JAMA Network Open

Original Investigation | Gastroenterology and Hepatology

Cost-Effectiveness of MASH Diagnosis and Management Approaches Among Those With Type 2 Diabetes

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Abstract

IMPORTANCE Metabolic dysfunction–associated steatohepatitis (MASH) represents a high, underprioritized burden among noncommunicable diseases (NCDs) and people living with type 2 diabetes (T2D).

OBJECTIVE To identify cost-effective management approaches to prevent, detect, and treat MASH and liver fibrosis in people living with T2D.

DESIGN, SETTING, AND PARTICIPANTS This economic evaluation consisted of a generalized cost-effectiveness analysis (GCEA) that was conducted for 12 countries (Brazil, Chile, Germany, Italy, Japan, Saudi Arabia, South Africa, Spain, Sweden, Tanzania, Thailand, and the United States), across all 6 World Health Organization (WHO) regions. A cohort state-transition model simulated liver disease development and its impact on a synthetic cohort, aged 19 years and older and living with T2D, over their lifespan across 10 liver health states.

EXPOSURES Using an 80% coverage level, 14 management approaches were compared, including screening via the Fibrosis-4 (FIB-4) test and Enhanced Liver Fibrosis (ELF) test or vibration-controlled transient elastography (VCTE) as well as treatment with pharmacological and nonpharmacological interventions.

MAIN OUTCOMES AND MEASURES The main outcomes were the average cost-effectiveness ratios (ACERs) and the incremental cost-effectiveness ratios (ICERs), which were used to construct care expansion paths by ranking the management approaches in order of cost-effectiveness. The main measures were the total incremental costs and the total incremental quality-adjusted life-years (QALYs) of each intervention.

RESULTS In this GCEA, the outcomes were evaluated with respect to country-specific willingness-to-pay thresholds. The standard of care had the lowest ACERs in 8 countries (not in Chile, Germany, Saudi Arabia, or the United States). Treatment with intensive lifestyle interventions (ILIs), after screening via ELF or VCTE, was cost-effective in all countries. ILIs and treatment with semaglutide was cost-effective in 11 countries (not in Tanzania); ILIs and treatment with resmetirom was cost-effective in 8 countries (not in Brazil, South Africa, Tanzania, or Thailand).

CONCLUSION AND RELEVANCE In this economic evaluation, screening followed by ILIs was found to be a cost-effective management approach for MASH and liver fibrosis among people living with T2D in all countries. Screening followed by pharmacological treatment was cost-effective in most

(continued)

Key Points

Question What are the most cost-effective management approaches for detecting, preventing, and treating metabolic dysfunction–associated steatohepatitis and liver fibrosis among people living with type 2 diabetes (T2D) in 12 countries?

Findings This economic evaluation found that the standard of care had the lowest average cost-effectiveness ratios in 8 countries; intensive lifestyle interventions (ILIs) after screening were cost-effective in all countries; and ILIs and semaglutide or resmetirom therapy were cost-effective in 11 and 7 countries, respectively.

Meaning In this study, most proposed management approaches among people living with T2D were cost-effective in most countries.

+ Supplemental content

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Abstract (continued)

countries. These results can inform health policy decision-making and further the development of WHO recommended interventions to address NCDs.

JAMA Network Open. 2025;8(11):e2542750. doi:10.1001/jamanetworkopen.2025.42750

Introduction

The global burden of cardiometabolic disease is high and expanding, posing major societal, economic, and health system implications.[1-3] Metabolic dysfunction–associated steatohepatitis (MASH), formerly nonalcoholic steatohepatitis, the advanced form of metabolic dysfunction–associated steatotic liver disease (MASLD), formerly nonalcoholic fatty liver disease, is an often-overlooked consequence of metabolic syndrome.[4] The prevalence of MASLD and MASH among the general adult population is respectively estimated at 38.0% and 5.3% globally, with variations depending primarily on the underlying prevalence of obesity and type 2 diabetes (T2D).[5] These figures are hence higher among adults living with T2D, with prevalence estimates of 65.0% and 31.6%, respectively.[6]

MASLD can result in liver damage (eg, fibrosis, cirrhosis, and cancer).[7] Globally, approximately 20% of cases of hepatocellular carcinoma (HCC), the most common primary liver cancer, are directly associated with MASH, with this proportion growing, particularly among those living with other cardiometabolic risk factors.[8,9] HCC is a common indication for liver transplantation.[10] The impact of MASLD extends beyond the liver, with the disease being associated with the risk of developing cardiovascular disease (CVD)—the leading cause of death among people living with MASLD—T2D, chronic kidney disease, and extrahepatic cancer.[11,12] The MASLD and MASH burden, including the associated costs, is expected to expand, leading to important consequences for at-risk populations and health systems.[13,14]

Despite the scale of the challenge, global policy responses to prevent and manage MASLD and MASH have been weak and fragmented. Of 102 countries studied in 2020, none had a strategy for addressing MASLD and MASH, and these were infrequently included in strategies for comorbidities such as diabetes.[15] MASLD and MASH are also not mentioned in the World Health Organization (WHO) global action plan for the prevention and control of noncommunicable diseases (NCDs),[16] and there is a dearth of technical guidance for countries seeking to design and deliver health system responses.

However, since 2020, the MASLD community of practice has grown, including through large multistakeholder initiatives to define research and action priorities.[15,17-19] Moreover, the approval of the first MASH-specific drug by the US Food and Drug Administration (FDA), in 2024, along with diagnostic innovations and other pharmacological treatments being tested in advanced-phase clinical trials, provide impetus for expanding care for people living with MASLD.[20-22]

In 2023, an updated list of WHO best buys, which are cost-effective interventions and other recommended interventions, was approved by the 76th World Health Assembly. These provide member states with a set of policy options to prevent and manage high-prevalence NCDs. While several interventions address factors that impact MASLD and MASH, including healthy diets and physical activity, none directly address their diagnosis and treatment requirements.[23,24]

Establishing cost-effective management approaches for the early detection of MASLD and MASH and linking people to care are key steps in improving health outcomes and making health systems more impactful. Therefore, it is essential to identify individuals and populations at risk of MASH and liver fibrosis (the most important prognostic determinant in MASLD[25]) to screen and intervene early, before complications develop. While some clinical guidelines recommend the screening of MASLD-associated liver fibrosis in high-risk populations (eg, people living with T2D),[26-29] this practice has not been systematically implemented, partly due to a lack of enabling guidance and policy. This study aimed to identify the most cost-effective approaches to prevent,

detect, and treat MASH and liver fibrosis due to MASLD among adults living with T2D around the world.

Methods

In this economic evaluation, a health system's perspective generalized cost-effectiveness analysis (GCEA) was conducted for 12 countries to identify the most cost-effective management approaches and corresponding expansion paths to prevent, detect, and treat MASH and liver fibrosis.[30-33] The analysis was based on WHO's Choosing Interventions that are Cost-Effective (WHO-CHOICE) methods and was conducted following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline for economic analyses.[34] Per the Common Rule, ethical approval was not required for this study because no patient data were used.

