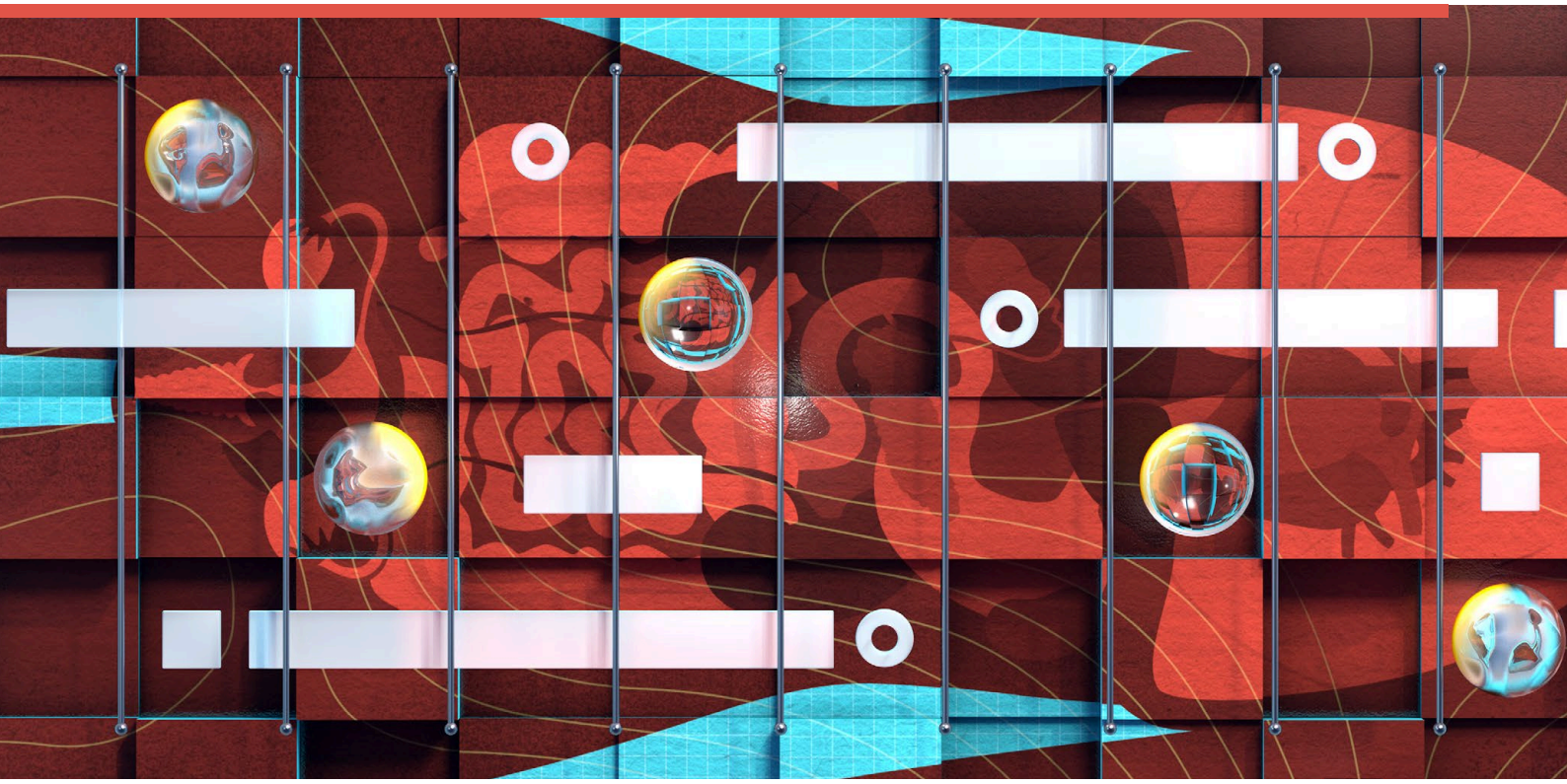


Appropriate use of tumour markers

The appropriate use of serum tumour marker testing is complex and patient harm can occur when testing is requested but not clinically indicated. The main role for a tumour marker test is in the management of a patient with a known malignancy. However, there are some tumour markers, e.g. CA 125, that can have a role in the detection of specific cancers.

