ePathWay
THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

AUGUST 2019 | PUBLISHED BY RCPA ISSUE #094

IN THIS ISSUE

INTERESTING FACTS

210,000

number of people affected by Hepatitis C in Australia[1]. In New Zealand more than 50,000 people have the virus[2].

2030

the target year for the elimination of Hepatitis C

30–100 million

the estimated number of people infected with strongyloidiasis worldwide[3].

Source:

[1] Burnet Institute and Kirby Institute.Australia's progress towards hepatitis C elimination: annual report 2019.

Welcome to the August issue of ePathWay

ePathway is an e-magazine designed for anyone interested in their health and wellbeing and the integral role pathology plays in the diagnosis, treatment and management of diseases.

This month's issue of *ePathway* looks at the following:

- Copeptin, a new prognostic marker
- Strongyloidiasis in remote communities
- Pathology, it's in the blood
- The global challenge to eliminate Hepatitis C by 2030

The need for quicker and more accurate diagnosis in various diseases has led to investigations of new biomarkers, and Copeptin has emerged as a promising new tool for the diagnosis of a number of diseases. We spoke to Associate Professor David Sullivan, Head of Chemical Pathology at Royal Prince Alfred Hospital, to learn why Copeptin is becoming more frequently used as a surrogate to other biomarkers such as Anti-Diuretic Hormone (ADH).

Strongyloidiasis is one of the world's most neglected tropical diseases. With reports that the disease is common in remote communities here in Australia, we spoke with Associate Professor Rob Baird, Director of Pathology and Infectious Diseases Physician at Territory Pathology, to find out why researchers are calling for a ramped-up health response to this potentially deadly parasitic disease.

Doctor Alessandra Bianchi and Professor David Gottlieb met whilst working in the same research lab in London in 1986. This month, they both kindly took the time to speak with us for our regular, Pathology, it's in the blood feature. Now married and with a family, Alessandra is currently Staff Specialist in Charge, Laboratory Haematology at South Western Sydney Local Health District, whilst David is currently Professor of Haematology at the University of Sydney.

Hepatitis C is often referred to as a silent epidemic due to its asymptomatic nature. In 2016, the World Health Assembly (WHA) adopted the Global Health Sector Strategy on Viral Hepatitis 2016–2021, which set the overarching goal of the elimination of viral hepatitis as a major public health threat by 2030. We spoke with Dr Jenny

Melbourne: Burnet Institute; 2019.

[2] https://www.health.govt.nz/your-health/conditions-and-treatments/diseases-and-illnesses/hepatitis-c

[3] https://www.who.int/intestinal_worms/epidemiology/strongyloidiasis/en/

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Robson, microbiologist at Sullivan Nicolaides Pathology to understand how Australia became one of only a few countries worldwide that is on track to reach this elimination goal.

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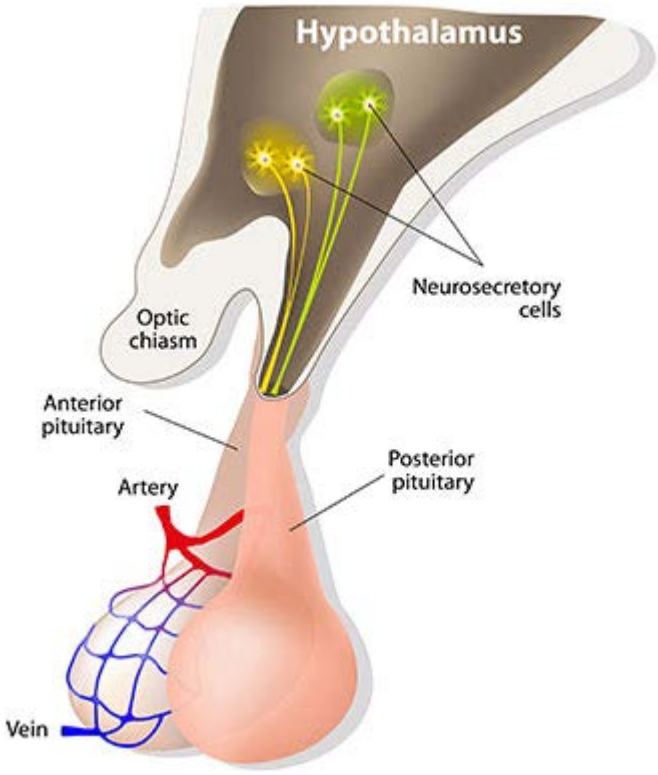
Copeptin, a new prognostic marker