Sites and Population

Twelve countries across all 6 WHO regions (African [AFR], Americas [AMR], Eastern Mediterranean [EMR], Europe [EUR], South-East Asia [SEAR], and Western Pacific [WPR]), were included: South Africa and Tanzania for AFR; Brazil, Chile, and the United States for AMR; Saudi Arabia for EMR; Germany, Italy, Spain, and Sweden for EUR; Thailand for SEAR; and Japan for WPR. The target population was adults aged 19 years and older living with T2D, as this population is at increased risk for developing MASH and liver fibrosis.[26,27,29] An 80% coverage level was assumed for the proposed management approaches. Total costs and quality-adjusted life-years (QALYs) were also estimated for 50% and 95% coverage levels.

Management Approaches

Fourteen multifaceted approaches, in addition to the standard of care (SoC), which was defined as the absence of any systematic testing and treatment, were analyzed. Following the SoC and first-line liver fibrosis screening via the Fibrosis-4 (FIB-4) test, a freely available noninvasive test to estimate the risk of scarring in the liver, all subsequent approaches were divided into 2 groups, each featuring a different second-line fibrosis screening test: Enhanced Liver Fibrosis (ELF) or vibration-controlled transient elastography (VCTE) (eTable 1 in Supplement 1).

Outcomes

Average cost-effectiveness ratios (ACERs), incremental cost-effectiveness ratios (ICERs), and the expansion paths were the 3 outcomes of interest. The ACER measures the average cost per unit of health benefit for a single intervention by dividing its total cost by its total effectiveness. The approach for estimating ACERs is conceptually equivalent to comparing each management approach with the null being set as the fixed comparator. The ICER represents the additional cost per unit of health benefit (ie, QALYs) gained when comparing among interventions, calculated as the difference in incremental costs divided by the difference in incremental effectiveness. While ACERs provide a stand-alone measure of efficiency,[30-32] ICERs are essential for constructing the expansion path, which is the set of cost-effective management approaches that lie on the efficiency frontier, representing the sequence of approaches that maximize health outcomes for incremental costs. By definition, the efficiency frontier connects nondominated approaches in order of increasing effectiveness and cost. Nondominated strategies (management approaches) are part of the expansion path, providing better ICERs than the alternatives. Dominated and extendedly dominated approaches were those that were more expensive and/or less effective than the alternatives. The WHO-CHOICE method does not use the SoC as a fixed comparator[30-32]; it identifies the management approach with the lowest ICER as the first comparator and expands this path in a stepwise fashion, comparing each new candidate management approach with the previously identified approach and not always with the SoC. This framework is used to prioritize interventions as resources expand.

Statistical Analysis

Model Structure

All analyses were performed using R version 4.3.0 in RStudio version 2024.04.2 (R Project for Statistical Computing) on a high-performance server. A Markov time-independent cohort state-transition model[33] was developed to simulate the natural history of liver fibrosis among people living with MASH and T2D and the outcomes associated with the aforementioned management approaches over a synthetic cohort with an initial and a final cycle at ages 19 and 100 years, respectively, and to estimate the corresponding long-term costs and health outcomes. The model included 10 health states (eFigures 1-12 in Supplement 1), and the cohort was assumed to be homogeneous within each one.[33] The cycle length between one state and the next was set at 1 year. Transition probabilities—which represent the chance that individuals within the cohort residing in a state in a given cycle transition to another or remain in the same state for stages F0 through F4—could remain stable, increase, or decrease in accordance with what is reported in the literature[14]; no regression was possible after stage F4. All cohort individuals started at F0 at the initial cycle and followed the natural history of liver fibrosis based on the most recent literature.[4,14] In line with WHO guidelines, no discount was applied to health utilities, and costs were discounted at an annual rate of 3%.[30-32]

Modeling Outcomes and Costs

To be conservative, the model considered that FIB-4, ELF, VCTE, semaglutide, intensive lifestyle interventions (ILIs), and resmetirom only affected transition probabilities from F2 to F2, F2 to F3, F3 to F2, and F3 to F3 within a 1% to 5% range, each. For approaches consisting of multiple interventions, a cumulative effect was assumed.[20,22,35] Based on prior literature, the assumed effects of FIB-4, ELF, VCTE, semaglutide, ILIs, and resmetirom on health outcomes corresponding to stages F2 and F3 were 0.03, 0.04, 0.04, 0.04, 0.06, and 0.08, respectively.[36,37] All management approach costs were assumed to be related to stages F0 through F4 only.

Sensitivity Analyses

To evaluate more optimistic scenarios with stronger effects on transition probabilities, a deterministic sensitivity analysis (DSA) was conducted, estimating prospective outcomes by doubling the baseline effects initially considered for semaglutide and resmetirom. These results are presented with the expansion paths.

To account for uncertainty in cost parameters, a probabilistic sensitivity analysis (PSA) was conducted with 1000 simulations. Cost and utility inputs were modeled using a uniform distribution with a range of −20% to 30% and −5% to 5% of the base values, respectively. This approach was used to capture potential asymmetry in cost variability, where costs are more likely to exceed the baseline than fall below it, and allowed for utility values to vary to a lesser extent. To reduce making additional assumptions about parameters, other distributions (eg, gamma, beta) were not used. Undertaking this analysis enabled a robust exploration of cost uncertainty and its impact on results, thereby enhancing the reliability of our findings.[38]

Model Inputs

The prevalence of MASH among adults aged 19 years and older living with T2D within each country was estimated by (1) obtaining the prevalence of T2D among adults, aged 19 years and older, from country-specific literature[39] and (2) using data from En Li Cho et al[6] to calculate the prevalence of MASH among adults aged 19 years and older living with T2D within each country. The resulting estimate was used as the number of people included in the synthetic cohort at the initial stage of the model. This allowed for estimating current costs for each approach.

Annual transition probabilities from one state to the next were obtained from country- and/or region-specific registries and studies (eTables 2-13 in Supplement 1) or the Global Burden of Disease Study 2021. For states F0 to F4, transition probabilities were adjusted for general mortality; for all

other states, transition probabilities were adjusted for general and liver-specific mortality. Management approach effects were applied to each corresponding fibrosis stage in a conservative manner, as detailed previously.