KEY PRACTICE POINTS

- Tumours markers have an increasing role in primary care as more evidence and guidance becomes available for their use. For example, the role of CA 125 has changed over time; testing serum CA 125 levels is now indicated in primary care as part of the diagnostic workup of a patient with suspected ovarian cancer.
- There are currently no tumour markers that have high enough sensitivity or specificity to be used alone as screening tests for malignancy in asymptomatic patients. Instead, specific tumour markers may be requested to determine which patients presenting with symptoms should be prioritised for further assessment.
- The main role for a tumour marker test is in the management of a patient with established malignancy, e.g. to assess response to treatment or to monitor for any secondary cancer or recurrence
- A tumour marker test should only be requested based on a specific clinical indication for investigating that parameter. Using these tests for general screening in asymptomatic patients can result in unnecessary follow-up and anxiety due to an abnormal test result, which turns out not to be cancer. Conversely, relying on tumour markers alone to rule out cancer in a symptomatic patient, can result in false reassurance.

This is a revision of a previously published article.
What's new for this update:

- General article revision
- Changes to the indications for requesting serum CA 125 in primary care

Prostate specific antigen (PSA) is also a tumour marker. PSA is not currently included in this article as existing national guidance from 2015 is now outdated and the role of PSA in primary care, particularly in screening, is inconsistent among the literature and in practice. New PSA guidelines for New Zealand are currently under development and are expected to be published later in 2023. A section on "Tumours markers in prostate cancer" will be added once new guidance becomes available. In the interim, a position statement about PSA testing is available from the Urological Society of Australia and New Zealand **here**, and further information about prostate cancer can be found **here**.

Tumour markers generally make poor screening tests

The term "tumour marker" encompasses a spectrum of molecules that are produced either by, or in response to, a tumour that contributes to the clinical detection, management or prognosis of a patient with cancer.[1, 2]

The clinical use of a tumour marker largely depends on its sensitivity, specificity and positive and negative predictive value for a particular cancer.[2, 3] An ideal tumour marker is one that is highly sensitive and specific.[3] Many of the currently available and frequently requested serum tumour markers (Table 1) can be produced by normal tissues and levels can be elevated in non-malignant conditions.[2, 3] They are also not always site- or organ-specific.[2, 4] In addition, not all people with a particular cancer have raised levels of the corresponding tumour marker(s).[2, 3] Therefore, clinical utility is currently limited.

Under certain clinical scenarios, testing specific serum tumour markers may be indicated in primary care as part of the diagnostic workup of a patient with suspected cancer, e.g. CA 125 for ovarian cancer.[5] Tumour markers are not appropriate to be used as screening tests for malignancy in patients who are asymptomatic due to low sensitivity and specificity.[1, 5] Instead they can be used to determine which patients presenting with symptoms should be prioritised for further assessment.

In general, the main role of a tumour marker test is in the management of a patient after diagnosis of a particular cancer, where it is used to assess response to treatment or to monitor for any secondary cancer or recurrence.[3–5] A rising tumour marker level usually requires further investigation, while an undetectable, low or falling level tends to be reassuring.[1]

Only request laboratory testing for a tumour marker when it is clinically indicated.[2, 5] If a tumour marker is inappropriately requested there is a higher risk of false positive and false negative results, e.g. as a screening test in an asymptomatic patient, as a diagnostic test in a patient with non-specific symptoms, for a suspected cancer that is not known to produce the marker. An elevated result may be due to reasons other than malignancy which can cause the patient anxiety and distress, lead to unnecessary investigations and a delay in reaching the correct diagnosis.[3, 4] Conversely, false reassurance is possible if normal/negative results are returned (and it is the only test used to exclude malignancy). In rare cases, requesting serum tumour markers when not clinically indicated may detect cancer, but this is likely to be outweighed by the potential for harm.

Table 1. Commonly requested tumour markers.

