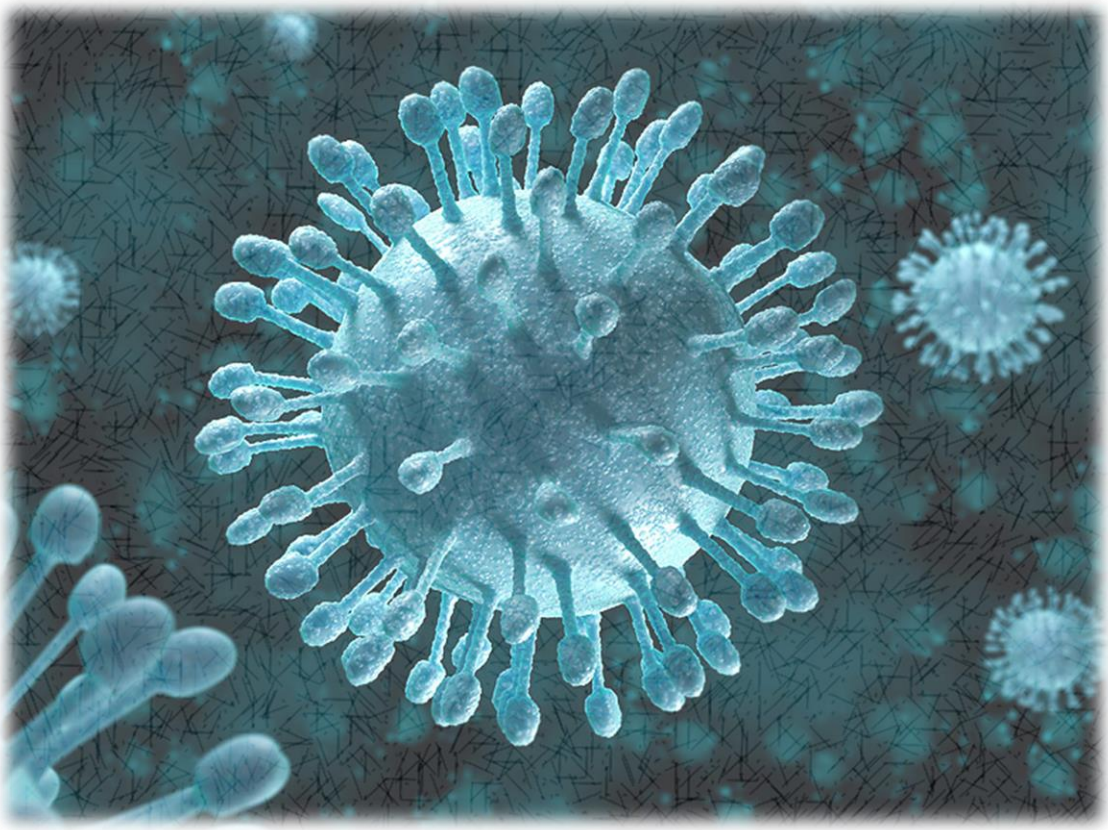

Joeun Mijoo Kim

# An audit study of the changes in hepatitis C virus (HCV) testing services among Labtests, Northland Pathology Laboratory and LabPLUS in New Zealand.

2018

Auckland University of Technology, School of Applied Science

A thesis submitted to Auckland University of Technology in partial fulfilment of the requirements for the degree of Master of Medical Laboratory Science (MMLS)

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Secondary Supervisor: Dr. Arlo Upton

# Abstract

Hepatitis C virus (HCV) is internationally recognised as a global burden according to the World Health Organisation (WHO). HCV is a major cause of chronic liver disease, including the liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC). With the development of direct-antiviral agents (DAAs), the treatment regimen of HCV has improved significantly. Medical laboratories play an important role in the diagnosis and monitoring of HCV treatment by using anti-HCV antibodies and HCV RNA. Prior to April 2016, laboratory pathologists had concerns regarding both under- and over-utilisation of HCV RNA tests, impacting on patient' outcomes and detrimentally affecting clinical resources. In April 2016, the HCV test protocol was changed at Northland Pathology Laboratory, Labtests, and LabPLUS to address this issue. An audit was performed to assess the effectiveness of the changes. This audit found evidence of mis-use of both anti-HCV antibody tests and HCV RNA tests. It was recognised that around 60% of reactive (or positive) anti-HCV antibody test results were inappropriately requested, reflecting an over-utilisation of anti-HCV antibody tests. Out of 70 appropriately requested reactive anti-HCV antibody tests, less than half had appropriate follow up HCV RNA testing, suggesting under-utilisation of the HCV RNA test. Follow up HCV RNA tests are important to determine active HCV infection from resolved HCV infection. Conversely, it was recognised that 35-50% of HCV RNA requests were inappropriately over-requested, resulting in over-utilisation of HCV RNA tests. The HCV protocol changes introduced in April 2016 improved the medical laboratory services to referrers where all reactive anti-HCV antibody results are reviewed, appropriate follow up HCV RNA and/or genotypes are added, and inappropriate HCV RNA requests are rejected by pathologists. This process change has been demonstrated in this audit to have improved the value of HCV tests and to have reduced unnecessary waste of resources. This audit emphasises the need for primary and secondary care to follow current guidelines for HCV testing protocols, from screening populations at high risk of HCV infection to better utilisation of available HCV tests. Hence I order to provide excellent patient care, both appropriate test requesting and minimising over-requesting where-ever possible is required.

**Keywords:** audit, hepatitis c virus (HCV), anti-HCV antibody, HCV RNA, test utilisation

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# Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgement), nor material which to substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Joeun Mijoo Kim

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I would also like to acknowledge Northland Pathology Laboratory and Labtests team for the support. I thank the laboratory teams for allowing me to use the company resources to collect and analyse the data used for this study.

# Ethics Approval

Ethics application was submitted to Health and Disability Ethics Committees (HDEC) and was approved on 6th of April 2017.

HDEC ref: 17/NTA/59

Study title: An audit of the changes in hepatitis C virus (HCV) testing services among Labtests, Northland Pathology and LabPLUS in New Zealand.

Approval letter from HDEC is attached to appendix.

Locality assessment was done by Wil Hermans, general manager of Northland Pathology Laboratory.

Locality assessment form is attached to appendix.

Approval to use TestSafe for this study was approved via e-mail correspondence on 23rd of May 2017 by Susan Hedges, Application Support Analyst.

TestSafe Request Number: 1782570

# Abbreviations

| Abbreviations: | Definition: |
|---|---|
| ALT | Alanine aminotransferase |
| Apo E | Apolipoprotein E |
| APRI | AST to platelet ratio index |
| AST | Aspartate aminotransferase |
| BPAC | Best Practice Advocacy Centre New Zealand |
| C | Core |
| CD4 | Cluster of Differentiation 4 |
| CD8 | Cluster of Differentiation 8 |
| CD81 | Cluster of Differentiation 81 |
| CDC | Centres for Disease Control and Prevention |
| DAA | Direct-acting antiviral |
| DNA | Deoxyribonucleic acid |
| dsRNA | Double stranded RNA |
| E1 | Envelope glycoprotein 1 |
| E2 | Envelope glycoprotein 2 |
| EASL | European Association for the Study of the Liver |
| ER | Endoplasmic reticulum |
| FDA | Food and Drug Administration |
| GP | General Practitioner |
| HAV | Hepatitis A virus |
| HBc IgM | Anti-hepatitis B core immunoglobulin M |
| HBcAg | Hepatitis B core antigen |
| HBe | Hepatitis B envelope |
| HBeAg | Hepatitis B envelope antigen |
| HBsAg | Hepatitis B virus surface antigen |
| HBV | Hepatitis B virus |
| HCC | Hepatocellular carcinoma |
| HCV | Hepatitis C virus |

| | |
|---|---|
| HCV RNA | Hepatitis C virus viral load |
| HDEC | Health and Disability Ethics Committees |
| HDV | Hepatitis D virus |
| HEV | Hepatitis E virus |
| HFV | Hepatitis F virus |
| HGV | Hepatitis G virus |
| HIV | Human immunodeficiency virus |
| HSC | Hepatic stellate cell |
| IgM | Immunoglobulin M |
| IL-8 | Interleukin-8 |
| IRES | Internal ribosome entry site |
| kDa | Unit for protein molecular weight |
| MIP-1α | Macrophage inflammatory protein type 1α |
| MIP-1β | Macrophage inflammatory protein type 1β |
| MOH | Ministry of Health New Zealand |
| NAFLD | Non-alcoholic fatty liver disease |
| NALD | Non-alcoholic liver disease |
| NANBH | Non-A, non-B hepatitis |
| NASH | Non-alcoholic steatohepatitis |
| NAT | Nucleic acid test |
| NCR | Non-coding region |
| NS | Non-structural |
| NZ | New Zealand |
| ORF | Open reading frame |
| PAMP | Pathogen-associated molecular pattern |
| PCR | Polymerase chain reaction |
| PEG-IFN | Pegylated interferon |
| PT | Prothrombin time |
| PWID | People who inject drugs |
| RANTES | A type of chemokine |
| RDT | Rapid diagnostic test |

| | |
|---|---|
| RIG-I | Retinoic acid-inducible gene I |
| RNA | Ribonucleic acid |
| rpm | Revolution per minute |
| SCARB1 | Scavenger receptor class B type 1 |
| ss | Single-stranded |
| ssRNA | Single-stranded RNA |
| STAT3 | Signal transducer and activator transcription 3 |
| SVR | Sustained virologic response |
| TAT | Turnaround time |
| TLR-3 | Toll-like receptor 3 |
| UTR | Untranslated regions |
| VLDL | Very-low-density-lipoprotein |
| WHO | World Health Organisation |

Chapter One

# *General Introduction*

## 1.1 Introduction

The World Health Organisation (WHO) has indicated that the global burden of hepatitis is high and is predicted to become higher. Approximately 325 million people are living with hepatitis worldwide and hepatitis is estimated to cause 2.7% of all deaths (World Health Organisation, 2013). The WHO Director-General made a statement in April 2017 stating that “viral hepatitis is now recognised as a major public health challenge that requires an urgent response” (World Health Organisation, 2017c). Viral hepatitis infects around 3% of the population worldwide (Andrade, Melo, Lins, Parana, & Lins, 2015). It caused 1.34 million deaths in 2015, which is comparable to deaths caused by tuberculosis and HIV (World Health Organisation, 2017c). New cases of viral hepatitis infection are predominantly due to hepatitis C virus (HCV); whereas the new infection rate of hepatitis B virus (HBV) is falling due to widespread HBV vaccination. To date, there is no vaccination for HCV (World Health Organisation, 2017c). According to the WHO Global Hepatitis Report in 2017, it is estimated 71 million people are living with HCV globally. In addition, 1.75 million people were infected with HCV in 2015 alone, and more than 350,000 people are estimated to die from HCV related diseases each year. The Global Hepatitis Report, 2017 also estimated that 20% of all HCV infections were diagnosed by 2015, and of those only 7% (estimated to be 1.1 million people) received treatment during that year (World Health Organisation, 2017a).

Diagnosis of HCV infection consists of serological screening for anti-HCV antibodies, followed by molecular confirmation of HCV viral replication by measuring HCV RNA and/or HCV antigens, and HCV genotype to determine the treatment regimen. Positive or reactive anti-HCV antibodies indicate HCV infection at some time, but does not differentiate between acute, chronic, or resolved HCV infection. Detection of the presence of HCV RNA differentiates current from past infection. Laboratories are crucial in the diagnosis of viral hepatitis as the clinical presentation of HCV is non-specific, and a diagnosis cannot be made on clinical grounds alone.

In New Zealand (NZ), it is thought that up to 1.2% of the NZ population is sero-positive for anti-HCV antibodies (Gane et al., 2014). There are several issues around HCV testing in NZ, including the expense of molecular HCV tests, and the perception of both under- and over-ordering of tests. Of particular concern is that some patients with reactive anti-HCV antibody tests have not had HCV RNA and HCV genotyping requested by their doctor. In response to

this, Labtests, Northland Pathology Laboratory, and LabPLUS worked together to institute new testing protocols. In April 2016, the changes were introduced. These included a review of all reactive anti-HCV antibody results, and a review and appropriate addition of reflex HCV RNA and genotyping where indicated. In addition, requests for HCV RNA and HCV genotyping in the absence of clinical indications were not processed.

This thesis is an audit study of the changes in HCV testing services by comparing HCV result data before and after the protocol changes.

The focus of this research is separated into four chapters to describe the evaluation of the changed HCV testing protocols. Chapter One provides an overview of viral hepatitis and HCV. Chapter Two provides clinical aspects of HCV test utilisation. Chapter Three provides a brief outline of current standards and recommendation of the management of HCV in terms of clinical guidelines, and cost effectiveness. And finlly, Chapter Four provides overview of the findings of this thesis and general discussion.

## 1.2 Hepatitis Overview

Hepatitis is a liver disease characterised by inflammation of the liver. Hepatitis is caused by either viral agents or non-viral aetiologies. Hepatitis caused by viral agents such as hepatitis A virus (HAV), HBV, or HCV, is commonly referred to as viral hepatitis. Viral hepatitis is the most common type of hepatitis worldwide followed by alcoholic hepatitis. Alcoholic hepatitis is caused by excessive alcohol consumption that leads to liver damage. Other aetiologies include: autoimmune hepatitis, drug-induced hepatitis, parasitic hepatitis, bacterial hepatitis, metabolic/non-alcoholic hepatitis [which include non-alcoholic liver disease (NALD), non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)], and secondary/ischemic hepatitis, but these are less common (Choudhuri & Chowdhury, 2009; Horn, Hecht, Babcock, & Heymann, 2011; Korsman, 2012).

Hepatitis has a wide range of symptoms that range from asymptomatic, hepatitis (liver) non-specific symptoms, hepatitis specific symptoms, to hepatic failure. Examples of hepatitis non-specific symptoms and clinical findings are fatigue, muscle and joint ache, nausea and vomiting, fever, abdominal pain, diarrhoea, headache, malaise, and anorexia (loss of appetite)

(Choudhuri & Chowdhury, 2009; Horn et al., 2011). Examples of hepatitis specific symptoms include: jaundice (yellowing of the skin), icterus (yellowing of the whites of the eye), hepatomegaly (enlarged liver), portal hypertension, ascites (fluid accumulation in the abdomen), coagulopathy (deranged haemostasis) and elevated liver specific enzymes (Choudhuri & Chowdhury, 2009; Madigan, Martinko, Dunlap, & Clark, 2009).

Hepatitis can be classified as acute hepatitis or chronic hepatitis depending on the duration of the disease. Acute hepatitis refers to liver inflammation that lasts less than six months, whereas chronic hepatitis refers to liver inflammation that lasts more than six months (Choudhuri & Chowdhury, 2009; Horn et al., 2011; Korsman, 2012; World Health Organisation, 2017b). Acute hepatitis can be self-limiting (resolve itself), or cause extrahepatic complications, hepatic failure and/or lead to chronic hepatitis. Chronic hepatitis can lead to liver fibrosis, liver cirrhosis, and hepatic failure, or HCC (liver cancer) (Choudhuri & Chowdhury, 2009; Madigan et al., 2009).

Identification of an early aetiology of the hepatitis, and the severity of the hepatitis, is important in treatment, management, and prognosis of the disease (Choudhuri & Chowdhury, 2009). Initial diagnosis of hepatitis involves assessing patients' medical history, signs and symptoms, as well as physical examination, laboratory testing, confirmatory imaging techniques, and confirmatory liver biopsy or elastography scan. However, lack of symptoms for hepatitis makes it hard to diagnose hepatitis on clinical grounds. Liver specific transaminases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and haematological and/or coagulation tests are used in laboratories to assess the degree of hepatitis and the presence of liver damage. Further testing with an elastography scan provide more accurate information in regards to the extent of liver fibrosis and damage (Choudhuri & Chowdhury, 2009; Madigan et al., 2009).

Treatment of hepatitis depends on the underlying aetiology and the type of hepatitis. The goal is to stop the infection from progressing and to prevent complications from hepatitis, which may lead to a liver transplant. The liver is the second most transplanted organ after the kidney.

## 1.3 Viral Hepatitis

There are five main viruses that cause viral hepatitis: HAV, HBV, HCV, hepatitis D virus (HDV) and hepatitis E virus (HEV). Whereas hepatitis G virus (HGV) is believed to be associated with hepatitis, however there are no reports of HGV being clinically significant. However, hepatitis F virus (HFV) is speculated to be a seventh hepatitis virus, however more research is needed to confirm this (Horn et al., 2011).

Viral hepatitis has common symptoms as described above, that vary from asymptomatic to hepatic failure. It has been reported that some people with viral hepatitis show no symptoms of hepatitis until the chronic phase, 20 or more years after infection (Choudhuri & Chowdhury, 2009; Horn et al., 2011). Therefore, a patient who does not show any symptoms of viral hepatitis may be (by chance) diagnosed accidently or never. Hence, the lack of hepatitis specific symptoms is an important factor to consider when trying to understand the global burden of viral hepatitis (Horn et al., 2011; World Health Organisation, 2017c).

### 1.3.1 Acute Viral Hepatitis

Acute viral hepatitis is characterised by viral hepatitis that is resolved within six months (Choudhuri & Chowdhury, 2009; Horn et al., 2011; Korsman, 2012). All HAV infections and HEV infections cause acute viral hepatitis; up to 95% of HBV infections cause acute viral hepatitis, and between 15 and 20% of HCV infections cause acute viral hepatitis (Choudhuri & Chowdhury, 2009).

Acute viral hepatitis can be divided into four phases: incubation phase, prodromal phase, icteric phase, and convalescent phase (Choudhuri & Chowdhury, 2009; Horn et al., 2011).

The incubation phase begins with initial viral infection and continues until the onset of symptoms. The duration of this phase varies from one week to many months, depending on the aetiology of the viral hepatitis and immune response of the infected individuals. During this phase the infected virus replicates rapidly and the individual becomes contagious (Choudhuri & Chowdhury, 2009; Korsman, 2012). The asymptomatic characteristic of hepatitis makes this period dangerous for other people because infected individuals may not know about the infection and will not be able to take precautions (Horn et al., 2011).

The prodromal phase begins with the onset of symptoms and the duration is between three to seven days (Choudhuri & Chowdhury, 2009; Horn et al., 2011). During this phase liver function tests appear abnormal and may include raised serum liver enzymes ALT, AST, some specific immunoglobulin M (IgM) and most nucleic acid markers (Choudhuri & Chowdhury, 2009; Horn et al., 2011; Korsman, 2012).

The icteric phase begins with jaundice and icterus, with the duration being four to eight weeks. The liver is palpable in up to 70% of individuals due to raised conjugated and unconjugated bilirubin. On rare occasions, some individuals may not develop jaundice and icterus, so in some cases the prodromal phase is not followed by the icteric phase (Choudhuri & Chowdhury, 2009; Horn et al., 2011; Korsman, 2012).

The convalescent phase or recovery phase begins when all symptoms disappear, and individuals recover. The duration of this phase typically lasts four to eight weeks but it can last up to six months (Choudhuri & Chowdhury, 2009; Horn et al., 2011). Not all instances of acute viral hepatitis result in clearance of the infection. Acute HBV infection in adolescents and adults typically does as with a proportion of cases of acute HCV infection. However, younger patients with HBV infection and over half of those with acute HCV infection will develop chronic hepatitis. Interestingly, patients with symptomatic acute HBV and HCV are more likely to self-clear the virus.

Acute viral hepatitis caused by HAV and HEV is usually self-limiting (resolves on its own), however supportive treatment can help to manage symptoms (Choudhuri & Chowdhury, 2009). Acute viral hepatitis caused by HBV, HCV and HDV can progress to chronic viral hepatitis if the infection is not resolved within six months.

### 1.3.2 Chronic Viral Hepatitis

Chronic viral hepatitis is characterised by viral hepatitis that is not resolved within six months (Choudhuri & Chowdhury, 2009; Horn et al., 2011; Korsman, 2012). HBV, HCV and HDV can cause chronic viral hepatitis which can lead to liver cirrhosis and HCC (Choudhuri & Chowdhury, 2009). An exceptional feature of HDV is that it can cause hepatitis only with the assistance of HBV (Horn et al., 2011). Chronic viral hepatitis develops when a patient's immune

system cannot eliminate the invading virus possibly due to the feature of the virus, such as virus mutation, or because the virus replicates faster than the immune system responds (Horn et al., 2011). During chronic hepatitis, some individuals may be asymptomatic, symptomatic, continuously symptomatic, or symptoms could disappear. Chronic hepatitis individuals remain infectious with or without the symptoms (Horn et al., 2011).

Chronic viral hepatitis can be divided into three phases: replicative phase, seroconversion phase, and non-replicative phase.

The replicative phase is a period where viruses are actively replicating. This is a dynamic process based on virus-host interaction, which is essential to the pathogenesis of the liver disease. The duration of this phase may last several years, which lead to viraemia (a large amount of virus in the blood). Individuals in this phase are most contagious (Horn et al., 2011).

The seroconversion phase is a period where a specific antibody develops and becomes detectable in the blood. After seroconversion has occurred, the disease can be detected in blood tests for the presence of antibody. For example, the average time from HCV exposure to seroconversion is between five to 23 weeks. Serum ALT and AST may be raised in this period due to damaged liver cells (Horn et al., 2011; World Health Organisation, 2017b).

