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Chronic hepatitis C:

Epidemiology, viral resistance, and public health implications

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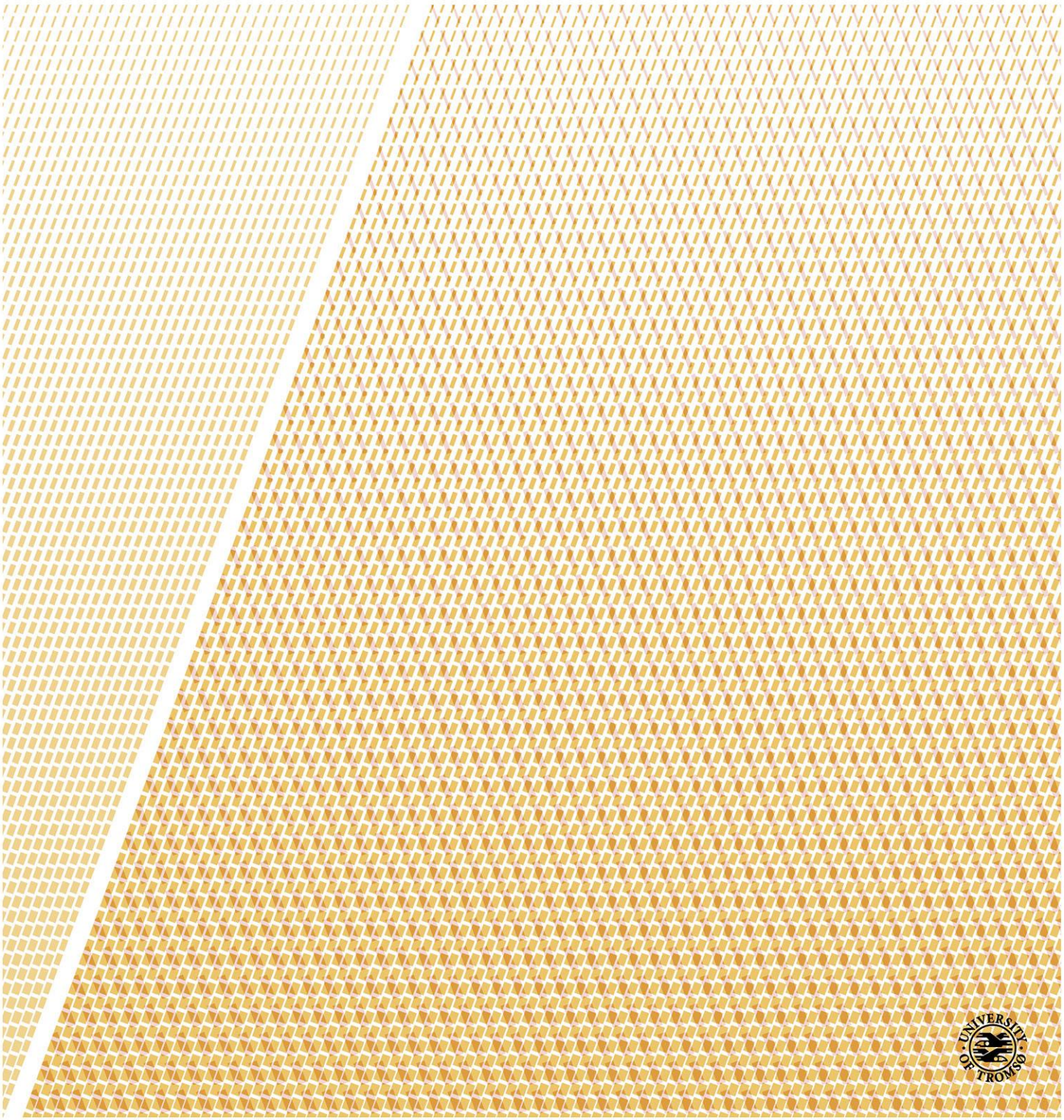

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PREFACE

In the last few years we have entered an important new chapter in the story of hepatitis C virus (HCV) infection. Troublesome interferon-based treatment regimens with severe side effects and moderate success rates are left behind. The advent of effective and well-tolerated therapies with cure rates above 95% in most patient groups has been a game-changer for the disease and made HCV infection, theoretically, an eliminable disease. Clinicians can offer treatment to potentially all HCV infected persons, regardless of the degree of liver disease, somatic or psychiatric comorbidities. In the last years, data on optimal regimens have been rapidly emerging and treatment guidelines subsequently rapidly changing. During the work with this thesis, I have been fortunate to witness this major breakthrough in modern medicine through my combined research and clinical work in this field.

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SUMMARY

Chronic hepatitis C virus (HCV) infection can progress to cirrhosis and end-stage liver disease in a substantial proportion of patients. The infection is frequently asymptomatic, leaving many infected individuals unaware of the diagnosis until complications occur. Worldwide, the total number of HCV infections is projected to remain stable or to decline, but the burden of the disease is expected to increase. The availability of potent direct-acting antiviral therapies (DAAs) provides an opportunity to reverse the rising burden of HCV-disease. However, viral resistance to DAAs has emerged as an important consideration in optimization of HCV-treatment.

There is an uncertainty regarding the prevalence of HCV infection in Norway due to limited availability of population-based data. The first aim of this thesis is to assess the prevalence of HCV infection and the proportion of undiagnosed HCV infection in a general adult population. In a cross-sectional study based on data from the Tromsø 7 Study, we found a low prevalence (0.2%) of viraemic HCV infection in the general population. A substantial number (13/33) of individuals with viraemic disease were unaware of their status.

Second, we aim to estimate future complications of chronic HCV infection towards 2050 in our presumed low-prevalence area by using a Markov cohort simulation model based on data from the Hepatitis C Study in Northern Norway. In this modelling approach, we estimated a stable low incidence of HCV infections towards 2050. The model predicted an almost three-fold increase in the prevalence of cirrhosis (68 per 100,000), of decompensated cirrhosis (21 per 100,000) and of hepatocellular carcinoma (4 per 100,000) by 2050, as well as a six-fold increase in the cumulated number of deaths from HCV-related liver disease (170 per 100,000 inhabitants).

Finally, we aim to investigate the effect of baseline HCV resistance-associated substitutions (RASs) on treatment outcome in patients with HCV genotypes 1a and 3 in a prospective, real-life, open label, non-randomized multi-center cohort study in Norway and Sweden (HCV Preexist). Baseline RASs appeared to be associated with lower cure rates.

To conclude, our findings suggest a substantial rise in HCV-related morbidity and mortality in the coming years, despite a low prevalence of chronic HCV infection in the general population. Baseline RASs appear to impair the treatment response to DAAs in patients with genotypes 1a and 3.

NORSK SAMMENDRAG

Infeksjon med hepatitt C-virus (HCV) gir i de aller fleste tilfellene en asymptomatisk kronisk hepatitt med gradvis utvikling av progredierende leverfibrose. Sykdommen oppdages ofte ikke før det er etablert levercirrhose og/eller cirrhoserelaterte komplikasjoner. Sykdomsbyrden av kronisk infeksjon med HCV er antatt å øke i årene fremover. Nye direktevirkende antivirale medisiner (DAAs) har revolusjonert behandlingen av hepatitt C med svært høye kurasjonsrater i de fleste pasientgruppene, men viral resistens kan påvirke behandlingseffekten.

Det er usikkerhet vedrørende prevalensen av HCV infeksjon i Norge ettersom det foreligger få populasjonsbaserte studier. I denne avhandlingen er det brukt data fra Tromsø 7 undersøkelsen for å undersøke prevalensen av HCV infeksjon i den generelle voksne befolkningen. Vi fant en lav prevalens på 0.2 % av viremisk HCV infeksjon. Et betydelig antall (13/33) av disse visste ikke at de hadde smitteførende sykdom, noe som taler for at gjeldende nasjonale screeningsanbefalinger er suboptimale for å finne de som er smittet.

Videre estimerte vi fremtidig insidens av komplikasjoner av kronisk HCV infeksjon frem mot 2050 i vårt antatte lavprevalens område. Til dette brukte vi en Markov kohortmodell med data fra Hepatitt C Studien i Nord-Norge. Vi estimerte en stabil, lav insidens av HCV infeksjon frem mot 2050, men en nesten tredobbel økning i prevalensen av cirrhose (68 pr 100,000), av dekompensert cirrhose (21 pr 100,000) og av hepatocellulært karcinom (4 pr 100,000) frem mot 2050, i tillegg til en nesten seksdoblet økning i kumulert antall dødsfall forårsaket av HCV-relatert leversykdom (170 pr 100,000).

Til sist undersøkte vi om resistensassosierte substitusjoner (RASs) i HCV påvirket behandlingseffekten av DAAs hos pasienter med HCV genotype 1a og 3. Data fra en prospektiv, multisenter, «real life» kohortstudie i Sverige og Norge (HCV Preexist) viste at tilstedeværelse av RASs syntes å ha innvirkning på behandlingsresultatet med høyere kurasjonsrater når behandlingen ble tilpasset funn ved resistensanalyse.

For å konkludere indikerer våre funn en betydelig økning i HCV relatert morbiditet og mortalitet i årene fremover til tross for en lav prevalens av kronisk HCV infeksjon i den generelle befolkningen. Tilstedeværelse av RASs kan ha negativ innvirkning på behandlingseffekten av DAAs.

LIST OF PRESENTED PAPERS

The thesis is based on the following papers:

I. Screening for hepatitis C in a general adult population in a low-prevalence area: The Tromsø Study.
Kileng H, Gutteberg T, Goll R, Paulssen EJ
BMC Infectious Diseases. 2019 February. DOI 10.1186/s12879-019-3832-7

II. Future complications of chronic hepatitis C in a low-risk area: projections from the hepatitis C study in Northern Norway.
Kileng H, Bernfort L, Gutteberg T, Moen OS, Kristiansen MG, Paulssen EJ, Berg LK, Florholmen J, Goll R.
BMC Infectious Diseases. 2017 September. DOI 10.1186/s12879-017-2722-0

III. Personalized treatment of hepatitis C genotype 1a in Norway and Sweden 2014-2016: a study of treatment outcome in patients with or without resistance-based DAA-therapy.
Kileng H, Kjellin M, Akaberi D, Bergfors A, Duberg A-S, Wesslén L, Danielsson A, Kristiansen MG, Gutteberg T, Goll R, Lannergård A, Lennerstrand J.
Scandinavian Journal of Gastroenterology. 2018 November. DOI 10.1080/00365521.2018.1511824

IV. Effect of the baseline Y93H resistance associated substitution in HCV genotype 3 for direct-acting antiviral treatment: Real-life experience from a multicenter study in Sweden and Norway.
Kjellin M, Kileng H, Akaberi D, Palanisamy N, Duberg A-S, Danielsson A, Gangsøy Kristiansen M, Nöjd J, Aleman S, Gutteberg T, Goll R, Lannergård A, Lennerstrand J.
Manuscript.

ABBREVIATIONS

ALT	alanine aminotransferase
Anti-HCV	antibodies to hepatitis C virus
DAA	direct-acting antiviral
DCV	daclatasvir
EIA	enzyme immunoassay
FC	fold change
GLE	glecaprevir
GT	genotype
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCV RNA	hepatitis C virus ribonucleic acid
Hep C North	The Hepatitis C Study in Northern Norway
HIV	human immunodeficiency virus
IDU	injecting drug use
IFN	interferon
kPa	kilopascal
LDV	ledipasvir
LSM	liver stiffness measurement
NGS	next generation sequencing
OST	opioid substitution therapy
PCR	polymerase chain reaction
PI	protease inhibitor
PIB	pibrentasvir
PWID	people who inject drugs
RAS	resistance-associated substitution

RBV	ribavirin
RdRp	RNA-dependent RNA polymerase
RIBA	recombinant immunoblot assay
SIM	simeprevir
SOF	sofosbuvir
SVR	sustained virologic response
SVR12	sustained virologic response 12 weeks after end of treatment
Tromsø 7	The seventh survey of the Tromsø Study
VEL	velpatasvir
VOX	voxilaprevir
WHO	World Health Organization

1. INTRODUCTION

Hepatitis C virus (HCV) infection is increasingly being recognized as a serious health threat worldwide, but still remains relatively unknown in the general population in low endemic countries. Chronic HCV infection is a major cause of chronic liver disease, liver cirrhosis, hepatocellular carcinoma (HCC) and end-stage liver disease [1, 2]. The total number of HCV infections is expected to decline in the years to come, but HCV-related mortality and morbidity is projected to increase as the aging population infected during peak HCV epidemics decades earlier progresses to more advanced liver diseases [3-6]. The infection is often asymptomatic until late stage, hence the term "the silent epidemic", where a substantial proportion of infected individuals are unaware of their diagnosis [7, 8]. Prevention of late complications requires treatment before patients reach advanced stages of the disease, which underlines the necessity of an early diagnosis.

The development of direct-acting antiviral agents (DAAs) is one of the major breakthroughs in modern medicine and has changed the scenario and perspective of HCV treatment [9]. Compared to previous interferon (IFN)-based therapies, oral DAA regimens are well tolerated, have shorter treatment durations, cure rates above 95% in the majority of patient groups, and can be administered to potentially all HCV infected persons with all aspects of liver disease, and also in the presence of somatic- and psychiatric comorbidities.

The improvement in HCV treatment has the potential to reverse the rising burden due to HCV infection, but undiagnosed infection is one major barrier to the health impact offered by DAAs. In 2016, the World Health Organization (WHO) released its first global strategy on viral hepatitis with aim on elimination of HCV as a major public health threat by 2030 [10]. This target includes a 90% reduction in new HCV infections and a 65% reduction in HCV liver-related mortality, requiring diagnosis of 90% and treatment of 80% of chronically infected patients. To achieve these goals for the care and management of HCV infection, countries need to develop national strategies based on reliable estimates of prevalence and disease burden. In Norway, the Ministry of Health and Care recently has launched a national strategy on viral hepatitis with aim on 90% reduction in new HCV infections by 2023 compared to 2018, and which stated that no one should die or become seriously ill of HCV [11].

Although DAAs offer exceptionally high cure rates in the majority of patient groups, a significant absolute number fail to achieve sustained virologic response (SVR), defined as undetectable HCV RNA 12 (SVR12) or 24 weeks after the end of treatment. The presence of

naturally occurring HCV viral variants which carry resistance-associated substitutions (RASs) is associated with impaired treatment effect of DAAs [12, 13]

In this work, the epidemiology and future complications of chronic HCV infection in a low-prevalence area have been explored. HCV viral resistance to DAAs has emerged as an important consideration in optimization of HCV-treatment, and the impact of baseline HCV RASs on treatment outcome has been investigated.

1.1 Epidemiology of HCV infection

1.1.1 Dissemination and transmission

HCV infection has shown a pandemic spread through the twentieth century. As a blood-borne virus, transmission was initially driven by parenteral transmission routes like unsafe medical injections, surgical procedures, mass vaccination campaigns and blood transfusions [14, 15]. One of the most notorious examples of iatrogenic HCV transmission took place in Egypt, where a parenteral mass population antischistosomal treatment program from 1950s to 1980s led to widespread infection of HCV. Consequently, Egypt became the country with the highest HCV prevalence in the world [16]. Iatrogenic transmission is still a major transmission route in resource-limited countries [17], unlike developed countries where safety improvements in health-care related procedures and blood transfusions the last 40 years have eliminated or significantly reduced these transmission routes [18, 19]. However, iatrogenic transmission has been reported in western countries in recent years, e.g. a case report of transmission of HCV from patient-to-surgeon, and the subsequent transmission of HCV to surgical patients [20].

In the Western world, injecting drug use (IDU) is the most important route for HCV transmission [21-23]. Worldwide, 25 countries have reported that 60- 80% of people who inject drugs (PWID) have antibodies to HCV (anti-HCV), and in 12 countries the prevalence is over 80% [21]. In Europe, a systematic review showed that 53- 97% (median 72%) of PWID had chronic HCV infection [24]. Approximately 30% of PWID in Western Europe are younger than 25 years of age [25].

Of lesser importance are sexual transmission, mother-to-infant transmission and tattooing. The risk of perinatal transmission of HCV from a viraemic mother to child is approximately 4-5% [22, 26]. While heterosexual transmission of HCV is not a significant contributor in the HCV epidemic [27], the incidence of HCV infection among men who have sex with men has

increased significantly in recent years, especially in individuals with human immunodeficiency virus (HIV) infection [22, 28]. HCV transmission has been associated with tattooing and piercing when performed under non-sterile conditions [29]. Finally, in about 10% of infections, no potential risk factor can be identified [30].

1.1.2 Global prevalence

There is considerable geographic variation in HCV prevalence, as well as significant differences between regions and between age- and risk groups within regions. Currently, the estimated global prevalence of viraemic HCV infection is 1.0% (95% CI: 0.8-1.1%), corresponding to 71.1 million (62.5-79.4) chronically infected persons [31]. In three modelling studies involving several countries, the estimated viraemic prevalence's ranged from 0.12% in the Netherlands to 7.3% in Egypt [4-6]. The highest HCV prevalence is found in Southeast Asia, North and Central Africa, and Russia [31]. In Europe, the highest prevalence is found in Italy and in countries in Eastern Europe, while in the Nordic countries the viraemic prevalence rates are 0.3-0.4% [31].

1.1.3 Prevalence of HCV infection in Norway

There is uncertainty regarding the prevalence of HCV infection in Norway as population-based data is limited. A prevalence survey based on The Oslo Health Study in 2001, included 11,456 individuals in the general population and revealed a prevalence of anti-HCV and HCV-RNA of 0.7% and 0.5%, respectively [32]. In a register study from Northern Norway in 2002, the prevalence of RIBA positive HCV infection was 0.24% [33]. A study of pregnant women in Norway in 2000, showed an anti-HCV prevalence of 0.7% [34].

1.1.4 Incidence of HCV infection

There is scarcity of data describing HCV incidence due the asymptomatic nature of acute HCV infection. In Norway, HCV infection has been a notifiable disease to The Norwegian Surveillance System for Communicable Diseases (MSIS) since 1990 [35]. However, the notification criteria have changed several times and MSIS cannot distinguish between resolved and chronic HCV infection. Consequently, there is no reliable data on the HCV incidence in the general population in Norway. Hatzakis et.al. supposed, by using historical data and expert consensus, a peak in HCV incidence in Norway in 1980 due to an increase in IDU, followed by a slowly decrease thereafter to 14.9 cases per 100 000 persons per year in 2013, corresponding to 750 new cases annually [4]. According to MSIS, there has been a decrease in the number of annual reported HCV cases since 2008. The number of reported

cases that are born outside Norway has been increasing and constitutes about 25% of reported cases [35].

1.1.5 Prevalence of HCV genotypes

HCV is classified into seven genotypes (GTs), with varying geographic distribution [36]. Globally, GT1 is the most common (46%), followed by GT3 (30%), GT2 (9%), GT4 (8%) and GT6 (5%) [37]. GT7 is only sporadically reported in Central Africa [37]. GT1 dominates in Europe, North- and South America, while GT3 is prevalent in many West European countries, South Asia, Russia and Australia [37, 38]. In Norway, GT3 accounts for 50% of HCV infections, GT1 36%, and GT2 9%, while in Sweden GT1 is most common (50%), followed by GT3 (30%) and GT2 (20%) [31].

1.1.6 Health burden of HCV disease

Chronic HCV infection is the leading cause of end stage liver disease, HCC, and liver-related death in the Western world and has a substantial effect on morbidity and mortality worldwide [1]. According to Pertz et al., 27% of cirrhosis and 25% of HCC worldwide are attributable to HCV infection [39]. In Western Europe, the attributable fractions of cirrhosis and HCC for HCV are 38% and 44%, respectively [39]. Individuals with chronic HCV infection has increased mortality from both hepatic and extrahepatic diseases [40]. Currently, complications of chronic HCV infection is the leading indication for liver transplantation in the Western world [1, 6, 41].

Even with a decline in the total number of HCV infections, the number of patients with late-stage liver disease and liver-related deaths is expected to increase until 2030 [4-6]. A modelling study from Sweden projects an increase in HCV-related decompensated cirrhosis, HCC, and liver-related deaths in the next two decades, unless an increased number of patients receive antiviral treatment [42]. In Norway, a modelling approach including active and former PWIDs, describes the estimated increase in people with cirrhosis, HCC, and liver transplantation until 2022 [43]. Findings from The Global Burden of Disease Study 2013 revealed that viral hepatitis (hepatitis B (HBV) and HCV) was the seventh leading cause of death worldwide in 2013, a rise from tenth place in 1990 [3]. In addition, viral hepatitis is a leading cause of disability worldwide [3].

1.1.7 Awareness of HCV infection

A substantial proportion of individuals with chronic HCV infection has not been tested and are unaware of their diagnosis. A recent modelling study including 28 EU countries estimated that only 36.4% of those with viraemic HCV infection have been diagnosed [44]. In Norway, the diagnosis rate is estimated to be 57% [4]. Studies from the US have indicated that about half of those infected with HCV were aware of their infection [7, 8]. In a French cross-sectional study, 40% of HCV RNA positive individuals were not aware of their infectious status [45].

1.1.8 Screening strategies for HCV infection

In 1968, Wilson and Jungner proposed ten criteria to guide the selection of diseases that would be suitable for screening [46]. Considering these criteria, and the revised version posed by WHO in in 2008 [47], screening for HCV infection meet the required conditions for a screening program:

- HCV infection is a global health problem that can cause serious, life threatening complications in a substantial proportion of patients.
- The infection is frequently asymptomatic, leaving many infected individuals unaware of the diagnosis until complications occur.
- A suitable diagnostic test is available for the early stages of the disease.
- The availability of potent antiviral therapies provides an opportunity to reverse the rising burden of HCV disease.

Screening strategies vary in different areas, based on the local epidemiology of HCV infection. In Norway, as well as in other low-prevalence countries, a limited screening of high-risk individuals is recommended, such as individuals with current or previous IDU, recipients of blood products prior to 1992, patients infected with HIV, haemodialysis patients, incarcerated individuals, children born to HCV-infected mothers, individuals with elevated alanine aminotransferase (ALT), and migrants from endemic regions [48].

In the new treatment landscape with highly effective and well tolerated DAA regimens, many countries are reconsidering their testing strategies to determine the optimal approaches for reaching persons who might not identify themselves as being at risk for HCV infection. In the US, it is recommended a one-time screening of persons in the 1945-1965 birth cohort, in addition to targeted risk-based testing [49]. In France, with a prevalence of viraemic HCV infection of 0.3%, a recent study showed that universal screening of all individuals aged 18-

80 years is the most effective screening strategy, and also the most cost-effective, assuming rapid initiation of treatment after diagnosis [50]. In Spain, with an HCV RNA prevalence of 0.35-0.41%, a recent modelling study concluded that screening of the general adult population would identify a larger number of additional individuals with chronic HCV infection than screening high-risk groups or screening the age-cohort with the highest anti-HCV prevalence plus high-risk groups [51].

1.2 The HCV genome and its genetic heterogeneity

1.2.1 The HCV genome

HCV, discovered in 1989, is a positive sense, single stranded RNA virus belonging to the family *Flaviviridae* and genus *Hepacivirus* [52, 53]. The genome is 9,600 nucleotides in length and encodes a single polyprotein of about 3,000 amino acids that is co- and post-translationally cleaved into ten polypeptides, including three structural (core (C), E1, E2) and seven non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B) [53, 54]. The NS proteins include enzymes necessary for viral replication (RNA polymerase) and protein processing (protease). Figure 1 shows the HCV open reading frame (ORF) encoding the polyprotein and the predicted secondary structures.

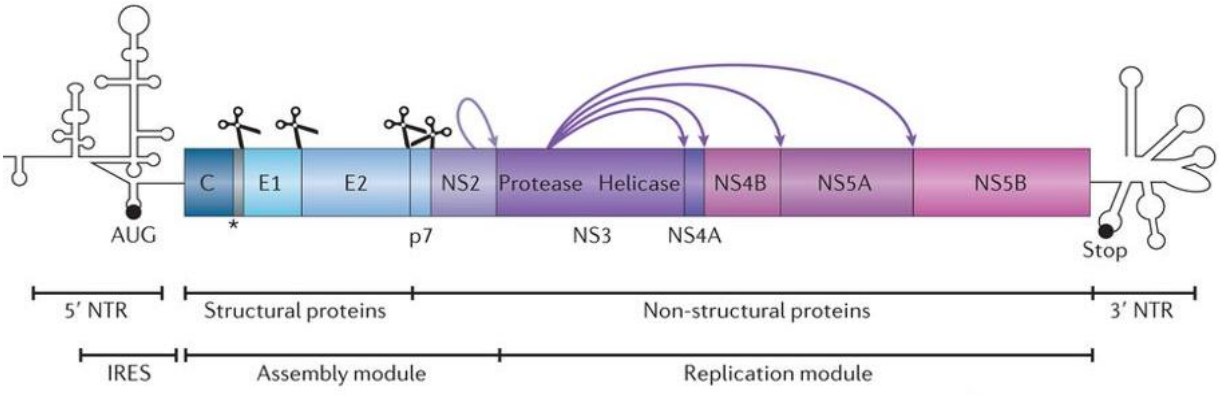


Figure 1. Hepatitis C virus genome organization. NTRs; non-translated regions, IRES; internal ribosome entry site. Polyprotein cleavage by cellular signal peptidases is indicated by scissors at the corresponding ORF position. Arrows refer to cleavage by the viral proteases. From: Bartenschlager et al 2013 [54]. Reprinted by permission from Springer Nature: Nature Reviews Microbiology.

1.2.2 HCV genetic heterogeneity

HCV displays a pronounced genetic heterogeneity at several different levels, resulting in seven different GTs, 67 confirmed subtypes and a large number of quasispecies [36, 53, 55, 56]. First, over decades and centuries a substantial genetic diversity has evolved, resulting in seven distinct HCV GTs, with a 30 – 35% variability in their nucleotide sequences [53]. Second, rapid sequence drift of HCV increases the sequence variability within the different GTs, identifiably as separate strains or isolates [53]. Third, the lack of proofreading activity of the RNA dependent RNA polymerase (RdRp) combined with a high production of up to 10^{12} virions per day, result in the production of quasispecies, which are different but closely related viral variants generated within an infected person over time [53, 56]. Quasispecies can differ by 1-5% in nucleotide sequences, and some variants bear polymorphisms in drug target genes. These polymorphisms, or baseline resistance associated substitutions (RASs), may confer reduced susceptibility to DAAs [12, 13, 57, 58]. Finally, inter- and intra-GT recombination can contribute to the tremendous genetic heterogeneity in HCV through the exchange of nucleotide sequences between different genomic RNA molecules [53, 55].

1.3 The natural course of HCV infection

HCV infection has some characteristics making it challenging to determine the accurate natural course of the infection [59]. Due to the asymptomatic course of the acute phase in the vast majority of cases, the onset of the disease is rarely identified. The phase of chronic infection may last several decades, and the progression of liver fibrosis, and ultimately development of liver cirrhosis, most often occurs without symptoms. Accompanying factors like comorbid conditions, co-infections with HBV and HIV, alcohol consumption, and antiviral treatment can modify the natural course of the disease.

1.3.1 Acute HCV infection

Clinical symptoms may develop in 15% to 30% of adults with acute infection, yet most acute HCV infections are asymptomatic [30, 60]. Reported rates of spontaneous clearance have varied widely (15-40%) due to the asymptomatic course of acute HCV infection [30, 61]. In a systematic review of 31 longitudinal studies, the estimated rate of spontaneous HCV clearance rate was 26% [62]. In a prospective study with pooled data from nine international cohorts of participants with well-defined HCV infection, spontaneous clearance of virus occurred in 25% and was associated with female sex, favorable IL28B genotype and GT 1 infection [63].

1.3.2 Fibrosis progression in chronic HCV infection

The majority of HCV infected individuals develop chronic HCV infection with subsequent progressive accumulation of fibrous tissue in the liver. The fibrosis progression is generally slow, leading to the development of cirrhosis in approximately 10-20% of patients after 20-30 years of infection. However, the progression varies widely and may be affected by several external, viral and host factors [1, 61, 64].

A systematic review of 111 studies revealed that fibrosis progression was non-linear, with an estimated risk of cirrhosis of 16% and 41% after 20 and 30 years of infection, respectively [65]. Others have also shown non-linear development, with major acceleration of fibrosis progression after 50 years of age [66]. A Norwegian autopsy study in injecting drug users, showed advanced fibrosis and cirrhosis in 35% of cases with disease duration of 25 years or longer [67].

On the other hand, slower rates of progression to cirrhosis have also been shown. In a cohort study of young healthy women who had been infected with HCV GT 1b-contaminated anti-D immunoglobulin, the cirrhosis prevalence was 14.2% (treatment-naïve patients) and 15,3% (non-SVR group) 35 years after infection [68].

When advanced fibrosis, i.e. METAVIR stage F3, has developed, the risk of progression to cirrhosis is approximately 10 percent per year [69].

Several host, environmental and viral factors can affect the rate of fibrosis progression. Male gender, age at time of infection >40 years, alcohol consumption, co-infection with HIV or HBV, type 2 diabetes mellitus, and obesity are factors shown to be associated with faster fibrosis progression [30, 66, 70]. An association between viral GT 3 and accelerated fibrosis progression has also been suggested [71, 72]. Moreover, the variable rates of fibrosis progression shown in different studies can in part be explained by different study populations with variable risk factors for fibrosis progression, different study designs and settings, and different methods used to estimate fibrosis progression [64, 65]. Sweeting et.al. demonstrated considerable differences in disease progression rates in three cohorts of patients with the same demographics with estimated 20-year risk of cirrhosis of 12%, 6% and 23% in a hospital-based cohort, a post-transfusion cohort, and in a cohort referred from a tertiary center, respectively [73].

1.3.3 Cirrhosis complications

When compensated cirrhosis is established, patients are in risk of progression to hepatocellular carcinoma (HCC) and hepatic decompensation with complications including ascites, encephalopathy, hepatorenal syndrome and variceal bleeding [74]. The annual risk of HCC and hepatic decompensation is described to be in the range 1-5% and 3-6%, respectively [1, 69, 74, 75]. Further, the annual rate of death or liver transplantation in compensated cirrhosis is estimated to be approximately 4% [74, 76].

When decompensation or HCC has been established, the prognosis is poor without a liver transplantation. The probability of survival at one and five years after decompensation is shown to be 81.8% and 50.8%, respectively [77]. Regarding HCC, the median overall survival time is a few months [78, 79].

Although a SVR to treatment has been shown to induce cirrhosis regression [80, 81] and reduce the risk of complications and mortality in cirrhotic patients [82-84], the risk of complications still remains significant. In one study, the annual risk of HCC after SVR ranged between 0.1% and 1.55% in various subgroups [85]. A recent study demonstrated that SVR was associated with a 76% reduced risk of HCC compared to non-SVR, however, the annual risk of HCC was 0.90% [86]. In individuals with decompensated cirrhosis, an SVR after antiviral therapy is associated with early improvement in liver function, however the long-term clinical benefits remains to be ascertained [87, 88].

1.3.4 Liver disease staging

Liver biopsy with histologic staging of liver fibrosis using the Ishak and METAVIR semi-quantitative scoring systems has historically been the gold standard for assessing liver fibrosis, and thus predicting the prognosis in chronic HCV infection [89-91]. The METAVIR fibrosis score is assessed on a five point scale; F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, bridging fibrosis; and F4, cirrhosis [90], while the Ishak fibrosis score grades fibrosis into seven stages (0-6) [91]. However, liver biopsy has several limitations, including sampling error, significant interobserver variability and risk of complications [92-94]. During the last decade, non-invasive liver stiffness measurement (LSM) has replaced liver biopsy as the recommended method for the assessment of liver fibrosis in HCV infection [95]. The most widely used and validated method is transient elastography, which measures the velocity of a low-frequency elastic shear wave propagating through the liver [96, 97]. The velocity of the shear wave is directly related to the LSM value and is expressed in kilopascals (kPa), ranging from 2.5 to 75 kPa. LSMs can be used as a

prognostic tool for risk stratification, as values in the cirrhotic spectrum (12.5-75 kPa) correlate well with the degree of portal hypertension [98].

Combination of serum markers of fibrosis, like the aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 (FIB-4 test), and LSM improves the accuracy of non-invasive diagnosis of liver fibrosis [99, 100]. The Child Pugh Score and the model for end-stage liver disease (MELD) are commonly used score models to assess the severity of liver dysfunction [101].

1.3.5 Extrahepatic manifestations

In addition to its effect in the liver, chronic HCV infection can have serious consequences for other organ systems. A number of extrahepatic manifestations, independent of the severity of the liver disease, have been associated with chronic HCV infection, including hematologic diseases such as cryoglobulinemia and lymphoma, autoimmune disorders such as thyroiditis, renal disease such as membranoproliferative glomerulonephritis, and dermatologic conditions such as lichen planus and porphyria cutanea tarda [102, 103]. Extrahepatic manifestations are common, presenting in two thirds of patients with chronic HCV infection, and are associated with increased mortality [40, 104].

1.4 Diagnosis of HCV infection

Diagnosis of HCV relies on serologic assays for detection of specific antibodies to HCV (anti-HCV) and molecular assays for detection and quantification of virus-specific molecules [105].

1.4.1 Immunoassays

Following the cloning of the HCV genome in 1989 [52], the first-generation enzyme immunoassay (EIA) for circulating anti-HCV immunoglobulin G was developed, reacting against an epitope from the NS4 region (C100-3) of the HCV genome [106]. The second generation EIA combined several antigens from the core, NS3, and NS4 regions, modifications which markedly improved the sensitivity and specificity of the test [107]. In the third-generation EIA, an additional antigen from the NS5 region was included [108], leading to a diagnostic specificity >99% [109]. However, in severely immunocompromised patients, patients on hemodialysis and transplant recipients, the third-generation EIAs can yield false-negative results [110]. In a systematic review of the accuracy of third-generation EIA used to screen asymptomatic adults, the sensitivity compared with RNA detection varied between 61-82% [111]. False-positive results are more likely to occur in populations with a low

prevalence of HCV-infection, i.e. low positive predictive values [110], and can be caused by increased gammaglobulins, liver diseases, nephritic syndrome, autoimmune diseases, or other viral or parasitic infections [112].

1.4.2 Recombinant Immunoblot Assays (RIBA)

RIBA is a more specific, supplemental test, in which antibody reactivity to four viral antigens is investigated. RIBA is used to confirm the result of the EIA, and is defined positive when antibodies to two or more antigens are detected, indeterminate when reaction to only one antigen occurs, and negative when there is no antibody reactivity detected [113]. RIBA can help distinguish between past infection (RIBA positive) and false-positive anti-HCV (RIBA negative) in individuals who have a reactive immunoassay and a negative HCV RNA test [114].

1.4.3 Detection of virus-specific molecules

Nucleic acid testing (NAT) directly detect the presence of HCV RNA and is the gold standard for diagnosing active HCV infection [105, 110]. Several methods can be used to detect (qualitative assays) and quantify (quantitative assays) HCV RNA, including polymerase chain reaction (PCR), transcription mediated amplification, and branched DNA signal amplification [105]. Most of the currently available quantitative methods can detect as little as 5 IU/mL of HCV RNA, making qualitative tests redundant [105]. The specificity of all NATs is up to 99% [105]. Immunoassays that detect the HCV core or nucleocapsid protein (HCVcAg) are alternatives to NAT to confirm viraemic infection, but is limited by a lower sensitivity than NAT [105].

1.4.4 Point-of care assays

Several rapid assays for detection of anti-HCV have been developed, based on recombinant antigens in an immunochromatographic format, and designed for point-of-care (PoC) testing to provide increased opportunities for HCV-testing outside of traditional clinical settings [105, 115, 116]. These assays can be run on serum, venous blood, plasma, finger stick blood, and oral fluid, and have a high specificity of >99% and sensitivity ranging from 86% to 99% [105]. The availability of a new PoC test with high sensitivity and specificity (close to 100%) for detection of HCV RNA might contribute to simplify HCV testing, i.e. to facilitate HCV RNA confirmation and diagnosis in a single visit [117].

1.4.5 HCV genotyping

HCV is classified into 7 GTs, which on average differ in their genetic sequences by 30-35% [53]. Determination of HCV GT has clinical implications regarding treatment regimen, duration of treatment, and predicting of treatment response. Assays for HCV genotyping use different approaches, like direct sequencing and reverse hybridization [105].

1.5 Antiviral therapy in chronic HCV infection

In recent years there has been a revolution in the treatment for chronic HCV infection. Troublesome regimens with pegylated (PEG)- IFN and ribavirin (RBV) for 12 to 48 weeks with limited success have been replaced with well-tolerated DAAs with cure rates exceeding 95% in most patient groups [118]. Figure 2 shows the changes in the standard of care for HCV infection, and the subsequent tremendous improvement in treatment response.

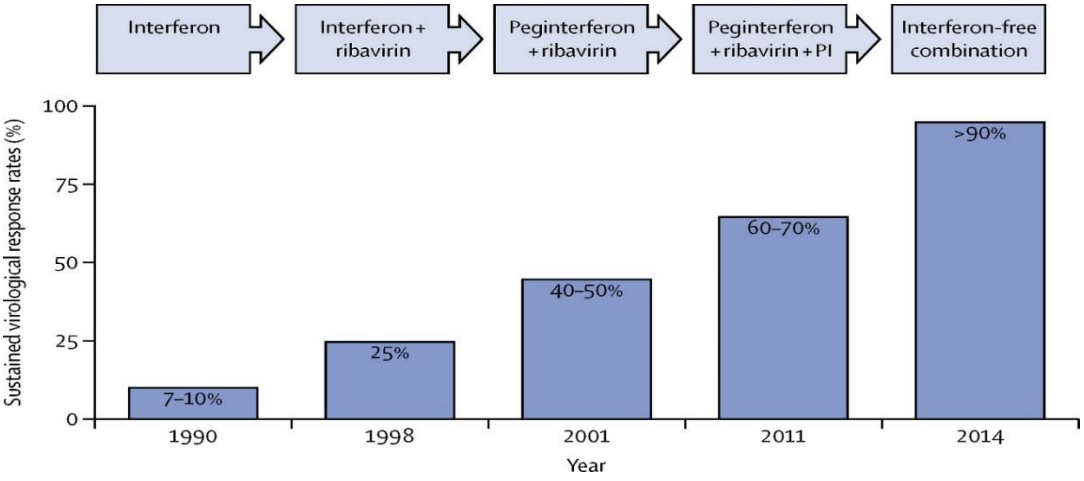


Figure 2. Changes in antiviral treatment for hepatitis C, and improvements in the number of SVR. PI= Protease inhibitor. From: Webster et al. 2015 [119]. Reprinted by permission from Elsevier: The Lancet 2015.

1.5.1 Direct-acting antiviral agents (DAAs)

The development of a HCV RNA replicon model, and later other cell-based culture systems, gave tremendous new insight into the HCV molecular virology, and facilitated the development of drugs that directly inhibit key steps in the viral replication [54]. In principle, every step of the HCV replication cycle is a potential target for antiviral therapy. Currently, four classes of DAAs are available, classified on the basis on their molecular target and mechanism of action: NS3/4A protease inhibitors (PI), NS5A inhibitors, nucleoside-and non-nucleoside inhibitors of the NS5B RdRp [54, 120]. Since 2014, an increasing number of new DAAs have been introduced, which differ with regard to efficacy, barrier to resistance and potential for drug interactions (Table 1).

Drug class	Efficacy	Genotypic coverage	Barrier to resistance	Drug
NS3/4AProtease inhibitors	High	1, 4, 6	Low to moderate (1a < 1b)	Grazoprevir Paritaprevir Simeprevir
		1-6		Glecaprevir Voxilaprevir
NS5A inhibitors	High	1-6	Low to moderate (1a and 3 <1b, 2, 4, 5 and 6)	Daclatasvir Elbasvir Ledipasvir Ombitasvir Pibrentasvir Velpatasvir
Nucleosid inhibitors of NS5B polymerase	High	1-6	High +++	Sofosbuvir
Non-nucleosid inhibitors of NS5B polymerase	Moderate	1	Low +	Dasabuvir

Table 1. General characteristics of different classes of DAAs. Adapted from Asselah et al. [121] and data from [12, 13, 122].

1.5.2 Treatment response of DAAs

Treatment with different combinations of DAAs with complementary mechanisms of action has made it possible to obtain SVR rates above 90-95% in most patient populations in randomized clinical trials [123-135]. High SVR rates are also shown in real-life clinical practice, e.g. a Spanish study of treatment with DAA regimens (ombitasvir/paritaprevir/ritonavir plus dasabuvir and ledipasvir (LDV)/sofosbuvir (SOF) in patients with GT1, which demonstrated SVR rates above 95% [136].

However, treatment responses are still compromised in patients with cirrhosis, previous treatment failure and infection with HCV GT3 [118, 137]. A phase 3 trial (ALLY-3), demonstrated significantly lower SVR rates in GT3 patients with cirrhosis (63%) compared to those without cirrhosis (96%) after treatment with daclatasvir (DCV) and SOF in 12 weeks [128]. In the ALLY-3+ study, SVR was achieved in 86% of treatment-naïve and treatment-experienced GT3 patients with cirrhosis who received DCV/SOF/RBV for 12 weeks, with no improvement by prolonging treatment to 16 weeks [132]. In a study assessing the treatment response of velpatasvir (VEL) and SOF (ASTRAL-3), the SVR was 98% in treatment-naïve, non-cirrhotic patients with GT3 infection, compared to 89% in cirrhotic patients with prior treatment failure [138]. In a large real-life study in individuals with GT3 infection, prior HCV treatment failure, cirrhosis and decompensated liver disease were significant predictors of reduced SVR rates, with reduced odds of SVR of 49%, 40%, and 32% respectively [139]. Lowest SVR rates were observed in treatment-experienced cirrhotic patients, where SVR rates ranged from 57 to 71% [139]. However, in a Scandinavian real-life SOF-based treatment study in GT3 patients, 89% of cirrhotic patients, including patients with decompensated cirrhosis, achieved SVR [140].

The recent approved DAA combinations glecaprevir (GLE)/pibrentasvir (PIB) and SOF/VEL/voxilaprevir (VOX) have greatly improved the SVR rates also for “difficult-to cure” groups, with SVR rates exceeding 95% [133, 141-144].

The presence of pre-treatment resistance-associated substitutions (RASs) may impair the efficacy of DAAs, especially in individuals infected with GT 1a and GT 3, and in patients with cirrhosis and/or prior treatment failure [13, 57, 122], as described below.

1.5.3 Goals of antiviral treatment and the impact of SVR

The primary goal for treatment of chronic HCV infection is to eradicate HCV, and thus prevent disease progression and complications [95]. Other goals are to improve quality of life, remove stigma and prevent onward transmission of HCV [95]. SVR, defined as undetectable HCV RNA 12 or 24 weeks after completion of antiviral therapy [145], corresponds to a definite cure of HCV infection in more than 99% of cases [146]. SVR is associated with marked improvements in liver necro-inflammation, liver stiffness and fibrosis scores [80, 147, 148]. Further, an SVR is associated with decrease in all-cause mortality, liver-related deaths, need for liver transplantation, HCC rates, and in liver-related complications, even among patients with advanced liver fibrosis [82, 84, 86, 149-152]. In addition, achievement of SVR can reduce extrahepatic manifestations related to chronic HCV infection [104].

1.5.4 Treatment recommendations

The impressive therapeutic improvement offered by potent and well-tolerated DAAs has changed the scenario and perspective of HCV treatment. DAAs can be administered to potentially all HCV infected persons with a wide spectrum of liver disease and somatic and psychiatric comorbidities, and provides an opportunity to reverse the rising burden of HCV-disease. This new reality is reflected in changes in treatment guidelines, e.g. The European Association for the Study of the Liver (EASL) and WHO now recommend that treatment must be considered for *all* patients with HCV infection, including individuals with high risk of transmitting HCV, like PWIDs [95, 153]. Historically, PWIDs has been excluded from treatment guidelines due to concerns about adherence, side effects and reinfection [154].

1.5.5 Treatment uptake

In a recent Markov modelling study, is was estimated that 4.6% of the total viraemic HCV population or 12.7% of the diagnosed viraemic population in Europe received antiviral treatment in 2015 [44]. Annual treatment rates in the infected population varies widely between countries; for instance 5.2% in France, 4.7 % in Germany, 2.8% in Sweden, and 0.5% in Denmark [6]. In 2013 in Norway, it was estimated, by modelling, that the annual treatment rate was 2.8% (610 of a total population of 21,900 HCV infections) [4]. In a Norwegian observational study of individuals who had received opioid substitution therapy (OST) between 2004 and 2013, 14% had received antiviral treatment, and the annual treatment rates varied between 1.3% and 2.6% [155]. In a Norwegian cohort of current or former PWIDs, approximately one-fourth of those alive at a median of 36 years of infection had received antiviral treatment [156].

In order to control the rising burden of HCV disease and achieve WHO elimination targets, treatment uptake has to be increased [4, 42, 157-159]. After the introduction of DAAs in 2014, a major barrier to increased treatment uptake has been the initially very high list prices of DAAs, which has restricted treatment to individuals with significant liver fibrosis or serious extrahepatic manifestations [160]. Lately, access to treatment has increased in several countries [160]. In Norway, unrestricted treatment has been available since February 2018 [161]. The annual number of treated patients in Norway has increased since the introduction of DAAs in 2014, from 799 in 2014 to 1955 in 2017 [162].

1.6 HCV resistance to DAAs

1.6.1 Resistance-associated substitutions (RASs)

Due to the extremely fast replication rate and the lack of proofreading activity of the viral RdRp, HCV exist as populations of genetically distinct but closely related viral variants in the infected person [13, 56]. These HCV quasispecies differ by amino acid polymorphisms that emerge during replication, and variants with reasonable good replicative capacity (fitness) can subsequently be selected during the chronic HCV infection. The term "resistance-associated substitutions" (RASs) is used to describe HCV amino acid substitutions associated with treatment failure and/or reduced susceptibility to DAAs [57].

