The Royal College of Pathologists of Australasia
ABN 52 000 173 231

Durham Hall 207 Albion Street Surry Hills NSW 2010 Australia
Telephone 61 2 8356 5858 Facsimile 61 2 8356 5828

The Royal College of Pathologists of Australasia
1956 - CELEBRATING 60 YEARS - 2016

Position Statement

Subject:	**Serum Tumour Marker Requesting, Testing and Reporting of Results**
Approval Date:	June 2016, June 2020
Review Date:	June 2024
Reviewed by:	BPPQ
Number:	3/2016

Introduction

This Statement is intended to provide guidance for clinicians who initiate testing and receive reports for serum tumour markers and for pathology practices providing these tests and reports. The appropriate use of tumour marker testing is complex and patient harm may occur when testing is performed inappropriately. In general, the best validated use is for monitoring of a known tumour. Measurement of tumour markers for case finding or diagnosis should only be done by those knowledgeable in the field. This Statement is current at the review date above and addresses only the areas described in “Scope” below. Every patient must be treated as an individual and therefore the College encourages use of this Statement by those requesting and interpreting tumour markers as a starting point to determine the best course of action for each patient.

Scope

This statement is intended to only cover the testing of serum specimens (not urine, tissue or cells) for common tumour markers such as carcinoembryonic antigen (CEA), CA 19-9; CA 125; CA 15-3; alpha-fetoprotein (AFP); and human chorionic gonadotrophin (hCG). The scope of this statement does not include markers such as prostate specific antigen or hormones, although the principles described with respect to tumour marker testing and the reporting of results may still apply. Routine analytes with other clinical uses (e.g. lactate dehydrogenase) may be useful surrogate markers for malignancy [Ref 1,2] but are not specifically covered by this statement.

The common tumour markers referred to above are neither tissue nor organ specific. It is important to note that raised levels of these markers are not necessarily indicative of neoplasia/malignancy and that results within the reference limits do not necessarily exclude the presence of malignancy.

Requesting

The use of tumour markers for the monitoring of a known cancer is the clinical setting with the strongest supporting evidence [1,2,3]. There may be a role, however, for tumour marker measurement in the initial investigation and assessment of high risk or symptomatic individuals [1,2,3] In some settings tumour marker levels measured prior to obtaining a tissue diagnosis may govern the approach to further management and in these cases it may be appropriate to consult with a specialist clinician or pathologist prior to testing.
Tumour marker measurement prior to a tissue diagnosis may have a role under the following circumstances:

- in the presence of a mass identified clinically or by investigations such as CT scan or ultrasound where a tissue diagnosis has not been made.
- where there is evidence of secondary neoplasia and a primary source cannot be identified.
- in clinical surveillance where there is a condition present associated with a significantly increased risk of malignancy, e.g. chronic hepatitis B or C predisposing to hepatocellular carcinoma.

- in the context of clinically validated algorithms that use a combination of analytical results to evaluate the risk of malignancy [1,2]

In patients with a tissue diagnosis of malignancy, measurement of appropriate tumour markers may be utilised to assess the outcome of surgery, radiotherapy and or chemotherapy as well as to confirm remission status or the presence of recurrence. Such monitoring should usually include testing prior to the therapeutic intervention to establish the likely utility of the marker in the patient and the baseline concentration. Tumour marker testing is not recommended early post-breast cancer treatment although there may be a role early post-treatment of other specific malignancies such as colorectal cancer, testicular cancer or ovarian cancer. This testing should be done under the guidance of the specialist managing the patient e.g. oncologist, gynaecologist, gastroenterologist or surgeon who can incorporate the results into the management plan for the patient.

General population testing of tumour markers for non-targeted assessment of asymptomatic patients or the "worried well" is not recommended [1,2,3] as the risk of malignancy reflects the background risk of the population sub-group into which such individuals fall. In a low risk population, there is a greater likelihood that raised tumour marker levels are associated with non-malignant conditions so that abnormal test results may not only generate additional anxiety but lead to further unnecessary and costly investigations.

