# Cost-Effectiveness Analysis of Cell-Based Therapy for Patients with Non-Alcoholic Fatty Liver Disease

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## BACKGROUND

- Non-alcoholic fatty liver disease (NAFLD) is a leading cause of liver disease and hepatocellular carcinoma worldwide. Its global prevalence was estimated to be 25%.
- Disease comprises a spectrum of hepatic conditions, including non-alcoholic fatty liver (NAFL), and non-alcoholic steatohepatitis (NASH). NAFL generally follows a benign non-progressive clinical course, while NASH may progress to cirrhosis and hepatocellular carcinoma (HCC).
- No NAFLD-specific therapy is approved, although there are several agents advancing to Phase 2 and 3 clinical trials.

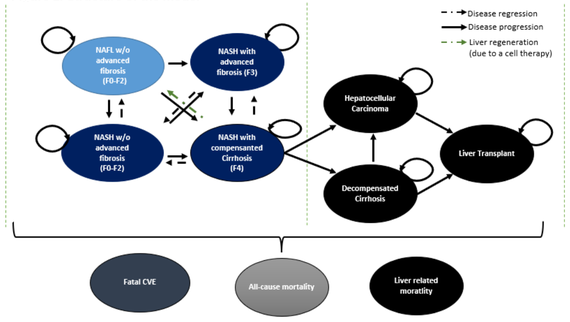
## OBJECTIVE

We investigated the cost-effectiveness of a hypothetical cell-based therapy used later in the disease course compared to the standard of care used in NAFLD patients, with the objective to inform the development of new therapies.

## METHODS

- A Markov cohort model was developed to simulate the therapeutic management and the course of NAFLD. The model structure was inspired by Tapper 2016 [2] (including steatosis-specific health states for modeling of NAFL and NASH) and Pearson 2016 [1] (including comprehensive fibrosis- and advanced complications-related health states for the later stages of liver disease). The structure of the combined model is presented in Figure 1.
- The analysis was conducted with the lifetime horizon from a US third-party payer perspective.

**Figure 1. Structure of the model**




- NASH resolution and slowing down of fibrosis progression are the key endpoints in the clinical trials for NASH and are recommended by the FDA [3] in the assessment of NASH-targeted drugs and thus were used in the model to reflect the effect of treatment.
- Therapeutic strategy with cell-based therapy used when cirrhosis is diagnosed and no other interventions targeting liver disease were compared to the current standard care strategies, i.e., lifestyle intervention in NAFL and NASH patients, and add-on with pioglitazone in NASH patients.

**Table 1. Methodology of the model**

| Methodology of the model | |
|---|---|
| **The baseline characteristics** | The simulation began with a hypothetical cohort of NAFL patients without advanced fibrosis (NAFL F0-F2). The baseline characteristics of the population were obtained from the NASH Clinical Research Network Study for patients with NAS ≤4 [4]. |
| **Transmission probabilities** | Transition probabilities across fibrosis stages were derived from a meta-analysis for patients with NAFLD [5], which allowed differentiating transitions across fibrosis stages according to NAFL and NASH.<br>Transition probabilities to and across advanced complications and to liver-related death were sourced from the evidence report published by the Institute for Clinical and Economic Review [1].<br>Mortality rates by cause were based on data published by the Centers for Disease Control and Prevention (CDC).<br>An increased fatal CVE mortality was applied based on the hazard ratios stratified by NAS and fibrosis stage following a published meta-analysis for patients with NAFLD [6]. |
| **Efficacy - Standard care (comparator)** | In the absence of comparative efficacy, NASH resolution and slowing down of fibrosis progression with lifestyle intervention and add-on with pioglitazone were derived from a randomized controlled trial [7], a meta-analysis [8], and a prospective cohort study [9].<br>Evidence for lifestyle interventions in NAFL patients is scarce, and endpoints are not applicable to the model. Thus, the efficacy of lifestyle intervention in NASH patients was used as a proxy and calculated based on the weight loss [10].<br>There was no data to inform the efficacy of pioglitazone and lifestyle intervention beyond 18 and 12 months. A conservative assumption of maintained efficacy on NASH resolution and slowing down of fibrosis progression was made. |
| **Efficacy - Intervention (cell-based therapy)** | Based on the advanced NASH pre-clinical model, a series of assumptions on the efficacy of innovative therapy were made: **50%, 70%, and 90% of patients with cirrhosis (F4) could be cured and stopped from progressing into DC and HCC**. |
| **Utilities and costs** | Utilities and costs for the model health states were retrieved from the Younossi 2016 [11], which used the micro-costing method to calculate costs and reported utilities elicited from Short Form-6D (SF-6D) in NAFLD patients.<br>Age-specific utilities in the US were taken from the evidence report published by the Institute for Clinical and Economic Review [1].<br>Treatment acquisition costs of lifestyle intervention and pioglitazone were collected from the previously published cost-utility analyses [2, 12].<br>Costs were adjusted to 2020 US dollars. |