RASs may exist prior to treatment, i.e. *baseline* RAS, or can emerge under the selective pressure of treatment with DAAs, i.e. *treatment- emergent* RASs [57]. RASs can contribute to treatment failure, depending on several factors: viral factors (GT, viral fitness, frequency within the HCV quasispecies, level of resistance), host factors (cirrhosis, previous treatment failure), and treatment factors (the DAAs genetic barrier to resistance, duration of treatment, addition of RBV, and adherence) [58, 163]. The level of resistance of different RASs, i.e. the effect on DAA susceptibility expressed as fold change (FC) in resistance (often expressed in EC_{50} values, i.e. the effective DAA-concentration that inhibits 50% of viral replication compared to wild-type HCV), can be assessed in phenotypic resistance analysis for each HCV subtype in cell cultures [12, 13, 57]. The EC_{50} FC is the ratio between the EC_{50} against the mutant and the wild-type virus in the replicon system in vitro.

1.6.2 Methods for sequencing HCV to detect RASs

Methods used for detecting RASs are based on DNA sequencing technologies. No standardized tests for resistance analysis to approved DAAs are available in Europe, only in USA [164]). These methods mostly rely on in-house techniques and include population (Sanger) sequencing and next generation sequencing (NGS) based on deep sequencing methods [165]. In a study reviewing methods for sequencing RASs in clinical samples, Sanger population sequencing was the most commonly performed method, followed by NGS [166].

In *population sequencing*, GT-specific or pan-genotypic PCR primers are used to amplify the target gene (NS3, NS5A or NS5B). This method has a sensitivity to detect the presence of RASs at an approximately 15-25% frequency within the HCV quasispecies [165, 167], compared to the *NGS methods* which provide detection of viral variants with a frequency down to 0.5 - 1% [12, 13]. However, as RASs present at low frequencies (1%-15%) do not impair the treatment response to DAAs with clinical relevance, the general consensus is to recommend a cut-off level of 15% for detecting RASs within the HCV quasispecies [13, 168, 169]. Using a 15% cut-off level also allows for comparison of results achieved with different sequencing methods [13].

1.6.3 Prevalence of baseline RASs and their level of resistance

Several RASs in the non-structural proteins NS3 and NS5A have been associated with reduced susceptibility to DAAs. RASs in the NS5B seem to be of less clinical significance [167, 170].

RASs in the HCV NS3 gene

Q80K is the most common RAS in the NS3 protease domain and is associated with impaired treatment response to the NS3/4A PI simeprevir (SIM) [171]. Q80K, mainly present in individuals with HCV GT1a, shows a geographically varying prevalence within Europe, ranging from 4.8% in Norway [171], 5.7- 15.2% in Sweden [172], to 75% in Poland [171]. In North America the prevalence is estimated to be 48% [173]. Q80K confers a 7-11 FC in resistance to SIM *in vitro* [57, 167].

The NS3 RAS *R155K* is rarely observed at baseline (< 1%) in GT1a infections [12, 174]. It is, however, frequently observed in patients who have failed treatment with PIs (boceprevir, telaprevir or SIM) [58], and confers a 90 FC in resistance to SIM *in vitro* [57, 167].

Combination of Q80K and R155K, results in an increased (1830) FC in resistance to SIM [57].

RASs in the HCV NS5A gene

In GT1a, the most clinically relevant NS5A RASs include variants at position Y93, M28, Q30, and L31 [57, 167]. The overall prevalence of baseline NS5A RASs as natural polymorphisms is 13-16%, using a 15% cut-off level [167, 169, 170]. However, clinically important NS5A RAS with high fold *in vitro* resistance are found at baseline in only 2-5% in GT1a [12, 58], e.g. RAS Y93H (prevalence <1.5%), which confers a very high FC in resistance to DCV (1600x), LDV (>1600x) and VEL (>600x) [12, 57].

Regarding GT3, the NS5A RASs Y93H and A30K are clinically the most relevant [57, 167]. NS5A RASs have been found at baseline in 8-16% of GT3a patients [128, 138]. RAS Y93H, which is detected quite frequently at baseline in GT3a (5-9%) [128, 138, 175], possesses a high FC in resistance to DAC (>3000x) and VEL (>700x) [57]. The A30K RAS is observed baseline in about 5-6% [167, 175], and confers a lower FC to DCV (100x) and VEL (50x) [57]. Both Y93H and A30K confers ≤1 FC to pibrentasvir [57].

1.6.4 Clinical relevance of RASs

RASs are typically associated with a change in HCV nonstructural proteins, which affect the binding or interaction with DAAs [12]. Many RASs confer a high FC in resistance in *in vitro* replicon assays, however, the level of resistance is not necessarily directly associated with treatment failure. Baseline RASs with high-fold level of resistance seem to contribute to treatment failure in the presence of factors like cirrhosis, prior treatment failure, suboptimal treatment regimen, and in viral GT1a and GT3 infections [13, 122, 167]. The clinical effect of RASs may be overcome by extension of treatment duration and/or by adding RBV [13, 57, 170]. Due to limited data, the clinical significance of RASs in less common GTs like GT5 and GT6 is less clear [57].

In patients who fail to achieve SVR after treatment with DAAs, RASs are selected in more than 80% of patients, dependent on treatment duration, the DAA class and regimen [12].

The impact of baseline NS3 RAS Q80K in treatment of patients with GT1a:

The impact of RASs on treatment outcome was first documented in patients treated with the PI SIM in combination with PEG-IFN and RBV. Individuals with HCV GT1a having a Q80K substitution at baseline within the NS3 protein, had lower SVR12 rates than those without

Q80K (46.7% versus 78.5%, respectively) [176]. However, treatment duration and the presence of cirrhosis seem to modulate the effect of Q80K. In a study with non-cirrhotic patients treated with SIM plus SOF (OPTIMIST-1), Q80K had an negative impact on treatment outcome in patients receiving treatment in 8 weeks compared to 12 weeks (SVR 73% and 96%, respectively), while there were no difference in SVR12 rates in those treated for 12 weeks [130]. In a study of patients with GT1a and cirrhosis (OPTIMIST-2), the SVR rate was 74% in individuals with baseline NS3 RAS Q80K, compared to 92% in individuals without Q80K [131].

In two phase 3 trials in individuals with GT1a treated with the pan-genotypic NS3 PI VOX combined with SOF and VEL for eight weeks, the SVR12 rate was lower in patients with baseline Q80K (88%) compared to those without Q80K (94%) [133].

The impact of baseline NS5A RAS in treatment of patients with GT1a:

In a study by Zeuzem and coworkers, the SVR12 rates in patients treated with LDV plus SOF were generally high regardless of the presence or absence of baseline NS5A RAS, however, lower SVR12 rates were observed in patients with previous treatment failure (SVR 76%) compared to treatment-naïve patients (SVR 97%) [169]. In treatment-naïve patients with cirrhosis, numerically lower SVR12 rates (86%) were observed, but the interpretability of this observation is limited due to a small number of patients [169].

In treatment with DCV combined with SOF, pooled resistance data has shown that baseline NS5A RAS was associated with a 22% lower SVR12 rate [57].

NS5A RASs at baseline did not affect treatment outcome of VEL plus SOF in patients without cirrhosis or with compensated cirrhosis (ASTRAL-1 trial) [135]. However, in patients with Child Pugh B cirrhosis, lower SVR12 rates were observed in patients with baseline NS5A RAS (ASTRAL-4 trial) [87].

The impact of baseline NS5A RASs in treatment of patients with GT3a:

In the phase 3 trial ALLY-3, which evaluated the treatment response of 12 weeks with DCV and SOF, the Y93H RAS was observed at baseline in 9% (13/147), of whom 67% (6/9) without cirrhosis and only 25% (1/4) with cirrhosis obtained SVR12 [128].

In the phase 3 study ASTRAL-3, which evaluated a 12-week treatment with the second generation NS5A inhibitor VEL combined with SOF, baseline NS5A RASs were observed in 16% (43/274), of whom 88% (38/43) reached SVR12, compared to 97% of the 231 patients without baseline NS5A RAS [138]. The Y93H RAS was detected at baseline in 9% (25/274), of whom 84% (21/25) achieved SVR12 [138].

In a recent pooled resistance analysis including eight studies, RAS A30K was identified in a few cases of treatment failure in regimen with the second generation NS5A inhibitor PIB. In treatment-naïve patients treated for 8 weeks, the SVR12 rates was 78% (14/18) in patients with baseline A30K, compared to 99% (161/163) in those without A30K [175]. Prolonging treatment to 12 weeks increased SVR to 93% (13/14) in patients with baseline A30K [175].

1.6.5 HCV resistance testing in treatment guidelines

Currently, baseline RASs do not appear to affect treatment response in GTs 1b, 2, 4, and 6, thus baseline RAS testing is not recommended in patients who are infected with these GTs [13]. The NS3 inhibitor SIM is no longer in use due to the advent of more effective DAAs. Since 2016, EASL guidelines recommend considering baseline resistance testing of clinically relevant NS5A RAS, using population sequencing or deep sequencing with a cut-off level of 15% in patients with GTs 1a and 3 [177]. NS5A RASs may influence the choice of first-line treatment regimen in the following situations [177, 178]:

- Elbasvir/grazoprevir in patients with GT 1a [129].
- Sofosbuvir/ledipasvir in treatment-experienced and cirrhotic patients with GT 1a [169].
- Sofosbuvir/velpatasvir in patients with GT 3 and cirrhosis [138].

1.7 Summary of Introduction: Key points

Globally, an estimated 71 million people are living with viraemic HCV infection. Norway is a low-prevalence country in this respect, as are most other Western European countries. Chronic HCV infection can progress to cirrhosis, HCC and end-stage liver disease in a substantial proportion of patients and the burden of disease is increasing. The infection is frequently asymptomatic, leaving many infected individuals unaware of the diagnosis until complications occur. The availability of effective and well tolerated DAAs has provided new opportunities to reverse the rising burden of “the silent epidemic”. HCV viral resistance to DAAs has emerged as an important consideration in order to optimize the antiviral treatment

and minimize the risk of treatment failure. Since the advent of DAAs, data on optimal regimens has been rapidly emerging and treatment guidelines subsequently rapidly changing. There are many challenges and remaining knowledge gaps that represent barriers to the care and treatment of HCV infection. Undiagnosed infection is one important barrier to the health impact of DAAs, and effective screening programs are urgently needed to diagnose and provide treatment to individuals who are unaware of their infection. There is uncertainty regarding the prevalence of diagnosed and undiagnosed HCV infection in Norway due to limited population-based data. Projection of future complications of HCV, based on local data, is warranted to enable an estimate of the future disease burden. Although DAAs are effective with overall response rates above 95% in most patient groups, the presence of baseline RASs can significantly compromise the treatment response in the individual patient. Implementation of HCV resistance testing may enhance the likelihood of successful treatment and minimize excessive healthcare costs wasted on suboptimal treatment.

2. AIMS AND HYPOTHESES

The overall research aims of the thesis were to describe epidemiological aspects and viral resistance in chronic HCV infection among the general adult population in a low-prevalence area. The specific research aims and corresponding hypotheses were:

- There is uncertainty regarding the prevalence of HCV infection in Norway and the proportion of undiagnosed HCV infection. It is assumed that 20-30,000 individuals live with chronic HCV infection, but population-based data are limited.
  Aim: To assess the prevalence HCV infection in the general adult population >40 years of age in the municipality of Tromsø, Northern Norway, and to evaluate the effectiveness of such an approach (Paper 1).
  Hypothesis: The prevalence of diagnosed and undiagnosed HCV infection in the general population in the municipality of Tromsø is low.
- Worldwide, the total number of HCV infections is expected to decline in the years to come, but HCV-related mortality and morbidity is projected to increase.
  Aim: To estimate the future prevalence and complications of chronic HCV infection towards 2050 in a low-risk area by using a Markov model (Paper 2)
  Hypothesis: The burden of HCV disease will increase in the coming years despite a low prevalence of chronic HCV infection in the region.
- DAAs offer high cure rates in the majority of HCV infected patients, however, a significant absolute number of patients fail to achieve SVR. The presence of baseline RASs can impair the treatment outcome.
  Aim: To assess the prevalence of baseline NS3- and NS5A RASs, and to investigate the impact of these RASs on the treatment outcome in patients infected with HCV GTs 1a and 3a receiving personalized treatment regimens based on resistance testing in a real-life setting in Sweden and Norway (Papers III and IV).

  Hypothesis: The prevalence of baseline NS3 RASs (Q80K and R155K) and NS5A RASs (Y93H and A30K) are low. The presence of baseline RASs may impair treatment response to DAAs in chronic HCV infection GTs 1a and 3a.

3. STUDY POPULATIONS AND METHODS

The individuals included in the studies referred to in this thesis were participants in the seventh survey of the Tromsø Study (Tromsø 7), the Hepatitis C Study in Northern Norway (Hep C North) and the HCV Preexist Study (Table 2).

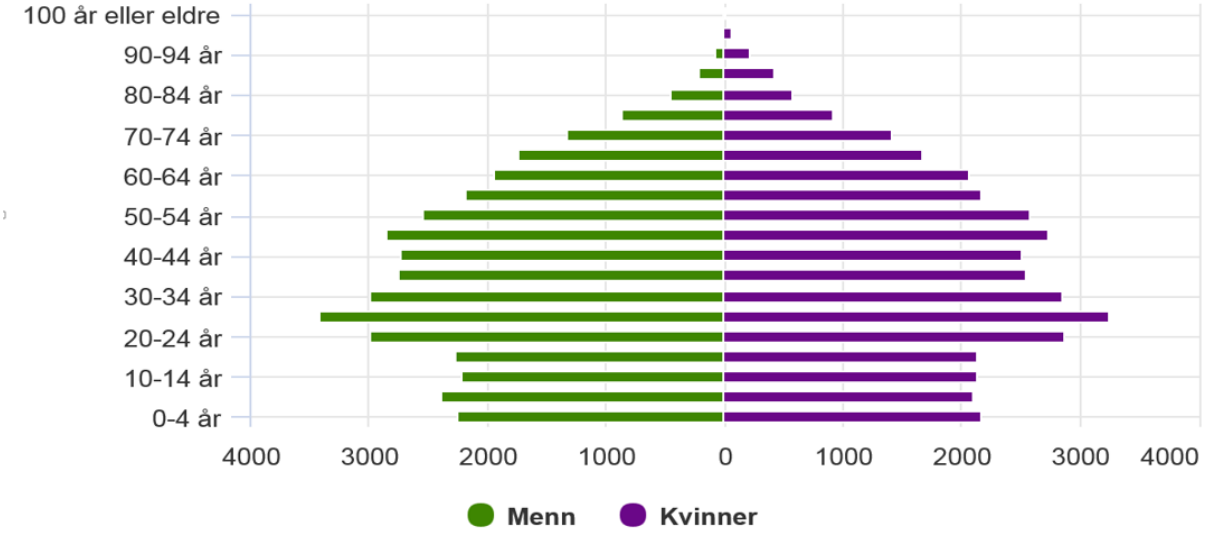
	Included	Period	Design
Paper I Tromsø 7	20 946	2015-2016	Cross-sectional population-based study
Paper II Hep C North	2 589	1992-2012	Markov cohort simulation model
Paper III HCV Preexist	193	2014-2016	Prospective, real-life, open label, non-randomized multi-center cohort study
Paper IV HCV Preexist	208	2014-2017	Prospective, real-life, open label, non-randomized multi-center cohort study

Table 2 Study participants included in the studies referred to in this thesis.

3.1 The Tromsø 7 Study (Paper I)

The Tromsø Study is a single-centre, population-based, prospective study with seven repeated health surveys since 1974 in the municipality of Tromsø in Northern Norway [179]. The study was initiated to explore the reasons for the high cardiovascular mortality in Northern Norway, but has gradually been expanded to include a broad spectrum of chronic diseases.

The present population in the municipality of Tromsø (2nd quarter of 2018) is 76,062 inhabitants [180]. The demographics of Tromsø is presented in Figure 3.



Kilde: Folkemengde, Statistisk sentralbyrå

Figure 3. The demographics of the municipality of Tromsø as of the 2nd quarter of 2018. Numbers of males (Menn) and females (Kvinner) in each 5-year age group. Reproduced with permission from Statistics Norway. År: years (age).

We used data from Tromsø 7, which was performed in 2015-2016. Microbiological analyses were performed at the Department of Microbiology and Infection Control, University Hospital of North Norway, Tromsø.

All 32,591 citizens aged 40 years and above were invited, and 21,083 (65%) attended. The participation rate was highest in the age group 60 to 69 years for both women and men, somewhat lower in younger age groups, and lowest among those older than 80 years.

Sera from 20,946 participants (64.3%) were tested for anti-HCV (ARCHITECT Anti-HCV Assay, Abbott System, Wiesbaden, Germany), of whom 11,004 (52.5%) were women and 9942 (47.5%) were men. A self-administered questionnaire (Appendix) was used to obtain

information concerning health, psychological problems, smoking habits, alcohol consumption, the use of drugs other than alcohol, level of education, marital status and main occupation/activity. There were two questions regarding hepatitis C (translated from Norwegian): “Have you been infected with the liver virus hepatitis C?”, and “If you have been infected with the liver virus hepatitis C: have you ever received treatment?”

Individuals with a positive anti-HCV test received a letter with information and a request for a second blood test. Two reminders were sent to those who did not have the follow-up test. The follow-up samples were retested for anti-HCV and further tested for the presence of HCV RNA (ROCHE RT-PCR Cobas Amplicor Hepatitis C Viral Polymerase Chain Reaction, Roche Molecular System Inc., Branchburg NJ, USA), and the result of any previous laboratory HCV data were recorded. Samples positive for the anti-HCV test and negative to the HCV RNA test were analyzed with a recombinant immunoblot assay (RIBA HCV 3.0 SIA test, Chiron Cooperation, Emeryville, CA, USA). RIBA was not carried out in cases were existing laboratory results were consistent with either spontaneous recovery or obtained SVR after antiviral treatment. HCV genotyping was performed as a hybridization assay on products from the HCV RNA PCR according to the manufacturer’s instructions (INNO-LIPA HCV II kit, INNOGENETICS, Ghent, Belgium).

All subjects with a positive HCV RNA test were offered a clinical evaluation, which included a thorough medical examination, blood tests, the recording of the medical history with questions concerning symptoms of chronic HCV and the assessment of risk factors for HCV infection. Liver fibrosis was assessed by LSM (expressed in kiloPascals, kPa), using transient elastography (FibroScan® 402, Echosens, Paris, France). Significant fibrosis and cirrhosis was defined as LSM values ≥7 kPa and 12,5 kPa respectively [97]. The Fibrosis-4 (FIB-4) index was calculated using ALT, aspartate aminotransferase, platelet count and age [181].

3.2 The Hep C North Study (Paper II)

Data from the Hep C North Study constituted an incidence cohort, which was used to estimate the future prevalence and complications of chronic HCV infection in Northern Norway until 2050.

In 1992, a screening and medical follow-up program of patients with community-acquired HCV infection was established in the Health Region of Northern Norway, as previous reported [33, 182]. In short, patients with positive anti-HCV and RIBA were registered at the

two microbiological laboratories in the health region (Tromsø and Bodø). Referring general practitioners were encouraged to refer patients with HCV infection for follow-up at one of the 11 medical centers in the region. An estimate of the year of transmission was made based on either the year of acute HCV infection or the first year of high-risk behavior. Liver biopsies were performed, and fibrosis was graded (0-6) according to Ishak et al. [91].

We performed a registration study to estimate the annual number of newly diagnosed individuals with HCV infection in the years 1998-2012 at the two microbiological laboratories in Northern Norway. Previous registered patients in the years 1992-1997 were included [33]. The year of diagnosis was defined as the first year of a positive anti-HCV test (ARCHITECT Anti-HCV Reagens kit. Abbott System, Wiesbaden, Germany). Until 2004, a positive anti-HCV test was directly confirmed with RIBA (RIBA HCV 3.0 SIA test, Chiron Cooperation, Emeryville, CA, USA). Individuals with a positive or indeterminate RIBA were included, while individuals with a negative RIBA were excluded. The result of the HCV RNA test was recorded if available: An in-house reverse transcriptase polymerase chain reaction (RT-PCR) until 2004, where after the ROCHE RT-PCR (Cobas Amplicator Hepatitis C viral Polymerase Chain Reaction, Roche Molecular System Inc., Branchburg NJ, USA) was used. The ROCHE PCR test replaced the RIBA test for confirmation of HCV infection from 2005. HCV genotyping was performed as a hybridization assay on products from the HCV RNA PCR according to the manufacturers' instructions (INNO-LIPA HCV II kit, INNOGENETICS, Ghent, Belgium). Individuals without a registered residence in Norway were excluded.

Markov model

Markov models are used to estimate the progression of a chronic disease through defined disease stages within a cohort [183]. We constructed a Markov model to simulate the natural course of HCV infection in our population over time. Patients were assumed to be in one of several defined disease stages (Markov states). All events were modelled as transitions from one stage to the next, based on probability estimates generated from different sources. The effect of medical treatment was modelled in three scenarios where 0%, 15%, and 50% of patients were assumed to receive medical treatment. The annual number of HCV-infected individuals entering the model and the fibrosis progression towards cirrhosis were based on local data. Individuals entered the Markov model at the time of contraction of HCV infection. Year of infection was known in a subgroup of the infected individuals, and had to be estimated for the remaining records.

The ***rate of fibrosis progression*** towards cirrhosis was estimated in an ordinal regression analysis, which included duration of infection and HCV GT as covariates of disease progression. A sub-cohort (n=237) with known duration of HCV infection and available liver biopsy were included. The distribution of gender and GTs in the sub-cohort was equal to the total cohort (n=2589).

As we did not have exact local data for the transition probabilities from compensated cirrhosis (Ishak 6) to more severe states of liver disease, the remaining transition probabilities were based on data from a Scottish HCV population of PWID [184]. The effect of medical treatment were modelled in three scenarios where 0%, 15% and 50% of all patients were assumed to receive treatment. The model accounted for the improvement in treatment response offered by DAAs, and was corrected for standardized mortality rate according to Norwegian population characteristics.

Handling of incomplete records

The registration of HCV infection revealed that 18% of the records were incomplete regarding confirmation testing, i.e. records with only a positive anti-HCV test or an indeterminate RIBA. In the incomplete records, we estimated the likelihood of a true positive test based on samples with complete diagnostics, resulting in estimated probabilities for a true positive test given a positive anti-HCV and an indeterminate RIBA of 0.63 and 0.21, respectively. Thus, the starting cohort in the Markov model was based on individuals with confirmed HCV infection (each weighted 1.0) and individuals with incomplete diagnostics (each weighted 0.63 or 0.21, respectively).

3.3 The HCV Preexist Study (Paper III and IV)

The HCV Preexist Study is a prospective, real-life, open label, non-randomized multi-center study in Sweden and Norway. The study was designed to investigate the effect of baseline RASs on treatment outcome in patients with HCV GT1a and HCV GT3 infection treated with DAAs. The Departments of Infectious Diseases in Uppsala and Gävle, Sweden, and of Gastroenterology in Tromsø, Norway, have performed routine NS3 resistance testing of HCV GT1a before treatment with DAAs since 2014, and NS5A resistance testing of HCV GT1a since 2015 and GT3 since 2014. At the initiation of the study there were no available guidelines regarding baseline resistance testing.

The inclusion criteria were ≥18 years of age, and HCV GT 1a (Paper III) or HCV GT 3 (Paper IV) and treatment according to Swedish and Norwegian consensus recommendations, as well as completed treatment course (per- protocol). Included patients were either treatment-naive or treatment-experienced to IFN-based therapy, including triple therapy containing the first generation NS3 protease-inhibitors boceprevir or telaprevir. Patients previously treated with other DAAs were excluded.

Liver fibrosis was assessed by liver biopsy (graded 0-4 according to METAVIR [90]) or by transient elastography (FibroScan ® 502,Echosens, Paris, France in Swedish study sites, and FibroScan 402® Echosens, Paris, France in Norwegian study sites). Cirrhosis was defined as METAVIR score F4 [90] or LSM values > 12,5 kPa [97].

In Paper III, the effect of baseline NS3 RASs (Q80K and R155K) and clinically relevant NS5A RASs on treatment outcome in patients with GT1a infection were investigated. Patients from Uppsala, Gävle and Tromsø (intervention group, n=92) were consecutively included. The control group consisted of patients from Örebro, Falun and Bodö (n=101). The inclusion period was from 1 April 2014 to 30 June 2015 (Sweden) and to 26 January 2016 (Norway).

In Paper IV, the effect of baseline NS5A RAS Y93H on treatment outcome in patients with GT3 infection were investigated. Patients from Uppsala and Tromsø (intervention group, n=130) were consecutively included from 1 April 2014 to 31 December 2017. The control group consisted of patients from Bodø, Falun, Stockholm and Örebro (n=78).

In both studies, a prospective intervention was performed. Treatment in the intervention group was tailored to baseline resistance findings. Recommended treatment, according to national guidelines, was given to patients without baseline RAS in the intervention group and to all patients in the control group. The primary endpoint was SVR 12 weeks after the end of treatment.

HCV RNA titer quantification was performed at the Department of Clinical Microbiology, University Hospital, Uppsala, and at the Department of Microbiology and Infection Control, University Hospital of North Norway (Roche COBAS® AmpliPrep/TaqMan® HCV Quantitative Test, v2.0 with a LOQ of 15 IU/mL, Roche Molecular Systems Inc., Branchburg NJ, USA). The Clinical Microbiology laboratory at the University Hospital, Uppsala, performed the resistance analysis of RASs (baseline and emerging). A nested PCR method was adopted for NS3- and NS5A resistance analysis, followed by Sanger sequencing (population sequencing, cut-off 20%). The methods for RNA extraction, reverse transcription,

nested PCR and sequencing in NS3- and NS5A resistance analysis are described in detail elsewhere [172, 185]. Presence of baseline RASs was analyzed for all patients in the control group retrospectively. Resistance analysis for emerging RAS was performed in all non-responders at the time of relapse.

3.4 Statistical methods

Statistical analysis were performed using Microsoft® Excel 2013 (Microsoft Office Professional Plus 2013, Microsoft Corporation) and the Statistical Package for Societal Science (SPSS), version 24 and 25 (IBM Corp., Armonk, N.Y., USA). Means, medians and proportions (%) were used to describe both baseline characteristics and outcomes, where appropriate.

The Chi-Square and Mann-Whitney U tests were used for comparison between groups. The Fisher's exact test was used to test the differences between groups in case of small sample numbers. In Paper 1, a multivariate logistic regression analysis were used to compare sociodemographic and behavioral characteristics between HCV exposed and anti-HCV negative. A two-tailed p-value <0.05 was considered statistically significant.

In Paper II, an ordinal regression model was used to estimate transition points on an ordinal scale (like the Ishak fibrosis scale). Sex, duration of infection in years, and HCV GT were included as predictors of Ishak fibrosis grade. The individual effect of each covariate was assessed in a multivariate analysis, leaving duration of infection and HCV GT as significant predictors. GTs 1 and 4 were analyzed as a single group due to few observations of GT 4. The model predicted 70% of the observed fibrosis grades correctly within a margin of error of one Ishak grade, but overestimated the fibrosis grade in 13% and underestimated in 17%. From this model, a matrix of estimated probabilities of transition to a higher fibrosis grade versus staying in the present grade for each year of infection could be constructed. It was assumed that fibrosis development could only either stay the same or change to a higher stage each year of infection.

3.5 Ethics

The Regional Committee for Medical and Health Research Ethics (REK) approved the Tromsø 7 study (ref: 2014/1406 and 2017/253) and the Hepatitis C Study in Northern Norway (ref: P-REK 55/2001), and all participants gave their written, informed consent to participate. The Data Protection Official at The University Hospital of North Norway approved processing of the microbiological data in the registration study in Paper II (Nr. 0552). The HCV Preexist study was a multicenter study carried out at the Uppsala University Hospital in Sweden. The regional committee of medical research ethics Committee in Uppsala (Dnr: 2013/185 and Dnr: 2013/185/1) and the Data Protection Official at The University Hospital of North Norway (Nr. 0574) approved the study. All participants received written information and the opportunity to withdraw from the study.

4. SUMMARIES OF PAPERS AND MAIN RESULTS

4.1 Paper I: Screening for hepatitis C in a general adult population in a low-prevalence area: The Tromsø Study

Background/aim: Chronic HCV infection can progress to cirrhosis and end-stage liver disease in a substantial proportion of patients. The infection is frequently asymptomatic, leaving many infected individuals unaware of the diagnosis until complications occur. This advocates the screening of healthy individuals. The aim of this population-based survey was to estimate the prevalence of chronic HCV infection in a presumed low-prevalence area and evaluated the efficiency of such an approach.

Methods: The study was part of the Tromsø 7 Study in 2015-2016. Sera from 20,946 individuals aged 40 years and older were analysed for anti-HCV. A positive anti-HCV test was followed up with a new blood test for HCV RNA and the result of any previous laboratory HCV data were recorded. Samples positive for anti-HCV and negative for HCV RNA were tested with a recombinant immunoblot assay. All HCV RNA positive individuals were offered clinical evaluation.

Results: Among 20,946 participants, HCV RNA was detected in 33 (0.2%; 95% CI: 0.1-0.3), of whom 13 (39.4%; 95% CI: 22.7-56.1) were unaware of their infection. The anti-HCV test was confirmed positive in 134 individuals (0.6%; 95% CI: 0.5-0.7) with the highest prevalence in the age group 50-59 years. Current or treatment-recovered chronic HCV-infection was found in 85 individuals (0.4%; 95% CI: 0.3-0.5) and was associated with an unfavorable psychosocial profile.

Conclusion: In this population-based study, the prevalence of viraemic HCV infection was 0.2%. A substantial number (13/33) of persons with viraemic disease was not aware of their infectious status, which suggests that the current screening strategy of individuals with high risk of infection may be an inadequate approach to identify chronic HCV infection hidden in the general population.

4.2 Paper II: Future complications of chronic hepatitis C in a low-risk area: projections from the hepatitis c study in Northern Norway

Background/aim: Screening for HCV infection has confirmed a low prevalence in the general population in Northern Norway. Despite this, late complications are increasing. In this study we aimed to estimate future complications of chronic HCV infection in the period 2013-2050 in our low-prevalence area.

Methods: In order to predict HCV-related morbidity and mortality, an open Markov model was constructed. The estimated HCV cohort of 2589 individuals were entered into the model at the time of contraction of the disease. The rate of fibrosis progression was estimated in an ordinal regression analysis. Yearly transitions between disease categories were done according to probability estimates generated from different sources. The effect of medical treatment was modelled in three different scenarios.

Results: It was estimated a stable low incidence of HCV infections in the projection period. The rate of fibrosis progression was relatively slow in the first 20-25 years of infection, followed by an accelerated fibrosis progression, especially in patients with GT 3. The model predicted an almost three-fold increase in the prevalence[1] of cirrhosis (68 per 100,000), of decompensated cirrhosis (21 per 100,000) and of hepatocellular carcinoma (4 per 100,000) by 2050, as well as a six-fold increase in the cumulated number of deaths from HCV-related liver disease (170 per 100,000 inhabitants). All estimates were made assuming an unchanged treatment coverage of 15%. The estimated numbers could be reduced by approximately 50% for cirrhosis, and by approximately one third for the other endpoints if treatment coverage was raised to 50%.

Conclusion: These projections from a low-prevalence area indicate a substantial rise in HCV-related morbidity and mortality in the coming years, despite a presumed stable incidence of HCV infection. Increased treatment coverage is necessary to reduce the burden of HCV disease.

[1] In the published journal article, the prevalence of complications is incorrectly referred to as incidence in the abstract and in the section Markov modelling on page 5.

4.3 Paper III: Personalized treatment of hepatitis C genotype 1a in Norway and Sweden 2014-2016: a study of treatment outcome in patients with or without resistance-based DAA-therapy

Background/aim: RASs, either naturally occurring or selected, may impair treatment response to DAAs in HCV infection. We aimed to investigate the presence of baseline NS3-RASs (Q80K and R155K) and clinical relevant NS5A-RASs together with treatment outcome in patients with GT 1a with and without resistance-based DAA-treatment.

Methods: A prospective intervention was performed where treatment in the intervention group (n= 92) was tailored to baseline resistance (population sequencing method): i.e. detection of NS3 RAS led to a switch to an NS5A- inhibitor based regimen, and opposite switch with NS5A RAS. Patients without baseline RAS in the intervention group and all patients in the control group (n=101) received standard recommended DAA-treatment.

Results: The overall prevalence of baseline NS3 RAS Q80K and R155K was 7.1% and 5.2%, respectively. The SVR12 rates in the intervention and control groups were 97.8% (90/92) and 93.1% (94/101), respectively (p=0.174). A trend toward higher SVR rate in cirrhotic patients was noticed in the intervention group compared to the control group, 97.5% (39/40) and 83.3% (35/42), respectively (p=0.058). All patients with baseline NS3 and NS5A RASs in the intervention group achieved SVR. In the control group, treatment failed in two of five patients with Q80K or R155K at baseline who were treated with the NS3/4A protease inhibitor SIM combined with SOF. Furthermore, one of three patients who failed treatment with the NS5A inhibitor LDV combined with SOF had NS5A RASs at baseline.

Conclusion: In line with the findings of the OPTIMIST-2 trial for Q80K and the EASL guidelines 2016 for NS5A RASs, baseline RASs appear to have an impact on treatment outcome, albeit a statistical significance could not be obtained in this low-prevalence population.

4.4 Paper IV: Effect of the baseline Y93H resistance-associated substitution in HCV genotype 3 for direct-acting antiviral treatment: Real-life experience from a multicenter study in Sweden and Norway

Background/aim: RAS may impair treatment response to DAAs in HCV infection. The NS5A RAS Y93H is found quite frequently (5 -10 %) at baseline in DAA treatment-naïve GT 3a patients when studied by the population (Sanger) sequencing method with a cut-off of 20%. This RAS possesses a high fold *in vitro* resistance to the NS5A inhibitors DCV and VEL in patients with HCV GT 3 infection.

Methods: Treatment in the intervention group (n=130) was tailored to baseline resistance findings by population sequencing method. Detection of baseline Y93H prompted a prolonged treatment duration of NS5A inhibitor plus SOF and/or addition of RBV at the responsible medical doctor`s discretion. Patients without baseline Y93H in the intervention group and all patients in the control group (n=78) received recommended standard DAA-treatment.

Results: The overall prevalence of baseline Y93H RAS was 4.3% (9/208). A higher SVR rate in the intervention group was shown compared to the control group, 95.4% (124/130) and 88.5% (69/78), respectively (*p=0.06*). All five patients with baseline Y93H in the intervention group achieved SVR with personalized treatment based on the results of baseline resistance testing; either with the addition of RBV or prolonged treatment duration (24w). In the control group, 2/4 patients with Y93H at baseline treated with LDV+SOF+RBV or DCV+SOF without RBV, failed treatment. Thereby, with baseline Y93H, a trend towards higher SVR rate was found in the intervention group compared to the control group (*p=0.07*).

Conclusion: The results from this real-life study are in accordance with the findings of the randomized controlled trials in 2015 (ALLY-3 and ASTRAL-3) and the EASL-guidelines of 2016, i.e. baseline Y93H impacts on DCV and VEL treatment outcome. However this could not be statistically determined in this low-prevalence population.

5. GENERAL DISCUSSION

Collectively, the studies referred to in this thesis have highlighted important aspects of HCV infection. The assumed low prevalence of chronic HCV infection in a general population was confirmed (Paper 1). However, the study indicate that a substantial number of individuals with viraemic HCV infection are unaware of their diagnosis, rendering them in risk of developing serious complications. In addition, the high proportion of undiagnosed infection suggests that the current risk-based screening strategy may be an inadequate approach to identify individuals with chronic HCV infection hidden in the general population. Despite an estimated stable incidence of HCV infection in the years to come, a substantial increase in liver cirrhosis, liver cancer, hepatic decompensation, and liver-related deaths is projected by 2050 (Paper II). The estimated numbers of complications can be reduced by approximately 50% for cirrhosis, and by approximately one third for the other endpoints if treatment-coverage is increased from the assumed base scenario of 15% to 50%. Effective and well-tolerated DAAs have provided an opportunity to reverse the rising burden of HCV-related disease, however, viral resistance has added a layer of complexity to the treatment of HCV infection. The presence of baseline RASs may have an impact on the treatment outcome in patients infected with HCV GTs 1a and 3, however this could not be statistically determined (Paper III and IV). Baseline resistance testing may be an important tool for tailoring personalized treatment and enhance the likelihood of treatment success for the individual patient, as well as in a perspective of evidence-based healthcare delivery.

5.1 Methodological considerations

5.1.1 Study populations, recruitment and study designs

An overview of the study populations and study designs in the respective papers has been presented in Table 2. In Paper 1, the HCV prevalence was determined in a population-based cross-sectional study of individuals aged 40 years and older. The main strength of this study is the large sample size in a general population, which reduces the risk of selection bias and enhances the probability that the study population is representative of the general population.

In Paper II, future HCV-related morbidity and mortality was predicted by using a Markov cohort simulation model. The study population consisted of individuals with community-acquired HCV infection registered at the two Departments of Microbiology in Northern Norway and referred from primary care to one of the medical centers in Northern Norway.

Fibrosis progression was modelled in an ordinal logistic regression analysis of 237 records with available liver biopsy and known duration of infection.

Markov models are well suited and widely used to simulate the progression of a chronic disease through defined disease stages within a cohort, with transition from a given category to the next based on probability estimates [183]. However, precision of dynamic modelling in estimating future complications of a disease depends on the quality of the data entered and the assumptions made. The strength of our Markov model is the use of locally acquired data whenever available. The HCV cohort entered into the model and the progression of liver fibrosis to cirrhosis was based on local data. The further development from established cirrhosis to more severe states of disease and the rate of spontaneous recovery are not likely to be very different from that of other cohorts, and the use of estimated transition probabilities from other studies should not affect the projections measurably. The transition probabilities from compensated cirrhosis to decompensated cirrhosis, HCC, and liver-related death were based on pooled transition estimates, which increase the accuracy of the transition estimates [184]. Model limitations will be discussed further in Section 5.3.4.

In Papers III and IV, the impact of baseline RASs on treatment outcome in patients with HCV GT 1a and GT 3 was investigated in two prospective, open label, non-randomized multi-center cohort studies. The patients were consecutively included and managed in a real-life setting. The real-life design, where patients are more diverse and complex compared to patients included in clinical trials, enhances the probability that the study population reflects the real patient population encountered in clinical practice.
Cohort studies are well suited for investigating risk factors and the natural history of a disease [186]. The temporal sequence of exposure/intervention (treatment tailored to baseline resistance analysis) and outcome (SVR) allows some indication of causality, however, an association between exposure and outcome in a prospective study is not enough to conclude with causality. The high number of participants required when studying rare conditions makes cohort studies less appropriate. In Papers III and IV, the prevalence of baseline RASs turned out to be lower than expected. As a consequence, statistically significant results could not be obtained when investigating the impact of baseline RASs on treatment outcome. Lastly, the non-randomized design of cohort studies make them prone to bias, which will be further discussed.

5.1.2 Validity

The aim of epidemiological studies is to obtain correct and precise results that can be generalized to other populations. The *validity* of a study refers the extent to which this aim is achieved [186]. *External validity* refers to the results' generalizability, whereas *internal validity* denotes to which extent it is possible to draw conclusions concerning the study population [186]. Most threats to internal validity can be classified as: selection bias, information bias, and confounding [186]. Internal validity is regarded as a prerequisite for external validity.

5.1.3 Bias

Bias is the result of a systematic error in the design or conduct of a study, which can influence both the internal and the external validity of a study [187].

Selection bias may occur when there are systematic errors in the recruitment and retention of study participants in a way that affects the conclusions of the study [187, 188]. This bias may arise as a result of participant selection procedures or from factors that influence participation in the study. In The Tromsø 7 Study (Paper 1), all inhabitants of the municipality of Tromsø aged 40 years and older were invited to participate. This age restriction was inherent to the overreaching study design of Tromsø 7, but clearly introduces a selection bias. IDU is the main mode of transmission of HCV [21] and it is estimated that approximately 30% of PWID in Western Europe are younger than 25 years of age [25]. There is no clear data available on the age distribution of PWIDs in the Tromsø population, but it is reasonable to assume that the proportion of young PWID in Tromsø is comparable to other countries in Western Europe.

In addition, ***self-selection bias*** may be an important issue that may threaten the external validity. The attenders in health surveys tend to be more educated and have a healthier life style than non-attenders [189], and various psychiatric disorders and alcohol abuse have been shown to be significant predictors of nonattendance in health surveys [190]. It is therefore reasonable to assume that PWID are less likely to participate in health surveys. Due to these biases, the true prevalence of HCV infection probably is underestimated.

In Paper II, the study participants included in the simulated fibrosis progression were referred from primary care to one of the medical centers in Northern Norway between 1992 and 2011. In this period, only IFN-based treatment was available, thus many HCV infected persons were not considered eligible for treatment due to concerns of side effects, compliance and reinfection. It is likely that persons with ongoing IDU, psychiatric comorbidities and heavy

alcohol consumption were referred from primary care to a lesser extent than the rest of the HCV population. Thus, the recruitment procedure was inherently subject to selection bias.

In Paper I, a self-administered questionnaire was used to obtain information regarding health, psychological problems, use of alcohol, and use of drugs other than alcohol. Self-administered questionnaires are prone to ***response bias*** that may promote more socially acceptable responses, e.g. response to alcohol use and current or past drug injection [191]. In the self-administered questionnaire used in the Tromsø 7 Study, only six of the 13 individuals with previous unknown HCV infection reported current (n=2) or past (n=4) IDU. In the follow-up examination, an additional three persons reported past IDU.

The non-randomised design in Papers III and IV makes them prone to selection bias. Cirrhosis and previous treatment failure to IFN-based therapy are well known negative predictors of non-SVR. In Paper III, the distribution of patients with cirrhosis was similar in the intervention and the control groups, however, in Paper IV, the distribution of cirrhosis was significantly higher in the control group compared to the intervention group, 61.5% (48/78) and 37.7% (49/130), respectively. Further in Paper IV, the proportion of treatment-experienced patients was significantly higher in the control group compared to the intervention group, 39.7% (31/78) and 21.5% (28/130), respectively. Thus in Paper IV, the observed trend of a lower SVR rate in the control group compared to the intervention group could be explained by the presence of more advanced liver disease and a higher proportion of previous treatment failure in the control group.

5.1.4 Confounding

Confounding refers to a situation where the association between an exposure variable and the outcome may be attributed to the influence of a third variable, which is independently related to both the exposure variable and the outcome [187]. Confounding represents a threat to the assessment of causal relationships in cohort studies, and may lead to underestimation, overestimation or even change in the direction of the observed association [187]. Age and gender are often confounding variables in population-based studies.

Confounding can be minimized by proper adjustment and by using multivariable statistical analysis, where potential confounding variables are included as covariates in multivariable regression models. In Paper 1, sociodemographic and behavioural characteristics between HCV exposed and anti-HCV negative individuals were compared. To control for confounders, we used multivariate logistic regression analysis, adjusted for age and gender. Significant

independent predictors of being exposed to HCV were thus: being disabled or unemployed, smoking, and current or previous use of drugs other than alcohol.

5.1.5 Sample size and study power

Statistical power is the probability that a given study will reject the null hypothesis when the alternative hypothesis is true [186]. This depends on the strength of the true association between risk and exposure, the number of participants in the study, and the distribution of the exposure in the population being studied. A type II error is the failure to reject a null hypothesis when it is false, i.e. to disregard an effect that is in fact present [186]. Type II errors are usually related to small sample sizes, which limits the possibility to stratify the population into subgroups for analysis.

In Papers III and IV, an important limitation is the relatively small sample sizes. In addition, the prevalence of observed baseline RASs was lower than expected based on previous reports. The failure of detecting statistically significant associations between baseline RASs and treatment outcome may therefore be attributable to a lack of statistical power.

5.1.6 Methods for HCV diagnosis

Diagnosis and monitoring of HCV infection in the four papers referred to in this thesis are based on two different kinds of tests; determination of specific antibodies against HCV and detection of HCV RNA.

Anti-HCV test (EIA)

The specificity of EIAs has improved from the start of the study in Paper II, from about 80% diagnostic specificity of first-generation EIAs to >99% specificity in third- generation EIAs [105]. As a result, some records might have been missed in the registration of early anti-HCV positive cases in Paper II. The sensitivity of third-generation EIAs is variable (61-82%), yielding low positive predictive values in low-prevalence populations [111]. In Paper I, the proportion of false-positive results was 38%. False-positive results can cause harm by way of anxiety and stigmatization [192]. According to the criteria for screening proposed by Wilson and Jungner, the screening test should be “suitable (simple, sensitive, specific)” [46]. The current HCV testing algorithm requires first the detection of anti-HCV. In people with positive anti-HCV, a new blood sample for HCV RNA is required to confirm viraemic infection. The consequence of this two-step algorithm is that a significant proportion of individuals with positive anti-HCV test never receive the confirmatory HCV RNA rest, as we observed in the registration study in Paper II, and also described by others [116]. The

availability of point-of-care diagnostics has the potential to simplify testing, thus obtaining HCV diagnosis in a single visit [116].

RIBA

RIBA can help distinguish between past infection (RIBA positive) and false-positive anti-HCV (RIBA negative) in individuals who have a reactive EIA and a negative HCV RNA test [114]. The interpretation and significance of RIBA-indeterminate reactions is unclear. In one study, 4.9% of cases with indeterminate RIBA were HCV RNA positive [114]. Still, in most RIBA-indeterminate cases the HCV RNA test is negative, which may indicate both spontaneously resolved HCV infection and unspecific antibody reactions [113]. Studies in blood donors have indicated that approximately half of RIBA indeterminate results could be explained in previous resolved HCV infections [193, 194]. The number of cases with indeterminate RIBA reactions in both Papers I and II were low, making the contribution of these records less significant.

