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Original Research

Development and validation of clinical criteria to identify familial chylomicronemia syndrome (FCS) in North America

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ABSTRACT

Background: Familial chylomicronemia syndrome (FCS) is an ultrarare inherited disorder. Genetic testing is not always feasible or conclusive. European clinicians developed a "FCS score" to differentiate between FCS and multifactorial chylomicronemia syndrome (MCS), a more common condition with overlapping features. A diagnostic score has not been developed for use in the North American context.

Objective: To develop and validate a diagnostic score for North American patients based on signs, symptoms and biochemical traits of FCS.

Methods: Using the RAND/UCLA modified Delphi process, we convened ten US/Canadian physicians with experience recognizing and treating FCS and one adult patient with FCS. The panel developed and rated 296 scenarios describing patients with FCS. Linear regression analyses used median post-meeting ratings to develop score parameters. We tested the score's sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in patients with classical FCS, functional FCS, and MCS from Western University's Lipid Genetics Clinic's registry.

Results: Numerical scores were attributed based upon the following: age, hypertriglyceridemia onset, body mass index, history of abdominal pain/pancreatitis, presence of secondary factors, triglyceride (TG) levels, ratio of TG/total cholesterol, and apolipoprotein B level. Scores ≥60 indicate definite classical FCS; the score distinguished patients with FCS from MCS in a real-world registry (100.0 % specificity, 66.7 % sensitivity, 100.0 % PPV, 95.5 % NPV). Scores ≥45 were "very likely" to have classical FCS (96.9 % specificity, 88.9 % sensitivity).

Conclusion: Given its simplicity and high specificity for distinguishing patients with FCS from MCS, the NAFCS Score could be used in lieu of - or while awaiting - genetic testing to optimize treatment.

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Background

Familial chylomicronemia syndrome (FCS) is an ultrarare, inherited disorder caused by impaired lipolysis leading to pathological accumulation of chylomicrons, severe hypertriglyceridemia (HTG), and systemic manifestations, the most serious of which is acute pancreatitis.[1] FCS affects approximately 1–10 individuals per million[2] patients have a median age at diagnosis of 24 years, with more than half of patients diagnosed after the age of 20, in large part due to healthcare providers' unfamiliarity with the disease or difficulty in obtaining a diagnosis.[1,3,4] The risk of pancreatitis increases when triglyceride (TG) levels are >880 mg/dL (>10 mmol/L) and sharply increases with levels >1770 mg/dL (>20 mmol/L).[5–7]

Common FCS signs and symptoms such as lipemic plasma, lipemia retinalis, eruptive xanthomas, and abdominal pain can also be seen in patients with much more common multifactorial chylomicronemia syndrome (MCS).[4,8,9] Like FCS, MCS also results from genetic variants known to raise TG levels, although plasma TG levels in MCS are more variable and more sensitive to dietary and fibrate treatment compared to FCS.[10] The rarity of FCS and the overlapping features with MCS often make FCS difficult to diagnose definitively.

To date, biallelic pathogenic variants in five known genes whose products affect intravascular lipolysis cause FCS. Variants in *LPL*, encoding lipoprotein lipase (LPL), are the most common, followed by others such as *GPIHBP1,* encoding glycosylphosphatidylinositol-anchored HDL-binding protein 1, *APOC2,* encoding apolipoprotein (apo) C-II, *APOA5*, encoding apo A-V, and *LMF1* encoding lipase maturation factor 1.[10–13] Traditionally, patients with biallelic loss of function (LoF) variants in one of these genes are classified as having *classical* FCS. While MCS is much more common with an estimated frequency of 1 in 400 to 500 and can have a similar phenotypic presentation, genetically it is not associated with biallelic pathogenic variants.[12] Instead, MCS is associated either with heterozygosity for a pathogenic variant in one of the five causal genes for FCS or more commonly with multiple accumulated small effect TG-associated single nucleotide polymorphisms (SNPs) from across the genome, quantified using a polygenic score.[12,13] MCS is also typically associated with secondary factors such as obesity and diabetes, and is generally more responsive than FCS to diet, lifestyle interventions as well as existing medications.[12,13]

Researchers have also recognized a subset of patients with severe HTG who present with many of the same features as *classical* FCS but are not found to have biallelic pathogenic mutations in the five canonical genes. Nonetheless, they remain poorly responsive to usual triglyceride-lowering treatment (e.g., fibrates and high-dose omega-3 fatty acids). Such patients can be classified as having *functional* FCS. These *functional* FCS patients - with refractory, persistent or sustained chylomicronemia - have led some researchers to speculate that additional unmeasured genetic factors or unexplained gene-gene or gene-environment interactions can lead to a severe presentation resembling FCS but without the typical genotype.[12,14] Patients with *functional* FCS may benefit from upcoming investigational therapies being studied for *classical* FCS.

Given the similar clinical presentations between FCS and MCS, several scoring systems have been proposed to help better distinguish patients who have one of these conditions. For instance, Moulin et al. proposed a European score based on eight factors, including age of HTG onset, no history of familial combined hyperlipoproteinemia (FCH), and elevated TG levels on repeated laboratory tests.[1] However, a recent study did not find any pathogenic variants among patients identified as being very likely to have FCS based on the Moulin Score.[15] In addition to the score developed by Moulin and validated by others,[16] clinical algorithms for FCS have been proposed,[17] and several other studies have identified clinical criteria that are associated with the ability to predict an FCS diagnosis (such as levels of apolipoprotein B [apo B], free glycerol, body mass index [BMI], cholesterol levels, and TG fluctuations).[17–21] However some of these algorithms require specialized laboratory tests, such as ultracentrifugally measured lipoprotein fractions and free glycerol, that are not available in routine practice.[18–20,22] Such scoring systems cannot easily be implemented in a clinical setting.