The non-replicative phase is a period where the virus stops replicating and viraemia is at a minimal level, this occurs with HBV but not with HCV (Horn et al., 2011).

### 1.3.3 Complication of Hepatitis

Complications of the acute viral hepatitis may require patient hospital admission. Symptoms and signs of complications include: deep jaundice with ascites, coagulopathy (prolonged prothrombin time (PT), bleeding tendency), altered sensorium, and acute liver failure (Choudhuri & Chowdhury, 2009; Horn et al., 2011; Korsman, 2012). Acute liver failure or fulminant hepatitis is a rare complication that can occur in 0.5 to 2% of patients and which can be fatal (Choudhuri & Chowdhury, 2009; Horn et al., 2011). With fulminant hepatitis, hepatocytes are destroyed. The liver function is impaired, toxic materials are not cleared leading to hepatic encephalopathy (cerebral oedema), sepsis or coma. Death from fulminant hepatitis can occur within two weeks of the onset of symptoms (Horn et al., 2011; Korsman, 2012). The

fulminant hepatitis is most often associated with HBV infection (1% of cases), but can also develop with HAV and HCV infections (Horn et al., 2011). Clinical management is supportive, and liver transplantation is indicated in some patients.

Complications of chronic viral hepatitis can include cirrhosis, extrahepatic manifestation (renal, neurological, haematological disorders), and HCC as previously mentioned (Choudhuri & Chowdhury, 2009; Horn et al., 2011; Korsman, 2012). Approximately 20% of chronic hepatitis cases progress to cirrhosis after ten or more years (Choudhuri & Chowdhury, 2009; Horn et al., 2011). Cirrhosis is end-stage liver disease, which is characterised by liver fibrosis and hepatic nodular regeneration. Chronic hepatitis B, D and C infections lead to progressive damage to the hepatocytes caused mainly by the immune system (Horn et al., 2011; Korsman, 2012). Killer T cells attempt to eliminate the hepatitis virus by attacking and destroying infected hepatocytes. As a result, the body forms scar tissues in the liver to repair the damaged hepatocytes (Horn et al., 2011). This immune response also causes cascade hepatitis complications such as extrahepatic manifestation. The scar tissues formed can extend onto other organs, which can lead to life-threatening haematernesis (vomiting of blood) (Korsman, 2012). HCC usually develops more slowly and appears later than liver cirrhosis. Most cases of HCC are preceded by cirrhosis. However, as HBV is an oncogenic virus, HCC can be seen in patients with chronic HBV infections without cirrhosis.

About 20% of chronic HBV infection and 5% of chronic HCV infection progress to HCC. With HCC, partial liver resection or liver transplant is the only available lifesaving procedure (Horn et al., 2011).

### 1.3.4 Hepatitis Virus Transmission

Viral hepatitis is a high global burden both in developing and developed countries. In developing countries HAV and HEV infections are common because they are commonly infected by ingestion of contaminated food or water (Horn et al., 2011; Madigan et al., 2009). HAV and HEV are commonly infected via the route of faecal-oral transmission, where viruses are spread through contaminated food or water. HBV, HCV and HDV are commonly infected via the route of blood-borne transmission, where viruses are spread through blood or blood products. Other transmissions include: vertical transmission where the viruses infect through mother to child

(Horn et al., 2011; Madigan et al., 2009). In NZ, HBV and HCV are the most common cause of viral hepatitis.

### 1.3.5 Diagnosis of Viral Hepatitis

As mentioned previously, early diagnosis and detection of viral hepatitis is important; however, it can be challenging especially if patients present without any noticeable symptoms until the emergence of severe liver damage. Therefore, diagnostic laboratories play a crucial role in diagnosis of viral hepatitis.

When viral hepatitis is suspected, specific tests are carried out to diagnose viral hepatitis. Laboratory tests for HCV are divided into screening and confirmatory tests. As shown below in Table 1.1, screening tests are performed in the first instance to detect antibodies or antigens to the specific viral hepatitis. Screening tests are cost-effective and quicker compared to the confirmatory tests. Confirmatory tests are performed either to detect specific antigens to the specific viral hepatitis or to detect specific nucleic acid of the virus.

Total antibody to anti-HAV is used as a screening assay for HAV infection or to check for immunity to HAV infection. The anti-HAV IgM antibody is used to diagnose acute HAV infection.

HBV surface antigen (HBsAg) is a key assay to screen for HBV infection. Total antibody to anti-HBV and/or antibody to HBV core antigen (HBcAg) are used to check for immunity to HBV infection. HBcAg, HBc IgM, HBV envelope antigen (HBeAg) and HBV DNA are used to diagnose and determine active or chronic HBV infection.

Total antibody to anti-HCV is used to screen for HCV infection. HCV RNA or HCV antigen is used to confirm HCV infection.

Diagnoses of HDV and HEV are not commonly performed in NZ. HDV and HEV infections are screened using total antibody to anti-HDV and anti-HEV for suspected HDV and HEV infection, respectively. Confirmatory tests are done by detecting RNA of HDV and HEV.

Imaging techniques and liver biopsy were considered the gold standard to determine the extent of the liver damage and the possibility of HCC by histopathologic analysis. However, the liver

biopsy is invasive and has a higher risk to the patients. Nowadays, liver ultrasound elastography is used to assess the extent of the liver damage (Gherlan, 2015).

Table 1.1 Markers to diagnose viral hepatitis

| Viral Hepatitis | Markers: | Screening | Immune Status | Acute Infection | Chronic Infection |
|---|---|---|---|---|---|
| **HAV** | Positive/reactive anti-HAV total | ✔ | ✔ | ✔ | |
| | Positive/reactive anti-HAV IgM | | | ✔ | |
| **HBV** | Positive HBsAg | ✔ | | ✔ | ✔ |
| | Positive HBsAg + positive/reactive HBc IgM | | | ✔ | |
| | | | | HBeAg, anti-HBe, and HBV DNA to assess viral activity. | |
| | Negative HBsAg + positive/reactive anti-HBc and/or anti-HBs | | ✔ | | |
| **HCV** | Positive/reactive anti-HCV | ✔ | | ✔ | ✔ |
| | | | | HCV RNA to assess viral activity | |
| **HDV** | Positive/reactive anti-HDV + positive HBV markers | ✔ | ✔ | ✔ | ✔ |
| | | | | HDV RNA to assess viral activity | |
| **HEV** | Positive/reactive anti-HEV | ✔ | ✔ | ✔ | |
| | | | | HEV RNA to assess viral activity | |

### 1.3.6 Treatment of Viral Hepatitis

As acute viral hepatitis is often self-limiting, the treatment is a supportive symptomatic management (Choudhuri & Chowdhury, 2009; Korsman, 2012). Treatment for fulminant hepatitis or hepatic failure is usually intensive care support and liver transplants. Treatment for chronic viral hepatitis is heavily dependent on the aetiology and the immune system of the patients. The main goal of treating chronic viral hepatitis is to prevent further complications such

as cirrhosis and HCC (Choudhuri & Chowdhury, 2009; Horn et al., 2011; Korsman, 2012). At present, the only treatment for HCC is liver resection and liver transplant. Liver transplants are performed on patients who meet strict criteria. The liver is the second most transplanted organ after the kidney, and liver transplants are becoming more and more common throughout the developed and developing world (Horn et al., 2011).

### 1.3.7 Prevention of Viral Hepatitis

As a common notion, prevention is better than a cure, and the primary goal of prevention of viral hepatitis is to minimise the global burden. Understanding the different route of transmission of viral hepatitis is important in preventing viral hepatitis. Common preventions of viral hepatitis include sanitation improvement and hygiene, vaccination of high-risk groups (vaccines are only available for HAV, HBV, and HDV indirectly), screening for blood products, prevention of high-risk behaviours (such as intravenous drug use and unprotected sexual intercourse), and extra caution with needles or any other biohazards for healthcare workers.

## 1.4 HCV Overview

HCV was first suspected in the 1970s, and it was originally called a non-A, non-B hepatitis (NANBH) virus as the virus could not be isolated (Rogo, Akogwu, Umar, Aliyu, & Aminu, 2011; Westbrook & Dusheiko, 2014). The virus and its genome were later identified in 1989 (Andrade et al., 2015; Horn et al., 2011; Rogo et al., 2011). Prior to 1992, HCV was responsible for most cases related to post-transfusion or post-transplant hepatitis; back then the cause of hepatitis after blood transfusion was unknown (Andrade et al., 2015; Horn et al., 2011). A reliable diagnostic test was developed and approved by the Food and Drug Administration (FDA) in the 1990s, leading to compulsory screening on all donated blood products in developed countries (Alter, Kuhnert, & Finelli, 2003; Andrade et al., 2015; Horn et al., 2011). This routine screening has eliminated post-transfusion hepatitis in most cases. However, in under-developed countries HCV is still a main blood transfusion hepatitis (Horn et al., 2011). Humans are the only known host of HCV, which causes about 50% of chronic liver disease worldwide, especially since the

invention of HBV vaccine (Andrade et al., 2015; Ascione, Tartaglione, & Costanzo, 2007; Bartenschlager & Lohmann, 2000; Westbrook & Dusheiko, 2014).

Anti-HCV antibody and HCV RNA testing are crucial in diagnosing active HCV infection. Until recently, the standard treatment for HCV infection was a combination of pegylated interferon (PEG-IFN) and ribavirin. However, the treatment is associated with significant adverse effects and the treatment duration was either 24 or 48 months. Recent developments of new DAA therapies have changed the treatment regimens particularly for HCV genotype 1 (Andrade et al., 2015).

## 1.5 Flaviviridae Hepacivirus C Taxonomy

HCV belongs to the family *Flaviviridae*. Most *Flaviviridae* viruses are host-specific pathogens that infect mammals and birds. This family of viruses is divided into four genera: *Hepacivirus, Flavivirus* (which include zika virus, dengue fever and yellow fever virus), *Pegivirus* and *Pestivirus*. HCV belongs to the genus *Hepacivirus*. There are 14 species of *Flaviviridae Hepacivirus*, from A to N. HCV belongs to the species *C*. There are six major genotypes (genetic makeup) of *Flaviviridae Hepacivirus C* with many subtypes, and HCV is yet to be classified (Andrade et al., 2015; Bartenschlager & Lohmann, 2000; Choudhuri & Chowdhury, 2009; Dubuisson & Cosset, 2014; Horn et al., 2011; ICTV, 2016a).

### 1.5.1 Virus Structure

HCV is spherical virus with a diameter of approximately 50 nm. HCV, *F. Hepacivirus C*, is a small enveloped single-stranded (ss) positive-sensed non-segmented RNA virus. The core genetic material (ss RNA) is surrounded by an icosahedral capsid, a protective single protein shell, also called a nucleocapsid. This nucleocapsid is further encased in a lipid envelope of cellular origin. The lipid envelope contains two glycoproteins (E1 and E2) embedded in the envelope, which plays a crucial role in the virus replication. A simplified diagram of HCV is shown in Figure 1.1 (Andrade et al., 2015; Bartenschlager & Lohmann, 2000; Choudhuri & Chowdhury, 2009; Dubuisson & Cosset, 2014; Horn et al., 2011; ICTV, 2016a, 2016b; Korsman, 2012; Madigan et al., 2009; Rogo et al., 2011).

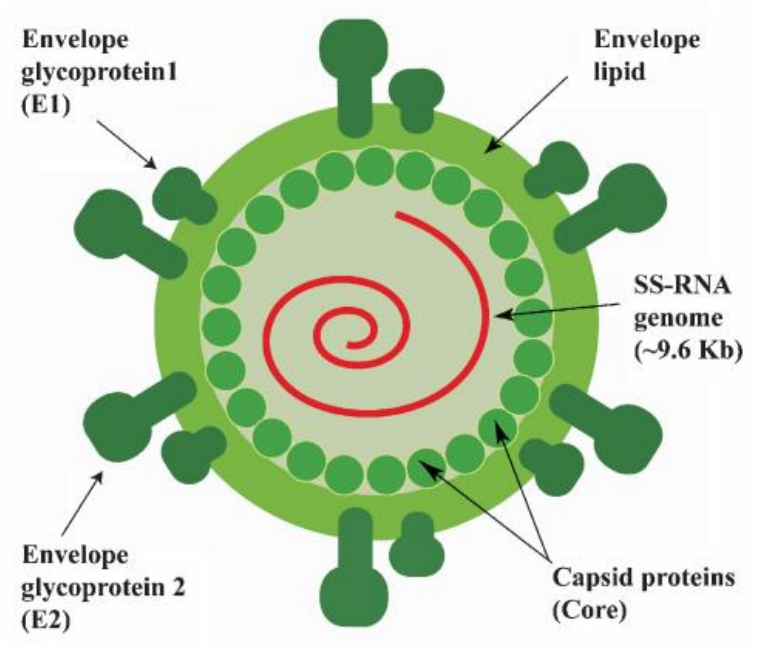


Figure 1.1. Simplified HCV structure (Rogo et al., 2011).

### 1.5.2 HCV Genome Organisation

The size of the HCV genome is around 9600 nucleotides. The HCV genome has a single large translational ORF (open reading frame) which means a single protein product is produced and then further cleaved to smaller proteins. This ORF encodes a single polypeptide with multiple transmembrane domains of approximately 3000 amino acids flanked by untranslated regions (UTR, which are not translated into proteins but are important to translation and replication of the virus) at both 5' and 3' ends. This polyprotein is later cleaved by cellular and viral proteases into the ten smaller proteins (Andrade et al., 2015; Bartenschlager & Lohmann, 2000; Horn et al., 2011; ICTV, 2016b; Rogo et al., 2011). HCV proteins are divided into structural and non-structural (NS) proteins. Structural proteins include core (C) protein, envelope glycoprotein 1 (E1), envelope glycoprotein 2 (E2) and non-structural proteins include p7/p13, NS2, NS3, NS4A, NS4B, NS5A and NS5B (Andrade et al., 2015; Bartenschlager & Lohmann, 2000; ICTV, 2016a; Rogo et al., 2011). The order of proteins encoded is N-terminal, C, E1, E2, p7/p13, NS2, NS3, NS4A NS4B, NS5A, NS5B and C-terminal. Figure 1.2 (ICTV, 2016b) shows HCV genome organisation and polyprotein processing. Table 1.2 Summarises HCV proteins, their size, and their role.

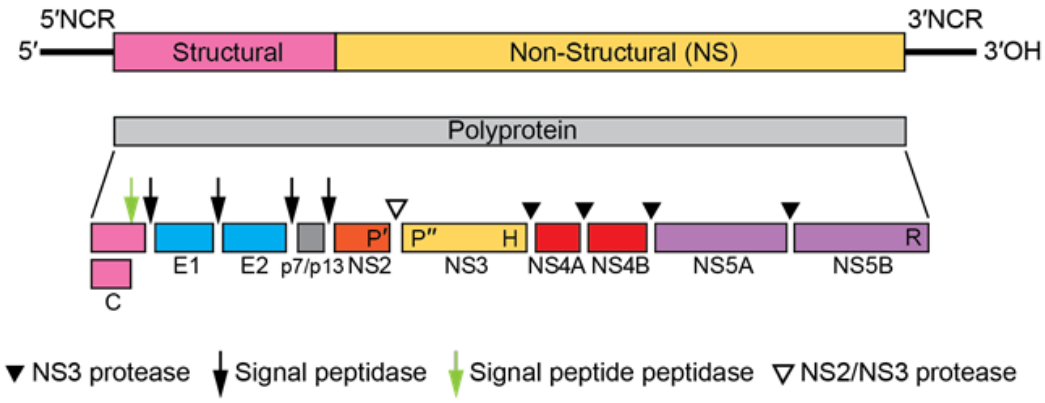


Figure 1.2 HCV genome organisation and polyprotein processing (ICTV, 2016b).

Table 1.2 HCV proteins and their role.

| Protein | Structural or Non-structural | Protein size | Role |
|---|---|---|---|
| **Core (C)** | Structural | 19-21 kDa | Nucleocapsid core protein and modulates cellular processes. |
| **Envelope 1 (E1)** | Structural | 31 kDa | Envelope glycoprotein |
| **Envelope 1 (E2)** | Structural | 70 kDa | Envelope glycoprotein |
| **P7/p13** | NS | 7 or 13 kDa | Ion channel and virus assembly. |
| **NS2** | NS | 21 kDa | Transmembrane proteins and virus assembly. |
| **NS3** | NS | 70 kDa | Serine protease, RNA helicase and NTPase activities. |
| **NS4A** | NS | 6-8 kDa | Co-factor |
| **NS4B** | NS | 27 kDa | Co-factor, and induces a membrane replication complex. |
| **NS5A** | NS | 56-58 kDa | Serine phosphoprotein, viral replication and virus assembly, IFN-resistance protein. |
| **NS5B** | NS | 68 kDa | RNA polymerase. |

In different HCV genotypes, there is over 30% variability in the nucleotide sequence and 20 to 25% difference in HCV subtypes (Andrade et al., 2015).

## 1.5.3 HCV Viral Replication

In general, viruses require a living host to replicate, and there are several steps of viral replication. The initial step involves attachment of the virus to the host cell, which involves penetration of the host and injection of viral nucleic acid. Once inside the host cell, the virus synthesis new viral proteins and nucleic acid, in order to assemble and pack the new viruses. Lastly, the virus is released from the host cell, it is estimated that ten trillion virion particles are produced per day in active HCV infection (Andrade et al., 2015; Horn et al., 2011; Madigan et al., 2009).

### *1.5.3.1 Attachment and Entry*

The initial step in a virus life-cycle is the attachment of infectious particle to host cell through which specific interaction between receptors on the cell surface and a viral attachment protein on the surface particle is required (Bartenschlager & Lohmann, 2000).

After an exposure to HCV, HCV attaches to serum very-low-density lipoprotein (VLDL) or apolipoprotein E (Apo E) via E1 (which is embedded in the lipid envelope of the HCV), as shown in Figure 1.3 (Bartenschlager, Cosset, & Lohmann, 2010).

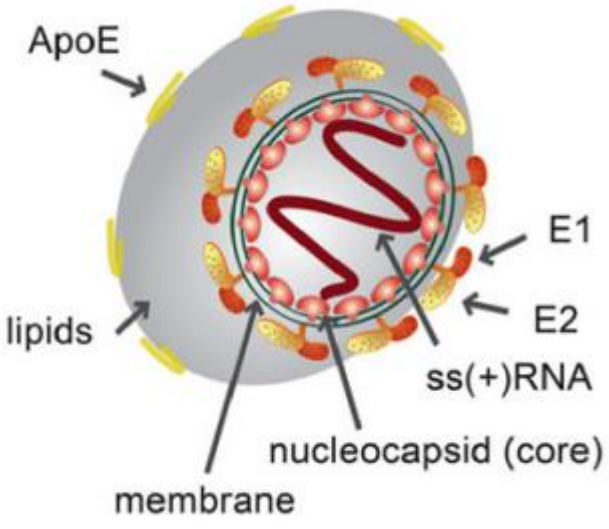


Figure 1.3 HCV attached to Apo E (Bartenschlager et al., 2010).

HCV enters the hepatocyte via receptor-medicated fusion. HCV attaches to the surface of the hepatocyte by attaching to specific receptors on the host cells (scavenger receptor class B type

1 (SCARB1, SR-BI), CD81, claudin-1 (CLDN-1), occluding (OCLN), receptor tyrosine kinases, epidermal growth factor receptor, ephrin receptor A2 and Niemann-Pick C1-like 1 cholesterol absorption receptor) via using a glycoprotein E2, that interact with host cell receptors (Andrade et al., 2015; Dubuisson & Cosset, 2014; ICTV, 2016b). Figure 1.4 demonstrates HCV attachment to hepatocytes using different receptors (Bartenschlager et al., 2010). This is mediated via clathrin-mediated endocytosis (entering the hepatocyte, surrounded by host cell lipid layer) (Andrade et al., 2015; Bartenschlager & Lohmann, 2000; Dubuisson & Cosset, 2014).

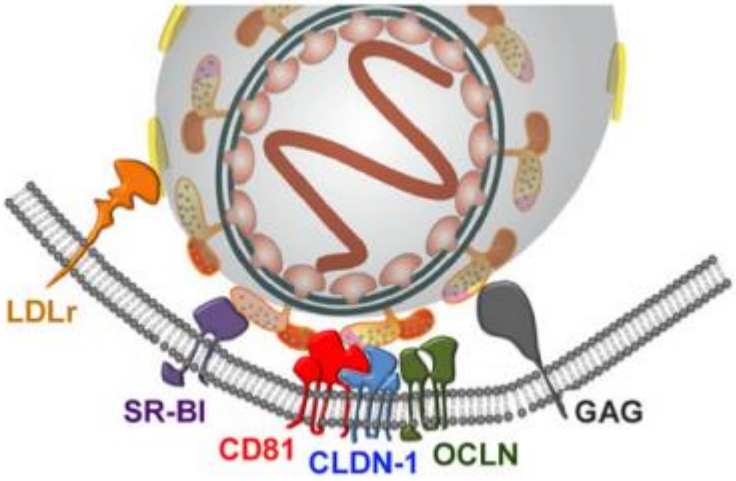


Figure 1.4 HCV attachment to hepatocytes using receptors (Bartenschlager et al., 2010).

