

## Serum tumour markers: how to order and interpret them

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### PRACTICE, p 859

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Cite this as: *BMJ* 2009;339:b3527  
doi: 10.1136/bmj.b3527

Tumour markers are molecules that may be present in higher than usual concentrations in the tissue, serum, urine, or other body fluids of patients with cancer.<sup>1-3</sup> Serum tumour 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 tumour markers are requested and interpreted correctly, they undoubtedly help clinical management. Somewhat alarmingly, however, a recent audit in a single Greek hospital found that only about 10% of requests for tumour markers were appropriate.<sup>4</sup> The cost of inappropriate testing of tumour markers was estimated to be about €23 974 (£21 000; \$35 000) a month, even without including the cost of unnecessary second level follow-up investigations such as colonoscopy and ultrasonography.<sup>4</sup> However, awareness of the limitations of tumour markers is crucial not only because of the economic implications of their misuse but even more importantly because inappropriately used tumour marker results can cause patients additional anxiety and distress. Unnecessary investigations (such as biopsy) may be associated with serious side effects and may delay correct diagnosis and treatment.

Here we focus on more commonly used serum tumour markers, reviewing recommendations for their optimal application.

### Which are the most clinically useful serum tumour markers and how should they be used?

Serum tumour markers may be used in screening, to help in diagnosis, or to monitor response to treatment. Although routinely available, tumour markers are specialised tests, ideally measured only after consideration of the likelihood that results will improve patient outcome, increase quality of life, or reduce overall cost of care.<sup>5</sup> Table 1 lists the 10 serum tumour markers most likely to be requested by non-specialists, with current recommendations for their use. PSA (prostate specific antigen) is the marker most often requested, and the increased incidence of prostate cancer in the United States during the past two decades is attributed largely to its widespread measurement.<sup>6</sup>

### When are tumour markers helpful for diagnosis?

With a few important exceptions (such as  $\alpha$  fetoprotein and human chorionic gonadotrophin in germ cell tumours), measuring more than one serum tumour marker is unlikely to be helpful when trying to establish a diagnosis. Table 2 outlines typical clinical presentations that would prompt requests for each of the seven most commonly requested tumour markers. The National Academy of Clinical Biochemistry recommends that requests for panels of tumour markers are actively discouraged, as are requests for prostate specific antigen in women or CA125 in men.<sup>1</sup> The likely benefit of the result to the individual patient must be considered before requesting any tumour marker. If decisions about treatment depend solely on the result of a single tumour marker, the result should be confirmed on a repeat specimen.

In carefully selected undiagnosed patients who are at medium to high risk of malignancy, highly raised levels of the appropriate tumour marker may provide helpful information—for example, in a patient unable or unwilling to have further, invasive investigations such as colonoscopy. Major recent improvements in the speed of access to ultrasonography in UK general practice may reduce the number of unfocused requests for tumour markers, which previously may have been made pragmatically while awaiting more definitive radiological testing.

Together with radiological testing, measurement of

### SUMMARY POINTS

Tumour markers can contribute usefully to patient management, but awareness of their limitations is essential

The main application of tumour markers is in monitoring

Measurement of a fetoprotein and human chorionic gonadotrophin is mandatory in the management of germ cell tumours

Carcinoembryonic antigen (CEA) is recommended for postoperative follow-up of patients with stage II and III colorectal cancer if further surgery or chemotherapy is an option

Prostate specific antigen (PSA) may be used for detecting disease recurrence and monitoring treatment in patients with prostate cancer

In some high risk patients, measurement of a fetoprotein, CA125, or CA19-9 may aid early detection of hepatocellular carcinoma, ovarian cancer, or pancreatic cancer, respectively

Opportunistic screening with panels of tumour markers is not helpful, nor is measurement of CA125 in men or PSA in women

**Table 1 | Most frequently requested serum tumour markers and the current recommendations of the National Academy of Clinical Biochemistry for the appropriate clinical use of these markers<sup>6</sup>**

