Abstract
The objective of this paper was to complete a retrospective audit on tumour marker requests at the Hawke’s Bay District Health Board's laboratory to determine if the requests had been ordered appropriately according to the guidelines issued by the Best Practice Advocacy Centre (BPACnz). A sample period of one month of tumour marker requests from 16.5.11 to 15.6.11 for AFP, β-hCG, CA 125, CA 15-3, CA 19-9 and CEA were viewed to identify whether the clinical information conformed to BPAC guidelines. Where no clinical details were provided, cumulative history was viewed to establish, if possible, the reason for the test request.

Requests were divided between the community General Practitioners and those that were hospital based as either in- or out-patients. With a few exceptions, the hospital based requests were found to be appropriate by the BPAC guidelines. However, there were a large number of requests from the community General Practitioners (49% overall) that were inappropriate by the same criteria.

Key words
Tumour markers, BPAC, guidelines, appropriate requests.


Introduction
Best Practice Advocacy Centre (BPACnz) is an independent New Zealand organization that examines evidence based information, cost effectiveness and New Zealand specific needs to make recommendations to primary health care professionals in New Zealand (1).

Tumour markers are a valuable addition to the test panel used for monitoring disease progression. However, their limitations must be kept in mind in order to ensure they are appropriately requested. Generally there is poor sensitivity and specificity for tumour markers. Values may not rise early enough, they may not rise in all occasions or they may rise due to other factors such as other concurrent disease, transient response to treatment or artefactual results due to testing limitations such as haemolysis, sample quality or delayed testing. This is undesirable, not only as a waste of resources, but also because it can be misleading giving false reassurances or false concern.

Methods
As a response to the BPAC publication entitled ‘Appropriate Use of Tumour Markers’ (BPAC, July 2010) it was decided to complete a retrospective audit on tumour marker requests at the Hawke’s Bay District Health Board Hospital laboratory. Requests were reviewed over a one month period from 16.5.11 to 15.6.11 for AFP, β-hCG, CA 125, CA 15-3, CA 19-9 and CEA to determine whether the clinical information provided with the request corresponded to the BPAC guidelines of appropriate use. Where no clinical details were provided, cumulative history was viewed to establish, if possible, the reason for the test request.

Results and Discussion
Alpha fetoprotein
Alpha fetoprotein (AFP) is a glycoprotein produced initially in the embryonic yolk sac and then later in the foetal liver thus foetal blood concentrations are relatively high (2–4 g/L). After birth AFP decreases to reach adult levels of 0-6 µg/L by about 10 months of age (2).

Analysis of AFP, outside of prenatal screening, takes place because it is raised in various cancers such as liver, germ cell testicular, bowel, stomach, lung, breast and lymphomas. It can also be raised in other situations such as chronic hepatitis or cirrhosis. As a tumour marker, AFP is most often used for testicular cancer or hepatocellular carcinoma (HCC).

With regards to testicular cancer, BPAC states that diagnosis should be made on “clinical signs and symptoms [and] investigations including ultrasound and CT scans” (3). AFP should be analysed for non-seminomatous tumours following diagnosis but before treatment with the rate of marker decline reflecting the response to treatment. BPAC guidelines indicate AFP measurements are not useful for seminomas (3).

The American Association for Clinical Chemistry produces the National Academy of Clinical Biochemistry (NACB) Laboratory Medicine Practice Guidelines. Their current guidelines on tumour markers indicate there is no place for screening for testicular cancers using AFP and that diagnosis is usually confirmed by ultrasonography. AFP, β-hCG and LD are “mandatory” before treatment and that AFP is important in evaluating the response to treatment and in early recognition of relapse (4).

The International Germ Cell Cancer Collaborative Group use AFP along with β-hCG and LD in a scheme to classify metastatic germ cell tumours and selection of treatment is based on tumour type and prognostic group (4).

In preparation of the NACB guidelines other group studies were evaluated, including those of the European Group on Tumour Markers (EGTM), the European Association of Urologists (EAU), the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), and all groups concur that AFP is important for staging/prognosis, detecting recurrence and monitoring treatment but not for screening (4).