Costs of Each Fibrosis Stage and Proposed Management Approach, and Utility Values

Unit costs were approximated based on country- or region-specific fee schedules obtained from the literature, governmental sources, and/or expert opinion (eTables 14 and 15 in Supplement 1). These costs were adjusted and converted into international dollars (I$) for the year 2023 based on the purchasing power parity reported by the World Bank.[40] Health outcomes were measured as QALYs obtained from country-specific studies (eTable 16 in Supplement 1). Thresholds for highly cost-effective and cost-effective management approaches were set at less than 1 gross domestic product per capita and per ICER, respectively (eTable 17 in Supplement 1).[41]

Results

For 8 of the 12 countries, the SoC was found to be the most cost-effective intervention, making it the starting point in their expansion path. After screening, treatment with ILIs, ILIs with semaglutide, and ILIs with resmetirom were identified as being cost-effective for 12 (all countries), 11 (all countries except Tanzania), and 8 (all countries except Brazil, South Africa, Tanzania, and Thailand) countries, respectively (**Table**). Estimates for total costs and QALYs according to coverage levels of 50%, 80%, and 95% are reported in eTables 18 to 23 in Supplement 1.

For both AFR countries, the SoC was the management approach with the lowest ACERs: I$74 (Tanzania) and I$145 (South Africa) for ELF, and I$80 (Tanzania) and I$151 (South Africa) for VCTE. For South Africa, all screening management approaches and treatment with ILIs and semaglutide were found to be cost-effective, with ACERs ranging from I$157 to I$5613 for ELF and from I$163 to I$2387 for VCTE. For Tanzania, all screening management approaches and treatment with ILIs were identified as being cost-effective, with ACERs ranging from I$81 to I$771 for ELF and from I$88 to I$2269 for VCTE. The management approach expansion paths are shown in the Table and eFigure 13 in Supplement 1.

For AMR, the most cost-effective management approach for Brazil was the SoC, with ACERs of I$71 for ELF and I$67 for VCTE. Additionally, all screening management approaches and treatment with ILIs and semaglutide, both independently and combined, were found to be cost-effective, with ACERs ranging from I$73 to I$17 598 for ELF and I$69 to I$17 606 for VCTE. For Chile, the SoC had the lowest ACERs for ELF and VCTE. For Brazil, all resmetirom and resmetirom with ILI approaches were not found to be cost-effective. For the United States, the SoC had the lowest ACER at I$403 for ELF, and FIB-4 (2B) alone had the lowest ACER at I$383 for VCTE, with these being the expansion path starting points (Table; eFigure 14 in Supplement 1).

For EMR, the management approaches with FIB-4 and ELF (2A) or FIB-4 and VCTE (2B) had the lowest ACERs, at I$920 and I$893, respectively. Nondominated management approaches are shown in the Table and eFigure 15 in Supplement 1.

For EUR, all management approaches were identified as being cost-effective, and the SoC had the lowest ACERs in Italy, Spain, and Sweden. For Germany, FIB-4 with ELF (2A) had the lowest ACER for ELF; FIB-4 only had the highest ACER for VCTE. As management approaches were added into the expansion path ACERs ranged from I$1180 to I$46 863 for ELF and I$188 to I$47 095 for VCTE. For Italy, the next most cost-effective management approaches after the SoC for ELF were FIB-4 only (1); FIB-4 with ELF (2A); FIB-4 with ELF, a hepatologist consult, and semaglutide prescription (6A); and FIB-4 with ELF, a hepatologist consult, ILIs, and resmetirom prescription (5A), with ACERs ranging from I$132 to I$30 025; for VCTE, they were FIB-4 with VCTE (2B); FIB-4 with VCTE, a hepatologist consult, and semaglutide prescription (6B); and FIB-4 with VCTE, a hepatologist consult, ILIs, and resmetirom prescription (5B), with ACERs ranging from I$143 to I$30 018. For Spain, management approaches involving FIB-4 with ELF (2A); FIB-4 with ELF, a hepatologist consult, and semaglutide

Table. Total Costs, QALYs, and ACERs for the WHO African, Americas, Eastern Mediterranean, European, South-East Asian, and Western Pacific Regions for the ELF and VCTE Groups[a]

Management approaches (using ELF)	Costs per 100 000, I$	QALYs per 100 000	Status	ACER per 100 000, $I/QALY	Management approaches (using VCTE)	Costs per 100 000, I$	QALYs per 100 000	Status	ACER per 100 000, $I/QALY
South Africa (WHO African region)									
0: Standard of care	301 621 428	2 085 511	ND	145	0: Standard of care	315 175 222	2 085 511	ND	151
2A: FIB-4 with ELF	358 178 793	2 118 222	ND	169	1: FIB-4 only	342 755 835	2 096 952	ND	163
3A: FIB-4 with ELF, a hepatologist consult, and ILIs	4 950 665 653	2 177 940	ND	2273	2B: FIB-4 with VCTE	403 133 103	2 118 222	ND	190
6A: FIB-4 with ELF, a hepatologist consult, and semaglutide	8 197 911 057	2 195 151	ND	3735	3B: FIB-4 with VCTE, a hepatologist consult, and ILIs	5 198 857 916	2 177 940	ND	2387
5A: FIB-4 with ELF, a hepatologist consult, ILIs, and resmetirom	57 504 456 194	2 200 827	ND	26 129	6B: FIB-4 + VCTE, a hepatologist consult, and semaglutide	8 447 974 155	2 195 151	ND	3848
1: FIB-4 only	328 809 376	2 096 952	ED	157	5B: FIB-4 with VCTE, a hepatologist consult, ILIs, and resmetirom	57 752 648 457	2 200 827	ND	26 241
7A: FIB-4 with ELF, a hepatologist consult, ILIs, and semaglutide	12 225 384 715	2 178 079	D	5613	7B: FIB-4 with VCTE, a hepatologist consult, ILIs, and semaglutide	12 472 700 506	2 178 079	D	5726
4A: FIB-4 with ELF, a hepatologist consult, and resmetirom	54 182 664 411	2 183 662	D	24 813	4B: FIB-4 with VCTE, a hepatologist consult, and resmetirom	53 632 159 401	2 183 662	D	24 561
Tanzania (WHO African region)									
0: Standard of care	155 296 540	2 095 737	ND	74	0: Standard of care	168 609 872	2 095 737	ND	80
1: FIB-4 only	170 923 221	2 106 529	ND	81	1: FIB-4 only	184 622 251	2 106 529	ND	88
2A: FIB-4 with ELF	211 189 605	2 126 319	ND	99	2B: FIB-4 with VCTE	255 346 366	2 126 319	ND	120
3A: FIB-4 with ELF, a hepatologist consult, and ILIs	1 681 602 337	2 180 881	ND	771	3B: FIB-4 with VCTE, a hepatologist consult, and ILIs	4 949 217 257	2 180 881	ND	2269
6A: FIB-4 with ELF, a hepatologist consult, and semaglutide	22 385 770 015	2 195 289	ND	10 197	6B: FIB-4 with VCTE, a hepatologist consult, and semaglutide	22 631 396 665	2 195 289	ND	10 309
5A: FIB-4 with ELF, a hepatologist consult, ILIs, and resmetirom	57 259 205 205	2 203 768	ND	25 982	5B: FIB-4 with VCTE, a hepatologist consult, ILIs, and resmetirom	57 502 994 211	2 203 768	ND	26 093
7A: FIB-4 with ELF, a hepatologist consult, ILIs, and semaglutide	26 330 707 414	2 182 258	D	12 066	7B: FIB-4 with VCTE, a hepatologist consult, ILIs, and semaglutide	26 573 635 497	2 182 258	D	12 177
4A: FIB-4 with ELF, a hepatologist consult, and resmetirom	53 227 437 320	2 186 603	D	24 343	4B: FIB-4 with VCTE, a hepatologist consult, and resmetirom	53 471 226 325	2 186 603	D	24 454
Brazil (WHO Americas region)									
0: Standard of care	128 699 225	1 818 607	ND	71	0: Standard of care	121 465 969	1 818 607	ND	67
2A: FIB-4 with ELF	140 714 569	1 865 640	ND	75	1: FIB-4 only	126 690 516	1 834 908	ND	69
3A: FIB-4 with ELF, a hepatologist consult, and ILIs	4 191 298 556	1 953 579	ND	2145	2B: FIB-4 with VCTE	137 398 078	1 865 640	ND	74
6A: FIB-4 with ELF, a hepatologist consult, and semaglutide	30 648 063 579	1 979 907	ND	15 480	3B: FIB-4 with VCTE, a hepatologist consult, and ILIs	4 207 551 724	1 953 579	ND	2154
5A: FIB-4 with ELF, a hepatologist consult, ILIs, and resmetirom	55 800 195 670	1 984 454	ND	28 119	6B: FIB-4 with VCTE, a hepatologist consult, and semaglutide	30 663 801 101	1 979 907	ND	15 487
1: FIB-4 only	134 135 283	1 834 908	ED	73	5B: FIB-4 with VCTE, a hepatologist consult, ILIs, and resmetirom	55 816 448 838	1 984 454	ND	28 127
7A: FIB-4 with ELF, a hepatologist consult, ILIs, and semaglutide	34 349 857 978	1 951 952	D	17 598	7B: FIB-4 with VCTE, a hepatologist consult, ILIs, and semaglutide	34 366 358 155	1 951 952	D	17 606
4A: FIB-4 with ELF, a hepatologist consult, and resmetirom	51 840 916 127	1 961 297	D	26 432	4B: FIB-4 with VCTE, a hepatologist consult, and resmetirom	51 857 169 295	1 961 297	D	26 440
Chile (WHO Americas region)									
0: Standard of care	380 253 677	1 818 670	ND	209	0: Standard of care	409 367 899	1 818 670	ND	225
2A: FIB-4 with ELF	395 600 162	1 865 689	ND	212	1: FIB-4 only	417 392 223	1 834 967	ND	227
6A: FIB-4 with ELF, a hepatologist consult, and semaglutide	3 100 753 629	1 979 908	ND	1566	2B: FIB-4 with VCTE	490 357 233	1 865 689	ND	263