HCV RNA

Testing for HCV RNA is the gold standard for diagnosing active HCV infection [105, 110]. In Papers I, III and IV, HCV RNA was detected with PCR methods with high specificity (up to 99%) and high sensitivity [105]. In Paper II, an in-house reverse transcriptase PCR with lower sensitivity was used until 2004, thus false negative HCV RNA results might have been obtained in early records.

Incomplete records

In Paper II, registration of HCV infection at the two microbiological departments in the study region revealed that 18% of the records were incomplete regarding confirmation testing, i.e. records with only a positive anti-HCV test or an indeterminate RIBA. Studies have revealed that only 46-73% of individuals with positive anti-HCV received a confirmatory HCV RNA test [116]. We estimated the likelihood of a true positive test, as described in Section 3.2 and in Paper II. Thus, the incidence cohort in the Markov model was based on individuals with confirmed HCV infection (each weighted 1.0) and individuals with incomplete diagnosis (weighted 0.63 when only positive anti-HCV and 0.21 when indeterminate RIBA, respectively). This estimation may have resulted in uncertainty regarding the number of individuals entering the Markov model. However, our estimate of 63% true positive among those who only had a positive anti-HCV test is in accordance with a reported value of 68%

true positive in a population with low prevalence of HCV infection [114]. The estimate is also in accordance with the findings in Paper I, where 62% of those with positive anti-HCV test were confirmed to be true positive.

5.1.7 Resistance testing

RASs can be detected by Sanger (population) sequencing and NGS method. In Papers III and IV, the Sanger method was used in the resistance analyses. The Sanger method has a 15-25% sensitivity for detecting RAS in the viral population, compared to the more sensitive NGS method with a cut-off of 1% [13, 167]. However, in order to be of clinical relevance in predicting treatment failure, the general consensus is to recommend a cut-off level of 15% for detecting RASs in all clinical trials, real-life studies and in clinical practice [13, 167, 177]. The viral load must be > 1000-2000 IU/mL in order to increase the likelihood of a successful test [167].

5.1.8 Liver fibrosis staging

Liver fibrosis was assessed by LSM in Paper I, by liver biopsy in Paper II, and by LSM or liver biopsy in Papers III and IV. The cut-off value for significant liver fibrosis and cirrhosis was defined as LSM values >7 kPa and ≥12.5 kPa, respectively, equivalent to METAVIR fibrosis stage F2 and F4, respectively.

Liver biopsy and histologic staging of liver fibrosis using the Ishak and METAVIR semi-quantitative scoring systems has been the traditional gold standard for assessing liver fibrosis. However, liver biopsy has several limitations, including sampling error and significant intra- and interobserver variability that may cause over- or understaging of fibrosis [90, 92, 93].

Non-invasive LSM has replaced liver biopsy as the recommended method for assessing the severity of the liver disease in HCV infection [95]. LSM correlates with METAVIR fibrosis stages, however, there is a substantial overlap of LSM output between adjacent fibrosis stages, particularly in the lower range [97]. LSM overestimate fibrosis in cases with acute liver inflammation (as reflected with ALT >3x upper limit of normal value) and postprandially [195, 196]. LSM can be difficult to perform in obese patients, and limited operator experience can give unreliable results [195]. In the studies referred to in this thesis, LSM was performed by experienced nurses and doctors. Furthermore, the positive predictive value for cirrhosis with a cut-off value of ≥12.5 kPa is 77%, compared to 90% when a cut-off value of 18.3kPa is used [197]. Thus, the risk of a false positive diagnosis of liver cirrhosis can not be ruled out, especially in patients with LSM values between 12.5-18.3 kPa. However,

the diagnosis of liver cirrhosis was not merely based on the LSM, but also on a clinical evaluation including serum markers of fibrosis and ultrasound.

5.2 Summarized study strengths and limitations

The main strengths of the study in Paper I is its population based approach and the high participation rate, providing a large sample in the general population. The main limitation is the age-restriction of 40 years and a possible self-selection, which likely led to an underestimation of the true HCV prevalence.

The main strengths of the study in Paper II are the use of locally acquired data regarding the HCV-infected subjects in the region and the use of local data in the simulated fibrosis progression. However, as with all modelling studies, our findings are only as valid as the quality of the data used and the assumptions made.

The main strength of the studies in Paper III and IV is the real-life design, which enhances the probability that the study populations reflect the real patient population encountered in clinical practice. The non-randomized design and the small sample sizes are important limitations. The failure of detecting statistically significant associations between baseline RASs and treatment outcome may be attributable to a lack of statistical power.

5.3 Discussion of main results

Detailed discussion of the main results can be found in the respective Papers I-IV. The following sections are focused on aspects which are relevant in view of the WHOs global strategy on eliminating HCV as a public health threat by 2030, i.e. a 90% reduction in new HCV infections and a 65% reduction in HCV liver-related mortality. This requires the diagnosis of 90% and treatment of 80% of chronically infected patients. The Norwegian Ministry of Health and Care has recently launched a national strategy on viral hepatitis, which defines challenges and aims in order to eliminate HCV in Norway [11]. In this context, local estimates on HCV epidemiology, disease dynamics, and barriers to screening and treatment are relevant.

5.3.1 Prevalence of HCV infection in the general population

There are uncertainties regarding the prevalence of HCV infection in Norway as population-based data is limited. We found a prevalence of anti-HCV and chronic (viraemic) HCV infection of 0.6% and 0.2%, respectively. The highest prevalence of anti-HCV (1.2%) and

chronic HCV infection (0.4%) was found in people born between 1956 and 1965, which may be explained by the epidemic of IDU in Norway, with a gradual increase in the number of PWID from the beginning of the 1970s until a peak was reached in 2000 [43]. We found that being exposed to HCV was associated with an unfavorable psychosocial profile, which is generally well established [32, 198]. The last population-based study in Norway was in 2001 and revealed a prevalence of chronic HCV infection of 0.5%, an estimate which also included treatment-recovered cases [32]. In our study, the prevalence of current and treatment-recovered HCV infection was 0.4%. In a register study from Northern Norway in 2002, the prevalence of RIBA positive HCV infection was 0.24% [33], and a study of pregnant women in Norway in 2000, showed an anti-HCV prevalence of 0.7% [34]. The last two studies did not report the viraemic prevalence. A modelling study in 2013 estimated the viraemic prevalence in Norway to be 0.43% [4]. The discrepancy of this estimate compared to our findings can be explained by different study designs, where the modelling study was based on historical data and expert opinions rather than measured values. Register studies in Sweden and Denmark have shown prevalence of chronic HCV infection of 0.36% and 0.38%, respectively [199, 200].

To summarize, the population-based study in a general population (Paper I) confirms the assumed low prevalence of HCV infection. Due to probable biases discussed in Section 5.1.3 above, the true prevalence is likely higher.

5.3.2 Undiagnosed HCV infection in the general population

In Paper I, we reported that 39.4% (13/33) of individuals with viraemic HCV infection were previous undiagnosed. In a modelling study from 2013 including several countries and based on historical data and expert opinion, the diagnosis rate in Norway was estimated to be 57% [4]. A recent modelling study including 28 EU countries estimated that only 36.4% of those with viraemic HCV infection were diagnosed in 2015 [44]. A population-based study in a small health area in Spain revealed a prevalence of viraemic HCV infection of 0.5%, of whom 38.5% were previously undiagnosed with HCV [201]. In a French cross-sectional study, 40% of HCV RNA positive individuals were not aware of their infectious status [45]. A large population-based study in the US (NHANES) indicated that fewer than half of those infected with HCV were aware of their infection [7]. An observational cohort study among adults with access to care in the US estimated that one-half of chronic HCV infections had been identified [8].

Based on LSM values, more than half of those with undiagnosed HCV infection in our study had developed significant liver fibrosis (LSM value >7 kPa), and two patients had advanced liver fibrosis or cirrhosis (LSM value >12.5 kPa). In an observational study, 17% of HCV infected patients had advanced liver disease at the time of diagnosis [202]. In a Danish study, 32% of patients had advanced liver fibrosis (LSM >9.5 kPa) at first evaluation in specialized care [203]. Another finding in our study was that a majority (69%) of those with undiagnosed infection reported previous or current IDU, thus should theoretically have been captured by a risk-based screening strategy.

Summarized, a high proportion of HCV infected individuals are unaware of their disease, which suggests that the current recommendation of screening of individuals with high risk of infection is an inadequate approach to identify all chronically infected persons. Undiagnosed HCV infection is an important barrier in the control of the HCV epidemic.

5.3.3 Screening in the general population

We estimated a prevalence of chronic HCV infection of 0.2% in a general population (Paper 1), yet due to the described biases, the true prevalence is likely higher, reducing the efficiency of such an approach. To be effective, people with the highest risk of infection must also attend the screening. With the availability of effective HCV-treatment, whom and how to screen has become a prioritized health policy issue.

In low-prevalence countries, routine screening of the entire population has not been considered cost-effective, however, recent studies indicate that universal screening of the general population may be an effective strategy. In a Spanish cross-sectional pilot study for an eventual population-based screening strategy, the participation rate was 46.2% (2637/5706) and the prevalence of viraemic HCV infection was 0.5% [201]. The study revealed that 5 of 13 viraemic individuals were unaware of their diagnosis, leading the authors to conclude that screening in the general population are “good means” to allow diagnosis and treatment of individuals who are unaware of their status. However, the same study points out that the high costs of a universal screening strategy makes it less feasible, [201], which is in correspondence with the cost estimations in Paper I. In France (HCV RNA prevalence 0.3%), a modelling study indicated that universal screening of all individuals aged 18-80 years was the most effective screening strategy [50]. A modelling approach in Spain (HCV RNA prevalence 0.35-0.41%) concluded that screening of the general adult population would identify a larger number of additional individuals with chronic HCV infection compared to

screening of high-risk groups or screening the age-cohort with the highest anti-HCV prevalence plus high-risk groups [51].

In population surveys, the attenders tend to be more educated and have a healthier life style than non-attenders [189]. Further, psychiatric disorders and alcohol use are significant predictors of nonattendance in health surveys [190], and non-response bias is a problem in alcohol and drug population surveys [204]. Thus, it is reasonable to assume that current and former PWIDs are less likely to participate in health surveys. Based on this, strategies to improve targeted screening of people in high-risk groups in various settings, like primary care, outpatient clinics, OST programs, jails, and psychiatric clinics may still be the most effective approach in low-prevalence regions [205-210].

5.3.4 Fibrosis progression

The critical aspect in HCV pathophysiology is the progressive development of hepatic fibrosis. In Paper II, the fibrosis progression model predicted a relatively slow development in the first 20-25 years of infection, followed by an accelerated fibrosis progression, especially in patients with GT 3. Most studies show that fibrosis generally is progressing slowly, leading to the development of cirrhosis in approximately 10-20% of patients 20-35 years after infection, however, the progression varies widely and may be affected by several external, viral and host factors [1, 61, 64, 68]. The non-linear fibrosis progression and the association between viral GT 3 and accelerated fibrosis progression are in line with other reports [65, 66, 71, 72].

The cohort, which was the basis for the simulated fibrosis progression, was relatively young with a mean age at liver biopsy of 40 years and median duration of infection of 13 years, resulting in few observations with long duration of infection and a limited number of observations with advanced liver fibrosis or cirrhosis (Ishak grade 4-6). This bias may have caused less precise estimates regarding progression through high fibrosis stages. In addition to duration of infection, age at infection may affect the fibrosis progression. Acquisition of HCV infection after the age of 50 years is associated with a more rapid progression of liver fibrosis [66, 70]. However, omitting this covariate from the model should not have a major impact on the estimated fibrosis progression as the cohort was relatively young.

Another limitation is the questionable accuracy in the duration of infection. Due to the asymptomatic course of acute HCV infection, the exact time of infection is often uncertain and estimates must rely on patient history. We used the first year of high-risk behavior as the

presumed year of transmission, e.g. the year of onset of IDU, like others have done [66, 211]. HCV infection is rapidly acquired after onset of IDU, however, it has been reported that time to HCV infection in developed countries has lengthened in recent years [212]. This may indicate that the duration of infection could be shorter than estimated in the model, resulting in a spurious slow fibrosis progression rate. If so, our estimates of fibrosis progression are relatively conservative.

Finally, several host and environmental factors which may affect the fibrosis progression were not included in the fibrosis model due to incomplete data. Moderate and excessive alcohol use, high body mass index, diabetes mellitus, and co-infection with HBV or HIV are important risk factor for accelerated fibrosis progression [68, 213-215]. The prevalence of co-infection with HBV or HIV were low in our HCV cohort, however, lack of data regarding the remaining cofactors may have reduced the accuracy of the simulated fibrosis progression.

5.3.5 Future complications of chronic hepatitis C

In Paper II, a Markov model was used to predict HCV-related morbidity and mortality until 2050, given various scenarios of HCV treatment coverage. Assuming a treatment coverage of 15%, an almost threefold increase in the prevalence of cirrhosis (68 per 100,000 inhabitants), of decompensated cirrhosis (21 per 100,000), and of HCC (4 per 100,000) by 2050 were estimated. Complications were expected to reach a peak around 2040. Further, we estimated a six-fold increase in the cumulated number of deaths due to HCV-related disease (170 per 100,000). By scaling up treatment coverage to 50%, the estimated numbers could be reduced by approximately 50% for cirrhosis, and by approximately one third for the other endpoints.

These projections from a low-prevalence area indicate a substantial rise in HCV-related morbidity and mortality in the coming years, in line with other reports. A modelling approach, including Norway and several other countries, estimated that the total number of viraemic infections in Norway will decline slightly from 22,000 cases in 2018 to 21,300 cases in 2030, based on treatment levels in 2013 [4]. However, complications were projected to rise considerably from 2013 until 2030, with an estimated increase in cases with cirrhosis, decompensated cirrhosis, and HCC of 90%, 20%, and 115%, respectively [4]. Further, liver-related mortality was expected to increase with 80% in the same period. Estimates from The Global Burden of Disease Study have demonstrated a continued upward trend in viral hepatitis (HBV and HCV) burden of disease and attributable mortality [3].

The focus of the study in Paper II was descriptive, showing the impact on disease burden given locally generated data and certain assumptions. The precision of the estimates depends of the quality of the data entered and the assumptions made. The remarkable advances in HCV treatment in recent years will likely change clinical practice in the future, however there are several uncertainties regarding how these new therapies will affect the care and management of HCV infection, which in turn may impact future complications and disease burden. Several aspects which can have an impact on our modelled projections will be discussed in the following.

Incidence

We estimated a constant *incidence* of 90 new HCV infections in Northern Norway per year from 2013 towards 2050 (Paper II). Currently, there is no reliable data on the HCV incidence in the general population in Norway. By using expert consensus, it is proposed an incidence of 14.9 HCV cases per 100 000 persons per year in Norway in 2013 [4]. Extrapolating this estimate to the population in Northern Norway (460,000 inhabitants) would imply 70 new HCV cases annually, which indicate that the incidence used in the Markov model is overestimated. However, IDU is an ongoing problem and accounts for 90% of all HCV infections in Norway [4], indicating a stable HCV incidence in the coming years. The model did not take into consideration the impact of *treatment as prevention*; i.e. scaling up treatment in individuals with high risk of transmitting HCV, like PWID, which can reduce the HCV incidence and have an impact on HCV prevalence and future disease burden [157, 216-218]. The possibility of reinfection after successful treatment and the impact of immigration were not considered in the model. In a Norwegian study among PWID, reinfection was observed in 27% of people who had relapsed to IDU after achieving SVR and in 11% of people with a history of IDU [219]. Harm reduction programmes may have a considerable impact on the incidence, e.g. in the Netherlands, where IDU as a risk factor for HCV infection is almost absent due to effective prevention programmes [4].

Undiagnosed HCV infection

The number of *undiagnosed* HCV infected persons was not included in the Markov model. In the Tromsø 7 Study, almost 40% (13/33) of those with viraemic HCV infection were unaware of their diagnosis (Paper I). This corresponds to a population prevalence of 0.06% (13/20946), which, when extrapolated to the population in Northern Norway, would imply 276 persons

with undiagnosed chronic HCV infection in the region. This may indicate that the projections in Paper II are underestimated.

The proportion of people with undiagnosed infection contrasts the WHO goal of diagnosing 90% of chronically infected. In the new therapeutic scenario with effective DAAs, many countries, including Norway [220], are reconsidering their screening and testing strategies. Implementation of effective screening strategies may contribute to reverse the increasing burden of HCV disease, making the modelling forecasts overestimated.

Treatment uptake

The estimated future complications can be reduced if *treatment uptake* is increased. Our estimates were based on a treatment coverage of 15%. By scaling up treatment coverage to 50% the estimated numbers of future complications could be reduced by approximately 50% for cirrhosis, and by approximately one third for the other endpoints.

In order to reach the WHOs aim on eliminating HCV as public health threat by 2013, 80% of chronically infected persons need to be treated [10]. By modelling, it has been estimated that the annual treatment rate in Norway was 2.8% in 2013 [4]. Estimates from Norway indicated that 14% of HCV-infected patients in OST had received HCV treatment between 2004-2013, with annual treatment rates varying between 1.3% and 2.6% [155].

Strategies to manage the burden of HCV disease were evaluated in a modelling study of several countries including Norway [221]. The analysis showed that a combined aggressive treatment and diagnosis strategy, requiring a 3- to-5-fold increase in diagnosis and/or treatment, were critical for achieving substantial reductions in future disease burden [221]. A significant barrier to increased treatment uptake has been the initially extremely high costs of DAAs. However, due to tender negotiations, unrestricted treatment has been available in Norway since February 2018 [161]. The annual number of treated individuals in Norway has increased in recent years, from 610 treatments in 2013 [4] to an average of approximately 1000 annual treatments since the introduction of DAAs in 2014 [11]. A continued substantial increase in treatment-uptake is likely to improve the projections presented in Paper II.

Altogether, the uncertainties regarding the future HCV incidence, treatment uptake, and the effect of more extensive prevention and screening strategies can have impact on the projections in Paper II. A recent modelling study including data from 190 countries evaluated what is required to achieve the WHO targets for 2030, and concluded that “a comprehensive

package of prevention, screening, and treatment interventions" has to be implemented [222]. The authors emphasize that the potentials of DAAs to reverse the burden of HCV disease only can be fulfilled with a considerably increase in the diagnosis rate. HCV testing must be implemented in a variety of settings and new technology such as PoC HCV RNA testing should be implemented. Further, the study emphasizes that strategies to control the HCV epidemic among PWID are of crucial importance to reach the incidence target of 90% reduction in new HCV infections.

5.3.6 Clinical relevance of RASs

The studies presented in Papers III and IV were performed when data on optimal treatment regimens were emerging and treatment guidelines were rapidly changing. At the initiation of the studies, there were no available guidelines regarding baseline resistance testing and the knowledge of the impact of baseline RASs in treatment with DAAs was very limited. The costs of DAAs were very high, rendering it important to find the most cost-efficient treatment approach.

In Paper III, baseline NS3 RASs Q80K and R155K and clinically relevant NS5A RASs appeared to have an impact on treatment outcome in patients with HCV GT 1a, although statistically significant results could not be obtained. The SVR12 rates in the intervention and control groups were 97.8% and 93.1%, respectively. In patients with cirrhosis, the difference in SVR12 rates were more pronounced, with SVR12 rates 97.5% and 83.3% in the intervention and control groups, respectively. Our findings appear to agree with prior studies. The COSMOS study in 2014 indicated lower SVR12 rates in patients with GT 1a and baseline Q80K RAS compared to patients without this RAS at baseline [123]. The OPTIMIST-1 study in 2016 showed that the presence of baseline Q80K RAS adversely affected SVR12 rates in patients treated with 8 weeks of SIM + SOF, but not in patients treated for 12 weeks [130]. In the OPTIMIST-2 study, the SVR12 rates in cirrhotic patients with baseline Q80K was 74%, compared to 92% in cirrhotic patients without baseline Q80K [131].

In Paper IV, the SVR12 rates in patients with GT 3 infection who received treatment tailored to the result of baseline resistance analysis was 95.4%, compared to 88.5% in the control group. All five patients with baseline Y93H in the intervention group achieved SVR with personalized treatment, compared to 2/4 patients with baseline Y93H in the control group. Although we could not obtain statistically significant results, our findings are in line with

previous randomised controlled trials (ALLY-3 and ASTRAL-3) and the EASL-guidelines of 2016 [128, 138, 177].

Since the introduction of DAAs, the treatment has improved steadily with SVR rates >95% in the majority of patients groups [9]. Pan-genotypic DAA combinations with high genetic barriers to resistance are available [133-135, 138, 142]. The study in Paper IV was conducted prior to the recent approved DAA combinations GLE/PIB and SOF/VEL/VOX. These regimens have greatly improved the SVR rates, even for patients with GT 3 infection, cirrhosis, previous treatment failure, and baseline NS5A RASs [133, 141, 144, 223]. In clinical practice, the impact of RASs will probably become less important with the availability of these effective DAA combinations. However, it could be noted that RAS Q80K was the most commonly observed baseline NS3 RAS in the few GT 1a patients experiencing treatment failure in a trial evaluating the efficacy of SOF/VEL/VOX (POLARIS-2 trial) [133]. Further, a pooled resistance analysis in patients treated with GLE/PIB suggested a negative effect of baseline Y93H and A30K in patients with GT 3 infection. In treatment-experienced, non-cirrhotic patients who received 12 weeks of GLE/PIB, lower SVR rates of 25% (1/4) and 50% (2/4) were observed for patients with baseline A30K and Y93H, respectively, compared to 96% (43/45) and 93% (42/45), respectively, in patients without these RASs [175]. The small number of patients limits the generalizability of these results, but they suggests that viral resistance may have a negative impact also in recently approved DAA therapies with high antiviral potency and high genetic barrier to resistance.
The proportion of patients who fail to achieve SVR after treatment with DAAs is small. However, given the size of the infected population, the absolute number of treatment failures is substantial and will probably increase as more patients receive treatment [224]. Effective and well-tolerated DAAs have improved the feasibility of HCV treatment among patients with ongoing IDU, psychiatric comorbidities, and alcohol abuse. However, reduced compliance to treatment may be likely in some of these patients, rendering non-adherence to treatment as the most important risk factor for non-SVR. In patients who fail DAA treatment, RASs are selected in more than 80% of patients and long-term persistence of NS5A RASs (>2 years) is likely [12, 167]. Onward transmission of resistant HCV variants [225] and new emerging mutations in the highly variable HCV genome may affect the current high SVR rates.

In the current “changeable and dynamic” treatment landscape, our understanding of resistance testing as a diagnostic tool is far from settled [122, 167]. The recently approved effective, pan-genotypic DAAs with high genetic barrier to resistance are more expensive than prior approved regimens and are currently not extensively available. Retreatment options are still limited for some patient groups, and resistance testing is an important tool for tailoring personalized treatment [122]. Also, in order to reach the WHO elimination goals, surveillance of HCV resistance must be addressed [163, 224].

6. CONCLUSIONS

- The prevalence of chronic HCV infection in Northern Norway is low. Still, a substantial number of persons with viraemic disease are not aware of their infection, suggesting that the current strategy of screening individuals with high risk of infection is an inadequate approach to identify all patients with chronic HCV infection. Screening of the general population may unmask asymptomatic infected individuals that do not define themselves as belonging to known risk groups, and may be a sensible approach in addition to screening of high risk groups.
- Despite a low prevalence of HCV infection, projections indicate a substantial rise in HCV-related morbidity (cirrhosis, decompensated cirrhosis and hepatocellular carcinoma) and mortality in the coming years.
- Baseline RASs appear to have a negative impact on treatment outcome in patients with HCV infection GTs 1a and 3. Some RASs do to some extent predict lower SVR rates, but the results are limited due to small sample sizes and a low prevalence of RASs. Personalized treatment tailored to baseline resistance analysis may be of importance to guide the selection of cost-effective treatment combinations and treatment durations, both in a perspective of evidence-based healthcare delivery and to avoid treatment failure in the individual patient.

7. FINAL REMARKS AND FUTURE PERSPECTIVES

Despite a low prevalence of HCV infection, the morbidity and mortality attributable to chronic HCV infection are projected to increase and clearly represent a challenge to the health care system. The availability of effective DAA therapies has provided an opportunity to reverse the rising burden of HCV disease, however, prevention of late complications requires early diagnosis and treatment. Effective screening strategies are urgently needed in order to achieve the WHO targets for elimination of HCV infection as a public health threat by 2030. Screening for HCV infection should identify asymptomatic, infected persons also outside of known risk groups. Screening in the general population in low prevalence areas may be a sensible approach in addition to strategies to improve targeted screening of people in high-risk groups. Implementation of PoC HCV RNA testing might contribute to simplify HCV testing, and thus enable decentralization of HCV care and treatment. Improvements in the entire HCV cascade of care from infection to cure are required in order to reach the WHOs elimination goals.

The availability of highly effective and well-tolerated DAAs play a major role in the elimination effort. DAAs will improve the feasibility of HCV treatment in a wide range of patient groups, including marginalized populations of PWIDs, persons with psychiatric comorbidities and alcohol abuse. This changing patient population presents some challenges, e.g. non-adherence to treatment as a risk factor for treatment failure. Although DAAs provide high SVR rates, selection of RASs in persons who fail treatment is almost certain. Given the approximately 5% failure rates of the currently approved DAA regimens, a significant number of patients in the global HCV-infected population will have resistant variants of HCV. Prevention of onward transmission of resistant HCV variants and effective rescue treatment strategies for patients who fail first line therapies are needed. The long-term effects of HCV resistance remain unclear, hence surveillance of RASs is necessary to provide data in order to handle the resistance issue adequately.

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Paper I

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Screening for hepatitis C in a general adult population in a low-prevalence area: the Tromsø study

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Abstract

Background: Chronic hepatitis C virus (HCV) infection can progress to cirrhosis and end-stage liver disease in a substantial proportion of patients. The infection is frequently asymptomatic, leaving many infected individuals unaware of the diagnosis until complications occur. This advocates the screening of healthy individuals. The aim of this study was to estimate the prevalence of HCV infection in the general adult population of the municipality of Tromsø, Norway, and to evaluate the efficiency of such an approach in a presumed low-prevalence area.

Methods: The study was part of the seventh survey of the Tromsø Study (Tromsø 7) in 2015–2016. Sera from 20,946 individuals aged 40 years and older were analysed for antibodies to HCV (anti-HCV). A positive anti-HCV test was followed up with a new blood test for HCV RNA, and the result of any previous laboratory HCV data were recorded. Samples positive for anti-HCV and negative for HCV RNA were tested with a recombinant immunoblot assay. All HCV RNA positive individuals were offered clinical evaluation.

Results: Among 20,946 participants, HCV RNA was detected in 33 (0.2%; 95% CI: 0.1–0.3), of whom 13 (39.4%; 95% CI: 22.7–56.1) were unaware of their infection. The anti-HCV test was confirmed positive in 134 individuals (0.6%; 95% CI: 0.5–0.7) with the highest prevalence in the age group 50–59 years. Current or treatment-recovered chronic HCV-infection was found in 85 individuals (0.4%; 95% CI: 0.3–0.5) and was associated with an unfavorable psychosocial profile.

Conclusion: In this population-based study, the prevalence of viraemic HCV infection was 0.2%. A substantial proportion (39%) of persons with viraemic disease was not aware of their infectious status, which suggests that the current screening strategy of individuals with high risk of infection may be an inadequate approach to identify chronic HCV infection hidden in the general population.

Keywords: Epidemiology, Hepatitis C, Norway, Population surveys, Prevalence

Background

Chronic infection with hepatitis C virus (HCV) is a leading cause of liver cirrhosis, resulting in increased risk of liver failure, hepatocellular carcinoma (HCC) and premature death [1]. Globally, an estimated 71 million people are living with viraemic HCV infection (HCV RNA positive) [2]. Norway is a low-prevalence country in this respect, as are most other Western European countries. There are uncertainties regarding the prevalence of HCV infection in Norway, as population-based data is limited. A cross-sectional study based on the Oslo Health Study in 2001 included 11,456 individuals and reported a prevalence of anti-HCV and HCV RNA of 0.7 and 0.5%, respectively [3]. In Sweden and Denmark, the estimated prevalence of chronic HCV infection is 0.36 and 0.38%, respectively [4, 5].

The incidence of HCV infection is projected to decline, but the burden of the disease is increasing [6]. According to a recent modelling approach from Norway, the HCV incidence among people who inject drugs (PWID) peaked in 2000, and has thereafter decreased. However, the occurrence of HCV-related cirrhosis and HCC in active and

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former PWID is expected to increase in the coming years [7]. Prevention of late complications requires treatment in the early stages of the disease, and the availability of potent direct-acting antiviral therapies (DAAs) has provided an opportunity to reverse the rising burden of HCV-related complications [8].

Surveillance of HCV is challenging for several reasons. Individuals infected with HCV are often asymptomatic until a late stage, and it is presumed that up to half of infected individuals are unaware of their status [5, 9, 10]. A recent modelling study including 28 EU countries, estimated that only 36% of those with viraemic HCV infection have been diagnosed [11].

HCV infection in Norway has by law been a notifiable disease to The Norwegian Surveillance System for Communicable Diseases (MSIS) since 1990. The surveillance system did not distinguish between resolved and chronic HCV infection prior to 2016, when it started to include only HCV RNA positive cases [12]. Yet it still does not adequately discriminate chronic HCV infection from acute infection with subsequent spontaneous clearance. Another limitation of the MSIS registration is the low notification rate. In a study of HCV treatment uptake among people who had received opioid substitution therapy (OST), only 57% of OST patients treated for HCV infection were notified to MSIS [13]. Notifications of HCV infection may reflect testing practices rather than real occurrence of the disease, thus rendering official surveillance in Norway incomplete.

In 2016, the World Health Organization (WHO) released its first global strategy on viral hepatitis aiming to eliminate HCV as a public health threat by 2030, including an 80% reduction in new HCV infections and a 65% reduction in HCV liver-related mortality, requiring diagnosis of 90% and treatment of 80% of chronically infected patients [14]. Several measures are necessary to achieve these goals. Ideally, screening for HCV infection should identify asymptomatic, infected persons before they develop cirrhosis and cirrhosis-related complications. The subsequent early treatment would improve clinical outcomes, reduce transmission risk and thus save health costs.

Screening strategies vary in different areas, based on the local epidemiology of HCV infection. In low-prevalence countries, routine screening of the entire population has not been considered cost-effective [15–18] and the approach to prevention and control of HCV infection has focused on testing persons with risk factors. Recent studies have, however, indicated that screening of the general population may be cost-effective compared to risk-based screening [19, 20]. In Norway, a limited screening of high-risk individuals is recommended, such as current or previous PWID, recipients of blood products prior to 1992, patients infected with human immunodeficiency virus (HIV), haemodialysis patients, incarcerated individuals, children born to HCV-infected mothers, individuals with elevated alanine aminotransferase (ALT), and refugees from endemic regions [21].

In the new treatment landscape with highly effective and well tolerated DAAs, many countries are reconsidering their testing strategies. Whom and how to screen has become a prioritized health policy issue.

The Norwegian Ministry of Health and Care recently launched a national strategy on viral hepatitis with aim of 90% reduction in new HCV infections by 2023 compared to 2018 [22]. Prevalence studies in the general population may be an important tool for assessing the number of infected with HCV and thus to enable an estimate of the future disease burden. The Tromsø Study is an established population survey in the municipality of Tromsø in Northern Norway, making such a prevalence study feasible.

The primary aim of the present study was to estimate the prevalence of diagnosed and undiagnosed HCV infection in the general adult population of Tromsø, Northern Norway, and second, to evaluate the efficiency of a screening approach to find individuals with undiagnosed hepatitis C infection.

Methods

Study population

The study was part of the seventh survey of the Tromsø Study (Tromsø 7) in 2015–2016. The Tromsø Study is a longitudinal population-based, prospective study with repeated health surveys since 1974 in the municipality of Tromsø in Northern Norway [23]. Tromsø is the largest city in Northern Norway, harbouring the world's northernmost university, thus having a high proportion of young people. The present population (per 2nd quarter of 2018) is 76,062 inhabitants, predominantly of Norwegian origin (14% immigrants) [24].

Tromsø 7 included more than 50 research projects, covering various health issues, symptoms and chronic diseases. HCV detection was included for the first time. Based on the official population registry, residents of the municipality of Tromsø aged 40 years and older were invited to participate. A personal invitation was sent about 2 weeks before a suggested time of appointment at one permanent study site. The subjects were free to attend whenever suitable within the opening hours of the study site and within the one year duration of the study. The invitation leaflet included all necessary information, and a questionnaire was enclosed, as well as username and password for an optional online response. Non-attenders were given one reminder. Information about the survey and invitation to participate were repeatedly provided in the local newspapers.

All 32,591 citizens aged 40 years and above were invited, and 21,083 (65%) attended. Sera from 20,946 participants (64.3% of invited citizens) were tested for anti-HCV, of whom 11,004 (52.5%) were women and 9942 (47.5%) were men. The participation rate was highest in the age group 60

to 69 years for both women and men, somewhat lower in younger age groups, and lowest among those older than 80 years (Table 1).

Questionnaire

The participants responded to a self-administered questionnaire with questions about health, psychological problems triggering contact to professional health care, anxiety or depression, smoking habits, alcohol consumption, the use of drugs other than alcohol, level of education, marital status and main occupation/activity. There were two questions regarding hepatitis C (translated from Norwegian): "Have you been infected with the liver virus hepatitis C?", and "If you have been infected with the liver virus hepatitis C: have you ever received treatment?"

Data collection and laboratory methods

Sera from 20,946 participants were stored frozen at − 20 °C and tested for anti-HCV (ARCHITECT Anti-HCV Assay, Abbott System, Wiesbaden, Germany) at the Department of Microbiology and Infection Control, University Hospital of North Norway, Tromsø, Norway. Individuals with a positive anti-HCV test received an information letter with their test results, describing the requirement for a second blood test to discriminate between current infection and previous exposure to HCV. The second blood test was performed at the University Hospital in Tromsø, where the result was followed up by the responsible medical doctor at the Department of Gastroenterology, and compared to any existing HCV test results. Two reminders were sent to those who did not have the follow-up test. The follow-up samples were retested for anti-HCV and further tested for the presence of HCV RNA (ROCHE RT-PCR Cobas Amplicor Hepatitis C Viral Polymerase Chain Reaction, Roche Molecular System Inc., Branchburg NJ, USA). Samples positive for the anti-HCV test and negative to the HCV RNA test were analyzed with a recombinant immunoblot assay (RIBA HCV 3.0 SIA test, Chiron Cooperation, Emeryville, CA, USA) as a secondary confirmation test of the first line anti-HCV test to rule out unspecific positive tests. Samples were considered anti-HCV positive with reactivity to two or more antigens in the RIBA test, indeterminate when reactivity to only one antigen was present, which may represent previous resolved HCV-infection or unspecific antibody reactions [25], and negative when no antigen-specific reactivity was observed. The RIBA test was not carried out in cases were existing laboratory results were consistent with either spontaneous clearance (previous positive RIBA test or positive HCV RNA test followed by at least two consecutive negative HCV RNA tests with at least three months interval) or obtained sustained virologic response (SVR) after antiviral treatment. HCV genotyping was performed as a hybridization assay on products from the HCV RNA PCR according to the manufacturer's instructions (INNO-LIPA HCV II kit, INNOGENETICS, Ghent, Belgium).

Definitions

The term HCV exposure is used in Tables 2 and 3 to include individuals with the following characteristics: (1) persons with chronic (viraemic) HCV infection; i.e. with positive HCV RNA: (2) persons with treatment-recovered HCV infection: (3) persons with spontaneously resolved HCV infection; i.e. with positive RIBA test or positive HCV RNA test followed by at least two consecutive negative HCV RNA tests with at least three months interval: (4) persons with positive anti-HCV test, negative HCV RNA and indeterminate RIBA test.

Estimated prevalence numbers of HCV exposure and chronic HCV infection

Estimated prevalence numbers of HCV exposure and chronic (viraemic) HCV infection in the Tromsø population were calculated based on the observed prevalence in each age group and corrected for different attendance rates between the groups. An equal prevalence between attenders and non-attenders was presumed for the calculation of expected numbers of infected individuals.

Clinical follow-up

All subjects with a positive HCV RNA test were offered a clinical evaluation, which included a thorough medical

Table 1 HCV testing in the Tromsø 7 Study ($n = 20,946$)

	Women		Men		Total	
Age (years)	Invited	Tested (%)	Invited	Tested (%)	Invited	Tested (%)
40–49	5195	3360 (64.7%)	5562	3033 (54.5%)	10,757	6393 (59.4%)
50–59	4534	3230 (71.2%)	4327	2767 (63.9%)	8861	5997 (67.7%)
60–69	3586	2652 (74.0%)	3543	2487 (70.2%)	7129	5139 (72.1%)
70–79	2001	1352 (67.6%)	1897	1310 (69.1%)	3898	2662 (68.3%)
80–89	981	386 (39.3%)	639	322 (50.4%)	1620	708 (43.7%)
90–104	242	24 (9.9%)	84	23 (27.4%)	326	47 (14.4%)
Total	16,539	11,004 (66.5%)	16,052	9942 (61.9%)	32,591	20,946 (64.3%)

Actual numbers for invitation to the Tromsø 7 Study, and rates (n (%)) of testing for anti-HCV according to sex and 10-year age groups

Table 2 Observed and estimated prevalence of HCV exposure and chronic HCV infection

Age (years)	Invited	Tested	Observed HCV exposure (n)	Prevalence of HCV exposure (% (95% CI))	Estimated HCV exposure* (n)	Observed chronic (viraemic) HCV infection (n)	Prevalence of chronic (viraemic) HCV infection (% (95% CI))	Estimated chronic (viraemic) HCV infection[a] (n)
40–49	10,757	6393	32	0.5% (0.4–0.7)	54	5	0.08% (0.0–0.2)	8
50–59	8861	5997	69	1.2% (0.9–1.5)	102	24	0.4% (0.2–0.6)	35
60–69	7129	5139	28	0.5% (0.4–0.8)	39	4	0.08% (0.0–0.2)	6
70–79	3898	2662	3	0.1% (0.0–0.3)	4	0	0% (0.0–0.1)	0
80–89	1620	708	2	0.3% (0.1–1.0)	5	0	0% (0.0–0.5)	0
90–104	326	47	0	0% (0.0–7.6)	0	0	0% (0.0–7.6)	0
Total	32,591	20,946	134	0.6% (0.5–0.7)	209	33	0.2% (0.1–0.3)	51

Observed prevalence of HCV exposure and chronic HCV infection in the Tromsø 7 Study according to 10-year age groups. Total prevalence is corrected for different attendance rate in the different age-groups

[a]Estimated numbers of individuals in the Tromsø population is based on an equal prevalence between attenders and non-attenders. All numbers are n or proportions (%) with 95% confidence intervals (95% CI)

examination, the recording of the medical history and the assessment of risk factors for HCV infection. An estimate of the time-point of transmission was made based on information on the first year of high-risk behaviour, such as injecting drug use (IDU), tattoos or transfusion of blood products prior to 1992 [26]. At this stage, an additional blood sample was analysed for platelet count, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) in order to calculate the Fibrosis-4 (FIB-4) index [27]. The blood sample was also analysed for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) and antigens/antibodies to human immunodeficiency virus (HIV Ag/Ab combo). Liver stiffness (kPa) was measured with transient elastography (FibroScan® 402, Echosens, Paris, France). Significant fibrosis and cirrhosis was defined as liver stiffness values ≥7 kPa and ≥ 12,5 kPa, respectively, equivalent to METAVIR fibrosis stage ≥F2 and F4, respectively [28]. Ultrasound was performed at the responsible medical doctor's discretion. Treatment was offered to all HCV RNA positive patients who met for clinical follow-up.

Statistical analysis

Data summaries were performed using SPSS 24.0 software and Microsoft Excel 2013. The Chi-Square test and Mann-Whitney U test, as well as multivariate logistic regression analysis, were used to compare sociodemographic and behavioral characteristics between HCV exposed and anti-HCV negative. The Fisher's exact test was used to test the differences between groups in case of small sample numbers. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Prevalence of hepatitis C

Figure 1 shows a flowchart of the study with associated results. The anti-HCV screening test was positive in 217 (1.0%) of 20,946 individuals. The follow-up test was negative for anti-HCV and/or RIBA in 83 samples. Thus, the prevalence of confirmed anti-HCV was 0.6% (95% CI: 0.5–0.7%) ($n = 134$), with a sex distribution of 71 (53%) men and 63 (47%) women. HCV RNA was detected in 33 (0.2%; 95% CI: 0.1–0.3) of 20,946 participants, 18 male (54.5%). Of these viraemic cases, 13 (39.4%; 95% CI: 22.7–56.1) were not aware of their infection. Two of the 33 persons with current positive HCV RNA reported that they had received antiviral treatment earlier, one of whom had interrupted the treatment before scheduled treatment-end and was considered to be a treatment failure. The second person did not meet for clinical follow up, rendering it unclear whether the vireaemia represents reinfection or treatment failure. Overall, current or treatment-recovered HCV infection was found in 85 (0.4%; 95% CI: 0.3–0.5) of 20,946 individuals, 48 (56.5%) men and 37 (43.5%) women. Of those, 52 (61.2%) had previously received antiviral treatment with achieved SVR.

Spontaneous clearance of HCV was demonstrated in 33 (24.6, 95% CI: 17.3–31.9) of 134 anti-HCV positive individuals. The RIBA test was indeterminate in 16 of the cases that were anti- HCV positive and HCV RNA negative.

Table 2 shows the observed prevalence of HCV exposure and chronic (viraemic) HCV infection according to sex and 10-year age groups, as well as the estimated over-all prevalence. The highest prevalence of HCV exposure (1.2%) and chronic HCV infection (0.4%) was seen in the age group 50–59 years.

HCV genotype

Data on HCV genotype (GT) was available in 75 of the 85 persons with current or recovered chronic HCV infection. HCV GT 1a was detected in 19 (25.3%) individuals, GT 1b in 10 (13.3%), GT 2b in 10 (13.3%), GT 3a in 33 (44%), GT 4 in one (1.3%) and GT 1 not available for subtyping in 2 (2.7%).