Copeptin has recently emerged as a new prognostic marker in a variety of diseases such as sepsis, community acquired pneumonia, polydipsia, chronic obstructive pulmonary disease, heart failure and myocardial infarction. We spoke to Associate Professor David Sullivan, Head of Chemical Pathology, and Julie Sherfan, Senior Hospital Scientist, in the Department of Chemical Pathology at Royal Prince Alfred Hospital to learn why Copeptin is becoming more frequently used as a surrogate for other biomarkers such as Anti-Diuretic Hormone (ADH).

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Strongyloidiasis in remote communities

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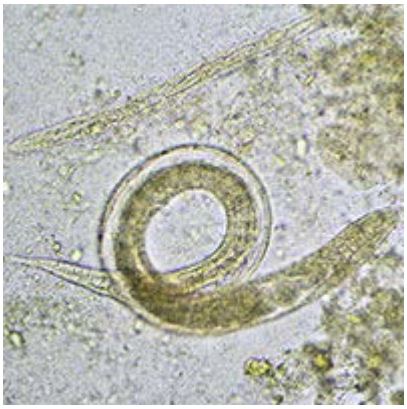

With reports that the disease is common in remote communities in Australia, we spoke with Associate Professor Rob Baird, Director of Pathology and Infectious Diseases Physician at Territory Pathology, to find out why researchers are calling for a ramped-up health response to this deadly parasitic disease.

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Pathology, it’s in the blood

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The global challenge to eliminate Hepatitis C by 2030

In 2016, the World Health Assembly (WHA) adopted the Global Health Sector Strategy on Viral Hepatitis 2016–2021, which has the overarching goal of eliminating viral hepatitis as a major public health threat by 2030. It is estimated that implementation of this strategy will prevent 7.1 million deaths worldwide between 2015 and 2030. By the end

of 2016, Australia was one of only a few countries worldwide which were on track to reach this elimination goal. We spoke with Dr Jenny Robson, microbiologist at Sullivan Nicolaides Pathology to understand more.

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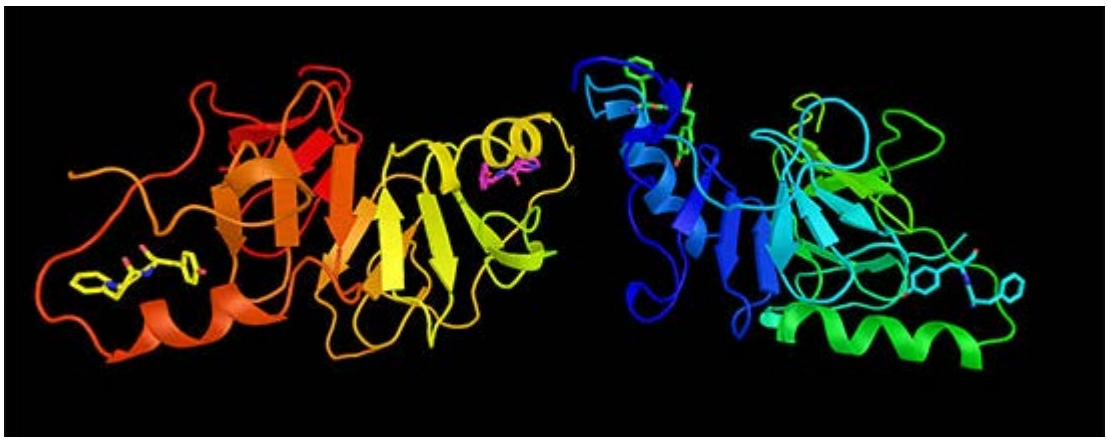
Copeptin, a new prognostic marker



