Clinical development of new technologies for non-alcoholic steatohepatitis: NICE perspective
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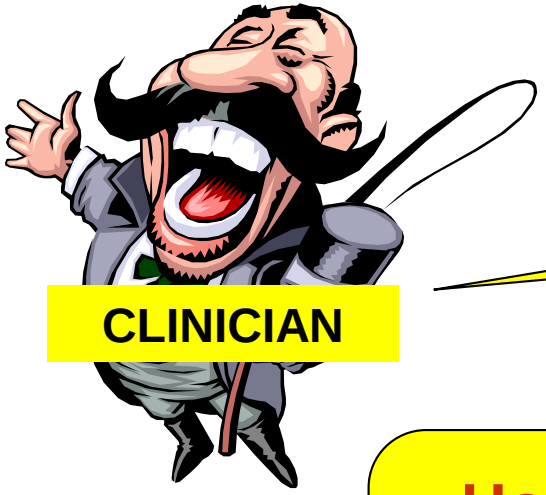
NICE

Balancing Clinical and Cost Effectiveness

A game of two halves?



CLINICIAN

How cheap does this technology need to be to make it cost effective?

How clinically effective does this technology have to be to make it worth paying that much for?

ECONOMIST

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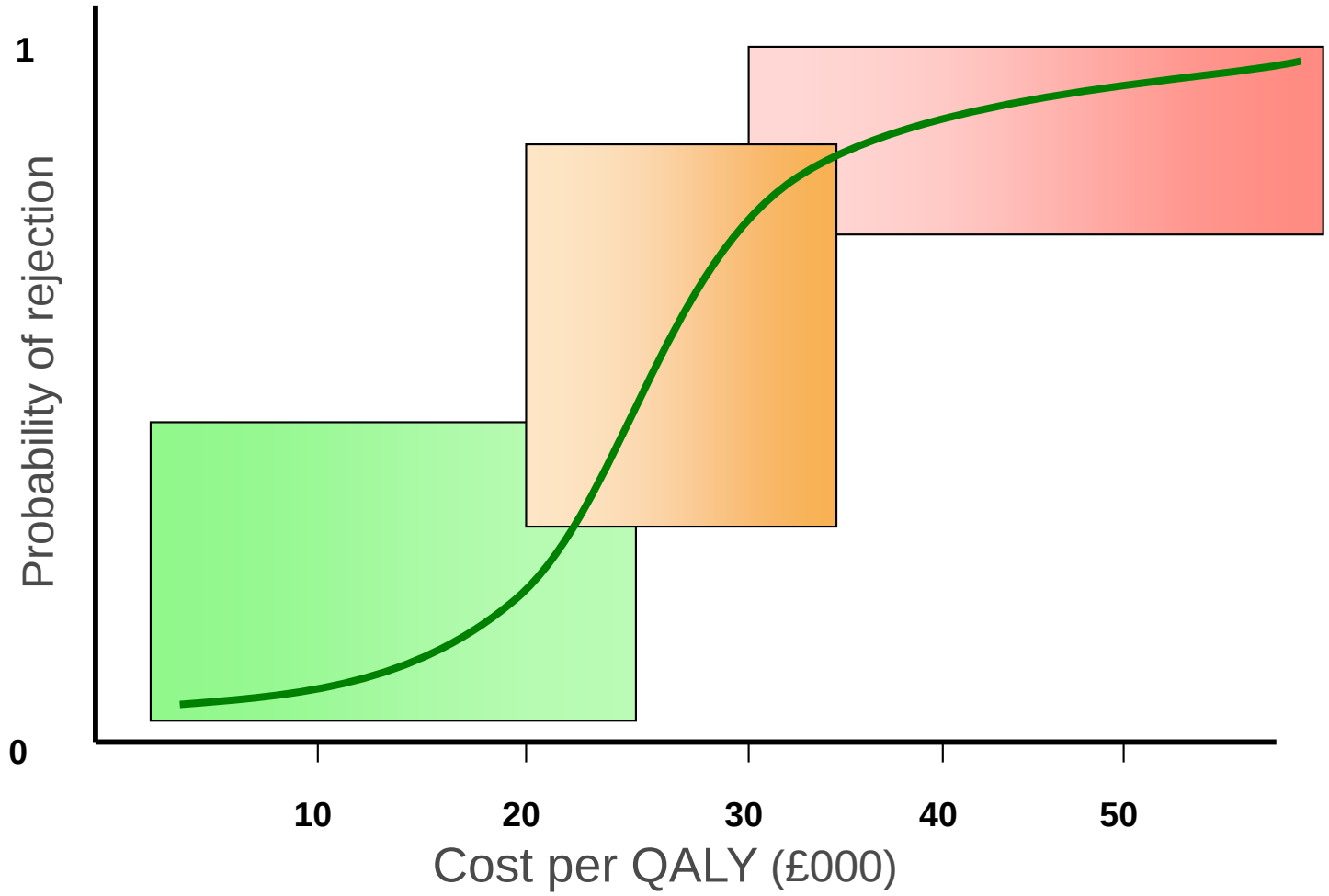
Assessing Cost Effectiveness

