MICROBiome-based biomarkers to PREDICT decompensation of liver cirrhosis and treatment response

D8.5 Draft of a model describing typical treatment paths in decompensated cirrhosis

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1. Executive Summary
Liver disease has been estimated to cost in the range of 500 USD annually per capita in the UK and up to 1238 USD in France (Younossi et al, 2016). The most severe patients, with decompensation and acute liver failure are the most expensive patients and new tests that can improve the treatments for these patients could have potentially large cost savings. In order to estimate how new tests that enable physicians to distinguish between patients that are low vs. high risk, and patients that respond vs. do not respond to treatments, we develop a benchmark model where the patient can be in one of four states: Cirrhosis (outpatient treatment), Decompensation (Hospital admissions), and Acute Chronic Liver Failure (ACLF, with treatment in intensive care units) and Death. We then collect information about the probability of going from one state to another, as well as the costs and quality of life in patients in each state. Next we create a model of typical treatment paths when we introduce new tests. The states are the same as the benchmark model, but in each state there is now a test that sorts patients to different treatments, which means that the transition probabilities will change: Knowing that a patient is high risk and/or a good candidate to respond to certain treatments, it is possible to avoid or delay progression to more severe states. These models will be used to calculate costs and benefits of the different interventions compared to the standard treatment when the data for the effectiveness of the tests becomes available at a later stage in the project.

2. Aim
The specific objective of this deliverable is to develop a draft model of treatments paths that can be used to evaluate the economic costs and benefits of the information and innovations that comes from the MICROB-PREDICT project.

The more general aim of the analysis is to provide information about costs and benefits that that is relevant to decision makers when they make decisions about whether to adopt new tests and treatments.

3. Background
The MICROB-PREDICT project seeks to identify and validate microbiome-based biomarkers and signatures for personalized prediction of decompensation and ACLF, and response to treatment. Moreover it aims to design three new tests as easy-to-use tools and point-of-care, smartphone-connected nanobiosensors.

To conduct an economic evaluation of the new tests, it is necessary to create a model of how patients are typically diagnosed and treated today - and the associated costs and benefits. We can then use the model to assess how the costs and benefits change when we, for instance, introduce improved personalized treatment based on the knowledge gained in the MICROB-PREDICT project.
It is useful to note that a model here means a framework for simulation. We first specify a
number of states, for instance: healthy (no disease), moderate disease, severe disease, and
death. At any point an individual can be in one of these states. The next step is to assign
probabilities, that is: For each time step how likely is it that a patient who has a moderate
disease will progress to a severe disease or go back to a healthy state. Using these
probabilities, we start with a large number of individuals and simulate how many that will be
in the different states, and for how long, over a long time period. Each state must also be
assigned a utility corresponding to the quality of life of a patient in that state, and a cost
Corresponding (treatment cost).

Using the model described above it is possible to estimate the costs and benefits of a new
diagnosis or a treatment because the new knowledge or innovation may change the
probability that a patient will become healthy but also the costs since the new intervention
may require tests that change the costs. By comparing the costs and benefits for an average
patient using today’s treatment in this model, and the costs and benefits we get when we
change the probabilities and the costs, we can calculate the cost per quality adjusted life
years. This is a key metric since it helps decision makers decide whether a new and possible
costly diagnostic tool gives enough benefit to recommend its implementation. For instance,
if an intervention is estimated to cost 10 000 Euro per life-year it saved, policy-makers may
conclude that the benefits are large enough to justify the costs. This is the type of analysis
and information we will provide. The first step in such an analysis is to build the model and
outline the relevant states a patient can be in.

Note that the costs and benefits are not only narrow economic costs and benefits. The
model includes all kinds of benefits, but must translate non-economic consequences to
something that affect the life quality or translate the non-monetary consequences into
something that can be measured in monetary units.

3.1 The burden of advanced chronic liver disease (aCLD)

Before moving to the specific case of cost-benefit studies and treatment paths, it is useful to
survey the literature on the economic costs of cirrhosis. The economic cost of an illness
provides an idea of potential improvements and economic savings that can be made with
better tests and treatments. It also suggests important categories of costs and benefits that
should be included in a cost-benefit analysis.