Following hepatocyte entry, the HCV RNA genome is released into the hepatocyte cytoplasm near the rough endoplasmic reticulum (ER) (Andrade et al., 2015; Dubuisson & Cosset, 2014).

### *1.5.3.2 Polyprotein Translation and Processing*

Viral replication occurs within the hepatic cell cytoplasm. A positive-sensed RNA strand is used as mRNA and encodes viral proteins directly. The genomic RNA is translated into a polyprotein that is rapidly processed both co- and post- translationally by host and viral proteases. Translation initiation occurs via an internal ribosome entry site (IRES) within the 5'- non-coding region (NCR) which is regulated by cellular proteins that vary in abundance or activity during the cell cycle, shown in Figure 1.5 (Bartenschlager et al., 2010). Directed by the IRES, the

polyprotein is translated at the rough ER and cleaved co- and post- translationally by host cell signalases and two viral proteinases. In the last few years, a wealth of information regarding the mechanism of polyprotein processing has been published. (Bartenschlager & Lohmann, 2000; Dubuisson & Cosset, 2014). It is beyond the scope of this study to summarise all of them.

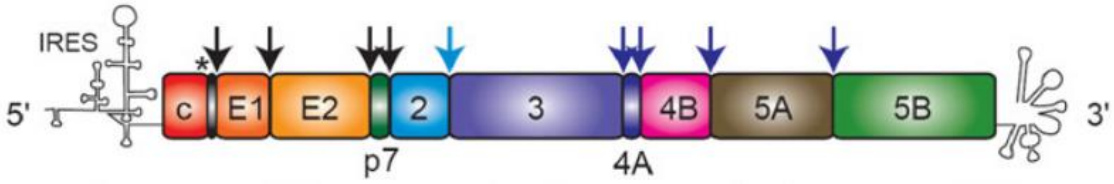


Figure 1.5 HCV genome structure and polyprotein processing with IRES (Bartenschlager et al., 2010).

#### *1.5.3.3 RNA Replication, Virion Assembly and Release*

Most of the non-structural proteins formed act as a replication complex, where HCV positive ssRNA will be replicated to a negative ssRNA. This negative ssRNA will then be used as a template by the replication complex to replicate many positive ssRNA. These ssRNA are then used for polyprotein translation and processing (Andrade et al., 2015; Bartenschlager & Lohmann, 2000; Dubuisson & Cosset, 2014). Virion assembly occurs in the ER and in Golgi, where virions are packaged up to a full virus. In this process, lipoprotein is attached to the newly assembled HCV. Newly assembled HCV virus leaves the hepatic cell by budding (Bartenschlager & Lohmann, 2000; Dubuisson & Cosset, 2014).

### 1.5.4 HCV Mutation

Understanding the mechanism of viral replication provides strategies for developing new treatments and vaccines. Unfortunately, HCV has a high mutation rate, and a mixed virus population gives HCV advantage to create multiple variant genomes. This makes the development of HCV vaccines difficult. Vaccines are developed to mimic specific antigens to provoke an immune response to produce antibodies. Due to the high mutation rate of the virus the specific antigens used in vaccines may be rendered ineffective and will be unrecognised to the antibodies when induced (Andrade et al., 2015; Horn et al., 2011).

HCV RNA-polymerase plays an important role for a high mutation rate. RNA-polymerase is an important enzyme for RNA replication. HCV RNA-polymerase does not detect errors during the RNA replication, unlike most RNA-polymerases. For example, an extremely high mutation rate of glycoprotein E2, due to RNA-polymerase aids, HCV to evade the immune system (Horn et al., 2011).

### 1.5.5 Immuno-pathogenesis of HCV

Viruses that are introduced in humans are targeted and destroyed by three immune mechanisms: by 1. innate and adaptive immunity; by 2. antibody-mediated immunity; and by 3. cell-mediated immunity (Madigan et al., 2009). Innate immunity results from interactions between virion and phagocytes. Adaptive immunity results from antigen-specific T cells, and antibody-mediated immunity results from specific virion antibodies produced by B-lymphocytes. The immune system is not very successful in defeating HCV as at least 80% of those infected develop the chronic disease. The primary immune response is cellular, mediated by CD4 and CD8 killer T-cells (Cashman, Marsden, & Dustin, 2014; Liang, Rehermann, Seeff, & Hoofnagle, 2000). The liver becomes chronically inflamed and over a span of ten to 20 years, scarring of the liver can develop into cirrhosis in 10% to 20% of infected people. HCC develops in about 5% of patients after 30 years. The Centres for Disease Control and Prevention (CDC) has summarised the progression of events associated with chronic HCV infection. For every 100 people infected with the HCV virus, 75 to 85 will develop chronic infection; 60 to 70 will develop chronic liver diseases, 5 to 20 will develop cirrhosis, and one to five will die from HCC (Horn et al., 2011; Liang et al., 2000).

#### *1.5.5.1 Adaptive Humoral Response*

The immune system has several roles in recognition and clearance of viral infections. It contributes to immune surveillance, directly neutralising infection as well as triggering inflammation, opsonizing pathogens, and modulating adaptive immunity (Liang et al., 2000). Initiation of a protective adaptive immune response to HCV infection follows inflammation and as such is dependent on an effective acute phase innate immune response. The inflammatory response is initiated by the presence of virus particles and subsequent infection of hepatocytes.

Binding of microbial pathogen-associated molecular patterns (PAMPs), such as HCV glycoproteins, to antigen presenting cells results in activation and initiation of the inflammatory response and presentation of viral antigens to T cells (Tarr, Urbanowicz, & Ball, 2012).

The humoral immune response plays an important role to assist in the direct neutralisation of cell free virion, but has a very limited role in the cell to clear HCV completely. However, the role of the humoral immune response in acute infection and spontaneous clearance is still not fully understood (Cashman et al., 2014).

#### *1.5.5.2 Cellular Response*

Recent studies have shown that the hepatic stellate cells play a novel role in liver immunity. Hepatic stellate cells (HSCs) represent 5 to 8% of the total human liver cells and reside in the Disse space. During the progression of HCV-related diseases, HSCs contribute to the inflammatory response triggered by HCV infection (Nishitsuji et al., 2013; Wang, Li, Wang, Sang, & Ho, 2013). The induction of proinflammatory cytokines and chemokines is triggered by viral proteins and double-stranded RNA (dsRNA) from HCV. The HCV core protein induces inflammatory cytokines through the signal transducer and activator of transcription 3 (STAT3) signalling pathway. Retinoic acid-inducible gene I (RIG-I) and Toll-like receptor 3 (TLR-3) are cellular sensors that recognize HCV dsRNA, resulting in production of chemokines such as interleukin-8 (IL-8), RANTES (a chemokine), macrophage inflammatory protein 1α (MIP-1α), and MIP-1β (Nishitsuji et al., 2013; Wang et al., 2013). Although direct induction of liver inflammation by HCV infection through cellular sensors or HCV proteins is well documented, little is known about the mechanisms governing the proinflammatory cytokines and chemokines which are produced during the interactions between HCV-infected hepatocytes and HSCs (Nishitsuji et al., 2013; Wang et al., 2013). Clearance of HCV during the acute phase of infection is associated with a robust CD4 and CD8 T-cell response to multiple viral epitopes.

The host shows response against HCV infection by helper T-cells and T-cytotoxic cells. T-helper and T-cytotoxic cells plays a major role in providing immunity at a cellular level and offer a very powerful defence mechanism. The activated T-cells can kill HCV hidden in hepatocytes and can make hepatocytes and Kupffer cells so strong that they do not exhibit any injurious or harmful events in the liver (Nishitsuji et al., 2013; Tarr et al., 2012; Wang et al., 2013).

### 1.5.6 Virus Route of Transmission

HCV is a blood-borne virus; it is spread commonly among intravascular drug users. Other possible modes of transmission include healthcare exposure, body modification (tattoo and piercing with non-sterile equipment), sexual intercourse, and vertical transmission. Some modes are less frequent now due to enhanced knowledge and precautions (Andrade et al., 2015; Ascione et al., 2007; Choudhuri & Chowdhury, 2009; Horn et al., 2011; Korsman, 2012; Westbrook & Dusheiko, 2014).

### 1.5.7 Epidemiology

WHO estimates that about 170 million people alive today are infected with HCV. One hundred ten million people have a history of hepatitis C infection and 80 million people have chronic viraemic hepatitis C infection (World Health Organisation, 2017b). The European Association for the Study of the Liver (EASL) stated that there are up to four million new incidents of HCV infection annually and 350,000 people die from HCV related causes annually (Westbrook & Dusheiko, 2014). The Global Burden of Disease study by WHO showed that the estimated number of deaths due to hepatitis C increased to 704,000 in 2013 (World Health Organisation, 2017b). Before blood screening began in the 1980s, there was an average of 242,000 new HCV infection recorded per year according to the CDC (Horn et al., 2011).

HCV genotype 1, genotype 2 and genotype 3 have a worldwide distribution whereas others are more specific to different regions of the world. HCV genotype 1a and 1b are the most common, accounting for about 60% of global HCV infection. HCV genotype 1a and 1b are most prevalent in US and Western Europe, and the HCV genotype 3 is most prevalent in Southeast Asia. HCV genotype 4 is most prevalent in the Middle East and Central Africa, HCV genotype 5 is prevalent in South Africa, and HCV genotype 6 is prevalent in South East Asia (Andrade et al., 2015; Horn et al., 2011).

The exact prevalence of chronic HCV infection is unknown in NZ. This is because there is no accurate HCV prevalence data, as only acute HCV infection is notifiable in NZ. It is assumed that the epidemiology of HCV in NZ follows that of Australia, which accounts for the HCV

prevalence in NZ (Gane et al., 2014; Vermunt et al., 2015). Ministry of Health of NZ (MOH) estimated in 2015 that 50,000 NZ adults (over 1% of the NZ population) are living with chronic HCV infection.

### 1.5.8 Laboratory Diagnosis

The impact of chronic infection of HCV demands early treatment and management for HCV infections, and therefore an early diagnosis is very important (Westbrook & Dusheiko, 2014). As mentioned earlier, diagnosis of hepatitis C infection involves serological screening of anti-HCV antibodies, followed by a nucleic acid test (NAT) to confirm the presence of the HCV RNA, or followed by recently developed HCV antigen tests (Andrade et al., 2015; Choudhuri & Chowdhury, 2009; Horn et al., 2011; World Health Organisation, 2017b). The serological screening test is used to determine exposure to HCV, and it is cost-effective compared to NAT. However, it does have some limitations with occasional false positive results, false negative results in occasional immunocompromised patients, and HCV antibody positivity does not always represent active infection. NAT for the detection of HCV RNA is the gold standard for diagnosing active HCV infection (Andrade et al., 2015). Serological assays and molecular assays are useful because they may detect early infection before clinical signs of disease appear and they may detect persistence of the virus or verify development of immunity (Andrade et al., 2015). Determination of the virus genotype is important because the duration and success of treatment depends on the HCV genotype (European Association for the Study of the Liver, 2016; Gupta, Bajpai, & Choundhary, 2014; Horn et al., 2011).

Rapid diagnostic tests (RDTs) are currently available for HCV, these are single-use disposable assays that are simple to use. Due to their simplicity, they can be performed by trained non-laboratory healthcare providers, support or peer workers. In addition, they are relatively inexpensive and have a rapid turnaround time (TAT) (World Health Organisation, 2017b).

### 1.5.9 Treatment

The primary goal of HCV treatment is to eradicate HCV which prevents progression to chronic liver disease. Sustained virologic response (SVR) is used to determine the effectiveness of

treatment. SVR is defined as having undetectable viral replication in a defined period of time after completion of therapy (Lam, Jeffers, Younoszai, Fazel, & Younossi, 2015). For several years, the standard treatment for chronic HCV infection involved a combination of interferon and indirect antivirals such as ribavirin. The duration of treatment varied from 24 or 48 weeks. This therapy has severe side effects and less than 50% efficacy (Andrade et al., 2015; Horn et al., 2011; Lam et al., 2015; Liang et al., 2000). The standard treatment for chronic HCV infection has changed since the introduction of new DAA (Andrade et al., 2015; Horn et al., 2011).

Interferon stimulates the immune system to fight the virus. PEG-INF, a modified form of interferon that makes the molecule more stable, is injected weekly depending on the HCV genotype. Ribavirin is an antiviral agent that stops viral replication. Ribavirin is taken orally multiple times a week depending on the HCV genotype. PEG-INF and ribavirin therapy has an average success rate of 40-60% depending on the HCV genotype; however, a major obstacle to this therapy is its adverse side effects. Almost all patients treated with PEG-INF and ribavirin present with side effects during the therapy which include influenza-like symptoms, neuropsychiatric effects, haematological abnormalities, and induction of autoimmune disorders. Extending the duration of therapy has increased the probability of side effects, which requires the therapies to be discontinued in some patients (Andrade et al., 2015; Horn et al., 2011; Lam et al., 2015). Furthermore, half of all patients with chronic HCV infection are either interferon-ineligible or intolerant to interferon (Gane et al., 2014; Lam et al., 2015).

The introduction of DAAs has transformed the treatment of HCV. These treatment regimens can be administered orally for a short duration (as short as six to eight weeks) with resulting cure rates of higher than 90%. DAAs are also associated with fewer serious adverse side effects in comparison to the standard PEG-INF and ribavirin therapy (Andrade et al., 2015; Lam et al., 2015; World Health Organisation, 2017b). Two DAAs are funded in NZ for treatment of patients infected with HCV genotype 1: VIEKIRA PAK ® (AbbVie Ireland) and Harvoni ® (Gilead Sciences). Different factors are considered before patients are treated with DAAs, these factors include: prior treatment history, presence of fibrosis, other underlying medical conditions, baseline HCV RNA level and HCV genotypes (Lam et al., 2015).

VIEKIRA PAK contains ombitasvir, paritaprevir, ritonavir and dasabuvir, and was approved by the FDA on 19th of December 2014 (Lam et al., 2015). VIEKIRA PAK utilises fixed-dose oral

tablets for the treatment of chronic HCV genotype 1 infection. VIEKIRA PAK is taken with or without ribavirin depending on HCV genotype (MEDSAFE, 2017). Harvoni contains ledipasvir and sofosbuvir, which was approved by the FDA on 10th October 2014 (Lam et al., 2015). Harvoni is an oral tablet used for the treatment of chronic HCV infection due to all HCV genotypes. Table 1.3 below summarises HCV treatments. Nationwide recommendations or guidelines for the DAAs are present in NZ Society of Gastroenterology HCV treatment guidelines for NZ.

There are other DAAs under development and are also in the approval process, however, further studies are required for special populations, such as patients with co-infection (HCV and HIV or HCV and HBV).

Table 1.3 Summary of HCV treatments available in NZ

| | **PEG-INF + Ribavirin** | **VIEKIRA PAK ®** | **Harvoni ®** |
|---|---|---|---|
| **Antiviral agents** | PEG-INF and ribavirin | Paritaprevir Ritonavir Ombitasvir Dasabuvir | Ledipasvir Sofosbuvir |
| **Mechanisms:** | Indirect antiviral agents | Inhibits NS3/4A, NS5A, NS5B | Inhibits NS5A and NS5B |
| **Mode of administration** | PEG-INF – injection Ribavirin – oral | Oral | Oral |
| **Treatment duration** | 24-48 weeks depending on genotype | 12 weeks | 8-12 weeks depending on genotype |
| **SVR** | Average of 40-60% | 96.7-100% | 95-100% |
| **Side Effects** | Anaemia, neutropenia, thrombocytopenia, flu-like symptoms, neuropsychiatric side effects, rash, insomnia | Headache, fatigue, nausea | Headache, fatigue, nausea, insomnia, diarrhoea |

Along with treatments, making lifestyle changes are recommended in managing HCV infection. This is to prevent and limit liver damage and to reduce the risk of spreading HCV (Andrade et al., 2015; Westbrook & Dusheiko, 2014).

### 1.5.10 Prevention

In the absence of a suitable vaccine for HCV prevention, the best prevention currently is to reduce the risk of exposure to HCV (World Health Organisation, 2016, 2017b). Prevention strategies involve the practice of universal precautions, blood screening, blood product purification, and risk reduction counselling (Choudhuri & Chowdhury, 2009).

## 1.6 Northland Pathology Laboratory and Labtests

Northland Pathology Laboratory and Labtests are community laboratories in Whangarei and Auckland, respectively. They are the two laboratories in the Northland and Auckland regions where almost all community tests are performed based on the agreed contract with their corresponding District Health Boards.

New protocols for community HCV testing protocols at Northland Pathology Laboratory, Labtests, and indirectly, LabPLUS were implemented in April 2016. Prior to the changes, HCV testing protocols involved testing HCV RNA and HCV genotypes on request regardless of clinical indications and history, as shown in Figure 1.6.

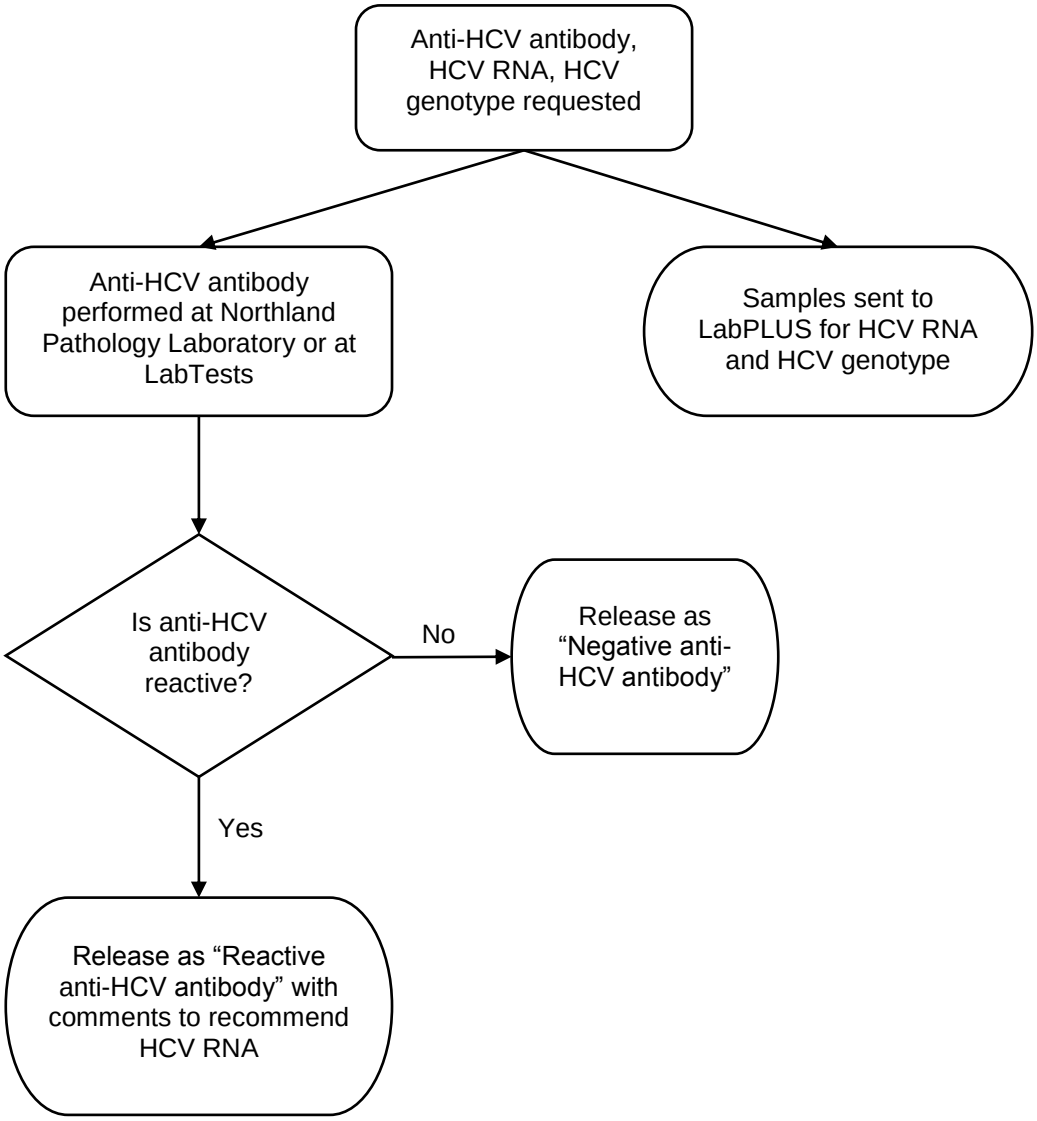


Figure 1.6 HCV test protocol prior to April 2016

Prior to the changes, testing was performed as requested by referrer. From April 2016, changes were implemented including: (a) pathologists' review of all reactive or positive anti-HCV antibody results with addition of comments as part of the result (to discourage repeated testing of anti-HCV antibody for known infections), as well as (b) the addition of reflex tests for HCV RNA and HCV genotype, if HCV RNA was detected, as indicated by reactive anti-HCV antibody results and the patient's history. In addition, (c) unnecessary repeat requests for HCV RNA and HCV genotyping were not processed as indicated by past results and the patient's history, refer to Figure 1.7 for anti-HCV antibody testing regime and Figure 1.8 for HCV RNA and HCV genotype testing regime below.