Tumour Marker	Description
Alpha fetoprotein (AFP)	Predominantly raised in liver cancers and testicular or ovarian germ cell tumours, but may also be raised in non-malignant conditions, e.g. chronic hepatitis, cirrhosis.[6] Less commonly, it is raised in other cancers, e.g. gastrointestinal.
Human chorionic gonadotropin (hCG) – particularly beta hCG	Secreted during pregnancy but may also be produced by cancers originating in the placenta (gestational trophoblastic disease) or germ cell tumours of the ovary or testes.[7] It may also be secreted by some gastrointestinal malignancies.[7]
Cancer antigen 125 (CA 125)	May be raised in ovarian cancer, but also in other gynaecological conditions such as menstruation, pregnancy, benign ovarian cysts, endometriosis.[8, 9]
Cancer antigen 15-3 (CA 15-3)	May be raised in breast cancer or other malignancies, e.g. bowel, lung, ovarian, pancreatic.[10] May also be elevated in some non-malignant conditions, e.g. cirrhosis.[10]
Cancer antigen 19-9 (CA 19-9)	May be raised in cancers of the gastrointestinal tract, in particular pancreatic cancer.[11, 12] Can also be raised in some mucinous ovarian cancers.[12]
Carcinoembryonic antigen (CEA)	May be raised in bowel cancer or other malignancies, e.g. ovarian, breast, lung, gastric, pancreatic, or in non-malignant conditions, e.g. inflammatory bowel disease, cirrhosis.[13, 14] May also be elevated in people who smoke.[13, 14]
Lactate dehydrogenase (LDH)	May be raised in lymphoma or germ cell tumours, or in non-malignant conditions when there is cellular damage, e.g. hepatitis, kidney disease.[15]

Tumour markers in ovarian cancer

Ovarian cancer is the second most common gynaecological cancer in New Zealand after endometrial cancer, and has a higher mortality than all other gynaecological cancers combined.[16]

Cancer antigen 125 (CA 125) is a cell-surface glycoprotein that is raised in more than 80% of people with advanced epithelial ovarian cancer, and in half of those with early-stage disease.[8, 9] It is less commonly raised in people with non-epithelial ovarian cancers.[8] Some non-malignant conditions are also associated with elevated CA 125 levels. These may include conditions involving or inflaming the peritoneum, pericardium or pleura, e.g. endometriosis, pelvic inflammatory disease, ascites, recent abdominal surgery, pleuritis, pericarditis or congestive heart failure with pleural effusion.[8, 9] Menstruation and first-trimester pregnancy can also cause up to three-fold elevations in CA 125.[8]

The role of CA 125 has changed over time, and testing serum CA 125 levels is now indicated in primary care as part of the diagnostic workup of a patient with suspected ovarian cancer.[17] CA 125 is not used as a screening test for ovarian cancer in asymptomatic people (including those at high-risk) due to low sensitivity and specificity.[8, 9] Instead, it is used to determine which females presenting with symptoms suggestive of ovarian cancer should be prioritised for further assessment.

Higher levels of CA 125 should increase suspicion of malignancy and patients with elevated levels will generally require referral for a pelvic ultrasound. Malignancy is suggestive at a CA 125 level of > 200 U/mL, or at a level of > 65 U/mL in patients with an ovarian mass, but there is no level that is exclusively associated with cancer.[8]

The specificity and positive predictive value of CA 125 is higher in females who are post-menopausal, compared to those who are pre-menopausal; an elevated serum CA 125 level in younger females is less likely to be due to epithelial ovarian cancer.[17–19]

Occasionally after a diagnosis of ovarian cancer, CA 125 is used to monitor response to treatment.[8]

Other tumour markers in ovarian cancer

Human chorionic gonadotrophin (hCG), lactate dehydrogenase (LDH) and alpha fetoprotein (AFP) may be elevated in pre-menopausal females with a non-epithelial ovarian cancer.[17] Other tumour markers, such as human epididymis protein 4 (HE4) show potential for the detection of ovarian cancer in international studies, but are not yet available in New Zealand and further research is needed.[17]

For information on the diagnosis of ovarian cancer, see: **bpac.org.nz/2023/ovarian-cancer.aspx**

Tumour markers in bowel cancer

Bowel cancer is the most commonly diagnosed cancer in New Zealand, and is the second leading cause of cancer mortality after lung cancer.[16]

Carcinoembryonic antigen (CEA) is the tumour marker most commonly used, along with clinical review and other appropriate investigations, to detect bowel cancer recurrence.[13] It is not recommended as a screening or diagnostic test for bowel cancer due to low sensitivity and specificity.[13, 14]

Production of CEA begins and peaks during fetal development; then declines with age and is found in low levels in healthy adults.[14] Bowel cancer may increase CEA levels; however it is non-specific and levels can be raised in people with other malignancies including ovarian, gastric, pancreatic, lung and breast cancer.[13, 14] In addition, not all people with bowel cancer have raised CEA levels.[13] CEA may also be elevated in other conditions including inflammatory bowel disease, pancreatitis and cirrhosis, and in people who smoke.[13, 14]