Unawareness of HCV infection

Thirteen of the 33 (39.4%) individuals with viraemic HCV infection were not aware of their infectious status,

Table 3 Characteristics of the subpopulation exposed to HCV in the Tromsø 7 Study

	Tested	HCV exposed $n = 134$	HCV-antibody negative $n = 20,812$	*P* value	OR[c] (95% CI)
Age (yrs), median (range)	20,946	54 (40–84)	56 (40–99)	$p = 0.004$	
Gender (%)	20,946			$p = 0.199$	
Male		71 (53%)	9871 (47%)		N.s.
Female		63 (47%)	10,941 (53%)		
Live with a spouse/partner (%)	19,767			$p < 0.0005$	
No		50 (43.5%)	4530 (23.1%)		N.s.
Yes		65 (56.5%)	15,122 (76.9%)		
Level of education (%)	20,573			$p = 0.001$	
< 12 years		85 (64.4%)	10,394 (50.8%)		N.s.
> 12 years		47 (35.6%)	10,047 (49.2%)		
Disability benefit recipient or unemployed (%). Retired excluded	15,870			$p < 0.0005$	2.5 (1.7–3.7)
Yes		46 (36.8%)	1973 (12.5%)		
No		79 (63.2%)	13,772 (87.5%)		
Self-reported health (%)	20,768			$p < 0.0005$	
Very bad		1 (0.8%)	73 (0.4%)		N.s.
Bad		18 (13.6%)	1065 (5.2%)		
Neither good nor bad		46 (34.8%)	5353 (25.9%)		
Good		61 (46.2%)	11,104 (53.8%)		
Excellent		6 (4.5%)	3041 (14.7%)		
Psychological problems (%)[a]	20,251			$p < 0.0005$	
Current		16 (12.9%)	879 (4.4%)		N.s.
Previous		12 (9.7%)	1801 (8.9%)		
No		96 (77.4%)	17,447 (86.7%)		
Daily smoking (%)	20,753			$p < 0.0005$	
Current		54 (40.3%)	2827 (13.7%)		4.4 (2.2–8.6)
Previous		65 (48.5%)	9129 (44.3%)		2.7 (1.4–5.1)
Never		15 (11.2%)	8663 (42.0%)		
Alcohol consumption (%)	20,816			$p = 0.419$	
4 or more times a week		5 (3.8%)	1235 (6.0%)		N.s.
2–3 times a week		30 (22.6%)	4920 (23.8%)		
2–4 times a month		48 (36.1%)	7795 (37.7%)		
Monthly or less frequently		34 (25.6%)	5067 (24.5%)		
Never		16 (12%)	1666 (8.1%)		
Use of drugs other than alcohol (%)[b]	20,498			$p < 0.0005$	
Yes, now		15 (11.5%)	65 (0.3%)		35.4 (17.4–71.9)
Yes, previously		53 (40.8%)	824 (4.0%)		15.7 (10.2–24.2)
No		62 (47.7%)	19,479 (95.6%)		

All numbers are n (%) or median (range). Chi Square, Fisher's exact or Mann-Whitney U test were used where appropriate
[a]Psychological problems triggering contact to professional health care
[b]E.g. cannabis, amphetamines, cocaine, heroin, hallucinogens, solvents, gamma hydroxybutyrate (GHB)
[c]Results from multivariate logistic regression analysis, adjusted for age and gender, shown as odds ratios (OR) with 95% confidence intervals (CI). N.s.: Not significant

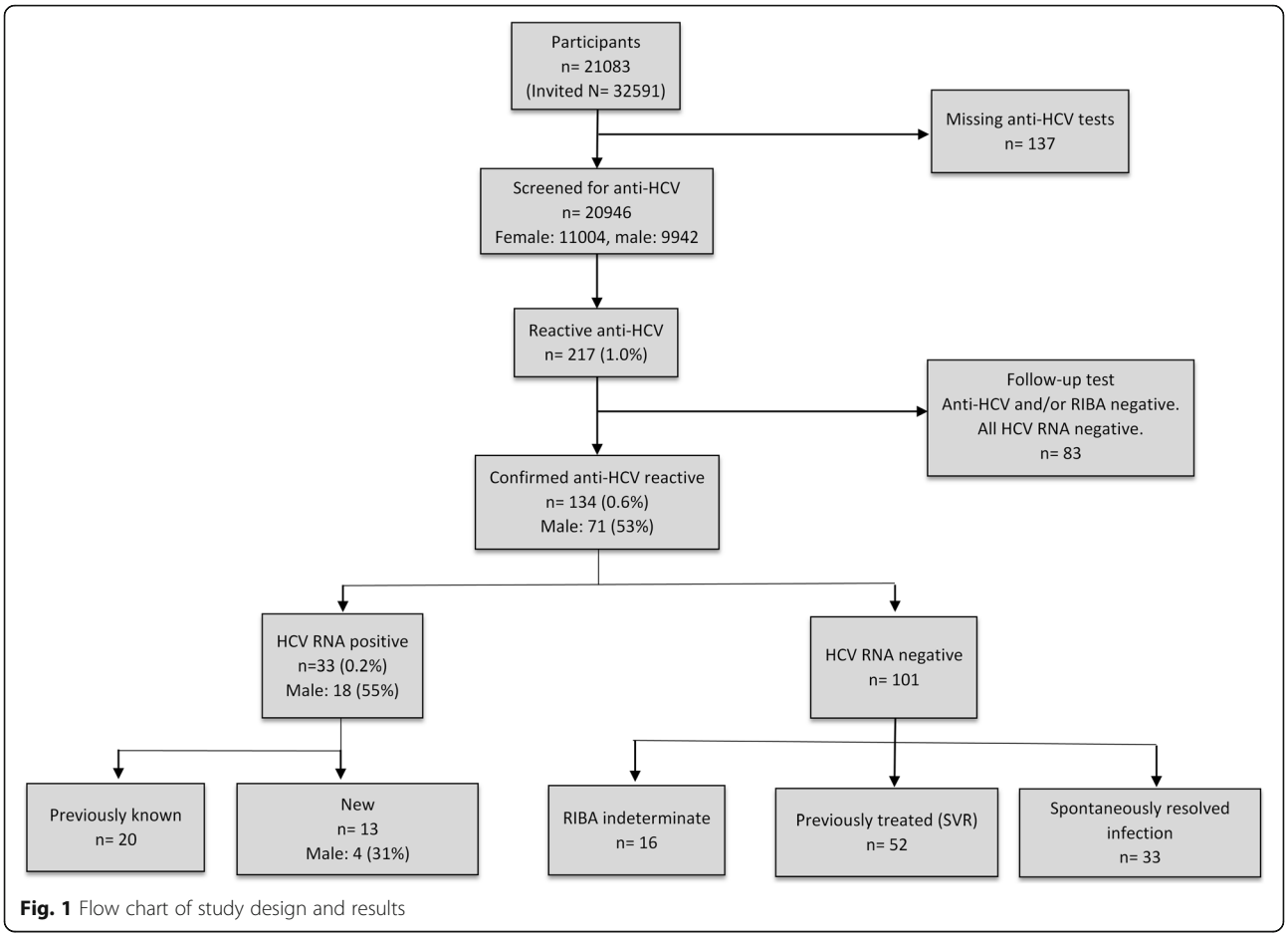

Fig. 1 Flow chart of study design and results

corresponding to a population prevalence of 0.06% (95% CI: 0.03–0.09). Nine of the 13 were women and the median age was 55 years. The distribution of genotypes 1 through 3 was six GT 1a, two GT 2 and five GT 3a. The median ALT value was 48 U/L (range 21–276 U/L), with eight of thirteen persons demonstrating a normal ALT value. The median liver stiffness value was 6.7 kPa (range 4.1–17.6). Liver stiffness values were < 7 kPa in five persons and between 7 and 12 kPa in six persons. Two persons had liver stiffness > 12.5 kPa, one of whom was considered to have established liver cirrhosis based on liver stiffness of 17.6 kPa and signs of cirrhosis on ultrasound. The second person had probable liver cirrhosis based on liver stiffness of 12.6 kPa and a FIB-4 index of 3.86. HBsAg was negative in all, and HBcAb was detected in three of the 13 persons. In the self-administered questionnaire, six of the 13 individuals reported current ($n = 2$) or past ($n = 4$) drug injection. In the follow-up examination, an additional three persons reported past drug injection, thus 69.2% reported a history of IDU. The median estimated time from infection to diagnosis was 30 years (range 10–40 years). Extrapolating the observed proportion of individuals who were unaware of their HCV infection to the whole population of Northern Norway (484,001 inhabitants) implies that 290 persons above 40 years of age in this region could be unaware of ongoing HCV infection.

All 13 persons with previously undiagnosed chronic HCV infection have been successfully treated with achieved SVR 12 or 24 weeks after completed treatment.

Factors associated with HCV exposure

Frequencies of socio-demographic characteristics in the HCV-exposed cohort compared to the background population are shown in Table 3. In univariate analysis, there was a positive association between HCV exposure and self-reported bad health, daily smoking, the use of drugs other than alcohol, lower level of education, living without a spouse/partner, being disabled or unemployed, and having psychological problems triggering contact to professional health care. In a separate question about anxiety or depression, the HCV-exposed cohort scored higher than the background population (data not shown). We found no association between alcohol consumption and HCV infection. In a multivariate logistic regression analysis including significant variables from

the univariate analysis and adjusting for age and gender, significant independent predictors of being exposed to HCV were: Being disabled or unemployed (OR 2.5; 95% CI 1.7–3.7), current daily smoking (OR 4.4; 95% CI 2.2–8.6), previous daily smoking (OR 2.7; 95% CI 1.4–5.1), current use of drugs other than alcohol (OR 35,4; 95% CI 17.4–71.9), and previous use of drugs other than alcohol (OR 15.7; 95% CI 10.2–24.2).

Estimated cost of screening

Table 4 shows the estimated costs for the screening project. The total cost for screening of 20,946 individuals was NOK 1177705 (€ 125,175), and the cost per newly detected chronic HCV infection ($n = 13$) was NOK 90593 (€ 9629).

Discussion

We have carried out a population-based screening for HCV infection in a presumed low-prevalence area. In clinical practice, the identification of individuals with viraemic HCV infection is most important. For surveillance purposes, however, reliable data for both current infection and recovered disease, either spontaneously or through treatment, is of interest. In this survey of individuals aged 40 years and older, the prevalence of chronic (viraemic) HCV infection was 0.2%. In comparison, the last population survey in Norway in 2001, including people aged 30 years and older, revealed a prevalence of chronic HCV infection of 0.5%, an estimate which also included treatment-recovered cases [3]. In our study, the prevalence of current and treatment- recovered chronic HCV infection was 0.4%, of which a high proportion (61.2%) had already received treatment with achieved SVR. A modelling study in 2013 estimated the viraemic prevalence in Norway to be 0.43% [29]. The slightly higher estimate in this study compared to ours might partly be explained by different study designs, where the modelling study was based on historical data and expert opinions.

The present study revealed that a substantial proportion (39.4%) of individuals with chronic HCV infection were unaware of their infectious status, a finding which is in line with the results of others [5, 9–11, 29]. Of the 13 previously undiagnosed individuals, 69% had a history of IDU, thus should theoretically have been detected by a risk-based screening strategy. This suggest that the current recommendation of risk-based screening is suboptimal in identifying all chronically infected persons hidden in the general population. One reason for this is that infected persons may not consider themselves as being at risk for HCV infection, i.e. persons with occasional drug use, especially in the remote past, and individuals who received blood transfusion before 1992 [9, 17]. Others have pointed out that the stigma associated with IDU; and the socio-demographic characteristics of PWIDs, create barriers that impede testing and linkage to care in this population [30].

Strengths and weaknesses

The strength of this study is the large sample size in a general population, which enhances the probability that the study population is representative of the general population. However, there are important limitations. First, The Tromsø 7 study only included individuals aged 40 years and older. This age restriction was inherent to the overreaching study design of Tromsø 7, but clearly introduces a selection bias. IDU is the main mode of transmission of HCV [31], and it is estimated that 29.8% (range 25.0–34.8) of PWIDs in Western Europe are younger than 25 years [32]. In the municipality of Tromsø, it is estimated that the number of PWIDs is approximately 300 (personal communication, Inger Hilde Trandem, MD, Social Medical Center, Tromsø, May 28, 2018). There is no clear data on their age distribution, but it is reasonable to assume that the proportion of young PWID in Tromsø is comparable to the findings in the above mentioned study. Due to the age restriction, the prevalence of HCV infection in our study is most likely underestimated.

Table 4 Cost of screening for HCV in the Tromsø 7 Study

	Cost per analysis	Analyses (n)	Total cost	Cost per newly detected chronic HCV infection (n = 13)
Reagents[a]		20,946	NOK 922705 (GBP 86,987, € 98,071)	NOK 70977 (GBP 6691, € 7544)
Labour costs[b]			NOK 180000 (GBP 16,969, € 19,132)	NOK 13846 (GBP 1305, € 1472)
Other[c]			NOK 75000 (GBP 7071, € 7972)	NOK 5769 (GBP 544, € 613)
Total	NOK 56.23 (GBP 5.30, € 5.98)	20,946	NOK 1177705 (GBP 111,028, € 125,175)	NOK 90593 (GBP 8541, € 9629)

Estimated costs for the HCV screening project in Norwegian Kroner (NOK), Pounds (GBP) and Euros (€). 1 GBP and 1 € approximated 10.69 and 9.48 NOK, respectively, as of 2. October 2018. 1 € = 1.15 US Dollars

[a]Reagents (anti-HCV test kits) for this study were provided by Abbvie AS, Norway. Cost is based on prices for test kits used for daily routine HCV testing

[b]Labour costs in this study were covered by the Northern Norway Regional Health Authorities with the sum mentioned, which was based on estimated time used for testing the samples in the study

[c]Participation fee for the Tromsø 7 Study

Second, even if participation rates were generally high across all age groups, self-selection is still an important issue that may affect the representativeness of the study sample. The attenders in population surveys tend to be more educated and have a healthier life style than non-attenders [33]. The second survey of the Tromsø study (Tromsø 2) showed that various psychiatric disorders and alcohol abuse were significant predictors of non-attendance in health surveys [34], and a Canadian study demonstrated that non-response bias is a problem in alcohol and drug use surveys [35]. It is therefore reasonable to assume that current and former PWIDs are less likely to participate in health surveys, also resulting in underestimation of the true HCV prevalence and reducing the efficiency of screening in the general population.

The interpretation and significance of indeterminate RIBA reactions are unclear. In one study, 4.9% of RIBA indeterminate cases were found to be HCV RNA positive [36]. Still, most individuals with indeterminate RIBA have a negative HCV RNA test, which may represent previous resolved HCV-infection as well as unspecific antibody reactions [25]. Reports have shown that approximately half of those with indeterminate RIBA have a resolved HCV infection [37, 38]. In this study, we have chosen to include persons with RIBA indeterminate result in the HCV-exposed cohort, which could have led to overestimation of anti-HCV positive. However, the number of RIBA-indeterminate records was low, making the contribution of these less important.

Screening strategies in a low-prevalence area: Whom and how to screen

Our study was integrated in an established population-based survey with repeated health surveys since 1974. The attendance rate was 64.3% and the estimated cost per newly detected chronic HCV infection was approximately NOK 90000 (€ 9629). HCV-screening of the general population outside such an established population survey would have been more laborious and at an expected considerably higher costs, thus making it less feasible. As discussed above, it is likely that persons belonging to risk groups for HCV infection attended the study to a lesser degree than the general population, reducing the efficiency of such an approach. On the other hand, the study has unmasked several individuals with chronic HCV infection that did not define themselves as belonging to known risk groups. A recent Spanish pilot study for an eventual population-based screening program included the adult population (20–75 years) in a small health area with a participation rate of 46.2% (2637/5706) [39]. HCV RNA was detected in 13 persons (0.5%), of whom five were unaware of the disease.

In low-prevalence countries, routine screening of the entire population has not been considered to be cost-effective [15–18], and screening are limited to high-risk populations. However, the high proportion of undiagnosed HCV infection clearly underscores the limitations of the risk-based screening approach and the need to reconsider screening strategies in order to achieve the diagnosis rate of 90% promoted by the WHO.

In the US, it is recommended a one-time screening of persons in the high-prevalence 1945–1965 birth cohort, in addition to targeted risk-based testing [40]. In the present study, the highest prevalence of anti-HCV and viraemic HCV infection was found in the age group 50–59 years, i.e. in people born between 1956 and 1965, which may be explained by a later onset of the epidemic of IDU in Norway, with a gradual increase in the number of PWID from the onset of IDU in 1973 until a peak was reached in 2000 [7]. In a birth-cohort analysis, 73% of the HCV-infected population in Norway was born between 1955 and 1980 [41]. A systematic review including several countries concluded that screening of birth cohorts, drug users, and high-risk populations was cost-effective [18]. However, recent studies indicate that universal screening of the general population may be an effective strategy. In France, where the prevalence of chronic HCV infection is 0.3% [2], a modelling study showed that universal screening of all individuals aged 18–80 years was the most effective screening strategy, and also the most cost-effective, assuming rapid initiation of treatment after diagnosis [19]. Likewise, in Spain with an HCV RNA prevalence 0.35–0.41%, a recent modelling study concluded that screening of the general adult population would identify a larger number of additional individuals with chronic HCV infection than screening high-risk groups or screening the age-cohort with the highest anti-HCV prevalence plus high-risk groups [20].

Others suggest strategies to improve targeted screening of people in high-risk groups in various settings. Primary care practitioners can play an important role in targeted screening, especially in former PWID, whereas screening of current PWID is more appropriate in settings like outpatient clinics, opioid substitution programs, jails, and psychiatric clinics [17, 42–46]. In a screening and medical follow-up programme in Northern Norway, primary care practitioners were encouraged to screen patients with former or present risk factors for HCV infection, which led to an increase in the number of newly diagnosed HCV infections in the subsequent years [47]. Technical bottlenecks in HCV testing can lead to missed opportunities in the HCV cascade of care, e.g., when a high proportion of anti-HCV positive individuals are not followed up with a confirmatory test for HCV RNA [48]. The availability of a new point-of-care (PoC) test with high sensitivity and specificity (close to 100%) for detection of HCV RNA might contribute to simplification of HCV testing and thus enable decentralisation of HCV care and treatment [49].

New technology, such as the use of dried blood spot and saliva sampling could increase access to HCV testing, e.g. in people with difficult venous access [50, 51].

There are potential negative effects associated with screening large numbers of persons in a population with low prevalence of HCV infection. In our study, the proportion of false positive anti-HCV tests was 38.2% (83/217). False-positive results can cause harm by way of anxiety and stigmatization, although such effects are difficult to quantify [52].

Implications

Modelling studies have indicated that screening in the general adult population may be an effective screening strategy [19, 20]. Universal screening may allow diagnosis and treatment of asymptomatic infected persons, avoiding the development of complications and onward transmission, thus saving health costs. To be effective, people with the highest risk of infection must also attend the screening project. Based on this, strategies to improve targeted screening of people in high-risk groups in various settings, including primary care-based interventions, may still be the most effective approach in low-prevalence regions. To overcome the high costs associated with screening in the general population, the use of a birth-cohort screening strategy could be considered, which in our case would be based on the finding of the highest prevalence of anti-HCV and chronic HCV infection in people born between 1956 and 1965. Finally, implementation of simplified testing methods may increase access to HCV testing in both risk groups and birth cohorts.

Conclusion

In this population-based survey the prevalence of chronic HCV infection in the general population in Tromsø was 0.2%, but due to biases the true prevalence is likely higher. A substantial proportion (39.4%) of individuals with viraemic infection was not aware of their diagnosis, suggesting that the current recommendation of screening of individuals with high risk of infection is an inadequate approach to identify all chronically infected persons. Strategies to improve HCV awareness and case-finding are needed, and for some communities, testing the general population may be a sensible approach.

Abbreviations

ALT: alanine aminotransferase; Anti-HCV: antibodies to HCV; DAA: direct acting antiviral; GT: genotype; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IDU: injecting drug use; PWID: people who inject drugs; RIBA: recombinant immunoblot assay; SVR: sustained virologic response; WHO: World Health Organization

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Availability of data and materials

Data from the seventh Tromsø Study is the property of UiT The Arctic University of Norway, Tromsø, Norway, and is available upon request at: https://uit.no/forskning/forskningsgrupper/gruppe?p_document_id=367276 The dataset of the HCV infection cohort is available from the corresponding author on reasonable request.

Authors' contributions

Conception and study design: HK, EP and TG; Data collection: HK; Clinical follow up: HK; Data analysis: HK and RG; Drafting the manuscript: HK; Data interpretation, discussion and preparation of the final manuscript: HK, TG, RG and EP. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Tromsø study was conducted by UiT The Arctic University of Norway. The Regional Committee for Medical and Health Research Ethics (REK) approved the study (ref: 2014/1406 and 2017/253), and all participants gave their written consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Paper II

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RESEARCH ARTICLE Open Access

Future complications of chronic hepatitis C in a low-risk area: projections from the hepatitis c study in Northern Norway

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Abstract

Background: Hepatitis C (HCV) infection causes an asymptomatic chronic hepatitis in most affected individuals, which often remains undetected until cirrhosis and cirrhosis-related complications occur. Screening of high-risk subjects in Northern Norway has revealed a relatively low prevalence in the general population (0.24%). Despite this, late complications of HCV infection are increasing. Our object was to estimate the future prevalence and complications of chronic HCV infection in the period 2013–2050 in a low-risk area.

Methods: We have entered available data into a prognostic Markov model to project future complications to HCV infection.

Results: The model extrapolates the prevalence in the present cohort of HCV-infected individuals, and assumes a stable low incidence in the projection period. We predict an almost three-fold increase in the incidence of cirrhosis (68 per 100,000), of decompensated cirrhosis (21 per 100,000) and of hepatocellular carcinoma (4 per 100,000) by 2050, as well as a six-fold increase in the cumulated number of deaths from HCV-related liver disease (170 per 100,000 inhabitants). All estimates are made assuming an unchanged treatment coverage of approximately 15%. The estimated numbers can be reduced by approximately 50% for cirrhosis, and by approximately one third for the other endpoints if treatment coverage is raised to 50%.

Conclusion: These projections from a low-prevalence area indicate a substantial rise in HCV-related morbidity and mortality in the coming years. The global HCV epidemic is of great concern and increased treatment coverage is necessary to reduce the burden of the disease.

Keywords: Disease burden, Fibrosis development, Hepatitis C, Markov modelling, Natural course

Background

Chronic hepatitis C virus (HCV) infection is a major cause of chronic liver disease and the burden of the disease is expected to increase [1–3]. Worldwide, 64–103 million people are persistently infected with HCV [4]. After acute HCV infection, between 75% and 85% of the patients establish a chronic infection [5]. In industrial countries, most of the patients infected with HCV will have contracted the disease in the 1970s and 1980s. Thus, at the beginning of the twenty-first century, a large pool of infected patients exists, and in many countries, the cohorts of patients with chronic HCV infection have come of age. Most infected individuals are asymptomatic, but the number of patients with liver cirrhosis and hepatocellular carcinoma (HCC) is increasing [6, 7]. Thus, 30–40 years after the start of the epidemic, the disease is a growing burden on the health care system in many countries.

The natural course of late-stage HCV infection is so far unsettled. The disease increases the risk of developing liver cirrhosis and its complications such as liver cancer and liver failure. The prognosis is highly dependent on the rate of progression of liver fibrosis

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towards cirrhosis. Most studies have shown that the rate of fibrosis is slow the first two decades. However, the estimated risk of cirrhosis varies as much as 3–30% in different populations [5, 8–10], suggesting that the progression of the disease may not be universal but rather depend on additional risk factors [11]. Beyond the two first decades, the rate of fibrosis progression is sparsely documented. One study reported that fibrosis progression is non-linear with an estimated a risk of cirrhosis of 41% after 30 years [8], whereas an autopsy study reported septal fibrosis or cirrhosis in 35% of cases with disease duration of 25 years or longer [12].

Among patients with liver cirrhosis the annual rate of progression to hepatic decompensation and HCC has been described to be in the range 4–8% and 2.4–3.4%, respectively [13–15]. In the absence of retrospective as well as prospective data for the long-term progression of the disease (>20 years), various mathematical models have been used to reconstruct the natural course and estimate future complications of HCV infection [1, 13, 16–18]. Even with a decline in the incidence rate after 1990, an increase in the number of patients with complicated disease and deaths from chronic HCV is expected in the coming decades [1–3, 19, 20].

Norway is a country with a low prevalence of HCV [21, 22]. Drug abuse is the primary transmission route, and low age at transmission indicates a low risk for rapid disease progression. Despite this, late complications of HCV infection is a growing problem [23] and health costs are expected to increase. Markov models are well suited for simulation of chronic diseases [24], and we have used a Markov model to estimate the future prevalence and complications of chronic HCV infection in the period 2013–2050 in a low-risk area.

Methods

The study population consists of individuals included in the Hepatitis C study in Northern Norway between 1992 and 2011 [21, 23]. In addition, we performed a registration study to assess the number of newly diagnosed individuals with HCV each year between 1998 and 2012 at the two microbiological departments in our region.

The Hepatitis C study in Northern Norway

In 1992, a screening and medical follow-up programme of patients with HCV infection was established in the Health Region of Northern Norway (460.000 inhabitants). In brief, general practitioners were encouraged to screen patients with former or present risk behavior for HCV infection. If chronic HCV infection was detected, the general practitioners were encouraged to refer the patient for follow-up at one of the 11 medical centers in the region. An estimate of the year of transmission was made for all referred patients based on either the year of acute HCV infection or the first year of high-risk behaviour [23]. Liver biopsies were performed, and fibrosis was graded (0–6) according to Ishak et al. [25]. Presence of concomitant alcoholic liver disease was assessed by clinical judgment.

The registry study

Individuals with a positive anti-HCV test registered at the two microbiological departments in Northern Norway between 1998 and 2012 were included. The year of diagnosis was defined as the first year of a positive anti-HCV test (ARCHITECT Anti-HCV Reagens kit. Abbott System, Wiesbaden, Germany). Until 2004, a positive anti-HCV test was directly confirmed with a recombinant immunoblot assay (RIBA HCV 3.0 SIA test, Chiron Cooperation, Emeryville, CA, USA). Individuals with a positive RIBA (two or more positive bands) or indeterminate RIBA (one band) were included, while individuals with a negative RIBA (no bands) were excluded. The result of the HCV RNA test was recorded if available: an in-house reverse transcriptase polymerase chain reaction (RT-PCR) until 2004, where after the ROCHE RT-PCR (Cobas Amplicor Hepatitis C Viral Polymerase Chain Reaction, Roche Molecular System Inc., Branchburg NJ, USA) was used. The ROCHE PCR test replaced the RIBA test for confirmation of HCV infection from 2005. HCV genotyping was performed as a hybridization assay on products from the HCV RNA PCR according to the manufacturers' instructions (INNO-LIPA HCV II kit, INNOGENETICS, Ghent, Belgium). Individuals without a registered residence in Norway were excluded. The results of HBsAg (hepatitis B surface antigen) and anti-HIV (human immunodeficiency virus) were recorded if available.

Markov model

In order to predict HCV-related morbidity and mortality an open Markov model was constructed (Fig. 1). Of infected patients, 20% were assumed to recover spontaneously during the first year of infection [26]. Yearly transitions between categories were done according to probability estimates generated from different sources. The effect of medical treatment was modelled in three scenarios where 0%, 15% and 50% of all patients were assumed to receive medical treatment. Before the introduction of direct acting antivirals (DAAs), treatment was offered to eligible patients irrespective of fibrosis stage, i.e. patients with Metavir fibrosis score F0/F1 were also treated. The treatment coverage at this time was approximately 15%. When the highly expensive DAAs became available, the Norwegian national guidelines restricted treatment to patients with fibrosis score ≥ F2. However, since DAAs offer a simple, tolerable, short-term and highly effective therapy, we consider an

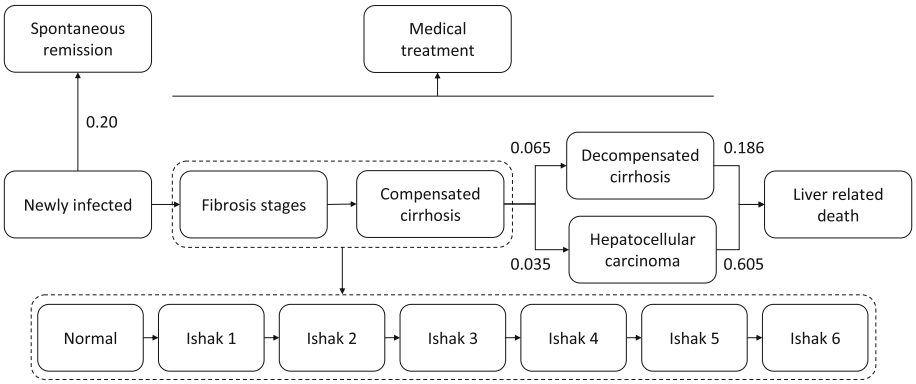

Fig. 1 The natural course of hepatitis C. The Markov model is based on simulation of transition from a given category to the next based on probability estimates. The progression of fibrosis towards cirrhosis is based on local data, whereas most of the remaining estimated probabilities are previously published from other cohorts. In all states of HCV, there is also an annual risk of dying from natural courses, which is implicitly included in the model

increased treatment coverage to 50% as possible. Recently (March 2017), updated national guidelines recommend treatment for all patients with genotype 1, irrespective of fibrosis grade. Treatment of genotype 2 and 3 is still restricted to patients with fibrosis score ≥ F2.

To estimate the rate of fibrosis progression in the cohort, 237 records with a positive HCV RNA test, known duration of infection, and available liver biopsy results were entered into an ordinal regression analysis, which can be described as a multilayer logistic regression. This method estimates points of transition on an ordinal scale (like the Ishak fibrosis scale). Sex, time after contraction of the disease and HCV genotype were included as predictors of Ishak fibrosis grade. Non-significant terms were removed from the model leaving time after contraction and genotype as significant predictors. Genotype 1 and 4 were analyzed as a single group due to few observations of genotype 4. The model predicted 70% of the observed fibrosis grades correctly within a margin of error of one Ishak grade, but overestimated fibrosis grade in 13% and underestimated in 17%. From this model, a matrix of estimated probabilities of transition to a higher fibrosis grade versus staying in the present grade for each year of infection could be constructed. It was assumed that fibrosis development during ongoing HCV infection could only either stay the same or change to a higher stage each year of infection. Additional file 1 shows the regression model in more detail. The Markov model was adjusted for genotypes in the estimation of fibrosis progression, according to the prevalence of the different genotypes in our population. For transitions from Ishak 6 (compensated cirrhosis) to more severe states, fixed probabilities were used. We did not have exact data from Northern Norway for the various transitions, and have thus used data from a Scottish HCV population of drug-injecting abusers (as in our study), as described by Hutchinson et al. [13], with transition probabilities similar to that reported by others [14, 27], as shown in Table 1. The model was corrected for standardized mortality rate according to Norwegian population characteristics. Non-cirrhotic subjects successfully treated for HCV with achieved sustained virological response (SVR) were removed from the model. Subjects with cirrhosis remain in risk of liver complications in spite of SVR, and of those, 50% were retained in the model [28]. All successfully treated subjects with decompensated cirrhosis and HCC were kept in the model.

The overall SVR rate until 2015 was 71.3%, based on the response of interferon-based treatment in our own

Table 1 Transition rates between different states of hepatitis C

Transition rates			
From state	To state	Yearly transition rate	Reference
Infection time	Spontaneous remission	0.200	Thomas Clin Liver Dis 2005 [26]
Compensated cirrhosis	Decompensated cirrhosis	0.065	Hutchinson Hepatol 2005 [13]
Decompensated cirrhosis	Liver-related death	0.186	Hutchinson Hepatol 2005 [13]
Cirrhosis	Hepatocellular carcinoma	0.035	Hutchinson Hepatol 2005 [13]
Hepatocellular carcinoma	Death	0.605	Hutchinson Hepatol 2005 [13]

The table shows the estimated rates of transition between different states of development of hepatitis C and its complications, as used in the Markov model

clinical practice. For individuals treated from 2015 onwards, the overall SVR rate was set to 90% to reflect the improved treatment response provided by DAAs.

Entering of data into the Markov model

Figure 2 shows the actual incidence of newly diagnosed HCV infection per year in the period from 1992 to 2012 (dark bars). After 2004, the incidence decreased to a stable level of approximately 90 newly diagnosed cases each year. In view of this stable number, we have projected a stable occurrence of 90 newly diagnosed cases each year from 2013 and forwards (light bars).

HCV-positive individuals were entered into the model at time of contraction. Since only a subgroup had a known time of transmission, this had to be estimated for the remaining records. First, we investigated the 402 records with known times of transmission. In 2004, all general practitioners in the area were subject to a HCV campaign encouraging screening of their patients with known risk behaviour. We found an increased amount of early diagnoses (within the first year of transmission) in the years after this campaign compared to before (35.5% vs. 21.3%). From these data, probability distributions could be derived in order to estimate time of contraction for records diagnosed before and after 2004, respectively. Records without known time of transmission were then entered into the model using these distributions as weights. From 2013 forward, the estimated number of 90 newly diagnosed cases each year were allocated due to the late probability distribution in order to estimate their time of contraction.

The registration of HCV infection revealed incomplete records regarding confirmation testing. A positive anti-HCV test normally should be followed up with a new blood sample for the confirmation with RIBA and/or HCV RNA. Not all the persons with positive anti-HCV tests had a recorded confirmation test. The starting cohort in the model thus consists of patients with confirmed HCV infection (either a positive RIBA or a positive HCV RNA test), as well as individuals with unconfirmed HCV (either only a positive anti-HCV or an indeterminate RIBA). We therefore estimated the likelihood of a true positive test in incomplete records in the following way: In a sample of 326 records with a positive anti-HCV-test where RIBA had been measured, 207 subjects (63%) had a positive RIBA test, and the probability of a true positive anti-HCV test was estimated to 0.63. Similarly, in a sample of 14 records with an inconclusive RIBA and a HCV RNA test, we found three individuals with a positive HCV RNA test, and the probability of a true positive record in case of inconclusive RIBA was estimated to 0.21. Summarized, individuals with either a positive HCV RNA or RIBA were weighted 1.0, and individuals with only a positive anti-HCV test or an inconclusive RIBA were weighted 0.63 and 0.21, respectively.

Results

Based on the registration and subsequent weighting described above, the estimated HCV cohort consists of

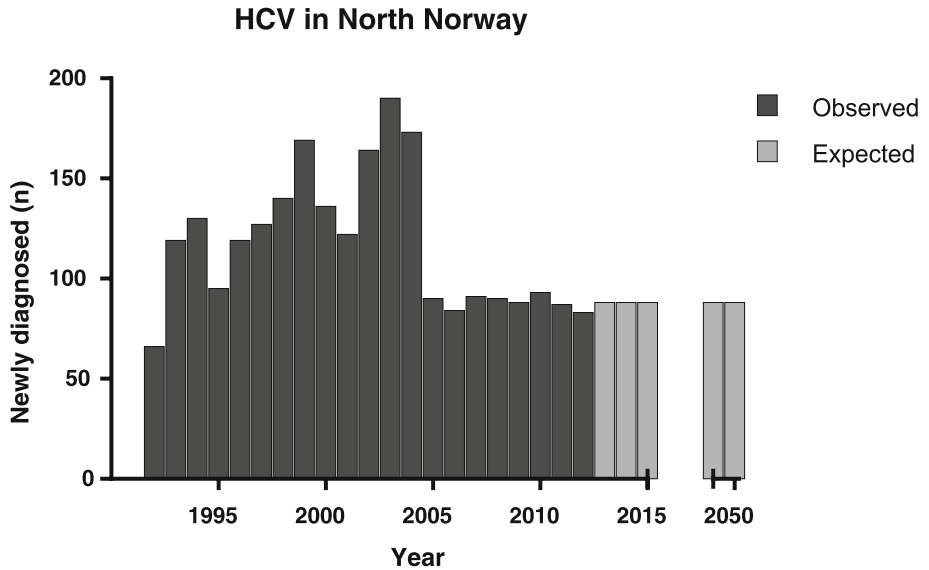

Fig. 2 Newly diagnosed hepatitis C in Northern Norway. The figure shows numbers per year of newly diagnosed individuals with hepatitis C in Northern Norway, from the first registration in 1992 to the end of 2012 (dark bars). The estimated yearly occurrence of newly diagnosed from 2013 and forward are also shown (light bars)

2589 individuals (positive HCV RNA or positive RIBA) with a sex distribution of 64% men and 36% women. Additional file 2 shows the estimation of the HCV cohort in more detail. The distribution between genotypes 1 through 4 was 45%, 8%, 46% and 1%, respectively. The prevalence of HBsAg and anti-HIV was 2.3% and 1%, respectively.

Modeled fibrosis progression

In the subgroup that was the basis for estimation of fibrosis progression ($n = 237$), the sex distribution was the same as in the total cohort and the distribution between HCV genotypes 1 through 4 were approximately equal to the total cohort, 45%, 10%, 44%, and 1%, respectively. The median duration of infection was 13 years (range 0–42 years) and the mean age at liver biopsy was 40 years. The rate of fibrosis progression was relatively slow in the first 20–25 years of infection, followed by an accelerated fibrosis progression, especially in patients with genotype 3 (Fig. 3).

Markov modelling

The Markov model projects the number of patients (per 100,000 inhabitants) in the different states of compensated cirrhosis, decompensated cirrhosis and HCC for the years 2013 to 2050, given various scenarios of HCV treatment coverage. It estimates an almost threefold increase in the incidence of cirrhosis (68 per 100,000), of decompensated cirrhosis (21 per 100,000) and of hepatocellular carcinoma (4 per 100,000) by 2050, as shown in Fig. 4a-c. Complications are expected to reach a peak around 2040. The model predicts a sixfold increase in the cumulated number of deaths from HCV-related liver disease (170 per 100,000 inhabitants), as shown in Fig. 4d. All estimates are made assuming an unchanged treatment coverage of approximately 15%. The estimated numbers can be reduced by approximately 50% for cirrhosis, and by approximately one third for the other endpoints if treatment coverage were scaled up to 50%.

Discussion

In our low-risk area of HCV infection, we have estimated the fibrosis progression in untreated hepatitis C. Fibrosis develops slowly the first 20–25 years of infection, where after an accelerated fibrosis progression, especially in genotype 3, is predicted.

Using a Markov model, we have estimated the future complications of HCV based on the actual number of infected individuals until the year 2012, followed by an estimated low and stable incidence rate. The model predicts a gradual increase in HCV-related liver cirrhosis, decompensated cirrhosis and HCC with an apparent peak around 2040, accompanied by a gradual increase in liver-related deaths.

Modelling

Precision of dynamic modelling for prognosis of prevalence, morbidity and mortality depends on the quality of the data entered and the assumptions made. We have used locally acquired data whenever possible. The critical aspect in HCV pathophysiology is the progressive development of fibrosis towards cirrhosis, and in this aspect, our model also made use of local data. The further

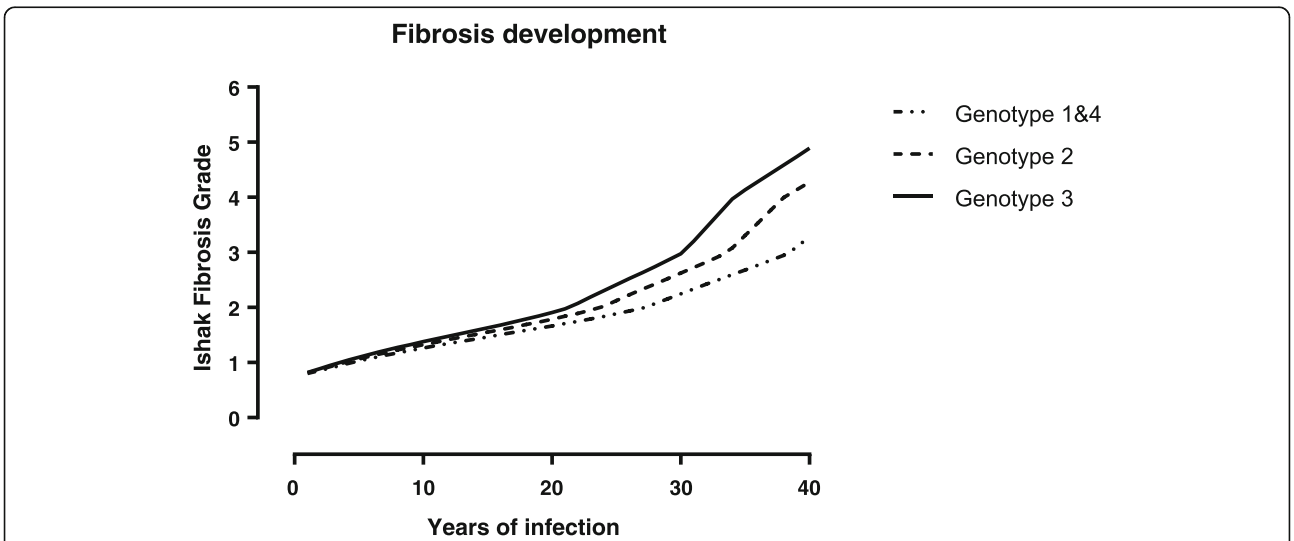

Fig. 3 Development of fibrosis in hepatitis C. The figure shows the time course of distribution of estimated median fibrosis grade according to genotype and duration of HCV disease. Estimates were derived by ordinal regression analysis of Ishak scores in 237 patients with duration of infection and genotype as independent variables

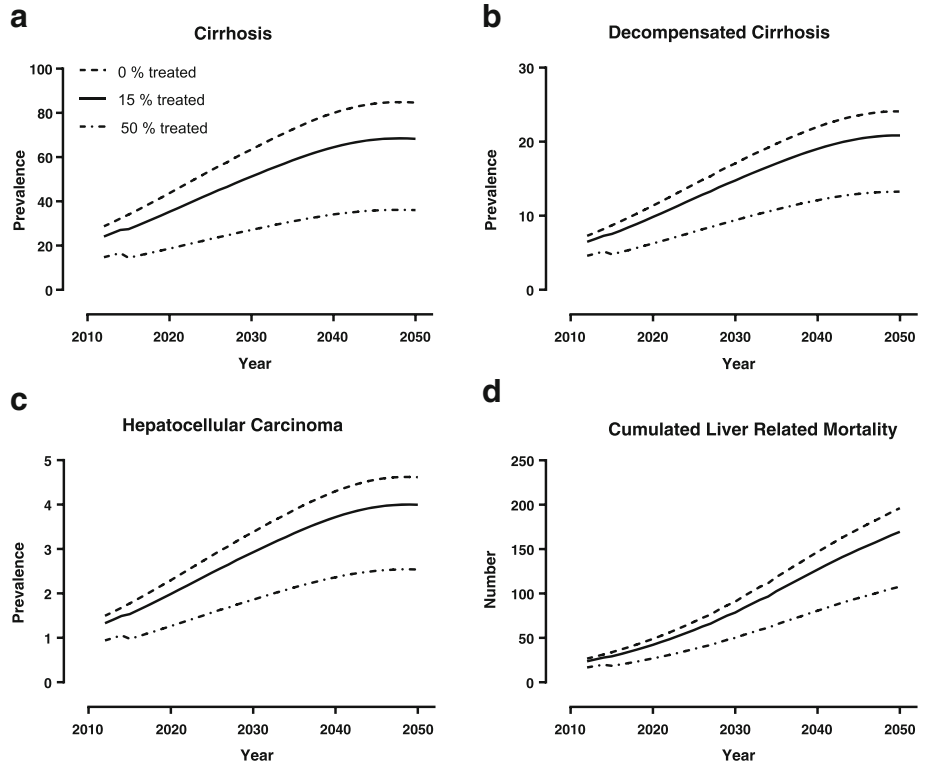

Fig. 4 Prediction of hepatitis C-related complications. The figure shows the predicted number of patients with cirrhosis, decompensated cirrhosis and hepatocellular carcinoma (panels **a**-**c**), and predicted cumulated number of deaths from liver disease (panel **d**) in the period 2013 to 2050 according to different treatment coverage. Numbers are given per 100,000 inhabitants

development from established cirrhosis is not likely to be very different from that of other cohorts, and the use of estimated transition rates from other studies [13] should not affect the prognosis measurably.

Our Markov model is based on an assumed low and stable incidence until 2050, whereas other reports estimate a declining or stable incidence [2]. The observed incidence peak in 2002–2004 in our data is probably a result of increased focus on HCV infection among general practitioners due to our encouragement of diagnosis in that period.

Our cohort is relatively young, and the liver biopsy data has a limited number of observations of severe fibrosis (Ishak grade 4–6). Hence, the estimates generated from these data are less precise regarding progression through high fibrosis stages.

Published data show variable rates of liver fibrosis progression, with 10%–40% developing cirrhosis after 20–35 years of infection [5, 8, 29]. A large systematic review supports nonlinear fibrosis progression [8] and other studies have shown that HCV genotype 3 is associated with a faster fibrosis progression [30–33]. Male sex is a reported risk factor for disease progression [5, 31]. However, we found no effect of sex in the progression of fibrosis, which is also observed in other studies [34].

Strengths and weaknesses

The strengths of this study are; first, we have reliable data on the HCV-infected subjects in our health region; second, the simulated fibrosis progression in the cohort is based on local data. However, there are apparent weaknesses. First, the number of undiagnosed HCV-infected individuals in the population is unknown. In Sweden, a comparable country regarding HCV epidemiology, it has been suggested that the rate of undiagnosed HCV infection is approximately 20% [35]. Second, incomplete records regarding confirmation testing has made it necessary to estimate the number of true positive cases, resulting in uncertainty regarding the true prevalence. However, our estimate of 63% true positives among those who only tested positive for anti-HCV is not controversial compared to another reported value of 68% true positive [36]. Moreover, the significance of RIBA-indeterminate reactions is unclear. Most individuals with indeterminate RIBA have a negative HCV RNA test, which may represent previous exposure to, but spontaneous recovery

from HCV [37]. Authors have shown that approximately half of those with indeterminate RIBA have a resolved HCV infection [38, 39]. The proportion of RIBA-indeterminate records in our HCV population was low, making the contribution of these records less significant.

Third, the future incidence may be underestimated. Most likely, transmission of HCV will still be mainly by drug abuse, which is an ongoing problem in our region as is the case in the rest of Europe [40]. On the other hand, the introduction of highly effective, simple, short-term and tolerable therapies has the potential to increase treatment coverage among people who inject drugs. Thus, scaling up treatment in people with a transmission risk could reduce the future incidence and have a major impact on the HCV prevalence [41]. Fourth, it is documented that both moderate and excessive alcohol intake increase fibrosis progression in patients with HCV [42, 43]. Presence of concomitant excessive alcohol use was in our study assessed by clinical judgment, and not by a validated questionnaire of drinking habits. We have therefore chosen to omit alcohol use from the model over concerns on the quality of the data. Several other factors have been shown to accelerate the fibrosis progression, like co-infection with hepatitis B virus or HIV, diabetes and obesity [9]. The prevalence of HBV or HIV co-infections in our HCV population were low, 2.3% and 1% respectively, and therefore not included in the model. Data regarding diabetes and obesity were incomplete and neither included in the model.

Fifth, the exact time of infection is often not known. In individuals with unknown time of infection, we have used the first year of high-risk behavior as the presumed year of transmission, as others have done [30, 44, 45]. However, it has been reported that the interval between onset of drug injection and HCV infection has lengthened in recent years [46], which may indicate that the duration of infection could be shorter than estimated in our model of fibrosis progression. If so, our fibrosis model produces a spuriously slow rate of fibrosis progression, making the prognosis relatively conservative.

Sixth, the Markov model assumes that HCC only occurs when liver cirrhosis is established (Ishak 6). However, HCC can develop in lower fibrosis stages in chronic HCV infection [47, 48]. Finally, regression of fibrosis, cirrhosis and cirrhosis complications is possible after achieving SVR [49–51]. We do not have data to assess the effect of SVR on fibrosis regression, i.e. available pretreatment and post-treatment liver biopsies, and this is another limitation of the model. However, removing subjects achieving SVR from the model can mimic fibrosis regression in non-cirrhotic cases. In patients with cirrhosis, about 60% can regress after SVR [49, 50], and much less likely in decompensated cirrhosis. In patients with HCV-induced cirrhosis who attain SVR, the risk of HCC declines, but persists [52, 53]. To reflect that model cases with cirrhosis and SVR still are in risk of cirrhosis complications, we have retained 50% of these in the model.

Implications

HCV is the leading cause of chronic liver disease and cirrhosis and is the main cause of liver transplantation in the Western world [10]. Although the total number of HCV-infected individuals is estimated to be stable or decline in the future, an increase in liver cirrhosis, liver cancer, hepatic decompensation and liver-related deaths is expected in the coming years.

This assessment is underlined by the World Health Organization (WHO) statement that the burden of HCV disease has been largely ignored as a health priority, and the organization has developed the first-ever global health sector strategy for addressing the viral hepatitis pandemic [54].

To reduce the future burden of hepatitis C it is necessary to meet the challenge at three levels. First, prophylaxis measures must focus on reducing the transmission rate among active injection drug users. In addition, recent guidelines suggest that treatment should be offered to this group of individuals at high risk of transmitting HCV due to a potential prevention benefit [55]. Second, HCV infection among apparently healthy subjects must be diagnosed by screening of high-risk groups. Strategies to expand screening beyond high-risk groups should be considered since a substantial proportion of infected are unaware of their status [56]. Third, antiviral treatment has been offered only to a small percentage of patients, as treatment is hampered by the high cost of the new direct-acting antiviral drugs (DAAs). Based on the unpredictable course of liver fibrosis at the individual level, delaying treatment of patients with early fibrosis stages will increase the risk of liver complications [11]. DAAs has the potential to reduce the future burden of disease of HCV, but this is restricted by the current treatment levels [19]. In spite of the high costs of DAAs, several studies show that interferon-free regimens are cost-effective compared to interferon-based regimens [57–61].