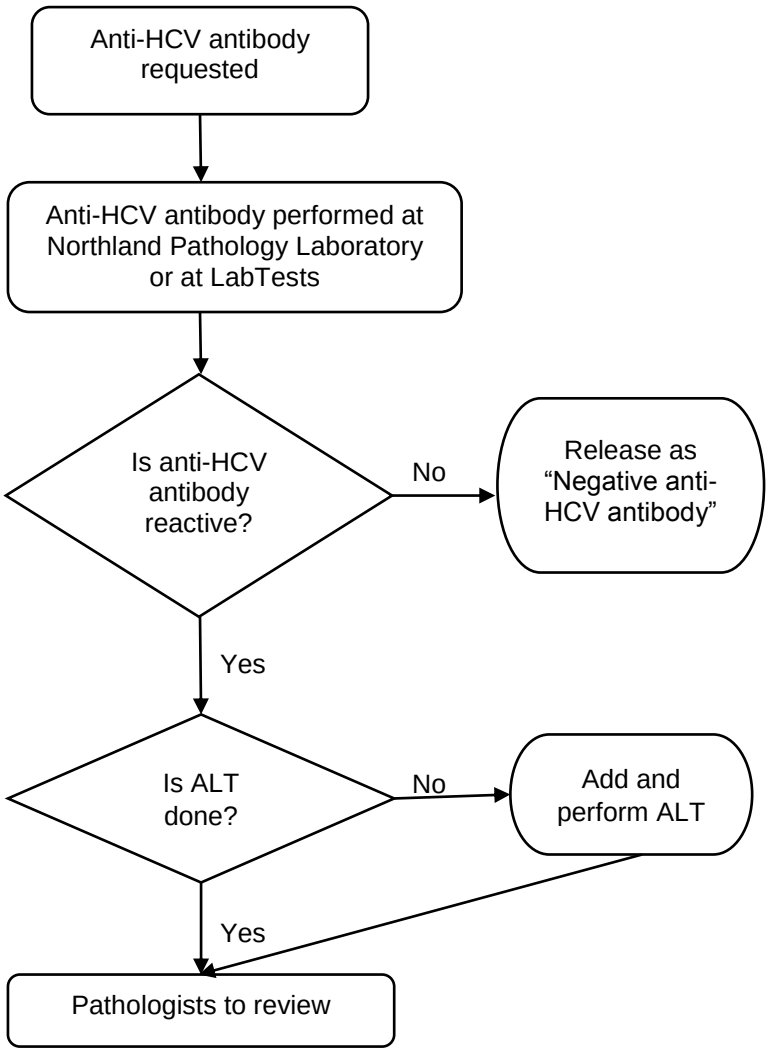


Figure 1.7 Anti-HCV antibody protocol after April 2016

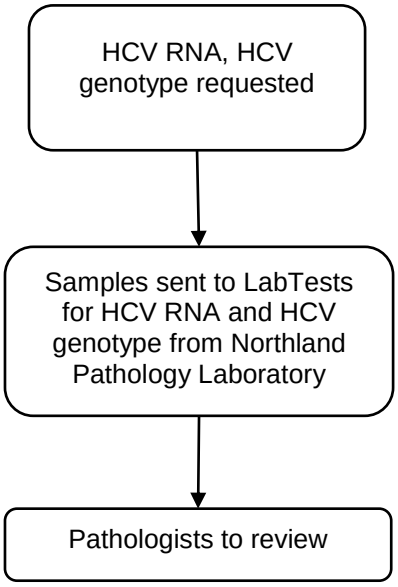


Figure 1.8 HCV RNA and HCV genotype protocol after April 2016

## 1.7 Aims

This thesis aims to conduct an audit of the three primary service providers to provide an overview of the impact of these changes in diagnosing HCV.

The objectives of this audit are to:

1. Assess the HCV testing services in a representative two months period using samples from 2015 and 2016 to determine the clinical appropriateness of tests requested and performed.
2. Provide objective evidence for possible improvement in current HCV testing protocols among service providers.
3. Identify whether there are impediments to best care in terms of resources, cost and turnaround times.

Chapter Two

# *Analytical and Clinical Aspects of HCV*

## 2.1 Introduction

HCV is recognised as an important global infection. Medical laboratories provide screening and confirmatory tests for the diagnosis of HCV infection. In 2015, pathologists at Northland Pathology Laboratory, Labtests, and LabPLUS had concerns that HCV tests were mis-utilised, resulting in possible delayed treatment and management, and impacting on healthcare resourcing. It was suspected that anti-HCV antibody screen tests were over-utilised, and HCV RNA and HCV genotypes were both over and under-utilised. Traditionally medical laboratories performed all the tests requested, regardless of clinical appropriateness of the requested tests. In April 2016, strategies were implemented at Northland Pathology Laboratory, Labtests, and LabPLUS to decrease mis-utilisation of HCV RNA and HCV genotyping testing. The strategies involved protocol changes: to review all reactive anti-HCV antibody results; to add reflex HCV RNA and/or HCV genotype if required depending on the anti-HCV antibody result and patient history; and to review all HCV RNA and HCV genotype requested.

A clinical audit was performed to compare the number, rate, and appropriateness of HCV testing before and after the protocol changes.

The aims of this chapter are to assess and compare the HCV testing services in a representative two-month period using samples (from 1$^{st}$ August to 30$^{th}$ September) in 2015 and 2016 to determine the clinical appropriateness of HCV tests requested and performed. This audit will provide objective evidence for possible improvement in current HCV testing protocols among service providers.

## 2.2 Laboratory Test Utilisation

The fundamental role of the medical laboratory service is to support and assist clinicians in the management of patients' outcomes. Like many other healthcare resources, the utilisation of medical laboratory services has increased during the past decade worldwide (Huck & Lewandrowski, 2013). Laboratory tests should not be requested without a proper plan for using the information gained. The elimination of unnecessary tests is becoming more and more important in the control and management of healthcare resources to help curb the rapid growth in healthcare costs (Huck & Lewandrowski, 2013). Excessive and redundant use of tests

contributes significantly to the problem of waste in healthcare. More and more laboratories are restricting some test requests and adding additional tests for a better patient service. While significant motivator to reduce the unnecessary testing is financial, there is also a drive to reduce false positive results, and to eliminate unnecessary follow-up tests and procedures (Hauser & Shirts, 2014). For instance, there have been many strategies reported in literature and have also been evaluated to control the use of laboratory utilisation.

Utilisation management is defined as reducing the over-utilisation, under-utilisation, and mis-utilisation of laboratory tests (Azadmanjir, Torabi, Safdari, Bayat, & Golmahi, 2015; Huck & Lewandrowski, 2013). The aim of utilisation management is to give rise to solutions and plans that will reduce the number of inappropriate laboratory test utilisations, in addition to increasing revenue (Azadmanjir et al., 2015).The goal of a laboratory utilisation model is to restrict use of tests that are over-utilised, increase use of tests that are under-utilised, and correct mis-use of tests that are requested incorrectly, at the wrong time, on the wrong patient, or at the wrong frequency (Snozek, Kaleta, & Hernandez, 2013). The concept of utilisation management is evidence-based improvement, where the criteria to determine the appropriateness of the test is based on medical evidence (Huck & Lewandrowski, 2013). Evidence-based criteria should include the timing and frequency of testing, choice of tests with common indications, clinical indication for testing, and determination of probability of out-of-range results (Huck & Lewandrowski, 2013). The main goal of utilisation management from the laboratory's perspective is to reduce the overall cost of health care without potential harm to the patient.

### 2.2.1 Appropriate Test Utilisation

Appropriate use of medical laboratory tests is necessary for optimal patient care and patient outcome. This has to be clinically valid, clinically effective, and cost effective (Horvath, 2013). Appropriate use of medical laboratory tests is based on a clinical question or intention to change patient management. Increased medical laboratory service is considered appropriate if it allows accurate diagnosis, provides ideal treatment and is monitored and provides accurate prognosis.

### 2.2.2 Inappropriate Test Utilisation

Inappropriate laboratory test utilisation includes both over-utilisation and under-utilisation. Over-utilisation occurs when tests are unnecessarily over-used and do not provide useful additional information. Under-utilisation occurs when tests are under-used and consequently fail to provide information that could benefit the outcome of patients (Snozek et al., 2013). Inappropriate use of medical laboratory services is likely to increase with advancing medical technology and increasingly sophisticated medical care and interventions. Preventing mis-utilisation of medical laboratory resources is acknowledged internationally, mainly to prevent adverse effect on patient's outcome and because of the pressure it places on health care costs (Huck & Lewandrowski, 2013; Snozek et al., 2013). A recent study reported that 26.5 to 42.8% of requested laboratory tests were unnecessary (Huck & Lewandrowski, 2013). It is generally accepted that between 10 and 50% of laboratory tests are unnecessary (Huck & Lewandrowski, 2013). Repeat test ordering is found to be a primary reason for increased laboratory use. It is often difficult to determine whether tests are appropriate or not.

### 2.2.3 HCV Test Utilisation

In 2016, pathologists from Northland Pathology Laboratory, Labtests, and LabPLUS identified areas of potential improvements in HCV test utilisation. Noting some requests for anti-HCV antibodies, HCV RNA, and HCV genotype are of questionable medical benefit as they are not providing any additional information in some patients (previously worked up for HCV infection), and that HCV RNA and HCV genotype are expensive. This initiative was undertaken to not only reduce costs but to also provide a better service by providing additional HCV RNA and/or HCV genotype that will contribute to earlier diagnosis and better HCV management. These changes should result in patients getting more accurate results (and fewer patients will get false positive results). This will also prevent unnecessary HCV RNA testing.

#### *2.2.3.1 Anti-HCV antibody*

Anti-HCV antibody is used as a screening assay for HCV infection, as it can detect early infection before clinical symptoms of liver disease appear. Anti-HCV antibodies are developed

from an exposure to HCV. Once the antibodies are produced, they will be present for life in healthy individuals. The anti-HCV antibody test is widely used for initial HCV infection screening worldwide. The test is optimised to maximise HCV detection rate and minimise false positive rate and is relatively faster and cheaper compared to a confirmatory test. Reactive or positive anti-HCV antibody results cannot be used to determine the status of HCV infection, they can only be used to indicate that the individual with the reactive anti-HCV antibody was once exposed to HCV. To determine whether it is active or resolved infection, a further NAT must be performed.

As previously mentioned, it was suspected that anti-HCV antibody tests were unnecessarily repeated, resulting in the over-utilisation of the test. Prior to April 2016, all reactive anti-HCV antibodies were released to clinicians with a comment to recommend HCV PCR. After April 2016, all reactive anti-HCV antibody results were reviewed by pathologists and HCV RNA and/or HCV genotypes were added where appropriate. Referrers no longer needed to request follow-up HCV RNA and/or HCV genotype testing. First time reactive anti-HCV antibody results had reflex HCV RNA and/or HCV genotype performed with an exception of the low-level antibody reactivity. Low-level results were tested on another platform with an alternative method to detect anti-HCV antibodies. If low-level results were consistently reactive, HCV RNA and/or HCV genotype were then performed. Reactive anti-HCV antibody results with previous reactive anti-HCV antibody results or with positive HCV RNA results were released with a generic comment stating that patient is anti-HCV antibody reactive, and HCV antibody persists for life so repeat antibody testing is not informative. HCV RNA were added to repetitive reactive anti-HCV antibody results without previous HCV RNA results, and the HCV RNA panel from Northland Pathology Laboratory and from Labtests were released and reported to clinicians with a comment stating specimen had been referred for HCV RNA and genotyping.

#### *2.2.3.2 HCV RNA*

HCV RNA is used as a confirmatory test for HCV infection. HCV RNA is a quantitative measure of viral load in patients with HCV infection. The HCV RNA test can be used as a first time confirmatory test, as well as to monitor the effectiveness of HCV treatment and for testing of a cure.

After April 2016, not all HCV RNA requests are performed. HCV RNA was performed with first time anti-HCV antibody reactive results, or where the patient did not have evidence of past HCV RNA testing. All HCV RNA requests were reviewed and vetted by pathologists daily at Northland Pathology Laboratory and at Labtests. This involved reviewing clinical details on laboratory request forms, past laboratory results, and clinical notes. If a patient was negative for anti-HCV antibody, HCV RNA was rejected as a negative anti-HCV antibody indicates that there has been no exposure to HCV. An example of a comment that is now attached to an over-utilised HCV RNA test request is 'HCV RNA has previously been not detected. This indicates PAST infection'. If there is a consistent history of re-exposure, a justification must be provided to perform HCV RNA testing. Another example is if the patient is known to be HCV RNA positive, repeat RNA testing is not indicated unless the patient is 12 weeks following completion of DAA treatment, or is undergoing interferon-based treatment.

## 2.3 HCV Assay Procedures and Principles

### 2.3.1 Anti-HCV antibody screening test

Current anti-HCV antibody screening tests used at Northland Pathology Laboratory and Labtests are based on third generation enzyme immunoassays. The third generation was developed in 1993 which measured anti-core antibodies, anti-NS3 antibodies, anti-NS4 antibodies and anti-NS5 antibodies. The fourth generation of anti-HCV antibody assay is yet to be used in medical laboratories, this is because it is yet to be proved by FDA. Table 2.1 demonstrates a summary of different generations of anti-HCV antibody assays and what they measure (Andrade et al., 2015).

Table 2.1 Summary of different generations of anti-HCV antibody assays

| | **Developed year** | **Measures:** | | | | |
|---|---|---|---|---|---|---|
| | | Capsid Antigen | Anti-Core antibodies | Anti-NS3 antibodies | Anti-NS4 antibodies | Anti-NS5 antibodies |
| **1st Gen.** | 1989 | | | | ✔ | |
| **2nd Gen.** | 1992 | | ✔ | ✔ | ✔ | |
| **3rd Gen.** | 1993 | | ✔ | ✔ | ✔ | ✔ |
| **4th Gen.** | NA | ✔ | ✔ | ✔ | ✔ | ✔ |

#### 2.3.1.1 Platform

At Northland Pathology Laboratory in Whangarei an instrument called cobas 6000 e601 by Roche Diagnostics is used for the anti-HCV antibody screening assay. At Labtests in Auckland, an instrument called ADVIA Centaur XPT by Siemens is used for the anti-HCV antibody screening assay.

#### 2.3.1.2 Principle

The principle of measuring anti-HCV antibodies is a sandwich immunoassay for both Roche cobas 6000 e601 and Siemens ADVIA Centaur XPT. Sandwich assays involve forming a "sandwich" structure with the target antibody or antigen with a complex of labelled antibodies.

For Roche cobas 6000 e601 and Siemens ADVIA Centaur XPT, the sample is incubated with reagent containing recombinant and synthetic HCV-specific antigens. Both Roche and Siemens use biotinylated HCV-specific antigens to capture anti-HCV antibodies. If the anti-HCV antibody is present in the sample, antigen-antibody complexes will form. Detection antibodies are added. Roche uses ruthenium-complex and tripropylamine bound antibodies and Siemens uses acridinium ester bound antibodies, either of which bind to the antigen-antibody complex to form the "sandwich" structure. Chemiluminescent emission is induced, and light emitted is measured (Roche Diagnostics, 2016; Siemens Healthcare Diagnostics, 2014).

#### 2.3.1.3 In-house Reactive anti-HCV antibody confirmation

If the anti-HCV antibody is reactive for the first time, an internal in-house confirmation test is done at Northland Pathology Laboratory and at Labtests. This involves a two-assay serological testing strategy where an aliquot sample is obtained from the primary sample and it is spun at 6000 rpm for ten minutes. It is then repeated for the anti-HCV antibody in duplicates. If the result is borderline low reactive, the sample is sent to a different laboratory for the anti-HCV antibody test which is repeated on a different platform. If there is evidence of acute HCV infection or the previous anti-HCV antibody was negative within the last year, the case is reported to the medical officer of health at the Northland District Health Board or Auckland District Health Board.

### 2.3.2 HCV RNA Confirmatory Test

NAT is used to confirm HCV infection by detecting and measuring HCV RNA. Measurement of HCV RNA is also used to monitor the response to HCV treatments.

#### *2.3.2.1 Platform*

At LabPLUS in Auckland, The COBAS AmpliPrep/COBAS Taqman HCV Quantitative Test is used to measure and detect HCV RNA.

#### *2.3.2.2 Principle*

Using TaqMan technology, real-time PCR measures quantitative results. The COBAS AmpliPrep/COBAS Taqman HCV Quantitative Test is based on three major processes: sample preparation to isolate HCV RNA; reverse transcription of the target RNA to generate complementary DNA; simultaneous PCR amplification of target complementary DNA and exposure of detection probe specific to the target (Roche Diagnostics, 2008).

Automatic sample preparation is done on the COBAS AmpliPrep Instrument by a generic silica-based capture technique, where HCV virus particles are lysed with a protease to release RNA and a buffer to protect the released HCV RNA. The reagent provided by Roche contains primers and probes specific for HCV RNA and the detection of amplified DNA is performed using a target-specific and a complex labelled probe that identifies HCV amplicons (Roche Diagnostics, 2008). Quantification of HCV RNA is expressed as the number of HCV RNA IU/mL and the logarithm of the number of HCV RNA IU/mL. Quantification value indicates potential infectivity and it is used to follow response in relation to HCV therapy.

## 2.4 Aims of the study

This audit was undertaken to estimate the size of inappropriate test utilisation of HCV tests at Northland Pathology Laboratory, Labtests, and indirectly at LabPLUS. This research examines the clinical appropriateness of HCV tests requested and performed. Ultimately this was

undertaken to provide evidence for possible improvement in current HCV testing protocols among service providers. These findings will be important as most NAT, for example, HCV RNA, tests are expensive and unnecessary repeat testing provides no additional useful clinical purpose especially for anti-HCV antibody and HCV RNA tests.

The aims of this chapter are (a) to assess the HCV testing services representing two months of samples collected in 2015 and 2016 to determine the clinical appropriateness of HCV tests requested and performed. It also aims to (b) provide objective evidence for possible improvement in current HCV testing protocols among service providers.

## 2.5 Materials and Methods

### 2.5.1 Study type

This is a descriptive audit study, where data were collected and analysed.

### 2.5.2 HCV Data Extraction

Data for all anti-HCV antibody, HCV RNA, and HCV genotype requests were extracted from Northland Pathology Laboratory and Labtests for the period between 1st of August to 30th of September 2015 and 2016. The following information from the data was extracted from the laboratories: referred year; laboratory request number; NHI; gender; age; requestor specialty; account code; practice suburb; practice city; date referred; date reported; panel (anti-HCV antibody, HCV RNA or HCV genotype); and anti-HCV antibody results. Additionally, six-years' worth of anti-HCV antibody test results with repeat frequency for negative anti-HCV antibody results were also extracted.

### 2.5.3 HCV Data Refinement

Refinement of the data was made using Microsoft excel. HCV genotype was disregarded as it was not part of the audit. Data from patients without an NHI were removed. Requests that were non-DHB funded (privately funded, immigration, insurance, commercial, patient requests, occupational health) were also removed. The following data was categorised for the audit: 1)

age into age groups; 2) requested doctor specialists into four groups: GP, specialists, alcohol/drug/sexual practice clinicians, and other. Specialists included: haematologists, Hepatitis Foundation doctors and nurses, doctors from oncology, renal and dialysis department, gastroenterology, fertility, cardiology, dermatologists, emergency department, surgery, liver transplant unit, general medicine, infectious disease, rheumatology, and mental health. Alcohol/drug/sex practice clinicians included: doctors or from rehab, alcohol, drug, or sexual clinic services. Other included: nurses and midwives.

For confidentiality reasons, any identifiable patient and requestor information (NHI, DOB, and address) was deleted after completion of data collection. Prior to data collection, ethics approval was requested from the National NZ ethics committee.

### 2.5.4 HCV Data Source and Ethics

Required data was collected for all reactive anti-HCV antibody results and all requested HCV RNA from the extracted data using Ultra and TestSafe. Ultra is the Northland Pathology Laboratory and Labtests laboratory information system and TestSafe is an Auckland regional patient data repository. Ethical approval was granted from HDEC and TestSafe.

#### *2.5.4.1 Anti-HCV Antibody Data*

Data were collected from all equivocal and reactive anti-HCV antibody results: past anti-HCV antibody results, a total frequency of anti-HCV antibody requests and HCV RNA results (if performed) in the past 10 years.

#### *2.5.4.2 HCV RNA Data*

Data were collected from all HCV RNA requests: past anti-HCV antibody results, past HCV RNA results, and total frequency of HCV RNA requests in the past 10 years.

### 2.5.5 Appropriateness of HCV Tests Analysis

Collected data were analysed for the appropriateness of anti-HCV and HCV RNA tests requested and performed. Table 2.2. showed the example criteria for determining appropriateness of HCV tests. These decisions were made by pathologists.

Table 2.2 Criteria for determining appropriateness of HCV tests

| | Appropriate | Inappropriate |
|---|---|---|
| **Anti-HCV antibody requests:** | • There were no previous reactive anti-HCV results | • There were previous reactive anti-HCV results<br>• There were previous positive HCV RNA results<br>• There were previous defined genotype results |
| **HCV RNA** | • Anti-HCV antibody reactive for the first time with no previous HCV RNA results<br>• Anti-HCV antibody reactive in the past without previous HCV RNA results<br>• Possible acute infection based on history and liver tests<br>• Indicated suspected re-infection of HCV<br>• Treatment monitoring<br>• Test of cure<br>• Patients known immunocompromised | • No previous anti-HCV results<br>• Anti-HCV antibody negative<br>• Repeated HCV RNA without clinical indications<br>• On treatment for HCV (DAA)<br>• Regular repeat without obvious clinical indications (e.g., risk of re-infection or on treatment)<br>• Repeat of negative HCV RNA<br>• Too early post-end of treatment for test of cure<br>• Past cure – repeat testing |

## 2.6 Results

Anti-HCV antibody and HCV RNA requested data from 1st of August to 30th of September 2015 and 1st of August to 30th of September 2016 were analysed. Each number represents a request, not a patient.