Liver disease are some of the leading causes of more serious, irreversible chronic liver
diseases such as cirrhosis and hepatocellular carcinoma (Younossi et al, 2016). Interventions
targeted at testing and preventing progression to serious liver disease can therefore spare
patients significant morbidity, or possibly early death, and in addition permit reallocation of
health spending to others in need. For instance, Baumeister et al. (2008) found in their
study of the general population in the German region of West Pomerania that when controlling for comorbidities, patients with a liver disease accumulated 26% higher healthcare costs over a five-year period. Another study, from Portugal, showed that the medical costs associated with the one subtype of liver disease was at least 54 million dollars annually or 5.4 USD per capita (Cortez-Pinto et al 2010).

The medical cost is only one of many components that should be included if one wants to estimate the overall social cost of the disease. In addition to medical costs, some studies also include lost productivity as a consequence of the disease. When this is included, the social costs increase manifold. For instance, the per capita cost of non-alcoholic liver disease was estimated to be around 74 USD per capita in a US study that did not include lost productivity (Martini et al, 2006). In contrast, a large and methodologically advanced study which included lost productivity, estimated the total cost to be more than five times higher, ranging from more than 500 USD annually per capita in the UK to 1238 USD in France (Younossi et al, 2016).

3.2 Moving from cost of illness to evaluating cost-benefits

Studies of costs of illness can inform decision makers about the maximum potential savings, but they do not give information about whether specific interventions are cost-effective. To do this it is necessary to measure both costs and benefits. One of the most commonly used measures to prioritize between different interventions, is to measure the benefits in terms of costs per quality adjusted life years (QALY, see Drummond et al, 2015). The intuition behind the method is simple. For each intervention, we estimate to what extent the intervention will increase the life expectancy and the quality of those years for the patients. The quality of life is here often measures using instruments such as EQ5-D or SF-36D and the life expectancy is often estimated using statistical models. For diseases with recurring states, the life history of a patient is modelled in a framework where patients flow between different states. In this way, it is possible to estimate the average costs and benefits for a cohort of patients with and without an intervention. Although it is commonly used, it should be noted that cost per QALY is not the most comprehensive measure of benefits. Quality adjusted life years focuses on the medical effects for the patient and do not capture wider social benefits such the value of productive work for the rest of society.

Despite the relevance of cost-benefit studies, there are in fact even fewer studies that focus on this than the cost of illness itself. One recent study concluded that “The main limitation with the current published studies of potential effective interventions for NALFD/NASH is that none of the studies reviewed collected robust data on effective treatments for patients with NASH and fibrosis” (Crossan et al, 2015).
4. Model

In order to decide on the appropriate model, we first collected information about models previously published in the scientific literature.

4.1 Previous models

Crossan et al. (2016) studied the ‘Cost-effectiveness of non-invasive liver fibrosis tests for treatment decisions in patients with chronic hepatitis B in the UK.’ They use a Markov model where patients can progress or stay put in different stages of the disease depending on how the disease progresses if they are tested and how their behaviour change after receiving a test result. They conclude that ‘For HBeAg-positive patients, using Fibroscan was the most cost-effective option with an Incremental Cost-Effectiveness Ratio (ICER) of £23 345.’ The model is illustrated in Figure 1:

![Image of Markov Model](image)

**Fig. 1** Illustration of the Markov Model used for economic analysis. The disease stages reflect the META VIR staging score for liver fibrosis and cirrhosis. The cohort represents people suspected of liver fibrosis who can enter the models in one of three disease stages: mild fibrosis (META VIR stages F0–F1), moderate fibrosis (META VIR stages F2–3) and compensated cirrhosis (META VIR stage F4) with the proportions determined by the prevalence estimated from the results of the systematic review. Within the model, people can remain within any disease stage for longer than one cycle (length of cycle is set as 1 year) except for the liver transplant disease stage where patients can only progress to either a post-liver transplant stage or death.