Conclusion

Based on the registration of patients with HCV in a low risk area, we estimate a relatively slow fibrosis progression within the first 20–25 years of infection, followed by an accelerated fibrosis progression, especially in subjects with HCV genotype 3. This may have important implications in the clinical management of patients infected with genotype 3.

Furthermore, we estimate a gradual increase in future complications with an estimated peak around 2040. The projected scenario implies a substantial increase in HCV-related morbidity and mortality in the coming years. An increased number of patients need to be treated to have an impact on the future burden of HCV disease.

Additional files

Additional file 1: Ordinal regression model for estimating fibrosis grade according to duration of infection. (DOCX 19 kb)

Additional file 2: Estimated HCV cohort 1992–2012. The file describes how we estimated our HCV cohort. (DOCX 15 kb)

Abbreviations

DAA: Direct acting antiviral; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; SVR: Sustained virological response; WHO: World Health Organization

Author's contributions

Conception and study design: RG, JF. Data collection: HK, OSM, MGK, LKB. Data analyses: LB, RG. HK and RG drafted the manuscript. Data interpretation, discussion and preparation of the final manuscript: HK, RG, JF, EP, TG, LB, OSM, MGK, LKB. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Regional Committee for Medical and Health Research Ethics approved of the Hepatitis C study in Northern Norway (ref: P-REK 55/2001), and all participants gave their written consent to participate. The Data Protection Official at The University Hospital of Northern Norway and Nordland Hospital approved processing of the microbiological data in the registration study.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Paper III

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Personalized treatment of hepatitis C genotype 1a in Norway and Sweden 2014–2016: a study of treatment outcome in patients with or without resistance-based DAA-therapy

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ORIGINAL ARTICLE

Personalized treatment of hepatitis C genotype 1a in Norway and Sweden 2014–2016: a study of treatment outcome in patients with or without resistance-based DAA-therapy

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ABSTRACT

Objectives: Resistance-associated substitutions (RASs) may impair treatment response to direct-acting antivirals (DAA) in hepatitis C virus (HCV) treatment. We investigated the effects of baseline NS3-RASs (Q80K and R155K) and clinically relevant NS5A-RASs in patients with HCV genotype (GT) 1a infection on treatment outcome, with or without resistance-based DAA-treatment. This multi-center study was carried out between 2014 and 2016.

Patients/methods: Treatment in the intervention group ($n = 92$) was tailored to baseline resistance. Detection of NS3-RAS led to an NS5A-inhibitor-based regimen and detection of NS5A-RAS to a protease-inhibitor regimen. Patients without baseline RAS in the intervention group and all patients in the control group ($n = 101$) received recommended standard DAA-treatment.

Results: The sustained virologic response rates (SVR) in the intervention and control groups were 97.8% (90/92) and 93.1% (94/101), respectively ($p = .174$). A trend toward higher SVR-rate in cirrhotic patients ($p = .058$) was noticed in the intervention group compared to the control group with SVR-rates 97.5% (39/40) and 83.3% (35/42), respectively. All patients with baseline NS3 (Q80K/R155K) or NS5A-RASs in the intervention group achieved SVR with personalized resistance-based treatment. In the control group, five patients with Q80K or R155K at baseline were treated with simeprevir + sofosbuvir and treatment failed in two of them. Furthermore, one of three patients who failed ledipasvir + sofosbuvir treatment had NS5A-RASs at baseline.

Conclusions: In line with the findings of the OPTIMIST-2 trial for Q80K and the EASL-guidelines 2016 for NS5A-RASs, baseline RASs appeared to have an impact on treatment outcome albeit a statistical significance was not observed in this low-prevalence population.

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Introduction

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, liver cirrhosis, hepatocellular carcinoma (HCC) and liver failure [1]. Globally, the prevalence of viremic HCV infection is estimated to be around 1.1%, corresponding to 64–103 million actively infected individuals [2]. In Sweden and Norway, about 0.4–0.5% of the population is infected with HCV, i.e., approximately 45,000 and 20,000 individuals, respectively [3–5]. HCV is classified into seven genotypes (GT) and several subtypes [6]. In Sweden, the most common GT is 1a, followed by 3a [7], while in Norway GT 3a is the most common, followed by 1a (personal communication Gutteberg T).

The development of direct-acting antiviral agents (DAAs) has led to major advances in the treatment of HCV infection, with substantially higher sustained virologic response (SVR) rates, shorter treatment duration and fewer side effects than previous interferon-based treatment. Currently, four classes of DAAs are available targeting three nonstructural proteins in HCV; NS3/4A protease inhibitors (PI), NS5A inhibitors and nucleoside and non-nucleoside inhibitors of the NS5B RNA-dependent RNA

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Supplemental data for this article can be accessed here.

polymerase (RdRP) [8]. Treatment with different combinations of these potent DAAs with or without ribavirin has made it possible to obtain SVR rates of above 95% in the majority of patients with chronic hepatitis C (CHC).

HCV displays a pronounced genetic heterogeneity due to the lack of proofreading activity of the RdRP and the rapid turnover rate in HCV replication [9]. In the resulting HCV quasispecies, resistance-associated substitutions (RASs) can emerge under the selective pressure of treatment with DAAs [10], but may also occur prior to treatment, i.e., baseline resistance [9]. Depending on their frequency within the HCV quasispecies and the level of resistance conferred, baseline RAS can contribute to treatment failure in the presence of other negative predictive factors such as advanced stages of liver fibrosis, previous treatment and suboptimal treatment [8].

These methods available for detecting RASs are the Sanger sequencing and the next-generation sequencing (NGS) methods. The Sanger sequencing method carries a 20% cutoff level for detecting RASs in the viral population compared to 1% with the NGS method. However, the general consensus is to recommend a cutoff level of 10–20%, for detecting RASs within the HCV quasispecies, in order to be of clinical relevance in predicting treatment failures [11].

The polymorphism Q80K, a naturally occurring amino acid substitution in the viral NS3 region, is mainly present in HCV GT 1a and is associated with reduced susceptibility to the NS3/4A protease inhibitor simeprevir, as indicated by the COSMOS and the first OPTIMIST studies [12,13]. The prevalence of baseline Q80K varies geographically and is reported to be 48% in the USA [14], compared to 5.7–15.2% in Sweden [7,15], and 4.8% in Norway [15].

The NS3 amino acid substitution R155K confers resistance to PI and is frequently observed in GT 1a-infected patients who failed to achieve SVR after treatment with boceprevir, telaprevir or simeprevir [10]. R155K can also be present in $<$1% of GT 1a PI treatment-naïve patients [16].

In current clinical practice, it is more important to consider baseline RASs in NS5A than NS3 for GT 1a. Many RASs confer a very high fold resistance, e.g., Y93H/N ($>$1000 fold), with GT 1a in *in vitro* replicon assays [8]. It should be noted that NS5A RASs at positions 30 and 31 confer a medium to high resistance, but these *in vitro* resistance profile might not be high enough to be of clinical importance for current approved NS5A inhibitors (with exception of elbasvir and ledipasvir). Nevertheless, these NS5A RASs are rarely found as baseline polymorphisms in GT 1a patients, i.e., in 2–5% of DAA treatment-naïve patients when using the population-sequencing method. However, EASL and AASLD guidelines recently recommended NS5A baseline testing for GT 1a prior to treatment with elbasvir and that testing should also be considered in treatment-experienced patients before treatment with ledipasvir regimens [17,18].

At the start of the study, there were no available guidelines regarding baseline resistance testing. The aim of this real-life study was initially to investigate the impact of Q80K, subsequently also including R155K and NS5A RASs, on treatment outcome in GT 1a infected patients treated with DAAs, and to evaluate the resultant economic consequences. Known factors influencing treatment outcome were evaluated. The study was conducted during 2014–2016 when simeprevir plus sofosbuvir combination was a recommended alternative to NS5A inhibitor based regimes.

Patients and methods

Patients diagnosed with chronic HCV GT 1a infection from Uppsala, Gävle and Tromsø received resistance-based treatment (intervention group) and from Örebro, Falun and Bodö received treatment according to the national guidelines [19,20] without previous resistance testing (control group). They were consecutively included in this real-life, open-label, non-randomized Nordic multi-center study from 1 April 2014 to 30 June 2015 (Sweden) and 26 January 2016 (Norway). During this period, baseline NS3 resistance testing (Q80K and R155K) of HCV GT 1a was performed routinely for the intervention group. In January 2015, when the fixed combination ledipasvir plus sofosbuvir was approved in Sweden and Norway, analysis of NS5A RAS was introduced and was performed in the intervention group, approximately 40% of 92 patients in the intervention group. The NS5A RASs considered important by us at that time were Q30E/H/R, L31M and Y93C/H/N. All these RASs were indicated by the HCV drug development advisory group to be clinically relevant with a $>$100 fold increase in resistance toward ledipasvir [10].

Recommended treatment, according to the National Boards [19,20], was, therefore, given to patients without baseline RASs in the intervention group and to all patients in the control group. For patients in the intervention group with Q80K or R155K mutation, the treatment was amended to a NS5A inhibitor-based regimen. In case of baseline NS5A RAS, treatment with a protease inhibitor-based regimen i.e., simeprevir plus sofosbuvir was considered. Presence of baseline NS3 RASs were analyzed for all patients in the control group retrospectively, whereas baseline NS5A analysis in the control group was only done (also retrospectively) for those that had failed ledipasvir plus sofosbuvir treatment.

Resistance analyses for emerging RASs were performed in all non-responders at the time of relapse; NS3A analysis in simeprevir failures and NS5A analysis in patients with failure after the treatment with NS5A inhibitor-based regimen.

Ribavirin was added at the responsible medical doctor's (MD) discretion, mainly due to the presence of cirrhosis.

The inclusion criteria were: infection with HCV GT 1a; $\geq$18 years of age; informed consent; and treatment according to Swedish and Norwegian consensus recommendations as well as completed treatment course (per-protocol). Patients included were either treatment-naive or treatment-experienced to interferon-based therapy, including triple therapy containing the first generation NS3 protease-inhibitors boceprevir or telaprevir. Patients previously treated with other DAAs were excluded.

Liver elasticity (kPa) was measured with FibroScan® 502 (Echosens, Paris, France) (Swedish study sites) and FibroScan® 402 (Norwegian study sites) by experienced nurses or doctors. For patients who had undergone a liver biopsy, the Metavir score was recorded [21]. Presence of cirrhosis was determined by FibroScan $>$12.5 kPa or Metavir

score 4 in liver biopsy. Child-Pugh score was estimated from available information on the level of liver elasticity [22], biochemical results and ultrasound. Patient data were extracted from the medical records by the responsible MD at each study site, anonymized and transferred to a joint database.

SVR was defined as undetectable HCV RNA 12 weeks after the end of treatment. Non-SVR was regarded as a viral breakthrough (a negative viral load nadir followed by a positive HCV RNA level during therapy), or viral relapse (non-detectable viral load at the end of treatment followed by an increase in HCV RNA level after therapy).

Laboratory methods

The Clinical Microbiology laboratory at the University Hospital, Uppsala, performed the resistance analysis of RASs (baseline and emerging). A nested PCR method, followed by Sanger sequencing (population sequencing, cutoff 20%) method was adopted for the NS3 resistance analysis. The pan-genotypic NS3 resistance method has been described elsewhere [7]. In brief, RNA extraction from the samples was done using the BioMerieux NucliSENS® easyMAG™ system (bioMérieux, Marcy-l'Étoile, France). cDNA was synthesized from RNA template with the SuperScript™ III Reverse Transcriptase (Invitrogen™, Thermo Fisher, Waltham, MA, USA) using random hexamers. First round PCR and nested PCR were performed with in-house primers targeting parts of the NS3 region using the Taq PCR Master Mix (Qiagen, Hilden, Germany). The integrity of the nested PCR products was verified by agarose-gel electrophoresis. PCR-positive samples were purified using QIAquick® PCR Purification Kit (QIAgen, Hilden, Germany). All protocols used were performed according to the manufacturer's instructions. The purified products were sequenced by the Sanger sequencing method using the same primers used in the nested PCR. The HCV NS3 sequences were analyzed using SeqScape® Software version 2.6 (Applied Biosystems, Foster City, CA). The NS3 sequence of GT 1a H77 strain was used as a reference template. The mutations were interpreted as relevant NS3 RASs by comparing with RASs reported in the literature [10,23]. The NS5A resistance analysis was performed with the same method and is described elsewhere [24].

HCV RNA titer quantification was performed at the Department of Clinical Microbiology, University Hospital, Uppsala, Sweden and at the Department of Microbiology and Infection Control, University Hospital of North Norway, Tromsø, Norway using Roche COBAS® AmpliPrep/TaqMan® HCV Quantitative Test version 2.0 with a LOQ of 15 IU/mL (Roche Molecular Systems Inc., Branchburg, NJ).

Outcomes

The primary objective was to study the treatment efficacy in the intervention group compared to the control group, with respect to the proportion of patients achieving SVR. Secondary objectives included to determine (1) the proportion of patients with baseline NS3 (Q80K and R155K) RASs, (2) the proportion of patients with baseline NS3 and NS5A RASs experiencing viral breakthrough or relapse, (3) the proportion of patients with baseline NS3 RASs not experiencing viral breakthrough or relapse and (4) to compare total expenditures (treatment and baseline analysis costs) per capita in the two study groups.

Statistics

The null hypothesis of this study was that the SVR rate is equal in the intervention and control groups. The basic statistical computing was done in Microsoft® Excel® 2013 (Microsoft Office professional plus 2013, Microsoft Corporation) and in Statistical Package for Societal Sciences (SPSS version 24, SPSS Inc., Chicago, IL). The Fisher's exact test was used to test the differences between groups (small expected cell count). A two-tailed p value $<.05$ was considered significant.

Ethics

The regional committee of medical research ethics Committee in Uppsala (Dnr: 2013/185 and Dnr: 2013/185/1) and the Data Protection Official at The University Hospital of Northern Norway (Nr. 0574) approved the study. All participants received written information and the opportunity to withdraw from the study.

Results

Patient baseline characteristics

In total, 200 patients were assessed to be eligible for the study. Samples from 196 patients were available for baseline resistance analyses (95 in the intervention group and 101 analyzed retrospectively in the control group). In the intervention group, three patients were omitted from further analyses; two of them died before the time of evaluation for SVR and one patient started treatment before the result of the baseline resistance analysis was available. Thus, week 12 follow-up data were obtained from 193 patients; 92 in the intervention group and 101 in the control group (Figure 1).

Demographic and baseline clinical characteristics are provided in Table 1. The majority of patients were treatment-naïve and male. The median age was 56 years. The distribution of patients with cirrhosis and baseline NS3 RASs (Q80K and R155K) in the intervention and the control groups were similar. The majority of cirrhotic patients were Child-Pugh A.

Table 2 shows treatment characteristics. The proportion of patients treated with simeprevir was higher in the intervention group compared to the control group. Most of the patients received treatment for 12 weeks and ribavirin was added to a minority.

Efficacy and baseline RASs

The overall prevalence of baseline Q80K and R155K polymorphisms was 7.1% (14/196) and 5.2% (10/196), respectively.

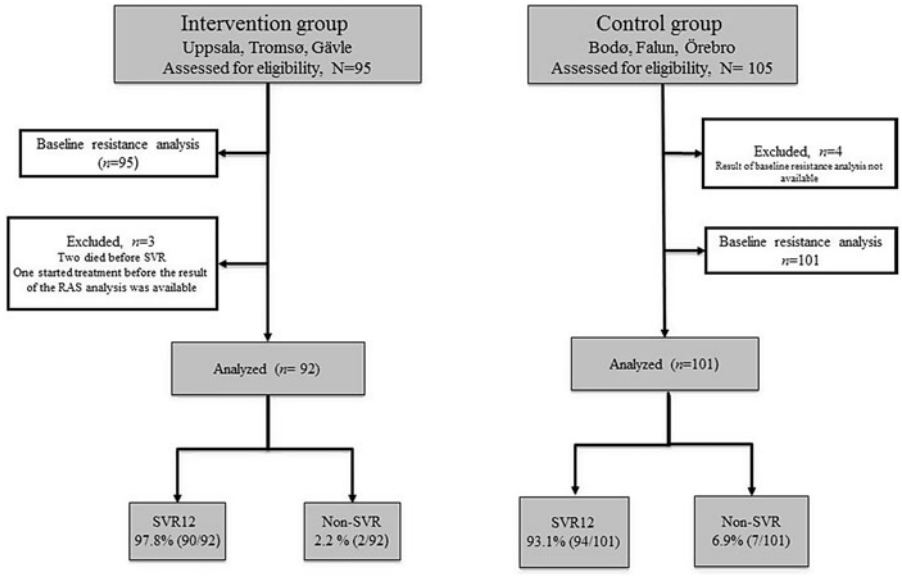

Figure 1. Flowchart of patients included in the study. Baseline resistance testing in the control group was performed retrospectively.

Table 1. Patient demographics and baseline characteristics.

	Intervention group ($N = 92$)	Control group ($N = 101$)	p
Median age, year (range)	56 (27–74)	56 (28–74)	.9
Sex, male, *n* (%)	61 (66)	70 (69)	.8
Cirrhosis, *n* (%)	40 (43)	42 (42)	.9
Child A, *n* (%)	35 (87.5)	40 (95.2)	–
Child B, *n* (%)	5 (12.5)	2 (4.8)	–
Child C, *n* (%)	0	0	–
Median HCV RNA, $\log_{10}$ IU/ml (range)	6.1 (3.3–7.5)	6.1 (4.4–7.2)	.7
Baseline Q80K and R155K RAS, *n* (%)	11 (12.0%)	13 (12.9)	.6
HCV antiviral treatment history, *n* (%)			.07
Treatment-naïve	45 (48.9)	67 (66.3)	–
Non-responder	21 (22.8)	14 (13.9)	–
Relapse/ breakthrough	19 (20.7)	12 (11.9)	–
Other[a]	7 (7.6)	8 (7.9)	–
Previous therapy with PI[b], *n* (%)	11 (12.0)	6 (5.9)	.2

[a]Reinfection, discontinuation.
[b]PI: protease inhibitor (boceprevir or telaprevir).

Table 2. Treatment characteristics.

	Intervention group ($N = 92$)	Control group ($N = 101$)	p
Treatment regime, *n* (%)			.023
Simeprevir + Sofosbuvir	46 (50.0)	30 (29.7)	–
Ledipasvir + Sofosbuvir	34 (37.0)	58 (57.4)	–
Daclatasvir + Sofosbuvir	11 (12.0)	11 (10.9)	–
OBV/PTV/r + DSV[a]	1 (1.0)	2 (2.0)	–
Addition of ribavirin, *n* (%)	14 (15.0)	9 (8.9)	.2
Treatment duration, week (%)			.4
8	5 (5.4)	3 (3.0)	–
12	73 (79.3)[b]	88 (87.1)	–
16	3 (3.3)	1 (1.0)	–
24	11 (12.0)	9 (8.9)	–

[a]Ombitasvir/paritaprevir/ritonavir + dasabuvir.
[b]One patient scheduled for 12 weeks of treatment discontinued after 4 weeks because of an accident, but achieved SVR.

The prevalence of Q80K in Sweden and Norway was 7.0% (11/158) and 10.5% (4/38), respectively. The prevalence of R155K in Sweden and Norway was 4.4% (7/158) and 7.9% (3/38), respectively. Prevalence data of NS5A RASs could not be specified since the mandatory screening of baseline NS5A RASs was not started until January 2015, and done only for a part of the intervention group. However, three patients with baseline NS5A RASs were found: two in the intervention group (M28T and Y93H), and one in the control group that harbored both M28A and Q30R.

The SVR rate in the intervention group and the control group was 97.8% (90/92) and 93.1% (94/101), respectively ($p = .174$). A trend toward higher SVR rates in cirrhotic patients ($p = .058$) was noticed in the intervention group compared to the control group, 97.5% (39/40) and 83.3% (35/42), respectively (Figure 2). Overall, liver cirrhosis was associated with a lower SVR12 rate compared to non-cirrhosis, 90 (74/82) and 99% (110/111), respectively ($p = .005$).

NS3 RASs

In the intervention group, all patients with baseline Q80K ($n = 5$) and R155K ($n = 6$) were successfully treated with a regimen containing a NS5A inhibitor. In the control group, the SVR rates in patients with baseline Q80K and R155K were 89% (8/9) and 75% (3/4), respectively. Only five of 13 patients with such RASs at baseline were treated with simeprevir plus sofosbuvir in the control group. Notable, of this one in four (1/4) patients with Q80K RAS and one in one (1/1) with R155K RAS failed treatment (Figure 2).

NS5A RASs

In the intervention group, all patients with baseline NS5A RASs ($n = 2$) were successfully treated. The patient with Y93H was treated with simeprevir plus sofosbuvir, whereas the patient with M28T was treated with ledipasvir plus sofosbuvir since the M28T was not considered a clinically relevant NS5A RAS. In the control group, three patients failed ledipasvir plus sofosbuvir treatment and one of these patients harbored a relevant NS5A RAS at baseline Q30R (together with M28A) (Supplementary Table S1).

In total, nine patients failed to achieve SVR, the reason for non-SVR was a viral relapse. In three of these nine patients, Q80K, R155K and Q30R one each, were detected at baseline (all in control group). Majority of the 10 observed baseline R155K was connected with prior boceprevir or telaprevir treatment failure, but in one patient, it was found as a natural polymorphism. Overall, patients with treatment failure were all male, had a median age of 56 years, 89% (8/9) of them had liver cirrhosis and most were treatment naïve (6/9) (Table 3).

Supplementary Table S1 gives an overview of the patients with detected baseline NS3 RASs (Q80K and R155K) and NS5A RASs.

Economic implications

In 2014/2015, the cost of simeprevir plus sofosbuvir treatment for 12 weeks was 750,000 NOK/650,000 SEK. In 2015, the price for 12 weeks of ledipasvir plus sofosbuvir treatment was 500,000 NOK/400,000 SEK. Baseline NS3 RAS was detected retrospectively in two patients who experienced virological relapse after treatment with simeprevir plus sofosbuvir. Switching these two patients to a NS5A inhibitor-based regimen could possibly have reduced treatment costs and in addition, contributed to a best practice approach. The same trend occurred with the use of simeprevir plus sofosbuvir treatment for the patient with NS5A Q30R RAS at baseline. Thus, in the control group, there was an economic loss of 2.0 million NOK/1.7 million SEK compared to the intervention group where no patients with Q80K/R155K or clinically important NS5A RAS at baseline experienced non-SVR. In comparison, the baseline analysis costs (2000 NOK/SEK per analysis) for the 95 patients in the intervention group were less than 0.2 million NOK/SEK.

Discussion

In this real-life study conducted in Q2 2014 to Q1 2016, we found a low prevalence of baseline Q80K RAS in HCV GT 1a

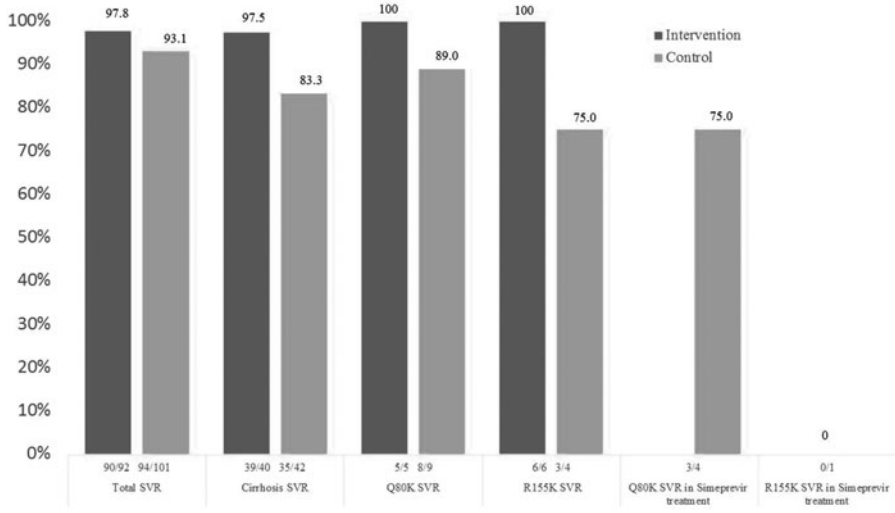

Figure 2. Sustained virologic response rates (SVR) in the intervention and control groups. SVR rates in the intervention group (dark grey bars) and the control group (light grey bars). The two bars to the right show SVR rates by simeprevir treatment in patients with baseline Q80K and R155K RAS in the control group.

Table 3. Clinical characteristics, baseline and emerging RASs (NS3 and NS5A) in the non-responders.

Age (year)	Study group	Metavir score (child pugh)	Fibro Scan (kPa)	Treatment	Previous treatment response	Baseline viral load, $\log_{10}$ (IU/ml)	Baseline RAS(s)	RAS(s) at relapse	Ribavirin	Treatment time (week)
60	I	4 (B)	42.8	S + S	*N*	5.2	0	R155K	Yes	12
54	I	3	10.4	S + S	NR	5.7	0	0	No	12
56	C	4 (A)	–	S + S	*N*	6.1	0	0	Yes	12
46	C	4 (A)	–	S + S	*N*	6.2	R155K	R155K	No	12
66	C	4 (A)	–	L + S	*N*	6.9	0	Q30R + L31M	No	12
59	C	4 (A)	–	L + S	NR	6.0	0	L31I	No	12
52	C	4 (A)	75	S + S	NR	5.8	0	D168A	No	12
52	C	4 (B)	75	S + S	*N*	4.8	Q80K	Q80K	No	12
65	C	4 (A)	47.2	L + S	*N*	6.4	M28A, Q30R	M28A, Q30R	Yes	12

I: intervention group; C: control group; L + S: ledipasvir plus sofosbuvir; N: naïve; NR: null responder to pegylated interferon plus ribavirin; S + S: simeprevir plus sofosbuvir

in Sweden and Norway (7.1%), which is in line with previous studies [7,15]. Liver cirrhosis was significantly associated with treatment failure. There were not enough GT 1a patients with Q80K RAS to detect a significant effect of baseline resistance-guided treatment on the SVR rate. However, our findings appear to agree with earlier studies. The COSMOS study in 2014 indicated lower SVR rates in GT 1a patients with baseline Q80K RAS compared to patients without Q80K at baseline [13]. The OPTIMIST-2 study revealed lower SVR rates for GT 1a patients with cirrhosis and baseline Q80K (SVR 74%) compared to those without Q80K (SVR 92%) [25].

In the control group, only 30% of the patients were treated with simeprevir + sofosbuvir combination compared to 50% in the intervention group, possibly due to new treatment guidelines introduced in February (Sweden) and March (Norway) 2015, which recommended treatment with the fixed combination of ledipasvir plus sofosbuvir. Thus, these guidelines recommended NS5A inhibitor-based regimens for previous treatment failures of boceprevir/telaprevir, without regard to baseline resistance analysis. Of note, the only patient in the control group with Q80K at baseline that failed treatment was one out of four patients with such RAS that were treated with simeprevir plus sofosbuvir (i.e., SVR 75%). Furthermore, the single patient with baseline R155K that underwent simeprevir plus sofosbuvir treatment in the control group also failed to attain SVR.

Our study also indicated that baseline resistance analysis may have an impact on treatment outcome in patients with liver cirrhosis, but the difference was not statistically significant, possibly due to the low prevalence of baseline NS3 and NS5A RASs.

Currently, the NS3 inhibitor simeprevir is no longer in use due to the development of more effective DAA treatment regimens. As a result, the focus has switched to study baseline NS5A RASs in predicting the most effective DAA combination and treatment duration [11]. Since 2016, NS5A baseline resistance analysis is mainly recommended before treatment of GT 1a with the NS5A inhibitor elbasvir, co-formulated with the NS3 inhibitor grazoprevir. However, it is also recommended to consider baseline analysis of the NS5A RASs for treatment-experienced GT 1a patients prior to treatment with ledipasvir plus sofosbuvir [17,18]. Therefore, it was relevant for this study, when conducted in 2015, to include also baseline NS5A analysis.

Although we cannot report any significant effect on baseline Q80K/R155K and NS5A resistance analyses on the treatment outcome, baseline resistance testing could have economic implications. However, today's considerably lower drug expenditures per patient combined with recommended regimens that are less dependent on the preexisting RASs addressed in this study, made our economic calculations somewhat obsolete.

In clinical practice, the impact of HCV RASs will probably become less important with the availability of new effective DAAs. However, drug resistance can be a problem in the context of other negative predictors for treatment response like the presence of cirrhosis, suboptimal treatment duration and prior treatment [8,11], and new emerging mutations in the highly variable HCV genome may affect the current high SVR rates. It could be noted that the Q80K RAS was the most commonly observed baseline NS3 variant in the few failures in the POLARIS-2 trial [26]. In patients with GT 1a treated with the pan-genotypic NS3 protease inhibitor voxilaprevir combined with sofosbuvir plus velpatasvir for eight weeks, the SVR rate was lower in patients with baseline Q80K compared to patients without (88 and 94%, respectively) [26].

Conclusion

We found a low prevalence of NS3 Q80K RAS in HCV GT 1a in Norway and Sweden. In this real-life study, baseline resistance analyses for NS3 RAS (Q80K and R155K) and clinically relevant NS5A RASs could not statistically determine the treatment outcome, probably due to small sample sizes. Liver cirrhosis was the most important predictor of treatment failure. However, the results indicate an adverse effect of RAS Q80K preexistence on the treatment outcome with simeprevir plus sofosbuvir, findings that were published in the OPTIMIST-2 trial in 2016. Furthermore, the results are in line with the recommendations by EASL in 2016 that NS5A RASs at baseline appeared to have an impact on ledipasvir plus sofosbuvir treatment outcome. Personalized treatment with regard to baseline resistance analyses could thereby be important to find the most cost-effective treatment combinations/duration, both in a perspective of evidence-based healthcare delivery and in the case of the individual patient to avoid relapse and reducing the retreatment options.

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Paper IV

Effect of the baseline Y93H resistance-associated substitution in HCV genotype 3 for direct-acting antiviral treatment: Real-life experience from a multicenter study in Sweden and Norway

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Running title: Personalized treatment of HCV genotype 3

Abstract

Background: Resistance-associated substitutions (RASs) may impair treatment response to direct-acting antiviral agents (DAAs) in hepatitis C virus treatment. The NS5A RAS Y93H is found quite frequently (5-10 %) at baseline in DAA-treatment-naïve genotype (GT) 3a patients when studied by the population (Sanger) sequencing method with a cut-off of 20%. This RAS possesses a high fold *in vitro* resistance to daclatasvir (DCV) and velpatasvir (VEL) in GT 3. We investigated the effect of baseline Y93H in patients with GT 3a infection on treatment outcome, with or without resistance-based DAA-treatment during 2014-2017.

Patients/Methods: Treatment in the intervention group (n=130 Uppsala and Tromsø) was tailored to baseline resistance-findings by population sequencing method. Detection of baseline Y93H above 20% prompted a prolonged treatment duration of NS5A inhibitor + sofosbuvir (SOF) and/or addition of ribavirin (RBV) at the responsible medical doctor's discretion. Patients without baseline Y93H in the intervention group and all patients in the control group (n=78 Örebro, Falun, Bodø and Stockholm) received recommended standard DAA-treatment.

Results: A higher sustained virologic response rate (SVR) in the intervention group was shown compared to the control group at 95.4% (124/130) and 88.5% (69/78), respectively (*p=0.06*). All five patients with baseline Y93H in the intervention group achieved SVR with personalized treatment based on results from resistance testing; either with the addition of RBV or prolonged treatment duration (24w). In the control group, 2/4 patients with Y93H at baseline treated with ledipasvir+ SOF+ RBV or DCV+ SOF without RBV, failed treatment. Thereby, a trend towards higher SVR rate was found in the intervention group with baseline Y93H compared to the control group (*p=0.07*).

Conclusion: The results from this real-life study are in accordance with the findings of the randomised controlled trials in 2015 and the EASL-guidelines of 2016, thus baseline Y93H impacts on DCV and VEL treatment outcome.

Keywords: baseline resistance, hepatitis C virus, NS5A, Y93H, resistance-associated substitution (RAS), sustained virologic response (SVR)

Introduction

Hepatitis C virus (HCV) infection is considered the leading cause of liver cancer and liver transplantations in the Western world [1]. Worldwide, an estimated 71 million people are living with viraemic HCV infection [2]. In Sweden and Norway, about 0.4 -0.5% of the population is infected with HCV, which approximately relates to 45,000 and 20,000 individuals, respectively [3-5]. HCV is classified into seven genotypes (GT) and >100 subtypes [6]. The most common GT in Sweden is 1a, followed by GT 3a [7], while in Norway GT 3a is the most common, followed by 1a [8].

Recently, HCV treatment has undergone a remarkable change and fixed-dose combinations containing two to three classes of DAAs have replaced the traditional interferon (IFN)-based treatment. The DAAs can be classified into four classes, targeting three non-structural proteins in HCV: NS3/4A protease inhibitors, NS5A inhibitors, and nucleoside and non-nucleoside inhibitors of the RNA-dependent NS5B polymerase [9]. By using the latest approved drug combinations, a complete cure is possible with sustained virologic response (SVR) rates above 95%. Despite this remarkable increase in effectiveness of DAA treatment for HCV infection, the treatment of GT 3 infection has shown lower SVR rates compared to the other GTs [10]. Drug resistance is the main problem when DAAs are employed sub-optimal. Of the 5% of the patients who fail treatment, almost all of these acquire resistance-associated substitutions (RASs), e.g. NS5A RAS with a long half-life [9]. Even treatment-naïve patients could have RASs against currently approved DAAs, i.e. resistance at baseline [10, 11]. Pre-existence of NS5A RASs with high fold resistance, together with other negative factors, such as high fibrosis stage, GT 3, or previous treatment with non-NS5A DAAs, could affect the efficacy of treatment with DAAs [10, 12].

RASs can be detected by Sanger sequencing and next generation sequencing (NGS) methods. The Sanger method carries a 15-20% cut-off level for detecting RAS in the viral population,

compared to 1% with NGS. However, the consensus is to recommend a cut-off level of 10-20% for detecting RASs within the HCV quasispecies, in order to be of clinical relevance in predicting treatment failures [10, 13, 14].

The RAS Y93H, a naturally occurring polymorphism in the viral NS5A region, where one nucleotide substitution in the first position of the codon that in wild type translates to amino acid tyrosine (Y), makes it a histidine (H) at position 93 in the mutant. The Y93H mutation is found quite often (5-10 %) at baseline for DAA-treatment-naïve GT 3a patients with the population sequencing method, i.e. as a dominant variant with >20% frequency within the HCV quasispecies [15]. This RAS possesses a high fold *in vitro* resistance to daclatasvir (DCV) and velpatasvir (VEL) used for treatment of GT 3 infection. In GT 3a replicon assay, the Y93H RAS exhibited >2000 increased fold resistance to DCV and >700 increased fold resistance to velpatasvir VEL [16-18]. Thus, although VEL has improved resistance profile compared to the earlier generations of NS5A inhibitors, it is still prone to high level of resistance by Y93H in GT 3 infection. This was further revealed in clinical studies during 2016. The ALLY-3 study, which evaluated a 12-week treatment with DCV plus sofosbuvir (SOF), showed that 33% without liver cirrhosis and 75% with liver cirrhosis of the GT 3 patients with baseline RAS Y93H failed treatment [19]. In the ASTRAL-3 study, which evaluated 12 weeks of VEL plus SOF treatment, the Y93H mutation was detected at baseline in 9% of patients and the study demonstrated that 4 out of 10 non-SVR patients had Y93H at baseline, and that all these non-SVR patients then had Y93H at relapse [20].

Another NS5A RAS, A30K, is found at a similar level (5-10 %) as a common baseline polymorphism in GT 3 patients. Its *in vitro* resistance in GT 3a replicon assay towards DCV and VEL is in the fold ranges of 50 [16, 17].

At the initiation of this study there were no available guidelines regarding baseline resistance testing. The aim of this real-life study was initially to investigate the impact of Y93H at

baseline on treatment outcome in GT 3 infected patients treated with DAAs, and to evaluate the resulting economic consequences. The A30K RAS was also investigated, but only in the later phases as it was not considered as a clinical relevant RAS in 2014-2015. Known factors influencing treatment outcome were also evaluated. The study was conducted during 2014-2017 when DCV or VEL plus SOF were the recommended treatment regimes.

Material and Methods

Patients and treatment

Patients were consecutively included in this real-life, open label, non-randomised Nordic multicenter study from April 1 2014 to December 31 2017, consisting of an intervention group and a control group. Patients with chronic HCV GT 3a infection from Uppsala and Tromsø received treatment based on the results from resistance testing prior to treatment initiation (intervention group). The control group consisted of patients from Bodø, Falun, Stockholm and Örebro, who received treatment according to national guidelines [21-24] without previous drug resistance testing.

In the intervention group (n=130), treatment was adjusted to baseline resistance findings detected by the population sequencing method. Detection of baseline Y93H prompted either prolonged treatment duration (during 2014-16 DCV plus SOF and during 2017 VEL plus SOF) and/or addition of ribavirin (RBV) at the responsible MD's discretion. At one occasion in 2016, 12 weeks SOF plus pegylated (PEG)-IFN with RBV was used. Patients without baseline Y93H in the intervention group and all patients in the control group (n=78) received recommended standard DAA-treatment according to the National Boards. Note that A30K was not initially implemented in the intervention group as it was an unknown baseline RAS at the start of the study in 2014.

Samples for NS5A resistance analysis in the intervention group were analysed consecutively in routine diagnostics, while samples from the control group were analysed retrospectively.

Resistance analysis for emerging NS5A RAS was performed on all non-SVR patients at the time of relapse in the intervention group and retrospectively for the patients in the control group.

The inclusion criteria were: infection with HCV GT 3a; ≥18 years of age; informed consent; and treatment according to Swedish and Norwegian consensus recommendations. Patients previously treated with SOF plus ribavirin or other DAAs were excluded.

Liver elasticity (kPa) was measured with FibroScan® 502 (Echosens, France) (Swedish study sites) and FibroScan® 402 (Echosens, France) (Norwegian study sites) by experienced nurses or doctors. For patients who had undergone a liver biopsy, the Metavir score was recorded [25]. Presence of cirrhosis was determined by FibroScan >12.5 kPa [26] or Metavir fibrosis score 4 in liver biopsy. The Child-Pugh score was estimated on the basis on available information from clinical examination, biochemical results and ultrasound. Patient data was extracted from the medical records by the responsible MD at each study site, anonymised and transferred to a joint database.

SVR was defined as undetectable HCV RNA 12 weeks after the end of treatment. Non-SVR was regarded as either viral breakthrough (a negative viral load nadir followed by a positive HCV RNA level during therapy), non-response (increase in HCV RNA levels after initial decrease during treatment), or viral relapse (non-detectable viral load at the end of treatment followed by an increase in HCV RNA-level beyond therapy).

The primary objective was to study the treatment efficacy in the intervention group compared to the control group, with respect to the proportion of patients achieving SVR. Secondary objectives included to determine: (1) the proportion of patients with NS5A baseline Y93H and

A30K RASs; (2) the proportion of patients with these baseline NS5A RASs experiencing viral breakthrough or relapse; (3) the proportion of patients with baseline NS5A RASs not experiencing viral breakthrough or relapse; and (4) to compare total expenditures (treatment and baseline analysis costs) per capita in the two study groups.

Laboratory methods

Resistance testing of RASs (baseline and emerging) was performed at the Department of Clinical Microbiology at Akademiska Hospital, Uppsala and was performed on all available samples at baseline, i.e. on samples collected prior to treatment initiation and at treatment failure. Viral gene from patient samples was amplified by the Nested PCR method and then sequenced by the Sanger sequencing method (population sequencing). This pan-genotypic NS5A resistance analysis protocol has been published previously [27]. In brief, RNA extraction from plasma samples was done using NucliSENS® easyMAG™ system (BioMérieux, Marcy-l'Étoile, France). cDNA was synthesized from RNA template with SuperScript™ III Reverse Transcriptase (Invitrogen™, Thermo Fisher, Waltham, MA; USA) using random hexamers. First round PCR and nested PCR were performed with in-house primers targeting parts of the NS5A-regions using the *Taq* PCR Master Mix (QIAgen, Hilden, Germany). The amplicons were verified by agarose-gel electrophoresis. PCR-positive samples and were purified using QIAquick® PCR Purification Kit (QIAgen, Hilden, Germany) before they were sent for sequencing.

The first two rounds of PCR amplification protocols preceding the sequencing step were revised on samples included in this study as of February 2017. cDNA synthesis and first round of PCR was done using Takara PrimeScript™ One Step RT-PCR Kit Ver.2 (Takara BIO Inc, Kusatsu, Shiga prefecture, Japan). Nested PCR was performed as previously. The nested PCR products were verified by e-Gel® 2% agarose electrophoresis (Invitrogen,

ThermoFischer Scientific, Waltham, MA, USA). Samples were purified before sequencing using ExoSAP-IT™ (Applied Biosystems™, ThermoFischer Scientific, Waltham, MA, USA).

The purified products were, at the start of this study, sent to the Uppsala Genome Center and as of Q3 2017 to EurofinsGenomics, Ebersberg, Germany for capillary electrophoresis (Sanger) sequencing, at both sites, on 3730xl DNA Analyzer (Applied Biosystems™, ThermoFischer Scientific, Waltham, MA, USA) using the same primer pair used in the nested PCR.

Sequence analysis

Population-based sequencing generates a consensus sequence of the viral quasispecies with a sensitivity of approximately 20% for (minority) variants, recognized as mixed peaks in the electropherogram. NS5A sequence results were aligned and analysed using SeqScape® Software v2.6 (Applied Biosystems™, Thermo Fisher Scientific, Waltham, MA, USA) to generate consensus sequences. The NS5A sequence of HCV GT1a H77 strain (accession number: NC_004102.1) was used as a reference template to which the sample sequences were aligned. To simplify, we considered this reference GT 1a template suitable for GT 3 as described in a previous report [7].

To detect relevant substitutions and evaluate their implications, the consensus sequences were submitted in the web-based mutation detection algorithm, Geno2Pheno [hcv] 0.92 (G2P) [28]. Substitutions scored by G2P were further interpreted as clinically relevant RASs by relating scores with EASL guidelines 2016 and 2018, in addition to RASs reported to bear impact on DAA treatment outcome *in vitro* and/or *in vivo* in literatures [10, 18, 29]. In this study, the NS5A RASs Y93H and A30K were defined as relevant for GT3 as reported in the literature [14].

HCV-RNA quantification of the patient samples was performed at the Department of Clinical Microbiology at Uppsala Akademiska Hospital (2014-2017: COBAS® AmpliPrep/TaqMan® HCVQuantitative Test (Roche, Basel, Switzerland), v2.0 with a LOQ of 15 IU/mL and 2017 onwards Abbott m2000 HCV Viral Load Assay (Abbott Laboratories, Chicago, IL, USA) with a LOQ of 12 IU/mL.) and at the Department of Microbiology, University Hospital of North Norway, Tromsø, Norway (ROCHE RT-PCR (Cobas Amplicor Hepatitis C Viral Polymerase Chain Reaction, Roche Molecular System Inc., Branchburg NJ, USA)). All protocols used were performed according to the manufacturer's instructions.

Statistics

The null hypothesis of this study was that the SVR12 rate was equal in the intervention and control groups. The basic statistical computing was done in Microsoft® Excel® 2013 (Microsoft Office professional plus 2013, Microsoft Corporation) and in Statistical Package for Societal Sciences, version 24 (IBM Corp., Armonk, N.Y., USA). The Chi-square-test was used to test the differences between groups (or Fishers exact test if expected cell count was small). A two-tailed p-value <0.05 was considered significant.

Ethics

The protocol of this multicentre study was in compliance with the Helsinki Declaration. The regional committee of medical research ethics, Committee in Uppsala (Dnr: 2013/185, Dnr: 2013/185/1 and Dnr: 2013/185/2) and the Data Protection Official at The University Hospital of Northern Norway (Nr. 0574) approved this study. All participants received written information and the opportunity to withdraw from this study.

Results

Patient baseline characteristics

In total, 226 patients with HCV GT3, 141 in the intervention group and 85 in the control group were assessed to be eligible for the study. Eleven patients from the intervention group were omitted from further analyses: one refrained from participation, one was re-infected with GT 1a, two were lost to follow-up, two could not give informed consent, and baseline resistance results could not be obtained from five of the patients. In the control group, seven patients were omitted; one deceased before SVR and six had no results from baseline resistance analysis. Thus, week 12 follow-up data were obtained from 208 patients; 130 in the intervention group and 78 in the control group (Figure 1).

Detailed demographic and baseline clinical characteristics are described in Table 1. Most patients were men, 73.1% (95/130) and 66.7% (52/78) in the intervention and control groups, respectively, and the majority was treatment-naïve to previous PEG-IFN/RBV regimen, 76.9% (100/130) and 59.0% (46/78) in the intervention and control groups, respectively. Amongst the patients who were PEG-IFN/RBV treatment-experienced, 77.4% (24/31) in the control group had relapsed compared to 60.7% (17/28) in the intervention group. The median age at start of treatment was 55 and 52 in the intervention and control groups, respectively. The distribution of patients with cirrhosis was 37.7% (49/130) and 61.5% (48/78) in the intervention and control groups, respectively. Median viral load at start of treatment was similar in both groups.

Most cirrhotic patients in both groups were Child-Pugh class A (data not shown).

Table 2 describes treatment characteristics. The distribution and variety of treatment regimens were higher in the intervention group. While the great majority of the patients in the control group were administered DCV plus SOF (93.6%, 73/78), the remaining were administered with ledipasvir (LED) plus SOF. Patients in the intervention group, on the other hand, were

treated with a greater variety of treatment regimens; 47.7% (62/130) were treated with DCV plus SOF, 10.0% (13/130) were treated with LED plus SOF, and furthermore, only patients in the intervention group were treated with VEL plus SOF (41.5%, 54/130). Of the patients on VEL plus SOF-treatment, 29.6% (16/54) also had RBV included in the treatment regime (data not shown). Most of the patients in both groups received treatment for 12 weeks, but it was more common in the intervention group compared to the control group, 76.9% (100/130) and 53.8% (42/78), respectively ($p<0.001$). Simultaneous prolonged treatment of 24 weeks and addition of RBV was administered to 32.1% (25/78) in the control group compared to only 3.8% (5/130) in the intervention group (data not shown).