### 2.6.1 Demographics and Geographic of all HCV Tests Requested

There were a total of 6083 and 6268 anti-HCV antibody and HCV RNA requests between 1st of August to 30th of September 2015 and 2016, respectively. More male test requested were evident in both 2015 and 2016. Table 2.3 demonstrates the gender distribution of all requested HCV tests in the stated timeframe. Unknown gender category consists of foreigners without

specified gender from their requestors, transgenders, and new born babies. Ages ranged from one year to 96 years in 2015 and zero to 94 years in 2016. The age group of 25 to 34 were most prevalent for requested HCV tests as shown in Figure 2.1 below.

Table 2.3 Gender distribution of all HCV tests requested

| | 2015 | | 2016 | |
|---|---|---|---|---|
| **Total no. of requests:** | 6083 | | 6268 | |
| **Gender:** | n | (%) | n | (%) |
| **Male** | 3275 | 53.8 | 3435 | 54.8 |
| **Female** | 2806 | 46.1 | 2831 | 45.2 |
| **Unknown** | 2 | 0.0 | 2 | 0.0 |

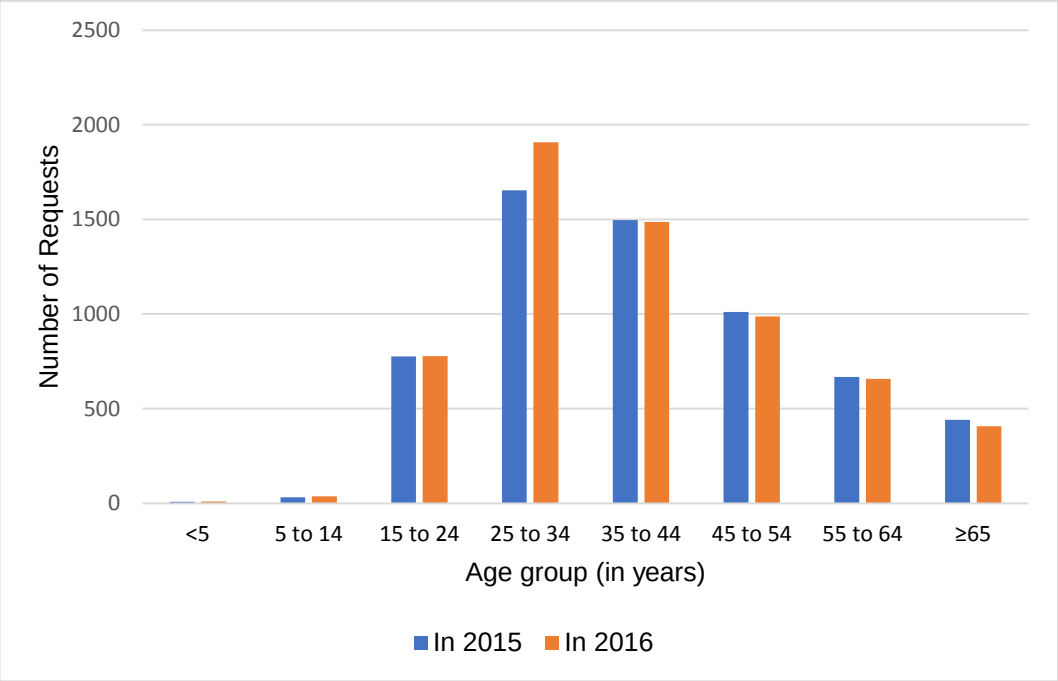


Figure 2.1 Age distribution of all HCV tests requested

## 2.6.2 HCV Data Summary

### *2.6.2.1 Refinement of HCV Data*

Of the original 12099 anti-HCV antibody requests, there were 271 HCV RNA and 49 HCV genotype requests from the 2015 dataset and 5836 (48.2%) of anti-HCV antibody and 247 (91.1%) of HCV RNA requests remained after data refinement. Data refinement involved: removal of HCV genotype results, removal of data without NHI, and removal of non-DHB funded

requests. Of the original 13498 anti-HCV antibody requests, there were 276 HCV RNA and 136 HCV genotype requests from the 2016 dataset and 6016 (44.6%) of anti-HCV antibody and 252 (91.3%) of HCV RNA requests remained after data refinement as mentioned previously and as mentioned in section 2.5.3.

#### *2.6.2.2 HCV Data used for the Audit*

Table 2.4 below summarises the number of anti-HCV antibody and HCV RNA requests that were used for this audit. 3.2% and 2.8% of anti-HCV antibody requests were reactive in 2015 and 2016, respectively. 35.7% of HCV RNA requests were rejected by pathologists in 2016 after the HCV testing protocol changes.

Table 2.4 Overview of anti-HCV antibody and HCV RNA test results

| | **2015** | | **2016** | |
|---|---|---|---|---|
| **Anti-HCV antibody:** | n | (%) | n | (%) |
| **Total** | 5836 | | 6016 | |
| **Negative** | 5640 | 96.6 | 5844 | 97.1 |
| **Reactive** | 188 | 3.2 | 171 | 2.8 |
| **Equivocal** | 8 | 0.1 | 1 | 0.0 |
| | | | | |
| **HCV RNA:** | n | (%) | n | (%) |
| **Total** | 247 | | 252 | |
| **Negative** | 128 | 51.8 | 73 | 29.0 |
| **Positive** | 116 | 47.0 | 88 | 34.9 |
| **NA (missed or mis-registered)** | 3 | 1.2 | 1 | 0.4 |
| **Rejected** | 0 | 0.0 | 90 | 35.7 |

## 2.6.3 Utilisation of Anti-HCV antibody tests

#### *2.6.3.1 Distribution of All Anti-HCV Antibody requests between Gender*

A total of 5836 requests from 1st of August to 30th of September 2015 data, and 6016 from 1st of August to 30th of September 2016 data, of all anti-HCV antibody requests were evaluated. Out of these 53.5% and 54.3% were categorised as males from 2015 and 2016, respectively. Out of these, 3.6% and 3.4% were reactive for anti-HCV antibody requests from 2015 and 2016, respectively. A total of 46.5% and 45.7% of requests were categorised as females from the 2015 and 2016 dataset, respectively. Out of these 2.8% and 2.1% requests were reactive for

anti-HCV antibody requests from 2015 and 2016, respectively. Table 2.5 illustrates anti-HCV antibody results distribution between gender.

Table 2.5 Anti-HCV antibody results distribution between gender

| | | 2015 | | 2016 | |
|---|---|---|---|---|---|
| | | n | (%) | n | (%) |
| **Total number of anti-HCV antibody requests:** | | 5836 | | 6016 | |
| **Gender:** | **Male:** | | | | |
| **Anti-HCV antibody Results:** | **Total** | 3122 | 53.5 out of total | 3266 | 54.3 out of total |
| | **Negative** | 3005 | 96.3 | 3153 | 96.5 |
| | **Reactive** | 111 | 3.6 | 112 | 3.4 |
| | | | | | |
| **Gender:** | **Female** | | | | |
| **Anti-HCV antibody Results:** | **Total** | 2712 | 46.5 out of total | 2748 | 45.7 out of total |
| | **Negative** | 2633 | 97.1 | 2689 | 97.9 |
| | **Reactive** | 77 | 2.8 | 59 | 2.1 |

### *2.6.3.2 Reactive Anti-HCV Antibody*

A total of 188 requests from 1st of August to 30th of September 2015 dataset, and 171 requests from 1st of August to 30th of September 2016 dataset were reactive for anti-HCV antibody and were evaluated. Of these, 59.0% and 65.5% were male from 2015 and 2016, respectively. An average of 90.6% of reactive anti-HCV antibody requests were from Auckland. Table 2.6 demonstrates gender distribution and area distribution of reactive anti-HCV requests. Age ranged from 1 to 81 years in 2015 and 0 to 77 years in 2016. The highest age group was 45 to 54 for both 2015 and 2016 as shown in Figure 2.2.

Table 2.6 Gender and area distribution of reactive anti-HCV antibody requested and performed

| | 2015 | | 2016 | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| **Total:** | 188 | | 171 | |
| **Gender:** | | | | |
| **Male** | 111 | 59.0 | 112 | 65.5 |
| **Female** | 77 | 41.0 | 59 | 34.5 |
| | | | | |
| **Area:** | | | | |

| | | | | |
|---|---|---|---|---|
| **Auckland** | 167 | 88.8 | 158 | 92.4 |
| **Northland (including Whangarei)** | 19 | 10.1 | 12 | 7.0 |
| **Other** | 2 | 1.1 | 1 | 0.6 |

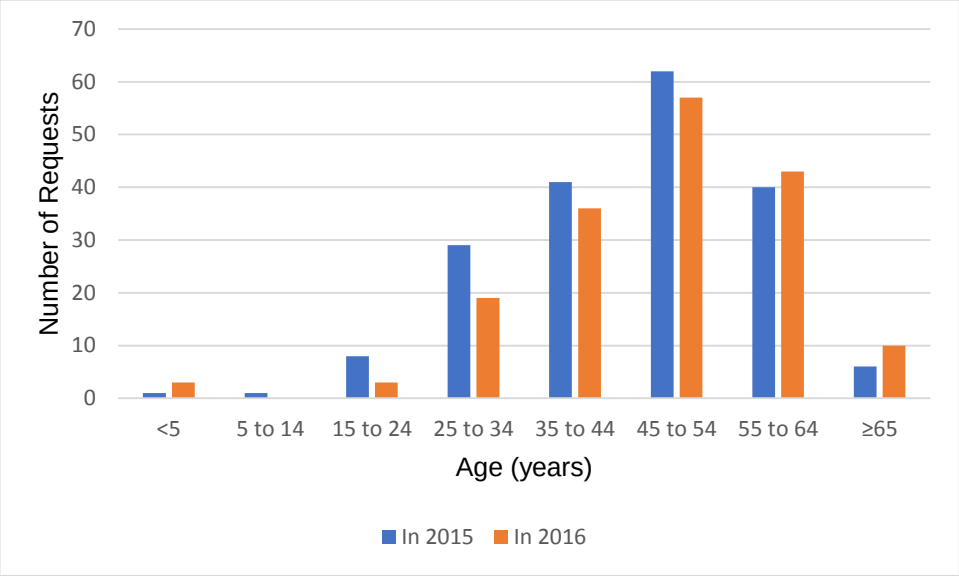


Figure 2.2 Age distribution of reactive anti-HCV antibody tests

Out of 188 total reactive anti-HCV antibody requests from 2015 dataset, 37.2% were considered appropriate, as they were new anti-HCV antibody reactive tests and they were not known to be previously reactive. Out of 171 total reactive anti-HCV antibody requests from 2016 dataset, 40.9% were considered appropriate. Table 2.7 below summarises the appropriateness of reactive anti-HCV antibody requests.

Table 2.7 Appropriateness of anti-HCV antibody requested

| | **2015** | | **2016** | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| **Total Reactive anti-HCV** | 188 | | 171 | |
| **Appropriate anti-HCV** | 70 | 37.2 | 70 | 40.9 |
| **Inappropriate anti-HCV** | 118 | 62.8 | 101 | 59.1 |

Out of 118 and 101 inappropriate anti-HCV antibody requests in 2015 and 2016, respectively, the frequency of inappropriate reactive anti-HCV antibody requests in the past 10 years for these patients are shown below in Figure 2.3. The number of repeats on patients known to be reactive in past 10 years prior to this audit ranged from one to greater than 10. 39 (33.1%) and 34 (33.7%) had two repeated reactive anti-HCV antibody tests.

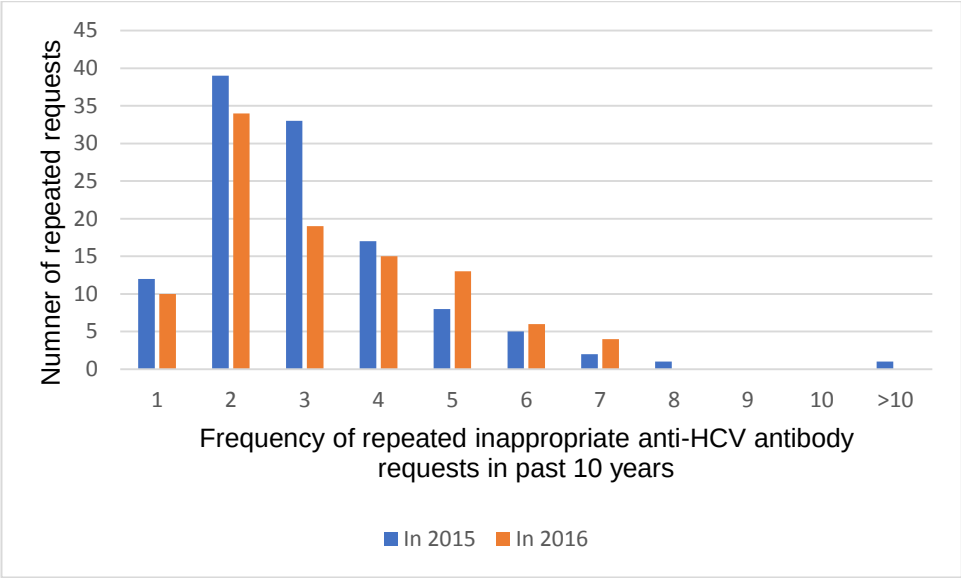


Figure 2.3 Frequency of inappropriate anti-HCV antibody requests on patients known to be reactive in past 10 years

As demonstrated in Table 2.8 below, out of the 70 appropriate anti-HCV antibody requests from 2015 dataset, 54.3% of the requests had HCV RNA test done; whereas from 2016 dataset, 98.6% had HCV RNA test done as part of the reflex testing regime.

Table 2.8 Number and percentage of HCV RNA performed on appropriate reactive anti-HCV antibody requests

| | 2015 | | 2016 | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| **HCV RNA performed** | 38 | 54.3 | 69 | 98.6 |
| **HCV RNA not performed** | 32 | 45.7 | 1 | 1.4 |

Out of all reactive anti-HCV antibody requests, both inappropriate and appropriate, 79.3% of the 2015 anti-HCV antibody tests had past HCV RNA tests done and 99.4% of the 2016 anti-HCV antibody tests had past HCV RNA tests done as demonstrated in Table 2.9 below.

Table 2.9 Number and percentage of HCV RNA performed from all reactive anti-HCV antibody requests

| | 2015 | | 2016 | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| **HCV RNA performed** | 149 | 79.3 | 170 | 99.4 |
| **HCV RNA not performed** | 39 | 20.7 | 1 | 0.6 |

### *2.6.3.3 Negative anti-HCV Antibody*

All negative anti-HCV antibody requests, on the basis of no previous reactive anti-HCV antibody result, were assumed to be clinically valid and therefore appropriate. Further data were collected on the patients with negative antibody tests – an extract was performed to collect anti-HCV antibody tests on these patients for the six years prior to the test reviewed in this audit. These are summarised in Table 2.10. A total of 5640 negative anti-HCV antibody requests were collected from 2015 data, and a total of 5844 negative anti-HCV antibody requests were collected from 2016 data. Repeated anti-HCV antibody testing ranged from zero to 26 times; a majority of patients (70.8%, 68.1% from 2015 and 2016 data, respectively) did not have repeated testing done, while a small number of patients had multiple repeat tests. No clinical information was available on why these tests were done.

Table 2.10 Frequency of repeated negative anti-HCV antibody requests

| **Frequency of repeated negative anti-HCV antibody test per patient** | **2015** | | **2016** | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| **0** | 3994 | 70.8 | 3981 | 68.1 |
| **1** | 1118 | 19.8 | 1206 | 20.6 |
| **2** | 286 | 5.1 | 372 | 6.4 |
| **3** | 96 | 1.7 | 156 | 2.7 |
| **4** | 57 | 1.0 | 52 | 0.9 |
| **5** | 30 | 0.5 | 31 | 0.5 |
| **6** | 16 | 0.3 | 12 | 0.2 |
| **7** | 14 | 0.3 | 4 | 0.1 |
| **8** | 4 | 0.1 | 7 | 0.1 |
| **9** | 6 | 0.1 | 6 | 0.1 |
| **10** | 11 | 0.2 | 4 | 0.1 |
| **>10** | 8 | 0.1 | 13 | 0.2 |

## 2.6.4 Utilisation of HCV RNA tests

From 1st of August to 30th of September 2015 there were 247 HCV RNA requested, and 252 test requested for the period 1st of August to 30th of September 2016 of requested HCV RNA tests were analysed. Of those 61.9% and 67.1% were categorised as males in 2015 and 2016, respectively. An average of 88.2% of requested HCV RNA test was from the Auckland regions. Table 2.11 illustrates gender distribution and area distribution of all HCV RNA requests. Age

ranged from 11 to 81 years in 2015 and 20 to 75 years in 2016. The highest age group was 55 to 64 for both 2015 and 2016 data as shown in Figure 2.4.

Table 2.11 Gender and area distribution of HCV RNA requested

| | 2015 | | 2016 | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| **total** | 247 | | 252 | |
| **Gender:** | | | | |
| **Male** | 153 | 61.9 | 169 | 67.1 |
| **Female** | 94 | 38.1 | 83 | 32.9 |
| | | | | |
| **Area:** | | | | |
| **Auckland** | 221 | 89.5 | 219 | 86.9 |
| **Northland (including Whangarei)** | 23 | 9.3 | 27 | 10.7 |
| **Other** | 3 | 1.2 | 6 | 2.4 |

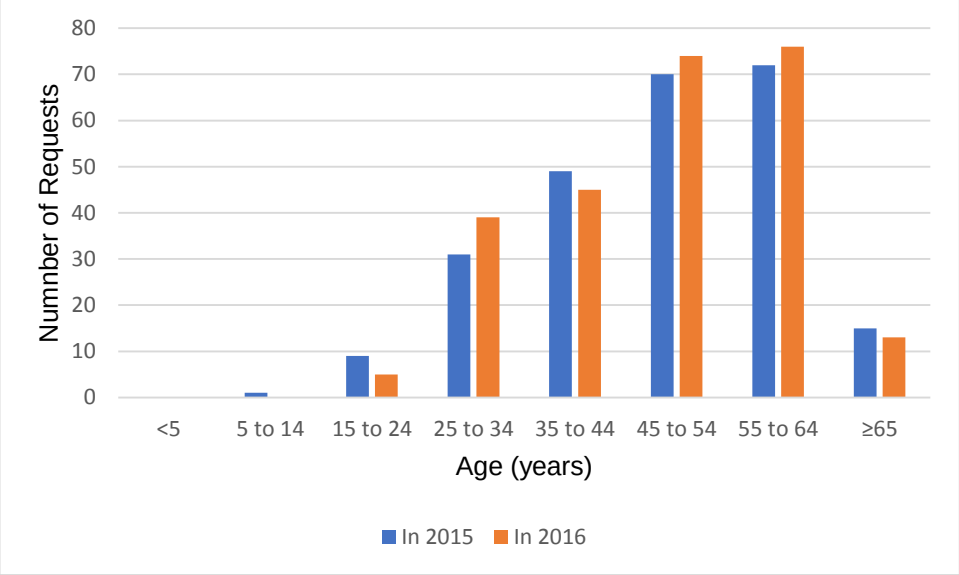


Figure 2.4 Age distribution of HCV RNA requested

Of 247 HCV RNA requests from 2015, 47.0% were positive, and 1.2% were missed or mis-registered with no available result. Of 252 HCV RNA requests from 2016, 34.9% were positive; 29.0% were negative; 0.4% were missed; and 35.7% were rejected due to the new HCV testing protocols. Of the 247 total HCV RNA requests from 2015, 49.4% were considered appropriate. Of 252 total HCV RNA requests from 2016, 64.3% were considered appropriate as summarised in Table 2.12. From 2015, out of 247 HCV RNA requests, 34 (13.8%) had no evidence of past HCV RNA testing. From 2016, out of 252 HCV RNA requests, 55 (21.8%) had no evidence of

past HCV RNA testing. Of the 125 inappropriate HCV RNA requests in 2015, 21 requests were negative for the anti-HCV antibody. Out of 90 inappropriate HCV RNA requests in 2016, one was negative for the anti-HCV antibody. Initially 93 out of 252 HCV RNA requests were rejected, but three of those rejected requests had HCV RNA performed after the referrer consulted with the pathologist. These information is presented in the raw data.

Table 2.12 HCV RNA results and appropriateness of HCV RNA requested

| | 2015 | | 2016 | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| **Total of HCV RNA requested** | 247 | | 252 | |
| **Positive HCV RNA** | 116 | 47.0 | 88 | 34.9 |
| **Negative HCV RNA** | 128 | 51.8 | 73 | 29.0 |
| **NA (missed, mis-registered)** | 3 | 1.2 | 1 | 0.4 |
| **Rejected** | 0 | 0.00 | 90 | 35.7 |
| | | | | |
| **HCV RNA Request Appropriateness** | n | (%) | n | (%) |
| **Appropriate HCV RNA** | 122 | 49.4 | 162 | 64.3 |
| **Inappropriate HCV RNA** | 125 | 50.6 | 90 | 35.7 |

The frequency of performed HCV RNA tests in the past 10 years from patients in this audit are shown below in Figure 2.5.