Very high CEA levels are usually associated with metastatic disease.[13] However, tumour differentiation also influences CEA levels but in an inverse relationship; CEA is more likely to be produced by a well differentiated bowel cancer than a poorly differentiated tumour.[13]

In general, the main application of CEA is for the monitoring of patients after surgical resection for bowel cancer to detect recurrence. However, pre-operative and early post-operative results do have prognostic significance. People with higher pre-operative levels tend to have a poorer prognosis as they are often diagnosed with more advanced bowel cancer.[13, 14] A pre-operative level > 5 micrograms/L is associated with a higher rate of recurrence and cancer-related mortality.[13]

A reduction in CEA levels post-operatively is associated with a good prognosis. In contrast, a CEA level that does not return to normal (e.g. within one month) following surgical resection, is associated with poorer survival and suggests residual or recurrent disease.[13, 14] Levels that are increasing or > 10 micrograms/L should prompt more urgent clinical review and investigations for recurrence.[13]

Recommendations for how frequently patients should have a CEA level requested post-operatively vary between international guidelines. The testing frequency will usually be determined for each patient by their secondary care specialist based on their specific clinical circumstances.

For further information on the follow-up and surveillance for patients after treatment for bowel cancer, see: **bpac.org.nz/2021/bowel-cancer.aspx**

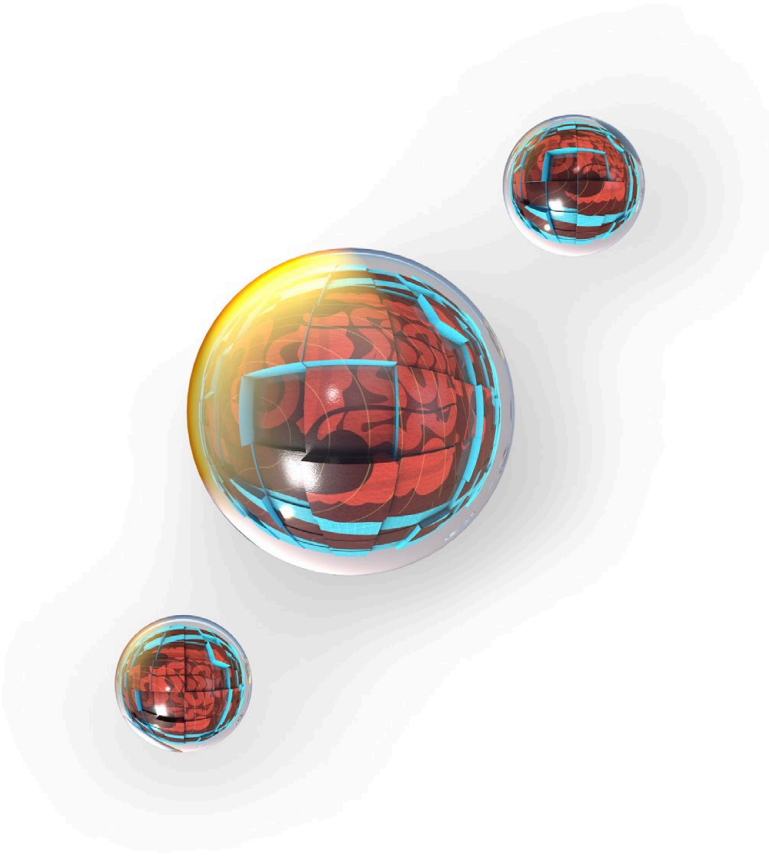
Tumour markers in testicular cancer

Testicular cancer accounts for a small proportion of the total cancer diagnoses in New Zealand; in 2020, 1.4% of all cancer diagnoses in males were testicular.[16] However, it is the most common solid tumour in younger males, and incidence is increasing.[20, 21]

Approximately 95% of testicular cancers originate in primordial germ cells and are classified into two main types: seminomas or non-seminomas.[20, 21] Most non-seminomatous tumours are associated with elevated levels of one or more of serum AFP, beta hCG and LDH, while only beta hCG and LDH are useful markers in people with seminomas.[6, 20] These tumour markers are non-specific and may also be raised in conditions other than testicular cancer, e.g.:[6, 7, 15]

- AFP: liver cancer, cirrhosis
- hCG: ovarian germ cell tumour, gastrointestinal cancer
- LDH: lymphoma, germ cell tumours, hepatitis