Baseline RASs

The prevalence of baseline Y93H RAS was similar in both the intervention and control groups; 3.8% (5/130) and 5.1% (4/78), respectively, and baseline A30K prevalence was 3.8% (5/130) and 2.6% (2/78), respectively. The prevalence of baseline Y93H in terms of country/cohort was also similar with 4.9% (6/122) and 3.5% (3/86) in the Swedish and Norwegian cohorts, respectively (Table 3/data not shown). In contrast, only one baseline A30K was found in the Swedish cohort as all the other A30K was found in the Norwegian patients, 0.8 % (1/122) and 7.0% (6/86), respectively. Detailed description of clinical characteristics of the patients harbouring baseline RASs A30K and Y93H are summarised in Table 3.

Of the five patients with baseline A30K in the intervention group, one was detected in a patient who subsequently relapsed. In the control group, prevalence of A30K was lower but found in one of the two patients who relapsed.

All five patients with baseline Y93H in the intervention group achieved SVR with treatment based on results from the resistance testing. These patients were treated with either 24 weeks

DCV or LED plus SOF treatment without RBV, 12 weeks VEL plus SOF with RBV, or 12 weeks SOF plus PEG-IFN with RBV.

One patient with A30K in the intervention group did not have the treatment adjusted since the A30K was not considered a clinically relevant NS5A RAS at the time of start of treatment in 2014 (and during 2015). This patient was treated 12 weeks with DCV plus SOF but subsequently failed and relapsed.

In the control group, 50.0% (2/4) patients with Y93H at baseline treated with 12 weeks of either LED plus SOF plus RBV or DCV plus SOF without RBV failed treatment and relapsed. The patient who failed LED plus SOF treatment harboured Y93H (Table 4).

In total, 15 patients failed to achieve SVR12. The main reason for non-SVR was viral relapse, however, in two patients viral breakthrough ensued, and one patient was non-responding. In three of these patients, one A30K and two Y93H were detected at baseline in the control group. One A30K was detected in the intervention group (Table 4).

SVR12 rates

SVR12 rates were consistently higher in the intervention group compared to the control group (Figure 2). The most distinct differences between the intervention and control groups are: (1) an overall SVR rate of 95.4% (124/130) and 88.5% (69/78), respectively *(p=0.06*); (2) a SVR rate in patients with baseline Y93H of 100% (5/5) and 50% (2/4), respectively (*p=0.07*); and (3) a SVR rate in 12-week treatment of 98% (98/100) and 90.2% (38/42), respectively (*p=0.04*).

Of the patients in the intervention group who received a 12-week treatment and relapsed, one was treatment-naïve and non-cirrhotic but harbored baseline A30K, and another had cirrhosis but did not have any baseline RAS but had failed previous treatment history with PEG-IFN/RBV. Neither had RBV added to their regimens with DCV plus SOF. In the control

group, 4/42 failed 12-week treatment regimens. All were male and had previous treatment history with PEG-IFN/RBV; three had relapsed and one was non-responding. Three were cirrhotic and had 12 weeks of DCV plus SOF and RBV. One was non-cirrhotic and did not receive RBV. Subsequent analyses for presence of baseline RAS showed that one of them had A30K at baseline (Table 4).

Discussion

This Nordic multicenter study from April 2014 to December 2017 was performed when data on optimal regimens were emerging and guidelines were rapidly changing. For GT 3 treatment, the EASL guidelines recommended DCV plus SOF during 2014– 2015 and a change to VEL plus SOF in 2016– 2017. Thereby, this study was conducted prior to recent approved (in Sweden Jan 2018 and in Norway February 2018) medications (glecaprevir (GLE) plus pibrentasvir (PIB) and VEL plus SOF plus voxilaprevir (VOX)). These regimens have greatly improved the SVR rates, even for GT 3 in presence of NS5A RASs. This is mainly due to the inclusion of GLE or VOX, which are effective NS3 protease inhibitors against GT 3.

When we started this real-life study, the knowledge on outcome of baseline NS5A RAS in GT 3 treatment was very limited. However, we suspected that the most clinically relevant RAS in GT 3 should be Y93H, which according to *in vitro* data from the literature confers a high level of resistance to DCV and VEL, where the fold-change values in resistance compared to GT 3a wild type replicon are 2100 and 700 fold, respectively [16, 17]. In the ALLY-3 and the ASTRAL-3 clinical studies, it was later shown that the Y93H in GT 3 was associated with lower SVR rates to treatment with DCV plus SOF and VEL plus SOF, especially in cirrhosis patients with baseline Y93H [19, 20]. Furthermore, the natural prevalence of Y93H is as high

as 5-10% in GT 3 patients with no prior exposure to NS5A treatment [10]. Thereby, since September 2016 it is stated in the EASL guidelines that physicians who have easy access to reliable resistance tests can use baseline testing of Y93H in GT 3 patients to guide their decisions prior to treatment with VEL plus SOF [14, 30]. In case of baseline Y93H findings, these guidelines recommend the addition of RBV and/or extended treatment duration, which were actually the same recommendations (during 2014 -2017) for retreatment of GT 3 patients with previous NS5A DAA-failure. In the recent report from the surveillance system against Antivirals in Norway (RAVN), resistance testing of Y93H at baseline is recommended in patients with GT 3 and cirrhosis [31].

It was therefore relevant for the study group, as early as 2014, to evaluate treatment outcome based on baseline analysis of Y93H. As displayed in Table 3, all five patients with baseline Y93H in the intervention group achieved SVR with personalized resistance-based treatment. In the control group, 2/4 patients with Y93H at baseline, one treated for 12 weeks with LED plus SOF and the other with DCV plus SOF, failed treatment. Thereby, Y93H appeared to have a negative impact on treatment outcome ($p=0.073$). However, because of the limited sample sizes and low prevalence of baseline Y93H this could not be statistically determined.

In our study, an overall higher SVR was shown in the intervention group compared to the control group with values at 95.4% (124/130) and 88.5% (69/78), respectively ($p=0.06$). However, there could be several confounding factors for the results in the intervention group compared to the control group. As shown in Table 1, some known negative predictors for SVR outcome were found in the control group compared to the intervention group in terms of the proportion of treatment naive patients (59.0% versus 76.9%), and more patients with cirrhosis (61.5% versus 37.7%). However, negative factors were also found in the intervention group, which had a higher rate of male patients; 73.1% compared to 66.7 % in the control group, and a lower proportion of patients receiving 24 weeks of treatment; 9.2%

compared to 35.9% in the control group. In addition, the newer treatment regimen VEL plus SOF was used in the intervention group (41.5%) and not at all in the control group. However, it has been shown in a recent large real-life study of 2824 GT 3 patients that the chance of obtaining SVR was the same irrespective of whether a patient received DCV plus SOF or VEL plus SOF [32]. It should also be noted that a few patients in our study, thirteen in the intervention group and five in the control group, were prescribed LED plus SOF. This was done in 2014 and early 2015, before DCV was available in Norway. At this time, it was actually not known that LED is less potent against GT 3 than DCV and VEL [14]. Despite the many dissimilarities between the intervention and control groups, still higher SVR rates for the intervention groups than for controls were found for all different parameters displayed in Figure 2.

The NS5A RAS A30K exists as a polymorphism in GT 3 in the same prevalence range 5-10% as Y93H. This RAS in GT 3a replicon assay confers resistance levels of 44 fold to DCV and 50 fold to VEL [16, 17]. Even though these resistance levels are lower than for Y93H, it could be a negative factor in patients who are difficult to treat, e.g. with severe cirrhosis. Combination of HCV RASs can often confer greater level of phenotypic resistance, however, we did not detect the combination of A30K and Y93H, neither at baseline or at treatment failure, which is in accordance with a recent report [33]. At the beginning of our study during 2014-2015, the RAS A30K was not considered a clinically relevant NS5A RAS but during 2016 the intervention group had its regimen tailored to this baseline RAS. It could be noted that a clinical study of the recently approved GLE plus PIB treatment suggests a negative effect of baseline A30K. In treatment-experienced (PEG-IFN or SOF) GT 3 patients without cirrhosis who received 12 weeks of GLE plus PIB treatment, significant lower SVR rate (25%) was observed for those patients with A30K at baseline, compared to those without A30K at baseline (SVR 96%) [34].

In 2014- 2016, the cost of DCV plus SOF treatment for 12 weeks was >0.5 M NOK/SEK. Baseline Y93H RAS was detected retrospectively in two patients who experienced virologic relapse after treatment with DCV or LED plus SOF. Switching these two patients to a prolonged NS5A inhibitor-based regimen (or in the case of LED to prolonged DCV) and/or addition of RBV could possibly have reduced treatment costs, and in addition, contributed to a "best practice" approach. Thus, in the control group there was an economical loss of >1 M NOK/SEK compared to the intervention group were no patients with Y93H at baseline experienced non-SVR. In comparison, the baseline analysis costs (2000 NOK/SEK per analysis) for the 130 patients in the intervention group were less than 0.3 M NOK/SEK.

The current Swedish and Norwegian recommendations for first-line treatment of treatment-naive GT 3 patients is, due to cost-effectiveness considerations, still VEL plus SOF [24, 35].

Conclusion

In this real-life study conducted in Q2 2014 to Q4 2017, we found a low prevalence of baseline Y93H RAS in HCV genotype 3 in Sweden and Norway. Even though a trend was observed for Y93H being a negative predictor for DCV plus SOF or VEL plus SOF treatment outcome (*p=0.07*), it could not be statistically determined, probably due to the small sample sizes. However, the findings are in line with the randomised controlled trials (ALLY-3 and ASTRAL-3) and the EASL-guidelines of 2016 and 2018. This could therefore have positive implications for the latest approved regimes, GLE plus PIB and VEL plus SOF plus VOX, combinations that are known to be more potent against Y93H. However, these regimes often are more expensive than VEL plus SOF and mainly considered as retreatment options. Since the resistance analysis cost per individual, even today, is 20-50 fold lower than the cost of current DAA-treatment, selection of cost-effective treatment combinations/duration should

still be of importance, both in a perspective of evidence-based healthcare delivery, resistance-surveillance, and for the individual patient to avoid relapse with uncertain retreatment options.

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Table 1. Baseline characteristics.

	Intervention group (n= 130)	**Control group (n=78)**	*p*
Median age, yr. (range)	**55 (22-77)**	**52 (25 – 67)**	
Male, n (%)	**95 (73.1)**	**52 (66.7)**	**0.3**
Cirrhosis, n (%)	**49 (37.7)**	**48 (61.5)**	**0.001**
Median HCV RNA, log_{10} IU/mL (range)	**6,1 (3.2 – 7.9)**	**6,0 (4.3 – 7.2)**	
Beseline Y93H (%)	**5 (3.8)**	**4 (5.1)**	**0.7**
Baseline A30K (%)	**5 (3.8)**	**2 (2.6)**	**0.6**
Previous HCV treatment[1], n (%)			
Treatment- naïve	**100 (76.9)**	**46 (59.0)**	**0.006**
Non-responder	**1 (0.8)**	**4 (5.1)**	
Partial responder	**6 (4.6)**	**2 (2.6)**	
Relapse	**17 (13.1)**	**24 (30.8)**	**0.002**
Intolerant	**4 (3.1)**	**1 (1.3)**	
NA	**2 (1.5)**	**1 (1.3)**	

[1]Treatment referring pegylated interferon (PEG-IFN) plus ribavirin
NA= Not available

Table 2. Treatment characteristics.

	Intervention group (n= 130)	**Control group (n=78)**	*p*
Treatment regime, n (%)			
Daclatasvir+sofosbuvir	**62 (47.7)**	**73 (93.6)**	**$2.0*10^{-11}$**
Velpatasvir+sofosbuvir	**54 (41.5)**	**-**	
Ledipasvir+sofosbuvir	**13 (10.0)**	**5 (6.4)**	**0.4**
Sofosbuvir+PEG-IFN+ribavirin	**1 (0.8)**	**-**	
Treatment duration, wk.			
4wk[1]	**1 (0.8)**		
8wk	**1 (0.8)**	**-**	
12wk	**100 (76.9)**	**42 (53.8)**	**0.0005**
16wk	**13 (10.0)**	**8 (10.3)**	
20wk	**3 (2.3)**	**-**	
24wk	**12 (9.2)**	**28 (35.9)**	**$2.0*10^{-6}$**
Addition of ribavirin, n (%)	**50 (38.5)**	**54 (69.2)**	**$2.0*10^{-5}$**

[1]Treatment was discontinued in one patient due to non-response.

Table 3. Clinical and treatment characteristics in patients with baseline A30K and Y93H RASs

Sex	Age	Study Group	Nationality	Metavir score (Child Pugh)	FibroScan (kPa)	Cirrhosis	Treatment	Previous treatment response with PEG-IFN/RBV	Baseline viral load log_{10}(IU/ml)	SVR	Ribavirin	Treatment duration (wk)
Baseline RAS A30K												
M	52	C	NO	(A)	NA	Yes	DCV/SOF	N	5.6	No	No	12
M	53	C	SE	NA	NA	Yes	DCV/SOF	N	4.6	Yes	Yes	24
F	54	I	NO	NA	8	No	DCV/SOF	N	6.4	No	No	12
M	65	I	NO	NA	12.4	Yes	VEL/SOF	N	6.2	Yes	Yes	12
M	30	I	NO	4 (A)	16	Yes	VEL/SOF	N	6.8	Yes	Yes	12
M	47	I	NO	NA	11.8	No	VEL/SOF	N	6.7	Yes	Yes	12
M	54	I	NO	NA	10	No	VEL/SOF	N	4.7	Yes	Yes	12
Baseline RAS Y93H												
M	49	C	SE	6 (A)	NA	Yes	DCV/SOF	Intolerant	5.0	Yes	Yes	24
F	63	C	SE	5	4.8	No	LED/SOF	NR	5.7	No	Yes	16
M	55	C	SE	4 (B)	NA	Yes	DCV/SOF	N	6.3	No	No	24
F	51	C	SE	(A)	14.3	Yes	DCV/SOF	N	6.3	Yes	Yes	12
F	58	I	NO	3 (A)	NA	Yes	SOF/PEG-IFN	PR	6.1	Yes	Yes	12
M	58	I	NO	NA	11.6	No	VEL/SOF	N	6.5	Yes	Yes	12
M	55	I	NO	NA	6.8	No	VEL/SOF	N	6.9	Yes	Yes	12
M	62	I	SE	NA	1.8	No	LED/SOF	N	5.7	Yes	No	24
M	49	I	SE	A	13.4	Yes	DCV/SOF	N	ND	Yes	No	24

6/7 (85.7%) patients with baseline A30K are from the Norwegian cohort.

3/9 (33.3 %) patients with baseline Y93H are from the Norwegian cohort.

Distribution of the cohorts regarding nationality in the intervention and control groups are 57.7% Norwegians versus 42.3% Swedish and 14.1% Norwegians versus 85.9% Swedish, respectively.

Table 4. Clinical characteristics, baseline, and emerging NS5A RASs in the non-SVR patients.

Sex	Age (yr)	Study group	Cirrhosis	Metavir (Child Pugh score)	Fibro Scan (kPa)	Treatment	Previous treatment response with PEG-IFN/ RBV	Baseline viral load, log_{10} (IU/ml)	Baseline RAS(s)	RAS(s) at relapse	Ribavirin	Treatment time (wk)
M	52	C	Yes	A	NA	DCV/SOF	N	5.6	A30K	ND	No	12
M	53	C	Yes	5(A)	NA	DCV/SOF	N	5.9	0	Y93H	No	16
M	63	C	Yes	5(A)	NA	DCV/SOF	RR	6.2	0	Y93H	Yes	12
M	56	C	Yes	6	39.7	DCV/SOF	N	5.8	0	NA	Yes	24
M	53	C	Yes	9	NA	DCV/SOF	N	6.3	0	Y93H	Yes	24
F	63	C	No	5	4.8	LED/SOF	N	5.7	Y93H	Y93H	Yes	16
M	55	C	Yes	4(B)	NA	DCV/SOF	N	6.3	Y93H	Y93H	No	24
M	53	C	No	NA	9.2	DCV/SOF	NR	6.3	0	Y93H	No	12
M	43	C	Yes	A	23.1	DCV/SOF	RR	6.5	0	Y93H	Yes	12
M	59	I	Yes	3(A)	NA	DCV/SOF	PR	6.7	0	Y93H	Yes	20
F	54	I	No	NA	8.0	DCV/SOF	N	6.4	A30K	A30K	No	12
M	58	I	Yes	A	22.8	DCV/SOF	RR	5.4	0	Y93H	No	12
M	55	I	Yes	A	48.0	LED/SOF	N	7.0	0	0	Yes	NR v16 (Sched. 24)
M	60	I	Yes	B	73.0	DCV/SOF	N	5.5	0	Y93H	No	VB v4 (Sched.16)
F	58	I	No	NA	11.1	VEL/SOF	NA	4.6	0	0	No	VB v4 (Sched.12)

Abbreviations: C= control group; DCV= Daclatasvir; F= female; I= intervention group; LED= Ledipasvir; M= male; N= naive; ND= not done; NO= Norway; NR= non-responder; PR= partial responder; RBV= ribavirin, R= relapse; SE= Sweden; SOF= Sofosbuvir; SVR= sustained virologic response; VB= viral breakthrough; VEL= Velpatasvir

Figure 1. **Flowchart of patients included in the study.**

Baseline resistance testing in the control group was performed retrospectively.

Figure 1.

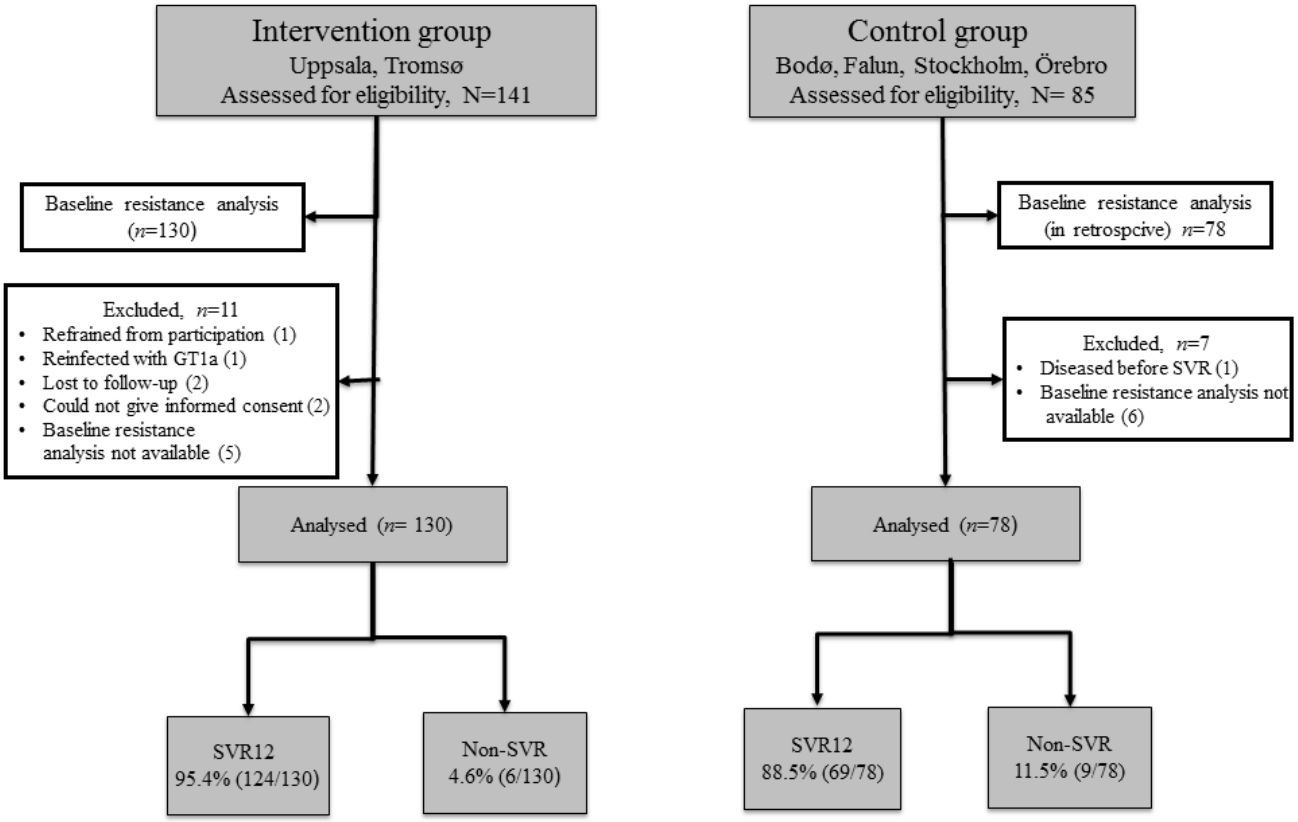
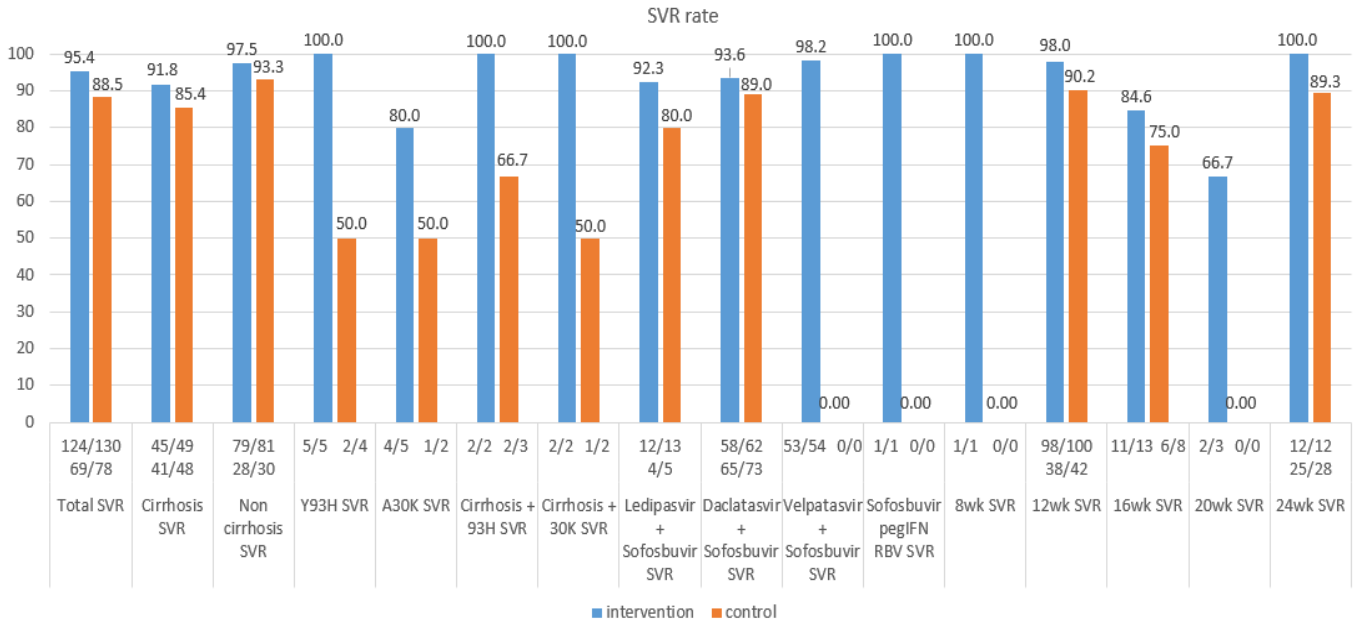


Figure 2. Sustained virologic response rates (SVR) in the intervention and control groups.

SVR rates in the intervention group (blue bars) and the control group (orange bars).



Appendix

Information brochure and questionnaires Tromsø 7

UiT

NORGES
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Vil du være med i **Tromsøundersøkelsen?**

UNIVERSITETET I TROMSØ

Forespørsel om deltakelse i Tromsøundersøkelsen

Hva er Tromsøundersøkelsen?

Tromsøundersøkelsen er en folkehelseundersøkelse. Formålet er å samle inn opplysninger til forskning som gir økt kunnskap om helse og sykdom, og hvordan folkehelsen kan forbedres gjennom forebygging og behandling.

Tromsøundersøkelsen startet i 1974 med bakgrunn i den høye forekomsten av hjerte -og karsykdom i Nord-Norge. Siden den gang er undersøkelsen gjennomført med 6-7 års mellomrom og dette er den sjuende runden.

Ved å delta bidrar du til viktig forskning om forekomst, forebygging og behandling av sykdom, hva som fremmer god helse, og hva som er årsak til helseproblemer.

Ditt bidrag teller!

Hvorfor spør vi deg?

Alle innbyggere i Tromsø kommune fra 40 år og oppover spørres om å delta. I tillegg inviterer vi ca.1000 personer i alderen 21-25 år. Hver deltaker er like viktig, enten du er ung eller gammel, frisk eller syk.

Sammen med denne informasjonsbrosjyren finner du en invitasjon med praktiske opplysninger om undersøkelsen.

Det er gratis å delta i Tromsøundersøkelsen. Trenger du videre undersøkelse eller oppfølging av fastlegen eller spesialisthelsetjenesten, betaler du vanlig egenandel.

Slik foregår undersøkelsen

Alle deltakere inviteres til en hovedundersøkelse som omfatter spørreskjema, intervju, blodprøver og undersøkelser. Et helt tilfeldig utvalg av deltakere inviteres tilbake til en spesialundersøkelse som omfatter flere prøver og mer omfattende undersøkelser. Alle undersøkelsene gjennomføres av helsepersonell.

Tilbakemelding

Noen uker etter undersøkelsen får du et brev med noen resultater, det vil si høyde, vekt, BMI, hemoglobin, blodtrykk, kolesterolnivå og om du har diabetes. Det gis ikke rutinemessig tilbakemelding om resultater av andre blodprøver eller målinger. Dersom prøveresultatet viser at det er nødvendig med oppfølging av lege eller henvisning til spesialist, vil du få råd om det. Ved behov for henvisning til spesialist, sørger vi for å sende henvisning.

Du kan reservere deg mot å få vite resultatene av prøvene dine. Men hvis et prøveresultat krever rask legebehandling, vil du likevel bli kontaktet.

Du vil også få informasjon om undersøkelsen underveis gjennom aviser, sosiale medier (Facebook, Twitter m.m) samt på arrangementer som "Lørdagsuniversitetet" og "Forskningsdagene".

Frivillig deltakelse

Det er frivillig å delta i Tromsøundersøkelsen.
Om du sier ja til å delta, kan du når som helst trekke tilbake samtykket.

Hva omfatter den sjuende Tromsøundersøkelsen?

Hva skal vi forske på?

I denne runden av Tromsøundersøkelsen er det mer enn 50 prosjekter som skal forske på forekomst, forebygging og behandling av folkehelseproblemer.

Det skal blant annet forskes på hjerte- og karsykdommer, kreft, lunge-sykdommer, aldring og demens, fedme, diabetes, legemiddelbruk, psykisk helse, kronisk smerte, tannhelse, muskel- og skjelettplager, risikofaktorer som alkohol, fysisk aktivitet og kosthold, nyrer og urinveier, hudproblemer, miljøgifter, infeksjoner og antibiotikaresistens, nervesystemet, sosial ulikhet, samspill mellom arv og miljø, søvn og bruk av helsetjenester.

Du finner mer informasjon om forskningen på vår internettside, www.tromsoundersokelsen.no

Spørreskjema

Deltakernes informasjon om egen helse er en svært viktig del av Tromsø-undersøkelsen. Vi ber deg derfor fylle ut to spørreskjema. Alle spørsmål kan besvares på nett. Det ene skjemaet er vedlagt i papirform, hvis du foretrekker det. Fyll det gjerne ut før du møter opp så sparer du tid under undersøkelsen. Hvis du trenger assistanse vil personalet hjelpe deg på undersøkelsen hvor det også er satt opp egne datamaskiner til dette.

Utfylte svar i spørreskjema er like viktig for forskningen som resultater fra blodprøver og kliniske undersøkelser.

Du kan delta på Tromsøundersøkelsen selv om du ikke ønsker å være med på alle deler av undersøkelsen.

Hovedundersøkelsen

Helsepersonell veileder deg gjennom undersøkelsen som varer ca. en time hvis du har fylt ut spørreskjemaene på forhånd. Du får også time til spesialundersøkelsen hvis du er valgt ut til denne.

Vi starter med noen enkle spørsmål knyttet til undersøkelsene du skal gjennomføre. Videre måler vi høyde, vekt, hofte- og livvidde, blodtrykk og puls.

Det tas deretter prøver og gjøres noen kliniske undersøkelser:

Blodprøve. Det tas blodprøver til bruk for forskning som samlet er mye mindre enn det en blodgiver gir. Det fryses ned prøver til bruk for senere analyser og forskning. Arvestoff (DNA/RNA) vil bli lagret til bruk for forskning.

Bakterieprøve fra nese og hals for å se etter gule stafylokokker, en bakterie som normalt finnes på hud og slimhinner hos mennesker, men som i enkelte tilfeller kan forårsake alvorlige infeksjoner. Prøvene tas med en fuktet vattpensel.

Spyttprøver til bruk for forskning knyttet til tannhelse, virusinfeksjon og kreft.

Smerteølsomhet måles med to metoder. Først holder du hånden i kaldt vann i opptil 90 sekunder,deretter får du en blodtrykksmansjett plassert rundt leggen som blåses opp. Underveis angir du hvor mye smerte du opplever, og kan avbryte testene når som helst hvis det blir for ubehagelig.

Tannsjekk som omfatter et røntgenbilde av kjeven, registrering av hull i tennene og betennelsessykdom i tannkjøttet.

Fysisk aktivitet og kosthold. Utvalgte deltakere blir bedt om å registrere fysisk aktivitet ved bruk av aktivitetsmåler og registrering av kosthold i en periode.

Du får også utdelt utstyr for innlevering av urin- og avføringsprøve hvis du er valgt ut til spesialundersøkelsen.

Spesialundersøkelsen

Et tilfeldig utvalg av deltakere inviteres til spesialundersøkelsen som gjennomføres noen uker etter hovedundersøkelsen. Denne varer totalt ca. 2 timer, avhengig av hvor mange deler du blir spurt om å være med på.

Ved oppmøte vil urinprøvene samles inn, og det tas noen nye blodprøver. Deler av blodprøvene fryses ned for senere forskning beskrevet i denne brosjyren.

Videre inviteres du til én eller flere av disse undersøkelsene:

EKG er en registrering av hjerterytmen som også kan gi informasjon om hjertesykdom. Ved registrering festes ledninger til kroppen.

Kognitiv funksjon testes ved hjelp av enkle spørsmål knyttet til gjenkjenning av ord, kopling av symboler og tall samt grad av fingerbevegelighet.

Fysisk funksjon undersøkes ved å teste balanse, gange og gripestyrke.

Ultralyd av halspulsåre gjøres for å se etter forkalkninger og innsnevringer av årene. Undersøkelsen kartlegger også blodforsyningen til hjernen.

Fotografering av øyebunnen gir bilder som både sier noe om synet og om tilstanden til blodkarene i kroppen. Det gis en øyendråpe i hvert øye en tid før fotografering for at pupillene skal utvide seg. Dette kan svi noe og synet kan forbigående bli noe uklart. Effekten går gradvis over, og er borte etter en time. I tillegg gjøres det en enkel synstest som du får svar på umiddelbart.

Lungefunksjonen testes ved at du puster så hardt du klarer gjennom et munnstykke. Hvor mye luft som blåses ut pr. sekund, er et mål på lungefunksjonen din. I tillegg vil det gjøres lydopptak av lungelyder og hjertelyder.

Måling av beintetthet. Ved hjelp av ultralyd foretas det beintetthetsmåling som brukes til å undersøke risiko for beinskjørhet og brudd.

Ultralyd av hjertet gjøres for å undersøke hjertets form og funksjon.

Videre bruk av opplysninger og prøver i forskning

Personvern

All informasjon du gir til Tromsøundersøkelsen behandles med respekt for personvern og privatliv, og i samsvar med lover og forskrifter.
Alle medarbeidere som jobber med undersøkelsen har taushetsplikt. Opplysningene som samles inn skal bare brukes til godkjente forskningsformål. Det vil ikke være mulig å identifisere deg når resultatene av forskningen publiseres.

UiT Norges arktiske universitet ved universitetsdirektøren er ansvarlig for behandlingen av personopplysninger. Tromsøundersøkelsen har konsesjon fra Datatilsynet. Regional komité for medisinsk og helsefaglig forskningsetikk i Nord-Norge (REK nord) har gjort en etisk og helsefaglig vurdering av undersøkelsene som gjennomføres, samt godkjent innsamlingen av prøver.

Hvilke data lagres i Tromsøundersøkelsen?

I Tromsøundersøkelsen lagres opplysninger gitt av deltakere i de forskjellige rundene av Tromsøundersøkelsen. Det lagres også opplysninger om kreftdiagnoser og dødsårsaker fra Kreftregisteret og Dødsårsaksregisteret.
For deltakere som har eller får diagnoser innen hjerte- og karsykdom, diabetes og beinbrudd, innhentes opplysninger fra sykejournalen i spesialist- og primærhelsetjenesten som er nødvendig for å kvalitetssikre aktuelle diagnoser. Dette for å sikre forskning av høy kvalitet. Tilsvarende vil også kunne bli aktuelt for andre sykdommer det forskes på i Tromsøundersøkelsen.

Hvordan lagres dine opplysninger og prøver?

Alle opplysningene og prøvene lagres uten navn og fødselsnummer.

En kode knytter deg til dine opplysninger og prøver. Det er kun noen få autoriserte personer som kan finne tilbake til deg gjennom en egen kodenøkkel.

De biologiske prøvene lagres i godkjent forskningsbiobank ved Institutt for samfunnsmedisin, UiT. Leder av Tromsøundersøkelsen er ansvarlig for biobanken. Den er registrert i Folkehelseinstituttets Biobankregister (nr 2397). Det biologiske materialet kan bare brukes etter godkjenning fra REK.

Utlevering av opplysninger og prøver til forskere

Hvis du sier ja til å delta i studien, samtykker du til at dine opplysninger og prøver kan brukes videre i forskning på ubestemt tid. Medisinsk forskning forandrer seg hele tiden, og i fremtiden kan data bli brukt i forskningsprosjekter forutsatt at det er i samsvar med gjeldende lover og forskrifter.

Alle forskningsprosjekter som får data fra Tromsøundersøkelsen må være i samsvar med lover og forskrifter. Prosjektleder må tilhøre en kompetent forskningsinstitusjon. Den enkelte forsker vil kun få tilgang til personidentifiserende opplysninger etter å ha innhentet nødvendige godkjenninger fra REK, og/eller Datatilsynet.

I noen forskningsprosjekter kan prøver og avidentifiserte opplysninger bli utlevert til andre land. Det vil skje i en slik form at våre utenlandske samarbeidspartnere ikke kan knytte prøvene opp mot deg som person.

I noen prosjekter kan det bli aktuelt å kontakte deg igjen for å samle inn flere data, f.eks. ved spørreskjema, intervju eller kliniske undersøkelser. Du vil da få ny informasjon og bes om nytt samtykke til det konkrete prosjektet.

Ved å delta i Tromsøundersøkelsen bidrar du til viktig forskning på sykdom og helse, oppbygging av fagmiljøer og bedre pasientbehandling.

Sammenstilling med andre registre

I noen forskningsprosjekter vil opplysninger om deg kunne bli sammenstilt med:

Opplysninger du har gitt i tidligere runder av Tromsøundersøkelsen hvis du har deltatt i Tromsøundersøkelsen før.

Opplysninger fra barn, søsken, foreldre og besteforeldre som har deltatt i Tromsøundersøkelsen.

Opplysninger om deg i nasjonale helseregistre som Reseptregisteret, Medisinsk fødselsregister, Kreftregisteret, Norsk pasientregister, Hjerte- og karregisteret, Dødsårsaksregisteret, infeksjonsregistre og andre nasjonale sykdoms- og kvalitetsregistre.

Helseopplysninger om deg fra primær- og spesialisthelsetjenesten.

Opplysninger om sosiale forhold som arbeid, utdanning, inntekt, boforhold osv. fra registre hos bl.a. Statistisk sentralbyrå og NAV.

Slike sammenstillinger krever som regel forhåndsgodkjenning av offentlige instanser, som REK og/eller Datatilsynet.

Rett til innsyn og sletting av dine opplysninger og prøver

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har også rett til å få korrigert eventuelle feil i opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller er brukt i vitenskapelige artikler.

Finansiering

Tromsøundersøkelsen er finansiert av UiT Norges arktiske universitet, Helse Nord RHF, Universitetssykehuset Nord-Norge (UNN) samt ulike forskningsfond.

Forsikring

Deltakere i Tromsøundersøkelsen er forsikret gjennom Norsk Pasientskadeerstatning.

Samtykke til deltakelse i studien

Hvis du vil delta i den sjuende Tromsøundersøkelsen, må du gi skriftlig samtykke ved oppmøte. Personalet vil gi mer informasjon og svare deg dersom du har spørsmål i forbindelse med samtykket.

Du kan når som helst trekke tilbake samtykket ditt.

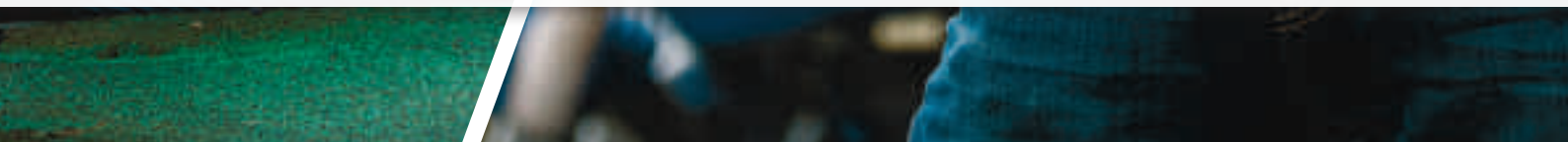
Her finner du oss:

Heiloveien 6 (tidligere Langnes legesenter)
9015 Tromsø

Telefon 77 62 07 00
Epost tromso7@uit.no
Nettside www.tromsoundersokelsen.no

Tromsø-undersøkelsen

UNIVERSITETET I TROMSØ



Tromsø-undersøkelsen
2015–2016

KONFIDENSIELT

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Bruk blokkbokstaver. Du kan ikke bruke komma.

Dato for utfylling: ☐☐☐☐☐☐

HELSE OG SYKDOMMER

1.1 Hvordan vurderer du din egen helse sånn i alminnelighet?

Meget god	God	Verken god eller dårlig	Dårlig	Meget dårlig
☐	☐	☐	☐	☐

1.2 Hvordan synes du at helsen din er sammenlignet med andre på din alder?

Mye bedre	Litt bedre	Omtrent lik	Litt dårligere	Mye dårligere
☐	☐	☐	☐	☐

1.3 Har du eller har du hatt?
Sett ett kryss per linje.

	Nei	Ja nå	Før, ikke nå	Alder første gang
Høyt blodtrykk	☐	☐	☐	☐☐
Hjerteinfarkt	☐		☐	☐☐
Hjertesvikt	☐	☐	☐	☐☐
Atrieflimmer *(hjerteflimmer)*	☐	☐	☐	☐☐
Angina pectoris *(hjertekrampe)*	☐	☐	☐	☐☐
Hjerneslag/hjerneblødning	☐		☐	☐☐
Diabetes	☐	☐	☐	☐☐
Nyresykdom *(unntatt urinveisinfeksjon)*	☐	☐	☐	☐☐
Kronisk bronkitt/emfysem/KOLS	☐	☐	☐	☐☐
Astma	☐	☐	☐	☐☐
Kreft	☐	☐	☐	☐☐
Revmatoid artritt *(leddgikt)*	☐	☐	☐	☐☐
Artrose *(slitasjegikt)*	☐	☐	☐	☐☐
Migrene	☐	☐	☐	☐☐
Psykiske plager *(som du har søkt hjelp for)*	☐	☐	☐	☐☐

1.4 Har du langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer?

☐ Nei ☐ Ja

TANNHELSE

2.1 Hvordan vurderer du din egen tannhelse?

	1	2	3	4	5	
Svært dårlig	☐	☐	☐	☐	☐	Svært god

2.2 Hvor fornøyd eller misfornøyd er du med tennene eller protesene dine?

	1	2	3	4	5	
Svært misfornøyd	☐	☐	☐	☐	☐	Svært fornøyd

BRUK AV HELSETJENESTER

3.1 Har du, grunnet egen helse, i løpet av de siste 12 måneder vært hos:

	Nei	Ja	Antall ganger
Fastlege/allmennlege	☐	☐	☐☐
Legevakt	☐	☐	☐☐
Psykiater/psykolog	☐	☐	☐☐
Legespesialist utenfor sykehus *(utenom fastlege/allmennlege/psykiater)*	☐	☐	☐☐
Tannlege/tannpleier	☐	☐	☐☐
Apotek *(for kjøp/råd om medisiner/behandling)*	☐	☐	☐☐
Fysioterapeut	☐	☐	☐☐
Kiropraktor	☐	☐	☐☐
Akupunktør	☐	☐	☐☐
Alternativ behandler *(homøopat, soneterapeut, healer etc)*	☐	☐	☐☐
Tradisjonell helbreder *(hjelper, «læser» etc)*	☐	☐	☐☐
Har du kommunisert via internett med noen av tjenestene over?	☐	☐	☐☐

3.2 Har du i løpet av de siste 12 måneder vært på sykehus?

	Nei	Ja	Antall ganger
Innlagt på sykehus	☐	☐	☐☐
Konsultasjon ved sykehus uten innleggelse:			
Ved psykiatrisk poliklinikk	☐	☐	☐☐
Ved annen sykehuspoliklinikk	☐	☐	☐☐

BRUK AV MEDISINER

4.1 Bruker du, eller har du brukt, noen av følgende medisiner? *Sett ett kryss per linje.*

	Aldri	Nå	Før, ikke nå	Alder første gang
Medisin mot høyt blodtrykk	☐	☐	☐	
Kolesterolsenkende medisin	☐	☐	☐	
Vanndrivende medisin	☐	☐	☐	
Annen medisin mot hjertesykdom *(f.eks. blodfortynnende, rytmestabiliserende, nitroglycerin)*	☐	☐	☐	
Insulin	☐	☐	☐	
Tabletter mot diabetes	☐	☐	☐	
Stoffskiftemedisin *(Levaxin/thyroxin)*	☐	☐	☐	

4.2 Hvor ofte har du i løpet av de siste 4 ukene brukt følgende medisiner? *Sett ett kryss per linje.*

	Ikke brukt siste 4 uker	Sjeldnere enn hver uke	Hver uke, men ikke daglig	Daglig
Smertestillende på resept	☐	☐	☐	☐
Smertestillende uten resept	☐	☐	☐	☐
Magesyrehemmende medisiner	☐	☐	☐	☐
Sovemidler	☐	☐	☐	☐
Beroligende medisiner	☐	☐	☐	☐
Medisin mot depresjon	☐	☐	☐	☐

4.3 Skriv alle medisiner (reseptfrie og reseptbelagte) du har brukt regelmessig siste 4 uker. *Ikke regn med reseptfrie vitamin-, mineral- og kosttilskudd, urter, naturmedisin etc.*

Får du ikke plass til alle medisinene, bruk eget ark.

