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PATHOLOGY FOCUS
Medical Newsletter

July 2018 – Newsletter 2

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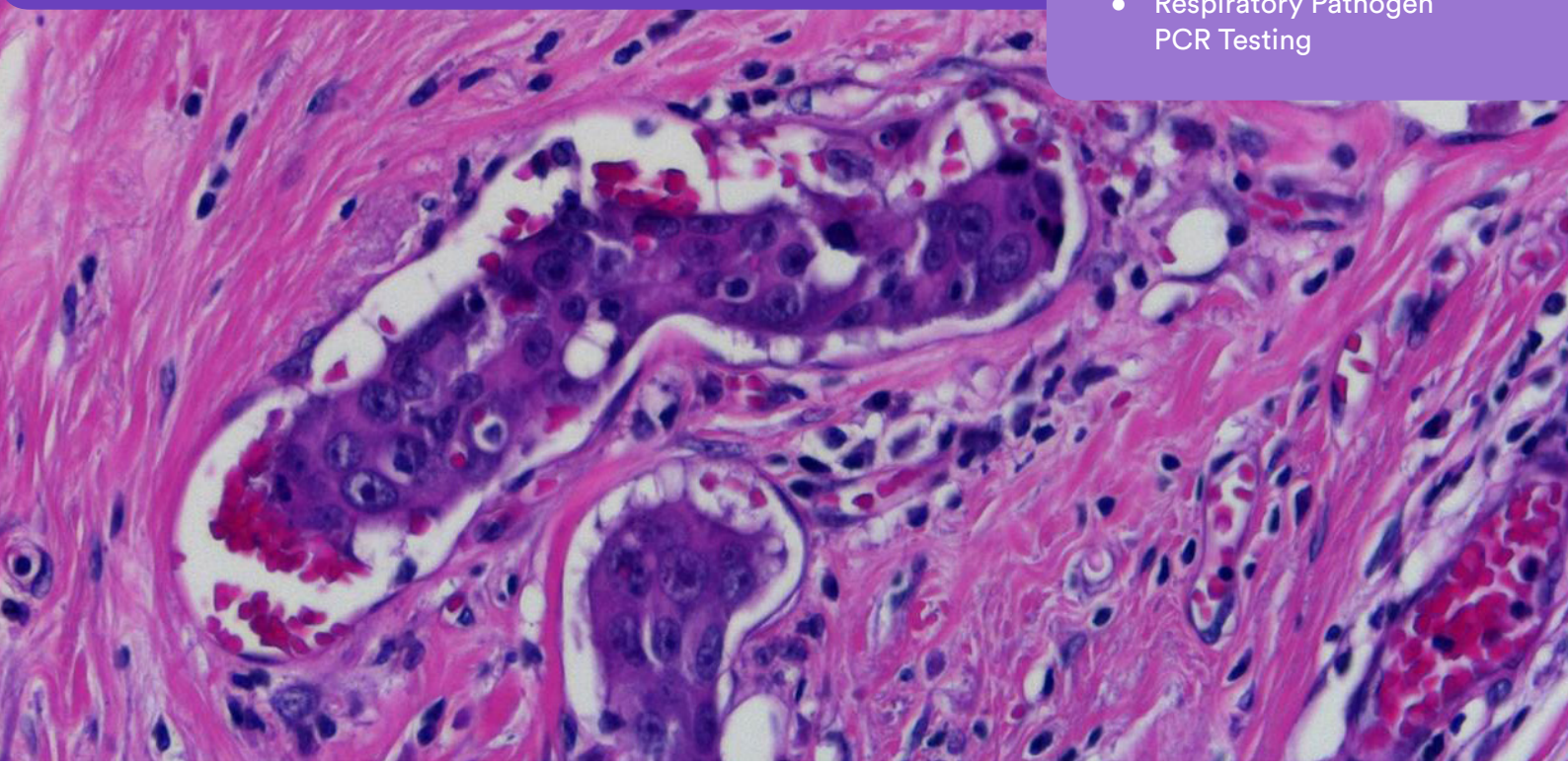

The vital role of breast cancer pathology in complex treatment decisions:

Interpreting breast cancer pathology reports and using molecular assays in ER positive breast cancer

Professor Sandra O'Toole

There has been a remarkable improvement in outcomes from breast cancer over the past 2 decades, with a 90%, 5-year survival. Detection of earlier stage lesions through mammographic screening has played a role, as has the use of biologically targeted treatments such as tamoxifen and aromatase inhibitors for estrogen receptor (ER) positive cancers and HER2 targeted therapies in HER2 amplified breast cancers. Chemotherapy and radiotherapy have also reduced the risk of breast cancer recurrence and death. Multi-disciplinary care has contributed through better communication between members of the clinical team. However, patients and their treating doctors must make complex, personalised decisions and information from the pathology report plays a vital role in determining the type of treatment and prognosis for the patient.