Tumour marker	Relevant cancer	Currently recommended clinical recommendations				
		Screening or early detection	Diagnosis or case finding	Prognosis (with other factors)	Detecting recurrence	Monitoring treatment
α fetoprotein	Germ cell/testicular tumour	No	Yes	Yes	Yes	Yes
	Hepatocellular carcinoma	Yes*	Yes†	Yes	Yes	Yes‡
Calcitonin	Medullary thyroid carcinoma	No	Yes	No	Yes	Yes
Cancer antigen 125 (CA125)	Ovarian cancer	Under evaluation§	Yes¶	Yes	Yes	Yes**
Cancer antigen 15-3 (CA15-3)	Breast cancer	No	No	No	Yes††	Yes‡‡
Cancer antigen 19-9 (CA19-9)	Pancreatic cancer	No	Yes§§	Yes	Yes	Yes¶¶
Carcinoembryonic antigen (CEA)	Colorectal cancer	No	No	Yes	Yes‡	Yes‡
Human chorionic gonadotrophin	Germ cell and testicular cancers; gestational trophoblastic neoplasia***	No	Yes	Yes	Yes	Yes
Paraproteins (M protein/Bence Jones protein); also measured in urine <sup>8</sup>	B cell proliferative disorders (such as multiple myeloma)	No	Yes	No	Yes	Yes
Prostate specific antigen	Prostate cancer	No	Yes	Yes	Yes	Yes
Thyroglobulin	Thyroid cancer (follicular or papillary)	No	No	No	Yes	Yes

\*Only for subjects in high risk groups (such as those with chronic hepatitis B or C, or cirrhosis) and only in conjunction with ultrasonography (impact on mortality unclear).

†In conjunction with liver imaging, α fetoprotein levels >200 µg/l are regarded as virtually diagnostic of hepatocellular carcinoma in patients with hypervascular lesions.

‡Especially for disease that cannot be evaluated by other means.

§Through the UK Collaborative Trial of Ovarian Cancer Screening<sup>19</sup> (see text) and (for women at high familial risk of ovarian cancer and in conjunction with genetic studies and transvaginal ultrasonography) through the UK Familial Ovarian Cancer Screening Study.

¶Only for differential diagnosis of pelvic masses, especially in post-menopausal women.

\*\*Preliminary results of a randomised trial show no survival benefit from early treatment based on a raised serum CA125 level alone,<sup>7</sup> so this recommendation may be modified to exclude asymptomatic patients.

††After surgery, when it may provide lead time for early detection of metastasis, but the clinical value is unclear.

‡‡Especially in patients with non-evaluable disease (for which carcinoembryonic antigen is also recommended in carefully selected patients).

§§In patients in whom pancreatic disease is strongly suspected CA19-9 may complement other diagnostic procedures.

¶¶Especially after chemotherapy and combined with imaging.

\*\*\* Use of human chorionic gonadotrophin in screening for gestational trophoblastic neoplasia, a rare malignancy which develops most often after a molar pregnancy, provides an excellent example of “best practice” in screening. Further information is available from the Trophoblastic Tumour Screening and Treatment Centre, Department of Medical Oncology, Charing Cross Hospital, London W6 8RF ([www.hmole-chorio.org.uk/](http://www.hmole-chorio.org.uk/)).

**Table 2 | The most frequently used tumour markers and typical clinical presentations that might prompt a request for them. Other cancers in which each marker is often raised are also listed**

Tumour marker	Relevant cancer	Typical clinical presentation	Other cancers in which marker may be raised*
α fetoprotein	Germ cell/testicular tumour	Diffuse testicular swelling; hardness	Colorectal; gastric; hepatobiliary; hepatocellular; lung; pulmonary
	Hepatocellular carcinoma	Ascites; encephalopathy; jaundice; upper abdominal pain; weight loss; early satiety in high risk subjects (that is, cirrhosis related to hepatitis B or C)	Colorectal; gastric; germ cell/testicular; lung; pulmonary
Cancer antigen 125 (CA125)	Ovarian cancer	Pelvic mass; persistent, continuous or worsening unexplained abdominal or urinary symptoms; bloating	Breast; cervical; endometrial; hepatocellular; lung; non-Hodgkin’s lymphoma; pancreas; peritoneal; uterus
Cancer antigen 19-9 (CA19-9)	Pancreatic cancer	Progressive obstructive jaundice with profound weight loss and/or pain in the abdomen or mid-back	Colorectal; gastric; hepatocellular; oesophageal; ovarian
Carcinoembryonic antigen (CEA)	Colorectal cancer	Intermittent abdominal pain, nausea, vomiting or bleeding; palpable abdominal mass	Breast; gastric; lung; mesothelioma; oesophageal; pancreatic
Human chorionic gonadotrophin	Germ cell/testicular tumour	Diffuse testicular swelling, hardness, and pain	Gestational trophoblastic neoplasia; lung
	Gestational trophoblastic neoplasia†	Symptoms leading to radiography showing cannon ball secondaries; history of hydatidiform mole/ molar pregnancy†	Germ cell/testicular; lung
Paraproteins (M protein/Bence Jones protein); also measured in urine <sup>8</sup>	B cell proliferative disorders (such as multiple myeloma)	Combination of symptoms including some/all of the following: anaemia; back pain; weakness or fatigue; osteopenia; osteolytic lesions; raised erythrocyte sedimentation rate or raised or lowered globulins; spontaneous fractures; recurrent infections	None known
Prostate specific antigen (PSA)	Prostate cancer	Frequency, urgency, nocturia, dysuria; acute retention; back pain, weight loss, anaemia	None known