KOSTHOLD

5.1 Spiser du vanligvis frokost hver dag?

☐ Nei ☐ Ja

5.2 Hvor mange porsjoner frukt og grønnsaker spiser du i gjennomsnitt per dag? *Med porsjon menes f.eks. et eple, en salatbolle.*

Antall porsjoner

5.3 Hvor ofte spiser du vanligvis disse matvarene? *Sett ett kryss per linje.*

	0–1 pr. mnd.	2–3 pr. mnd.	1–3 pr. uke	4–6 pr. uke	1 eller mer pr. dag
Rødt kjøtt *(alle produkter av storfe, får, svin)*	☐	☐	☐	☐	☐
Grønnsaker, frukt, bær	☐	☐	☐	☐	☐
Mager fisk *(torsk, sei)*	☐	☐	☐	☐	☐
Feit fisk *(laks, ørret, uer makrell, sild, kveite)*	☐	☐	☐	☐	☐

5.4 Hvor mange glass/beger drikker/spiser du vanligvis av følgende? *Sett ett kryss per linje.*

	Sjelden/ aldri	1–6 pr. uke	1 pr. dag	2–3 pr. dag	4 eller mer pr. dag
Melk/yoghurt tilsatt probiotika *(Biola, Cultura, Activia, Actimel, BioQ)*	☐	☐	☐	☐	☐
Fruktjuice	☐	☐	☐	☐	☐
Brus/leskedrikker:					
med sukker	☐	☐	☐	☐	☐
med kunstig søtning	☐	☐	☐	☐	☐

5.5 Hvor mange kopper kaffe og te drikker du daglig? *Sett 0 for de typene du ikke drikker daglig.*

	Antall kopper
Filterkaffe *(trakterkaffe)*	
Kokekaffe og/eller presskannekaffe	
Pulverkaffe	
Espressobasert kaffe *(fra kaffemaskin, kapsler etc)*	
Sort te *(f.eks. Earl Grey)*	
Grønn/hvit/oolong te	
Urtete *(f.eks. nype, kamille, Rooibos)*	

HELSEBEKYMRING

	Ikke i det hele tatt	Litt	Noe	En hel del	Svært mye
6.1 **Tror du at det er noe alvorlig galt med kroppen din?**	☐	☐	☐	☐	☐
6.2 **Er du svært bekymret over helsen din?**	☐	☐	☐	☐	☐
6.3 **Er det vanskelig for deg å tro på legen din dersom hun/han forteller deg at det ikke er noe å bekymre seg for?**	☐	☐	☐	☐	☐
6.4 **Er du ofte bekymret for muligheten for at du har en alvorlig sykdom?**	☐	☐	☐	☐	☐
6.5 **Hvis du blir gjort oppmerksom på en sykdom (f.eks. via TV, radio, internett, avis eller noen du kjenner), bekymrer du deg da for selv å få sykdommen?**	☐	☐	☐	☐	☐
6.6 **Opplever du at du plages av mange ulike symptomer?**	☐	☐	☐	☐	☐
6.7 **Har du tilbakevendende tanker (som er vanskelig å bli kvitt) om at du har en sykdom?**	☐	☐	☐	☐	☐

FYSISK AKTIVITET

7.1 **Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt?** *Sett kryss i den ruta som passer best.*

- ☐ For det meste stillesittende arbeid *(f.eks. skrivebordsarbeid, montering)*
- ☐ Arbeid som krever at du går mye *(f.eks. ekspeditørarbeid, lett industriarbeid, undervisning)*
- ☐ Arbeid der du går og løfter mye *(f.eks. pleier, bygningsarbeider)*
- ☐ Tungt kroppsarbeid

7.2 **Angi bevegelse og kroppslig anstrengelse i din fritid det siste året.** *Hvis aktiviteten varierer gjennom året, ta et gjennomsnitt. Sett kryss i den ruta som passer best.*

- ☐ Leser, ser på TV / skjerm eller annen stillesittende aktivitet
- ☐ Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uka *(inkludert gang eller sykling til arbeidsstedet, søndagsturer etc)*
- ☐ Driver mosjonsidrett, tyngre hagearbeid, snømåking etc minst 4 timer i uka
- ☐ Trener hardt eller driver konkurranseidrett regelmessig flere ganger i uka

7.3 **Siste uka, omtrent hvor lang tid tilbrakte du <u>sittende</u> på en typisk hverdag og fridag?** *F.eks. ved arbeidsbord, hos venner, mens du så på TV / skjerm.*

☐☐ timer sittende på en hverdag *(både jobb og fritid)*

☐☐ timer sittende på en fridag

ALKOHOL

8.1 **Hvor ofte drikker du alkohol?**

- ☐ Aldri
- ☐ Månedlig eller sjeldnere
- ☐ 2–4 ganger hver måned
- ☐ 2–3 ganger per uke
- ☐ 4 eller flere ganger per uke

8.2 **Hvor mange enheter alkohol (flaske øl, glass vin eller drink) tar du vanligvis når du drikker?**

1–2	3–4	5–6	7–9	10 eller flere
☐	☐	☐	☐	☐

8.3 **Hvor ofte drikker du 6 eller flere enheter alkohol ved en anledning?**

- ☐ Aldri
- ☐ Sjeldnere enn månedlig
- ☐ Månedlig
- ☐ Ukentlig
- ☐ Daglig eller nesten daglig

RØYK OG SNUS

9.1 **Har du røykt/røyker du daglig?**

☐ Aldri ☐ Ja, nå ☐ Ja, tidligere

9.2 **Har du brukt/bruker du snus eller skrå daglig?**

☐ Aldri ☐ Ja, nå ☐ Ja, tidligere

SPØRSMÅL OM KREFT

10.1 **Har du noen gang fått**

	Nei	Ja	**Hvis ja:** alder første gang	**Hvis ja:** alder siste gang
Utført mammografi	☐	☐		
Målt PSA (prostataspesifikt antigen)	☐	☐		
Utført tykktarmsundersøkelse (koloskopi, avføringsprøve)	☐	☐		

10.2 **Har noen i din nære biologiske familie hatt**

	Egne barn	Mor	Far	Mormor	Morfar	Farmor	Farfar	Tante	Onkel	Søsken
Brystkreft	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Prostatakreft	☐		☐		☐		☐		☐	☐
Tykktarmskreft	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

UTDANNING OG INNTEKT

11.1 **Hva er din høyeste fullførte utdanning?** *Sett ett kryss.*

- ☐ Grunnskole/framhaldsskole/folkehøyskole inntil 10 år
- ☐ Fagutdanning/realskole/videregående/gymnas minimum 3 år
- ☐ Høyskole/universitet mindre enn 4 år
- ☐ Høyskole/universitet 4 år eller mer

11.2 **Hva var din husstands samlede bruttoinntekt siste år?** *Ta med alle inntekter fra arbeid, trygder, sosialhjelp og lignende.*

- ☐ Under 150 000 kr
- ☐ 150 000–250 000 kr
- ☐ 251 000–350 000 kr
- ☐ 351 000–450 000 kr
- ☐ 451 000–550 000 kr
- ☐ 551 000–750 000 kr
- ☐ 751 000 –1 000 000 kr
- ☐ Over 1 000 000 kr

FAMILIE OG VENNER

12.1 **Hvem bor du sammen med?**

	Nei	Ja	Antall
Ektefelle/samboer	☐	☐	
Andre personer over 18 år	☐	☐	
Personer under 18 år	☐	☐	

12.2 **Har du nok venner som kan gi deg hjelp når du trenger det?**

☐ Ja ☐ Nei

12.3 **Har du nok venner som du kan snakke fortrolig med?**

☐ Ja ☐ Nei

12.4 **Hvor ofte deltar du vanligvis i foreningsvirksomhet som syklubb, idrettslag, politiske, religiøse eller andre foreninger?**

Aldri, eller noen få ganger i året	1–2 ganger i måneden	Omtrent 1 gang i uka	Mer enn 1 gang i uka
☐	☐	☐	☐

SPØRSMÅL TIL KVINNER

13.1 **Hvor gammel var du da du fikk menstruasjon første gang?**

Alder

13.2 **Er du gravid nå?**

☐ Nei ☐ Ja ☐ Usikker

13.3 **Hvor mange barn har du født?**

Antall barn

13.4 **Hvis du har født, fyll ut for hvert barn: fødselsår og vekt samt hvor mange måneder du ammet.** *Angi så godt du kan. Hvis flere barn, bruk ekstra ark.*

	Fødselsår	Fødselsvekt i gram	Ammet ant. mnd.
Barn 1			
Barn 2			
Barn 3			
Barn 4			
Barn 5			
Barn 6			

SPØRSMÅL TIL MENN

14.1 **Har du fått behandling for betennelse i prostata eller urinblæra?**

☐ Nei ☐ Ja

14.2 **Har du fått utført steriliseringsoperasjon?**

☐ Nei ☐ Ja **Hvis ja:** hvilket år

Tusen takk for ditt bidrag.

1 DIN HELSETILSTAND

Under hver overskrift ber vi deg krysse av den ENE boksen som best beskriver helsen din I DAG.

1.1 Gange

Jeg har ingen problemer med å gå omkring
Jeg har litt problemer med å gå omkring
Jeg har middels store problemer med å gå omkring
Jeg har store problemer med å gå omkring
Jeg er ute av stand til å gå omkring

1.2 Personlig stell

Jeg har ingen problemer med å vaske meg eller kle meg
Jeg har litt problemer med å vaske meg eller kle meg
Jeg har middels store problemer med å vaske meg eller kle meg
Jeg har store problemer med å vaske meg eller kle meg
Jeg er ute av stand til å vaske meg eller kle meg

1.3 Vanlige gjøremål

(f.eks. arbeid, studier, husarbeid, familie- eller fritidsaktiviteter)

Jeg har ingen problemer med å utføre mine vanlige gjøremål
Jeg har litt problemer med å utføre mine vanlige gjøremål
Jeg har middels store problemer med å utføre mine vanlige gjøremål
Jeg har store problemer med å utføre mine vanlige gjøremål
Jeg er ute av stand til å utføre mine vanlige gjøremål

1.4 Smerter/ubehag

Jeg har verken smerter eller ubehag
Jeg har litt smerter eller ubehag
Jeg har middels sterke smerter eller ubehag
Jeg har sterke smerter eller ubehag
Jeg har svært sterke smerter eller ubehag

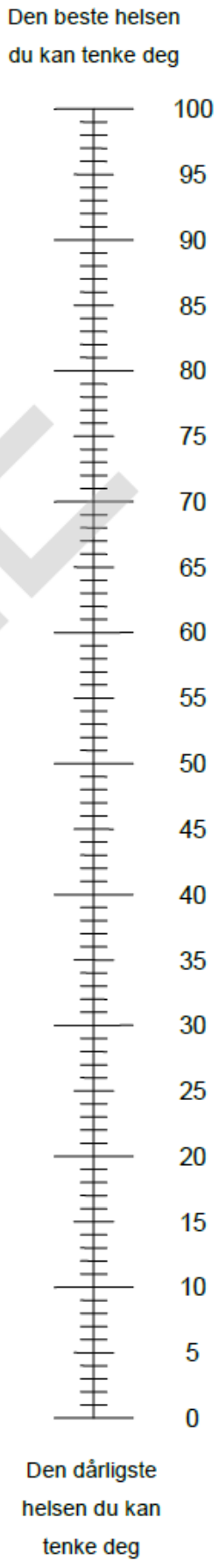
1.5 Angst/depresjon

Jeg er verken engstelig eller deprimert
Jeg er litt engstelig eller deprimert
Jeg er middels engstelig eller deprimert
Jeg er svært engstelig eller deprimert
Jeg er ekstremt engstelig eller deprimert

For å kunne vise hvor god eller dårlig din helsetilstand er, har vi laget en skala hvor den beste helsen du kan tenke deg er markert med 100 og den dårligste med 0. Hvor på denne skalaen vil du plassere din nåværende helse?

1.6 Fyll inn et tall mellom 0 og 100 for å angi hvordan din nåværende helse er:

___


Den beste helsen
du kan tenke deg
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
Den dårligste
helsen du kan
tenke deg

2 OPPVEKST OG TILHØRIGHET

2.1 Hvor bodde du størstedelen av din oppvekst?

(Sett ett kryss)

- Tromsø
- Troms, andre kommuner enn Tromsø
- Finnmark
- Nordland
- Resten av Norge
- Utlandet

2.2 Hvor lenge har du bodd i din nåværende bolig?

Antall år___

2.3 Hvordan var de økonomiske forhold i familien under din oppvekst?

- Meget gode
- Gode
- Vanskelige
- Meget vanskelige

2.4 Hvilken betydning har religion i ditt liv?

- Stor betydning
- En viss betydning
- Ingen betydning

2.5 Hva regner du deg selv som?

(Sett ett eller flere kryss)

- Norsk
- Samisk
- Kvensk/Finsk
- Annet

2.6 Hvor mange søsken har du/har du hatt?

Antall søsken

Hvor mange barn har du/har du hatt?

Antall

2.7 Biologiske barn
2.8 Adoptivbarn
2.9 Stebarn
2.10 Fosterbarn

2.11 Lever din mor?

Nei Ja

Hvis Ja, hopp til spm 2.9.
Hvis Nei:

2.11.1 Hva var din mors alder ved død?

Alder ved død __

2.12 Lever din far?

Nei Ja

Hvis Ja, hopp til spm 2.10.
Hvis Nei:

2.12.1 Hva var din fars alder ved død?

Alder ved død__

Hva var/er den *høyeste fullførte utdanning* til dine foreldre og din ektefelle/samboer?

Grunnskole/framhaldsskole/folkehøyskole inntil 10 år
Fagutdanning/realskole/videregående/gymnas minimum 3 år
Høyskole/universitet, mindre enn 4 år
Høyskole/universitet, 4 år eller mer

12.13 Mor
12.14 Far
12.15 Ektefelle/samboer

3 TRIVSEL OG LIVSFORHOLD

Nedenfor står tre utsagn om tilfredshet med livet som et hele. Deretter står fem utsagn om syn på din egen helse, og mestring av egen helse. Vis hvor enig eller uenig du er i hver av påstandene ved å sette et kryss i rubrikken for det tallet du synes stemmer best for deg.

Helt uenig						Helt enig
1	2	3	4	5	6	7

3.1 På de fleste måter er livet mitt nær idealet mitt
3.2 Mine livsforhold er utmerkede
3.3 Jeg er tilfreds med livet mitt
3.4 Jeg ser lyst på min framtidige helse
3.5 Ved å leve sunt kan jeg forhindre alvorlige sykdommer
3.6 Jeg vet hvordan jeg skal forebygge forverring av min helsetilstand
3.7 Jeg kan finne løsninger når det oppstår nye situasjoner eller problemer med min helsetilstand
3.8 Når alt kommer til alt er jeg selv ansvarlig for å ta hånd om min egen helse

Angi hvor godt følgende påstander beskriver deg og familien din:

Helt uenig				Helt enig
1	2	3	4	5

3.9 Jeg stoler fullt ut på mine vurderinger og avgjørelser
3.10 Jeg trives svært godt i familien min
3.11 Troen på meg selv får meg gjennom vanskelige perioder
3.12 Det er godt samhold i familien min
3.13 I motgang klarer jeg å finne noe bra å vokse på
3.14 Familien min ser positivt på fremtiden selv i vanskelige perioder

3.15 Hvordan vurderer du din økonomi?

Svært god
God
Middels
Dårlig
Svært dårlig

4 ARBEID OG YRKE

4.1 Hvilken arbeids- eller livssituasjon er du i?

(Sett ett eller flere kryss)

Yrkesaktiv heltid
Yrkesaktiv deltid
Hjemmeværende
Alderspensjonist
Sykemeldt
Uføretrygdet/mottar arbeidsavklaringspenger
Mottar sosialstønad
Arbeidsledig
Student/militærtjeneste

Hvis Yrkesaktiv heltid, Yrkesaktiv deltid, Hjemmeværende, Alderspensjonist, Student/militærtjeneste, hopp til spørsmål 4.2.
Hvis Sykemeldt, Uføretrygdet/mottar arbeidsavklaringspenger, Mottar sosialstønad, Arbeidsledig:

4.1.1 Hvor lenge har du vært uten lønnet arbeid?

3 månder eller mindre
4-6 måneder
7-12 måneder
1-2 år
3-5 år
6-9 år
10 år eller mer

4.2 Jeg opplever at yrket mitt har/hadde følgende sosiale status i samfunnet (dersom du ikke er i arbeid nå, tenk på det yrket du hadde sist):

Meget høy status
Ganske høy status
Middels status
Ganske lav status
Meget lav status

Hvis ikke Yrkesaktiv heltid eller Yrkesaktiv deltid på spm 4.1 hopp til spm 4.1.3.
Hvis Yrkesaktiv heltid eller Yrkesaktiv deltid på spm 4.1:

4.1.2 Hvilken av følgende yrkesfelt beskriver best ditt nåværende arbeid?

(Sett ett kryss)

- Administrativ leder, politiker
- Akademisk yrke (minst 4 års høyskole- eller universitetsutdanning)
- Yrke med kortere høyskole- eller universitetsutdanning (1-3 år) og teknikere
- Kontor- og kundeserviceyrker
- Salgs-, service- og omsorgsyrker
- Jordbruks-, skogbruks- og fiskeyrker
- Håndverker, bygningsarbeider, fagarbeider o.l.
- Prosess- og maskinoperatør, sjåfør o.l.
- Yrke uten formelt krav til utdanning

4.1.2.1 Beskriv virksomheten på det arbeidstedet (avdelingen) der du utførte inntektsgivende arbeid i lengst tid de siste 12 mnd (f.eks. regnskapsbyrå, ungdomsskole, sykehus, snekkerverksted, bilverksted, bank, dagligvarehandel eller lignende):

Virksomhet: _____

4.1.2.2 Hvilket yrke/tittel har eller hadde du på dette arbeidsstedet? (f.eks. sekretær, lærer, barnepleier, møbelsnekker, avdelingsleder, selger, sjåfør eller lignende)

Yrke:_____

4.1.4 På en skala fra 0 til 10, hvordan vil du beskrive din arbeidsprestasjon siste 7 dager?

0 Jeg har prestert svært dårlig 10 Jeg har prestert svært godt

Hvis Yrkesaktiv heltid eller Yrkesaktiv på spm 4.1 deltid hopp til spm 5.1.
Hvis ikke Yrkesaktiv heltid eller Yrkesaktiv deltid på spm 4.1:

4.1.3 Hvilken av følgende yrkesfelt beskriver best ditt siste arbeid?

(Sett ett kryss)

- Administrativ leder, politiker
- Akademisk yrke (minst 4 års høyskole- eller universitetsutdanning)
- Yrke med kortere høyskole- eller universitetsutdanning (1-3 år) og teknikere
- Kontor- og kundeserviceyrker
- Salgs-, service- og omsorgsyrker
- Jordbruks-, skogbruks- og fiskeyrker
- Håndverker, bygningsarbeider, fagarbeider o.l.
- Prosess- og maskinoperatør, sjåfør o.l.
- Yrke uten formelt krav til utdanning

4.1.3.1 Beskriv virksomheten på det arbeidstedet (avdelingen) der du utførte inntektsgivende arbeid siste periode du var i arbeid. (f.eks. regnskapsbyrå, ungdomsskole, sykehus, snekkerverksted, bilverksted, bank, dagligvarehandel eller lignende)

Virksomhet: _____

4.1.3.2 Hvilket yrke/tittel hadde du på dette arbeidsstedet? (f.eks. sekretær, lærer, barnepleier, møbelsnekker, avdelingsleder, selger, sjåfør eller lignende)

Yrke: _____

5 SYKDOMMER OG SYMPTOMER

Har du hatt følgende sykdommer eller plager?

Nei Ja Alder første gang

5.1 Har du gjennomgått operasjon (bypass) av trange blodårer (kransårer) til hjertet?

5.2 Har du gjennomgått utblokking (stenting) av trange blodårer (kransårer) til hjertet?

5.3 Har du eller har du hatt trange blodårer i beina (åreforkalkning, "røykebein")?

Hvis Nei på spm 5.1-5.3, hopp til spm 5.4.
Hvis Ja på spm 5.1:

5.1.1 Hvis du har gjennomgått operasjon (bypass) av trange blodårer (kransårer) til hjertet, hva var din alder første gang?

Alder første gang___

Hvis Ja på spm 5.2:

5.2.1 Hvis du har gjennomgått utblokking (stenting) av trange blodårer (kransårer) til hjertet, hva var din alder første gang?

Alder første gang___

Hvis Ja på spm 5.3:

5.3.1 Hvis du har eller har hatt trange blodårer i beina (åreforkalkning, "røykebein"), hva var din alder første gang?

Alder første gang___

Får du smerter i tykkleggen når du

Nei Ja

5.4 Går?
5.5 Er i ro?

Hvis Nei på 5.4 og 5.5, hopp til spm 5.6.
Hvis Ja på 5.4:

Hvis du får smerter i tykkleggen når du går

Nei Ja

5.4.1 Forverres smertene ved raskere tempo eller i bakker?
5.4.2 Gir smertene seg når du stopper?

Får du smerter eller ubehag i brystet når du går

Nei Ja

5.6 I bakker, trapper eller fort på flat mark
5.7 I vanlig takt på flat mark

Hvis Nei på 5.6 og 5.7, hopp til spm 5.8.
Hvis Ja på 5.6 eller 5.7 eller begge:

5.6.1 Hvis du får smerter eller ubehag i brystet ved gange, pleier du å
Stanse
Saktne farten
Fortsette i samme takt

5.6.2 Hvis du stanser eller saktner farten, forsvinner smertene etter
10 minutter eller mindre
Mer enn 10 minutter

5.8 Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste året?
Nei Ja

5.9 Hoster du omtrent daglig i perioder av året?
Nei Ja

Hvis Nei, hopp til spm 5.14.
Hvis Ja:

Hvis du hoster omtrent daglig i perioder av året

Nei Ja

5.9.1 Er hosten vanligvis ledsaget av oppspytt?
5.9.2 Har du hatt slik hoste så lenge som i en 3 måneders periode i begge de to siste årene?

Blir du tungpustet når du

Nei Ja

5.10 Går hurtig på flatmark eller svak oppoverbakke?
5.11 Spaserer i rolig tempo på flatmark?
5.12 Vasker deg eller kler på deg?
5.13 Er i hvile?

5.14 Har du Crohns sykdom eller ulcerøs kolitt?
Nei Ja

5.15 Har du vært smittet med leververiruset hepatitt C?
Nei Ja Vet ikke

Hvis Nei eller Vet ikke, hopp til spm 6.1.
Hvis Ja:

5.15.1 Har du fått behandling for hepatitt C?

Nei Ja Vet ikke

6 MUSKEL- OG LEDDSMERTER

Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende?
(Sett ett kryss for hver linje)

Ikke plaget En del plaget Sterkt plaget

6.1 Nakke, skuldre
6.2 Armer, hender
6.3 Øvre del av ryggen
6.4 Korsryggen
6.5 Hofter, ben, føtter
6.6 Andre steder

Har du vært plaget av smerter og/eller stivhet i muskler og ledd i i løpet av de siste fire ukene?
(Sett ett kryss for hver linje)

Ikke plaget En del plaget Sterkt plaget

6.7 Nakke, skuldre
6.8 Armer, hender
6.9 Øvre del av ryggen
6.10 Korsryggen
6.11 Hofter, ben, føtter
6.12 Andre steder

7 HODEPINE

7.1 Har du vært plaget av hodepine det siste året?

Nei Ja

Hvis Nei, hopp til spm 8.1.
Hvis Ja:

7.1.1 Hva slags hodepine er du plaget av?

Migrene
Annen hodepine

7.1.2 Omtrent hvor mange dager per måned har du hodepine?

Mindre enn 1 dag
1-6 dager
7-14 dager
Mer enn 14 dager

7.1.3 Hvor sterk er hodepinen vanligvis?

Mild *(hemmer ikke aktivitet)*

Moderat *(hemmer aktivitet)*
Sterk *(forhindrer aktivitet)*

7.1.4 Hvor lenge varer hodepinen vanligvis?

Mindre enn 4 timer
4 timer – 1 døgn
1-3 døgn
Mer enn 3 døgn

Er hodepinen vanligvis preget eller ledsaget av:

Nei Ja

7.1.5 Bankende/dunkende smerte?
7.1.6 Pressende smerte?
7.1.7 Ensidig smerte (høyre eller venstre)?
7.1.8 Forverring ved fysisk aktivitet?
7.1.9 Kvalme og/eller oppkast?
7.1.10 Lys- og/eller lydskyhet?

Før eller under hodepinen, kan du ha forbigående:

Nei Ja

7.1.11 Synsforstyrrelse (takkede linjer, flimring, tåkesyn, lysglimt)?
7.1.12 Nummenhet i halve ansiktet eller i hånden?

7.1.13 Angi hvor mange dager du har vært borte fra arbeid eller skole siste måned på grunn av hodepine:

Antall dager borte ___

8 PLAGER

8.1 Hvor ofte har du vært plaget av halsbrann og/eller sure oppstøt i løpet av de siste tre måneder?

Aldri Månedlig Ukentlig Daglig

Hvis Aldri, hopp til spm 8.2.
Hvis > Aldri:

8.1.1 Hvor plaget har du vært av halsbrann og/eller sure oppstøt?

Ikke noe Litt Mye

8.1.2 Hvor lenge har du vært plaget av halsbrann og/eller sure oppstøt?

Mindre enn 3 måneder
3-5 måneder
6-12 måneder
Mer enn 1 år

8.2 Har du falt siste året?

Nei
En gang
Mer enn en gang

8.3 Er du redd for å falle?

Ikke i det hele tatt
Noe redd
Svært redd

8.4 Hvordan har du opplevd følelse av tretthet og utmattelse den siste uken?

Marker på linjen nedenfor det punktet som best passer med den følelse av tretthet og utmattelse som du har opplevd siste uke.

Ingen problemer med tretthet Så mye tretthet og utmattelse som det er mulig å ha

9 HUKOMMELSE

Nedenfor ber vi deg besvare noen spørsmål om din hukommelse:
(Sett ett kryss for hvert spørsmål)

Nei Ja

9.1 Synes du at din hukommelse har blitt dårligere?
9.2 Glemmer du ofte hvor du har lagt tingene dine?
9.3 Har du problemer med å finne vanlige ord i en samtale?
9.4 Har du fått problemer med daglige gjøremål som du mestret tidligere?
9.5 Har du vært undersøkt for sviktende hukommelse?

Hvis Nei på 9.1-9.4, hopp til spm 10.1.
Hvis Ja på ett eller flere av 9.1-9.4:

9.1.1 Er din hukommelse et problem i hverdagen?

Nei Ja

10 UFRIVILLIG BARNLØSHET

10.1 Har du opplevd ufrivillig barnløshet i mer enn 1 år?

Nei Ja

Hvis Nei, hopp til spørsmål 11.1.
Hvis Ja:

Dersom du har opplevd ufrivillig barnløshet i mer enn 1 år

Nei Ja Vet ikke

10.1.1 Skyldtes dette forhold hos deg selv?
10.1.2 Skyldtes dette forhold hos din partner?

10.1.3 Har du/dere fått behandling for ufrivillig barnløshet?

Nei Ja

Hvis Nei, hopp til spm 11.1.
Hvis Ja:

Hvis du/dere har fått behandling for ufrivillig barnløshet, hva slags behandling har du eller din partner fått?

Antall ganger

10.1.3.1 Stimulering med tabletter
10.1.3.2 Stimulering med tabletter og sæddonasjon (ikke ektemann/samboer)
10.1.3.3 Sæddonasjon (ikke ektemann/samboer)
10.1.3.4 Prøverørsbefruktning (IVF/ICSI)
10.1.3.5 Annet

Hvor mange barn har du/dere fått ved infertilitetsbehandling?

Antall barn

10.1.3.6 Ved Universitetssykehuset Nord-Norge
10.1.3.7 Annet sted i Norge
10.1.3.8 I utlandet

11 DINE SLEKTNINGERS SYKDOMMER

Kryss av for de slektningene som har eller har hatt noen av sykdommene:

Mor Far Barn Søsken Ingen av disse

11.1 Hjerteinfarkt før fylte 60 år
11.2 Angina pectoris (hjertekrampe)
11.3 Hjerneslag/hjerneblødning
11.4 Astma
11.5 Diabetes
11.6 Psykiske plager
11.7 Rusproblemer

12 SØVN

Hvor mange dager pr uke
(marker antall dager) Antall dager pr uke 0 1 2 3 4 5 6 7

12.1 bruker du mer enn 30 minutter for å sovne inn etter at lysene ble slukket?
12.2 er du våken mer enn 30 minutter innimellom søvnen?
12.3 våkner du mer enn 30 minutter tidligere enn du ønsker uten å få sove igjen?
12.4 føler du deg for lite uthvilt etter å ha sovet?
12.5 er du så søvnig/trett at det går ut over skole/jobb eller privatlivet?
12.6 er du misfornøyd med søvnen din?

12.7 Om du har søvnplager, hvor lenge har de vart?

Mindre enn 1 uke
1-3 uker

1 måned
2 måneder
3 måneder
4-6 måneder
7-12 måneder
1-5 år
6-10 år
Mer enn 10 år
Har ikke søvnplager

12.8 Har du vanligvis skiftarbeid/nattarbeid?

Nei Ja

Når pleier du vanligvis å legge deg for å sove?

12.9 På arbeidsdager/hverdager

kl. 00:30-24:00 (rullegardinmeny)

12.10 På fridager/helgedager

kl. 00:30-24:00 (rullegardinmeny)

Hvor lenge ligger du våken før du sovner?

12.11 På arbeidsdager/hverdager

Antall minutter___

12.12 På fridager/helgedager

Antall minutter___

Når pleier du vanligvis å våkne?

12.13 På arbeidsdager/hverdager

kl. 00:30-24:00 (rullegardinmeny)

12.14 På fridager/helgedager

kl. 00:30-24:00 (rullegardinmeny)

12.15 Hvor ofte tar du deg en lur på dagtid?

Aldri eller sjeldnere enn en gang i måneden
Sjeldnere enn en gang i uken
1-2 dager i uken
3-5 dager i uken
Hver dag eller nesten hver dag

Hvis Aldri eller sjeldnere enn en gang i måneden, hopp til spm 12.16.
Hvis > Aldri eller sjeldnere enn en gang i måneden:

12.15.1 Hvis du tar deg en lur, hvor lenge pleier den vanligvis å vare?

Antall minutter___

12.16 Snorker du når du sover?

Aldri eller sjeldnere enn en natt i måneden

Sjeldnere enn en natt i uken
1-2 netter i uken
3-5 netter i uken
Hver natt eller nesten hver natt
Vet ikke

12.17 Har du opplevd pustestopp (søvnapné) når du sover?

Aldri eller sjeldnere enn en natt i måneden
Sjeldnere enn en natt i uken
1-2 netter i uken
3-5 netter i uken
Hver natt eller nesten hver natt
Vet ikke

Hvor sannsynlig er det at du døser av eller sovner i følgende situasjoner?
Bruk skalaen fra 0 til 3 for hver situasjon:
0=ville aldri døse/sovne
1=liten sjanse for å døse/sovne
2=moderat sjanse for å døse/sovne
3=stor sjanse for å døse/sovne

Situasjon Sjanse for å døse/sovne (0-3)

12.18 Sitte og lese
12.19 Se på TV
12.20 Sitte, inaktiv på et offentlig sted (f.eks. på teater eller et møte)
12.21 Som passasjer på en en-times biltur uten pause
12.22 Legge deg for å hvile om ettermiddagen hvis omstendighetene tillater det
12.23 Sitte og snakke med noen
12.24 Sitte stille etter lunsj (uten å ha inntatt alkohol)
12.25 I en bil, som har stoppet for noen få minutter i trafikken

14 MAGE

14.1 Hvor ofte har du hatt ubehag eller smerte i mageregionen de siste 3 månedene?

Aldri
Mindre enn en dag i måneden
En dag i måneden
To til tre dager i måneden
En dag i uken
Mer enn en dag i uken
Hver dag

Hvis Aldri, hopp til spm 14.2.
Hvis > Aldri og mann, hopp til spm 14.1.2.
Hvis >Aldri og kvinne:

MAGESMERTER

14.1.1 Har du hatt dette ubehaget eller denne smerten kun under menstruasjon og ikke på andre tidspunkt?

Nei Ja Jeg har ikke hatt menstruasjon siste 3 måneder

Hvis Ja, hopp til spm 14.2.
Hvis Nei eller Jeg har ikke hatt menstruasjon siste 3 måneder:

MAGESMERTER

14.1.2 Har du hatt dette ubehaget eller disse smertene i 6 måneder eller mer?

Nei Ja

Hvis Nei, hopp til spm 14.2.
Hvis Ja:

MAGESMERTER

Aldri eller sjelden Av og til Ofte Nesten alltid Alltid

14.1.2.1 Hvor ofte har ubehaget eller smerten blitt bedre eller helt borte etter at du har hatt avføring?
14.1.2.2 Hadde du oftere avføring da ubehaget eller smerten begynte?
14.1.2.3 Hadde du sjeldnere avføring da ubehaget eller smerten begynte?
14.1.2.4 Hadde du løsere avføring da ubehaget eller smerten begynte?
14.1.2.5 Hvor ofte hadde du hardere avføring da ubehaget eller smerten begynte?
14.1.2.6 Hvor ofte har du hatt hard eller klumpete de siste 3 månedene?
14.1.2.7 Hvor ofte har du hatt løs, grøtaktig eller vandig avføring de siste 3 månedene?

14.2 Hvor ofte har du vanligvis avføring?

4 ganger eller mer per dag
1-3 ganger per dag
4-6 ganger per uke
1-3 ganger per uke
Sjeldnere enn 1 gang per uke

15 HELSETJENESTER

15.1 Hvor lenge har du hatt din nåværende fastlege?

Mindre enn 1 år
1-2 år
3-4 år
Mer enn 4 år

15.2 Har du vært hos fastlegen siste 12 måneder?

Nei Ja

Hvis Nei, hopp til spm 15.3.
Hvis Ja:

15.2.1 Ved siste konsultasjon hos fastlegen, ble du henvist til

(Sett ett eller flere kryss)

fysioterapeut

kiropraktor
psykiater/psykolog
røntgenundersøkelse/billeddiagnostikk
sykehuspoliklinikk
legespesialist utenfor sykehus
annen henvisning
ble ikke henvist

15.2.2 Har du de siste 12 måneder bedt om eller ønsket å bli henvist til røntgenundersøkelse eller spesialist, men ikke blitt henvist av fastlegen?

Ja, en gang
Ja, flere ganger
Nei, jeg har blitt henvist når jeg har bedt om eller ønsket det
Nei, henvisning har ikke vært aktuelt

Hvis Nei, jeg har blitt henvist når jeg har bedt om eller ønsket det eller Nei, henvisning har ikke vært aktuelt, hopp til spm 15.3.
Hvis Ja:

15.2.2.1 Hvis du ikke ble henvist av fastlegen, fikk det konsekvenser for din helse at du ikke ble henvist?

Nei Ja, forbigående konsekvenser Ja, varige konsekvenser

Hvor ofte *det siste året* har du benyttet internett til informasjon og råd om helse og sykdom?

	Aldri	En gang	Noen ganger	Ofte
15.3 Apper for smarttelefon eller nettbrett				
15.4 Søkemotorer (som Google)				
15.5 Sosiale medier (som Facebook e.l.)				
15.6 Videotjenester (som Youtube)				

Hvis Aldri på alle de foregående, hopp til spørsmål 16.1.
Hvis >Aldri:

På grunnlag av informasjon du har funnet via internett, har du:

	Aldri	En gang	Noen ganger	Ofte

15.3.1 Bestemt deg for å oppsøke lege?
15.3.2 Bestemt deg for ikke å oppsøke lege?
15.3.3 Diskutert informasjonen med lege?
15.3.4 Endret din medisin uten å snakke med lege?
15.3.5 Blitt usikker på om du har fått riktig diagnose?
15.3.6 Blitt usikker på om du har fått riktig behandling?
15.3.7 Bestemt deg for å oppsøke alternativ behandler?
15.3.8 Endret din livsstil?
15.3.9 Følt deg engstelig?
15.3.10 Følt deg betrygget?
15.3.11 Følt deg mer kunnskapsrik?
15.3.12 Følt deg mer forvirret?

16 ALTERNATIV MEDISIN

16.1 Har du i løpet av de siste 12 måneder brukt urtemedisin, naturmidler eller naturlegemidler?

Nei Ja

16.2 Har du i løpet av de siste 12 måneder brukt meditasjon, yoga, qi gong eller thai chi som egenbehandling?

Nei Ja

17 SMERTESTILLENDE OG BETENNELSESDEMPENDE MEDISINER

17.1 Har du *det siste året regelmessig* brukt smertestillende og/eller betennelsesdempende medisiner (f.eks. acetylsalicylsyre, paracetamol, ibuprofen, diklofenak, naproxen)?

Dette inkluderer både reseptfrie og reseptbelagte legemidler, også acetylsalisylsyre som brukes i lav dose som blodfortynnende middel.

Nei Ja

Hvis Nei, hopp til spm 18.1.
Hvis Ja:

Hvilke smertestillende/betennelsesdempende medisiner har du brukt siste året?
(Sett ett eller flere kryss)

17.1.1 Acetylsalisylsyre lav dose som brukes som blodfortynnende middel

(75 mg eller 160 mg per tablet, f.eks. Acetylsalisylsyre® Albyl-E® Asasantin Retard®)

Nei Ja

17.1.2 Acetylsalisylsyre høy dose

(300-500 mg acetylsalisylsyre per tablett, f.eks. Aspirin® Dispril® Globoid®)

Nei Ja

17.1.3 Paracetamol

(f.eks. Pamol® Panodil® Paracet® Paracetamol® Pinex® Paracetduo®)

Nei Ja

17.1.4 Paracetamol kombinert med kodein/tramadol
(Paralgin forte® Codaxol® Paralgin major® Paralgin minor® Paramax Comp Vitabalans® Pinex Forte® Pinex Major® Trampalgin®)

Nei Ja

17.1.5 Fenazon
(Fanalgin® Fenazon-koffein® Fenazon-koffein sterke®)

Nei Ja

17.1.6 Ibuprofen og lignende
(f.eks. Brufen Retard® Burana® Ibumax® Ibumetin® Ibuprofen Ibuprox® Ibux® Orudis® Seractiv® Ketesse® Orodek®)

Nei Ja

17.1.7 Diklofenak og lignende
(f.eks. Cataflam® Diclofenac® DiclofenacKalium® Modifenac® Voltaren® Voltarol® Arthrotec® Toradol®)

Nei Ja

17.1.8 Naproksen
(f.eks. Napren-E® Naproxen-E® Naproxen® Vimovo®)

Nei Ja

17.1.9 Andre smertestillende og/eller betennelsesdempende medisiner
(f.eks. Brexidol® Piroxicam® Meloxicam® Migea® Celebra® Dynastat® Arcoxia® Relifex®)

Nei Ja

Hvis Nei på spm 17.1.1, hopp til spm 18.1.
Hvis Ja på spm 17.1.1:

17.1.1.1 Har du brukt lavdose acetylsalisylsyre ukentlig eller oftere siste år?

Nei Ja

Hvis Nei, hopp til spm 18.1.
Hvis Ja:

Hvis du har brukt acetylsalisylsyre lavdose ukentlig eller mer siste år

17.1.1.1.1 Hvor mange dager per uke?

1
2-3
4-5
6+ dager

17.1.1.1.2 Hvor mange tabletter totalt per uke?

1-2
3-5
6-14
15+

17.1.1.1.3 Hvor mange år har du hatt dette forbruket?

Antall år__

Hvis Nei på spm 17.1.2, hopp til spm 18.1.
Hvis Ja på spm 17.1.2:

17.1.2.1 Har du brukt høydose acetylsalicylsyre ukentlig eller oftere siste år?

Nei Ja

Hvis Nei, hopp til spm 18.1.
Hvis Ja:

Hvis du har brukt acetylsalisylsyre høydose ukentlig eller mer siste år

17.1.2.1.1 Hvor mange dager per uke?

1
2-3
4-5
6+ dager

17.1.2.1.2 Hvor mange tabletter totalt per uke?

1-2
3-5
6-14
15+

17.1.2.1.3 Hvor mange år har du hatt dette forbruket?

Antall år__

Hvis Nei på spm 17.1.3, hopp til spm 18.1.
Hvis Ja på spm 17.1.3:

17.1. 3.1 Har du brukt paracetamol ukentlig eller mer oftere år?

Nei Ja

Hvis Nei, hopp til spm 18.1.
Hvis Ja:

Hvis du har brukt paracetamol ukentlig eller mer siste år

17.1.3.1.1 Hvor mange dager per uke?

1
2-3
4-5
6+ dager

17.1.3.1.2 Hvor mange tabletter totalt per uke?

1-2
3-5
6-14
15+

17.1.3.1.3 Hvor mange år har du hatt dette forbruket?

Antall år__

Hvis Nei på spm 17.1.4, hopp til spm 18.1.
Hvis Ja på spm 17.1.4:

17.1.4.1 Har du brukt paracetamol kombinert med kodein/tramadol ukentlig eller oftere siste år?

Nei Ja

Hvis Nei, hopp til spm 18.1.
Hvis Ja:

Hvis du har brukt paracetamol med kodein/tramadol ukentlig eller mer siste år

17.1.4.1.1 Hvor mange dager per uke?

1
2-3
4-5
6+ dager

17.1.4.1.2 Hvor mange tabletter totalt per uke?

1-2
3-5
6-14
15+

17.1.4.1.3 Hvor mange år har du hatt dette forbruket?

Antall år__

Hvis Nei på spm 17.1.5, hopp til spm 18.1.
Hvis Ja på spm 17.1.5:

17.1.5.1 Har du brukt fenazon ukentlig eller oftere siste år?

Nei Ja

Hvis Nei, hopp til spm 18.1.
Hvis Ja:

Hvis du har brukt fenazon ukentlig eller mer siste år

17.1.5.1.1 Hvor mange dager per uke?

1
2-3
4-5
6+ dager

17.1.5.1.2 Hvor mange tabletter totalt per uke?

1-2
3-5
6-14
15+

17.1.5.1.3 Hvor mange år har du hatt dette forbruket?

Antall år__

Hvis Nei på spm 17.1.6, hopp til spm 18.1.
Hvis Ja på spm 17.1.6:

17.1.6.1 Har du brukt ibuprofen og lignende ukentlig eller oftere siste år?

Nei Ja

Hvis Nei, hopp til spm 18.1.
Hvis Ja:

Hvis du har brukt ibuprofen og lignende ukentlig eller mer siste år

17.1.6.1.1 Hvor mange dager per uke?

1
2-3
4-5
6+ dager

17.1.6.1.2 Hvor mange tabletter totalt per uke?

1-2
3-5
6-14
15+

17.1.6.1.3 Hvor mange år har du hatt dette forbruket?

Antall år__

Hvis Nei på spm 17.1.7, hopp til spm 18.1.
Hvis Ja på spm 17.1.7:

17.1.7.1 Har du brukt diklofenak og lignende ukentlig eller oftere siste år?

Nei Ja

Hvis Nei, hopp til spm 18.1.
Hvis Ja:

Hvis du har brukt diclofenac og lignende ukentlig eller mer siste år

17.1.7.1.1 Hvor mange dager per uke?

1
2-3
4-5
6+ dager

17.1.7.1.2 Hvor mange tabletter totalt per uke?

1-2
3-5
6-14
15+

17.1.7.1.3 Hvor mange år har du hatt dette forbruket?

Antall år__

Hvis Nei på spm 17.1.8, hopp til spm 18.1.
Hvis Ja på spm 17.1.8:

17.1.8.1 Har du brukt naproksen ukentlig eller oftere siste år?

Nei Ja

Hvis Nei, hopp til spm 18.1.
Hvis Ja:

Hvis du har brukt naproksen ukentlig eller mer siste år

17.1.8.1.1 Hvor mange dager per uke?

1
2-3
4-5
6+ dager

17.1.8.1.2 Hvor mange tabletter totalt per uke?

1-2
3-5
6-14
15+

17.1.8.1.3 Hvor mange år har du hatt dette forbruket?

Antall år__

Hvis Nei på spm 17.1.9, hopp til spm 18.1.
Hvis Ja på spm 17.1.9:

17.1.9.1 Har du brukt andre smertestillende og/eller betennelsesdempende medisiner ukentlig eller oftere siste år?

Nei Ja

Hvis Nei, hopp til spm 18.1.
Hvis Ja:

Hvis du har brukt andre smertestillende og/eller betennelsesdempende medisiner ukentlig eller mer siste år

17.1.9.1.1 Hvor mange dager per uke?

1
2-3
4-5
6+ dager

17.1.9.1.2 Hvor mange tabletter totalt per uke?

1-2
3-5

6-14
15+

17.1.9.1.3 Hvor mange år har du hatt dette forbruket?

Antall år__

18 INFORMASJON OM MEDISINER

18.1 Har du brukt medisiner (reseptfrie og reseptbelagte) *regelmessig siste 4 uker*?

(Ikke regn med reseptfrie vitamin-, mineral- og kosttilskudd, urter, naturmedisin etc)

Nei Ja

Hvis Nei, hopp til spm 19.1.
Hvis Ja:

Tenk på informasjonen om dine medisiner som du får hos *din fastlege*. Angi i hvilken grad du er enig i følgende utsagn.

Jeg får informasjon om…	Helt uenig	Uenig	Usikker	Enig	Helt enig

18.1.1 Hvorfor jeg skal bruke medisinene
18.1.2 Hvordan jeg skal bruke medisinene (antall tabletter, inntak, med eller uten mat osv)
18.1.3 Hvilke bivirkninger medisinene kan ha
18.1.4 Hvilke andre medisiner eller matvarer som kan påvirke effekten av mine medisiner

Tenk på informasjonen om dine medisiner som du får når du er *på apoteket*. Anig i hvilken grad er er enig i følgende utsagn.

Jeg får informasjon om…	Helt uenig	Uenig	Usikker	Enig	Helt enig

18.1.5 Hvorfor jeg skal bruke medisinene
18.1.6 Hvordan jeg skal bruke medisinene (antall tabletter, inntak, med eller uten mat osv.)
18.1.7 Hvilke bivirkninger medisinene kan ha
18.1.8 Hvilke andre medisiner eller matvarer som kan påvirke effekten av mine medisiner

18.1.9 Har du hjelp med dine medisiner?

Nei Ja

18.1.10 Uavhengig av om du har hjelp eller ikke med dine medisiner, trenger du mer hjelp?

Jeg trenger ikke mer hjelp
Jeg trenger litt mer hjelp
Jeg trenger mye mer hjelp

18.1.11 Trenger du mer informasjon om dine medisiner?

Jeg trenger ikke mer informasjon

Jeg trenger litt mer informasjon
Jeg trenger mye mer informasjon

18.1.12 Generelt sett, hvor viktig mener du at dine medisiner er for deg?

Ikke viktig i det hele tatt
Ikke veldig viktig
Viktig
Veldig viktig

18.1.13 Er du bekymret for dine medisiner?

Ikke bekymret i det hele tatt
Bekymret
Veldig bekymret

Hvis Ikke bekymret i det hele tatt, hopp til spm 18.1.13.
Hvis Bekymret eller Veldig bekymret:

18.1.13.1 Kryss av for hvilke bekymringer du har for dine medisiner

(Sett ett eller flere kryss)

Jeg er bekymret for
Langtids-effekter av mine medisiner
Bivirkninger av mine medisiner
At medisinene skal ha negativ innvirkning på livet mitt
At jeg ikke tar mine medisiner på rett måte
Å bli avhengig av mine medisiner
At medisinene mine skal miste effekten
At medisinene mine gjør mer skade enn nytte
Kostnader med mine medisiner
Annet

Mange mennesker tar ikke sine medisiner hele tiden, enten fordi de ikke kan, glemmer, eller fordi de ikke vil. De følgende spørsmålene omhandler hvordan *du* tar *dine* medisiner.