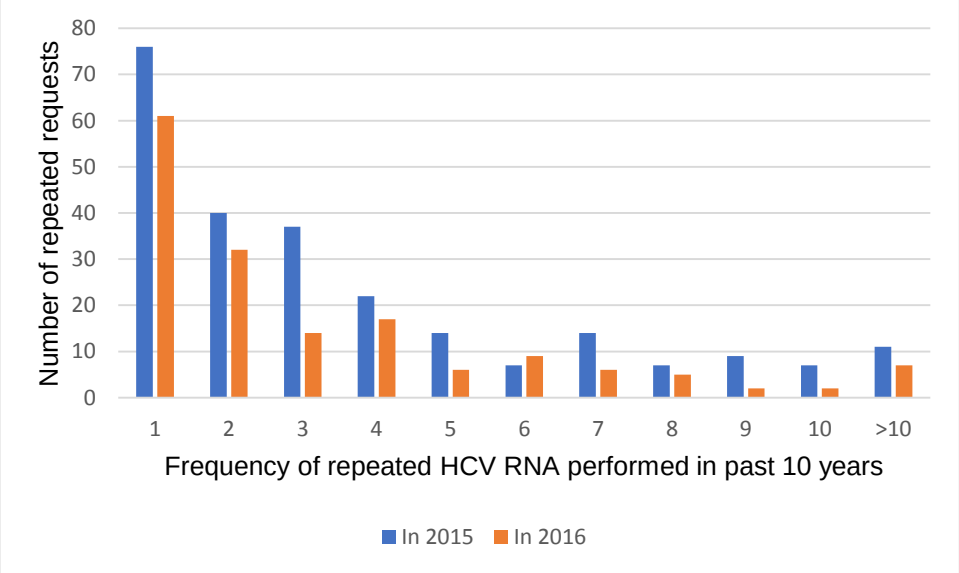


Figure 2.5 Frequency of HCV RNA performed in 10 years

## 2.7 Discussion

### 2.7.1 Demographic and prevalence

From this audit, 3.2% of the study group were reactive for the anti-HCV antibody from 2015 dataset, and 2.8% were reactive for the anti-HCV antibody from 2016 data. Sero-positive prevalence in this audit was higher than that estimated (1.2% anti-HCV antibody reactivity rate) in NZ, which is to be expected given that referrers are supposed to be requesting testing on the basis of an assessment of risk. A recent study in Dunedin, NZ, by Vermunt et al., 2015, found a sero-positive rate of 3.3% to 4.0% amongst the 40 to 59 year old Dunedin population.

In this audit, a peak prevalence of the reactive anti-HCV antibody occurred in 45 to 54 year old patients from this audit. However, the peak prevalence from this audit may not be truly representative of the NZ population. A recent study in Europe identified a peak prevalence for anti-HCV antibody that occurred in 55 to 65 year old patients (Westbrook & Dusheiko, 2014). If a full-scale NZ population study is to be performed, a peak sero-prevalence for anti-HCV may be in the 55 to 64 year old group, which could be similar to what is observed in Europe.

However, there are a number of limitations encountered with this audit, such as the audit design, ethnicity, socio-economic status, and clinical details not being available.

Future direction for the study of HCV in NZ may include a population-based study; this would be beneficial in terms of accurate measurement of HCV prevalence in different regions or even for the whole of NZ. This would allow healthcare utilisation to be studied within a geographical area. It has been emphasised that there is no existing survey or qualitative data regarding HCV prevalence in NZ.

### 2.7.2 HCV Test Utilisation

#### *2.7.2.1 Under-utilisation of anti-HCV antibody requests*

As mentioned earlier in section 2.7.1, within Europe peak prevalence for anti-HCV antibody occurs in 55 to 65 year old patients. From this audit, peak prevalence for HCV testing occurred in the 25 to 34 year old age group. This might suggest under-utilisation of anti-HCV antibody tests to screen for other age groups and those who are in the at-risk group for HCV infection.

Vermunt et al., 2015 suggested that more people need to be screened, as approximately 75% of individuals with HCV infection may be unaware of the infection. Lack of diagnosis of HCV infection could be a reason why the estimated annual treatment rate of 1.8% is low for HCV infection in NZ (Gane et al., 2014). This enforces the need for a HCV screening program to target those who are in high risk groups in NZ. Early diagnosis of HCV would greatly reduce HCV-related chronic liver diseases and reduce economic burden from HCV-related chronic liver diseases. It is noted that Europe's epidemiology of HCV may be different from NZ, and more epidemiology data are needed to support these data.

#### *2.7.2.2 Over-utilisation of anti-HCV antibody requests*

From the data gathered between 1st of August to 30th of September 2015 and 2016, it was evident that more than half of the requests from reactive anti-HCV antibody were inappropriate; 62.8% were considered inappropriate from 2015 data, and 59.1% were considered inappropriate from 2016 data. The reduction percentage of 3.7% after the HCV protocol change may not be significant for anti-HCV antibody tests. This is because only reporting comments have changed to reactive anti-HCV antibody results released to the referrers after April 2016. It may be that many of the negative anti-HCV antibody requests were also not clinically indicated (if patients did not have risk factors for infection); however, we were unable to determine whether or not this was the case in this audit.

All of the inappropriate reactive anti-HCV antibody results were repeated requests where the patient had already had a reactive test. It is unnecessary to repeat reactive anti-HCV antibody tests as an individual who has developed anti-HCV antibodies will remain antibody reactive for life. Repeated reactive anti-HCV antibody testing is unnecessary. It will not provide any extra information even if the patient is immunocompromised. This may be due to requester inexperience or lack of knowledge about the appropriate use of the anti-HCV antibody test, or it may be due to change of practice by patients or clinicians. Increasing awareness of what reactive anti-HCV antibodies means for both referrers and patients might reduce unnecessary repeat testing of anti-HCV antibodies.

With negative anti-HCV antibody requests, around 30% were repeated requests. From 2015 data repeat frequency of negative anti-HCV antibody ranged from zero times to 26 times; from

2016 data, repeat frequency of negative anti-HCV antibody ranged from zero times to 23 times. It is impossible to determine if those repeats were well utilised from this audit. It would be hard to determine the appropriateness of repeated negative anti-HCV antibody results as it is not possible to assess the clinician's rationale for test ordering.

#### *2.7.2.3 Under-utilisation of HCV RNA requests.*

From 2015 data, it was apparent that 20.7% of all reactive anti-HCV antibody results did not have HCV RNA performed. Without HCV RNA results, the status of HCV infection cannot be determined and therefore could result in delay or no treatment of possible HCV infections. In addition, it was also apparent that 45.7% of appropriate reactive anti-HCV antibody results did not have follow up HCV RNA performed in the timeframe studied. Appropriate reactive anti-HCV antibodies possibly indicate a newly diagnosed HCV infection. But without HCV RNA appropriate patient care management cannot be initiated. This would be classified as under-utilisation of HCV RNA requests which may have an adverse outcome on patients with active HCV infection. After the HCV test protocol change in April 2016, from 2016 data, there was only 0.6% of reactive anti-HCV antibody results that did not have HCV RNA performed. This significant reduction confirms that the new protocol implemented significantly reduced under-utilisation of HCV RNA tests, which in turn has reduced possible adverse outcomes to patients.

#### *2.7.2.4 Over-utilisation of HCV RNA requests.*

Over-utilisation of HCV RNA was reduced significantly after the implementation of HCV testing protocol changes in 2016. Approximately, 98.1% of HCV RNA tests performed were considered appropriate from 2016 data, whereas from 2015 data less than half (49.6%) were considered appropriate. This was largely due to the clinical review and vetting process undertaken by the pathologists. We found that 35.7% of HCV RNA requests were rejected in 2016. Of those rejected requests, three were re-added and had HCV RNA performed. This could be due to the fact that there was no clinical indication for the HCV RNA test to be performed on the request form. These cases highlight the importance of communication between the referrers and pathologists, and also shows that laboratory's decisions are not always 'set in stone'.

Requesting and performing HCV RNA with negative anti-HCV antibody results is highly inappropriate unless the patient is known to be immunocompromised and there is a specific reason for testing for HCV RNA. From 2015 data, there were 21 HCV RNA requests where HCV RNA was performed with a negative anti-HCV antibody results. From 2016 data there was one HCV RNA performed with an associated negative anti-HCV antibody result. The one HCV RNA performed with negative anti-HCV antibody results may have slipped through the new protocol due to human error.

From this audit, one of the challenges was to identify which patient is considered appropriate or inappropriate for HCV RNA testing without clinicians' notes. The current criteria for HCV test appropriateness rely on minimal standard recommendations or guidelines set by pathologists or a professional society. In addition, resources set in literature and local consensus are used to set rules and criteria to form validated and individual opinions (Hauser & Shirts, 2014). From 2016 data, it was apparent that the referrers would contact pathologists to discuss HCV RNA to be performed if the requests were rejected.

A frequency study for anti-HCV antibody and HCV RNA would have been more useful if it had defined a test repeat period. From an accurate repeat period of HCV tests, accurate repeated tests in percentage of the total workload could have been calculated. Repeating HCV RNA can provide useful information if clinically indicated. Unnecessary repeated HCV RNA could not be determined with this audit, as the appropriateness of HCV RNA and frequency of HCV RNA were done separately. Therefore, HCV RNA frequency cannot be used as an indication of over-utilisation of HCV RNA as repeated HCV RNA can be classified appropriate dependent on the history and clinical indications. One HCV RNA request that was rejected by Northland Pathology Laboratory and Labtests pathologists as it was considered inappropriate was later performed at LabPLUS. This patient showed 'spontaneous' clearance after 30 years. It may have been that the patient accessed DAA therapy overseas which was not available to our pathologists on their review.

One limitation of this audit is that the database repositories used may not have all data from all patients as the data held is restricted to the upper north of NZ. Another limitation is that decisions made with regards to the appropriateness or inappropriateness of HCV tests is partially subjective, mainly because clinical details including history could be missing from the

database. Further, it is difficult to obtain patients' lifestyle information to determine accurate appropriateness of HCV tests requested.

## 2.8 Recommendations

Since the HCV test protocol changes, there had been a slight decrease in inappropriate anti-HCV antibody test requests (from 118 to 101). For HCV RNA requests, the number of appropriate HCV RNA requests have increased from 122 to 162, and inappropriate HCV RNA requests have decreased from 125 to 90. The protocol change implemented at Northland Pathology Laboratory, Labtests and LabPLUS has increased the value of HCV tests. Interestingly, this audit was done six months after the new change had been implemented. A follow up audit is recommended perhaps after a few years and perhaps a full clinical audit is warranted if the clinical notes from referrers can be obtained.

The increase in the utilisation of diagnostic tests raised concerns about the appropriate use of medical laboratory services. Inappropriate test ordering by clinicians can cause excessive laboratory cost and healthcare cost. Many suggestions have been made to manage utilisation of tests, such as education for the requestors, redesign of request forms and the reintroduction of new recommendations, guidelines or diagnostic algorithms (Huck & Lewandrowski, 2013; Smellie, 2012). It is required to introduce standards for the proper testing and proper frequency of repeating tests in NZ to reduce mis-utilisation of HCV tests. National or regional standardisation is important. However, before implementing national or regional standardisation, as accurate data are required to help plan and design a standard.

Clinicians expect a high quality of service from the medical laboratories. It is the responsibility of the laboratories to ensure that services are in place that will lead to the delivery of such a quality service. From a medical laboratory perspective, computer-based order entry could reduce mis-utilisation of HCV tests. At Northland Pathology Laboratory and at Labtests, electronic ordering is currently in progress and this should improve test ordering and promote active utilisation of screening tests (promote anti-HCV antibody tests for those who are in a high-risk groups).

Chapter Three

# *Utilisation management of HCV*

## 3.1 Introduction

Medical laboratory services influence 60 to 70% of clinical decision-making in healthcare (Huck & Lewandrowski, 2013; Lewandrowski & Sluss, 2013). Laboratories are continuously faced with increasing workload providing a higher demand to reduce turnaround time while also maintaining and improving quality of service even though they only account for about 2% of total healthcare spending (Badrick, Gutscher, Sakamoto, & Chin, 2017). An audit is commonly used as a quality improvement tool to identify issues, and to provide an evidence-based approach to overcome issues. Quality indicators such as turnaround time (TAT), cost analysis, or feedbacks are also quality improvement tools used to monitor and improve aspects of services provided by laboratories. A combination of audit and quality indicators are used to measure efficiency and effectiveness for test utilisation management (Azadmanjir et al., 2015; Badrick et al., 2017).

Medical laboratories are faced with a challenge to continuously improve quality of service at the same or reduced cost. This is why more and more laboratory services are moving towards the value of service provided approach. Good value of service means that laboratories must provide useful information to improve the outcome of patient management. In April 2016, a change of HCV tests protocol was implemented to reduce unnecessary cost from mis-utilised HCV tests and to provide better service, as previously mentioned in Chapter One and Chapter Two. However, it is more concerning that individuals in high-risk groups for HCV are not getting screened properly. A recent study in NZ by Gane et al., 2014 estimated less than one half of HCV-infected New Zealanders have been diagnosed and less than 10 per cent have accessed treatment. Of those, only half have been cured. Gane et al., 2014 also stated that a recent cost analysis estimated that more than a half billion dollars would be required for the health burden of the HCV in NZ over the next 20 years, and that HCV-related mortality will be tripled by 2030 (Gane et al., 2014). Mis-utilisation of anti-HCV antibody tests results in the unnecessary use of healthcare resources. Over-utilisation of HCV RNA testing generates even greater unnecessary use of healthcare resources, while under-utilisation of HCV RNA testing can result in delay in diagnosis, treatment and management of HCV infection and therefore potentially lead to an adverse outcome for the patient. Delayed diagnosis and treatment of HCV infection will affect healthcare costs if complications with HCV infections are encountered.

Lack of following the available guidance on HCV testing is believed to be a major factor contributing to inappropriate HCV test requests. Because initial HCV infection is often asymptomatic, a guideline or recommendation is required to screen for those who are unaware of the HCV infection; (a) to provide best value of HCV tests to diagnose HCV infection; (b) to treat HCV infection with more effective treatment; and (c) to monitor the patient management and therefore patient outcome. In 2017, international organisations such as WHO and CDC have worked and planned to reduce the global burden of HCV by releasing their first international guidelines for HCV and HBV management. National recommendations or guidelines, and an awareness of HCV is required to decrease sero-prevalence of HCV and to decrease HCV-related mortality.

## 3.2 Benefit of Clinical Audit

The evaluation of HCV test utilisation was done by a way of this clinical audit. The term 'clinical audit' is "usually closely followed by a negative feeling. This is often due to a lack of appreciation of its origin, the exact process of audit and the importance that it has for patient outcome" (Levy & Rockall, 2009). A clinical audit is defined as "a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change" (Erasmus & Zemlin, 2009; Levy & Rockall, 2009). An audit is a form of research where the results are intended to bring additional knowledge and a better understanding of the issue investigated. The additional and new knowledge could be used to change the management of patient care and therefore patient outcome (Levy & Rockall, 2009). It is a process to improve the care, the outcome and quality of life of patients by measuring the performance and taking corrective actions. This is done by analysing the quality of service, including the procedures used for the diagnosis, treatment, care provided, use of resources and the outcome (Waise, 1999). The clinical audit can be used as a tool to review clinical practices based on evidence of improved service, and to assess HCV test protocol changes that were implemented in April 2016. However, the process of a clinical audit is very time consuming, and labour intensive, and it requires following careful and dedicated plans. Most importantly it requires continuous teamwork from all involved parties (Waise, 1999). For an audit to be effective, it must meet several criteria. For example, it must be professionally

led; it has to be seen as an educational process and; form part of laboratory and clinical practice; it must be based on the setting of standards; it must generate results that can be used to improve outcome of quality care, and it must involve management in both the process and outcome of audit.

It is beneficial to assess laboratory and clinical practices that range from the use of services to the clinical effectiveness of laboratory tests, as well as their impact on clinical outcomes. Various quality indicators are used to measure the efficacy of specific interventions as well as identify healthcare improvement opportunities. These quality indicators include measuring and monitoring turnaround time (TAT) and assessing the costs involved (Erasmus & Zemlin, 2009).

## 3.3 Turnaround Time

TAT is a type of quality indicator used to measure the laboratory process time. TAT is calculated based on that which is to be measured, for example, TAT is calculated from collection time to transported time; from collection time to time of processing; or from collection time to when the results are released and reported to clinicians. Usually in the laboratories they are separated into three categories: pre-analytical, analytical and post-analytical (Badrick et al., 2017). TAT is also commonly used as a performance indicator to measure the effect of the quality of medical laboratory services.

## 3.4 Cost

The healthcare sectors, including medical laboratories, are under continuous pressure to improve their processes, methods, and using technologies to perform at lower cost to meet the expectations of patients. Calculation of cost is used as a quality indicator to measure the effectiveness of laboratory services. Different cost analysis methods can be used depending on what is to be measured and monitored.

## 3.5 Current Guidelines for HCV testing

There are three HCV-related documents publicly available in NZ: the Hepatitis C Communicable Disease Control Manual by the MOH, Action on Hepatitis C Prevention by the MOH and the NZ Society of Gastroenterology HCV Treatment Guidelines. Both MOH documents and Best Practice Advocacy Centre New Zealand (BPAC) cover general information about HCV, however they do not recommend or provide guidelines for managing HCV infection. The NZ Society of Gastroenterology HCV Treatment Guidelines provide detailed information on the treatment plans and the monitoring of the treatments for HCV genotype 1 to genotype 6. However, the document does not provide enough information regarding who should be screened and tested for HCV infection, and how the different HCV tests can be best utilised. Nevertheless, BPAC guidelines and articles provide information regarding who should be screened and tested for HCV infection.

WHO was the first to introduce international HCV care and management guidelines, where their strategies include: a 90% reduction in new cases of chronic HCV, a 65% reduction in HCV death, and treatment of 80% of eligible people with chronic HCV. This is with a note that the trend of HCV infection is changing, for example, co-infection with HIV and HBV are more common as they share the same transmission routes. To achieve goals set by WHO, NZ needs to develop national policies based on evidence such as reliable and accurate epidemiological data. Different suggestions and plans need to be thoroughly executed to manage HCV tests. This is in order to achieve a higher value of HCV tests; screen targeted population; reduce mis-utilisation of HCV tests; provide the best management plan to achieve the best patient outcome, and to reduce the economic burden from HCV-related complications. Poor patient care, management, and cost effectiveness of HCV tests will continue without proper recommendations and guidelines.

Current recommendations and guidelines from the different organisations are summarised in Table 3.1 below.

Information was gathered from:

The WHO document on “Guidelines on hepatitis B and C testing” and the WHO document on “Guidelines for the screening, care and treatment of persons with hepatitis C infection” were used for WHO. A combination of CDC documents and Morbidity and Mortality Weekly Report

(MMWR) documents were used for CDC. The MOH document “Action on Hepatitis C Prevention” and NZ Society of Gastroenterology HCV treatment guidelines for NZ.

Table 3.1 Summary of recommendations and guidelines of HCV testing from different documents

| Criteria | WHO | CDC | NZ |
|---|---|---|---|
| **Stated 'who to test for'** | Individuals in high-risk group,<br>based on evidence-based research to:<br>Focus testing in most affected populations.<br>General population testing.<br>Birth cohort testing. | No information provided. | No information provided. |
| **High-risk group** | MSM, PWID, people with HIV, indigenous population, migrants, people in prison, mother with HCV and the baby, sex workers, transgender people, healthcare workers, persons living with HIV | PWID, history of PWID, received clotting factor concentrates produced before 1987, on long-term haemodialysis, persistently abnormal ALT, people with HIV, people who received blood, blood components, or an organ transplant before July 1992, healthcare workers, children born to HCV-positive women. | Injecting drug users, blood product recipients. |
| **Diagnostic steps:** | Serological test: Anti-HCV antibody<br>Confirmatory test: HCV RNA or HCV core Antigen. | Initial testing: Anti-HCV antibody<br>Confirmatory test: HCV RNA or recombinant immunoblot assay | Serology: Anti-HCV antibody<br>Viral load: HCV RNA<br>HCV genotype to determine treatment regimen. |
| **Diagnosis interpretation provided?** | Yes. Flowchart is provided. | Yes.<br>Separate document provided as a the guidelines for laboratory testing and result reporting of antibody to HCV.<br>Also, in a form of table which includes additional testing or evaluation steps. | Only states: anti-HCV indicates HCV exposure; HCV RNA confirms HCV infection; HCV genotype determines treatment regimen. |
| **Liver staging criteria established** | Refers to APRI score. | No | Yes |
| **Treatment guidelines** | Brief mention of DAAs | No | Yes |

| | | | |
|---|---|---|---|
| **Treatment monitoring guidelines** | Yes – provided.<br>Assessment of cure using HCV RNA and detection of HCC using ultrasound. | Brief mention of using ALT and HCV RNA. | Yes |
| **Prevention** | Enhance safety procedures in healthcare settings, prevent mother-to-child transmission, provide harm reduction services (sterile needle and syringe programmes, risk reduction programmes), promoting safer sex | Screening and testing of blood, plasma, organ, tissue, and semen donors; virus inactivation of plasma-derived products; risk-reduction counselling and services; implementation and maintenance of infection-control practices; identification, counselling, and testing for persons at risk; medical management of infected persons; professional and public education; surveillance and research to monitor disease trends and the effectiveness of prevention activities and to develop improved prevention methods. | Harm minimisation including needle and syringe exchange programmes, methadone maintenance treatment and education and counselling.<br>Targeting groups at risk. |
| **Other recommendations** | Promoting awareness, creating an enabling environment, providing pre-test information, post-test counselling services | No information provided. | Awareness, diagnosis/ identification, staging of the liver and HCV genotypes. |

## 3.6 Aims of the study

The aim of this chapter is to provide a snapshot of TAT, cost effectiveness, resource and management related to HCV tests since the HCV test protocol changes in April 2016. This chapter will also briefly discuss HCV-related clinical guidelines.

