Alcoholic Liver Disease (ALD): Medication and clinical parameters associated with course of disease

Andreas Teufel, Timo Itzel

Medical Faculty Mannheim, Heidelberg University, Germany

**Contact**

Prof. Dr. Dr. Andreas Teufel

Timo Itzel, M. Sc.

University Medical Center Mannheim

Department of Medicine II

Medical Faculty Mannheim

Heidelberg University

Theodor Kutzer Ufer 1-3

68167 Mannheim

Germany

Phone: +49 (0)621 383 4983 / -4077

Fax: +49(0)0621 383 1467

email: andreas.teufel@medma.uni-heidelberg.de

# Abstract

Chronic excessive alcohol consumption can then lead to significant liver damage, particularly, fatty liver disease, alcoholic hepatitis, cirrhosis of the liver. As a result of liver cirrhosis, liver failure and hepatocellular carcinoma may develop, both of which may require liver transplantation.

Treatment of alcoholic liver disease is difficult therapies available for these patients. Alcohol abstinence is the decisive factor, but is not achieved by many patients despite accompanying behavioral therapy or psychosocial support. As a last option, liver transplantation may be considered. However, the current criteria of the German Medical Association require patients to abstain from alcohol for at least 6 months. Since this is not fulfilled by many patients at the time of diagnosis, liver transplantation is ruled out for many patients with rapid decompensation of alcoholic liver disease.

Therefore, the proposed study will be an observational cohort study based on routinely-collected health care data which has been mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). Cohorts of individuals with ALD will be identified and stratified for co-occurrence of viral hepatitis B or C. Clinical features and drug responses linked to deterioration of alcoholic liver disease will be described with regard to an influence on the patient's survival.

# Rationale & Background

In Germany, but also in many other countries around the world, alcohol consumption is deeply rooted in society. Alcoholic drinks are indispensable at celebrations and festivals of all kinds. However, alcohol consumption in Western countries is considerable. In Germany, for example, it is estimated that around 2.1-3% of the adult population have an alcohol problem or meet the criteria of alcohol dependence [1].

The limit for supposedly “safe” alcohol consumption is currently assumed to be around 20g/d for men and around 10g/d for women. A possible reason for these gender-specific alcohol quantities could be that women have less alcohol dehydrogenase in their gastric mucosa, which means that more alcohol reaches the liver unmetabolized.

Excessive alcohol consumption can then lead to significant liver damage. In this regard, the following pathological changes should be mentioned in particular

• fatty liver (> 90%)

• Alcoholic hepatitis (10–35%)

• cirrhosis of the liver (10–20%)

As a result of liver cirrhosis, liver failure and hepatocellular carcinoma may develop, both of which may require liver transplantation. Overall, there appears to be a generally linear correlation between the amount and duration of alcohol consumption and the development of liver disease in affected persons. The risk of liver disease increases significantly for men who drink >80g of alcohol per day over a period of more than 10 years. If the alcohol consumption is even higher than 230 g/day over 20 years, the risk of cirrhosis is around 50%. However, only some alcohol-dependent people develop liver disease, which is why the influence of additional factors can be assumed. A better understanding of these factors could lead to improved therapeutic options in the future [2].

**Symptoms**

Symptoms usually appear relatively late, and the initial fatty liver is often asymptomatic. In one third of patients, the liver is enlarged and soft, but usually not tender to pressure. Raised liver values ​​during routine check-ups, fatigue, fever, jaundice, pain in the right upper abdomen or pressure-sensitive liver enlargement may be the first findings that trigger further diagnostics and ultimately lead to the diagnosis of alcoholic liver disease. Compensated liver cirrhosis can also be asymptomatic.

If the patients are already symptomatic as part of their alcoholic liver disease, pancreatitis, myopathies and peripheral neuropathies are common symptoms. In men, chronic alcohol abuse can lead to hypogonadism and feminization. Malnutrition with multiple vitamin deficiencies, parotid enlargement and nail changes are also observed. Finally, thiamine deficiency can lead to psychiatric changes such as Wernicke encephalopathy and Korsakoff psychosis in severely alcohol-dependent patients. Pancreatitis is common [2].

At this stage, however, symptoms of portal hypertension such as Esophageal varices and upper gastrointestinal bleeding, splenomegaly, ascites or hepatic encephalopathy are prominent as well as jaundice and the development of liver tumors. The risk of developing HCC is estimated to be as high as 2.6% per year in patients with alcoholic cirrhosis [3].

**Therapy**

Treatment of alcoholic liver disease is difficult. Alcohol abstinence is the decisive factor, but is not achieved by many patients despite accompanying behavioral therapy or psychosocial support.

The benefit of corticosteroids in the treatment of alcoholic hepatitis is controversial; there is speculation about an improvement in the course and survival in patients with severe forms without complications such as infections, gastrointestinal bleeding, kidney failure or pancreatitis. Various clinical decision-making aids have been formulated for the use of corticoids (including Maddrey discriminant function [4], Lille Score [5]), but these have not yet established themselves as the clear standard in therapy. Antioxidants, pentoxifylline, anti-TNF-alpha antibodies (e.g. infliximab, etanercept), penicillamine, propylthiouracil or silymarin are discussed, but a clear effectiveness of these substances has not yet been proven [6].

In contrast, drug therapy can be very helpful in treating withdrawal symptoms. Opioid antagonists (e.g. naltrexone) and drugs, GABA receptor inhibitors (e.g. baclofen) and benzodiazepines (e.g. diazepam) are well established in therapy and can effectively alleviate the symptoms of withdrawal.

The focus of treatment is on accompanying measures. A nutrient-rich diet with added vitamins (especially B vitamins) is important during the first few days of alcohol abstinence.

As a last option, liver transplantation may be considered, whereby the survival rates of patients with alcoholic liver disease are in principle good. The 5-year survival rates are around 80% comparable to those of non-alcoholic liver diseases [7]. However, the current criteria of the German Medical Association require patients to abstain from alcohol for 6 months. Since this is not fulfilled by many patients at the time of diagnosis, liver transplantation is ruled out for many patients with rapid decompensation of alcoholic liver disease. There are currently no established therapies available for these patients.