$$ICER = \frac{\text{Incremental costs}}{\text{Incremental effectiveness}} = \frac{\text{Cost}_A - \text{Cost}_B}{QALY_A - QALY_B}$$

$$= \text{Cost per 1 } QALY$$

QALY: Quality Adjusted Life Years

Assessing Cost Effectiveness



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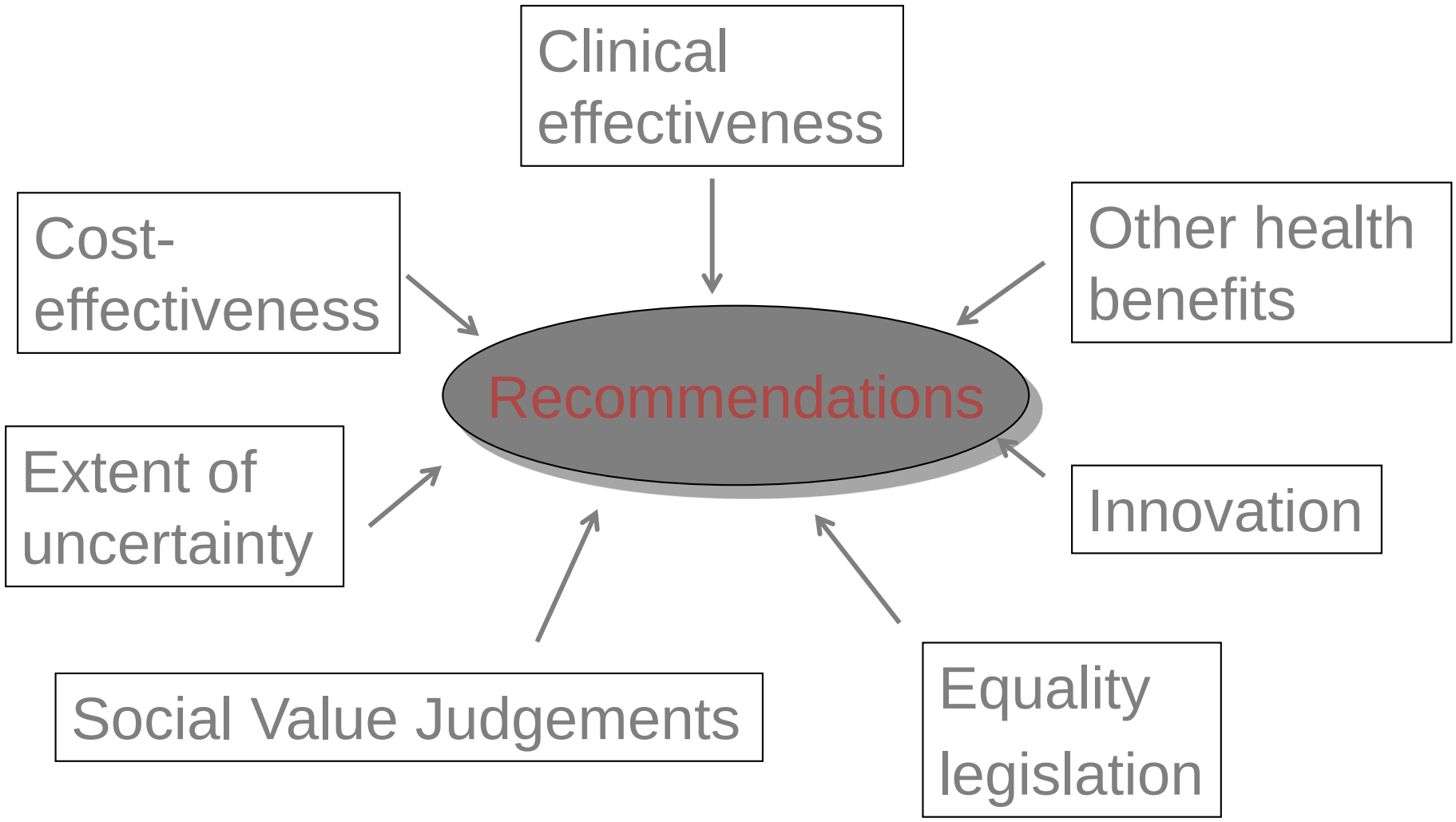
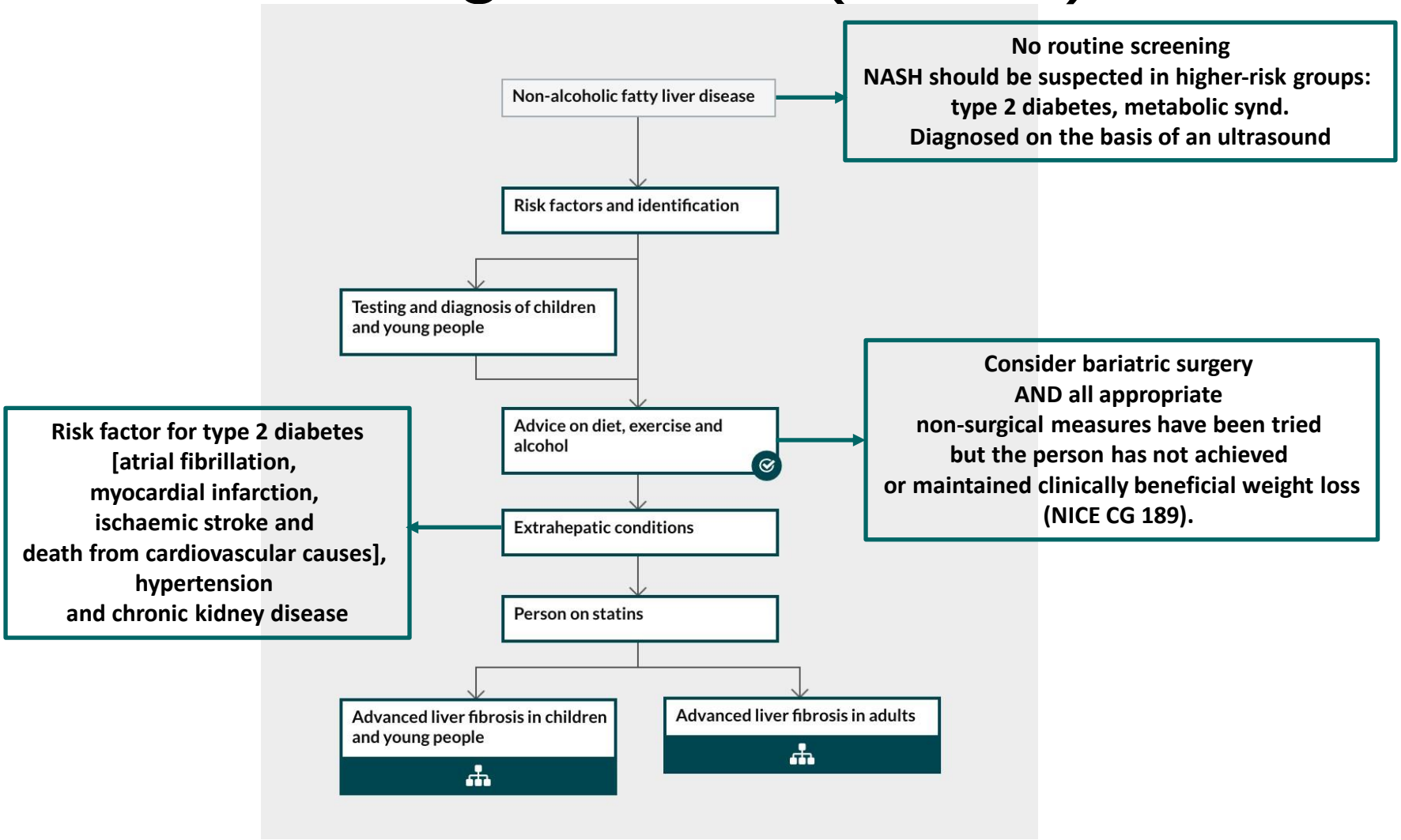
NICE Committee decision making