(continued)

Table. Total Costs, QALYs, and ACERs for the WHO African, Americas, Eastern Mediterranean, European, South-East Asian, and Western Pacific Regions for the ELF and VCTE Groups[a] (continued)

Management approaches (using ELF)	Costs per 100 000, I$	QALYs per 100 000	Status	ACER per 100 000, $I/QALY	Management approaches (using VCTE)	Costs per 100 000, I$	QALYs per 100 000	Status	ACER per 100 000, $I/QALY
5A: FIB-4 with ELF, a hepatologist consult, ILIs, and resmetirom	56 208 806 675	1 984 471	ND	28 324	6B: FIB-4 with VCTE, a hepatologist consult, and semaglutide	3 493 862 218	1 979 908	ND	1765
1: FIB-4 only	387 426 657	1 834 967	ED	211	5B: FIB-4 with VCTE, a hepatologist consult, ILIs, and resmetirom	56 597 164 306	1 984 471	ND	28 520
3A: FIB-4 with ELF, a hepatologist consult, and ILIs	4 599 906 257	1 953 596	D	2355	3B: FIB-4 with VCTE, a hepatologist consult, and ILIs	4 988 263 888	1 953 596	D	2553
7A: FIB-4 with ELF, a hepatologist consult, ILIs, and semaglutide	7 111 969 927	1 951 977	D	3643	7B: FIB-4 with VCTE, a hepatologist consult, ILIs, and semaglutide	7 498 047 508	1 951 977	D	3841
4A: FIB-4 with ELF, a hepatologist consult, and resmetirom	52 249 526 878	1 961 315	D	26 640	4B: FIB-4 with VCTE, a hepatologist consult, and resmetirom	52 637 884 510	1 961 315	D	26 838
United States (WHO Americas region)									
0: Standard of care	772 102 602	1 917 415	ND	403	2B: FIB-4 with VCTE	750 059 899	1 959 401	ND	383
1: FIB-4 only	777 610 131	1 932 160	ND	402	6B: FIB-4 with VCTE, a hepatologist consult, and semaglutide	6 988 014 371	2 056 161	ND	3399
2A: FIB-4 with ELF	798 900 413	1 959 401	ND	408	5B: FIB-4 with VCTE, a hepatologist consult, ILIs, and resmetirom	72 070 792 078	2 066 592	ND	34 874
6A: FIB-4 with ELF, a hepatologist consult, and semaglutide	7 190 971 291	2 056 161	ND	3497	0: Standard of care	755 776 591	1 917 415	D	394
5A: FIB-4 with ELF, a hepatologist consult, ILIs, and resmetirom	72 275 649 286	2 066 592	ND	34 973	1: FIB-4 only	762 225 850	1 932 160	D	394
3A: FIB-4 with ELF, a hepatologist consult, and ILIs	7 764 529 526	2 035 717	D	3814	3B: FIB-4 with VCTE, a hepatologist consult, ILIs	7 559 672 318	2 035 717	D	3714
7A: FIB-4 with ELF, a hepatologist consult, ILIs, and semaglutide	13 598 945 625	2 036 817	D	6677	7B: FIB-4 with VCTE, a hepatologist consult, ILIs, and semaglutide	13 393 189 164	2 036 817	D	6576
4A: FIB-4 with ELF, a hepatologist consult, and resmetirom	65 967 527 291	2 043 436	D	32 283	4B: FIB-4 with VCTE, a hepatologist consult, and resmetirom	65 762 670 083	2 043 436	D	32 182
Saudi Arabia (WHO Eastern Mediterranean region)									
2A: FIB-4 with ELF	1 801 689 236	1 959 401	ND	920	2B: FIB-4 with VCTE	1 750 165 026	1 959 401	ND	893
6A: FIB-4 with ELF, a hepatologist consult, and semaglutide	7 494 662 322	2 056 161	ND	3645	6B: FIB-4 with VCTE, a hepatologist consult, and semaglutide	7 280 908 607	2 056 161	ND	3541
5A: FIB-4 with ELF, a hepatologist consult, ILIs, and resmetirom	57 969 678 801	2 066 592	ND	28 051	5B: FIB-4 with VCTE, a hepatologist consult, ILIs, and resmetirom	57 758 508 690	2 066 592	ND	27 949
3A: FIB-4 with ELF, a hepatologist consult, and ILIs	6 360 781 494	2 035 717	ED	3125	3B: FIB-4 with VCTE, a hepatologist consult, and ILIs	6 149 611 383	2 035 717	ED	3021
0: Standard of care	1 843 719 270	1 917 416	D	962	0: Standard of care	1 827 888 373	1 917 416	D	953
1: FIB-4 only	1 921 621 060	1 932 160	D	995	1: FIB-4 only	1 905 327 243	1 932 160	D	986
7A: FIB-4 with ELF, a hepatologist consult, ILIs, and semaglutide	11 807 381 209	2 036 817	D	5797	7B: FIB-4 with VCTE, a hepatologist consult, ILIs, and semaglutide	11 597 450 878	2 036 817	D	5694
4A: FIB-4 with ELF, a hepatologist consult, and resmetirom	54 010 399 514	2 043 436	D	26 431	4B: FIB-4 + VCTE, a hepatologist consult, and resmetirom	53 799 229 132	2 043 436	D	26 328
Germany (WHO European region)									
2A: FIB-4 with ELF	272 371 576	1 904 867	ND	143	1: FIB-4 only	304 221 773	1 889 260	ND	161
6A: FIB-4 with ELF, a hepatologist consult, and semaglutide	2 292 712 326	1 943 642	ND	1180	2B: FIB-4 with VCTE	358 552 418	1 904 867	ND	188
7A: FIB-4 with ELF, a hepatologist consult, ILIs, and semaglutide	6 362 124 453	1 951 491	ND	3260	6B: FIB-4 with VCTE, a hepatologist consult, and semaglutide	2 751 501 800	1 943 642	ND	1416
5A: FIB-4 with ELF, a hepatologist consult, ILIs, and resmetirom	92 354 301 957	1 970 734	ND	46 863	7B: FIB-4 with VCTE, a hepatologist consult, ILIs, and semaglutide	6 818 274 466	1 951 491	ND	3494

