Physician/Provider Order Entry Systems (CPOE) from a number of different suppliers are in use in a number of hospitals nationwide. Few ICT systems are capable of effectively integrating primary/community with secondary care facilities, though there are examples of “bridging” solutions such as Healthlink which is used for laboratory test reporting and other applications (including possibly test ordering). At present in Ireland, there is no national electronic health patient record, and there is no agreed unique national health identifier. In order to make progress on appropriate utilisation of laboratory services in the interim, it is necessary to consider the laboratory test ordering modules that are currently available in these different settings.

It is also likely that paper laboratory request forms will continue (e.g. in primary care) until the provision of effective ICT systems improves. Improved forms in some cases may help to encourage better provision of relevant clinical information.

Laboratory Test Requesting Ordering Modules in Primary Care

It is not recommended that the tumour markers in this Guideline are used in primary care settings except where it is clear that the patient has a malignancy and is being managed at an oncology clinic.

Laboratory Test Requesting Modules in Hospital-based CPOE Systems

CPOE systems from a number of different suppliers are available in several hospitals nationwide. The national MedLIS will also provide an order-entry system. It is recommended that a user-friendly screen for ordering Tumour Markers is developed and implemented at the point of ordering. The information required for requesting Tumour Markers is as stated above.

National Laboratory Information System (MedLIS)

The recommendations given for Primary Care and Hospital-based CPOE systems would apply to circumstances where MedLIS will be providing the CPOE functionality (e.g. where its test ordering Module is implemented throughout the hospital).

A pre-laboratory Module in MedLIS should check for (1) absence of any clinical details; (2) repeat testing; (3) correct indication for testing provided, and generate an alert and an appropriate laboratory report as described above.

References

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Appendix: Quick Reference Card

Any request which does not fulfil the agreed criteria will not be analysed.

Many benign and malignant conditions are associated with increased tumour marker levels.

Results should be interpreted in conjunction with clinical and other diagnostic findings.

Tumour Marker	Clinical Indications for Measurement	Other conditions associated with elevated levels
AFP	Monitoring of NSGCTs (+hCG) Diagnostic aid in patients at high risk of HCC Aid to exclusion of NSGCT in investigation of cancers of unknown origin	Hepatitis Cirrhosis Biliary tract obstruction Alcoholic liver disease NAFLD Hepatoblastoma Advanced Adenocarcinoma
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