Non-alcoholic steatohepatitis (NASH)

- NASH is a non-alcoholic fatty liver disease characterised by hepatocellular injury, inflammation, and progressive fibrosis.
- NASH may lead to cirrhosis, hepatic decompensation, hepatocellular carcinoma and death.
- NHS practice reflected in NICE guidance published in NICE guideline 49 (6 July 2016).

NICE guideline (NG49)



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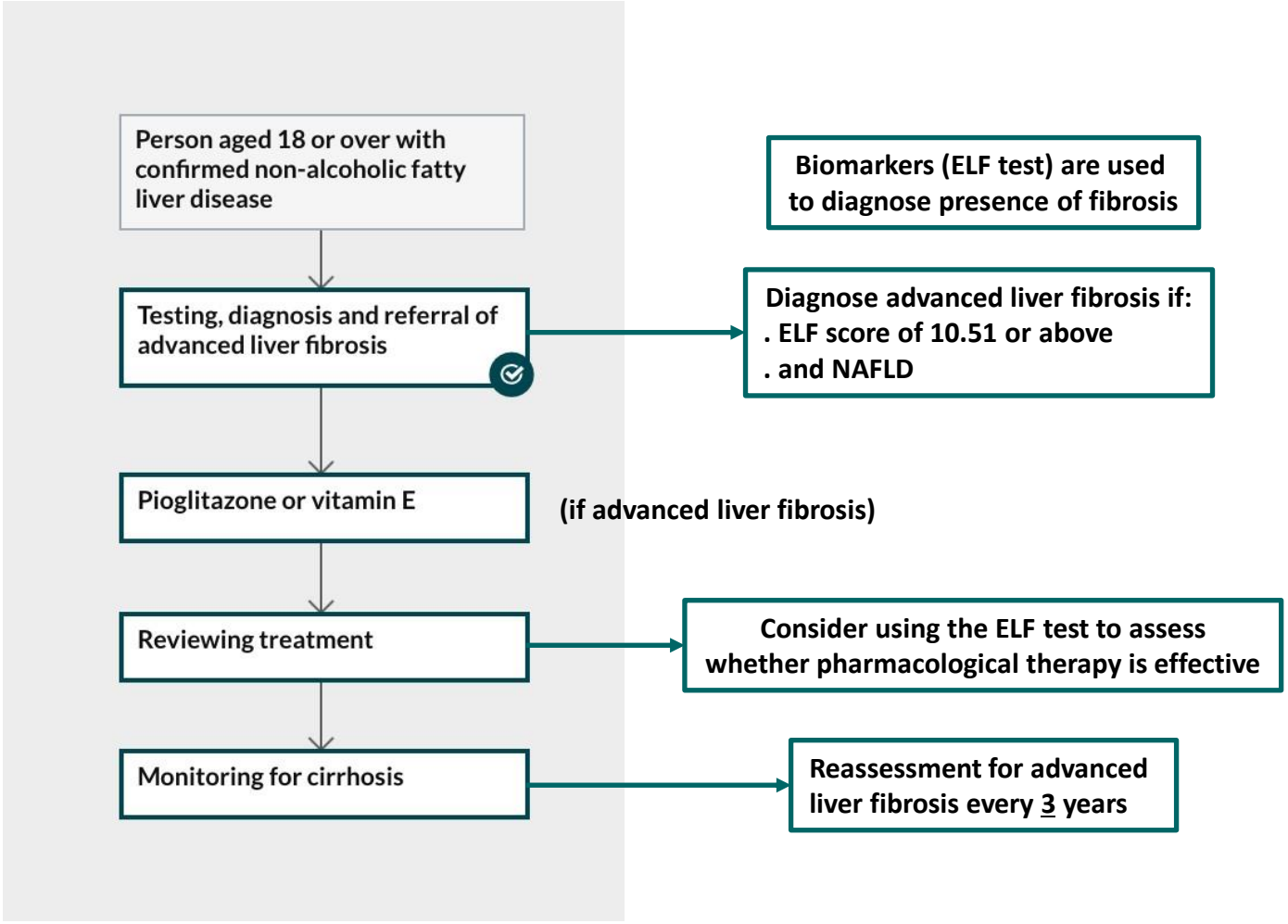
Advanced liver fibrosis in adults (NG49)