## 3.7 Materials and Methods

### 3.7.1 Study type

This is a descriptive audit study, where data are collected and analysed.

### 3.7.2 HCV Data

Data collected and analysed from Chapter Two was used for this chapter.

#### *3.7.2.1 Referrer Specialties*

The Specialties of requesting clinicians were divided into four groups: (1) GP, (2) specialists, (3) alcohol/drug/sexual practice clinicians, and (4) others. GP consists of general practitioners. Specialists consist of specialists from the hospital, surgery, fertility associates, hepatitis foundation clinicians. Alcohol/drug/sex practice clinicians include: doctors or from rehab, alcohol, drug, or sex clinic services. Other consist of midwives and nurses.

### 3.7.3 HCV TAT Analysis

For all anti-HCV antibody and HCV RNA requests, TAT was calculated. The difference of time in days was calculated from ‘date serviced’ to ‘date reported’. ‘Date serviced’ indicates the date at which the request was entered into Ultra (after the sample got to the laboratories or when the request form was scanned at collection centres post-patient visit), while ‘date reported’ indicates the date at which the results for the request were released to the requesting clinicians.

### 3.7.4 HCV Cost Analysis

Cost analysis was done using the publicly available fees from Northland Pathology Laboratory and from Labtests. Fees for anti-HCV antibody sit at $23.50 per test and HCV RNA at $200 per test. Publicly available fees were also used to take into account the bleeding fee of $12 per request, send-away fee to LabPLUS of $22 per request, reagent and consumable costs, labour cost and other costs associated with HCV tests.

## 3.8 Results

### 3.8.1 Referral specialty Groups

Referral based on specialty groups for all anti-HCV requests are shown in Table 3.2 below. Approximately 76% are from GPs, 22% are from specialists and less than 1% from alcohol/drug/sex practice clinicians and other clinicians. Requests were taken from both 2015 and 2016 data.

Table 3.2 Referral specialty for all anti-HCV antibody requests

| | **2015** | | **2016** | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| **Total number of requests** | 5836 | | 6016 | |
| **GP** | 4449 | 76.2 | 4572 | 76.0 |
| **Specialists** | 1275 | 21.9 | 1320 | 21.9 |
| **Alcohol/drug/sex practice clinicians** | 44 | 0.6 | 59 | 1.0 |
| **Other** | 68 | 1.2 | 65 | 1.0 |

54.3% of GP requests of reactive anti-HCV antibody tests were considered inappropriate from 2015 dataset, and 48.0% of GP requests of reactive anti-HCV antibody tests were considered inappropriate from 2016 dataset. 33.5% of GP requests of reactive anti-HCV antibody tests were considered appropriate from 2015 data, and 32.2 %of GP requests of reactive anti-HCV antibody requests were appropriate from 2016 data as shown in Table 3.3 below.

Table 3.3 Referral specialty for reactive anti-HCV requests

| | 2015 | | 2016 | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| **Total number or reactive anti-HCV antibody requests** | 188 | | 171 | |
| **Appropriate requests** | 70 | | 70 | |
| **GP** | 63 | 33.5 | 55 | 32.2 |
| **Specialist** | 3 | 1.6 | 5 | 2.9 |
| **Alcohol/drug/sex practice clinicians** | 3 | 1.6 | 9 | 5.3 |
| **Other** | 1 | 0.5 | 1 | 0.6 |
| | | | | |
| **Inappropriate requests** | 118 | | 101 | |
| **GP** | 102 | 54.3 | 82 | 48.0 |
| **Specialist** | 10 | 5.3 | 8 | 4.7 |
| **Alcohol/drug/sex practice clinicians** | 6 | 3.2 | 9 | 5.3 |
| **Other** | 0 | 0.0 | 2 | 1.2 |

70.5% requests for HCV RNA were from GP from 2015 data and 56.8% requests for HCV RNA were from GP from 2016 data. 40.9% of GP requests for HCV RNA tests were considered inappropriate from 2015 data, and 25.4% of GP requests for HCV RNA tests were considered inappropriate from 2016 data. 29.6% of GP requests for HCV RNA tests were considered appropriate from 2015 data and 31.4 %of GP requests for HCV RNA requests were considered appropriate from 2016 data as shown in Table 3.4 below.

Table 3.4 Referral specialty for HCV RNA requests

| | 2015 | | 2016 | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| **Total number of HCV RNA requests** | 247 | | 252 | |
| **Appropriate requests** | 122 | | 162 | |
| **GP** | 73 | 29.6 | 79 | 31.4 |
| **Specialist** | 25 | 10.1 | 38 | 15.1 |
| **Alcohol/drug/sex practice clinicians** | 7 | 2.8 | 26 | 10.3 |
| **Other** | 17 | 6.9 | 19 | 7.5 |
| | | | | |
| **Inappropriate requests** | 125 | | 90 | |
| **GP** | 101 | 40.9 | 64 | 25.4 |
| **Specialist** | 15 | 6.1 | 9 | 3.6 |
| **Alcohol/drug/sex practice clinicians** | 6 | 2.4 | 12 | 4.8 |
| **Other** | 3 | 1.2 | 5 | 2.0 |

### 3.8.2 Turnaround Times (TAT)

For negative anti-HCV antibody requests, the majority had a TAT of zero days. 91.8% of negative anti-HCV antibody requests from 2015 data and 93.3% of negative anti-HCV antibody requests from 2016 data were released and reported on the same day. This is demonstrated in Figure 3.1 below.

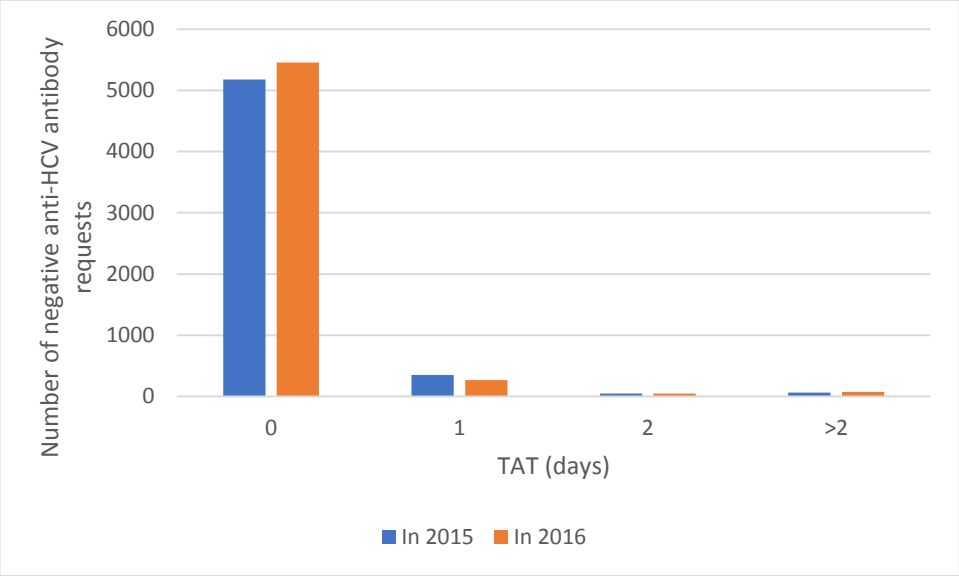


Figure 3.1 TAT of negative anti-HCV antibody requests

For reactive anti-HCV antibody results, it was found that 58.2% of reactive anti-HCV antibody tests had a TAT of zero days from 2015 data; 7.6% of reactive anti-HCV antibody tests had a TAT of zero days from 2016 data. 38.3% of reactive anti-HCV antibody tests had a TAT of one day from 2015 data; 67.4% of reactive anti-HCV antibody tests had TAT of 1 day from 2016 data. 20.9% of reactive anti-HCV antibody tests with a TAT of more than two days from 2016 data. This is demonstrated in Figure 3.2 below.

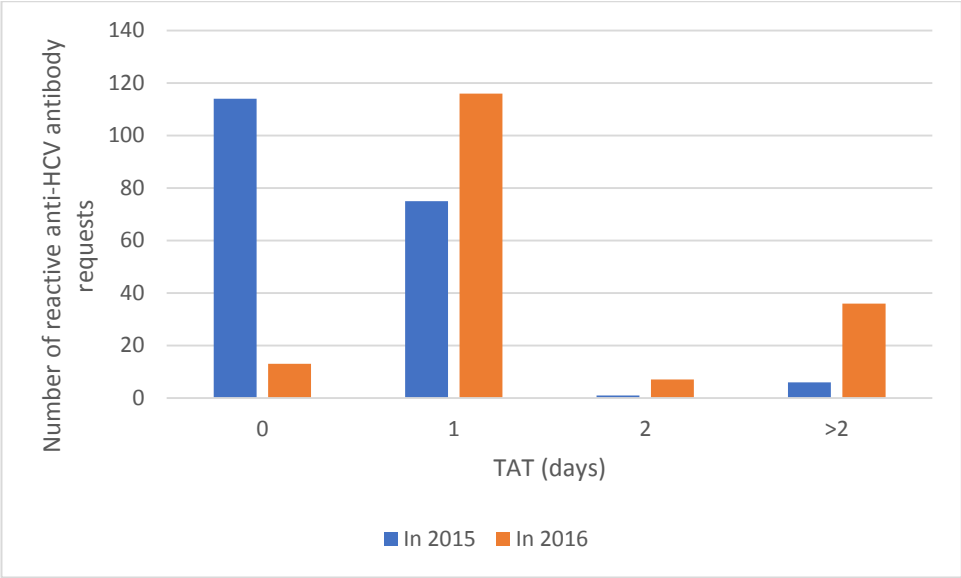


Figure 3.2 TAT of reactive anti-HCV antibody requests

86.6% of HCV RNA requests had a TAT of zero days from 2015 data; 4.0% of HCV RNA requests had a TAT of zero days from 2016 data. 12.1% of HCV RNA requests had a TAT of one day from 2015 data; 61.4% of HCV RNA had a TAT of one day from 2016 data. 17.9% of HCV RNA requests had a TAT of more than two days from 2016 data. This is demonstrated in Figure 3.3 below.

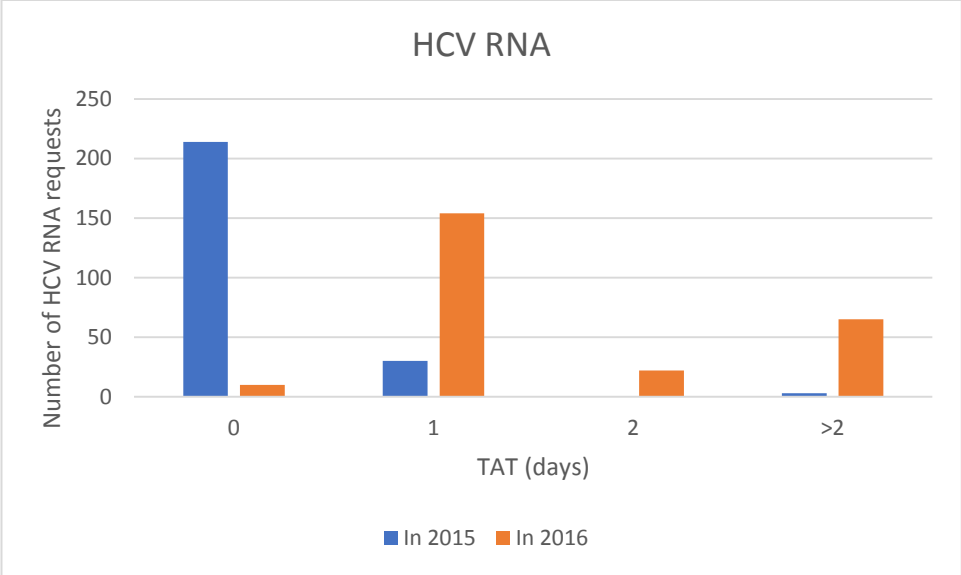


Figure 3.3 TAT of HCV RNA requests

### 3.8.3 Cost

A total cost of $137,146.00 was spent on anti-HCV antibody tests from 2015 data; a total cost of $141,376.00 was spent on anti-HCV antibody tests from 2016 data. This is demonstrated in Table 3.5 below. The cost was calculated by multiplying $23.50 by the total number of anti-HCV antibody performed (from Chapter Two).

Table 3.5 Cost involved with anti-HCV antibody tests

| | **2015** | | **2016** | |
|---|---|---|---|---|
| | n | Total cost | n | Total cost |
| **Performed anti-HCV antibody** | 5836 | $137,146.00 | 6016 | $141,376.00 |

For reactive anti-HCV antibody requests, a total of $4418.00 was spent on reactive anti-HCV antibody requests from 2015 data; a total of $4018.50 was spent on reactive anti-HCV antibody requests from 2016 data. A total of $2773.00 was spent on inappropriate anti-HCV antibody requests from 2015 data; a total of $2373.50 was spent on inappropriate anti-HCV antibody requests from 2016 data. This is demonstrated in Table 3.6 below.

Table 3.6 Cost involved with reactive anti-HCV antibody requests

| | **2015** | | **2016** | |
|---|---|---|---|---|
| | n | Total cost | n | Total cost |
| **Total Reactive HCV** | 188 | $4418.00 | 171 | $4018.50 |
| **Appropriate HCV** | 70 | $1645.00 | 70 | $1645.00 |
| **Inappropriate HCV** | 118 | $2773.00 | 101 | $2373.50 |

A total of $49,400.00 was spent on HCV RNA requests from 2015 data. A total of $50,400.00 was spent on HCV RNA requests from 2016 data. $25,000.00 was spent inappropriately on HCV RNA from 2015 data; $18,000.00 could have been inappropriately spent based on 2016 data had the protocol not been changed. This is demonstrated in Table 3.7 below.

Table 3.7 Cost involved with HCV RNA requests

| | 2015 | | 2016 | |
|---|---|---|---|---|
| | n | Total cost | n | Total cost |
| **Total HCV RNA performed** | 224 | $44,800.00 | 161 | $32,200.00 |
| **Appropriate HCV RNA performed** | 121 | $24,200.00 | 161 | $32,200.00 |
| **Inappropriate HCV RNA performed** | 123 | $24,600.00 | 0 | $0 |
| | | | | |
| **Rejected HCV RNA** | NA | NA | 90 | $18,000.00 |

## 3.9 Discussion

### 3.9.1 Referral specialty

Approximately 76% of anti-HCV antibody requests were from GPs, and around 22% of anti-HCV antibody requests were from different specialists from both 2015 and 2016 data. GPs are the most common referrers, which was indicated in the data as the most common requestor. It is evident that approximately half of the reactive anti-HCV antibody requests were inappropriate from GPs. As mentioned in Chapter Two, 90% of the reactive anti-HCV antibody requests were unnecessary repeats. This strongly indicates that GPs need to be aware of the purpose of anti-HCV antibody testing, and understand that once the anti-HCV antibody is produced, it remains reactive for the life time of healthy individuals. Around 5% of inappropriate anti-HCV antibody requests were from specialists, indicating that some specialists need to be aware of the purpose of anti-HCV antibodies also.

An estimated 70.45% of HCV RNA requests were from GPs from 2015 data and 56.75% of HCV RNA requests were from GPs from 2016 data. The reduction of 13.70% could be due to the dissemination of information resources regarding the new HCV test protocols by pathologists from Northland Pathology Laboratory, Labtests and LabPLUS. The information stated that blood samples received from the Primary Care sector requesting Hepatitis C antibody testing will undergo reflex testing for Hepatitis C RNA where appropriate. Referrers will no longer need to request HCV RNA testing under most circumstances (Upton & Croxson, 2016).

It was also noted that repeated reactive anti-HCV antibody requests and HCV RNA requests were performed with dialysis patients. When pathologists consulted dialysis specialists, an Auckland hospital specialist stated that an anti-HCV antibody test is performed on the first haemodialysis treatment. And with long-term haemodialysis patients, anti-HCV antibody tests are performed twice a year (in April and in October) along with monthly blood tests. A Waitemata District Health Board specialist stated that an anti-HCV antibody test is performed when starting haemodialysis and then annually. If the anti-HCV antibody test is reactive, HCV RNA is subsequently performed. A Middlemore hospital specialist stated that there is no written policy or protocol, but anti-HCV antibody testing is routinely done every six months (in May and in November) as per monthly blood request form. If the anti-HCV antibody is reactive HCV RNA is done. There is no consensus protocol and recently almost all renal dialysis patients in NZ have been cured using DAA treatments accessed by a clinical trial (personal communication, Professor Gane).

With this audit, specialists could have been separated further into GPs, liver specialists (including nurses specialising in liver diseases), specialists other than liver specialists, alcohol and sexual clinics, drug clinics and other. It would have yielded more information if specialists were separated into liver specialists and others. It would have also yielded more information if sexual clinics were separated from drug clinics. If patients have history of intravenous drug use, they should be screened for HCV, but less so for the sexual clinics.

One limitation worth noting is that the data from 2016 for referral specialty for HCV RNA may be obscured, due to reflex addition of HCV RNA by pathologists based on reactive anti-HCV antibody results. So, the increase of 1.8% of appropriate HCV RNA requests and the decrease of 15.49% for inappropriate HCV RNA requests could be from HCV RNA addition by pathologists. This was not differentiated from the data collection and data analysis.

### 3.9.2 TAT

There was no significant difference in TAT for negative anti-HCV antibody requests. This is because samples are processed, and negative results are automatically released and reported to clinicians. However, there was an increase in TAT for reactive anti-HCV antibody requests and HCV RNA by one day. This is hugely impacted due to the fact that all reactive anti-HCV

antibody results and HCV RNA requests are reviewed by pathologists. Northland Pathology Laboratory and Labtests pathologists review all reactive anti-HCV antibody results and HCV RNA requests everyday morning. It is evident that since April 2016, extra regime resources have been put in place by pathologists to increase the value of HCV tests. Erasmus & Zemlin, 2009 stated that “it is the pathologist’s duty to help clinicians order the appropriate tests, at the correct time, in the correct order. Combination of practice guidelines, modification to the laboratory requisition form and funding policy changes has been found to significantly decrease the use of several tests”.

The TAT for HCV RNA does not truly represent the TAT of HCV RNA. Calculation of TAT for HCV RNA is based on the process from the time requests are registered, to the time the HCV RNA panel is released and reported to clinicians with appropriate comments by pathologists. It was not calculated to take into account HCV RNA test completion at LabPLUS. It would have been more useful to have TAT of HCV RNA to completion, accounting for when the HCV RNA results are released and reported to clinicians.

### 3.9.3 Cost

An estimated cost of $142,950.50 was spent on anti-HCV antibodies between 1st of August to 30th of September in 2015 and $147,298.00 in the corresponding 2016 period. There was no significant difference between the cost from 2015 data and 2016 data. This is because anti-HCV antibody requests are all processed without vetting. As mentioned in Chapter Two, the audit would have yielded more information if appropriateness was determined for negative anti-HCV antibody results to estimate the cost of inappropriate anti-HCV antibody requests.

For reactive anti-HCV antibody requests, $2773.00 was adjudged wasted from 2015 data and $2373 from the 2016 data for inappropriately requested anti-HCV antibody requests. Again, there was no significant difference between the costs because all anti-HCV antibody requests are performed.

An estimated cost of $24,600.00 was wasted from 2015 data in regards to inappropriate HCV RNA testing. A cost of $18,000.00 could be considered saved from 2016 data due to rejected HCV RNA by pathologists. The change of HCV test protocol has reduced and saved costs

involved with HCV RNA tests. Cost analysis done in this audit was a basic analysis. Site-specific data should have been used to evaluate the impact of the HCV protocol changes because the operating costs will be different between laboratories. When calculating cost savings, it is important to understand the entire process involved in a laboratory setting. Calculating the cost of a laboratory test or test panel can be challenging. Consequently, determining the savings if the test is not ordered is equally problematic. Cost (to produce laboratory tests) must be differentiated from charges to patients or third-party payers (Huck & Lewandrowski, 2013). When assessing the financial impact of reducing test utilisation, Huck & Lewandowski, 2013 suggest to view the problem from five different perspectives: the cost to the laboratory; potential revenues to the laboratory; the charges to the payer; the cost and impact on clinicians; and the downstream cost of clinical care (Huck & Lewandrowski, 2013). This is because the total cost of a test includes pre-analytical costs, analytical costs, and post-analytical costs. One study estimated that a 10% reduction in automated testing lead to only a 1.32% reduction in cost because only the marginal cost of the tests are saved (Huck & Lewandrowski, 2013). So, the cost reduction achieved from HCV tests may only result in a tiny reduction in cost to the laboratory. On the other hand, for NAT, HCV RNA or HCV genotype, the marginal cost saving may be significant by reducing the volume of HCV RNA and HCV genotypes. There are many different methods to perform cost analysis; however, they were not covered for the scope of this thesis.