(continued)

Table. Total Costs, QALYs, and ACERs for the WHO African, Americas, Eastern Mediterranean, European, South-East Asian, and Western Pacific Regions for the ELF and VCTE Groups[a] (continued)

Management approaches (using ELF)	Costs per 100 000, I$	QALYs per 100 000	Status	ACER per 100 000, $I/QALY	Management approaches (using VCTE)	Costs per 100 000, I$	QALYs per 100 000	Status	ACER per 100 000, $I/QALY
3A: FIB-4 with ELF, a hepatologist consult, and ILIs	4 554 884 261	1 946 449	ED	2340	5B: FIB-4 with VCTE, a hepatologist consult, ILIs, and resmetirom	92 812 175 198	1 970 734	ND	47 095
4A: FIB-4 with ELF, a hepatologist consult, and resmetirom	88 314 201 008	1 952 521	ED	45 231	3B: FIB-4 with VCTE, a hepatologist consult, and ILIs	5 012 757 502	1 946 449	ED	2575
1: FIB-4 only	278 674 205	1 889 260	D	148	4B: FIB-4 with VCTE, a hepatologist consult, and resmetirom	88 772 074 250	1 952 521	ED	45 465
0: Standard of care	280 062 135	1 880 383	D	149	0: Standard of care	304 817 683	1 880 383	D	162
Italy (WHO European region)									
0: Standard of care	258 487 078	2 041 244	ND	127	0: Standard of care	257 708 923	2 041 244	ND	126
1: FIB-4 only	272 144 736	2 057 538	ND	132	2B: FIB-4 with VCTE	298 081 523	2 089 742	ND	143
2A: FIB-4 with ELF	300 682 143	2 089 742	ND	144	6B: FIB-4 with VCTE, a hepatologist consult, and semaglutide	2 140 984 919	2 218 272	ND	965
6A: FIB-4 with ELF, a hepatologist consult, and semaglutide	2 155 520 816	2 218 272	ND	972	5B: FIB-4 with VCTE, a hepatologist consult, ILIs, and resmetirom	66 799 991 256	2 225 306	ND	30 018
5A: FIB-4 with ELF, a hepatologist consult, ILIs, and resmetirom	66 814 366 187	2 225 306	ND	30 025	1: FIB-4 only	271 335 885	2 057 538	ED	132
3A: FIB-4 with ELF, a hepatologist consult, and ILIs	5 444 641 700	2 192 357	D	2483	3B: FIB-4 with VCTE, a hepatologist consult, and ILIs	5 430 266 769	2 192 357	D	2477
7A: FIB-4 with ELF, a hepatologist consult, ILIs, and semaglutide	6 868 746 218	2 186 962	D	3141	7B: FIB-4 with VCTE, a hepatologist consult, ILIs, and semaglutide	6 854 468 817	2 186 962	D	3134
4A: FIB-4 with ELF, a hepatologist consult, and resmetirom	620 106 265 291	2 200 594	D	28 222	4B: FIB-4 with VCTE, a hepatologist consult, and resmetirom	62 091 890 360	2 200 594	D	28 216
Spain (WHO European region)									
0: Standard of care	604 843 485	2 085 873	ND	290	0: Standard of care	604 115 681	2 085 873	ND	290
2A: FIB-4 with ELF	722 462 848	2 118 502	ND	341	2B: FIB-4 with VCTE	720 048 917	2 118 502	ND	340
6A: FIB-4 with ELF, a hepatologist consult, and semaglutide	347 710 834	2 195 156	ND	1584	6B: FIB-4 with VCTE, a hepatologist consult, and semaglutide	3 463 673 088	2 195 156	ND	1578
5A: FIB-4 with ELF, a hepatologist consult, ILIs, and resmetirom	58 434 096 699	2 200 925	ND	26 550	5B: FIB-4 with VCTE, a hepatologist consult, ILIs, and resmetirom	58 420 769 411	2 200 925	ND	26 544
1: FIB-4 only	662 916 022	2 097 288	ED	316	1: FIB-4 only	662 167 133	2 097 288	ED	316
3A: FIB-4 with ELF, a hepatologist consult, and ILIs	5 880 293 437	2 178 038	D	2700	3B: FIB-4 with VCTE, a hepatologist consult, and ILIs	5 866 966 150	2 178 038	D	2694
7A: FIB-4 with ELF, a hepatologist consult, ILIs, and semaglutide	7 564 238 414	2 178 219	D	3473	7B: FIB-4 with VCTE, a hepatologist consult, ILIs, and semaglutide	7 550 958 190	2 178 219	D	3467
4A: FIB-4 with ELF, a hepatologist consult, and resmetirom	54 402 326 795	2 183 760	D	24 912	4B: FIB-4 with VCTE, a hepatologist consult, and resmetirom	54 388 999 507	2 183 760	D	24 906
Sweden (WHO European region)									
0: Standard of care	1 905 442 298	718 368	ND	2652	0: Standard of care	1 973 159 450	718 368	ND	2747
2A: FIB-4 with ELF	2 414 595 312	727 092	ND	3321	1: FIB-4 only	2 244 237 701	721 983	ND	3108
3A: FIB-4 with ELF, a hepatologist consult, and ILIs	6 024 170 633	734 520	ND	8202	2B: FIB-4 with VCTE	2 685 277 054	727 092	ND	3693
7A: FIB-4 with ELF, a hepatologist consult, ILIs, and semaglutide	9 819 319 581	738 855	ND	13 290	3B: FIB-4 with VCTE, a hepatologist consult, ILIs	6 701 672 952	734 520	ND	9124
5A: FIB-4 with ELF, a hepatologist consult, ILIs, and resmetirom	30 441 096 107	743 342	ND	40 952	7B: FIB-4 with VCTE, a hepatologist consult, ILIs, and semaglutide	10 496 756 441	738 855	ND	14 207
1: FIB-4 only	2 176 366 870	721 983	ED	3014	5B: FIB-4 with VCTE, a hepatologist consult, ILIs, and resmetirom	31 118 598 426	743 342	ND	41 863