This article will highlight the impact of key information from a pathology breast cancer report and will also update practitioners on the use of molecular prognostic tools such as Endopredict and Oncotype Dx to assist with adjuvant therapy decision making in ER positive breast cancer.

First diagnosis of early breast cancer:

Breast cancer diagnosis is made through the "triple test" – correlating clinical and imaging features with a tissue pathology diagnosis. Fine needle aspiration can be used to confirm a diagnosis of malignancy but cytological preparations do not provide a reliable distinction between ductal carcinoma in situ (DCIS) and invasive carcinoma and also generally does not allow determination of hormone and Her2 receptor status. Increasingly, needle core biopsies are used to make the tissue diagnosis which allows pre-operative assessment of tumour grade, type (invasive or DCIS, lobular or ductal invasive carcinoma) and receptor status, which assists with decisions about potential neoadjuvant chemotherapy as well as planning for surgery.

The definitive excision report:

Detailed pathological assessment of the definitive excision specimen (whether a wide local excision or a mastectomy) provides a wealth of information on prognosis for the patient to guide further decisions about adjuvant therapy (chemo- and radiation therapy) or additional surgery. Pathology reports use a structured approach to ensure all key information is included but can be quite long. Some of the most important information is explained below:

Breast cancer type and grade:

Invasive carcinoma is most commonly ductal carcinoma of no special type, with invasive lobular carcinoma the next most common. Invasive lobular carcinoma may show more extensive disease than appreciated clinically, or on imaging pre-operatively, and is useful for this identification to assist with planning surgery.

Tumour grade is a measure of tumour differentiation and is an important prognostic variable that influences decisions about additional treatment such as chemotherapy. Grading takes into account the ability of the tumour to make glands, the degree of nuclear pleomorphism and the proliferative rate measured by counting mitoses (Figure 1 – grade 1 invasive carcinoma, Figure 2 – grade 3 invasive carcinoma).

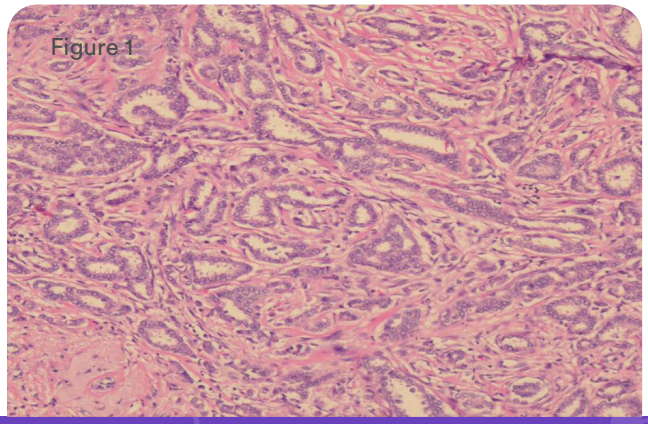
Figure 1

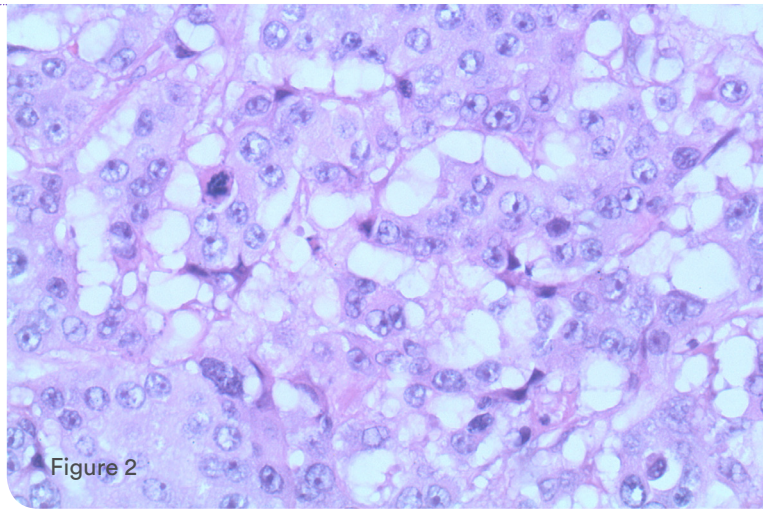
Figure 2

Identification of invasive carcinoma within the blood vessels or lymphatics, lymphovascular invasion is an adverse prognostic finding and may influence the use of chemotherapy (See cover image).