18.1.14 Hvor mange ganger i uka glemmer du å ta dine medisiner?

Sjeldnere enn 1 gang per uke
1 gang per uke
2-4 ganger per uke
5 ganger per uke eller mer

18.1.15 Hvor mange ganger i uka bestemmer du deg for å ikke ta dine medisiner?

Sjeldnere enn 1 gang per uke
1 gang per uke
2-4 ganger per uke
5 ganger per uke eller mer

19 FYSISK AKTIVITET

19.1 Hvor ofte driver du mosjon?

(Med mosjon mener vi gå en tur, gå på ski, svømme eller drive trening/idrett)

Aldri
Sjeldnere enn en gang i uken
En gang i uken

2-3 ganger i uken
Omtrent hver dag

Hvis Aldri, hopp til spm 20.1.
Hvis >Aldri:

19.1.1 Hvor hardt mosjonerer du i gjennomsnitt?

Tar det rolig uten å bli andpusten eller svett
Tar det så hardt at jeg blir andpusten og svett
Tar meg nesten helt ut

19.1.2 Hvor lenge mosjonerer du per gang i gjennomsnitt?

Mindre enn 15 minutter
15-29 minutter
30 minutter – 1 time
Mer enn 1 time

20 MATVANER

Hvor ofte spiser du vanligvis følgende?
Sett ett kryss for hver linje

0-1 g per mnd 2-3 g per mnd 1-3 g per uke Mer enn 3 g per uke

20.1 Ferskvannsfisk (ikke oppdrett)
20.2 Saltvannsfisk (ikke oppdrett)
20.3 Oppdrettsfisk (laks, røye, ørret)
20.4 Tunfisk (fersk eller hermetisert)
20.5 Fiskepålegg
20.6 Skjell
20.7 Den brune innmaten i krabbe
20.8 Hvalkjøtt/sel/kobbekjøtt
20.9 Innmat fra rein eller elg
20.10 Innmat fra rype
20.11 Tomater og tomatbaserte produkter (f.eks. tomat, ketchup)

Hvor mange ganger i året spiser du/spiste du vanligvis følgende?

Som voksen: antall ganger i året I din barndom: antall ganger i året

20.12 Mølje
20.13 Måsegg
20.14 Reinsdyrkjøtt
20.15 Elgkjøtt
20.16 Villsopp (for eksempel kantarell) og villbær (for eksempel blåbær/tyttebær/multe)

Bruker du følgende kosttilskudd?
(Sett ett kryss per linje)

Nei Iblant Daglig i vinterhalvåret Daglig

20.17 Tran, trankapsler
20.18 Omega 3 (fiskeolje, selolje)
20.19 Kalktabletter
20.20 Vitamintilskudd med vitamin D

Nei Iblant Kun ved reiser Daglig

20.21 Melkesyrebakterier/probiotika

21 SOLING

21.1 Har du vært på solferie siste 2 måneder?
Nei Ja

21.2 Tar du solarium?
Ja, ukentlig Ja, iblant Aldri

22 VEKTEN DIN

22.1 Hvilken vekt ville du være tilfreds med (din trivselsvekt)?
Antall kg___

22.2 Er du fornøyd med vekta di nå?
Ja Nei

22.3 Anslå din vekt da du var 25 år gammel
Antall kg___

22.4 Har du ufrivillig gått ned i vekt siste 6 måneder?
Ja Nei

Hvis Nei, hopp til spm 23.1 eller 24.1 avhengig av kjønn.
Hvis Ja:

22.4.1 Hvis du har gått ufrivillig ned i vekt siste 6 måneder, hvor mange kilo har du gått ned?
Antall kg___

23 MENNS HELSE

23.1 Har du i løpet av de siste 3 mnd hatt problemer med ereksjonsevnen?
Nei Ja

Hvis Nei, hopp til spm 23.2.
Hvis Ja:

23.1.1 Hvordan rangerer du tilliten din til å oppnå og opprettholde en ereksjon
Veldig lav Lav Moderat Høy Veldig høy

23.1.2 Når du har hatt ereksjoner med seksuell stimulering, hvor ofte var ereksjonene stive nok for penetrering (innføring i partner)?

(Nesten) aldri Noen få ganger Noen ganger Oftest (Nesten) alltid

23.1.3 Når du forsøkte å ha samleie, hvor ofte klarte du å vedlikeholde ereksjonen etter penetrering (innføring) hos partner?

(Nesten) aldri Noen få ganger Noen ganger De fleste ganger Oftest (alltid)

23.1.4 Når du forsøkte samleie, hvor vanskelig var det å vedlikeholde din ereksjon til fullendt samleie?

Store vansker Veldig vanskelig Vanskelig Litt vanskelig Ikke vanskelig

23.1.5 Når du forsøkte samleie, hvor ofte var det tilfredsstillende for deg?

(Nesten) aldri Noen få ganger Noen ganger De fleste ganger Oftest (alltid)

23.2 Har noen av dine partnere blitt gravid med deg og spontanabortert?

Nei Ja Vet ikke

Hvis Nei eller Vet ikke, hopp til spm 25.1.
Hvis Ja:

23.2.1 Antall ganger dine partnere har blitt gravid med deg og spontanabortert

Antall ganger__

24 KVINNERS HELSE

24.1 Har du spontanabortert?

Nei Ja Vet ikke

Hvis Nei eller Vet ikke, hopp til spm 24.2.
Hvis Ja:

24.1.1 Antall ganger du har spontanabortert

Antall ganger__

MENSTRUASJON

24.2 Har du menstruasjon fremdeles?

Nei Ja

Hvis Ja, hopp til spm 24.3.
Hvis Nei:

24.2.1 Hvorfor stoppet menstruasjonen?

(sett ett kryss)

Den stoppet av seg selv
Operasjon på livmoren
Operert bort begge eggstokkene
Satte inn hormonspiral
Annen grunn (for eksempel stråling, cellegiftbehandling)

24.2.2 Hvor gammel var du da menstruasjonen stoppet?

Alder___

24.3 Har du i løpet av livet vært plaget av menstruasjonssmerter?

Nei Ja

Hvis Nei, hopp til spm 24.4.
Hvis Ja på spm 24.3 + Nei på spm 24.2:

Hvor gammel var du da menstruasjonssmertene var mest plagsomme?

24.3.1 Fra alder_
24.3.2 Til alder _

24.3.3 Hvor lenge varte menstruasjonssmertene vanligvis da?

Mindre enn 1 dag
1 dag
2 dager
3 dager
4 dager
mer enn 4 dager

24.3.4 På en skala fra 0 til 10, der 0 er ingen smerte og 10 er sterkest tenkelige smerte, hvor sterke var menstruasjonssmertene vanligivis?

Ingen smerte 0 1 2 3 4 5 6 7 8 9 10 Sterkest tenkelige smerte

24.3.5 Hendte det at du var borte fra skole eller jobb på grunn av menstruasjonssmerter?

Aldri Sjelden Ganske ofte Svært ofte

Hvis Ja på spm 24.3 + Ja på spm 24.2:

24.3.6 Hvor lenge varer menstruasjonssmertene vanligvis nå?

Mindre enn 1 dag
1 dag
2 dager
3 dager
4 dager
mer enn 4 dager

24.3.7 På en skala fra 0 til 10, der 0 er ingen smerte og 10 er sterkest tenkelige smerte, hvor sterke er menstruasjonssmertene vanligivis?

Ingen smerte 0 1 2 3 4 5 6 7 8 9 10 Sterkest tenkelige smerte

24.3.8 Hender det at du er borte fra skole eller jobb på grunn av menstruasjonssmerter?

Aldri Sjelden Ganske ofte Svært ofte

BRUK AV PREVENSJON MED HORMONER

24.4 Bruker du nå, eller har du brukt prevensjon med hormoner (p-piller/minipiller/plaster/hormonspiral/implantat)?

Nei Ja, før Ja, nå

Hvis Nei, hopp til spm 24.5.
Hvis Ja, før på spm 24.4:

24.4.1 Alder første gang du brukte prevensjon med hormoner
Alder første gang __

24.4.2 Alder når du sluttet med prevensjon med hormoner
Alder når sluttet __

24.4.3 Hvor mange år har du til sammen brukt prevensjon med hormoner?
Antall år__

Hvis Ja, nå på spm 24.4:

24.4.1 Alder første gang du brukte prevensjon med hormoner
Alder første gang __

24.4.3 Hvor mange år har du til sammen brukt prevensjon med hormoner?
Antall år__

24.4.5 Hvilken type p-pille/minipille/p-plaster/hormonspiral/implantat bruker du nå?
P-piller (Loette Microgynon Oralcon Marvelon Mercilon Yasmin Yasminelle Yaz Zoely Synfase Qlaira)
Minipille (Conludag Cerazette)
Plaster (Evra)
Implantat (Depo-Provera Nexplanon)
Hormonspiral/skjedeinnlegg (Jaydess Mirena NuvaRing)

HORMONBEHANDLING VED NEDGANG I EGNE KJØNNSHORMONER
24.5 Bruker du nå, eller har du brukt østrogenpreparater (tabletter/plaster/vaginalring/tabletter/kremer) for enten plager i overgangsalderen eller av andre årsaker som behandling av beinskjørhet etc?
Nei Ja, før Ja, nå

Hvis Nei, hopp til spm 24.6.
Hvis Ja, før på spm 24.5:

24.5.1 Alder første gang du brukte østrogenpreparater
Alder første gang __

24.5.2 Alder når du sluttet med østrogenpreparater
Alder når sluttet __

24.5.3 Hvor mange år har du til sammen brukt østrogenpreparater?
Antall år__

Hvis Ja, nå på spm 24.5:

24.5.1 Alder første gang du brukte østrogenpreparater
Alder første gang __

24.5.3 Hvor mange år har du til sammen brukt østrogenpreparater?
Antall år__

24.5.4 Hvilke hormonpreparater bruker du nå?

Plaster (Evorel Estalis Estradot Sequidot)
Tabletter (Activelle Cliovelle Eviana Indivina Novofem Trisekvens Progynova Livial)
Ovesterin tabletter
Ring/tablett til skjeden (Estring Vagifem)
Ovesterin vaginalkrem, Ovesterin vagitorier

Ja, helt klart Ja, noen ganger Nei, ikke så mye Nei, ikke i det hele tatt

24.6 Har du eller har du hatt hetetokter?
24.7 Er du eller har du vært plaget av nattesvette?

FRAMFALL I SKJEDEN
24.8 Kjenner du et framfall i skjeden?

Med framfall (genital prolaps) menes her et framfall av livmor og/eller skjedevegg som er så stort at det kjennes.

Ikke
Litt
Ganske mye
Svært mye

Hvis Ikke, hopp til spm 25.1.
Hvis Litt, Ganske mye eller Svært mye:

FRAMFALL I SKJEDEN

Ikke Litt Ganske mye Svært mye

24.8.1 Har du nedtrykk-følelse i skjeden eller underlivet som blir verre utover dagen?
24.8.2 I hvor stor grad har fremfallet innflytelse på ditt liv?
24.8.3 Har framfallet en innflytelse på dine fysiske aktiviteter (for eksempel: å spasere, sykle, gå på trim)?
24.8.4 Må du presse for å tømme blæren?
24.8.5 Har du følelse av at framfallet er sjenerende under samleie?

24.8.6 Hvis behov, kan du presse framfallet tilbake i skjeden?

Aldri
Av og til
Ofte
Alltid

24.8.7 Kjenner du deg fullstendig tømt (avføring) etter toalettbesøk?

Alltid
Som oftest
Ganske ofte
Som oftest ikke

24.8.8 Har du søkt hjelp for framfall/prolaps

Nei Ja

25 SEKSUALHELSE

25.1 Har du i løpet av de siste 12 måneder vært seksuelt aktiv ?

Nei Ja

25.2 Hvor mange seksualpartnere har du hatt totalt (Sett 0 dersom du ikke har hatt seksualpartner)?

Antall seksualpartnere__

25.3 Har du noen gang praktisert munnsex (utført på partner og/eller mottatt)?

Nei Ja

Hvis Nei, hopp til spm 26.1.
Hvis Ja:

25.3.1 Har du i løpet av de siste 12 måneder praktisert munnsex (utført på partner og/eller mottatt)?

Nei Ja

26 VANNLATNING

26.1 Har du hatt vannlatningsbesvær i løpet av den siste måneden?

(f.eks. svak stråle, følelse av ufullstendig blæretømning eller hyppig vannlatning)

Nei Ja

Hvis Nei, hopp til spm 27.1.
Hvis Ja:

VANNLATNINGSBESVÆR

Aldri Mindre enn 1 av 5 ganger Mindre enn halvparten av gangene Omtrent halvparten av gangene Mer enn halvparten av gangene Nesten alltid

26.1.1 Hvor ofte har du hatt følelsen av at blæren ikke er fullstendig tømt etter avsluttet vannlatning?
26.1.2 Hvor ofte har du måttet late vannet på nytt mindre enn to timer etter forrige vannlatning?
26.1.3 Hvor ofte har du måttet stoppe og starte flere ganger mens du lot vannet?
26.1.4 Hvor ofte har det vært vanskelig å utsette vannlatningen?
26.1.5 Hvor ofte har du hatt svak stråle
26.1.6 Hvor ofte har du måttet trykke eller presse for å late vannet?
26.1.7 Hvor ofte har du vanligvis måttet stå opp i løpet av natten for å late vannet?

27 URINLEKKASJE

27.1 Hvor ofte lekker du urin?

(Sett ett kryss)

Aldri
Omtrent en gang i uken eller sjeldnere
2-3 ganger i uken

ca 1 gang per dag
Flere ganger per dag
Hele tiden

Hvis Aldri, hopp til spm 28.1.
Hvis >Aldri:

URINLEKKASJE

27.1.1 Hvor mye urin lekker du vanligvis?

(Sett ett kryss)

Ikke noe
En liten mengde
En moderat mengde
En stor mengde

27.1.2 Hvor mye påvirker urinlekkasje ditt hverdagsliv?

Sett kryss for et tall mellom 0 (ikke i det hele tatt) og 10 (svært mye).

Ikke i det hele tatt 0 1 2 3 4 5 6 7 8 9 10 Svært mye

27.1.3 Når lekker du urin

(Sett ett eller flere kryss)

Aldri, jeg lekker ikke urin
Lekker før jeg når toalettet
Lekker når jeg hoster eller nyser
Lekker når jeg sover
Lekker når jeg er fysisk aktiv/trimmer
Lekker når jeg er ferdig med å late vannet og har tatt på meg klærne
Lekker uten noen opplagt grunn
Lekker hele tiden

27.1.4 Har du søkt hjelp for urinlekkasje

Nei Ja

28 PSYKISK HELSE

Under finner du en liste over ulike problemer. Har du opplevd noe av dette *den siste uken* (til og med i dag)?
(Sett ett kryss for hver plage)

	Ikke plaget	Litt plaget	Ganske mye	Veldig mye

28.1 Plutselig frykt uten grunn
28.2 Føler deg redd eller engstelig
28.3 Matthet eller svimmelhet
28.4 Føler deg anspent eller oppjaget
28.5 Lett for å klandre deg selv
28.6 Søvnproblemer
28.7 Nedtrykt, tungsindig
28.8 Følelse av å være unyttig, lite verd
28.9 Følelse av at alt er et slit
28.10 Følelse av håpløshet mht. framtida

Her kommer noen spørsmål om hvorledes du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser *den siste uken*. Ikke tenk for lenge på svaret – de spontane svarene er best.

28.11 Jeg føler meg nervøs og urolig

Mesteparten av tiden
Mye av tiden
Fra tid til annen
Ikke i det hele tatt

28.12 Jeg gleder meg fortsatt over tingene slik jeg pleide før

Avgjort like mye
Ikke fullt så mye
Bare lite grann
Ikke i det hele tatt

28.13 Jeg har en uroføIelse som om noe forferdelig vil skje

Ja, og noe svært ille
Ja, ikke så veldig ille
Litt, bekymrer meg lite
Ikke i det hele tatt

28.14 Jeg kan le og se det morsomme i situasjoner

Like mye nå som før
Ikke like mye nå som før
Avgjort ikke som før
Ikke i det hele tatt

28.15 Jeg har hodet fullt av bekymringer

Veldig ofte
Ganske ofte
Av og til
En gang i blant

28.16 Jeg er i godt humør

Aldri
Noen ganger
Ganske ofte
For det meste

28.17 Jeg kan sitte i fred og ro og kjenne meg avslappet

Ja, helt klart
Vanligvis
Ikke så ofte
Ikke i det hele tatt

28.18 Jeg føler meg som om alt går langsommere

Nesten hele tiden
Svært ofte
Fra tid til annen
Ikke i det hele tatt

28.19 Jeg føler meg urolig som om jeg har sommerfugler i magen

Ikke i det hele tatt
Fra tid til annen
Ganske ofte
Svært ofte

28.20 Jeg bryr meg ikke lenger om hvordan jeg ser ut

Ja, jeg har sluttet å bry meg
Ikke som jeg burde
Kan hende ikke nok
Bryr meg som før

28.21 Jeg er rastløs som om jeg stadig må være aktiv

Uten tvil svært mye
Ganske mye
Ikke så veldig mye
Ikke i det hele tatt

28.22 Jeg ser med glede frem til hendelser og ting

Like mye som før
Heller mindre enn før
Avgjort mindre enn før
Nesten ikke i det hele tatt

28.23 Jeg kan plutselig få en følelse av panikk

Uten tvil svært ofte
Ganske ofte
Ikke så veldig ofte
Ikke i det hele tatt

28.24 Jeg kan glede meg over gode bøker, radio og TV

Ofte
Fra tid til annen
Ikke så ofte
Svært sjelden

29 BEKYMRINGER

Hvor typisk er utsagnene for deg:
(Sett ett kryss for hver påstand, fra 1=Ikke typisk til 5=Meget typisk)

	Ikke typisk		Noe typisk		Meget typisk
	1	2	3	4	5

29.1 Jeg bekymrer meg hele tiden
29.2 Mange situasjoner får meg til å bli bekymret
29.3 Jeg bekymrer meg alltid for et eller annet

30 TRAUMER

Har du noen gang opplevd noen av disse hendelsene?
(Sett ett eller flere kryss for hver linje)

	Nei	Ja, før fylte 18 år	Ja, etter fylte 18 år	Ja, siste året

30.1 En livstruende sykdom eller vært utsatt for en alvorlig ulykke (f.eks. brann, arbeids- eller bilulykke)
30.2 Blitt utsatt for vold (f. eks. slått, sparket, banket opp, ranet, eller truet med skytevåpen)
30.3 Blitt utsatt for seksuelle overgrep, det vil si utsatt for seksuelle handlinger uten at du selv ønsket det
30.4 Blitt kalt noe negativt, holdt utenfor, truet eller plaget av medelever, studiekamerater eller arbeidskollegaer over lengre tid
30.5 Vært vitne til at noen som står deg nær er blitt utsatt for vold eller seksuelle overgrep (f. eks. slått, sparket, banket opp, ranet, truet med skytevåpen, eller drept)
30.6 Opplevd noe annet som har vært skremmende, farlig eller voldelig (f.eks. naturkatastrofe, krig, terrorhandlinger, holdt fanget, etc)
30.7 Dødsfall hos noen som stod deg nær og har vanskelig for å akseptere tapet, lengter etter den avdøde og opplever intens følelsesmessig smerte knyttet til tapet
30.8 Fått smertefull eller skremmende medisinsk behandling da du var på sykehus fordi du var syk eller alvorlig skadet
30.9 Fått smertefull eller skremmende behandling hos tannlege
30.10 At noen som står deg nær har vært livstruende syk eller utsatt for en alvorlig ulykke (f. eks. brann, arbeids- eller bilulykke)
30.11 Omsorgssvikt under oppveksten, det vil si ikke fått det nødvendige av mat, klær, beskyttelse og omsorg/kjærlighet fra foreldre/foresatte

Nei Ja

Hvis Nei på alle 30.1-30.11, hopp til spm 31.1.
Hvis Ja på minst ett av 30.1-30.11:

30.1.1 Tenker du fortsatt mye på det som skjedde?

Nei Ja

31 ALKOHOL

31.1 Har du drukket alkohol det siste året?

Nei Ja

Hvis Nei, hopp til spm 31.1.1.15.
Hvis Ja:

Prøv så godt du kan å gi et "gjennomsnitt" av dine alkoholvaner. Ha det siste året i tankene når du fyller ut.

31.1.1-*31.1.8.2*

9. Alkoholholdige drikker

Svar enten pr. måned eller pr. uke. Merk at porsjonsenhetene er forskjellige, 1/5 liter tilsvarer ett glass (2 dl), mens 1/3 liter tilsvarer 0,33 liter glassflaske/boks.

	Gang pr. måned eller Gang pr. uke								Mengde pr. gang						
	Aldri/ sjelden	1	2	3	1	2-3	4-5	6-7							
Øl, sterk øl, pils	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/3 ☐	½ ☐	1 ☐	2 ☐	3 ☐	4+ ☐
Lettøl	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/3 ☐	½ ☐	1 ☐	2 ☐	3 ☐	4+ ☐
Rusbrus, Cider m/alkohol	☐	☐	☐	☐	☐	☐	☐	☐	(liter)	1/5 ☐	1/3 ☐	½ ☐	1 ☐	1½ ☐	2+ ☐
Rødvin	☐	☐	☐	☐	☐	☐	☐	☐	(vinglass)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐
Hvitvin	☐	☐	☐	☐	☐	☐	☐	☐	(vinglass)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐
Hetvin (portvin, sherry o.l.)	☐	☐	☐	☐	☐	☐	☐	☐	(1 glass = 4cl)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐
Brennevin, likør	☐	☐	☐	☐	☐	☐	☐	☐	(1 dram = 4cl)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐
Blandede drinker, cocktail	☐	☐	☐	☐	☐	☐	☐	☐	(drink)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐

Hvor ofte har du det siste året:

Aldri Sjeldnere enn månedlig Månedlig Ukentlig Daglig eller nesten daglig

31.1.1.9 Ikke klart å stoppe og drikke alkohol når du først har begynt?
31.1.1.10 Ikke klart å gjøre det som normalt forventes av deg fordi du har drukket?
31.1.1.11 Trengt alkohol om morgenen for å få komme i gang etter en rangel?
31.1.1.12 Følt skyld eller anger etter at du har drukket?
31.1.1.13 Ikke klart å huske hva som skjedde kvelden før på grunn av at du hadde drukket?
31.1.1.14 Drukket så mye at du har kjent deg sterkt beruset (full)?

Aldri Ja, men ikke det siste året Ja, det siste året

31.1.1.15 Har du eller andre noen gang blitt skadet på grunn av at du har drukket?
31.1.1.16 Har en slektning, venn, lege, eller annet helsepersonell vært bekymret for din drikking, eller foreslått at du reduserer inntaket?

32 ANDRE RUSMIDLER

32.1 Bruker du eller har du brukt andre rusmidler enn alkohol (f.eks hasj, amfetamin, kokain, heroin, hallusinogener, løsemidler, GHB)?

Nei Ja, nå Ja, tidligere

Hvis Nei hopp til spm 32.2.
Hvis Ja, nå eller Ja, tidligere:

32.1.1 Hva var din alder første gang du brukte andre rusmidler enn alkohol (f.eks. amfetamin, kokain, heroin, hallusinogener, løsemidler, GHB)?

Alder første gang__

32.1.2 I løpet av det siste året, hvor ofte har du brukt andre rusmidler enn alkohol (f.eks hasj, amfetamin, kokain, heroin, hallusinogener, løsemidler, GHB)?

Ikke brukt siste 12 måneder
1 gang i måneden eller sjeldnere
2-4 ganger i måneden
2-3 ganger i uken
4 ganger i uken eller mer

32.2 Bruker du eller har du brukt reseptbelagte legemidler for å oppnå rus (f.eks beroligende medisin, sovemedisin, smertestillende medisin, ADHD-medisin)?

Nei Ja, nå Ja, tidligere

Hvis Nei hopp til spm 33.1.
Hvis Ja, nå eller Ja, tidligere:

32.2.1 Hva var din alder første gang du brukt reseptbelagte legemidler for å oppnå rus (f.eks beroligende medisin, sovemedisin, smertestillende medisin, ADHD-medisin)?

Alder første gang__

32.2.2 I løpet av de siste 12 måneder, hvor ofte har du brukt reseptbelagte legemidler for å oppnå rus (f.eks beroligende medisin, sovemedisin, smertestillende medisin, ADHD-medisin)?

Ikke brukt siste 12 måneder
1 gang i måneden eller sjeldnere
2-4 ganger i måneden
2-3 ganger i uken
4 ganger i uken eller mer

33 RØYK OG SNUS

DAGLIG RØYKING

33.1 Røyker du daglig eller har du tidligere røykt daglig?

Aldri Ja, nå Ja, tidligere

Hvis Aldri, hopp til spm 33.2.
Hvis Ja, nå eller Ja, tidligere:

DAGLIG RØYKING

33.1.1 Hvor gammel var du da du begynte å røyke daglig?

Alder__

33.1.2 Hvor mange år til sammen har du røykt daglig?

Antall år__

33.1.3 Hvor mange sigaretter røyker/røykte du vanligvis daglig?

Antall sigaretter__

Hvis Ja, tidligere på spm 33.1:

DAGLIG RØYKING

33.1.4 Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet?

Antall år__

AV-OG-TIL RØYKING

33.2 Røyker du av og til men ikke daglig, eller har du tidligere røykt av og til men ikke daglig?

Aldri Ja, nå Ja, tidligere

Hvis Aldri, hopp til spm 33.3.
Hvis Ja, nå eller Ja, tidligere:

AV-OG-TIL RØYKING

33.2.1 Hvor mange sigaretter røyker/røykte du vanligvis per uke?

Antall sigaretter__

DAGLIG SNUSING

33.3 Bruker du eller har du tidligere brukt snus eller skrå daglig?

Aldri Ja, nå Ja, tidligere

Hvis Aldri, hopp til spm 33.4.
Hvis Ja, nå eller Ja, tidligere:

DAGLIG SNUSING

33.3.1 Hvor gammel var du da du begynte å snuse daglig?

Alder__

33.3.2 Hvor mange år til sammen har du snust daglig?

Antall år__

33.3.3 Hvis du snuser daglig nå eller har snust daglig tidligere, hvor mange porsjoner snus bruker/ brukte du vanligvis daglig?

Antall porsjoner__

Hvis Ja, tidligere på spm 33.3:

DAGLIG SNUSING
33.3.4 Hvis du har snust daglig tidligere, hvor lenge er det siden du sluttet?
Antall år__

AV-OG-TIL SNUSING
33.4 Bruker du eller har du tidligere brukt snus av og til, men ikke daglig?
Aldri Ja, nå Ja, tidligere

Hvis Aldri, hopp til spm 34.1.
Hvis Ja, nå eller Ja, tidligere:

AV-OG-TIL SNUSING
33.4.1 Hvor mange porsjoner snus bruker/brukte du vanligvis per uke?
Antall porsjoner__

34 STØY

Hvor følsom er du for støy? Sett kryss ved det utsagnet som passer best.

34.1 Jeg er følsom for støy
Helt enig
Ganske enig
Litt enig
Litt uenig
Ganske uenig
Helt uenig

34.2 Har du nedsatt hørsel (ett/begge ører)?
Nei Ja

34.3 Har du i løpet av de siste 12 måneder hatt øresus i perioder som varer lengre enn 5 minutter?
Nei Ja

Hvis Nei hopp til spm 34.4.
Hvis Ja:

ØRESUS
34.3.1 Hvor ofte har du øresus?
(Sett ett kryss)
Sjeldnere enn hver uke
Hver uke, men ikke hver dag
Hver dag, men ikke hele tiden
Nesten alltid

34.3.2 Hvor lenge varer vanligvis periodene med øresus?
(Sett ett kryss)
Noen få minutter
10 minutter til 1 time
Lengre enn 1 time

34.3.3 Noen bryr seg ikke om lyden, for andre oppleves det svært plagsomt å ha øresus. Angi hvor plaget du er av øresusen med det tall mellom 0 og 10, der 0 er inger plager og 10 er verst tenkelige plager.

0 Ingen plager 10 Verst tenkelige plager

Hvis du tenker på de siste 12 månedene, hvor plaget er du av støy hjemme fra kildene nedenfor? (Sett ett kryss for hver linje)

Ikke plaget Litt plaget Middels plaget Mye plaget Ekstremt plaget

34.4 Veitrafikk
34.5 Helikopter
34.6 Fly
34.7 Båt/skip/havn
34.8 Bygge- og anleggsvirksomhet
34.9 Industri- og næringsvirksomhet
34.10 Nabo/andre utenfor din bolig
34.11 Andre innenfor din bolig (f. eks. som spiller høy musikk, snorkende partner, barn som våkner og skriker om natten o.l.)
34.12 Annen støykilde

34.13 Hvor mange år til sammen har du arbeidet på steder med støy der det har vært nødvendig å rope for å bli hørt?

Antall år___

Hvis ikke Yrkesaktiv heltid eller Yrkesaktiv deltid på spm 4.1 hopp til spm 35.1.
Hvis Yrkesaktiv heltid eller Yrkesaktiv deltid på spm 4.1:

34.13.1 Hvis du tenker på de siste 12 månedene, hvor plaget er du av støy (fra musikk, prating, ventilasjonsanlegg, maskiner og utstyr el.l.) som virker forstyrrende i ditt arbeide?

Ikke plaget
Litt plaget
Middels plaget
Mye plaget
Ekstremt plaget

35 TANNHELSE

Her kommer noen spørsmål om hvordan tennenes og munnhulens tilstand kan påvirke deg i dine daglige gjøremål. Først vil vi stille noen spørsmål om ulike **plager med tennene, eventuelt gebiss, løstenner eller tannprotese**.

PLAGER MED TENNER/TANNPROTESER

Hver dag eller nesten hver dag En til to ganger i uka En til to ganger i måneden
Sjeldnere enn en gang i måneden Aldri

35.1 I løpet av de siste 6 månedene, hvor ofte har slike plager gjort det vanskelig for deg å spise og nyte maten?
35.2 I løpet av de siste 6 månedene, hvor ofte vil du si at slike plager har gjort det vanskelig for deg å snakke og uttrykke deg tydelig?
35.3 I løpet av de siste 6 månedene, hvor ofte har slike plager gjort tannrengjøringen vanskelig?
35.4 I løpet av de siste 6 månedene, vil du si at slike plager har gjort det vanskelig for deg å sove og slappe av?
35.5 I løpet av de siste 6 månedene, hvor ofte vil du si at slike plager har gjort det vanskelig for deg å smile og vise tenner uten å bli brydd?
35.6 I løpet av de siste 6 månedene, hvor ofte vil du si at slike plager har gjort det vanskelig for deg å være følelsesmessig stabil uten å bli irritabel?
35.7 I løpet av de siste 6 månedene, hvor ofte vil du si at slike plager har gjort det vanskelig for deg å glede deg over samvær med andre mennesker?
35.8 I løpet av de siste 6 månedene, hvor ofte vil du si at slike plager har gjort det vanskelig for deg å utføre daglig gjøremål?

35.9 Hvor ofte pusser du vanligvis tennene dine?

Sjeldnere enn 1 gang per uke
Noen ganger i uka
En gang daglig
To eller flere ganger daglig

35.10 Går du regelmessig til tannlege/tannpleier?

Ja, mer enn en gang i året
Ja, hvert år
Ja, hvert annet år
Ja, med lengre mellomrom enn 2 år
Nei, bare for akutte problemer
Nei, går aldri

Bruker du selv noen av følgende hjelpemidler og i tilfelle hvor ofte?

Aldri/Sjelden Noen ganger i måneden Noen ganger i uka Daglig

35.11 Fluortannkrem
35.12 Tanntråd, mellomromsbørste og eller tannstikker
35.13 Fluortabletter
35.14 Fluorskyllevæske (Flux; Fluorid tannskyll; Nicodent)
35.15 Antibakteriell skyllvæske (Listerine, Corsodyl, Klorhexidin)

Her kommer noen spørsmål om hvordan du opplever tannlegebesøk. Føler du, eller føler du ikke engstelse ved tannlegebesøk?

Ikke engstelig i det hele tatt Litt engstelig Ganske engstelig Meget engstelig
Ekstremt engstelig

35.16 Dersom du skulle til tannlegen i morgen, hvordan vil du føle deg?
35.17 Når du sitter i tannlegens venteværelse og venter på tur, hvordan føler du deg?
35.18 Hvordan føler du det når du sitter i tannlegestolen og venter på at tannlegen skal bore i tannen/tennene dine?
35.19 Tenk deg at du sitter i tannlegestolen og venter på at tannlegen skal får rengjort tennene dine. Hvordan føler du deg når tannlegen tar fram instrumentene for å fjerne tannsten?
35.20 Hvis du måtte ta bedøvelse («sprøyte») for behandling av en jeksel i overkjeven, hvordan vil du føle deg?

36 HUD- OG LEDDPLAGER

Har du eller har du noen gang hatt følgende hud- eller leddsykdommer?

Nei Ja

36.1 Psoriasis
36.2 Psoriasis artritt (psoriasis leddgikt)
36.3 Atopisk eksem (barneeksem)
36.4 Tilbakevendende (kronisk) håndeksem
36.5 Tilbakevendende, store, smertefulle kuler (verkebyller) som ofte tilheler med arr, i armhuler, lysker eller under brystene (sykdom kalt hidradrenitis)?

Hvis Ja på spm 36.1:

PSORIASIS
36.1.1 Har du fått diagnosen psoriasis av lege?

Nei Ja

36.1.2 Har du vært plaget av psoriasis i løpet av de siste 12 månedene?

Nei Ja

Hvis Ja på spm 36.2:

36.1.2.1 Hvilken beskrivelse passet/passer best til din psoriasis siste 12 måneder?

(Sett ett kryss)

Plutselige, bitte små flekker over hele kroppen (mindre enn 1 cm)
Flekker på albuer/knær/hodebunn som kommer av og til
Flekker på albuer/knær/hodebunn som er nærmest konstant til stede
Flekker på albuer/knær/hodebunn men også enkelte flekker på overkroppen, som nærmest konstant er til stede
Utslett på større områder på kroppen som kommer av og til
Utslett på større områder på kroppen som er nærmest konstant til stede

Hvis Ja på spm 36.2:

PSORIASIS ARTRITT (PSORIASIS LEDDGIKT)
36.2.1 Har du vært plaget av psoriasis artritt i løpet av de siste 12 månedene?

Nei Ja

Hvis Nei på spm 36.3

ATOPISK EKSEM (BARNEEKSEM)

36.3.1 Har du vært plaget av atopisk eksem i løpet av de siste 12 månedene?

Nei Ja

Hvis på spm 36.4:

TILBAKEVENDENDE (KRONISK) HÅNDEKSEM

36.4.1 Har du vært plaget av tilbakevendende håndeksem i løpet av de siste 12 månedene?

Nei Ja

Hvis Ja på spm 36.5:

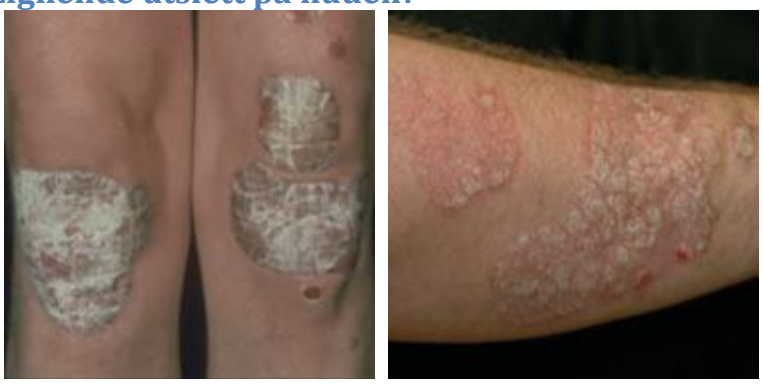
VERKEBYLL (HIDRADRENITIS)

36.5.1 Har du vært plaget av verkebyll i løpet av de siste 12 månedene?

Nei Ja

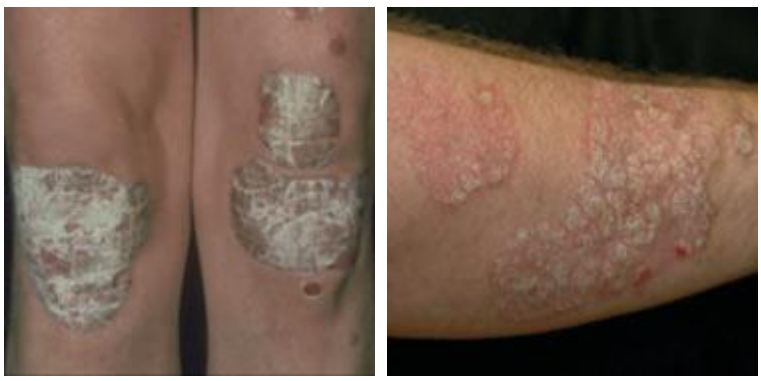
Har du eller har du hatt:
(Sett ett eller flere kyss)

36.6 Lignende utslett på huden?



Nei Ja

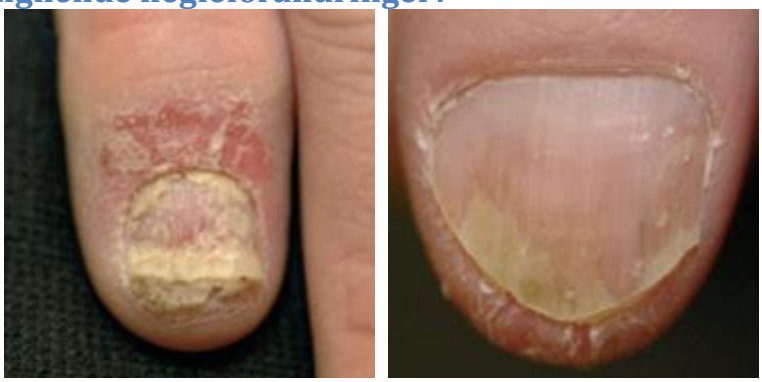
Hvis Nei, hopp til spm 36.7.
Hvis Ja:



36.6.1 Har du hatt slikt utslett på huden i løpet av de siste 12 månedene?

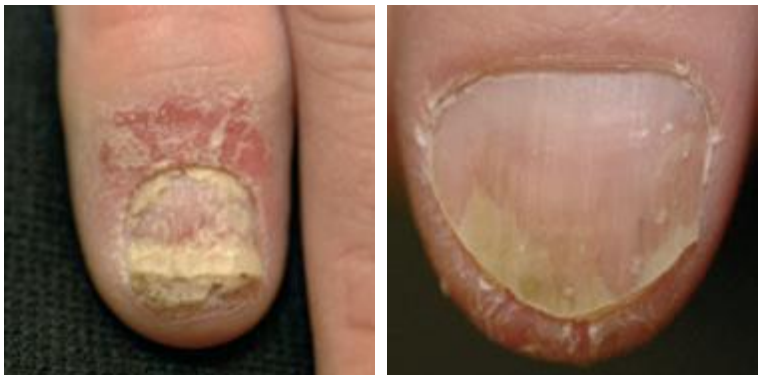
Nei Ja

36.7 Lignende negleforandringer?



Nei Ja

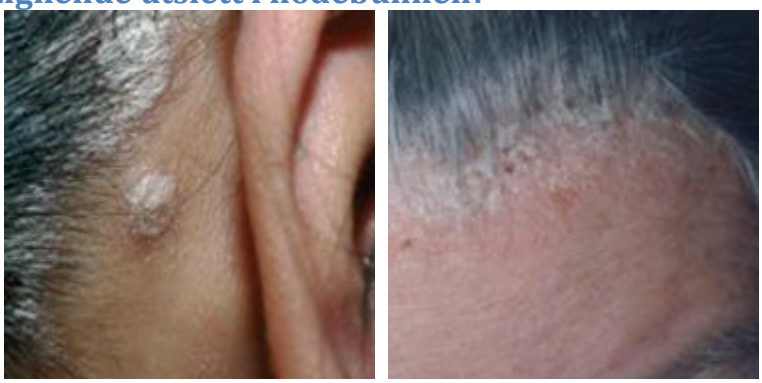
Hvis Nei, hopp til spm 36.8.
Hvis Ja:



36.7.1 Har du hatt slike negleforandringer i løpet av de siste 12 månedene?

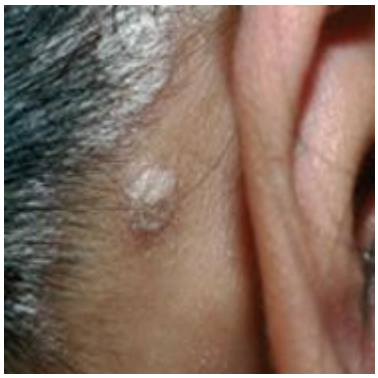
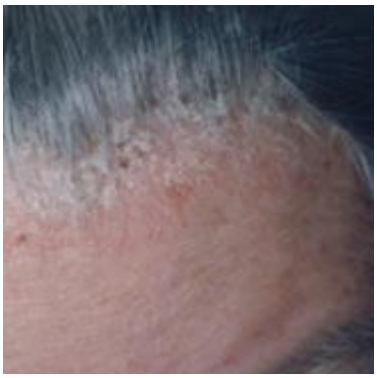
Nei Ja

36.8 Lignende utslett i hodebunnen?



Nei Ja

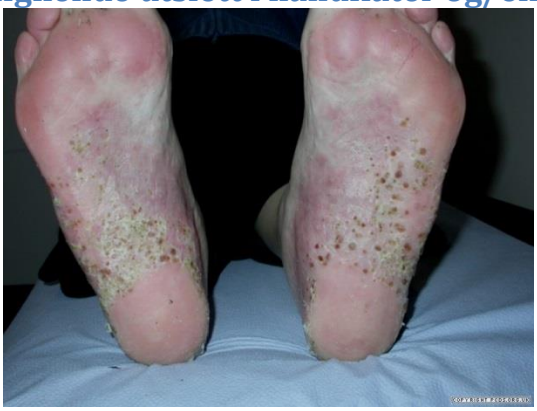
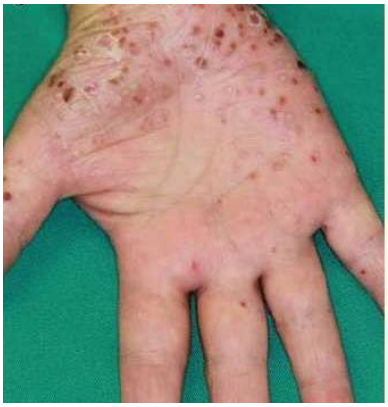
Hvis Nei, hopp til spm 36.9.
Hvis Ja:

36.8.1 Har du hatt slikt utslett i hodebunnen i løpet av de siste 12 månedene?

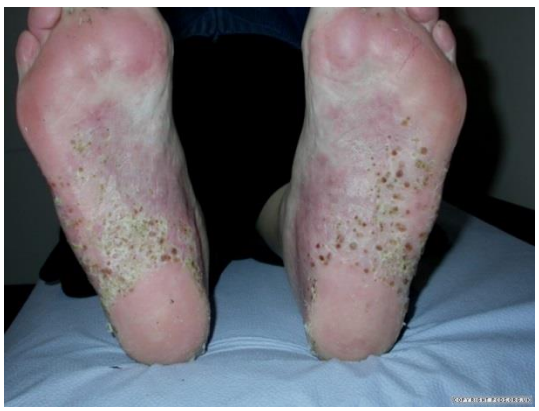
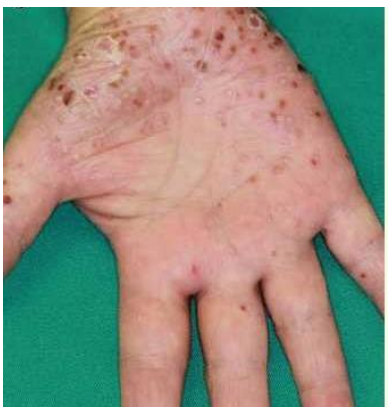
Nei Ja

36.9 Lignende utslett i håndflater og/eller fotsåler?

Nei Ja

Hvis Nei, hopp til spm 36.10.
Hvis Ja:

36.9.1 Har du hatt slikt utslett i håndflater og/eller fotsåler i løpet av de siste 12 månedene?

Nei Ja

36.10 Har du hatt utslett eller rødhet/irritasjon i lyskene, under/mellom rumpeballene eller under armene som har vart i mer enn 2 uker?

Nei Ja

37 REISER UTENFOR NORDEN

37.1 I løpet av de siste 12 måneder, hvor mange reiser har du hatt utenfor Norden med varighet lengre enn en uke?

(Sett 0 dersom du ikke har reist lengre enn en uke utenfor Norden siste 12 måneder)

Antall reiser i rullegardinmeny (1-20 reiser)

Hvis Reiser =0, hopp til spm 38.1.
Hvis Reiser >0:

For hver reise utenfor Norden med varighet lengre enn en uke, kryss av for landet du opphold deg lengst i, om du hadde diare i forbindelse med reisen, og dersom du var sykehusinnlagt, hvor mange ganger:

For reise 1-20:

37.1.1 Land

Rullegardinmeny land alfabetisk (200 land)

37.1.2 Diare

Nei Ja

37.1.3 Antall ganger sykehusinnlagt

(Sett 0 dersom du ikke var sykehusinnlagt i forbindelse med oppholdet)

Antall ganger__

Hvis Antall ganger sykehusinnlagt =0, hopp til spm 38.1.
Hvis Antall ganger sykehusinnlagt >0:

For hver sykehusinnleggelse i land utenfor Norden siste 12 måneder, i hvilket land var du sykehusinnlagt, hvilken måned du ble sykehusinnlagt, og hvor mange dager var du sykehusinnlagt:

37.1.3.1 Land

Rullegardinmeny land alfabetisk (200 land)

37.1.3.2 Måned sykehusinnlagt

Mars 2015 etc

37.1.3.3 Varighet sykehusinnleggelse

Antall dager__

38 ANTIBIOTIKAKJØP I UTLANDET

38.1 Har du kjøpt antibiotika i utlandet i løpet av de siste 12 måneder (penicillinlignende medisin til behandling av infeksjon)?

Nei Ja

Hvis Nei, ferdig med skjema.
Hvis Ja:

38.1.1 Hvordan foregikk kjøpet?

Behandlingen var etter resept fra lege/tannlege
Kjøpte direkte fra apotek uten resept