\* Not a comprehensive list. All markers listed in this table are not specific for malignancy but may also be raised in patients with certain benign diseases (see box).

†Use of human chorionic gonadotrophin in screening for gestational trophoblastic neoplasia, a rare malignancy which develops most often after a molar pregnancy, provides an excellent example of “best practice” in screening. Further information is available from the Trophoblastic Tumour Screening and Treatment Centre, Department of Medical Oncology, Charing Cross Hospital, London W6 8RF ([www.hmole-chorio.org.uk/](http://www.hmole-chorio.org.uk/)).

**Table 3 | Factors that may influence interpretation of tumour markers\***

Factor	Tumour marker
<b>Lifestyle</b>	
Smoking	CEA—minor increase in some assays
Cannabis use	Human chorionic gonadotrophin—transient increase
<b>Medication</b>	
5 $\alpha$ reductase inhibitors (such as finasteride, dutasteride)	PSA—median decrease of about 50%
<b>Medical investigation/intervention</b>	
Catheterisation	PSA†
Chemotherapy	Most tumour markers, especially with bulk disease, transient
Cystoscopy	PSA‡
Digital rectal examination	PSA (in some men)‡
Laparoscopy	CA125
Prostatic needle biopsy	PSA§
Prostatic massage	PSA‡
Prostate ultrasonography	PSA‡
Transurethral prostatic biopsy	PSA§

\*Not comprehensive; other factors may be relevant for some of these markers.

†Measure PSA before catheterisation.

‡Measure PSA before or one week after the investigation or intervention.

§Measure PSA before biopsy or >6 weeks after the investigation.<sup>12</sup>

**Benign conditions that may cause rises (some transient) in serum tumour marker levels that may lead to incorrect interpretation\***

- Acute cholangitis (CA19-9)
- Acute hepatitis (CA125, CA15-3)
- Acute and/or chronic pancreatitis (CA125, CA19-9)
- Acute urinary retention (CA125, PSA†)
- Arthritis/osteoarthritis/rheumatoid arthritis (CA125)
- Benign prostatic hyperplasia (PSA)
- Cholestasis (CA19-9)
- Chronic liver diseases—such as cirrhosis, chronic active hepatitis (CA125, CA15-3, CA19-9, carcinoembryonic antigen (CEA))
- Chronic renal failure (CA125, CA15-3, CEA, human chorionic gonadotrophin)
- Colitis (CA125, CA15-3, CEA)
- Congestive heart failure (CA125)
- Cystic fibrosis (CA125)
- Dermatological conditions (CA15-3)
- Diabetes (CA125, CA19-9)
- Diverticulitis (CA125, CEA)
- Endometriosis (CA125)
- Heart failure (CA125)
- Irritable bowel syndrome (CA125, CA19-9, CEA)
- Jaundice (CA19-9, CEA)
- Leiomyoma (CA125)
- Liver regeneration ( $\alpha$  fetoprotein)
- Menopause (human chorionic gonadotrophin)
- Menstruation (CA125)
- Non-malignant ascites (CA125)
- Ovarian hyperstimulation (CA125)
- Pancreatitis (CA125, CA19-9)
- Pericarditis (CA125)
- Peritoneal inflammation (CA125)
- Pregnancy ( $\alpha$  fetoprotein, CA125, human chorionic gonadotrophin)
- Prostatitis (PSA)
- Recurrent ischaemic strokes in patients with metastatic cancer (CA125)
- Respiratory diseases—such as pleural inflammation, pneumonia (CA125, CEA)
- Sarcoidosis (CA125)
- Systemic lupus erythematosus (CA125)
- Urinary tract infection (PSA‡)

\*Not a comprehensive list of conditions.