Ductal carcinoma in situ (DCIS) is commonly seen in association with invasive carcinoma or alone. Detailed assessment of DCIS nuclear grade may also impact decisions regarding further surgery and/or radiotherapy. Descriptions of association with microcalcification (as commonly seen with necrosis in high grade DCIS) allow correlation with mammographic findings and may be helpful in monitoring patients by imaging in follow up.

Margins:

Complete excision of both invasive carcinoma and DCIS is the goal of surgery and involved margins identified in the pathology report may prompt discussion in the clinical team and with the patient about the need for further surgery or radiotherapy.

Staging:

In early breast cancer, this is primarily based on the size of the invasive carcinoma and the status of the associated axillary lymph nodes. For patients with clinically node negative disease, sentinel lymph node biopsies are often used to assess the nodal status. In some cases, often those patients with higher risk tumours, an intraoperative "frozen section" will be performed proceeding to axillary lymph node dissection in the same procedure if positive (Figure 3 –metastatic carcinoma in a lymph node). In others, the sentinel nodes will be assessed post-operatively with the definitive breast excision specimens. The most recent international staging system (AJCC 8th Edition) also incorporates grade, hormone and HER2 receptor status to assign a prognostic stage, highlighting the significant impact of targeted therapies on outcome.

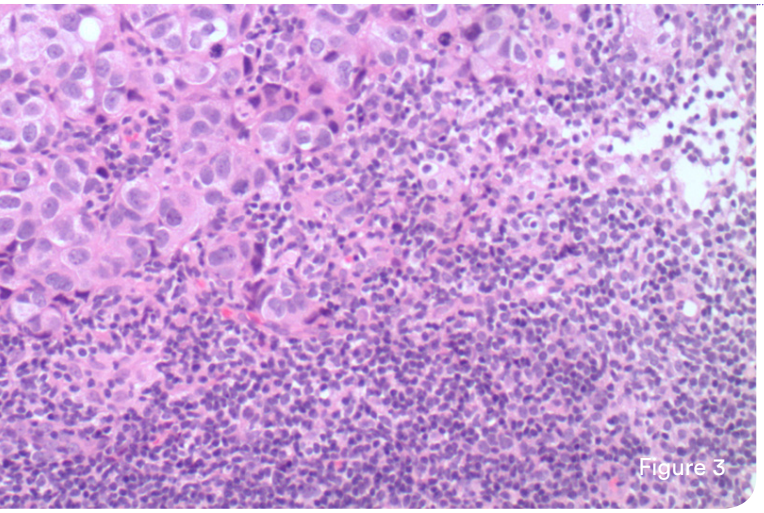

Figure 3

Hormone and HER2 receptors:

The hormone receptors for estrogen (ER) and progesterone (PR) are detected by immunohistochemistry in formalin fixed, paraffin embedded sections of invasive breast cancer and a positive result in as little as 1% of tumour nuclei showing expression (Figure 4 – ER positive case). Proper handling of the specimen including optimal fixation is essential for reliable results. Around 80% of invasive carcinomas are ER positive with higher grade tumours less likely to be positive.

HER2 is assessed by immunohistochemistry (IHC) and by in situ hybridisation (ISH) where a DNA probe is used to directly label the HER2 gene and count the number of copies present. Around 15% of invasive breast carcinomas show amplification (extra copies) of the HER2 gene and these patients may receive HER2 targeted therapies such as trastuzumab. It has been estimated that the use of HER2 targeted therapies has resulted in a 50% reduction in death from this previously poor prognosis subtype of breast cancer. It is critically important to identify these patients so they receive the correct treatment, again highlighting the importance of optimal fixation and handling of breast cancer pathology specimens.