The use of AFP is, however, recommended by NACB to screen for HCC, in conjunction with liver ultrasound, in high risk but asymptomatic groups in order to give “early identification of tumours while they are still potentially curable” (5). Examples of high risk patients are those with cirrhosis, chronic viral hepatitis, haemachromatosis. NACB state an AFP result greater than 20ug/L and increasing should prompt further investigation.

Diagnosis of HCC should be through imaging, with AFP levels used as “an adjunct in diagnosis”. The European Association for the Study of the Liver (EASL), the British Society of Gastroenterology and the EGTM also all recommend this (5).

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In this audit there were 77 requests for AFP over the month concerned. Of these, 28 came from the community GPs, 27 from hospital in-patients and out-patient clinics, and 22 from the Hepatitis Foundation. Of the 28 GP requests, 18 were hepatitis patients being serially monitored, two others were cirrhosis monitoring and seven were inappropriate requests from primary care by BPAC recommendations. The inappropriate requests had no cumulative results or past history to indicate a valid reason for testing and had the following clinical details:

- abnormal liver function tests, weight loss
- testicular mass
- ovarian cysts
- seminoma review*
- two samples with no clinical details

*BPAC guidelines state AFP is not useful for seminomas; β-hCG and LD should be used instead, but is useful for non-seminomatous tumours (3).

Of the 27 hospital AFP requests, six were for HCC monitoring in hepatitis patients, 18 were appropriate requests for suitable oncology reviews or high risk patient HCC screening. The three inappropriate hospital requests were for seminoma reviews.

β-human chorionic gonadotropin (β-hCG)

β-hCG is a glycoprotein synthesized mainly in the placenta hence its use as a pregnancy marker. However, it is also produced in small amounts in the pituitary with normal ranges of 0-5 IU/L. The alpha subunit is common to FSH, LH, TSH and hCG but the beta unit is unique to hCG which is why it is used to analyse hCG concentrations (2).

β-hCG is raised in trophoblastic tumours, testicular tumours, melanoma, breast cancer, GI, lung and ovarian cancer. It can also be raised in cirrhosis, duodenal ulcers, inflammatory bowel disease, menopausal women and pregnancy. β-hCG’s main use as a tumour marker is for testicular cancer. Recommendations are for its use alongside AFP however it can also be useful for seminomatous tumours where AFP is not (3).

There were 16 β-hCG tumour marker requests during the audited period, three from GPs and 13 hospital based. One of the GP requests was appropriate by BPAC standards as it was a seminoma review. However, the other two GP requests were inappropriate in that they were querying testicular masses and had no cumulative review history or clinical history to indicate a diagnosed cancer. The 13 hospital requests were all considered appropriate, being tumour and seminoma reviews.

Cancer Antigen 125 (CA 125)

CA 125 is raised in ovarian cancer as well as other situations such as during menstruation, pregnancy, benign ovarian cysts and endometriosis. The reference range is 0-35 kIU/L, however, values do decline with menopause and aging (2).

BPAC guidelines recommend that CA 125’s main role is in the management of ovarian cancer and that it should not be used for screening or diagnostic purposes as it has poor sensitivity for early stage disease (6). It can be used to monitor serial type ovarian cancers and levels following chemotherapy are a strong indicator of disease outcome. It can also be used to detect recurrent disease.

NACB guidelines agree with BPAC that CA 125 is unsuitable for screening. However, they indicate that it can be used with transvaginal ultrasound in the detection of hereditary ovarian cancer in asymptomatic individuals. The NACB also supports the use of CA 125 in differential diagnosis in post-menopausal women with pelvic masses and in correlating sample concentrations with tumour burden and stage, with declining concentrations showing a response to treatment and rises predicting a relapse (4).

The audit identified 47 requests for CA 125, 13 from GPs and 34 hospital based. Of the GP samples only two were appropriate by BPAC standards having been requested for ovarian cancer monitoring. The other 11 GP requests were considered inappropriate as they had the following clinical details with no result or clinical history found to support the case for testing:

- RA
- 2 x ovarian cysts
- weight loss, immune suppressed
- pelvic scan
- adnexal mass, ?ovarian
- 5 x no clinical details provided

All hospital CA 125 requests were appropriate by BPAC guidelines as they were for monitoring diagnosed patients.