†Delay PSA measurement for at least two weeks.<sup>12</sup>

‡Repeat PSA no earlier than two to four weeks after urinary tract infection.<sup>12</sup>

both human chorionic gonadotrophin and  $\alpha$  fetoprotein is mandatory in patients in whom testicular or other germ cell cancers are strongly suspected, although these markers are not raised in all such patients.<sup>6</sup>

A recently developed UK consensus statement on ovarian cancer recommends measurement of CA125 and pelvic ultrasonography in women aged over 50 years presenting with persistent, continuous, or worsening unexplained abdominal or urinary symptoms and in whom abdominal palpation gives cause for concern.<sup>9</sup> The rationale is to reduce the risk of delaying diagnosis if women with ovarian cancer are referred to non-gynaecological specialists.

Inadequate sensitivity and specificity limit the use of CA 19-9 measurement in the early diagnosis of pancreatic cancer.<sup>10</sup> In patients without jaundice, however, CA19-9 measurement may complement other diagnostic procedures, especially in the absence of cholestasis.

In conjunction with abdominal ultrasonography, the National Comprehensive Cancer Network, like other expert groups, recommends  $\alpha$  fetoprotein measurements at six-monthly intervals in patients at high risk of hepatocellular carcinoma (especially those with liver cirrhosis related to hepatitis B or hepatitis C) and further investigation if increases in  $\alpha$  fetoprotein persist.<sup>11</sup> The effectiveness of such testing will reflect prevalence of disease in the screened population.

Although PSA is essentially organ specific (table 2), it is not cancer specific (box). Sustained high levels of PSA occur in benign prostatic hyperplasia, and transient increases may occur in some patients with urinary tract infections, in prostatitis, and after catheterisation (table 3). Provided these latter conditions are excluded, the higher the PSA level, the greater the probability of prostate cancer. About 15% of men with a PSA <4  $\mu$ g/l will have cancer on biopsy, as will about 25% with a PSA 4-10  $\mu$ g/l and 50% with a PSA >10  $\mu$ g/l.<sup>13</sup> Confirmed levels >100  $\mu$ g/l are usually consistent with metastatic disease. Prostatic biopsy or radiological evidence of bone metastases is generally required for definitive diagnosis.

**Are tumour markers helpful for diagnosis in patients with non-specific symptoms?**

Tumour markers are not helpful for diagnosis in patients with non-specific symptoms. Many tumour markers (particularly carcinoembryonic antigen (CEA), CA125, CA15-3, and CA19-9) are raised in several cancers (table 2) but may also be raised in certain benign diseases (box). They therefore cannot either identify or exclude suspected malignancy (especially early stage disease) reliably, owing to low diagnostic sensitivity (the ability to identify the true cases of a particular cancer type) and low specificity (the ability not to identify people as having a particular cancer type when they do not have it).

For example, the proportion of patients with early stage (Dukes's type A) colorectal cancer who have CEA levels >5  $\mu$ g/l is only 3%, compared with 25%, 45%, and 65% for Dukes's type B, C, and D respectively.<sup>14</sup> Measurement of these markers is therefore not recommended in patients with non-specific symptoms

(a presentation most likely to be encountered in primary care) before imaging or a definitive diagnosis of malignancy by biopsy.

#### **Are tumour markers effective for screening asymptomatic populations?**

Population based screening of asymptomatic people with most serum tumour markers is not recommended owing to low diagnostic sensitivity and specificity. Screening for prostate cancer with PSA has the potential to detect malignancy at least five years before clinical evidence of disease but remains controversial, with some expert groups in favour and others not.<sup>6</sup> Interim results of two large prospective trials of PSA screening are contradictory, one suggesting no mortality benefit<sup>15</sup> and the other concluding that 1410 men would need to be offered screening and 48 men treated to prevent one death from prostate cancer during a 10 year period,<sup>16</sup> a benefit achieved only at the cost of substantial overdiagnosis and overtreatment.<sup>17</sup> Until these studies finally report their findings, asymptomatic men should be informed of the benefits and limitations of PSA screening before deciding whether to have the test.<sup>6 18</sup> The Prostate Cancer Risk Management Programme (part of the NHS Cancer Screening Programmes) provides helpful information packs intended for distribution through primary care ([www.cancerscreening.nhs.uk/prostate/informationpack.html](http://www.cancerscreening.nhs.uk/prostate/informationpack.html)).