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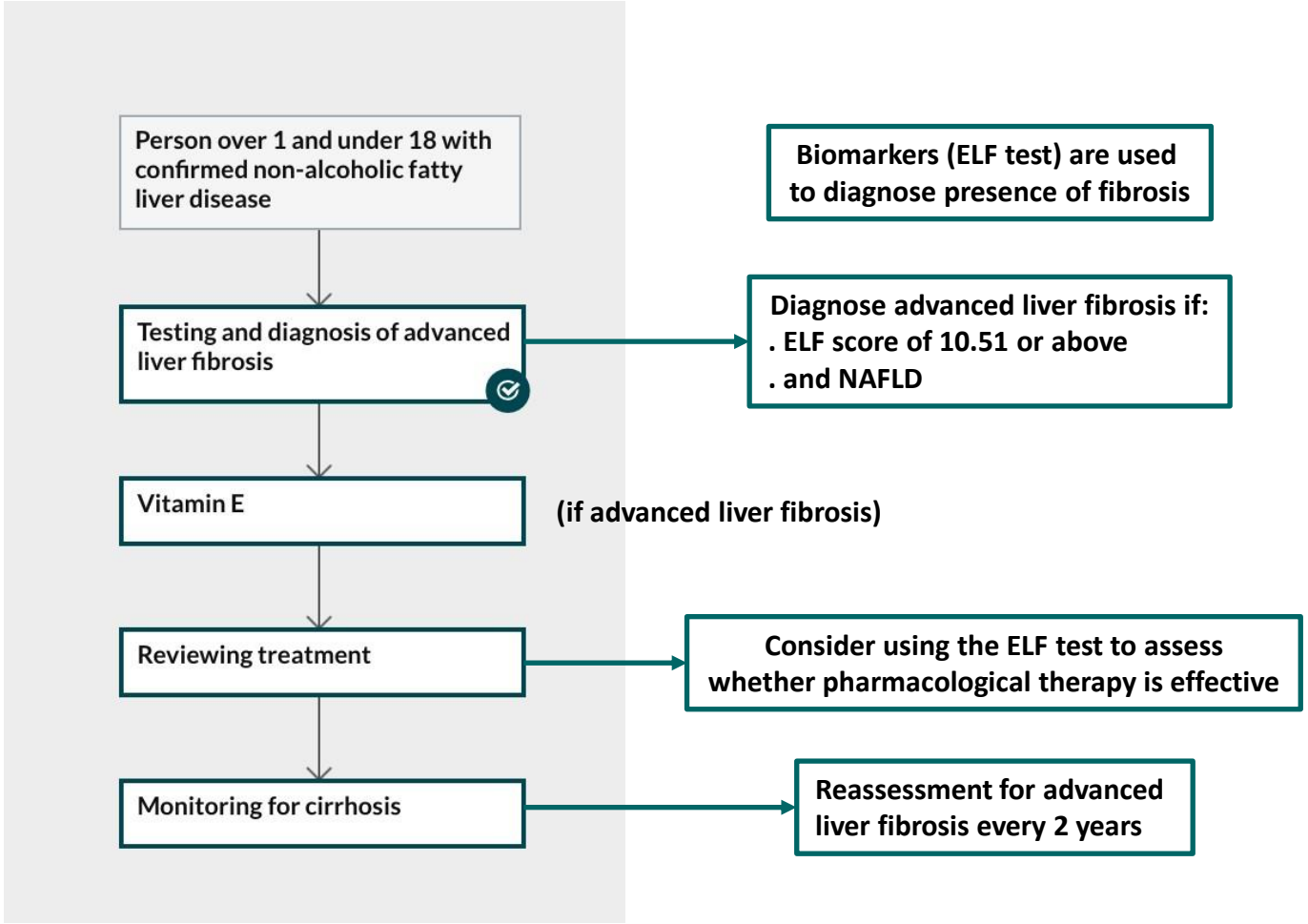
Advanced liver fibrosis in young children and young people (NG49)