Test and Laboratory Selection

The selection of tumour marker tests is generally determined by the malignant condition present, e.g. CEA for colorectal cancer. The selection of an appropriate tumour marker, however, should not necessarily be restricted according to the primary tissue or organ site involved as the measurement of other markers may be useful for identifying the presence of malignancy [1,3], e.g. CA 19-9 rather than CEA may be the predominantly abnormal marker in a patient with colorectal cancer. Testing for more than one tumour marker may be appropriate for some conditions such as AFP and hCG for germ cell tumours [1,2,3] and AFP, hCG and other markers, such as chromogranin A for carcinoma of unknown primary origin [4].

It is not appropriate to write a request for 'tumour markers' or non-specific panels of tumour marker tests. Requests for tumour markers must individually specify the markers to be tested and expert advice should be sought if there is uncertainty. When used for the purpose of monitoring patients, it is desirable that tumour markers are measured using the same analytical method (to avoid changes due to between-method biases or different analytical specificity) and preferably by the same pathology service (to support continuity of reporting).

Reporting Results

The usual requirements for reporting numerical pathology results should be followed. Specifically the test name should be clear, the units and reference interval should be provided and elevated results should be flagged. The numerical result should be rounded so that the reported level reflects the precision of the analytical method used as well as any dilution factor applied to obtain the result and the lower limit of reporting should be valid for the assay method used.

Tumour markers reports should be provided in a cumulative format and specify the test method, as levels obtained on the same specimen by different methods may not be comparable. Where there is a change of analytical method, results obtained using both the old and new method should be provided during a suitable overlap period (e.g. six months) to facilitate patient monitoring. Reports may also include appropriate comments related to the following factors:

- a negative result does not exclude the presence of neoplasia.
- a raised level may be associated with non-malignant conditions.

- a significantly elevated result may be associated with a greater probability of malignancy.
- borderline results should be assessed in terms of the clinical context.
- the presence of malignancy should not be assumed without other corroborative evidence such as imaging or tissue biopsy.
- the likely significance of a change in results relative to background random variation.

Interpreting Results

Tumour markers results must always be interpreted in the context of the clinical setting and the reason for the request. Some general principles are as follows:

- For results related to monitoring response to therapy, the change in results should be compared with the change expected from successful therapy.
- For assessing possible tumour recurrence or growth, changes should be assessed against expected analytical and biological variation.
- For testing in patients prior to a tissue diagnosis consideration should be given to the likelihood of a malignancy and possible benign causes of elevated tumour marker levels.
- If unexpected or inconsistent tumour marker results are obtained, the laboratory should be contacted to ensure that the reported results are clinically valid

Laboratory Practice

- Laboratories should review results for unexpected changes (e.g. with delta checking) and perform confirmatory testing where indicated.
- If performed, confirmatory testing should be carried out using the primary specimen rather than an aliquot tube.
- A protocol should be in place to assess the possibility of analytical interference, e.g. human anti-mouse antibody (HAMA), by employing one or more of the following: analysis by other methods; detection of interfering antibodies, dilution studies; heterophilic blocking agents, polyethylene glycol (PEG) separation.
- When unexpectedly low or normal results are obtained, a protocol should be in place to assess the possibility of high dose hook effect.
- The laboratory may choose to include the results or comments concerning additional/confirmatory testing in the final report.
- The selection of a sensitive assay method is preferable where the early detection of tumour recurrence may be optimal for patient management.
- Where possible, specimens should be retained for an extended period of time to allow re-testing in the event that a clinician notes a possibly inconsistent result.

References

1. Sturgeon CM & Diamandis E. The national academy of clinical biochemistry Laboratory medicine practice guidelines Use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. The American Association for Clinical Biochemistry 2009.
2. Gilligan TD et al. American society of clinical oncology clinical practice guideline on uses of serum tumour markers in adult males with germ cell tumours. American Society of Clinical Oncology 2010:1-22.
3. Sturgeon C. Practical guidelines for tumour marker use in the clinic. Clin Chem 2002;48:1151-59.
4. Pavlidis N. & Fizazi K. Critical reviews in Oncology/Hematology 69 (2009) 271-278.