Molecular assays in breast cancer:

Studies of gene expression conducted in the early 2000s highlighted the potential of molecular assays to provide additional information beyond traditional pathology about prognosis. A number of assays were developed including Oncotype Dx, Endopredict and the Prosigna assays among others. These assays have all been shown to provide useful prognostic information to ER positive patients about their risk of developing breast cancer recurrence and their use is supported by international guidelines. A recent large clinical trial using Oncotype Dx published in the New England Journal of Medicine (1) showed that women with ER positive, lymph node negative breast cancer over age 50 with low and intermediate scores had no difference in outcome when treated with endocrine therapy alone in comparison to the group who also received chemotherapy. This study highlights the clinical utility of molecular testing in sparing patients chemotherapy from which they are unlikely to derive significant benefit. Oncotype Dx is a first generation assay but a number of studies have shown that the second generation assays such as Endopredict (provided by Clinical Labs) which also incorporate clinical variables such as lymph node status and tumour size are better able to predict late recurrence (5-10 years post treatment) and may also identify a larger group of low risk patients (2,3).

These assays are not currently funded by Medicare in Australia and are a significant out-of-pocket cost but are worth discussing with suitable patients given the potential benefits.

Summary:

High quality pathology is a vital part of breast cancer diagnosis and management and molecular assays such as Endopredict can provide important additional information to support complex decision making about the use of chemotherapy in ER positive breast cancer.

To find out more about EndoPredict visit clinicallabs.com.au/endopredict

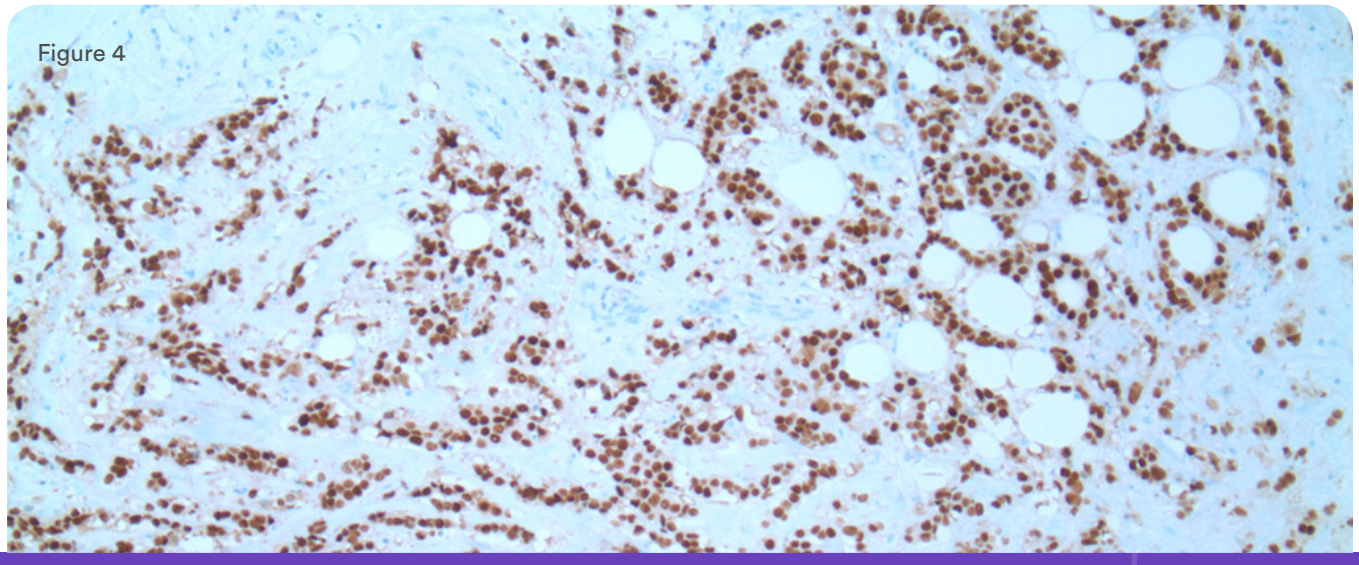

Figure 4

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1. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. Sparano JA, et al N Engl J Med. 2018 Jul 12;379(2):111-121.
2. Comparison of EndoPredict and EPclin With Oncotype DX Recurrence Score for Prediction of Risk of Distant Recurrence After Endocrine Therapy. Buus R, et al J Natl Cancer Inst. 2016 Jul 10;108(11).
3. Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor-Positive Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial. Sestak I, et al. JAMA Oncol. 2018 Apr 1;4(4):545-553.