Serial measurements of CA125 are included in a UK collaborative trial of ovarian cancer screening involving 208 638 women aged 50-74 years.<sup>19</sup> The final results of this trial will not be known until 2015, and in the meantime the National Academy of Clinical Biochemistry does not recommend opportunistic screening of asymptomatic women with CA125.<sup>6</sup>

#### **What are the pros and cons of monitoring response to treatment?**

Serial monitoring of patients after treatment is the most appropriate use of tumour markers (table 1), but its effect on outcome varies. In patients with a diagnosis of cancer, measurement of markers before and after treatment can provide evidence of efficacy of treatment and identify recurrence some months before clinically evident. Whether the latter benefits an individual patient depends on the availability of further treatment (such as chemotherapy or resection).

For patients with germ cell tumours, all guidelines recommend measurement of  $\alpha$  fetoprotein and human chorionic gonadotrophin according to well established protocols,<sup>20</sup> as further treatment can be started after a confirmed increase in markers even without radiological evidence of progression.

Similar benefit in monitoring can be achieved in patients with colorectal cancer by measuring CEA; serial measurement as part of an intensive surveillance programme improves survival when compared with less intensive follow-up.<sup>6</sup> Most expert groups recommend measurement of CEA at three-monthly intervals for at least three years in patients with stage II or III colorectal cancer who are candidates for surgery or

systemic treatment of metastatic disease.<sup>6</sup> Current trials are investigating whether intervention (such as chemotherapy) is similarly beneficial after a rise in CA125 in patients with ovarian cancer. Results of one such trial suggest not, probably reflecting the current lack of curative treatments.<sup>7</sup>

The National Academy of Clinical Biochemistry recommends monitoring with PSA measurements after treatment for prostate cancer but cautions that the clinical utility varies depending on the disease stage of the individual patient.<sup>6</sup> Importantly, cancer progression may occur without increases in the concentration of the relevant tumour marker, and a tumour may occasionally lose its ability to produce a marker, perhaps as a result of dedifferentiation.

Sustained decreases in marker concentrations provide reassuring and objective evidence of tumour regression. However, as rising levels provide early evidence of progression, if alternative treatment is not available then monitoring with marker measurements can cause psychological distress without much clinical benefit. The ultimate decision about whether to monitor with tumour markers requires close cooperation between clinicians and patients.<sup>6</sup> A recent article provides insight into these issues from the perspective of a patient with ovarian cancer monitored with CA125 measurement.<sup>21</sup>

#### **Why is non-selective requesting of tumour markers undesirable?**

If they are inappropriately requested, tumour marker measurements may lead to additional and unnecessary investigations, as recently illustrated for a cirrhotic patient extensively investigated for ovarian cancer because her serum CA125 was raised.<sup>22</sup> Raised markers may lead to suspicion of disease in organs not relevant to the patient's presentation, potentially causing undue alarm, while normal levels may provide false reassurance. Either scenario can result in additional cost (such as admission to hospital), risk of side effects (such as endoscopy, which carries a small risk of mortality), and/or delayed diagnosis.

#### **What evidence exists that tumour markers are often requested inappropriately?**

A recent audit of practice in Northern Ireland found that, although 80% of tumour marker requests were associated with the relevant organ, 54% of clinicians used tumour markers to screen for malignancy, with a low index of suspicion in 35% of these requests.<sup>23</sup> Another audit in a single UK hospital found that 26% of all tests for the marker of breast cancer CA15-3 were for men—even though none of these men had breast biopsies in the year of the study or in the two years before—as were 17% of requests for the marker of ovarian cancer CA125.<sup>24</sup> In the Greek study mentioned earlier, only 20% of 10291 retrospectively reviewed tumour marker results for 1944 patients were for patients with cancer.<sup>4</sup> The lowest level of appropriate requesting was for the pancreatic marker CA19-9 (1.9%), and 26% of CA125 requests were for men.<sup>4</sup> The colorectal cancer marker CEA was most often correctly requested (27%).<sup>4</sup>

**A PATIENT'S PERSPECTIVE**

In an area of medicine with conflicting views about at what point it is even necessary to investigate if a patient has prostate cancer, and with similar conflicting claims about the efficacy or even desirability of different forms of treatment, two words sum up the experience of the average male patient—uncertain and vulnerable.

