The tool developed from the analysis by Brunner and colleagues[5] could facilitate shared decision making in primary prevention by estimating lifetime risk of atherosclerotic cardiovascular disease up to 75 years of age, as well as the potential for individualised benefit from lowering non-HDL cholesterol or LDL cholesterol concentrations over a lifetime. The investigators should develop an online calculator in addition to the risk circle tools in their Article that could facilitate the widespread incorporation of their recommendations into future guidelines for cholesterol lowering in European-ancestry populations. For populations of non-European ancestry and those in low-income and middle-income countries, more prospective cohort data are needed.

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Obeticholic acid: towards first approval for NASH

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See **Articles** page 2184

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease, affecting about a quarter of the global population.[1] Non-alcoholic steatohepatitis (NASH), the progressive form of NAFLD, is characterised by hepatic inflammation with balloon degeneration, and portends progression to fibrosis and cirrhosis. Some people with NASH can develop hepatocellular carcinoma, even those who do not have cirrhosis. NASH is a multisystem disease; although it is on course to become the main indication for liver transplantation,[2] it also increases the risk of type 2 diabetes and cardiovascular disease.[3,4]

The current standard of care for fatty liver disease includes lifestyle modification that focuses on weight loss and exercise.[5] Although about 8–10% reduction in bodyweight reverses not only steatosis but also fibrosis, most patients fail to achieve and, more importantly, maintain this degree of weight loss. No pharmacological treatment has been licensed for the treatment of NASH, and thus it is not surprising that the drug development pipeline exploded with more than 300 agents in clinical trials in 2018.[6] The market for approved drugs for NASH is estimated to be worth US$20–35 billion per year by 2025.

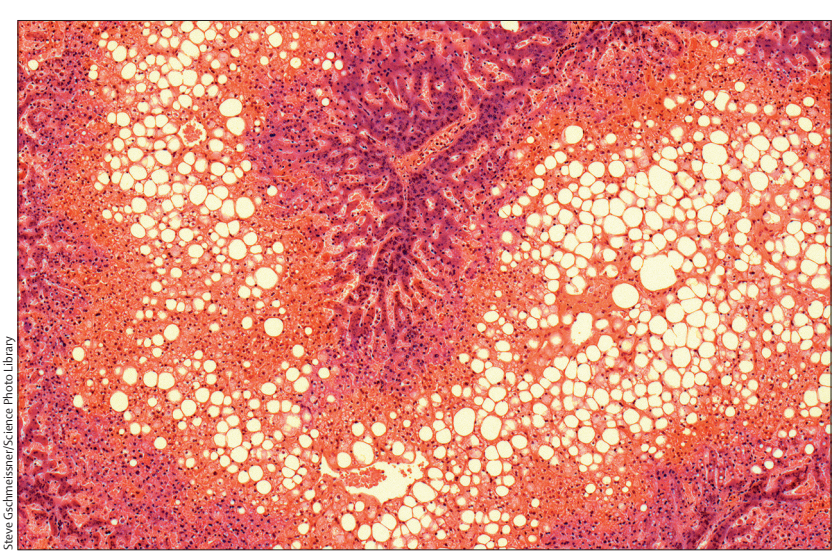
Accumulating evidence from multiple longitudinal studies suggests that patients with intermediate and advanced fibrosis, but not other histological features of NASH, are at greatest risk of overall and disease-specific mortality.[7] Hence, this subgroup has been identified as

the principal target population for investigational drugs in current phase 3 trials. For all current trials, histological features as surrogates of liver-related outcomes have been accepted by the regulatory authorities for accelerated or conditional approval.[8]

In *The Lancet*, Zobair Younossi and colleagues[9] report findings of the 18-month interim analysis of a phase 3 study that evaluated the safety and efficacy of two doses of obeticholic acid, 10 mg or 25 mg daily, relative to placebo in 931 patients (539 [58%] females) with biopsy-proven stage F2–F3 fibrosis. Obeticholic acid is a synthetically modified analogue of chenodeoxycholic acid and acts as a potent agonist of farnesoid X receptor, which is a bile-acid binding transcription factor with a master regulatory role in glucose and lipid metabolism, and inflammation.[10]

The primary outcome of the study was defined as NASH resolution with no worsening of fibrosis or fibrosis improvement by at least one stage without worsening of NASH. One of these outcomes (improvement of fibrosis) was achieved in 71 (23%) of 308 patients in the obeticholic acid 25 mg group compared with 37 (12%) of 311 patients in the placebo group (p=0·0002). The study is ongoing with patients expected to have follow-up for at least 4 years to evaluate the long-term clinical benefits of treatment.