**Study objectives**

Alcoholic liver disease (ALD) has the highest mortality of the alcoholism associated diseases and remains a major cause of liver-related mortality worldwide. The first line of treatment for ALD and the most important one is alcohol abstinence, which can be aided by psychotherapy or pharmacologic agents. Other standard treatments for ALD include nutritional therapy, pharmacological therapy and liver transplant, however, these standard treatments have not changed in the last 40 years due to the lack of an experimental models for ALD and because of the difficulty to perform clinical trials in ALD patients.

Therefore, the aim of this project is to analyze survival depending on existing co-medication or medical procedures. Therefore, we are instantiating a series of cohorts then generating a subset of features on these cohorts and ultimately putting this into a survival model. Result reporting back to the ALD group at Heidelberg University will be **only be aggregate results**. **Patient level data will not be reported**. As a benefit to patients, the obtained results may lead to recommendations on treatment or co-medication for these patients who otherwise have often limited treatment options.

**Goals**

The proposed project study will be an observational cohort study based on routinely-collected health care data which has been mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). Cohorts of individuals with ALD will be identified and stratified for co-occurrence of viral hepatitis B or C. Clinical features and drug responses linked to deterioration of alcoholic liver disease will be described with regard to an influence on the patient's survival Overall, this study aims to improve the treatment of patients with alcoholic liver disease (ALD) in the future. Sites will run the study analysis package locally on their data coded according to OMOP CDM. Only aggregate results will be shared with the study coordinator. For this purpose, the following work steps should be implemented:

* A data frame will be created locally, in which the individuals’ course of disease and feature variables will be aggregated for summarized an anonymous reporting to the study center.
* Cohorts of individuals with ALD will be identified and stratified for co-occurrence of viral hepatitis B or C.
* Evaluation of the concomitant medication of patients with alcoholic liver disease with regard to an influence on the patient's survival
* Sites will run the study analysis package locally on their data coded according to OMOP CDM. Only aggregate results will be shared with the study coordinator.

# Research Methods

## Study Design

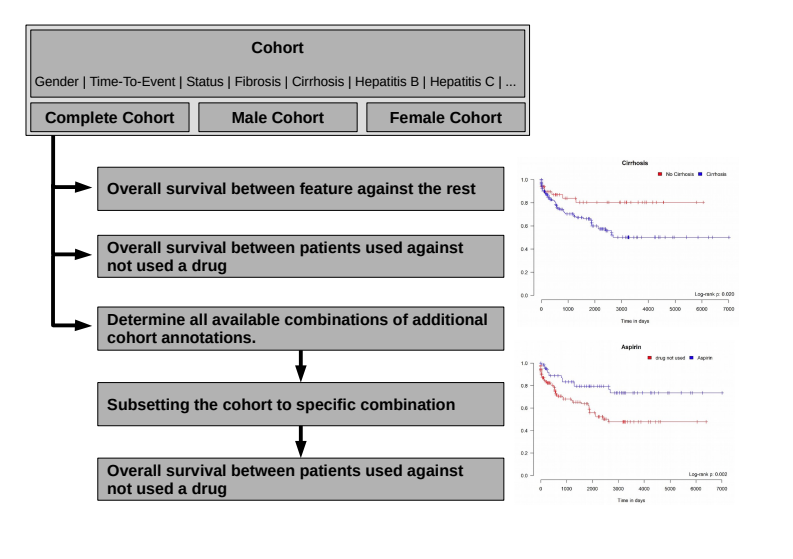
**Evaluation of clinical data set from within the OHDSI program**

Utilizing virtual machine provided by the OHDSI Community a data frame will be created locally, in which the individuals’ course of disease and feature variables will be aggregated for summarized an anonymous reporting to the study center. Export of anonymous, aggregated data will be prepared for semi-automatic export using the enclosed R / postgreSQL script for local storage. This allows final review (and data protection) of the data for the local researcher team before submitting aggregated results via email to the study coordinating team at Heidelberg University. At Heidelberg University (Campus Mannheim University Hospital) all aggregated and anonymized data from the individual working groups are merged into a global file for further analyzes.

**Evaluation of prognostic markers for the course of alcoholic liver disease**

Required for the analysis of prognostic markers are the clinical conditions of the patient, working conditions, initial diagnosis, date of death and therapeutic interventions.

For the evaluation of prognostic markers, two groups will be separated, patients with good and poor survival. All relationship parameters (concept IDs) will then be applied to these two groups, by means of Kaplan-Meier analyzes. Thereby all makers will be evaluated for statistical significance in terms of patient survival.



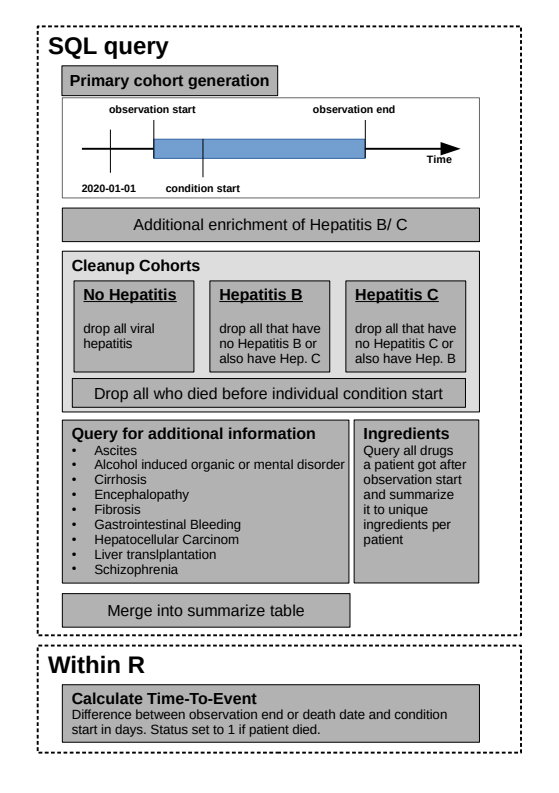
1. **Evaluation of the concomitant medication for patients with ALD with regard to its influence on the patient's survival**
2. To evaluate the influence of the accompanying medication on the survival of the patient or the course of the disease, all medications of a patient will be evaluated. Multiple or repeated administration to a patient is initially disregarded. Only the general intake of one of a substance is considered. Patients who have taken a certain drug are then compared with patients who have not taken this drug with regard to their survival.