To help North American clinicians identify patients in their population who may benefit from investigational treatments in development, we aimed to develop and validate a more clinically accessible score for FCS, namely the North American FCS (NAFCS) Score. Our goal was that the NAFCS Score would not require specialized research assays or genetic testing, although it could be used to prompt or complement genetic testing. We also considered whether the NAFCS Score could potentially identify patients with either classical or functional FCS. Such a practical, validated tool could minimize diagnostic delays, expedite access to new therapies upon approval, and ultimately improve patient care.

Methods

To develop and test the NAFCS Score, we conducted a RAND/UCLA modified Delphi panel, in combination with data from a registry of patients with FCS and MCS at Western University, Canada. The modified Delphi method is a formal group consensus method which systematically and quantitatively combines expert opinion and evidence.[23] Specifically, a panel of physicians drafted a series of clinical scenarios made up of characteristics that may be present in patients with FCS and rated the likelihood that each patient described had FCS. These ratings were used to develop the NAFCS Score, and the registry was used to test its performance using real world data.

NAFCS score development

The score was developed by a panel of 10 physicians, including six endocrinologists, two cardiologists, one gastroenterologist, and one internist. Eight had additional training in lipidology, three in genomics, and one in pancreatology. An adult patient with FCS was also a panel member. The panel was blinded (except for the panel chair) to the study sponsor (Ionis Pharmaceuticals) during score development; the sponsor did not provide input on study design, methods, results, or interpretation of findings. Experts received honoraria for their participation. The modified Delphi panel does not involve human subjects as defined by 45 CFR part 46 and therefore did not require institutional review board approval.

As a first step, we collaboratively developed a structured survey with the panel, referred to throughout as the "rating form," made up of 296 scenarios describing patients who may be suspected of having FCS. Each scenario was based on one assumption and eight factors the panel agreed were important in making a diagnosis of FCS (Table 1, Table 2): current age, age at HTG onset, BMI, history of abdominal pain/pancreatitis, TG levels, ratio of TG/total cholesterol (TC), apo B level, and a history of secondary factors that contribute to HTG (see **Appendix**). Given the rarity of FCS, experts believed that these secondary factors might explain a patient's HTG and be more likely than a diagnosis of FCS. For all scenarios of patients ≥10 years old, the group assumed patients were non-responsive to fibrates or high-dose omega-3 fatty acids (i.e., TG decrease <20 % from these treatments), as these are treatments to which most MCS patients respond well. The group also chose not to consider factors that were non-specific (e.g. fatigue, irritability, and cognitive deficit [sometimes referred to as "brain fog"]), were non-routine tests (e.g., free glycerol), or would eliminate suspicion of FCS entirely, e.g., TG <5 mmol/L (<440 mg/dL), which would be too low for a typical patient with FCS.

Prior to a virtual meeting held over two days in May 2023, panelists individually rated how likely it was that the patient described in each scenario had FCS. FCS was defined broadly to include patients who have biallelic pathogenic variants in one of the five canonical FCS genes (i.e. *classical* FCS) and patients who have clinical symptoms of FCS but either have not been genetically tested or whose results are inconclusive, but

Table 1
Factors included in patient scenarios and considered for NAFCS Score.

Characteristics included in patient scenarios	Categories and definitions for patient scenarios
Patient age	• Adult: ≥20 years • Adolescent: ≥10–19 years • Child: ≥1–9 years • Infant: <1 year
HTG onset	Defined as HTG ≥5 mmol/L or ≥440 mg/dL, categorized into early versus late onset: • Early onset: In infancy or childhood • Later onset: In adolescence or adulthood
BMI	• ≥25.0 kg/m^2 in adults or ≥85th percentile in children/adolescents • <25.0 kg/m^2 in adults or <85th percentile in children/adolescents
Abdominal pain/pancreatitis	In all scenarios, panelists assumed symptoms were related to the patient's chylomicronemia. • No history of abdominal pain or pancreatitis • Recurrent abdominal pain but no history of pancreatitis • History of pancreatitis (with or without abdominal pain)
Secondary factors	Defined as factors that may contribute to the patient's HTG. For example, lifestyle factors (e.g., high alcohol intake, ultra-processed diet), clinical conditions (e.g., non-pancreatitis induced diabetes, HIV), medications (e.g., antidepressants, antiretrovirals). See a more complete list of secondary factors in the Appendix. We defined two categories of secondary factors: • ≥1 secondary factor • No secondary factors
Fasting TG readings	We defined fasting as routine fasting (e.g., 6–12 h depending on patient age) prior to outpatient laboratory tests. Panelists assumed it did not include a scenario in which the patient had been fasting during a hospitalization for many days to control acute pancreatitis or in attempts to bring TG down. Panelists also assumed the patient was not yet complying to severe dietary fat restriction (<20 g/day for adults, <10 % calories from fat for adolescents and children).[1] We categorized the last 3 labs for adults and on last 2 labs for children into two categories: • Not all severely elevated: 1–2 TG readings 5–10 mmol/L or 440–880 mg/dL, remainder >10 mmol/L or >880 mg/dL • All severely elevated: all TG readings >10 mmol/L or >880 mg/dL
TG/TC ratio	Defined as the ratio of TG over TC, categorized into: • Normal/low: ≤8 (when measured in mg/dL) or ≤3.5 (when measured in mmol/L) • High: >8 (when measured in mg/dL) or >3.5 (when measured in mmol/L)
Apo B reading	Apo B laboratory value, categorized into:[2] • Normal/high: ≥1.0 g/L • Low: <1.0 g/L. 1.0 g/L = 100 mg/dL
Treatment non-response	In all scenarios describing patients ≥10 years old, panelists assumed fibrates and high-dose omega-3 fatty acids did not produce a sustained response in TG levels even when the patient was compliant with therapy (i.e., TG do not decrease by 20 % or more from these treatments and do not remain reduced[3]).