Cancer Antigen 15-3

CA 15-3 is a MUC1 protein antigen that is elevated in breast cancer and also in cases of cirrhosis and benign diseases of the ovaries and breast (4). Because CA 15-3 testing lacks sensitivity in early disease BPAC consider it to have no role in screening or diagnosis of breast cancer, but that its use should be limited to monitoring for recurrence or treatment effectiveness (3).

NACB guidelines also state “current blood-based biomarkers are of no value in early detection of breast cancer” and even that the clinical benefit of CA 15-3 following primary surveillance is unclear (4). This thinking is echoed by the American Society of Clinical Oncology (ASCO), ESMO and NCCN. These groups also concur that CA 15-3 can be useful in palliative care to help decide if a particular type of therapy should be continued (4).

There were 20 CA 15-3 requests during the period of this audit and all of them were hospital based. Only one of these was considered inappropriate by BPAC standards as it had clinical details indicating colon cancer. However, a further look showed this was probably an error on the request form as the clinical history showed a diagnosis of breast cancer.

Carcinoembryonic antigen (CEA)

CEA is a family of glycoproteins. Production starts during foetal development but is found in low levels (0-3ug/L) in healthy adults (2). One of the first tumour markers to be used, levels are raised in colon cancer but also in lung, breast, liver, pancreas, thyroid, stomach and ovarian cancers as well as in ulcerative colitis, cirrhosis and smoking (3). The most common use of CEA results is in the management of colorectal cancer (CRC) patients. BPAC recommendations are that CEA results not be used for screening or diagnosis due to its poor sensitivity and specificity and the low prevalence of CRC in non-symptomatic individuals. It may provide some prognostic information but should only be requested in management of patients with established malignancy (6).

NACB also recommends that CEA not be used as a screening test. They indicate that a preoperative CEA concentration may be used, with other factors, to plan surgical treatment but not to select a patient for adjuvant chemotherapy (4). CEA is widely used in surveillance of CRC but there is no agreement between groups as to the magnitude of change that would be clinically significant.

During the period of this audit there were 109 CEA requests, 30 from GPs and 79 hospital-based. Of the 30 GP requests, 13 were appropriate by BPAC standards (monitoring of diagnosed CRC patients) and 17 were inappropriate, i.e. clinical information given did not meet BPAC criteria and there was no clinical or result history to indicate otherwise. The clinical details give were:

- adenexal mass, ?ovarian
- alternating D&V, ?diverticulitis or cancer
- 2 x change of bowel habit, tenesmus
- iron deficient anaemia
- weight loss, change of bowel habit
- ?ceolon cancer
- ovarian cysts
- 8 x no clinical details provided
It is worth noting that two of the requests caveated the CEA request with “yes I know, not for primary screening” yet that is just what they appeared to be.

Of the 79 hospital requests, 78 were appropriate by BPAC guidelines but one was a request from the emergency department with clinical details of constipation and abdominal pain with no indicative result or clinical history.

Cancer Antigen 19-9 (CA 19-9)
CA 19-9 is a glycolipid synthesized by normal pancreatic, biliary duct, gastric, colon, endometrial and salivary epithelial cells. The normal reference range is 0-37 kIU/L but this can be raised in cancer of the stomach, bowel and particularly pancreas (2). BPAC recommends that it is not used for screening but only for monitoring known malignancies. It is recognized that use of CA 19-9 has been proposed to differentiate between benign and malignant situations but this has not yet been established with evidence based studies (3). The NACB guidelines state routine measurement of CA 19-9 is not recommended as it is less sensitive for CRC that CEA (4).

During the audit period there were 38 requests for Ca 19-9. One of these was from a GP and the rest were hospital based. All requests were appropriate as per BPAC guidelines being monitoring of diagnosed CRC patients.

In summary, aside from using AFP for hepatocellular carcinoma in high risk patients, tumour markers should not be used as screening tests for malignancies as the lack of sensitivity and specificity is too great. However, the individual markers do all have a role in the management of the already diagnosed patient when used appropriately. During the course of the audited period there were 42 inappropriate (as per BPAC guidelines) tumour marker requests, which resulted in a cost of over $800 for the one month audited.

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References