**Survival analysis**

All survival analyses will be performed using the R package ‘survival’.

## Study Population

The target cohort contains all patients with a first condition ‘Alcoholic liver damage’ (201612) or any of the downstream dependent codes. First diagnosis / documentation of ‘Alcoholic liver damage’ must be after January 01, 2000.



Since concomitant viral hepatitis may significantly influence outcome of patients with alcoholic liver disease, we furthermore excluded all patients linked to the condition ‘Viral hepatitis’ (4291005) or any of the downstream codes. The resulting cohort was labeled ‘no hepatitis’.

Further subgroup will be evaluated by only excluding Hepatitis B (‘no hepB’) or Hepatitis C (‘no hepC’).

Finally, all patients with documented death prior to initial documentation of ‘Alcoholic liver damage’ were excluded.

# Strengths & Limitations

## Strengths

* “Real world” data on alcoholic liver disease
* Data on alcoholic liver disease from diverse countries and continents
* Large number of patient records

## Limitations

* Different treatment standards in different countries
* Results from different Hospitals can´t be pooled / combined

# Protection of Human Subjects

All patient’s data will be retrieved anonymously. Thus, identification of individuals is not possible.

# Plans for Disseminating & Communicating Study Results

The results will be published in international peer review journals. All contributing investigators will be included in the author list.

# References

1. Robert Koch Institut, Gesundheitsberichterstattung des Bundes, Heft 40, https://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsT/alkoholkonsum.pdf
2. Cojocariu CE et al Alcoholic liver disease--epidemiology and risk factors. Rev Med Chir Soc Med Nat Iasi. 118: 910-7, 2014
3. Joshi K et al. Alcoholic Liver Disease: High Risk or Low Risk for Developing Hepatocellular Carcinoma? Clin Liver Dis. 20: 563-80, 2016
4. Rambaldi A et al. Systematic review: Glucocorticosteroids for alcoholic hepatitis—A Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial sequential analyses of randomized clinical trials. Aliment Pharmacol Ther 27: 1167-1178, 2008
5. Louvet A et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology 45: 1348-54, 2007
6. Fung P et al. Emerging concepts in alcoholic hepatitis. World J Hepatol. 9: 567-585, 2017
7. Marot et al. Liver transplantation for alcoholic hepatitis: A systematic review with meta-analysis. PLoS One. 13: e0190823, 2018

# Appendices

## Study Generation Version Information

## Code list

### Primary Cohort Definition

Based on any of the code set dowstream of ‘Alcoholic liver damage’ (201612).

|  |  |
| --- | --- |
| **Code Set** | **Title** |
| 193256 | Alcoholic fatty liver |
| 196463 | Alcoholic cirrhosis |
| 201343 | Acute alcoholic liver disease |
| 201612 | Alcoholic liver damage |
| 4146181 | Chronic alcoholic hepatitis |
| 4195620 | Zieve's syndrome |
| 4340383 | Alcoholic hepatitis |
| 4340386 | Alcoholic hepatic failure |
| 37017009 | Chronic alcoholic liver disease |
| 37017151 | Acute on chronic alcoholic liver disease |

### Exclusive list for ‘No Hepatitis cohort’

Excluded will be all patient that are marked with code set downstream of ‘Viral hepatitis’ (4291005).