Copeptin has recently emerged as a new prognostic marker in a variety of diseases such as sepsis, community acquired pneumonia, polydipsia, chronic obstructive pulmonary disease, heart failure and myocardial infarction. We spoke to Associate Professor David Sullivan, Head of Chemical Pathology, and Julie Sherfan, Senior Hospital Scientist, in the Department of Chemical Pathology at Royal Prince Alfred Hospital to learn why Copeptin is becoming more frequently used as a surrogate for other biomarkers such as Anti-Diuretic Hormone (ADH).

“ADH is one of the key hormones in the human body. It is secreted in response to circulatory stress and has a pivotal role in intravascular volume control. However, despite its clinical relevance, ADH is not often measured in clinical practice due to its short plasma half-life, interaction with platelets, and small size, which makes measurement difficult and subject to error. The need for robust and accurate diagnosis in various conditions related to ADH action has led to investigations of alternative biomarkers, and Copeptin has emerged as a promising new entity.”

“Copeptin is a hormone made by an endocrine part of the brain known as the hypothalamus. It is stored in the posterior pituitary gland and is released along with ADH in a 1:1 ratio. Since Copeptin directly reflects the concentration of ADH, it can be used as a surrogate marker of ADH secretion. Copeptin has been found to be more stable since ADH has a half-life of 5–20 min in plasma compared to 60-86 minutes for Copeptin,” said A/Prof Sullivan.

Copeptin has been found to be useful in a number of situations, including distinguishing people with Diabetes Insipidus (DI); a condition of water imbalance, from those with primary polydipsia; behavioural water drinking. There are two types of DI: Central

Diabetes Insipidus (CDI) and Nephrogenic Diabetes Insipidus (NDI). CDI occurs when the hypothalamus in the brain does not produce enough (or any) ADH. As a result, those affected produce large amounts of urine and will become dangerously dehydrated if they do not maintain an adequate intake of fluids. NDI occurs when there is damage to the kidneys and therefore the kidneys become unresponsive to ADH. A baseline morning blood sample for Copeptin can diagnose the two types CDI and NDI with 100 % accuracy.

“Traditionally, patients who are suspected of DI had to undergo a water deprivation test. The patient would be deprived of water for more than 16 hours, have urine collected every hour and blood collected every 3-4 hours. They would then be given desmopressin, a synthetic form of ADH, and have blood and urine collected for another two hours. This test is potentially dangerous because of the risk of dehydration and requires close monitoring of patients. With Copeptin, a morning baseline measurement is all that is required to diagnose the patient with CDI or NDI. Measuring Copeptin reduces the number of patients admitted to hospital for the water deprivation test and means that treatment can be initiated earlier.

“Analytically, the measurement of Copeptin is relatively quick with results reported to clinicians within the day. As the Copeptin molecule is larger than ADH, it is more stable and therefore does not require special blood collection tubes or collection conditions. NSW Health Pathology has replaced the ADH test with Copeptin as the preferred test for the diagnosis of Diabetes Insipidus (DI),” said Sherfan.

Copeptin measurement has been approved in the diagnosis of Acute Myocardial Infarction (AMI). Whilst it does not have specific diagnostic value in diagnosing AMI as a stand-alone test, it is proposed to ‘fill in the gap’ between the onset of symptoms and the detectability of troponin. The Copeptin level is high when troponin or other cardiac markers are not detectable. Copeptin measurement is thought to be useful in patients presenting within three hours after the onset of symptoms to assist with exclusion of AMI as the cause.