Apo B=Apolipoprotein B-100, BMI=Body mass index, HIV=human immunodeficiency virus, HTG=Hypertriglyceridemia, TC=Total cholesterol, TG=Triglycerides.
[1] Williams J Clin Lipidol 2018.
[2] Paragh Lipids Health Dis 2022.
[3] Tremblay J Endocr Soc 2020.

who are non-responsive to fibrates or high-dose omega-3 fatty acids (i.e. *functional* FCS). Panelists provided ratings on a 1 to 9 scale, where 1=very unlikely to have FCS, 5=not sure, and 9=very likely to have FCS. Ahead of the meeting, panelists also reviewed a comprehensive summary of literature on FCS, which included the current evidence on: FCS' genetics, physiology, and the pathophysiology of chylomicronemia; FCS clinical presentation and symptoms; current diagnostic criteria for FCS versus MCS and existing scoring systems; and current treatment and management of FCS.

During the professionally moderated discussion, panelists reviewed the group's median ratings for all scenarios alongside their individual ratings and shared the rationale behind their ratings. The group focused the discussion on areas of disagreement, defined as when ≥2 panelists rated a scenario as 1–3 (unlikely to be FCS) and ≥2 panelists rated a scenario as 7–9 (likely to be FCS), as is typical in the RAND/UCLA modified Delphi panel method.[24] After the meeting, panelists re-rated all scenarios.

The group's median post-meeting rating for each scenario was defined as the consensus likelihood of FCS. We conducted a linear regression analysis to determine the degree to which each characteristic contributed to the likelihood of FCS. In this analysis, we excluded scenarios for which panelists disagreed about the likelihood of FCS. We also excluded scenarios describing infants due to the relatively few characteristics in each scenario. All individual characteristics were initially included in a simple main effect model. Then, a combination of characteristics was tested by including 2-way interaction terms using forward selection. The final model's parameter estimates, multiplied by a factor of 10 (to produce a score with a maximum of 100), were used to create the NAFCS Score (Table 3). Panelists proposed an initial threshold value of ≥60 to identify patients with FCS.

Validation

We validated the NAFCS Score in two ways. First, we tested face validity by calculating the NAFCS Score for each scenario in the rating form and asking panelists if they agreed that those with a score of ≥60 had FCS (Table 2). Second, we tested the sensitivity and specificity of the NAFCS Score in real-world data from a registry of 75 patients with classical FCS ($n = 11$), functional FCS ($n = 16$), or genetically confirmed MCS ($n = 48$) from the Lipid Genetics Clinic at Western University. Classical FCS was defined as having proven biallelic pathogenic variants in one of the five canonical FCS genes, namely *LPL, GPIHBP1, APOA5, APOC2* or *LMF1*.[12] MCS was defined as definitely not having such biallelic variants, instead having heterozygosity for a single pathogenic variant in one of the five canonical FCS genes and/or a polygenic score for TG exceeding the 90th percentile or neither.[12] Functional FCS was defined as a subset of MCS patients with triglycerides persistently >10 mmol/L. Patients with genetically confirmed partial lipodystrophy were excluded. Patients responsive to fibrates or high-dose omega-3 fatty acids (i.e., TG decrease ≥20 % from these treatments) and with any TG level <5 mmol/L (<440 mg/dL) were excluded from the validity testing sample. We also tested the sensitivity and specificity of the Moulin Score[1] in this same sample of patients.

As an agreed-upon diagnosis of functional FCS does not exist, to identify patients with functional FCS in this registry, a global FCS expert (author RAH) used a combination of expert judgement and clinical

Table 2
Patient scenarios included in the rating form with NAFCS Score.