(continued)

Table. Total Costs, QALYs, and ACERs for the WHO African, Americas, Eastern Mediterranean, European, South-East Asian, and Western Pacific Regions for the ELF and VCTE Groups[a] (continued)

Management approaches (using ELF)	Costs per 100 000, I$	QALYs per 100 000	Status	ACER per 100 000, $I/QALY	Management approaches (using VCTE)	Costs per 100 000, I$	QALYs per 100 000	Status	ACER per 100 000, $I/QALY
6A: FIB-4 with ELF, a hepatologist consult, and semaglutide	7 939 331 838	732 619	D	10 837	6B: FIB-4 with VCTE, a hepatologist consult, and semaglutide	8 617 108 791	732 619	D	11 762
4A: FIB-4 with ELF, a hepatologist consult, and resmetirom	28 567 903 066	736 726	D	38 777	4B: FIB-4 with VCTE, a hepatologist consult, and resmetirom	29 245 405 385	736 726	D	39 696
Thailand (WHO South-East Asia region)									
0: Standard of care	202 065 284	2 016 906	ND	100	0: Standard of care	202 692 015	2 016 906	ND	100
2A: FIB-4 with ELF	252 454 077	2 042 627	ND	124	2B: FIB-4 with VCTE	254 661 986	2 042 627	ND	125
3A: FIB-4 with ELF, a hepatologist consult, and ILIs	6 154 741 137	2 077 025	ND	2963	3B: FIB-4 with VCTE, a hepatologist consult, and ILIs	6 171 311 477	2 077 025	ND	2971
7A: FIB-4 with ELF, a hepatologist consult, ILIs, and semaglutide	12 042 951 232	2 084 943	ND	5776	7B: FIB-4 with VCTE, a hepatologist consult, ILIs, and semaglutide	12 059 521 519	2 084 943	ND	5784
5A: FIB-4 with ELF, a hepatologist consult, ILIs, and resmetirom	58 845 952 939	2 092 943	ND	28 116	5B: FIB-4 with VCTE, a hepatologist consult, ILIs, and resmetirom	58 862 523 729	2 092 943	ND	28 124
1: FIB-4 only	222 447 706	2 025 902	ED	110	1: FIB-4 only	223 091 832	2 025 902	ED	110
6A: FIB-4 with ELF, a hepatologist consult, and semaglutide	12 043 151 585	2 073 190	D	5809	6B: FIB-4 with VCTE, a hepatologist consult, and semaglutide	12 059 722 800	2 073 190	D	5817
4A: FIB-4 with ELF, a hepatologist consult, and resmetirom	54 803 641 465	2 081 005	D	26 335	4B: FIB-4 with VCTE, a hepatologist consult, and resmetirom	54 820 211 805	2 081 005	D	26 343
Japan (WHO Western Pacific region)									
0: Standard of care	1 437 929 390	1 551 105	ND	927	0: Standard of care	1 438 031 849	1 551 105	ND	927
2A: FIB-4 with ELF	1 444 742 922	1 597 737	ND	904	2B: FIB-4 with VCTE	1 445 160 238	1 597 737	ND	905
6A: FIB-4 with ELF, a hepatologist consult, and semaglutide	1 878 988 801	1 646 304	ND	1141	6B: FIB-4 with VCTE, a hepatologist consult, and semaglutide	1 879 834 032	1 646 304	ND	1142
7A: FIB-4 with ELF, a hepatologist consult, ILIs, and semaglutide	5 216 966 859	1 670 404	ND	3123	7B: FIB-4 with VCTE, a hepatologist consult, ILIs, and semaglutide	5 217 811 962	1 670 404	ND	3124
5A: FIB-4 with ELF, a hepatologist consult, ILIs, and resmetirom	48 333 731 568	1 686 695	ND	28 656	5B: FIB-4 with VCTE, a hepatologist consult, ILIs, and resmetirom	48 334 576 707	1 686 695	ND	28 656
3A: FIB-4 with ELF, a hepatologist consult, and ILIs	4 828 149 010	1 654 223	ED	2919	3B: FIB-4 with VCTE, a hepatologist consult, and ILIs	4 828 994 149	1 654 223	ED	2919
1: FIB-4 only	1 457 132 762	1 567 726	D	929	1: FIB-4 only	1 457 237 859	1 567 726	D	930
4A: FIB-4 with ELF, a hepatologist consult, and resmetirom	44 996 113 973	1 662 341	D	27 068	4B: FIB-4 with VCTE, a hepatologist consult, and resmetirom	44 996 959 113	1 662 341	D	27 068

Abbreviations: ACER, average cost-effectiveness ratio; D, dominated; ED, extendedly dominated; ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis-4; ILI, intensive lifestyle intervention; I$, international dollars (for the year 2023); ND, non-dominated; QALYs, quality-adjusted life years; VCTE, vibration-controlled transient elastography.