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Elements of an appraisal: scope

Item of the appraisal	Content of the scope
Population	When the technology is a medicine, the marketing authorisation will generally specify the therapeutic indications.
Intervention	The scope includes information about the marketing authorisation (or CE mark for medical devices) of the technology, and the stage of regulatory approval for technologies not yet licensed.
Comparator	Established NHS practice.
Outcomes	The clinical outcome measures usually quantify an impact on **survival** or **health-related quality of life** that translates into quality-adjusted life years (QALYs) for the evaluation of cost effectiveness.

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Population

Main advice on patients selected in trials:

- NASH diagnosis is not made on the basis of a liver biopsy in the NHS.
- Biomarkers (ELF test) can be used to diagnose presence of fibrosis.
- If liver biopsies are performed, possible to correlate the findings with biomarkers information.

Population

- Heterogeneous population with different degrees of severity of the disease: liver fibrosis (stages 1 – 3).
- Treatment could be relevant in patients who have not responded to lifestyle modification advice:
  - Standardisation of eligibility criteria,
  - Consider including patients with compensated liver cirrhosis.

Comparators

NHS current practice:

- Pioglitazone and vitamin E in patients with advanced disease (stages 2 and 3).

NHS current practice may change if a new medicine is authorised and becomes reference treatment in the NHS.

- Consider indirect treatment comparisons.

Outcomes

- NICE uses outcomes of relevance to patients and their carers:
  - Survival
  - Improved quality of life (EQ-5D)
- NICE generally supported endpoints aimed at assessing evolution of fibrosis.
- Fibrosis assessed with ELF test are associated with disease progression (Sanyal et al. 2017).

Outcomes

- Other relevant endpoints for NASH:
  - Hepatic conditions:
    - Progression to cirrhosis,
    - Liver transplant,
    - Hepatocellular carcinoma,
    - Death.
  - Extra-hepatic conditions:
    - Type 2 diabetes, hypertension and chronic kidney disease,
    - Cardiovascular diseases and death.

Outcomes

- Important to determine the relationship between improvement and resolution of NASH with changes in fibrosis and changes in quality of life (HRQL), survival and resource use.