### 3.9.4 HCV management recommendations or guidelines

It is evident that recommendations or guidelines are required to be followed by referrers in response to WHO and CDC strategies. This would allow screening for 75-80% of the population who may be unaware of the HCV infection in NZ and worldwide. As mentioned in Chapter One, WHO has estimated that 20% of all HCV infections were diagnosed and of those only 7% underwent treatment in 2015. However, these figures may be from poorer countries with less accessible healthcare, so it may not be the case for NZ. This is considered unreasonable when reliable diagnostic tools and effective treatments are available. With a set of proper screening methods, testing guidelines and treatment regimens the burden of HCV-related disease could be reduced significantly. Based on the audit performed in this research, a personal

recommendation of three protocols can be considered: (1) a protocol for vetting anti-HCV antibody requests; (2) a protocol for interpretation of anti-HCV antibody results; and (3) a protocol for vetting HCV RNA requests as shown in Figure 3.4, 3.5 and 3.6 below.

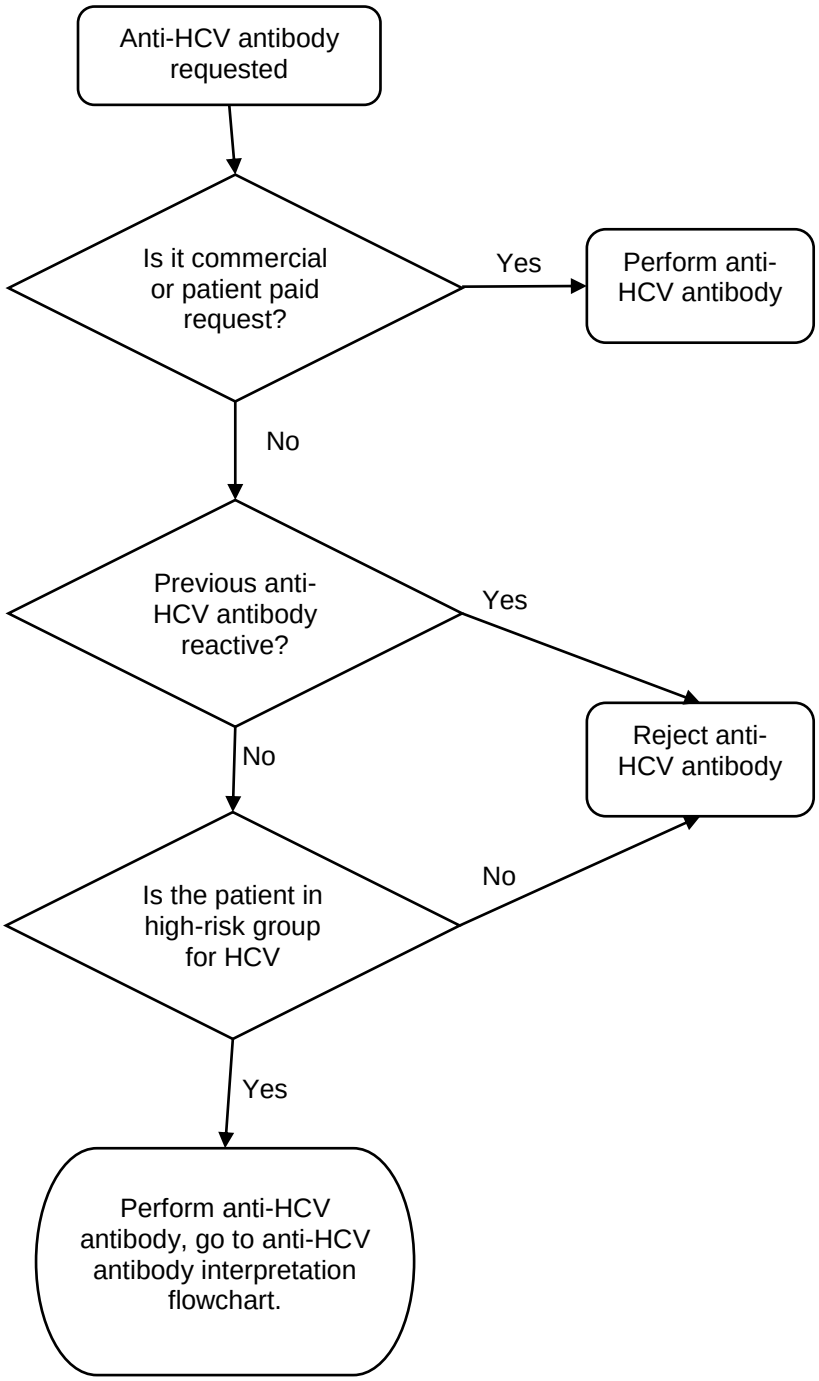


Figure 3.4 Proposed anti-HCV antibody request vetting protocol

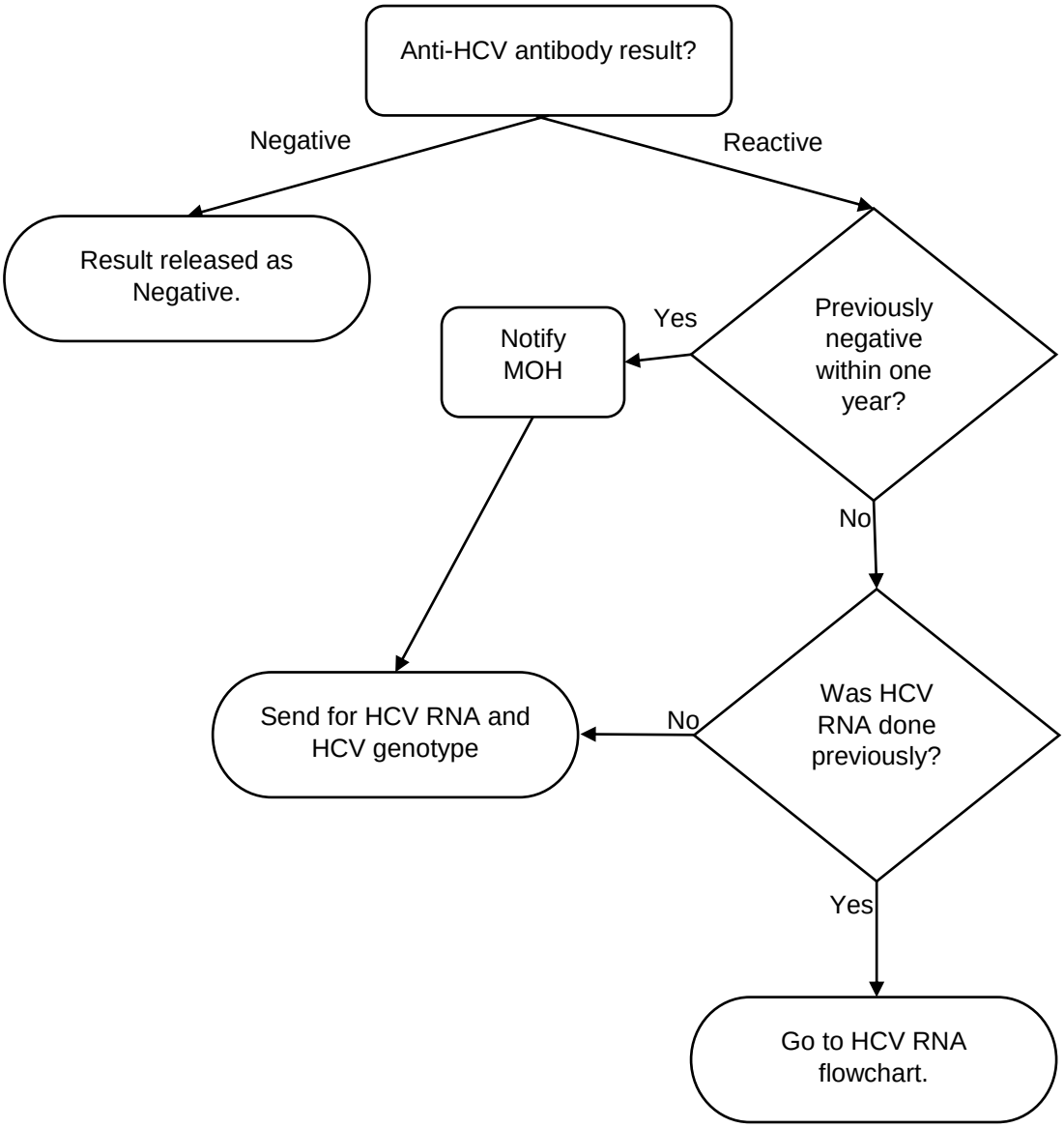


Figure 3.5 Proposed anti-HCV antibody interpretation protocol

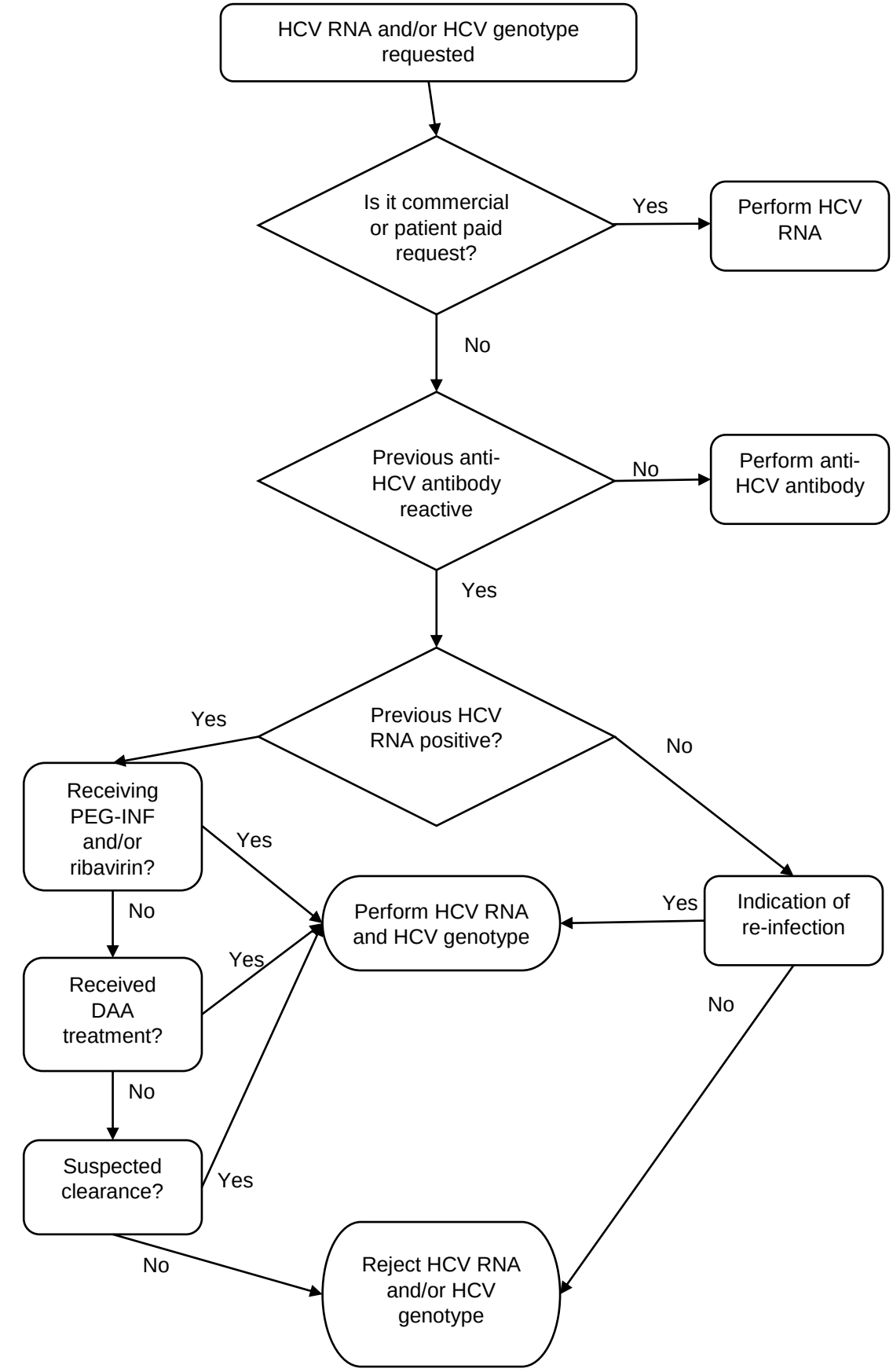


Figure 3.6 Proposed HCV RNA and/or HCV genotype vetting protocol

The proposed protocols are my own ideas, an evidence-based guideline for HCV management must be planned and designed by a group of specialists. It also must take into account theoretical considerations and practical considerations (Horvath, 2013). The protocol for HCV RNA and/or the HCV genotype will have multiple factors involved in decision making.

WHO has stated key elements for national testing services for HCV, these include: national framework; building capacity for testing services; product selection; assuring the quality of testing services; assuring the safety of testing series (World Health Organisation, 2017b). The author wishes to advise that this is not covered in detail for this thesis.

# Chapter Four

## *Final remarks*

## 4.1 Final remarks

HCV infection is a leading cause of cirrhosis, HCC, liver transplants and liver-related death worldwide, with more than 40% of liver transplants due to HCV-related liver disease internationally (Vermunt et al., 2015). The HCV-related disease burden is growing internationally due to its effect on morbidity and mortality. The economic burden from HCV-related treatment and complications is estimated to continuously increase. An estimated HCV-related health burden in NZ is more than 0.5 billion dollars over the next 20 years (Gane et al., 2014).

This thesis was an audit study to evaluate the changes that were made to the HCV testing protocol at Northland Pathology Laboratory, Labtests and LabPLUS. Overall, the change to the HCV testing protocol had no effect on the anti-HCV antibody tests because only reactive anti-HCV antibody results were reviewed, and released to clinicians with changed comments, However, the change to the HCV testing protocol had a greater effect on the HCV RNA tests. The change implemented has increased the value of HCV tests.

The arrival of new DAA will dramatically change the care of patients chronically infected with HCV. An effective screening program is still required as HCV infection is often diagnosed at the late stage or is rarely diagnosed at all and the use of DAA does not provide a cure for already established liver disease or HCC. To be able to reduce the global burden of HCV infection, a nationwide recommendation or guidelines is required to screen for high-risk groups and to promptly treat patients with HCV infection. However, recommendations or guidelines require reliable population-based data. Currently in NZ, there is no existing HCV prevalence data to identify those with HCV and to treat it before HCV-related complications arise. This would also be beneficial to increase the value of HCV tests and to maintain cost-effectiveness.

Furthermore, there was a time limitation with this audit. The HCV test protocol was changed in April 2016, so data used from 1$^{st}$ of August to 30$^{th}$ September 2016 may not truly represent the impact of changed HCV test protocol. Further audit should be done in 18 months or later to determine the impact of changed HCV test protocols.

Among healthcare sectors, there is a strongly held belief that ‘if you just get the science right, everything else will fall into place or become irrelevant’. From a personal perspective this belief is false, as the success or failure of the different healthcare sectors is heavily dependent on the

management, including in medical laboratories. Therefore, different tools are required to measure and monitor the performance of healthcare, particularly in medical laboratories. These tools include auditing and the use of different quality indicators. Outcome measurement in healthcare has become more important worldwide, where delivering value has become the goal.

Achieving high value for patients must become the overarching goal of health care delivery, with value defined as the health outcomes achieved per dollar spend (Epner, 2017).

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# Appendices

## Appendix A: Ethics Approval

Health and Disability Ethics Committees

Health and Disability Ethics Committees
Ministry of Health
133 Molesworth Street
PO Box 5013
Wellington
6011

04 816 3985
hdecs@moh.govt.nz

06 April 2017

Miss Joeun Mijoo Kim
19 Selwyn Avenue
Whangarei 0110

Dear Miss Kim

| | | |
|---|---|---|
| Re: | **HDEC ref:** | **17/NTA/59** |
| | Study title: | An audit of the changes in hepatitis C virus (HCV) testing services among Labtests, Northland Pathology and LabPLUS in New Zealand. |

Thank you for submitting your application for HDEC review on 04 April 2017. The Secretariat has assessed the information provided in your application and supporting documents against the Standard Operating Procedures.

This application has not been validated, as on the basis of the information you have submitted, it does not appear to be within the scope of HDEC review. This scope is described in section three of the *Standard Operating Procedures for Health and Disability Ethics Committees*.

This project is an audit of the Hepatitis C testing protocol changes at Labtests and LabPLUS. This audit does not involve the use of tissue, only the use of health information. As this health information is being accessed for the purposes of an audit rather than research this project is outside HDEC scope of review.

As your study is an Audit or related activity it does not require HDEC review as it does not involve the use, collection, or storage of human tissue without consent (paragraph 33 of the Standard Operating Procedures for Health and Disability Ethics Committees).

If you consider that our advice on your project being out of scope is in incorrect please contact us as soon as possible giving reasons for this.

This letter does not constitute ethical approval or endorsement for the activity described in your application, but may be used as evidence that HDEC review is not required for it.

Please note, your locality may have additional ethical review policies, please check with your locality. If your study involves a DHB, you must contact the DHB's research office before you begin. If your study involves a university or polytechnic, you must contact its institutional ethics committee before you begin.

Please don't hesitate to contact us for further information.

Yours sincerely,

Fox Swindells
Advisor
Health and Disability Ethics Committees
hdecs@moh.govt.nz

Appendix B: Locality Assessment

NORTHLAND DISTRICT HEALTH BOARD
*Te Poari Hauora Ā Rohe O Te Tai Tokerau*

## Locality Assessment by Northland District Health Board

### Locality Assessment Sign Off

All research conducted in the Northland DHB must be conducted with the knowledge of the Northland DHB, and must meet all the requirements of the Health & Disability Ethics Committees (HDECs), though not all research will require HDEC review.

A locality assessment must be undertaken to review all research conducted at Northland District Health Board. Locality Assessments will consider resource implications, suitability of the local researcher and research environment, and cultural issues.

### Part One: General

| | |
|---|---|
| Full project title: | An audit of the changes in hepatitis C virus (HCV) testing services among Labtests, Northland Pathology and Lab PLUS in New Zealand. |
| Short project title: | HCV Audit |
| Locality to be assessed: | Northland Pathology |
| Brief outline of study: | An audit will be performed on the HCV testing protocol changes at Labtests, Northland Pathology, and LabPLUS to assess the effectiveness of the changes. The changes were made between 2015 and 2016 to ensure accurate and timely results for patients from a single blood sample, and to prevent unnecessary HCV viral load and HCV genotype testing. These are the criteria that will be audited by comparing the number and rates of HCV testing: the number and proportion of patients testing positive; onward referral; rates of specialist assessment and treatment in control and intervention practices. |
| Principal investigator (for this locality): | Joeun Mijoo Kim |
| Contact details: | Mijoo.Kim@norpath.co.nz<br>021 0255 1647 |
| Other local investigators (list all at this site): | Dr. Arlo Upton<br>Joe Chang |
| Contact details: | Dr. Arlo Upton: Arlo.Upton@labtests.co.nz<br>Joe Chang: wee.leon.chang@aut.ac.nz |

## Part Two: Locality Issues

Identify any local issues and specify how these issues will be addressed.

| | | | |
|---|---|---|---|
| 1. | **Suitability of local researcher**<br>For example, are all roles for the investigator(s) at the local site appropriate (for example, has any conflict the investigator might have between her or his local roles in research and in patient care been adequately resolved)? | ✓ Yes | ☐ No |
| 2. | **Suitability of the local research environment** | | |
| | a) Are all the resources (other than funding that is conditional on ethical approval) and/or facilities that the study requires appropriate and available (for example, is staffing adequate? Is this site accessible for mobility-impaired people where necessary)? | ✓ Yes | ☐ No |
| | b) Have all potentially affected managers of resources such as clinical records or laboratory managers been notified? | ✓ Yes | ☐ No |
| 3. | **Have issues such as cultural issues specific to this locality or to people being recruited at this locality been addressed?** | ✓ Yes | ☐ No |
| 4. | **Have the local investigator contact details and other important contact details been provided to the locality organisation for checking?** | ✓ Yes | ☐ No |

## Part Three: Declaration by locality organisation

I am authorised to complete locality approval on behalf of this locality organisation. I understand that I may withdraw locality approval if any significant local concerns arise. I agree to advise the principal investigator and then the relevant ethics committee should this occur.

I confirm the organisation has sufficient indemnity insurance to compensate participants for harm that does not qualify for compensation under the Injury Prevention, Rehabilitation and Compensation Act 2001.

| | | | |
|---|---|---|---|
| Signature: | | Date: | 30/03/2017 |
| Name: | Wil Hermans | Position: | Lab manager |
| Contact details: | Wil.Hermans@norpath.co.nz | | |