In this situation one thing men have to cling on to is their PSA reading. It appeals to men, or at least to those men who wish to know the detail of what is happening to them. It is something tangible, non-conceptual. We're also used to scouring the football or rugby results for the measurable minutiae of progress, decline, movement, and the like.

I doubt that my own case is particularly exceptional. A PSA reading of 7 µg/l was identified through the ProtecT Study (a randomised controlled trial evaluating treatments for localised prostate cancer, comparing surgery (radical prostatectomy), radiotherapy (radical conformal), and monitoring with regular check-ups). My GP told me that with that particular reading he would have said not to worry and to come back to the surgery the following year. (I subsequently talked to other men who visited their GPs only to be told it was not the policy of the practice to do PSA tests unless there were "symptoms" and that PSA readings were often inaccurate and could create unnecessary anxiety for patients.)

I did extensive research and felt my PSA was high enough to warrant a biopsy. The PSA reading was the definitive catalyst for my action. It was also all I really had, and still have, even though it would seem to be a test that's been around a long time by current medical standards.

My biopsy gave a Gleason reading of 7 (3+4). On that basis, in consultation with my urologist, I had a laparoscopic prostatectomy. The subsequent laboratory report showed a Gleason reading of 7, but 4+3, with a 50% chance of spread. After two and four months my PSA was 0.1 µg/l, but after a further four months it had risen to 0.2 µg/l. Is this a "blip," or a sign that cancer cells are active and thus requiring more treatment? I will find out at my next appointment. So believe me, my PSA reading is very important to me. It does dominate my thinking and I have little doubt that it will be a factor for the rest of my life.

**TIPS FOR NON-SPECIALISTS**

- Tumour marker results are rarely diagnostic and cannot replace biopsy for establishing the primary diagnosis of cancer. A raised tumour marker result does not necessarily indicate a particular malignancy but may provide some indication of its likelihood. Results within normal limits do not exclude malignancy or progression
- Measurements of tumour markers are not recommended for patients with vague symptoms when the population likelihood of cancer is low, as in general practice
- The main clinical use of existing serum tumour markers is in postoperative surveillance and in monitoring after chemotherapy, endocrine therapy, or radiotherapy
- Tumour marker results are often method dependent—patients should, ideally, be monitored using the same method and its name indicated on the report form
- Tumour marker results should always be interpreted in the context of all available information including clinical findings, imaging investigations, and other blood tests (such as renal and liver function and haematological tests). The possible influence of other factors (such as medication) should be carefully considered
- Laboratory staff should be alerted to any results that are unexpected or do not accord with the clinical picture in order to minimise the risk of clinical error or misinterpretation. Where doubt exists about a result a confirmatory specimen is usually desirable

**ST ELSEWHERE HOSPITAL**

Department of Clinical Biochemistry      Hospital Name: \_\_\_\_\_  
 Tel: \_\_\_\_\_

<b>PATIENT:</b> Smith John	<b>PATIENT No:</b> 123456789Z	← Standard patient demographics including patient number ← Space for recording relevant information
<b>DOB:</b> 01/02/03	<b>CONSULTANT/GP:</b> Dr Jane Doe	
<b>WARD/PRACTICE:</b> Medical Centre 1	<b>HOSPITAL:</b>	

**ADDITIONAL DETAILS:**

← Possibility of graphical reporting - logged or not  
  
 ← Relevant clinical decision limit

LAB/SPECIMEN/METHOD	DATE	TUMOUR MARKER (4.0 units)	CLINICAL DETAIL
Lab A 244347 Method 1	03.03.1999		Post-surgery
Lab A 578221 *	04.05.2000	2.5 units	
Lab B 613365 Method 2	15.06.2000		For change of treatment?
Continued....			