In patients with Chronic Kidney Disease (CKD), ADH secretion is proportional to the destruction of the cells in the kidneys. Copeptin measurement can be used in place of ADH to monitor progressive damage of the kidneys. It is currently used by dietitians to monitor and control water intake in patients with Polycystic Kidney Disease, with the premise that maintaining adequate water intake leads to better prognosis for this group of patients. Studies of Copeptin levels in patients with stroke have shown that those with high Copeptin levels have a higher risk of mortality and poor functional outcomes. Copeptin may also be useful to stratify patients with transient ischemic attacks (known as mini-strokes) and predict those that may go on to have a full stroke.

“Whilst there are obvious benefits to its use, Copeptin is a haemodynamic stress marker. This means many forms of adjustment in the body - be it after a meal, physiological or psychological stress - can cause Copeptin levels to change acutely, so this needs to be considered. Currently Copeptin is approved for use in DI and AMI only; however, the potential use of Copeptin as a biomarker in the diagnostic laboratory is already increasing. Improved awareness of its potential will most likely see it commonly used in routine laboratories,” said A/Prof Sullivan.

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Strongyloidiasis in remote communities

Strongyloidiasis is a soil transmitted parasitic infection. It is one of the world's most neglected tropical diseases and it exists in Australia[1]. With reports that the disease is common in remote communities in Australia, we spoke with Associate Professor Rob Baird, Director of Pathology and Infectious Diseases Physician at Territory Pathology, to find out why researchers are calling for a ramped-up health response to this deadly parasitic disease.

"Strongyloidiasis is a human infection which is caused by worms, the common species being Strongyloides stercoralis. Largely, it is associated with inadequate sanitation and spreads when there is human faeces in the open environment. The worms are shed in faeces and the infected larvae live in the soil for a short period of time. Consequently, if a person comes into contact with the contaminated soil then the worm can enter the body through the skin" said A/Prof Baird.

An estimated 30–100 million people are infected with strongyloidiasis worldwide; precise data on prevalence are unknown in endemic countries[2]. In Australia, strongyloidiasis is most commonly seen in those living in or travelling to Aboriginal communities, World War II veterans, refugees from Southeast Asia, and African and South American tropical and subtropical regions. Some remote Aboriginal and Torres Strait Islander communities in Australia have previously had prevalence of the disease reported in up to 60% of participants. The parasite is endemic in tropical Australia, defined as above the tropic of Capricorn.

"The presence of the parasite is directly associated with poverty. Unfortunately, the highest rates of strongyloidiasis tend to be in remote aboriginal communities which have numerous health hardware issues, from poor housing, unemployment, poor education,

drug and alcohol problems, overcrowding, and other disease burdens, all of these are inter-related issues.

“This particular worm is special as infections can be lifelong, and in particular patient groups. It is important to diagnose and treat strongyloidiasis quickly to prevent cases of fatal hyperinfection. Unless strongyloidiasis is deliberately considered, the diagnosis is not always made. Many infected people have no symptoms, and the worm can live inside a human for 30-40 years. One of the current issues with strongyloides infection is re-activation of the worm in later life when a person becomes immune suppressed; for example, if they have been on steroids or receiving chemotherapy. This can cause an overwhelming hyper-infection, which blocks up the lungs and brain and can be fatal.

“Interestingly, in the Northern Territory, we test and treat everyone who is undergoing chemotherapy as the infection is common and it is devastating if the worm reactivates. We assume that indigenous patients from remote communities have probably been exposed, as current diagnostics are not 100% reliable to determine inactive infection,” said A/Prof Baird.

Exposure to strongyloidiasis can be determined with a blood test. The infection may also be diagnosed by detecting larvae in a stool sample when examined under the microscope. Nucleic acid based diagnostic methods have also recently come to the fore as an alternative technique for diagnosing the disease, and may prove more sensitive. Once diagnosed the parasite can be treated with specific anti-worm medication, depending on the age of the person with the infection. For a community response, improvements in health hardware are required.