[a] Highly cost-effective thresholds for all management approaches were defined using gross domestic product (GDP) per capita criterion (cost-effective if <1 GDP per capita in purchasing power parity, constant 2023 international dollars, per QALY gained). The values are as follows: Brazil, I$18 554; Chile, I$29 507; Germany, I$61 909; Italy, I$52 700; Japan, I$46 268; Saudi Arabia, I$49 568; South Africa, I$14 284; Spain, I$46 357; Sweden, I$64 191; Tanzania, I$3581; Thailand, I$21 113; and the United States, I$73 637.

prescription (6A); FIB-4 with ELF, a hepatologist consult, ILIs, and resmetirom prescription (5A); FIB-4 with VCTE (2B); FIB-4 with VCTE, a hepatologist consult, and semaglutide prescription (6B); and FIB-4 with VCTE, a hepatologist consult, ILIs, and resmetirom prescription (5B) were nondominated and followed the SoC in the expansion path. For Sweden, the management approaches identified as being most cost-effective after the SoC were FIB-4 with ELF (2A); FIB-4 with ELF, a hepatologist consult, and ILIs (3A); FIB-4 with ELF, a hepatologist consult, ILIs, and semaglutide prescription (7A); FIB-4 with ELF, a hepatologist consult, ILIs, and resmetirom prescription (5A); FIB-only (1); FIB-4 with VCTE (2B); FIB-4, VCTE, a hepatologist consult, and ILIs

(3B); FIB-4 with VCTE, a hepatologist consult, ILIs, and semaglutide (7B); and FIB-4 with VCTE, a hepatologist consult, ILIs, and resmetirom (5B) (Table; eFigure 16 in Supplement 1).

For SEAR, the SoC had the lowest ACERs for ELF and VCTE (Table). Nonpharmacological interventions with ILIs and pharmacological interventions, both independently and combined, were found to be cost-effective, with ACERs ranging from I$2963 to I$28 116 for ELF and I$2971 to I$28 124 for VCTE. Pharmacological management approaches were dominated by those including pharmacological and nonpharmacological treatments (eFigure 17 in Supplement 1).

For WPR, the SoC had the lowest ACER. All management approaches were identified as being cost-effective, and FIB-4 with ELF (2A); FIB-4 with ELF, a hepatologist consult, and semaglutide prescription (6A); FIB-4 with ELF, a hepatologist consult, ILIs, and semaglutide prescription (7A); FIB-4 with ELF, a hepatologist consult, and resmetirom prescription (5A); FIB-4 with VCTE (2B); FIB-4 with VCTE, a hepatologist consult, and semaglutide prescription (6B); FIB-4 with VCTE, a hepatologist consult, ILIs, and semaglutide prescription (7B); and FIB-4 with VCTE, a hepatologist consult, and resmetirom prescription (5B) for VCTE were nondominated and ordered as such in the expansion paths for ELF and VCTE (Table; eFigure 17 in Supplement 1).

In the DSA, pharmacological management approaches were dominated by management approaches combining nonpharmacological and pharmacological treatment across all countries. The PSA showed that ACERs did not vary, and thus, the order of the management approaches did not change in the expansion path (eTables 24-33 and eFigures 18-27 in Supplement 1).

Discussion

This study provides a cost-effectiveness assessment of management approaches to prevent, detect, and treat MASH and liver fibrosis among adults living with T2D across all 6 WHO regions.[26,27] Fourteen approaches were ranked according to their cost-effectiveness within 2 groups: ELF or VCTE. This evaluation was conducted across 12 countries, each with a different health care system, economic context, and epidemiological profile. Although cost-effectiveness studies are not new,[42-44] no study to our knowledge has applied the WHO-CHOICE method in this area to date.

For 8 countries, the SoC was found to be the most cost-effective management approach. These results were affected by the limited availability of country-specific model parameters. Only screening and nonpharmacological treatment with ILI management approaches were cost-effective across all countries. However, it is important to highlight that cost-effectiveness is only one of several factors that should be considered when determining whether a disease management approach is feasible. WHO has emphasized the limitations of dismissing interventions based solely on cost-effectiveness thresholds.[41]

Management approaches that involved screening followed by ILIs and pharmacological treatment to halt or reverse MASH and liver fibrosis were found to be cost-effective for most countries. However, systematic screening for MASLD and MASH is not well integrated in any health system as an SoC for at-risk populations, such as people living with T2D. Such a gap should be addressed to avoid late diagnoses, which lead to higher health risks—such as cardiovascular events, the leading cause of death among people living with MASH—and costs, and to enable good quality of life. As for ILIs and pharmacological treatment, upon approving the use of resmetirom to treat MASH, the US FDA noted that it should "be used along with diet and exercise."[45] Therefore, health care professionals and systems must consider how to best support people being treated for MASH. Expanding the community of practice to include nutritionists, for instance, coupled with social prescribing and a recognition of the central role of social nutrition, is a key step in ending the MASLD and MASH public health threat.[46,47]

Systematic screening for MASH for people living with T2D could lead to a timely diagnosis[48] and provision of appropriate treatment options with new pharmacological therapies, in addition to ILIs.[49] Assuming that health outcomes remain at current levels, prospective price reductions for ELF and resmetirom would make the corresponding management approaches even more cost-effective.

Additionally, as more biomarker-based noninvasive tests are developed, diagnosing will be more easily implemented outside of specialist care.[37,38]

Reducing premature NCD mortality is a key sustainable development goal to be reached by 2030.[50] Continuing to exclude MASH from being recognized as a major NCD would undermine the achievement of this goal, given the impact that it alone represents and its strong link to T2D and CVD.[17,26,27] This study provides decision-makers in the included countries with an efficiency-ranked portfolio of management approaches for addressing the high and growing burden of MASH, enabling targeted resource allocation to maximize health gains.[14,17,18]

Limitations

Several limitations should be considered when interpreting these findings. First, limited availability of country-specific data necessitated reliance on key parameters—particularly disease progression probabilities—derived primarily from US epidemiological studies.[7] While this approach is common in global health modeling, it may not fully reflect the specific clinical context and natural history of MASH in all included countries, potentially affecting the precision of health state definitions, cost assignments, and long-term disease projections. This limitation also cautions against direct cross-country comparisons of absolute values. Second, the use of a time-independent Markov model does not capture potential temporal variations in parameters, such as treatment efficacy waning, disease progression rates, or changing resource costs, over longer time horizons. Therefore, while this analysis provides a robust efficiency-based ranking of interventions, policymakers should consider these findings as one component of comprehensive decision-making. Final resource allocation decisions should integrate these economic evaluations with additional critical factors including budgetary impact, equity considerations, health system capacity, implementation feasibility, and alignment with local health care priorities.

Conclusions

Screening for MASH and liver fibrosis among individuals living with type 2 diabetes—and offering appropriate nonpharmacological and pharmacological interventions—was cost-effective across all countries analyzed and in most regions. These results provide strong evidence for integrating liver health into diabetes management pathways globally.

Given the growing burden of MASH as a major NCD disproportionately affecting people living with T2D, our findings offer timely guidance for national and international health policymakers. The analysis spanned a diverse set of countries, encompassing various income levels and health systems, and highlighted strategic opportunities to improve outcomes through cost-effective interventions.

Future research should extend this work by including additional countries, broadening the range of management approaches, and adopting a societal perspective that accounts for indirect costs. WHO could play a critical role in supporting such efforts, as it has done for other leading NCDs. Recognizing MASLD and MASH as global health priorities is essential to addressing their high and rising public health and economic impact.

ARTICLE INFORMATION

Accepted for Publication: September 17, 2025.