|  |  |
| --- | --- |
| **Code Set** | **Title** |
| 192240 | Chronic viral hepatitis B with hepatitis D |
| 192242 | Acute hepatitis C |
| 192824 | Mumps hepatitis |
| 193693 | Viral hepatitis without hepatic coma |
| 194574 | Chronic type B viral hepatitis |
| 196625 | Viral hepatitis A without hepatic coma |
| 197490 | Acute hepatitis E |
| 197493 | Hepatitis D superinfection of hepatitis B carrier |
| 197494 | Viral hepatitis C |
| 197795 | Acute type B viral hepatitis |
| 198683 | Viral hepatitis B without hepatic coma |
| 198964 | Chronic hepatitis C |
| 439672 | Viral hepatitis C with coma |
| 439673 | Acute hepatitis B with delta-agent (coinfection) without hepatic coma |
| 439674 | Chronic viral hepatitis B without delta-agent |
| 439675 | Acute hepatitis B with delta agent (coinfection) with hepatic coma |
| 763021 | Chronic viral hepatitis C with hepatic coma |
| 4009793 | Chronic aggressive type B viral hepatitis |
| 4012113 | Chronic viral hepatitis |
| 4027854 | Acute fulminating type B viral hepatitis |
| 4055219 | Hepatitis in yellow fever |
| 4059294 | Hepatitis caused by adenovirus |
| 4063037 | Viral hepatitis complicating pregnancy, childbirth and the puerperium |
| 4078071 | Acute fulminating type A viral hepatitis |
| 4092685 | Cytomegalovirus hepatitis |
| 4098652 | Acute type A viral hepatitis |
| 4103088 | Posttransfusion viral hepatitis |
| 4119142 | Epstein-Barr virus hepatitis |
| 4168151 | Anicteric viral hepatitis |
| 4173584 | Chronic active type B viral hepatitis |
| 4183882 | Relapsing type A viral hepatitis |
| 4193635 | Anicteric type A viral hepatitis |
| 4203326 | Anicteric type B viral hepatitis |
| 4211974 | Acute viral hepatitis |
| 4223947 | Viral hepatitis, type A |
| 4232466 | Chronic aggressive viral hepatitis |
| 4238508 | Relapsing viral hepatitis |
| 4260842 | Acute fulminating viral hepatitis |
| 4263363 | Hepatitis in coxsackie viral disease |
| 4281232 | Type B viral hepatitis |
| 4283078 | Chronic active viral hepatitis |
| 4287644 | Viral hepatitis, type G |
| 4291005 | Viral hepatitis |
| 4296554 | Chronic persistent type B viral hepatitis |
| 4313600 | Viral hepatitis A without hepatic coma, without hepatitis delta |
| 4341652 | Acute hepatitis B with hepatitis D |
| 35624866 | Chronic hepatitis C caused by hepatitis C virus genotype 6 |
| 35624867 | Chronic hepatitis C caused by hepatitis C virus genotype 5 |
| 35625040 | Chronic hepatitis C caused by Hepatitis C virus genotype 3 |
| 35625139 | Chronic hepatitis C caused by Hepatitis C virus genotype 2 |
| 35625140 | Chronic hepatitis C caused by Hepatitis C virus genotype 4 |
| 35625141 | Chronic hepatitis C caused by Hepatitis C virus genotype 1 |
| 35625295 | Chronic hepatitis C caused by Hepatitis C virus genotype 1b |
| 35625296 | Chronic hepatitis C caused by Hepatitis C virus genotype 1a |
| 36715820 | Hepatitis caused by sexually transmissible virus |
| 36716708 | Acute hepatic failure caused by hepatitis virus |
| 36716709 | Subacute hepatic failure caused by hepatitis virus |
| 37017654 | Occult chronic type B viral hepatitis |
| 40482214 | Hepatitis B associated with Human immunodeficiency virus infection |
| 40483136 | Hepatitis B and hepatitis C |
| 40488872 | Reactivation of hepatitis B viral hepatitis |
| 42536529 | Chronic viral hepatitis D |
| 42872885 | Chronic hepatitis E |
| 43531723 | Cirrhosis of liver due to chronic hepatitis C |
| 44809233 | Hepatitis C genotype 1 |
| 44809234 | Hepatitis C genotype 2 |
| 44809236 | Hepatitis C genotype 3 |
| 44809237 | Hepatitis C genotype 4 |
| 44809238 | Hepatitis C genotype 5 |
| 44809239 | Hepatitis C genotype 6 |
| 45757141 | Viral hepatitis in mother complicating childbirth |
| 45757142 | Viral hepatitis in mother complicating pregnancy |
| 45757252 | Herpes simplex hepatitis |
| 45757726 | Chronic hepatitis C with stage 3 fibrosis |
| 45766656 | Chronic hepatitis C with stage 2 fibrosis |
| 45768827 | Viral hepatitis D |
| 45769525 | Chronic active hepatitis C |
| 45769824 | Viral hepatitis E |
| 45773146 | Reactivation of hepatitis C viral hepatitis |

### Hepatitis B

| **Code Set** | **Title** |
| --- | --- |
| 192240 | Chronic viral hepatitis B with hepatitis D |
| 194574 | Chronic type B viral hepatitis |
| 197795 | Acute type B viral hepatitis |
| 198683 | Viral hepatitis B without hepatic coma |
| 439674 | Chronic viral hepatitis B without delta-agent |
| 439675 | Acute hepatitis B with delta agent (coinfection) with hepatic coma |
| 4009793 | Chronic aggressive type B viral hepatitis |
| 4027854 | Acute fulminating type B viral hepatitis |
| 4173584 | Chronic active type B viral hepatitis |
| 4203326 | Anicteric type B viral hepatitis |
| 4281232 | Type B viral hepatitis |
| 4296554 | Chronic persistent type B viral hepatitis |
| 4341652 | Acute hepatitis B with hepatitis D |
| 37017654 | Occult chronic type B viral hepatitis |
| 40482214 | Hepatitis B associated with Human immunodeficiency virus infection |
| 40483136 | Hepatitis B and hepatitis C |
| 40488872 | Reactivation of hepatitis B viral hepatitis |

### Hepatitis C

|  |  |
| --- | --- |
| 192242 | Acute hepatitis C |
| 197494 | Viral hepatitis C |
| 198964 | Chronic hepatitis C |
| 439672 | Viral hepatitis C with coma |
| 763021 | Chronic viral hepatitis C with hepatic coma |
| 35624866 | Chronic hepatitis C caused by hepatitis C virus genotype 6 |
| 35624867 | Chronic hepatitis C caused by hepatitis C virus genotype 5 |
| 35625040 | Chronic hepatitis C caused by Hepatitis C virus genotype 3 |
| 35625139 | Chronic hepatitis C caused by Hepatitis C virus genotype 2 |
| 35625140 | Chronic hepatitis C caused by Hepatitis C virus genotype 4 |
| 35625141 | Chronic hepatitis C caused by Hepatitis C virus genotype 1 |
| 35625295 | Chronic hepatitis C caused by Hepatitis C virus genotype 1b |
| 35625296 | Chronic hepatitis C caused by Hepatitis C virus genotype 1a |
| 40483136 | Hepatitis B and hepatitis C |
| 43531723 | Cirrhosis of liver due to chronic hepatitis C |
| 44809233 | Hepatitis C genotype 1 |
| 44809234 | Hepatitis C genotype 2 |
| 44809236 | Hepatitis C genotype 3 |
| 44809237 | Hepatitis C genotype 4 |
| 44809238 | Hepatitis C genotype 5 |
| 44809239 | Hepatitis C genotype 6 |
| 45757726 | Chronic hepatitis C with stage 3 fibrosis |
| 45766656 | Chronic hepatitis C with stage 2 fibrosis |
| 45769525 | Chronic active hepatitis C |
| 45773146 | Reactivation of hepatitis C viral hepatitis |