**Figure 1: Model developed by Crossan et al. (2016)**

Another article, Tanjewski et al. (2016) focused on evaluating the costs and benefits of stratifying patients with non-alcoholic fatty liver disease. They used a combination of a decision tree, where the choice is whether to employ the new stratification or not, and a Markov model to analyze the average costs and utility for patients (see Figure 2).
Figure 2: Model developed by Tanjewski et al. (2016). In their words: Decision tree and Markov model for the economic evaluation of risk stratification pathway in non-alcoholic fatty liver disease. Markov model states: NMD, no/mild disease: a patient can be identified (NMD+) or not identified (NMD−) to be at risk of developing disease; SLD, significant liver disease: a patient can be diagnosed (SLD+) or not (SLD−); CC, compensated cirrhosis: a patient can be diagnosed (CC+) or not (CC−); DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant. Death possible from every state.

4.2 Model for MICROB-PREDICT

Based on these models, as well as similar models by Tapper et al. (2016) and Phisalprapa et al. (2017) we created our own model that is designed to capture the aspects relevant for the aim of the project. Most importantly the model has to be able to analyze the outcome of introducing tests that increase personalized care. This is similar to Tanjewski et al. (2016) and to capture this it is useful to have a decision tree with tests that sort individuals into different groups that receive different further tests or treatments.
In the MICROB-PREDICT project there are three types of interventions that need to be modelled (see Figure 3): Test N1 (Risk of progression), Test N2 (Response to Rifaximin) and Test N3 (Response to Albumin). The key feature of all these tests is to make treatment better targeted: Instead of giving all patients the same treatment, the tests will split patients into groups: Low vs. High risk patients, and patients that respond/do not respond to a treatment. From the perspective of economic evaluation the main consequence is to reduce the probability of developing a more severe disease (since high risk individuals are identified and can be treated) and to reduce some treatment costs (since low risk individuals are identified and they need not be given the same treatment). However, the new tests and treatments also create some costs, and the cost of testing the patients and for the new test(s) to be cost-effective we must analyze whether the gains from the new individualized care is larger than the costs of the new tests. This will, to a large extent, depend on the sensitivity and specificity of the tests.

Figure 3: Typical treatment path before and after MICROB-PREDICT

Based on the treatment paths illustrated in Figure 3 we have created a model with four main states as the benchmark model (i.e. standard treatment path today, Figure 4): A person with liver cirrhosis can be in outpatient care, in a decompensation state with frequent hospital admissions or have Acute Chronic Liver Failure (ACLF) with treatment in intensive care unit and a high rate of mortality within a relatively short time period.
Figure 4: Benchmark model to calculate average costs and outcome for patient in the standard model.

The benchmark model will be used to simulate the costs and outcomes for a large number of individuals. This will be compared to the costs and outcomes with the innovations introduced in MICROB-PREDICT. Figure 5 shows the structure of the alternative interventions. People with cirrhosis will now be tested with new diagnostic tools and, depending on the outcome of the test, the high-risk individuals will receive different treatment than the low-risk individuals. This pattern is repeated at all states: Patients are tested and receive different care depending on the tests and their response to these tests. This means that the structure changes from the Benchmark case (Figure 4) to a structure where a test is used in every state (Figure 5).
Figure 5: Paths with new interventions: Example of treatment paths with new tests/treatments and more individualized care. In addition to the states visualized, the patient can also die in any of the states above.

In order to estimate the average costs and outcomes in this model, we need information about the probability of going from one state to another, and the average costs and utility (for patients in the different states (for a given time period). Each of these are discussed below.

4.3 Quality of life in the different states
Quality of life in the different states is estimated using previous surveys (Steel, 2005, see also Hessel, 2006), including the range of uncertainty:
Table 1: Estimated quality of life

Health state utility values

<table>
<thead>
<tr>
<th>All health states less severe than 1 decompensated cirrhosis</th>
<th>Low</th>
<th>Mean</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>0.85</td>
<td>0.88</td>
<td>0.91</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>0.74</td>
<td>0.66</td>
<td>0.82</td>
</tr>
<tr>
<td>ACLF</td>
<td>0.40</td>
<td>0.32</td>
<td>0.48</td>
</tr>
</tbody>
</table>