Published: November 6, 2025. doi:10.1001/jamanetworkopen.2025.42750

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Conflict of Interest Disclosures: Dr Lazarus reported receiving grants to the institution (ISGlobal) from Gilead Science, Echosens, Novo Nordisk, Pfizer, Madrigal Pharmaceuticals, Boehringer Ingelheim, AbbVie, Moderna, MSD, and Roche Diagnostics; receiving personal fees from GSK, Echosens, Novovax, Novo Nordisk, and Pfizer; having held a paid leadership role at the Global NASH/MASH Council; receiving honoraria from AbbVie, Echosens, Gilead Science, GSK, Moderna, MSD, Novo Nordisk, Pfizer and Prosciento; participating on a data safety monitoring board for the QuickStart Study; having a leadership role in Healthy Livers, Health Lives; and serving as director of the Global Think-tank on Steatotic Liver Disease and MASH Cities outside the submitted work. Dr Kondili reported receiving grants to her institution from Gilead Science and personal fees from Gilead Science for participation in a scientific meeting outside the submitted work. Dr Hagström reported receiving grants to his institution from AstraZeneca, Echosens, Gilead Science, Intercept, MSD, Novo Nordisk and Pfizer; receiving consulting fees from AstraZeneca and Novo Nordisk; receiving payment for lectures from Gilead Science and Novo Nordisk; and participating on hepatic events adjudication committees for Arrowhead, KOWA, GW Pharma, and Boehringer Ingelheim outside of the submitted work. Dr Takahashi reported receiving honoraria for lectures from Novo Nordisk, Tisho Pharma, and Kowa outside of the submitted work. Dr Pericàs reported receiving consulting fees from MSD, Madrigal Pharmaceuticals, Boehringer Ingelheim, and Novo Nordisk; receiving speaking fees from Madrigal Pharmaceuticals, Gilead Science, Intercept, Boehringer Ingelheim, Novo Nordisk, Asociación Española para el Estudio del Hígado, and International Meeting on Therapy in Liver Diseases; travel expenses from Gilead Science, Rubió, Pfizer, Astellas, MSD, and Novo Nordisk; receiving educational and research support from Madrigal Pharmaceuticals, Boehringe Ingelheim, Gilead Science, Pfizer, Astellas, Accelerate, Novartis, AbbVie, ViiV, Siemens and MSD; and receiving competitive funding from Vall d'Hebron University Hospital Campus (research

intensification grant 2024-2025), ISCIII PI19/01898, PI22/01770, European Commission/EFPIA IMI2 853966-2, IMI2 777377, H2020 847989, HLTH-2023-TOOL-05-03, MICIN IBEC_ProyectCompl22, DTS24/00035, and "La Caixa" Foundation and Barcelona City Council (COVID-SHINE and StopALD) outside of the submitted work. Dr Spearman reported receiving honoraria for lectures from Novo Nordisk, Gilead Science, and Sanofi; receiving travel support from Gilead Science, and having a leadership or fiduciary role for the Society on Liver Disease in Africa (SOLDA) outside the submitted work. Dr Oliveira reported receiving consulting fees from Novo Nordisk, Boehringer Ingelheim, Inventiva AstraZeneca, and Pfizer; receiving payment or honoraria for lectures from Novo Nordisk, Boehringer Ingelheim, Inventiva, AstraZeneca, and Pfizer, and receiving support for attending meetings from Novo Nordisk and Mertz outside of the submitted work. Dr Villela-Nogueira reported receiving honoraria from Novo Nordisk, Boehringer Ingelheim, and Mantecorp; receiving travel support from Novo Nordisk; and serving on the advisory boards of Novo Nordisk and Boehringer Ingelheim outside of the submitted work. Dr Schattenberg reported receiving speaker fees from AbbVie, Boehringer Ingelheim, Echosens, Gilead Science, Ipsen, Eli Lilly and Co, Madrigal Pharmaceuticals, MedScape, MSD, and Novo Nordisk; receiving personal fees from Akero, Alentis, Alexion, Altimmune, AstraZeneca, 89Bio, Bionorica, Boehringer Ingelheim, Boston Pharmaceuticals, Gilead Science, GSK, HistoIndex, Ipsen, Inventiva Pharma, Madrigal Pharmaceuticals, Kríya Therapeutics, Eli Lilly and Co, MSD Sharp & Dohme GmbH, Northsea Therapeutics, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Siemens Healthineers; and having stock options in Hepta Bio outside the submitted work. Mrs Grip reported receiving consulting fees from Quantify Research outside of the submitted work. Dr Alkhouri reported receiving grants to Arizona Liver Health from 89bio, Akero Therapeutics, Allergan, Arbutus Biopharma, AstraZeneca, Better Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Corcept Therapeutics, CymaBay Therapeutics, DSM, Galectin Therapeutics, Genentech, Genfit, Gilead Science, Healio, Hepagene Therapeutics, Intercept Pharmaceuticals, Inventiva Pharma, Ionis Pharmaceuticals, Ipsen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Noom, NorthSea Therapeutics, Novo Nordisk, Perspectum, Pfizer, Poxel, Viking Therapeutics, and Zydus Pharmaceuticals during the conduct of the study as well as receiving personal fees from 89bio, Akero, Boehringer Ingelheim, Echosens, Fibronostics, Gilead Science, Intercept Pharmaceuticals, Ipsen, Madrigal Pharmaceuticals, NorthSea Therapeutics, Novo Nordisk, Perspectum, Pfizer, Regeneron, and Zydus Pharmaceuticals; receiving honoraria for lectures from AbbVie, AstraZeneca, Intercept Pharmaceuticals, Ipsen, Madrigal Pharmaceuticals, and Perspectum outside the submitted work. Mr Mark reported being a director of HEM Consultancy and receiving consulting fees from Panorma Global, Barcelona Institute for Global Health, the European Association for the Study of the Liver, GBCHealth, and the United Nations University-IIGH outside of the submitted work. Dr Allen reported receiving grants to Mayo Clinic from the National Institutes of Health, Novo Nordisk, Madrigal Pharmaceuticals, Target Pharma, Siemens, Oncoustics, Escopics, and Pfizer as well as receiving consulting fees from Boehringer Ingelheim, Madrigal Pharmaceuticals, Novo Nordisk, and GSK outside the submitted work. Mr Brachowicz reported receiving support from the Ministerio de Ciencia, Innovación y Universidades/Agencia Estatal de Investigación (MCIN/AEI) and the Generalitat de Catalunya, through the CERCA Programme. No other disclosures were reported.

Data Sharing Statement: See Supplement 2.

Additional Information: Prof Lazarus, Ms Agirre-Garrido, and Mr Brachowicz acknowledge institutional support to ISGlobal from grant CEX2023-0001290-S, funded by MCIN/AEI/10.13039/501100011033, and the Generalitat de Catalunya, through the CERCA Program.

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SUPPLEMENT 1.