### Gastrointestinal Bleeding

|  |  |
| --- | --- |
| **Code Set** | **Title** |
| 23245 | Esophageal bleeding |
| 26727 | Hematemesis |
| 192671 | Gastrointestinal hemorrhage |
| 193249 | Acute hemorrhagic gastritis |
| 193250 | Gastric hemorrhage |
| 316457 | Mallory-Weiss syndrome |
| 4100660 | Acute gastrointestinal hemorrhage |
| 4139411 | Massive gastrointestinal bleed |
| 4143871 | Bleeding gastric erosion |
| 4144926 | Recurrent gastrointestinal bleeding |
| 4145805 | Vomiting blood - fresh |
| 4246979 | Coffee ground vomiting |
| 4291649 | Upper gastrointestinal bleeding |
| 4308202 | Acute upper gastrointestinal hemorrhage |
| 36717237 | Obscure gastrointestinal hemorrhage |
| 45757570 | Gastric hemorrhage due to idiopathic erosive gastritis |
| 45757783 | Gastric hemorrhage due to alcoholic gastritis |
| 45768629 | Gastric hemorrhage due to erosive gastritis |
| 46269908 | Gastric hemorrhage due to vascular ectasia of gastric antrum |
| 46273183 | Intestinal hemorrhage |

### Cirrhosis

|  |  |
| --- | --- |
| **Code Set** | **Title** |
| 192675 | Biliary cirrhosis |
| 194692 | Cirrhosis - non-alcoholic |
| 196463 | Alcoholic cirrhosis |
| 4003673 | Obstructive biliary cirrhosis |
| 4046016 | Toxic cirrhosis |
| 4046123 | Secondary biliary cirrhosis |
| 4048057 | Nutritional cirrhosis |
| 4048083 | Advanced cirrhosis |
| 4050640 | Mixed micro AND macronodular cirrhosis |
| 4059284 | Cirrhosis and chronic liver disease |
| 4064161 | Cirrhosis of liver |
| 4135822 | Primary biliary cholangitis |
| 4140536 | Parasitic cirrhosis |
| 4143008 | Drug-induced cirrhosis of liver |
| 4153294 | Cirrhosis secondary to cholestasis |
| 4159158 | Early cirrhosis |
| 4163687 | Cruveilhier-Baumgarten syndrome |
| 4232955 | Cryptogenic cirrhosis |
| 4340948 | Hepatic fibrosis with hepatic sclerosis |
| 37396401 | Decompensated cirrhosis of liver |
| 43531723 | Cirrhosis of liver due to chronic hepatitis C |
| 44805713 | Cirrhosis associated with cystic fibrosis |
| 45772057 | Cirrhosis of liver due to hepatitis B |

### Ascites

|  |  |
| --- | --- |
| **Code Set** | **Title** |
| 200528 | Ascites |
| 4342883 | Hepatic ascites |
| 46269816 | Ascites due to alcoholic cirrhosis |
| 46269817 | Ascites due to alcoholic hepatitis |
| 46269835 | Hepatic ascites due to chronic alcoholic hepatitis |
| 46273476 | Hepatic ascites co-occurrent with chronic active hepatitis due to toxic liver disease |

### Alcohol induced Organic or Mental Disorders

|  |  |
| --- | --- |
| **Code Set** | **Title** |
| 372607 | Alcohol hallucinosis |
| 374014 | Alcoholic paranoia |
| 374317 | Alcohol-induced psychosis |
| 374623 | Alcohol amnestic disorder |
| 375519 | Alcohol withdrawal syndrome |
| 375794 | Alcohol-induced sleep disorder |
| 376383 | Alcohol-induced organic mental disorder |
| 377830 | Alcohol withdrawal delirium |
| 378726 | Dementia associated with alcoholism |
| 439277 | Alcohol withdrawal hallucinosis |
| 442582 | Alcohol-induced psychotic disorder with delusions |
| 4088373 | Alcohol intoxication delirium |
| 4098164 | Pathological alcohol intoxication |
| 4101139 | Chronic alcoholic brain syndrome |
| 4146660 | Alcohol-induced anxiety disorder |
| 4205002 | Alcohol-induced mood disorder |
| 4310679 | Uncomplicated alcohol withdrawal |

### Liver transplantation

|  |  |
| --- | --- |
| **Code Set** | **Title** |
| 2003164 | Liver transplant |
| 2003165 | Auxiliary liver transplant |
| 2003166 | Other transplant of liver |
| 2109321 | Liver allotransplantation, orthotopic, partial or whole, from cadaver or living donor, any age |
| 4001373 | Liver implantation |
| 4067458 | Orthotopic liver transplant |
| 4067459 | Heterotopic liver transplant |
| 4076862 | Transplantation of liver |
| 4099299 | Liver transplant with recipient hepatectomy |
| 4101838 | Liver transplant without recipient hepatectomy |
| 4139049 | Orthotopic transplantation of whole liver |
| 44809584 | Living donor liver transplantation |

### Fibrosis

|  |  |
| --- | --- |
| **Code Set** | **Title** |
| 4046017 | Septal fibrosis of liver |
| 4194229 | Congenital hepatic fibrosis |
| 4267417 | Hepatic fibrosis |
| 4342775 | Pericellular fibrosis of congenital syphilis |
| 4345477 | Symmer's pipe-stem fibrosis |
| 36686081 | Stage 3 hepatic fibrosis |
| 36715922 | Fibrosis of liver caused by alcohol |
| 42537672 | Fibropolycystic disease of liver |
| 45766656 | Chronic hepatitis C with stage 2 fibrosis |