← Cumulated results across hospitals and including method and clinical details

**COMMENTS:**  
 Confirms recent increase. [Report copied to Urology and Oncology, as requested.]

← Comments - selected from presented choices depending on marker, level, and age of patient

**Is the method by which tumour markers are measured important?**

When interpreting results, particularly serial results, clinicians need to be aware that results obtained using different methods are not necessarily comparable.<sup>25</sup> The National Academy of Clinical Biochemistry recommends that laboratories indicate the method used when reporting the results for tumour markers, provide cumulative (ideally graphical) reporting, and append an interpretative comment, especially if there have been intervening method changes (figure).<sup>1</sup> Early discussion with laboratory staff about any results that do not accord with the clinical picture facilitates early identification of analytical errors.<sup>1 12</sup> Such identification is helped by the provision of relevant clinical information when tests are ordered, which is strongly recommended by the National Academy of Clinical Biochemistry.<sup>1</sup>

**How can the process of requesting tumour markers be improved?**

Guidelines provide a helpful framework for initiatives to promote best practice, with local ownership being essential for successful implementation.<sup>26</sup> Encouraging effective communication between clinical and laboratory staff—such as through laboratory provision of more informative reports (figure)—is likely to improve test requesting, particularly if underpinned by audit.

**What new tumour markers are emerging?**

New tumour markers may complement existing markers.<sup>6</sup> The gene product human epididymis 4

**SOURCES AND SELECTION CRITERIA**

This review is based on recently published guidelines for tumour markers from the National Academy of Clinical Biochemistry, which include summaries of relevant recommendations of other clinical organisations including the American Society for Clinical Oncology, the European Group on Tumour Markers, the National Comprehensive Cancer Network, the National Institute for Health and Clinical Excellence, and the Scottish Intercollegiate Guideline Network. We also searched PubMed and the Cochrane database to identify the best available evidence using search words including “tumour marker”, “guidelines”, and the names of relevant tumour markers. We supplemented these sources with our own knowledge of the literature and relevant authoritative reviews

**ONGOING AND FUTURE RESEARCH**

- Prospective trials to evaluate utility of tumour markers in screening for early malignancy are in progress for  $\alpha$  fetoprotein, CA125, and PSA
- Prospective trials to evaluate whether early intervention based on tumour marker increases in the absence of other clinical evidence of progression benefits outcome are about to report for CA125; similar trials are needed for CA15-3 in patients with breast cancer
- Validation is needed of emerging promising markers. Studies are currently in progress to evaluate PCA-3 in prostate cancer, epididymis 4 protein in ovarian cancer, and progastrin releasing peptide in small cell lung cancer
- New markers are needed for certain cancers—such as cervical and gastric malignancies (currently, serum markers are lacking for these cancers)
- Development of predictive markers is needed for cytotoxic therapies and the new biological therapies. Predictive markers are particularly important for the latter, as these agents are usually effective in only a small proportion of patients and are also expensive. Emerging predictive markers include the mutational status of k-ras for predicting benefit from cetuximab and panitumumab in patients with advanced colorectal cancer and the mutational status of epidermal growth factor receptor in predicting benefit from gefitinib (still being tested in research trials) or erlotinib in patients with advanced non-small cell lung cancer

protein has been cleared by the US Food and Drug Administration as an aid for monitoring patients with ovarian cancer.<sup>27</sup> Measurement of PCA-3 in urine may help to stratify patients according to their risk of prostate cancer before biopsy, although large scale validation studies are needed.<sup>28</sup> Similar studies are needed to assess the utility of methylated genes in the management of patients with cancer.<sup>29</sup>

Serum tumour markers currently contribute relatively little to treatment decisions, often owing to the lack of effective second line treatment. As treatments improve, predictive serum tests may help to identify patients most likely to benefit from new and expensive drugs. Personalised treatment is most advanced for

**ADDITIONAL EDUCATIONAL RESOURCES****Resources for healthcare professionals**

- European Group on Tumour Markers ([www.egtm.eu/](http://www.egtm.eu/))—The group’s website provides information about tumour markers for several cancer sites
- McAllister EJ, Sturgeon CM. Tumour markers. In: Marshall WJ, Bangert SK, eds. *Clinical biochemistry. Metabolic and clinical aspects*. 2nd ed. Edinburgh: Churchill Livingstone Elsevier, 2008:891-913.
- National Academy of Clinical Biochemistry ([www.aacc.org/members/nacb/Pages/default.aspx](http://www.aacc.org/members/nacb/Pages/default.aspx))—This part of the American Association of Clinical Chemistry and Laboratory Medicine provides consensus based guidelines for the laboratory evaluation and monitoring of patients with specified disorders, including those with cancer
- National Comprehensive Cancer Network ([www.nccn.org](http://www.nccn.org))—The network, an alliance of 20 of the world’s foremost cancer centres, provides detailed clinical practice guidelines for most malignancies
- Scottish Intercollegiate Guideline Network (<http://sign.ac.uk>)—Provides summaries of evidence based guidelines for more than 12 cancer sites, together with guidelines related to other aspects of medicine