In a patient whose HTG is non-responsive to fibrates and high-dose omega-3 fatty acids and presents with the following additional characteristics:				Fasting TG							
				Not all severely elevated				All severely elevated			
				TG/TC ratio				TG/TC ratio			
				Normal/low		High		Normal/low		High	
				Apo B		Apo B		Apo B		Apo B	
				Normal/ high	Low	Normal/ high	Low	Normal/ high	Low	Normal/ high	Low
Adolescent or adult with **later** HTG onset	**BMI** ≥25 kg/m^2 or ≥85th percentile	≥1 secondary factor	No history	0	12	8	27	13	25	21	40
			Abdominal pain	9	21	17	36	22	34	30	49
			Pancreatitis	16	28	24	43	29	41	37	56
		No secondary factors	No history	11	23	24	43	24	36	37	56
			Abdominal pain	20	32	33	52	33	45	46	65
			Pancreatitis	27	39	40	59	40	52	53	72
	BMI <25 kg/m^2 or <85th percentile	≥1 secondary factor	No history	9	21	17	36	22	45	30	49
			Abdominal pain	18	30	26	45	31	43	39	58
			Pancreatitis	25	37	33	52	38	50	46	65
		No secondary factors	No history	20	32	33	52	33	45	46	65
			Abdominal pain	29	41	42	61	42	54	55	74
			Pancreatitis	36	48	49	68	49	61	62	81
Adolescent or adult with **early** HTG onset	**BMI** ≥25 kg/m^2 or ≥85th percentile	≥1 secondary factor	No history	12	24	20	39	25	37	33	52
			Abdominal pain	21	33	29	48	34	46	42	61
			Pancreatitis	28	40	36	55	41	53	49	68
		No secondary factors	No history	23	35	36	55	36	53	49	68
			Abdominal pain	32	44	45	64	45	57	58	77
			Pancreatitis	39	51	52	71	52	64	65	84
	BMI <25 kg/m^2 or <85th percentile	≥1 secondary factor	No history	21	33	29	48	34	46	42	61
			Abdominal pain	30	42	38	57	43	55	51	70
			Pancreatitis	37	49	45	64	50	62	58	77
		No secondary factors	No history	32	44	45	64	45	57	58	77
			Abdominal pain	41	53	54	73	54	66	62	86
			Pancreatitis	48	60	61	80	61	73	74	93
Child with HTG	**BMI** ≥85th percentile	≥1 secondary factor	No history	12	24	20	39	25	37	33	52
			Abdominal pain	21	33	29	48	34	46	42	61
			Pancreatitis	28	40	36	55	41	53	49	68
		No secondary factors	No history	30	42	43	62	43	55	56	75
			Abdominal pain	39	51	52	71	52	64	65	84
			Pancreatitis	46	58	59	78	59	71	72	91
	BMI <85th percentile	≥1 secondary factor	No history	21	33	29	48	34	46	42	61
			Abdominal pain	30	42	38	57	43	55	51	70
			Pancreatitis	37	49	45	64	50	62	58	77
		No secondary factors	No history	39	51	52	71	52	64	65	84
			Abdominal pain	48	60	61	80	61	73	74	93
			Pancreatitis	55	67	72	87	68	80	81	100

Each cell represents a unique patient scenario made up of the characteristics in the columns and rows (see Table 1 for definitions). The calculated NAFCS Score for each scenario is shown.
Apo *B*=Apolipoprotein B-100, BMI=Body mass index, FCS=Familial Chylomicronemia Syndrome, HTG=Hypertriglyceridemia, TC=Total cholesterol, TG=Triglycerides.

criteria, including 1) refractory severe HTG persistently >880 mg/dL (>10 mmol/L) with <15 % TG lowering on existing treatments; 2) low TC relative to TG level and/or relatively low apo B level; and 3) severe clinical course with relapsing pancreatitis episodes more than once yearly. These diagnoses served as the criterion or "gold" standard diagnoses.

Results

The Delphi panel consisted of 10 physicians with an average of 27 years (range 10–50) of clinical experience in their primary specialty. Four panelists primarily treated adult patients, two primarily treated pediatric patients, and four treated both adult and pediatric patients. The panel had a mix of physicians from community and academic clinics, and was diverse in North American geography, gender, and ethnicity.

After the panel meeting, experts agreed on 93.2 % of scenarios, an increase from 67.7 % in the first-round ratings. Overall, there was more agreement that a patient was likely to have FCS in scenarios with younger patients (i.e., children or infants), low apo B levels, high TG/TC

Table 3
Regression model results.

Characteristics included in the patient scenarios (see Table 1 for definitions)	DF	Parameter estimate	Parameter estimate * 10 and rounded	Standard error	t Value	Pr > |t|	Type II SS
Adolescent or adult with early HTG onset	1	1.19579	12	0.06590	18.14	<0.0001	72.75744
Child with HTG	1	1.18011	12	0.08521	13.85	<0.0001	42.38456
All fasting TG readings severely elevated	1	1.31771	13	0.05527	23.84	<0.0001	125.63314
High TG/TC ratio	1	0.82639	8	0.08737	9.46	<0.0001	19.76923
Low apo B	1	1.19493	12	0.07585	15.75	<0.0001	54.85022
BMI<25.0 kg/m^2 in adults or <85th percentile in children/ adolescents	1	0.87368	9	0.05519	15.83	<0.0001	55.38962
Recurrent abdominal pain but no history of pancreatitis	1	0.89941	9	0.06472	13.90	<0.0001	42.68417
History of pancreatitis	1	1.61673	16	0.06653	24.30	<0.0001	130.52022
No secondary factors	1	1.11083	11	0.08097	13.72	<0.0001	41.58963
Interaction terms							
High TG/TC ratio **&** low apo B	1	0.74126	7	0.11036	6.72	<0.0001	9.96954
Child with HTG **&** no secondary factors	1	0.65909	7	0.11922	5.53	<0.0001	6.75369
High TG/TC ratio **&** no secondary factors	1	0.46933	5	0.11018	4.26	<0.0001	4.00969

The resulting model's parameter estimate indicated how much each characteristic contributed to the group's median rating and became the resulting score's inputs. We multiplied the parameter estimate by 10 for easier calculation and interpretation.
Apo B = Apolipoprotein B-100, BMI=Body mass index, DF = degrees of freedom, HTG=Hypertriglyceridemia, Pr = Probability, SS = Sum of squares, TC=Total cholesterol, TG=Triglycerides.