### Encephalopathy

|  |  |
| --- | --- |
| **Code Set** | **Title** |
| 194856 | Hepatic coma due to viral hepatitis A |
| 196029 | Hepatic coma due to viral hepatitis |
| 200031 | Hepatic coma due to viral hepatitis B |
| 377604 | Hepatic coma |
| 439672 | Viral hepatitis C with coma |
| 439675 | Acute hepatitis B with delta agent (coinfection) with hepatic coma |
| 763020 | Hepatitis with hepatic coma |
| 763021 | Chronic viral hepatitis C with hepatic coma |
| 4029488 | Hepatic encephalopathy |
| 4308946 | Hepatic coma due to chronic hepatitis B |
| 4314443 | Hepatic coma due to acute hepatitis B |
| 35622780 | Hepatoencephalopathy due to combined oxidative phosphorylation defect type 1 |
| 42710029 | Hepatic encephalopathy in fulminant hepatic failure |
| 42710030 | Portal systemic encephalopathy |
| 46269697 | Hepatic coma due to hepatitis |
| 46269814 | Hepatic coma due to acute hepatic failure |
| 46269818 | Hepatic coma due to alcoholic liver failure |
| 46269836 | Hepatic coma due to chronic hepatic failure |
| 46269949 | Hepatic coma due to subacute liver failure |
| 46270037 | Hepatic coma due to acute hepatitis C |
| 46270142 | Hepatic coma due to chronic hepatitis C |
| 46270152 | Hepatic coma due to chronic hepatitis B with delta agent |

### Hepatocellular Carcinoma

|  |  |
| --- | --- |
| **Code Set** | **Title** |
| 4001171 | Liver cell carcinoma |
| 4099699 | Fibrolamellar hepatocellular carcinoma |
| 4166154 | Combined hepatocellular carcinoma and cholangiocarcinoma |

### Schizophrenia

|  |  |
| --- | --- |
| **Code Set** | **Title** |
| 432299 | Subchronic paranoid schizophrenia |
| 432598 | Subchronic schizophrenia with acute exacerbations |
| 432864 | Acute schizophrenic episode |
| 433442 | Subchronic residual schizophrenia |
| 433450 | Paranoid schizophrenia |
| 433990 | Subchronic catatonic schizophrenia |
| 433996 | Catatonic schizophrenia |
| 434318 | Paraphrenia |
| 434332 | Catatonic schizophrenia in remission |
| 434901 | Acute exacerbation of subchronic paranoid schizophrenia |
| 435217 | Paranoid schizophrenia in remission |
| 435218 | Chronic residual schizophrenia with acute exacerbations |
| 435219 | Schizophrenia in remission |
| 435782 | Chronic schizophrenia |
| 435783 | Schizophrenia |
| 436067 | Simple schizophrenia |
| 436071 | Acute exacerbation of chronic catatonic schizophrenia |
| 436384 | Subchronic disorganized schizophrenia with acute exacerbations |
| 436385 | Chronic disorganized schizophrenia with acute exacerbations |
| 436673 | Chronic residual schizophrenia |
| 436944 | Chronic paranoid schizophrenia |
| 436947 | Disorganized schizophrenia in remission |
| 437243 | Acute exacerbation of chronic paranoid schizophrenia |
| 438724 | Subchronic disorganized schizophrenia |
| 439004 | Residual schizophrenia |
| 439275 | Acute exacerbation of subchronic catatonic schizophrenia |
| 440368 | Chronic disorganized schizophrenia |
| 440373 | Subchronic schizophrenia |
| 440686 | Residual schizophrenia in remission |
| 441538 | Chronic catatonic schizophrenia |
| 441828 | Disorganized schizophrenia |
| 444396 | Subchronic residual schizophrenia with acute exacerbations |
| 4008566 | Undifferentiated schizophrenia |
| 4085662 | Schizophrenic prodrome |
| 4100365 | Schizophrenic disorders |
| 4100366 | Acute exacerbation of chronic schizophrenia |
| 4102660 | Cenesthopathic schizophrenia |
| 4103254 | Acute exacerbation of chronic disorganized schizophrenia |
| 4105330 | Chronic undifferentiated schizophrenia |
| 4194671 | Chronic undifferentiated schizophrenia with acute exacerbations |
| 4213979 | Undifferentiated schizophrenia in remission |
| 4219539 | Late onset schizophrenia |
| 4244059 | Involutional paraphrenia |
| 4310121 | Subchronic undifferentiated schizophrenia |
| 4321694 | Subchronic undifferentiated schizophrenia with acute exacerbations |
| 40480879 | Lethal catatonia |

## Predefined Code Sets inside study package

### Target drugs of interests

For discovery the drugs we define a target list of drugs we are most interested in