**Resources for patients**

- Labs Are Vital ([www.labsarevital.com](http://www.labsarevital.com))—Provides information about how laboratories contribute to the healthcare community with up to date bulletins on new tests, including tumour markers
- Lab Tests Online UK ([www.labtestsonline.org.uk/](http://www.labtestsonline.org.uk/))—Provides information about how clinical laboratory tests contribute to diagnosis and treatment of all diseases, including cancer. Facility for searching for tests or for specific conditions and diseases
- National Institute for Health and Clinical Excellence ([www.nice.org.uk/](http://www.nice.org.uk/))—Provides national guidance on the promotion of good health and the prevention and treatment of ill health, including guidance relating to several cancer sites
- NHS Choices: Your health, your choices ([www.nhs.uk/Livewell/cancer/Pages/Cancerhome.aspx](http://www.nhs.uk/Livewell/cancer/Pages/Cancerhome.aspx))—Includes advice about prevention, diagnosis, and treatment for several cancers
- NHS National Cancer Screening Programmes ([www.cancerscreening.nhs.uk/prostate/informationpack.html](http://www.cancerscreening.nhs.uk/prostate/informationpack.html))—An updated information pack (July 2009) about PSA testing and the UK Prostate Cancer Risk Management Informed Choice programme

breast cancer, with tissue markers such as oestrogen receptor and HER-2 (human epidermal growth factor receptor 2) predicting response to endocrine therapy and trastuzumab respectively.<sup>30</sup>

We thank Sheila Liggat, Ranjit Manchanda, Orest Mulka, Julietta Patnick, Carole Shahin, and Simon Walker for their careful reading of the manuscript and most helpful comments.

**Contributors:** All authors contributed to the preparation of this paper. Orest P Mulka read the manuscript at an early stage and commented on it from a general practice perspective. CMS is the guarantor.

**Competing interests:** None declared.

**Provenance and peer review:** Commissioned; externally peer reviewed. Patient consent obtained.

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## A tale of mind and body

I have always been a firm believer in the so called mind-body connection. As a family doctor, I have witnessed time and again the effects of depression and anxiety on patients with chronic illness, and likewise the conundrum of unexplained physical symptoms that defy all attempts to reduce them into a particular diagnostic category. Indeed patients with multiple unexplained symptoms are a tremendous challenge to the general practitioner as well as an economic burden on already strained healthcare systems.

Just over a year ago my mother died aged 94, after six years of steadily worsening Alzheimer's disease. The last months of her life were disturbed by repeated admissions to hospital with aspiration pneumonia secondary to an inadequate swallowing mechanism. Thankfully for her, insertion of a feeding gastrostomy led to complications that brought about her rapid demise.

In the following weeks I developed pain on swallowing that, apart from raising in my medical mind visions of various neoplastic disorders, failed to respond to the usual remedies for common complaints. Inevitably, I was referred for investigation: a gastroenterologist performed a normal gastroscopy and anti-helicobacter treatment was started after a (barely) positive result on the breath

test. Eventually, the symptom disappeared and I resumed life to the full.

Exactly one year after my mother's death—the “Yahrzeit” or anniversary day for the dead in the Jewish tradition—I woke up in preparation for the traditional service at the cemetery, and lo and behold it was back, that nagging pain every time I swallowed.

At that moment I was struck by a connection which in retrospect seemed so obvious. Was this an example of the well known anniversary phenomenon?<sup>1 2</sup> Almost certainly, and it occurred to me that the symptom itself was possibly an unconscious identification with my late mother's last complaint. With insight came cure, and by the next day the pain had gone.

Perhaps this experience will help me to relate to my patients' complaints without splitting mind from body by assuming that one or the other is causative—instead accepting that our mind-body is an indivisible entity.

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Cite this as: *BMJ* 2009;339:b2383