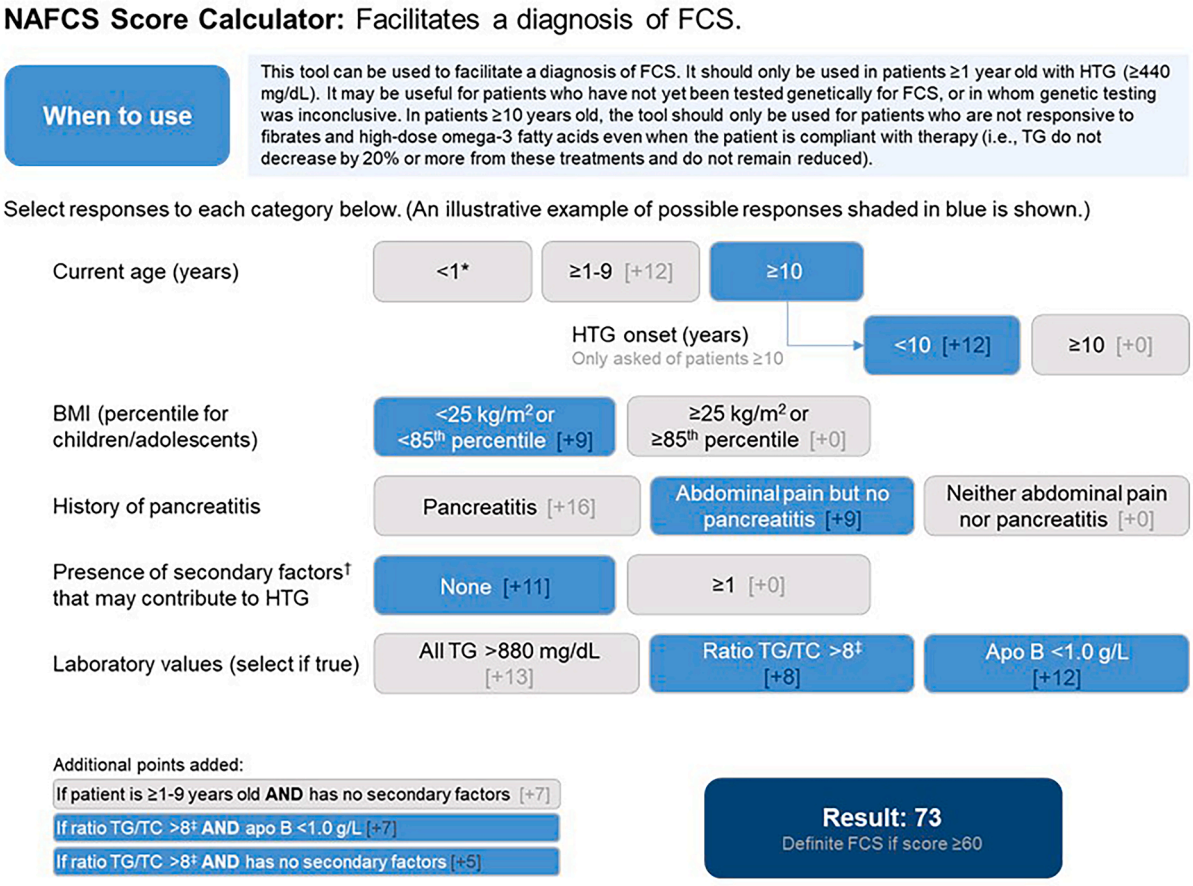

Fig. 1. NAFCS Score Calculator.
The figure above represents a static version of what we hope will eventually become an interactive calculator. The values in gray brackets would be calculated automatically and produce a NAFCS Score for the user. Items currently shown in blue are example selections shown for illustrative purposes. If a patient were to select these responses, they would receive a score of 73.
*Calculator cannot be used for patients <1 year old. If infant presents with no secondary factors that may contribute to HTG, consider a diagnosis of FCS. If infant presents with ≥1 secondary factor that may contribute to HTG, but with 2 TG readings >880 mg/dL and unexplained failure to thrive, consider a diagnosis of FCS. †See Appendix for complete list. ‡When measured in mg/dL.

ratio, or history of pancreatitis. Panelists agreed patients were less likely to have FCS when TG levels were lower, secondary factors were present, and there was no history of abdominal pain or pancreatitis.

Expert consensus likelihood of FCS, defined by post-meeting ratings, was used as the dependent variable in a linear regression model. The eight individual characteristics in the scenarios were used as

independent variables, first individually, and then with a series of interaction terms determined by forward selection. All eight independent variables and three interaction terms (high TG/TC ratio combined with low apo B level, child with HTG combined with no secondary factors, high TG/TC ratio combined with no secondary factors) remained in the best fit model (Table 3). The parameter estimates were multiplied by 10 for ease of computation and combined to create the final NAFCS Score, illustrated in Fig. 1.

The NAFCS Score was tested in a sample of 75 patients with classical FCS ($n = 11$), functional FCS ($n = 16$), or MCS ($n = 48$) from Western University (Table 4). Patients with classical FCS were younger at diagnosis (54.6 % were <20 years old vs 6.3 % of patients with functional FCS and 4.2 % of patients with MCS) and had a lower BMI (66.7 % <25 kg/m^2 [or <85th percentile in children] vs 6.3 % of patients with functional FCS and 4.2 % of patients with MCS). They were also more likely to have severely elevated TG (27.3 % only had TG levels >880 mg/dL [>10 mmol/L] vs 6.3 % of patients with functional FCS and 4.2 % of patients with MCS). None of the classical FCS patients had any secondary factors that might explain their HTG vs 62.5 % of patients with functional FCS and 70.8 % of patients with MCS who had one or more secondary factor. The relatively high prevalence of secondary factors in functional FCS patients distinguishes them from those with classical FCS. Patients with either classical or functional FCS were more likely to have a history of pancreatitis prior to diagnosis, i.e. 63.6 % of patients with classical FCS and 62.5 % of patients with functional FCS vs 39.6 % of patients with MCS.