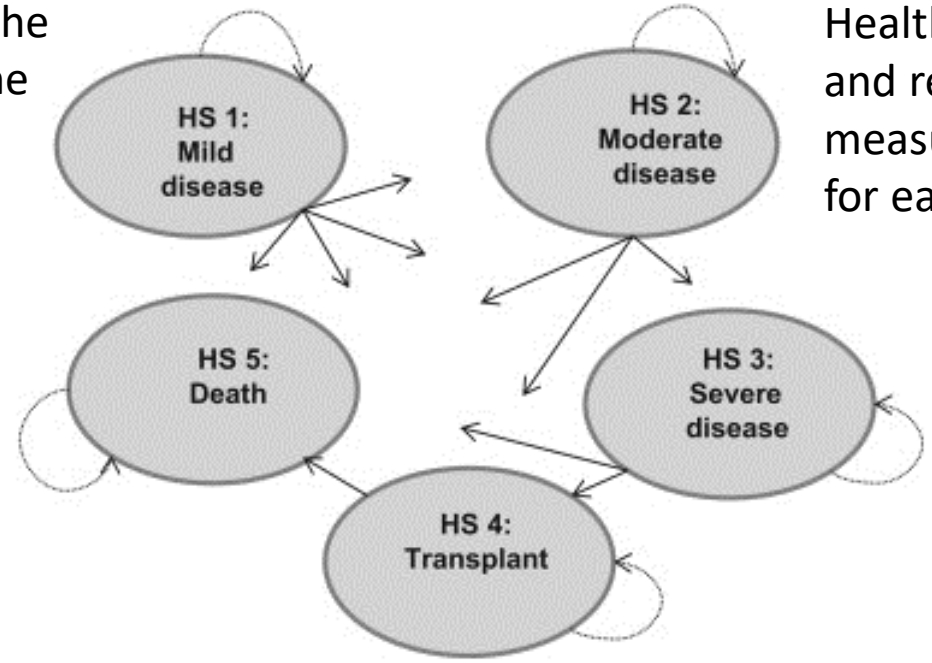
- Long term follow-up of patients is important (generally beyond the duration of clinical trials).

Quality of life

- HRQL of patients with NASH not adversely affected even in advanced disease: mostly fatigue.
  - Difficult to disentangle decrement in HRQL linked to NASH or to co-morbidities (type 2 diabetes).
  - Regular administration of HRQL questionnaires (e.g. every 3 months).

Economic Modelling: principles

Model should reflect the natural evolution of the disease.



Health benefits (QALY gain) and resources measured and modelled for each state.

Derive cost/QALY

Economic Modelling

General comments:

- NICE does not have any preferred model.
- Health states should represent homogeneous and clinically distinct groups.
- Robustness and plausibility of assumptions.

Specific modelling issues:

- Discrete event simulation may better capture the intrinsic variability within population of diseases such as NASH.

Economic Modelling

- Liver transplant stage:
  - Only patients with (advanced) liver cirrhosis or hepatocellular carcinoma would be eligible for a liver transplant in the NHS.
  - Post liver transplant stage.

- Important to include a “Death” stage.

- Consider stopping rules based on treatment response (e.g. ELF test).

Remember to …

- Incorporate HTA requirements in addition to regulatory requirements.
- Develop a sound value proposition of the new technology (delay or reversal of fibrosis, prevent liver transplant or improve survival).
- Plan economic evaluation with clinical development.
- Engage with HTA agencies and regulators thorough the development cycle, do not hesitate to seek HTA scientific advice.

Useful links

Non-alcoholic fatty liver disease overview
https://pathways.nice.org.uk/pathways/non-alcoholic-fatty-liver-disease

Non-alcoholic fatty liver disease (NAFLD): assessment and management. NICE guideline [NG49]
https://www.nice.org.uk/guidance/ng49

Office for Market Access
https://www.nice.org.uk/about/what-we-do/office-for-market-access

Technology appraisal guidance
https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-technology-appraisal-guidance

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