As part of the diagnostic workup of a patient with suspected testicular cancer, international guidelines and some local HealthPathways recommend testing AFP, beta hCG and LDH.[21] These results also help to inform staging, prognosis and management decisions in a patient with testicular cancer.[20, 21]

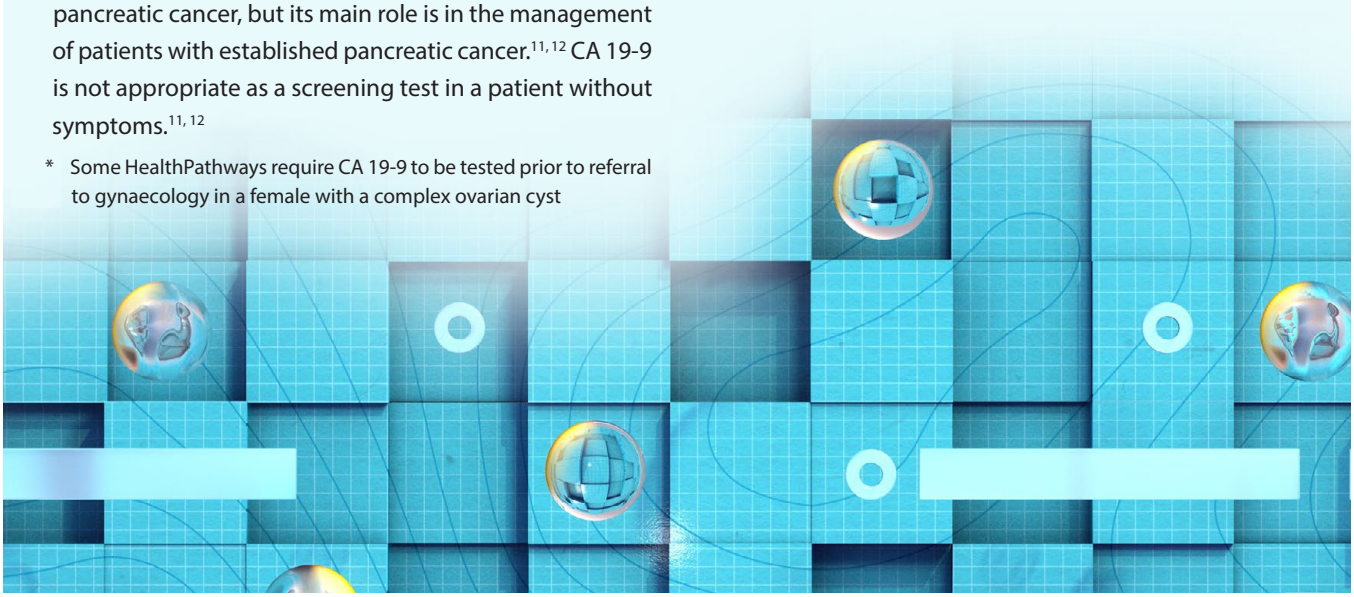


The use of tumour markers CA 19-9 and CA 15-3

CA 19-9 is a tumour marker that is elevated in approximately 80% of people with pancreatic cancer.[11] It may also be raised in other gastrointestinal tract malignancies such as biliary, liver, bowel and gastric cancers, or in non-malignant conditions, e.g. cholecystitis, cirrhosis.[11, 12] CA 19-9 may also be elevated in some mucinous ovarian cancers.*[12] CA 19-9 may be requested to aid in the diagnosis of a patient with suspected pancreatic cancer, but its main role is in the management of patients with established pancreatic cancer.[11, 12] CA 19-9 is not appropriate as a screening test in a patient without symptoms.[11, 12]

* Some HealthPathways require CA 19-9 to be tested prior to referral to gynaecology in a female with a complex ovarian cyst

CA 15-3 is a tumour marker that is elevated in some people with breast cancer.[10] Levels can also be elevated in other malignancies, e.g. bowel, pancreatic, lung or ovarian cancer, or non-malignant conditions, e.g. cirrhosis.[10] CA 15-3 is not an appropriate screening or diagnostic test for breast cancer due to low sensitivity and specificity.[10] Instead, it is most useful for the monitoring of a patient after treatment for breast cancer.[10]