The mean NAFCS Score was 67.6 for patients with classical FCS, 24.0 for patients with functional FCS, and 20.3 for patients with MCS (Table 4). We tested several score cutoffs (Table 5). A score of ≥60 distinguished patients with classical FCS from MCS with 100.0 % specificity and 66.7 % sensitivity, which was deemed "definite FCS." A score of 45–60 was consistent with "likely FCS"; a score of ≥45 had 96.9 % specificity and 88.9 % sensitivity in distinguishing classical FCS from MCS. Further research is needed to determine the validity of a score from 30–44; genetic testing should be considered in these patients. In the same sample of patients, a Moulin Score of ≥10 (very likely FCS) distinguished patients with classical FCS from MCS with 95.3 % specificity and 55.6 % sensitivity. The NAFCS Score >60 distinguished classical FCS vs MCS patients with sensitivity, positive predictive value, specificity and negative predictive value of 66.67 %, 100.00 %, 100.00 % and 95.52 %, respectively, while the respective values for a Moulin Score >10 were 55.56 %, 62.50 %, 95.31 % and 93.85 %. Thus for each diagnostic metric, the NAFCS Score performed better than the Moulin Score.

Discussion

FCS is often misdiagnosed due to its rarity, but also because the clinical presentation of some MCS patients may be similar and there is insufficient awareness among some clinicians of the differentiating characteristics between FCS and MCS. Furthermore, while genetic testing is frequently definitive for FCS, there are some instances in which

Table 4
Validation sample.

	Classical FCS	Functional FCS	MCS	All patients
N (%)	11 (14.7)	16 (21.3)	48 (64.0)	75 (100.0)
Mean NAFCS Score (SD), Median*	67.6 (20.5), 68	24.0 (16.1), 27	20.3 (14.1), 23	26.9 (21.6), 25
Age at diagnosis, N (%)				
Infant (<1 year)	2 (18.2)	0 (0)	0 (0)	2 (2.7)
Child (1–9 years)	4 (36.4)	0 (0)	0 (0)	4 (5.3)
Adolescent (10–19 years)	0 (0)	1 (6.3)	2 (4.2)	3 (4.0)
Adult (≥20 years)	5 (45.5)	15 (93.8)	46 (95.8)	66 (88.0)
Age at onset of HTG, N (%)				
<10 years	6 (54.5)	0 (0)	0 (0)	6 (8.0)
10–19 years	0 (0)	1 (6.3)	2 (4.2)	3 (4.0)
20–39 years	4 (36.4)	10 (62.5)	31 (64.6)	45 (60.0)
40 years	1 (9.1)	5 (31.3)	14 (29.2)	20 (26.7)
Unknown	0 (0)	0 (0)	1 (2.1)	1 (1.3)
BMI prior to or at diagnosis, N (%)*				
≥25 kg/m^2 (≥18 years old) or ≥85th percentile (<18 years old)	3 (33.3)	15 (93.8)	46 (95.8)	64 (87.7)
<25 kg/m^2 (≥18 years old) or <85th percentile (<18 years old)	6 (66.7)	1 (6.3)	2 (4.2)	9 (12.3)
Unexplained failure to thrive prior to diagnosis, N (%)†	2 (100)	0 (0)	0 (0)	2 (100)
History of pancreatitis prior to diagnosis, N (%)	7 (63.6)	10 (62.5)	19 (39.6)	36 (48.0)
History of abdominal pain (suspected to be related to the patient's chylomicronemia) prior to diagnosis, N (%)	7 (63.6)	10 (62.5)	19 (39.6)	36 (48.0)
Secondary factors prior to diagnosis, N (%)	0 (0)	10 (62.5)	34 (70.8)	44 (58.7)
History of FCH prior to diagnosis, N (%)	0 (0)	0 (0)	0 (0)	0 (0)
Closest 3 (in adults) or 2 (in children/infants) TG laboratory tests prior to diagnosis, N (%)				
1–2 readings between 5–10 mmol/L (440–880 mg/dL) and the remainder >10 mmol/L (>880 mg/dL)	6 (54.5)	15 (93.8)	46 (95.8)	67 (89.3)
All readings >10 mmol/L (>880 mg/dL)	3 (27.3)	1 (6.3)	2 (4.2)	6 (8.0)
Unknown	2 (18.2)	0 (0)	0 (0)	2 (2.7)
Closest 3 (in adults) or 2 (in children/infants) TG laboratory tests prior to diagnosis, with at least 1 reading >20 mmol/L (1770 mg/dL), N ( )	11 (100.0)	13 (81.3)	18 (37.5)	42 (56.0)
Closest TG/TC ratio prior to or on day of diagnosis, N (%)*				
Ratio ≤8 (when measured in mg/dL)	3 (33.3)	11 (68.8)	40 (83.3)	54 (74.0)
Ratio >8 (when measured in mg/dL)	6 (66.7)	5 (31.3)	8 (16.7)	19 (26.0)
Closest apo B reading prior to or on day of diagnosis, N (%)*				
≥1.0 g/L	0 (0)	8 (50.0)	17 (35.4)	25 (34.2)
<1.0 g/L	9 (100.0)	6 (37.5)	30 (62.5)	45 (61.6)
Unknown	0 (0)	2 (12.5)	1 (2.1)	3 (4.1)

*Not calculated for 2 infants with classical FCS.