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Professor O'Toole is recognised as one of Australia's leading molecular pathologists, with major research and diagnostic interests in breast cancer as well as the molecular pathology of melanoma and lung cancer. She was an expert member of the working group for Cancer Australia on Influencing Best Practice in Breast Cancer and is a National Breast Cancer Foundation Practitioner Fellow. Professor O'Toole is Clinical Professor at Sydney Medical School and head of Breast Cancer Translational Research at the Garvan Institute of Medical Research where she collaborates with researchers and clinicians nationally and internationally to promote the rapid translation of scientific discoveries. Her work has appeared in more than 100 scientific publications and she has secured over $20 million in research funding as a chief investigator. She is Chair of Cancer Services for the Royal College of Pathologists of Australasia.

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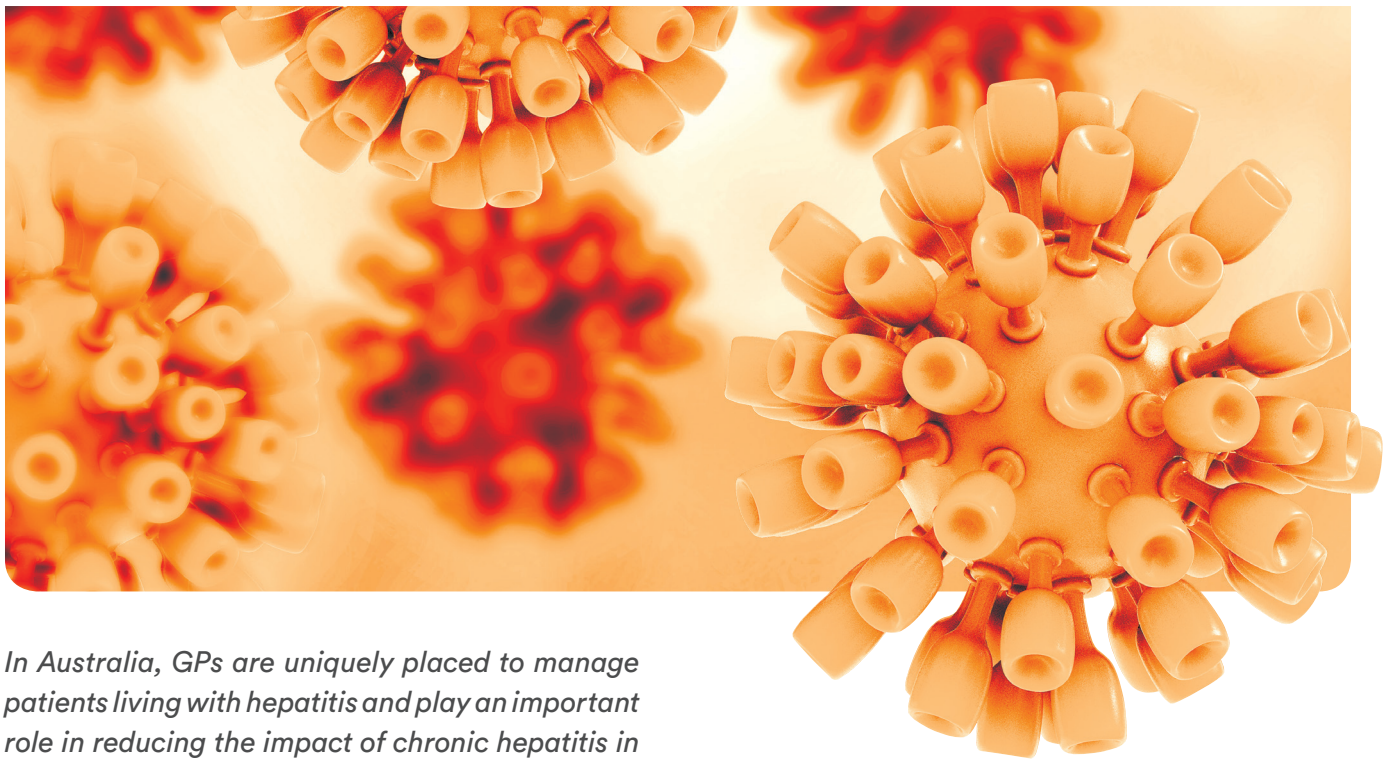
The A-B-Cs of Diagnosing Viral Hepatitis in General Practice

Dr Stella Pendle



In Australia, GPs are uniquely placed to manage patients living with hepatitis and play an important role in reducing the impact of chronic hepatitis in the community. Due to the often sensitive nature of the condition, GPs have a greater chance of identifying individuals living with viral hepatitis.