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References

1. Sonic Healthcare Limited. Tumour markers. In: Sonic pathology handbook. Available from: https://www.sonicedu.com.au/publications/document/5cce50/048e0f (Accessed May, 2023).
2. Srinivasan S, Boran G. Laboratory testing for tumour markers. 2017. Available from: https://www.hse.ie/eng/about/who/cspd/ncps/pathology/resources/lab-testing-for-tumour-markers1.pdf (Accessed May, 2023).
3. Sarhadi VK, Armengol G. Molecular biomarkers in cancer. Biomolecules 2022;12:1021. doi:10.3390/biom12081021
4. The Royal College of Pathologists of Australasia (RCPA). Position Statement - Serum tumour marker requesting, testing and reporting of results. 2020. Available from: https://www.rcpa.edu.au/getattachment/4b603b63-29f8-4f9b-856f-4141ffed9749/Serum-Tumour-Marker-Requesting,-Testing-and-Report.aspx (Accessed May, 2023).
5. Choosing Wisely Australia. Recommendations from The Royal College of Pathologists of Australasia. Available from: https://www.choosingwisely.org.au/recommendations/rcpa4 (Accessed May, 2023).
6. Sonic Healthcare Limited. Alpha fetoprotein (AFP). In: Sonic pathology handbook. 2014. Available from: https://www.sonicedu.com.au/publications/document/5cce50/53f7b6 (Accessed May, 2023).
7. Sonic Healthcare Limited. Human chorionic gonadotrophin (hCG). In: Sonic pathology handbook. 2014. Available from: https://www.sonicedu.com.au/publications/document/5cce50/67158f (Accessed May, 2023).
8. Sonic Healthcare Limited. Cancer antigen 125 (CA 125). In: Sonic pathology handbook. 2014. Available from: https://www.sonicedu.com.au/publications/document/5cce50/3e967d (Accessed May, 2023).
9. Scottish Intercollegiate Guidelines Network (SIGN). Management of epithelial ovarian cancer: a national clinical guideline. 2013 (revised 2018). Available from: https://www.sign.ac.uk/media/2010/sign135_oct2022.pdf
10. Sonic Healthcare Limited. Cancer antigen 15-3 (CA 15-3). In: Sonic pathology handbook. 2014. Available from: https://www.sonicedu.com.au/publications/document/5cce50/a6ff70 (Accessed May, 2023).
11. O'Neill RS, Stoita A. Biomarkers in the diagnosis of pancreatic cancer: are we closer to finding the golden ticket? World J Gastroenterol 2021;27:4045–87. doi:10.3748/wjg.v27.i26.4045
12. Sonic Healthcare Limited. Cancer antigen 19-9 (CA 19-9). In: Sonic pathology handbook. Available from: https://www.sonicedu.com.au/publications/document/5cce50/bded57(Accessed May, 2023).
13. Hall C, Clarke L, Pal A, et al. A review of the role of carcinoembryonic antigen in clinical practice. Ann Coloproctol 2019;35:294–305. doi:10.3393/ac.2019.11.13
14. Sonic Healthcare Limited. Carcinoembryonic antigen (CEA). In: Sonic pathology handbook. 2014. Available from: https://www.sonicedu.com.au/publications/document/5cce50/3a661a (Accessed May, 2023).
15. Sonic Healthcare Limited. Lactate dehydrogenase (LD). In: Sonic pathology handbook. 2014. Available from: https://www.sonicedu.com.au/publications/document/5cce50/ddaccd (Accessed May, 2023).
16. Ministry of Health NZ. Cancer: historical summary 1948–2022. Available from: https://www.health.govt.nz/publication/cancer-historical-summary-1948-2020 (Accessed May, 2023).
17. National Institute for Health and Care Excellence (NICE). Ovarian cancer: the recognition and initial management of ovarian cancer. 2011. Available from: https://www.nice.org.uk/guidance/cg122/evidence/full-guideline-pdf-181688799.
18. Sundar S, Neal RD, Kehoe S. Diagnosis of ovarian cancer. BMJ 2015;351:h4443. doi:10.1136/bmj.h4443.
19. Doubeni CA, Doubeni AR, Myers AE. Diagnosis and management of ovarian cancer. Am Fam Physician 2016;93:937–44.
20. Sonic Healthcare Limited. Testicular pathology and testicular cancer. In: Sonic pathology handbook. 2014. Available from: https://www.sonicedu.com.au/publications/document/5cce50/8f801b (Accessed May, 2023).
21. Gilligan T, Lin DW, Aggarwal R, et al. Testicular cancer, version 2.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2019;17:1529–54. doi:10.6004/jnccn.2019.0058

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