4.4 Transition probabilities

In the benchmark model, the probability of going from one state to another is given by the key statistics describing the median times spend in each state (10 years in the cirrhosis stage, 2-3 years for those entering the decompensation stage and a median of 1-2 months for those with ACLF). In our model, these numbers are recalculated to the probability of dying in a given month as well as adjusted for the length of time a patient has spent in one state: The longer the patient stays in a state, the higher the probability of transferring to another state. The average transition annual probabilities, to get the median times before transitioning (10 years, 3 years, 2 months) is calculated in Table 2:

Table 2: Estimated (annual) transition probabilities

<table>
<thead>
<tr>
<th>From cirrhosis to decompensation</th>
<th>10</th>
<th>0.669</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decompensated cirrhosis to ACLF</td>
<td>3</td>
<td>0.206</td>
</tr>
<tr>
<td>ACLF to death</td>
<td>1/6</td>
<td>0.984</td>
</tr>
</tbody>
</table>

The probability of dying is also dependent on the state and the time spent in that state (with averages of less than 1% annually for patients with cirrhosis only, 10% annually in the decompensation state and 40% for a given month in the ACLF state).
The transition probabilities for the model with the tests described in the MICROB-PREDICT project have not yet been estimated and will depend on the specificity and sensitivity of the tests and the treatment responses. Note also that the new data may also lead to revision of the transition probabilities in the benchmarks model.

4.5 Costs

Each time unit the patient is in a state is associated with average costs given by the costs of the drugs and the tests/treatments /care they receive. In order to calculate these costs, the model uses information on the following variables:

- The frequency and cost of an outpatient visit to the physician
- The cost and frequency of a hospital admission
- The cost of and frequency of infusions and drugs given in hospitals
- The cost and frequency of intensive care
- The cost and frequency of transplants

And for the model with the new tests and interventions:

- The costs and frequency of the tests/new treatments

Table 3 presents an overview of some of the costs that we have collected information about so far. These costs do not only include the direct cost of the tests themselves, but also the costs of the time of a physician, the nurses and so on who are involved.

Table 3 Health state costs (2018 $) and health state utilities

(Source and references: Asphaug et al. (2019))

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Expected value</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health care costs of diagnostic testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver function tests</td>
<td>$37.2</td>
<td>(27.9, 46.5)</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>$97.2</td>
<td>(72.9, 121.5)</td>
</tr>
<tr>
<td>LSM</td>
<td>$297</td>
<td>(222.8, 371.3)</td>
</tr>
<tr>
<td>Treatment costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief intervention</td>
<td>$124</td>
<td>(93, 155)</td>
</tr>
<tr>
<td>Treatment compensated cirrhosis</td>
<td>$4 883</td>
<td>(3 662, 6 103)</td>
</tr>
<tr>
<td>Treatment cirrhosis with ascites</td>
<td>$5 650</td>
<td>(4 237.5, 7 062.5)</td>
</tr>
<tr>
<td>Treatment cirrhosis with bleeding oesophageal varices</td>
<td>$9 463</td>
<td>(7 097.3, 11 829)</td>
</tr>
<tr>
<td>Treatment for cirrhosis with ascites and bleeding oesophageal varices</td>
<td>$9 463</td>
<td>(7 097.3, 11 829)</td>
</tr>
</tbody>
</table>
### Parameter | Expected value | (95% CI)
---|---|---
Treatment hepatic encephalopathy | $6,791 | (5,093.3, 8,488.8)
Treatment hepatocellular carcinoma | $4,438 | (3,328.5, 5,547.5)

## 5. Conclusions

This document has described a draft model for how to capture the costs and benefits of a typical treatment path for cirrhosis patients under the current system and under an alternative system with tests and treatments that are studied in the MICROB-PREDICT project. Moreover, it has described the data collected so far that will be used in the model. After receiving the results from the clinical trial, we will have the information necessary to simulate the model and get numeric estimates of costs and benefits of the different tests based on the model described in this document.

## 6. References


7. **Acknowledgement and Disclaimer**

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This report reflects only the author’s view and the Commission is not responsible for any use that may be made of the information it contains.