Hepatitis can be caused by the classical hepatitis viruses (hepatitis A, hepatitis B, hepatitis C, hepatitis D, and increasingly, hepatitis E) as well as other viruses (especially CMV and EBV).

Briefly outlined in this article are five common viruses, and how our pathology services can help you diagnose your patients suffering from hepatitis.

> **The diagnosis of hepatitis A may be established by serological testing.**

Hepatitis A

Hepatitis A is transmitted by the faecal–oral route through close person-to-person contact or after ingestion of food or water contaminated by the hepatitis A virus (HAV). Being a small non-enveloped virus, it can withstand environmental stress and maintain its infectivity. The incubation period is usually 30 days, but can be between 15 to 50 days.

It usually does not cause chronic infection, but in patients who are immunosuppressed, prolonged viral replication can be observed. While usually self-limiting, patients with other liver pathology may present with severe disease.

Diagnosis & Prevention:

The diagnosis of hepatitis A may be established by serological testing.

If acute hepatitis A infection is suspected, request HAV IgM, as this is a marker of acute infection. For routine screening or immunisation status HAV total antibody (HAV Ab) should be requested. Hepatitis A vaccination is recommended for travellers to endemic countries and other high risk groups, e.g. men who have sex with men. Routine serology testing after HAV vaccination is not recommended.

Hepatitis B

Hepatitis B virus (HBV) can be transmitted by contact with infected blood or body fluids containing the virus, including semen and saliva, or by contaminated needles. The incubation period is usually 45 to 180 days. HBV may also be transmitted vertically between an infected mother and her neonate, usually at the time of birth (vertical transmission).

Diagnosis & Prevention:

The majority of adults will recover with clearance of the virus from the blood after a few months. The development of chronic hepatitis B occurs when there is a failure of the immune response to eradicate the virus. A highly effective hepatitis B vaccine is available. Testing for HBV should be performed routinely as part of an antenatal screen on all pregnant women (request hepatitis B surface antigen - HBsAg). Serological testing for evidence of past or current hepatitis B can be performed on individuals at risk, including injecting drug users, sex industry workers, immunocompromised persons and migrants. Routine post-immunisation testing for hepatitis B is not recommended except in high risk groups.

Hepatitis C

Hepatitis C is transmitted through exposure to body fluids containing the hepatitis C virus (HCV). The incubation period can range from two weeks to six months, though a six to nine week incubation period is common. Chronic infection can occur in up to 70% of individuals while up to 30% will spontaneously resolve their infection. All persons with risk factors should have a serology test for HCV antibody. Both chronic carriers and those who have resolved the infection will remain HCV antibody positive for life.

Diagnosis & Treatment:

Because HCV is a major cause of chronic liver disease, cirrhosis and liver cancer, it is essential to diagnose chronically infected people so that treatment can be provided. Direct acting antiviral treatment for chronic hepatitis C is highly effective and well tolerated. Approximately 95% of patients will be cured. The treatment is available on the PBS and has a wide prescriber base that includes GPs.

Persons at risk of contracting a blood borne disease should be tested for hepatitis C as should persons with chronic liver disease or abnormal liver enzymes. Patients should be screened initially with a hepatitis C antibody test (HCV ab) and if this is positive, confirmed with a molecular test (HCV PCR) and genotyping.

Molecular testing for hepatitis C is also useful in diagnosing early acute infection when the serology may be negative or equivocal due to the long window period. This is a Medicare rebateable item, provided the test has not been performed in the previous 12 months. Genotyping may also be performed on HCV PCR positive patients who are awaiting treatment.

There is currently no vaccination for hepatitis C, however people who have been diagnosed or are at high risk are recommended to be vaccinated against hepatitis A and B.

Hepatitis D

Hepatitis D virus (HDV) also known as delta virus is only detectable in HBV infected individuals as it requires HBV to replicate. Transmission is the same as HBV but it is uncommon in Australia. It should be considered in chronic HBV carriers who have an exacerbation of their liver disease.

Hepatitis E

Hepatitis E virus (HEV) is transmitted by the faecal-oral route after ingestion of contaminated food and water. Although classically thought to be a disease seen in travellers returning from the developing world, it has been increasingly described in Europe especially in relation to pig farming and may be underdiagnosed in Australia. Hepatitis E infection is a serious disease in pregnancy and may lead to fulminant liver failure in up to 20% of cases.