“In addition to use of individual anti-worming medication, there have been some really interesting developments in the past five years in regard to treatment. A drug commonly used for scabies, called ivermectin, has a secondary action as an anti-worming drug. There is developing evidence that in areas of high ivermectin use decreases in worm infections have occurred. It is suspected that this association is related because, unfortunately, the people who get scabies are the individuals most at risk for strongyloidiasis. This has been recognised in Queensland and the Northern Territory, so there may be a very beneficial secondary effect of treating scabies with newer agents. However, it is important to note that improvements in sanitation is the best way to prevent strongyloidiasis. Improving aboriginal socio-economic circumstances would be just as beneficial as concentrating on individual diseases such as this,” said A/Prof Baird.

References:

[1] https://nt.gov.au/wellbeing/health-conditions-treatments/parasites/strongyloidiasis

[2] https://www.who.int/intestinal_worms/epidemiology/strongyloidiasis/en/

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Doctor Alessandra Bianchi

"When I was studying, I did a rotation in a haematology department in Bergamo, my home town in Italy, and this is when I discovered pathology. During my time there I became very interested in the interplay that haematology has with its laboratory component. My interest grew into a passion and in 1985 I specialised in haematology in Italy where I focused on allogeneic bone marrow transplantation. It's a very challenging area from a clinical perspective, but also a very interesting and evolving area of research into the pathophysiology of engraftment, rejection and recurrence of disease.

"In 1990, I migrated to Australia after a few years doing research at the Royal Free Hospital in London. Upon arriving in Australia, it was my aim to have my qualifications recognised right away, however RCPA guidelines stated that more laboratory training was needed along with an examination. This was quite a challenge for me as my haematology training in Italy was very focused on the clinical side. Unfortunately, I had to postpone this goal for few years while I had three children and managed health problems.

"Finally, in 1997, a friend who is an Infectious Disease (ID) specialist at Concord, asked

if I was interested in an ID training position in his Department. I was so desperate to be able to go back to work that I accepted, even if that meant starting from scratch. By absolute chance, there was a vacancy in a haematology training position in the same hospital, so when I was approached by the head of department, I very happily accepted. After 2.5 years of working and studying full time with three young kids I managed to pass the RCPA examination and I eventually started working at Concord as a Laboratory Haematologist with a newly discovered passion for morphology, coagulation and blood banking. Though it has been 18 years since, I still remember saying to David shortly after we arrived in Australia, 'over my dead body I'm going to spend my life at a microscope!" Famous last words.

"David and I met when we were working in the same research lab in London. I used to live a long train ride from the Royal Free Hospital and, at times, some of my experiments finished late in the evenings and I was anxious about the journey home alone on the dark streets. David was sharing a gorgeous apartment in Hampstead close to hospital and when one of the tenants left, he asked me if I wanted to move in. I discovered the "Australians" and how much fun they are and some months later a romance was born!

"For the most part, our personalities are different. I am much quieter and love to take weekend trips down to Jervis bay and lose track of time by gardening or reading books or through creating textile art pieces. Though I favour order and organisation, I can be moody and inconsistent too. While he is quiet too, David is charming, gregarious and has a beautiful sense of humour. He is a strong workhorse, hugely dedicated to his work and is the backbone of our family. "Pathology is the backbone of clinical medicine. It helps to achieve a diagnosis, understand the prognosis or severity of a disease and it allows us to monitor progression or treatment. Many of our most important modern treatments were born from understanding the specific pathophysiology of the disease. We now have medications that target the specific mutation or abnormal pathway that results from a mutation. Pathology is in a constant state of development and expansion with almost limitless possibilities for improvement."