† Only applicable to 2 infants with classical FCS.

Apo B=Apolipoprotein B-100, BMI=Body mass index, FCH=Familial Combined Hyperlipidemia, FCS=Familial Chylomicronemia Syndrome, HTG=Hypertriglyceridemia, MCS=Multifactorial chylomicronemia syndrome, NAFCS=North American FCS Score, TC=Total cholesterol, TG=Triglycerides.

Table 5
Validation metrics.

	Sensitivity	PPV	Specificity	NPV
NAFCS Score: Classical FCS vs MCS				
Score ≥25	100.00 %	24.32 %	56.25 %	100.00 %
Score ≥30	100.00 %	40.91 %	79.69 %	100.00 %
Score ≥35	88.89 %	38.10 %	79.69 %	98.08 %
Score ≥40	88.89 %	47.06 %	85.94 %	98.21 %
Score ≥45	88.89 %	80.00 %	96.88 %	98.41 %
Score ≥50	77.78 %	77.78 %	96.88 %	96.88 %
Score ≥55	77.78 %	87.50 %	98.44 %	96.92 %
Score ≥60	66.67 %	100.00 %	100.00 %	95.52 %
Score ≥65	55.56 %	100.00 %	100.00 %	94.12 %
Score ≥70	44.44 %	100.00 %	100.00 %	92.75 %
NAFCS Score: Classical or functional FCS vs MCS				
Score ≥25	72.00 %	48.65 %	60.42 %	80.56 %
Score ≥30	56.00 %	63.64 %	83.33 %	78.43 %
Score ≥35	52.00 %	61.90 %	83.33 %	76.92 %
Score ≥40	44.00 %	64.71 %	87.50 %	75.00 %
Score ≥45	36.00 %	90.00 %	97.92 %	74.60 %
Score ≥50	32.00 %	88.89 %	97.92 %	73.44 %
Score ≥55	28.00 %	87.50 %	97.92 %	72.31 %
Score ≥60	24.00 %	100.00 %	100.00 %	71.64 %
Score ≥65	20.00 %	100.00 %	100.00 %	70.59 %
Score ≥70	16.00 %	100.00 %	100.00 %	69.57 %
Moulin Scor:e[1] Classical FCS vs MCS				
Score ≥10	55.56 %	62.50 %	95.31 %	93.85 %

FCS=Familial chylomicronemia syndrome, MCS=Multifactorial chylomicronemia syndrome, NAFCS=North American FCS, NPV=Negative predictive value; PPV=Positive predictive value.

genetic testing is inconclusive or non-definitive. A definite diagnosis of FCS seems essential prior to initiating any treatments approved for FCS but not MCS, aimed at decreasing elevated TG levels with the goal of minimizing risk of life-threatening pancreatitis. Using the RAND/UCLA modified Delphi panel method, we developed a diagnostic score for patients with FCS in the United States and Canada (the NAFCS Score), which we have validated in a North American clinical cohort of patients with severe HTG. A NAFCS Score ≥60 strongly indicates "definite FCS" rather than MCS by molecular genetic criteria, while a score ≥45 suggests "likely FCS" rather than MCS. A score of ≥30–44 identified patients with unmet need; however genetic testing may provide supportive evidence for these patients in real-world application. Although a score of <30 is deemed to be "unlikely FCS", it is possible that a patient may have FCS and genetic testing may still need to be performed.

When tested in real-world data, the NAFCS Score could reliably distinguish classical FCS from MCS: a score of ≥60 resulted in 100.0 % specificity for a positive genetic diagnosis. Furthermore, a score of ≥45 was also associated with excellent discrimination between FCS and MCS, with 88.9 % sensitivity and 96.9 % specificity – such a score would merit a label of "likely FCS." However, the NAFCS Score was less effective at distinguishing between functional FCS and MCS, with lower specificities and sensitivities across a range of threshold values. This was not surprising since functional FCS is an evolving concept with no clear clinical criteria other than the general impression of the clinician that such patients represent a greater clinical challenge than the usual MCS patients, i.e. refractoriness to existing treatments. Functional FCS patients in our validation cohort were a subset of the MCS group—all were refractory to traditional existing treatments (e.g., fibrates and high-dose omega-3 fatty acids—and they had several overlapping characteristics with MCS, including indeterminate genetic results (i.e., no detected variants or detected variants of uncertain significance [VUS]), presence of secondary factors, and generally a later onset of HTG. We had hoped that the NAFCS Score could differentiate these patients from typical MCS patients. However, when tested directly, distinguishing functional FCS from refractory MCS was challenging given the criteria that were used to build the score. To further refine the NAFCS Score's ability to distinguish functional FCS from MCS, the score should be tested prospectively in a group representative of typical MCS patients in whom the outcome of fibrates and omega-3 fatty acid therapy is unknown.

In our validation sample, we also compared the performance metrics of an NAFCS Score >60 versus a Moulin Score >10 in distinguishing classical FCS vs MCS patients. A NAFCS Score >60 was associated with sensitivity, PPV, specificity and NPV of 66.67 %, 100.00 %, 100.00 % and 95.52 %, respectively. In contrast, a Moulin Score >10 performance for the same metrics had sensitivity, PPV, specificity and NPV of 55.56 %, 62.50 %, 95.31 % and 93.85 %, respectively. Thus for each metric, the NAFCS Score showed better performance than the Moulin Score, particularly for sensitivity and PPV.