Diagnosis:

Hepatitis E infection may be diagnosed by antibody testing followed by HEV PCR if other tests for hepatitis (A, B and C) are negative.

Cost

Medicare Bulk Billing available.

Hepatitis E infection may be diagnosed by antibody testing followed by HEV PCR if other tests for hepatitis (A, B and C) are negative.

Diagnostic Recommendations

The provision of clinical notes greatly aids in the correct test assignment. Where it is unclear what tests should be performed, request "Hepatitis Serology" and the laboratory will assign testing based on the clinical notes.

- All of the serological testing can be performed on serum samples. PCR testing requires a dedicated tube.
- Please refer to the table below for guidance.

There are a range of tests available to diagnose viral hepatitis:

Clinical Notes	Test Request
Acute hepatitis	HAV IgM, HBsAg, HBV core antibody (HBcAb), HCV Ab
Routine hepatitis screen	HB sAg HCVAb, HAV Ab
Monitoring infection or response to therapy	HBsAg, HBeAg, HBcAb, HCV Ab Consider HBV DNA, HCV PCR & genotyping Monitor LFTs
Determination of immunity	HBV surface antibody (HBsAb), HAV Ab
Antenatal screen	HBsAg, HCV Ab

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Areas of interest: Antimicrobials, Infection Control and Molecular Diagnostic Assays in Contemporary Clinical Microbiology

Correction

In our last edition, we mistakenly referred to A/P Mirette Saad as a Molecular Genetic Pathologist.

Mirette is a Chemical Pathologist, with interests in: Molecular Genetics & Precision Medicine, Antenatal Screening & NIPT, Fertility and Endocrine Testing. She is the National Clinical Director of Molecular Genetic Pathology at Australian Clinical Labs.

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Respiratory Pathogen PCR Testing

In Australia, the arrival of the winter months often sees a spike in respiratory disease among the population, with the young, elderly and patients with compromised cardiac, pulmonary or immune systems at greatest risk of serious disease.

Approximately 15% of pneumonias in children are caused by Parainfluenza Virus whilst an additional 20% are due to Respiratory Syncytial Virus (RSV) infection. RSV is the most commonly identified agent in 75% of children under two years of age who are hospitalised for bronchiolitis. Early identification is vital to support more timely clinical management and minimise progression to more serious illness.

Australian Clinical Labs is now offering a rapid respiratory viral assay that detects 10 viral respiratory pathogens improving identification of the causative agent, allowing the clinician to instigate appropriate treatment in a more timely manner.

	>>> RAPID TEST >>>		
What to request:	**"Rapid Flu"**	**"Respiratory Viral Screen"**	**"Multiplex PCR"**
Turnaround time:	**24 hrs - Urgent**	**24 hrs - Urgent**	**> 24 hrs**
Tests included:	Influenza A & B RSV (A&B)	Influenza A & B RSV (A&B) Parainfluenza 1, 2, 3, & 4 Human Metapneumovirus Human Adenovirus Human Rhinovirus	Influenza A & B RSV (A&B) Parainfluenza 1, 2 & 3 Human Metapneumovirus Human Adenovirus Human Enterovirus/Rhinovirus Mycoplasma pneumoniae Bordetella pertussis Bordetella parapertussis

Benefits to the patient

Assists in the specific and differential diagnosis of acute respiratory tract infections.

- Increased assay specificity and sensitivity improves the accuracy and speed of diagnosis.
- Enables the clinician to instigate earlier targeted treatment of viral or bacterial infections avoiding inappropriate antibiotic therapy.

Flu A & B **99.3% Sensitivity** **Specificity 98%**

Samples required (One of the below)

- Nose/throat or nasopharyngeal swab(s) (must use dry flocked swab) ***or***
- Nasopharyngeal/tracheal aspirates ***or***
- Sputum

Test ordering

Our rapid respiratory viral assay is performed daily, 7 days a week, during flu outbreaks. To assist the laboratory during flu outbreaks, please limit testing to suspected pathogens to ensure rapid result delivery.

If influenza or RSV testing is required, urgently order "**Rapid Flu**".

If investigation for bacterial respiratory infective agents is required, please specify "**Multiplex PCR**".

Cost

Medicare bulk billing available and subject to Medicare guidelines and criteria.

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