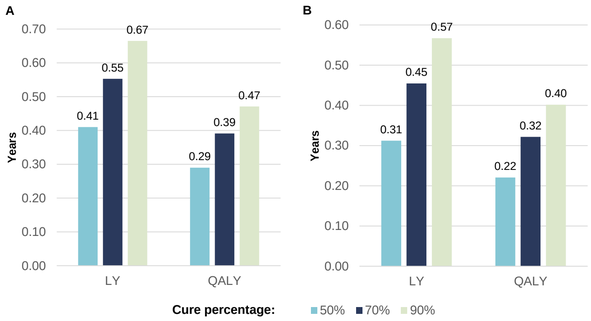
- Life years (LY) and quality-adjusted life years (QALY) gained were used as a measure of health outcomes.
- The economically justifiable price (EJP) was defined as the maximum price (one-time cost) for which a cell-based therapy would be cost-effective compared to standard care therapies considering a certain willingness-to-pay threshold per QALY gained. A series of hypothetical thresholds of $50,00, $100,000, and $150,000 per QALY was considered.
- One-way sensitivity analysis (SA) was performed to investigate the impact of variations in values of key parameters.

**Table 2. Input parameters**

| Parameters of the model | Base case | SA | Source |
|---|---|---|---|
| **Discount rate for costs and QALYs** | 3% | 1.5%, 5.0% | US Public Health Service [13] |
| **Percentage of female** | 55.8% | ±10% | NASH Clinical Research Network Study [6] |
| **Age of patients** | 47.7 | ±10% | |
| **Probability of NASH resolution** | | | |
| Lifestyle intervention | 20% | ±20% | Vilar-Gomez 2015 [9], Dudekula 2014 [10] |
| Add-on with pioglitazone | 53% | ±20% | |
| **Risk reduction of fibrosis progression** | | | Mahady 2011 [8], Cusi 2016 [7] |
| Lifestyle intervention | 98% | ±20% | |
| Add-on with pioglitazone | 79% | ±20% | |
| **Cure probability** | | | |
| Cell-based therapy | 50% | - | Assumption |
| | 70% | - | |
| | 90% | - | |
| **Annual costs [$]** | | | |
| NAFL F0-F2 1st year | 2,028 | ±30% | |
| NAFL F0-F2 after 1st year | 1,687 | ±30% | |
| NASH F0-F2 1st year | 2,443 | ±30% | |
| NASH F0-F2 after 1st year | 1,687 | ±30% | |
| F3 | 17,905 | ±30% | Younossi 2016 [11] |
| F4 (CC) | 29,688 | ±30% | |
| DC | 106,371 | ±30% | |
| HCC, LT 1st year after DC or HCC | 215,504 | ±30% | |
| LT after 1st year after DC or HCC | 53,043 | ±30% | |
| Lifestyle intervention | 2,083 | ±30% | Tapper 2016 [2] |
| Add-on with pioglitazone | 2,311 | ±30% | Zhang 2016 [12] |
| **Utilities** | | | |
| F0-F3 | 0.73 | ±10% | |
| F4 | 0.71 | ±10% | |
| DC | 0.57 | ±10% | Younossi 2016 [11] |
| HCC | 0.50 | ±10% | |
| LT | 0.57 | ±10% | |

## RESULTS

**Figure 2. Health outcomes for the strategy with cell-based therapy after diagnosis of cirrhosis compared to lifestyle intervention (A) and add-on with pioglitazone (B), for different levels of cure percentage**




- In the base case for each cure probability tested, about 22% of NAFL patients without advanced fibrosis progressed to compensated cirrhosis and were treated using cell-based therapy.

**Table 3. EJP of cell-based therapy for various levels of cure percentage, WTP threshold and comparisons**

| Comparison | Cure probability | EJP of cell-based therapy at WTP threshold: | | |
|---|---|---|---|---|
| | | $50,000 | $100,000 | $150,000 |
| vs Lifestyle intervention | 50% | $530,945 | $645,452 | $759,960 |
| | 70% | $621,799 | $774,072 | $926,345 |
| | 90% | $702,083 | $882,955 | $1,063,827 |
| vs Add-on with pioglitazone | 50% | $496,266 | $583,414 | $670,562 |
| | 70% | $587,599 | $712,890 | $838,181 |
| | 90% | $668,356 | $822,620 | $976,884 |

- For each cure probability tested, results of sensitivity analysis implied that the EJP of cell-based therapy was the most sensitive to variation in the cost of standard care, CC-specific health-state cost and discount rates for costs and outcomes.

## Limitations

- Efficacy and mode of action of a cell-based therapy were assumed.
- The quality of evidence for standard care interventions in NAFL and NASH patients is poor. The efficacy of the comparator was based on various data sources and conservative assumptions.

## CONCLUSIONS

- Cell-based therapy applied in the advanced stage of disease was estimated to provide meaningful life years (LY) and quality-adjusted life-years (QALY) gains for adult patients with NAFL and NASH.
- If highly effective in producing long-term NASH resolution and slowing down of fibrosis progression, cell-based therapy may also be a cost-effective alternative for prices in a range from $500,000 to $1 million per patient.
- Results of clinical trials for cell-based therapy are required to confirm the validity of these findings.

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