Professor David Gottlieb

"I didn't always to plan to go into medicine but there were a lot of doctors in my family and I suppose it was a natural evolution for me to follow the same path. I had a lot of good role models growing up, so I think that is what set me on the same course. When it comes to pathology, I initially had a keen interest in haematology, but I was more interested in the clinical side not so much pathology at all! However, at that time part of the training to be a haematologist required joint clinical and lab training, so I was more or less forced to do it. I'm pleased I was led down this path as I it turned out I really enjoyed pathology, especially once I understood its relevance.

"I realised that pathology was a really important branch of medicine, and that almost everything in medicine relies on it in some form or another. Everybody uses pathology testing to diagnose and treat patients which is something I learnt during my training. I realised the huge significance and relevance that pathology has on all branches of medicine which was the gradual awakening for me.

"Alessandra and I chose very different areas of interest in pathology which means that work issues aren't covered too much at home. At night we may tell each other about the things that we've done during the day and discuss some of the problems, but we rapidly conclude that most of the things that happen in hospitals are insoluble and move onto other things. I don't think there is one personality that fits pathology. Alessandra and I definitely don't have similar personalities, I would say she is much more focused on specifics than I am. I think of myself as the big picture person and she tends to sweat the detail – we balance each other out!

"Perhaps it seems unusual to have a husband and wife who are both pathologists, but I don't think it's so uncommon for people to find their partner at a time when they are working together - it's probably a lot more common than people realise. We were both doing research when we met in London, and I know a number of other couples that met under similar circumstances. Having similar areas of focus and interests can be further binding, it's the same for other professions beyond the medical realm.

“Fundamentally, pathology is important because it underpins every branch of medicine that there is. There is almost nothing in the current day, including psychiatry, which doesn’t have pathology as a very core part of its function, including the diagnostics, the therapeutics, the treatment, the information about pathogenesis of disease. All of this comes down, in some form (and often in very large form), to pathology. That’s why pathology is one of the bedrock disciplines of medicine; because in its absence, every doctor would be a whole lot poorer and his or her patients would be a whole lot worse off.”

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The global challenge to eliminate Hepatitis C by 2030

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“Hepatitis C virus (HCV) primarily affects the liver. Like Human Immunodeficiency Virus (HIV) and Hepatitis B, Hepatitis C is a blood-borne virus, passed on by blood-to-blood contact. Similar to Hepatitis B virus, and in contrast to other hepatitis viruses such as Hepatitis A and Hepatitis E, infection can become chronic. This occurs in 70-80% of individuals who are infected and can lead to inflammation of the liver causing fibrosis or scarring, cirrhosis, liver failure and subsequent increased risk of liver cancer and early death. HCV has been the most common reason for liver transplant in Australia.

“It is estimated that about 210,000 individuals in Australia[1], or 1% of the population, is infected. In New Zealand more than 50,000 people have the virus[2]. Individuals may remain asymptomatic for years and it is thought that up to 20% of those living with Hepatitis C remain undiagnosed. Unless pathology testing is performed to detect this lurking virus, many people will remain unaware that they are infected,” said Dr Robson.

The most common modes of HCV infection are through exposure to small quantities of infected blood. In Australia this occurs most commonly through injecting drug use. Prior

to 1992 and the introduction of accurate screening tests, HCV was commonly transmitted by transfusion of blood and blood components, however the blood supply is now safe from transmission of this virus. Poor infection control practices such as reuse of contaminated needles, which has occurred in vaccination programmes in some countries, have resulted in many infections. Healthcare workers may be at risk through blood and body fluid exposure, especially needle stick injuries from an infected individual. Similarly, body piercing and tattoos using non-sterile equipment can transmit the virus from an infected to uninfected persons[3]. Although rare, the virus can be sexually transmitted, and babies born to mothers with Hepatitis C can become infected during childbirth.