| CodeSet | Title |
| --- | --- |
| 19105879 | Ajmaline |
| 1753745 | Albendazole |
| 1344143 | Albumin Human, USP |
| 42903427 | Aldosterone |
| 1167322 | Allopurinol |
| 19010337 | aminosalicylate |
| 1726228 | aminosalicylic acid |
| 1309944 | Amiodarone |
| 710062 | Amitriptyline |
| 1713332 | Amoxicillin |
| 714785 | Amphetamine |
| 1717240 | Amphotericin B |
| 1717327 | Ampicillin |
| 1322207 | argatroban |
| 919839 | Arnica extract |
| 19011773 | Ascorbic Acid |
| 1112807 | Aspirin |
| 1314002 | Atenolol |
| 914335 | Atropine |
| 1593273 | avelumab |
| 19014878 | Azathioprine |
| 1734104 | Azithromycin |
| 19015123 | Azlocillin |
| 1715117 | Aztreonam |
| 19015346 | Barbital |
| 19015423 | BCG Vaccine |
| 19016754 | Benzbromarone |
| 1397141 | bevacizumab |
| 19022956 | Bezafibrate |
| 1338005 | Bisoprolol |
| 1329241 | Bleomycin |
| 40238770 | boceprevir |
| 42900350 | caffeic acid |
| 1134439 | Caffeine |
| 42900359 | Calcitonin |
| 19035631 | Calcitriol |
| 19018910 | Cannabinol |
| 1337620 | capecitabine |
| 1346823 | carvedilol |
| 36879077 | Catumaxomab |
| 19028286 | cefodizime |
| 1777806 | Ceftriaxone |
| 1149196 | Cetirizine |
| 1315411 | cetuximab |
| 1792515 | Chloroquine |
| 794852 | Chlorpromazine |
| 19095164 | Cholecalciferol |
| 1797513 | Ciprofloxacin |
| 1397599 | Cisplatin |
| 797617 | Citalopram |
| 997881 | Clindamycin |
| 1322184 | clopidogrel |
| 800878 | Clozapine |
| 1001419 | Cocaine |
| 1101554 | Colchicine |
| 1507705 | Cortisone |
| 19071967 | Creatine |
| 19071968 | Creatinine |
| 19010482 | Cyclosporine |
| 45775372 | dabigatran |
| 1311409 | Dacarbazine |
| 1786617 | Daptomycin |
| 1124300 | Diclofenac |
| 19026180 | Digitoxin |
| 1326303 | Digoxin |
| 1328165 | Diltiazem |
| 735850 | Disulfiram |
| 1337720 | Dobutamine |
| 1337860 | Dopamine |
| 1363053 | Doxazosin |
| 1594034 | durvalumab |
| 1341927 | Enalapril |
| 1743222 | Enoxacin |
| 1301025 | Enoxaparin |
| 1711246 | entecavir |
| 904453 | Esomeprazole |
| 1151789 | Etanercept |
| 1749301 | Ethambutol |
| 19011440 | everolimus |
| 1549686 | fluvastatin |
| 19111620 | Folic Acid |
| 956874 | Furosemide |
| 797399 | gabapentin |
| 1757803 | Ganciclovir |
| 1560278 | Glucagon |
| 766529 | Haloperidol |
| 19066747 | Halothane |
| 1367571 | heparin |
| 596876 | Hepatitis A Vaccine, Inactivated |
| 44814322 | Hepatitis A Virus |
| 528323 | Hepatitis B Surface Antigen Vaccine |
| 43532406 | Hepatitis B Virus |
| 44814323 | Hepatitis C virus |
| 19022417 | Heroin |
| 974166 | Hydrochlorothiazide |
| 975125 | Hydrocortisone |
| 1126658 | Hydromorphone |
| 1177480 | Ibuprofen |
| 1778262 | Imipenem |
| 19069107 | indobufen |
| 937368 | infliximab |
| 42903441 | Influenza A virus |
| 46275993 | influenza A virus (H1N1) antigen |
| 46275996 | influenza A virus (H3N2) antigen |
| 40220901 | influenza A virus (H5N1) antigen |
| 43013137 | influenza A virus antigen, Panama 2007-99 (H3N2) |
| 42873918 | Influenza A virus vaccine, A-California-7-2009 (H1N1)-like virus |
| 45776076 | Influenza A virus vaccine, A-Texas-50-2012 (H3N2)-like virus |
| 42873956 | Influenza A virus vaccine, A-Victoria-361-2011 (H3N2)-like virus |
| 42904068 | influenza A-B virus immunoserum rabbit |
| 40166605 | influenza A-California-7-2009-(H1N1)v-like virus vaccine |
| 42903442 | Influenza B virus |
| 46275999 | influenza B virus antigen |
| 43013138 | influenza B virus antigen, Hong Kong 330-2001 |
| 43531942 | Influenza B virus vaccine, B-Brisbane-60-2008-like virus |
| 43531944 | Influenza B virus vaccine, B-Massachusetts-2-2012-like virus |
| 42873961 | Influenza B virus vaccine, B-Wisconsin-1-2010-like virus |
| 42903602 | influenza B virus, B Panama-45-90 hemmagglutinin antigen, inactivated |
| 36878617 | Influenza Virus Fragmented, Inactivated, Strain A / Switzerland / 9715293/2013 H3N2 - Analogue Strain A / South Australia / 55/2014 Ivr-175 |
| 36879023 | Influenza Virus Fragmented, Inactivated, Strain A / Switzerland / 9715293/2013 H3N2 - Analogue Strain A / Switzerland / 9715293/2013, Nib-88 |
| 36878713 | Influenza Virus Fragmented, Inactivated, Strain B / Phuket / 3073/2013 |
| 36879091 | Influenza Virus Surface Antigen, Inactivated, Strain A / Switzerland / 9715293/2013 H3N2 - Analogue Strain A / South Australia / 55/2014 Type Wild |
| 36878953 | Influenza Virus Surface Antigen, Inactivated, Strain B / Phuket / 3073/2013 & ndash; Analogue strain B / Utah / 9/2014, Wild Type |
| 36878619 | Influenza Virus Surface Antigen, strain A / Victoria / 361/2011 H3N2 - Derived Strain Used Ivr-165 |
| 36879025 | Influenza Virus Surface Antigens, strain A / Switzerland / 9715293/2013 H3N2 - Analogue Strain Nib-88 |
| 532460 | Influenza Virus Vaccine, Inactivated A-Brisbane-10-2007 (H3N2)-like virus (A-Uruguay-716-2007 NYMC X-175C) strain |
| 532552 | Influenza Virus Vaccine, Inactivated A-Brisbane-59-2007 (H1N1) strain |