This study is a pivotal step for the development of drugs to treat NASH and is likely to be the first to receive regulatory approval. The strengths include the stringent protocol adherence and the central assessment of all biopsies by two designated pathologists.



Steve Gschmeissner/Science Photo Library

Although the study has yielded encouraging results and is the first phase 3 trial in NASH to show a beneficial treatment effect, some questions remain. The effect of obeticholic acid on the co-primary endpoint of NASH resolution was not achieved. Furthermore, patients receiving obeticholic acid were more likely to use a statin during the study than those receiving placebo, raising the question as to whether the observed reduction in fibrosis stage with obeticholic acid might at least partly be attributed to a statin effect. However, the authors note that no clear pattern of fibrosis response by statin use was observed.

The safety and metabolic consequences of obeticholic acid also remain a concern. Obeticholic acid has several side-effects, including pruritus and elevated LDL cholesterol levels. The deaths of 19 patients treated with obeticholic acid for primary biliary cholangitis, its current approved indication, have also raised concerns about safety post marketing, but it should be noted that the deaths are likely to be attributable to inappropriate dosing.[11] In particular, the effect of obeticholic acid on the lipid profile is of particular relevance because patients with NAFLD exhibit a substantial increase in the risk of cardiovascular disease, the main cause of death in this population.[3] A recent modelling study suggests that moderate increases in LDL cholesterol in patients with biopsy-proven NAFLD would result in worsening of cardiovascular disease risk in about 7·8% of all patients without a history of cardiovascular disease, which might blunt the beneficial effects from improved liver fibrosis.[12] In this study,[9] LDL cholesterol increased by approximately 20% from baseline levels, which is similar to other reports.[13,14] However, the increase in LDL cholesterol was suggested to be transient and controlled with statins, as it returned to baseline levels at month 6 and baseline levels were sustained through month 18. Therefore, LDL cholesterol would need to be monitored and managed as required. Notably, studies of the combination of obeticholic acid with lipid-lowering agents are ongoing.

In summary, the study by Younossi and colleagues[9] has introduced obeticholic acid as a treatment option for patients with NASH. Final results will hopefully clarify effects of obeticholic acid on liver and cardiovascular clinical outcomes. If approved, in the long term, safety and efficacy must be assessed in real-world populations, especially with regard to tolerability and cardiovascular risk.

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Should doctors have a legal duty to warn relatives of their genetic risks?

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On Nov 18–25, 2019, a legal case (QB-2013-009529, ABC *vs* St George's Healthcare NHS Trust) was heard in the Royal Courts of Justice in London, UK. The case concerns a man who killed his wife in 2007. He was convicted of manslaughter and while in a forensic psychiatric unit, in 2009, was diagnosed with Huntington's disease, a progressive neurological condition that confers a 50/50 inherited risk to first-degree relatives.[1] His daughter was pregnant at the time and the man told his doctors not to disclose his genetic diagnosis to her as he feared she would terminate her pregnancy. The doctors respected his confidentiality and did not tell the daughter. In 2013, the daughter was diagnosed with Huntington's disease. The daughter, known as ABC in the legal case, is suing the doctors who cared for her father for neglecting to warn her of her own risks of having Huntington's disease; she claims that had she been told in time, she would have had an abortion.

The case centres on whether doctors should have a legal duty to warn a patient's relatives about disease risks from an inherited condition. This case considers the balancing act between a duty to protect patient confidentiality versus a duty to warn, and thus prevent harm, in relatives.[2] How much weighting should be given to an individual's views, when they wish to withhold information that could be important for their relatives? If it is decided that health-care professionals have a legal duty to warn other at-risk relatives, then this case will have wide-ranging implications for how genetic medicine is practised.

In the UK, a duty to warn is already recognised in professional guidance from the General Medical Council[3] and the Joint Committee on Genomics in Medicine (JCGM)[4] for clinicians working with patients who have genetic conditions. For example, the JCGM states that "the rule of confidentiality is not absolute. In certain circumstances it may be justified to break confidence where the avoidance of harm by the disclosure outweighs the patients' claim to confidentiality".[4] Thus, it is acceptable for clinicians to forewarn unaffected relatives about their potential heritable disease risks, even if the affected relative