Because of the nature of acquisition, there are a number of at-risk populations including injecting drug users, prison inmates and migrants or refugees from high prevalence countries such as Egypt, Pakistan, the Mediterranean and Eastern Europe, Africa and Asia. Infection in the Aboriginal and Torres Strait Islander population is also thought to be four times higher than in the non-indigenous population. Although the reasons are uncertain, baby boomers in the US (1945 -1965) are five times more likely to be infected and it is recommended that, in that country, every baby boomer should have a test for Hepatitis C.

“Hepatitis C is often referred to as a silent epidemic due to its asymptomatic nature, therefore laboratory testing is absolutely essential for control of the disease. Symptoms may appear only decades after infection and are often then a sign of advanced liver disease, such as fever, fatigue, loss of appetite, nausea, dark urine and pale stools, and jaundice. Often the first warning that someone is infected with HCV may be slightly abnormal liver enzymes – especially alanine aminotransferase (ALT) - that have been found incidentally upon having a blood test.

“If abnormal liver enzymes are found, then this will lead to testing for antibodies to HCV. The likelihood that the result is a true positive result increases if a second antibody test using a different assay is also positive. Once a person has been infected, they will always have antibodies in their blood. Therefore, a positive antibody test identifies both those that have either past resolved or chronic active infection. Chronic infection requires the detection of nucleic acid from HCV through RNA testing,” said Dr Robson.

Follow up RNA testing is essential to identify those with chronic disease. RNA testing is also valuable to monitor treatment as well as to determine if an infection has resolved or spontaneous viral resolution (SVR), usually after treatment, has occurred. Laboratory tests can be used to quantify the degree of liver damage when liver biopsy and ultrasound (fibroscans) are difficult for patients to access. A number of markers measured in serum can be used to assess the degree of liver fibrosis or cirrhosis. These include the AST to Platelet Ratio Index (APRI), Hepascore and Enhanced Liver Fibrosis (ELF) tests.

Treatment of HCV with new Directly Acting Antiviral (DAA) treatments is the most significant advance in clinical management of Hepatitis C in decades and has brought with it an unprecedented opportunity to change the course of the epidemic. In 2016 the Australian Government made a major investment in DAA treatment and initiated changes to prescribing rules to support the broadest possible access to these medicines, with no restrictions in terms of stage of liver disease or drug and alcohol abuse. This has been coupled with a push to allow non-specialist and primary care prescribing by general practitioners and trained nurse practitioners.

“The use of DAAs has been one of the major success stories in medical treatment in the last decade, providing a cure to more than 90% of those treated. This is one of the few viruses where there is successful and effective treatment available that is well tolerated and with very few side effects. More than 70,000 individuals in Australia had accessed DAA treatment by the end of 2018, although there are indications of the number slowing down.

“At the end of 2016 it was estimated that 81% of people living with HCV had been diagnosed. Less than 50% of these had the additional RNA test to establish whether the infection was chronic. Now that there is effective treatment it is important to capture all those who might be infected and support the completion of follow up Hepatitis C RNA

testing to confirm any ongoing infection. Some regional and rural locations, prisons and Aboriginal and Torres Strait Islander (ATSI) groups remain a focus for improving access to diagnosis and treatment," said Dr Robson.

In order to reach target populations who may otherwise not seek help from traditional medical settings, rapid point-of-care testing (POCT) technologies, similar to those that have been introduced for the control of HIV may be adopted in the future, although none are currently registered on the Australian Register of Therapeutic Goods (ARTG). In order to remove barriers for treatment, there are calls to further relax restrictions on PBS prescribing by scrapping age restrictions (>18 years) and also the requirements for genotype testing prior to starting therapy. These measures need to be a coupled with innovative preventative strategies that are effective for the target populations.

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[1] Burnet Institute and Kirby Institute. Australia's progress towards hepatitis C elimination: annual report 2019. Melbourne: Burnet Institute; 2019.

[2] https://www.health.govt.nz/your-health/conditions-and-treatments/diseases-and-illnesses/hepatitis-c

[3] https://www.who.int/news-room/fact-sheets/detail/hepatitis-c

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