| 40164866 | Influenza Virus Vaccine, Inactivated A-Brisbane-59-2007, IVR-148 (H1N1) strain |
| 40224997 | Influenza Virus Vaccine, Inactivated A-California-07-2009 X-179A (H1N1) strain |
| 40225012 | Influenza Virus Vaccine, Inactivated A-California-07-2009 X-181 (H1N1) strain |
| 40240922 | Influenza Virus Vaccine, Inactivated A-Christchurch-16-2010 NIB-74 (H1N1) (A-California-7-2009) strain |
| 532582 | Influenza Virus Vaccine, Inactivated A-Uruguay-716-2007 (H3N2) (A-Brisbane-10-2007-like) strain |
| 40164826 | Influenza Virus Vaccine, Inactivated A-Uruguay-716-2007, NYMC X-175C (H3N2) strain |
| 40225028 | Influenza Virus Vaccine, Inactivated A-Victoria-210-2009 X-187 (H3N2) (A-Perth-16-2009) strain |
| 40164828 | Influenza Virus Vaccine, Inactivated B-Brisbane-60-2008 strain |
| 532584 | Influenza Virus Vaccine, Inactivated B-Florida-4-2006 strain |
| 532424 | Influenza Virus Vaccine, Inactivated, A-H1N1 (A-Brisbane-59-2007) strain |
| 532430 | Influenza Virus Vaccine, Inactivated, A-H3N2 (A-Uruguay-716-2007) strain |
| 532488 | Influenza Virus Vaccine, Inactivated, B-Florida-4-2006-like virus (B-Florida-4-2006) strain |
| 532452 | Influenza Virus Vaccine, Inactivated, Influenza B (B-Florida-4-2006) strain |
| 40225031 | Influenza Virus Vaccine, Live Attenuated, A-California-7-2009 (H1N1) strain |
| 40225038 | Influenza Virus Vaccine, Live Attenuated, A-Perth-16-2009 (H3N2) strain |
| 532512 | Influenza Virus Vaccine, Live Attenuated, A-South Dakota-6-2007 (H1N1) (A-Brisbane-59-2007-like) strain |
| 532516 | Influenza Virus Vaccine, Live Attenuated, A-Uruguay -716-2007 (H3N2) (A-Brisbane-10-2007-like) strain |
| 40164833 | Influenza Virus Vaccine, Live Attenuated, B-Brisbane-60-2008 strain |
| 532518 | Influenza Virus Vaccine, Live Attenuated, B-Florida-4-2006 strain |
| 1531601 | Insulin, Aspart Protamine, Human |
| 1567198 | Insulin, Aspart, Human |
| 1544838 | Insulin, Glulisine, Human |
| 46221581 | insulin, isophane |
| 42899447 | Insulin, Pork |
| 1513876 | Insulin, Protamine Lispro, Human |
| 1379969 | Interferon Alfa-2a |
| 1380068 | Interferon Alfa-2b |
| 40798893 | Interferon Alfa-2c |
| 19044394 | Interferon Alfa-n1 |
| 1385645 | Interferon Alfa-n3 |
| 1781314 | interferon alfacon-1 |
| 722424 | Interferon beta-1a |
| 713196 | interferon beta-1b |
| 42903737 | Interferon gamma-1a |
| 1380191 | Interferon gamma-1b |
| 19122123 | Interferon Type II |
| 19109079 | Interferon-beta |
| 40238188 | ipilimumab |
| 782043 | Isoflurane |
| 1782521 | isoniazid |
| 45775020 | ledipasvir |
| 791967 | Lorazepam |
| 1367500 | Losartan |
| 19019131 | Magnesium Aspartate |
| 908464 | magnesium carbonate |
| 19009022 | meclocycline |
| 19000498 | Mefloquine |
| 1301267 | Melphalan |
| 1503297 | Metformin |
| 906780 | Metoclopramide |
| 1307046 | Metoprolol |
| 907879 | Miconazole |
| 708298 | Midazolam |
| 1309068 | Minoxidil |
| 725131 | Mirtazapine |
| 710650 | modafinil |
| 1110410 | Morphine |
| 1716903 | moxifloxacin |
| 19080436 | nadoxolol |
| 1114220 | Naloxone |
| 1714319 | Naltrexone |
| 1314577 | nebivolol |
| 915981 | Neomycin |
| 1318853 | Nifedipine |
| 19020021 | Nitrazepam |
| 19020061 | Nitrendipine |
| 920293 | Nitrofurantoin |
| 1361711 | Nitroglycerin |
| 19020994 | Nitroprusside |
| 45892628 | nivolumab |
| 1321341 | Norepinephrine |
| 721724 | Nortriptyline |
| 922570 | Nystatin |
| 36250189 | obeticholic acid |
| 923081 | Ofloxacin |
| 19106973 | Omega-3 Fatty Acids |
| 1714165 | peginterferon alfa-2a |
| 45775965 | pembrolizumab |
| 19126544 | Penicillin |
| 1728416 | Penicillin G |
| 19022570 | pentifylline |
| 43012882 | PENTYLAMINE |
| 734275 | Phenobarbital |
| 19035344 | Phenprocoumon |
| 19035577 | Phenylalanine |
| 740910 | Phenytoin |
| 1746114 | Piperacillin |
| 1550557 | prednisolone |
| 1551099 | Prednisone |
| 734354 | pregabalin |
| 19051285 | Prenylamine |
| 1552310 | Progesterone |
| 753626 | Propofol |
| 1334456 | Ramipril |
| 961047 | Ranitidine |
| 40225716 | resveratrol |
| 1735947 | rifaximin |
| 964407 | Salicylic Acid |
| 1316262 | sildenafil |
| 1539403 | Simvastatin |
| 19034726 | Sirolimus |
| 44785094 | sofosbuvir |
| 836208 | Succinylcholine |
| 1836391 | Sulfadiazine |
| 950637 | Tacrolimus |
| 1436678 | Tamoxifen |
| 40239330 | telaprevir |
| 19011093 | Tenofovir |
| 35605546 | tenofovir alafenamide |
| 19119253 | terlipressin |
| 1836948 | Tetracycline |
| 19041746 | tetrazepam |
| 19137042 | Thalidomide |
| 1837289 | Thiabendazole |
| 19137312 | Thiamine |
| 700253 | Thiopental |
| 1387104 | trastuzumab |
| 40161532 | ustekinumab |
| 40799173 | Vaccine (Unspecified) |
| 40799175 | Vaccine, Human Papillomavirus Type-6,11,16,18,31,33,45,52,58 |
| 19056615 | VALEPOTRIATE |
| 745466 | Valproate |
| 1707687 | Vancomycin |
| 45774639 | vedolizumab |
| 40241937 | Vemurafenib |
| 1307863 | Verapamil |
| 744740 | zolpidem |
| 1336926 | tadalafil |
| 42800040 | avanafil |