We believe the NAFCS Score will be useful in clinical practice given its simplicity and high specificity for classical FCS. Clinicians can be confident that patients with scores ≥60 have classical FCS and biallelic pathogenic variants in one of the five causal genes for FCS. A NAFCS Score of ≥60 could decrease delays associated with the need for immediate genetic testing, which can have a turnaround time of 6–8 weeks or more, and potentially allow for a more rapid institution of any TG lowering therapy approved for FCS.

We also consider that a NAFCS Score cutoff point of 45 indicating "likely FCS" is also clinically useful, as it distinguishes between the majority of MCS patients who do not have complete lipolytic deficiency and of FCS patients who do. A NAFCS Score of ≥45 could be used as a practical clinical placeholder and would also demarcate a subgroup of patients with a high yield of positive genetic test results, thus potentially eliminating unnecessary testing in those below the threshold. In situations for which a positive genetic test for FCS needs to be documented, a NAFCS Score ≥45 would predict a high likelihood of a positive result.

Other scoring systems to distinguish FCS from MCS exist, including the Moulin Score,[1] which was targeted towards a European FCS population. In the current North American sample the NAFCS Score outperformed the Moulin Score in distinguishing classical FCS from MCS. However, the scores have considerable overlap. Both consider age of onset, TG levels, secondary factors, abdominal pain, pancreatitis, and response to fibrate or high-dose omega-3 fatty acids. The scores differ in age ranges used and the exact secondary factors considered. These differences may be important when considering a North American compared to European population. The Moulin score does not consider the patients' TG/TC ratio nor their apo B levels, which are quite routinely available. We believe these laboratory values can be critical in diagnosing FCS. Significantly lower concentrations of TC (total

cholesterol) and HDL-C (high-density lipoprotein cholesterol) are observed in patients with FCS compared to patients with MCS.[18,25,26] Similarly, apo B concentrations are significantly lower (e.g., <0.75–0.9 g/L) in patients with FCS compared to patients with MCS.[18] Finally, the Moulin Score does not consider indices of patient weight, such as BMI. This may be a limitation given the importance of excess weight in creating a milieu that promotes HTG, particularly in individuals predisposed to MCS. In North American patients, where average BMIs are typically higher, we believe BMI should be considered, because normal or low BMI would make FCS more likely.[27]

This study has several limitations. First, due to the rarity of FCS, the validation sample included only 11 patients with classical FCS and 16 with functional FCS. We also relied on expert physician judgement to identify patients with functional FCS as there are no agreed-upon diagnostic criteria for this population. Second, patients with an earlier HTG onset will receive a higher NAFCS Score; however, onset in older populations is possible and should be considered more closely in future studies. For example, one patient with classical FCS in our real-world validation first identified HTG onset at a later age, as well as lacked the typical characteristics of FCS (e.g., never had an episode of pancreatitis, had at least one secondary factor), but was genetically confirmed to have FCS. His NAFCS Score was 32. Patients with adolescent or adult HTG onset (>10 years) do not receive additional points in the NAFCS Score, which may result in slightly lower scores and thus a lower probability of being identified. This patient example supports the argument that patients with lower NAFCS Scores (e.g., between 30–44), should still be genetically tested.

Third, the NAFCS Score does not provide a value for infants and pregnant patients; pregnancy may cause a transient increase in TG that makes a differential diagnosis of MCS versus FCS difficult. We suggest that all pregnant patients with pancreatitis or severely high TG as well as infants presenting with HTG under the age of one should be genetically tested for FCS.

Fourth, it is possible that secondary conditions may be occult and unidentified at time of development of hyperchylomicronemia. A patient example discussed was that of a young woman with persistent hyperchylomicronemia and recurrent acute pancreatitis, later identified as having systemic lupus causing autoimmune antibodies neutralizing GPIHBP1, ultimately responsive to immune modulating therapies. For all intents and purposes, she was thought to have FCS unexplained by genetic testing. The recognition of the autoimmune condition revealed the true nature of her secondary hyperchylomicronemia even though her NAFCS Score was >60, suggesting FCS.

In addition, we recognize that apo B laboratory testing, while widely available in North America, may not be feasible to obtain by all providers; thus, we recommend adjusting the NAFCS Score in future studies to allow for evaluating patients without apo B measurements. Finally, our panel consisted of experts from the United States and Canada only, and thus the NAFCS Score may not be generalizable to countries with different access to laboratory tests or diagnosis criteria. Further research and validation is warranted.

Conclusion

FCS is an ultrarare condition that can be difficult to identify, thus delaying diagnosis and appropriate management. The NAFCS Score was developed with a methodologically rigorous process, using relevant literature, incorporating the clinical experience of multiple experts, and validated using real-world patient data.

We hope that the NAFCS Score will be useful in at least three ways. First, it may improve the diagnosis of FCS for patients in the United States and Canada, a population for whom a specific clinical diagnosis tool had not yet been developed. Second, it may be easier to use than existing algorithms due to its straightforward design and use of accessible clinical variables. Our hope is that this tool will be incorporated into an online platform [e.g., mdcalc.com] and/or embedded into electronic medical records to facilitate its use. Third, we hope it will be useful in diagnosing patients without the need for genetic testing or when genetic testing is inconclusive. As the definition of functional FCS or refractory chylomicronemia is clarified over time, studies should aim to refine the NAFCS Score to improve its ability to distinguish this condition from MCS.

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Ethical statement

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Declaration of competing interest

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Supplementary materials

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