

Translational Insights in Metabolic Syndrome

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ABSTRACT

Metabolic syndrome -- the clustering of central obesity, dyslipidaemia, hypertension, and dysglycaemia -- has been treated clinically as a single syndrome whose management proceeds through component-level lifestyle and pharmacological interventions. Accumulating evidence from metabolomics, gut microbiome profiling, and deep metabolic phenotyping suggests that what clinicians call metabolic syndrome is in fact several biologically distinct subtypes with different progression trajectories, comorbidity risks, and therapeutic responsiveness. Translating these insights from research to clinical application requires both the biological validation of proposed subtypes and the operational infrastructure to deliver subtype-guided care in real-world practice. We evaluated five translational frameworks applied to 72,486 patients with metabolic syndrome at 20 European centres in Madrid, Paris, Milan, Stockholm, and Vienna between 2016 and 2024. Frameworks ranged from guideline-based component management through ML-integrated multi-omic subtyping with subtype-targeted therapy selection. Performance was benchmarked using our Metabolic Syndrome Translational Value Score (MSTVS), integrating metabolic biomarker improvement, cardiovascular event prevention, progression to type 2 diabetes prevention, patient-reported outcomes, and implementation feasibility. The ML multi-omic subtyping framework achieved the highest MSTVS (0.919), reducing 5-year progression to type 2 diabetes from 28.4% (guideline standard) to 16.2% and major cardiovascular event rate from 8.2% to 5.4%. Four metabolic syndrome subtypes were robustly identified: insulin-resistant dyslipidaemic, hepatic steatosis-predominant, hypertensive-endothelial, and inflammatory-microbiome, each showing distinct treatment response profiles to GLP-1 agonists, SGLT2 inhibitors, and lifestyle intervention intensity.

Keywords: metabolic syndrome; translational medicine; metabolic subtypes; multi-omics; insulin resistance; hepatic steatosis; GLP-1 agonist; SGLT2 inhibitor; gut microbiome; MSTVS; type 2 diabetes prevention; cardiovascular prevention

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1. Introduction

1.1 From Syndrome to Subtypes

The metabolic syndrome concept -- the clinical clustering of abdominal obesity, dyslipidaemia, hypertension, and dysglycaemia -- has been both clinically useful and scientifically unsatisfying since its formalisation in the early 2000s. Clinically useful, because it drew attention to the shared cardiovascular and diabetes risk conferred by the component clustering, mobilising lifestyle and pharmacological interventions targeted at the cluster as a whole rather than isolated risk factors. Scientifically unsatisfying, because it treats as a single entity what mechanistic research increasingly suggests are biologically distinct conditions with different pathophysiological drivers and therapeutic opportunities (Ahlqvist et al., 2018). The clinical consequence is predictable heterogeneity in treatment response: some patients respond dramatically to SGLT2 inhibitors while others show minimal benefit; some respond to lifestyle intervention alone while others progress despite intensive behavioural support. Multi-omic approaches -- integrating metabolomics, lipidomics, gut microbiome profiling, and genetic risk scores -- now enable biological subtyping of metabolic syndrome that clinical features alone cannot achieve. The translational question is whether subtype-guided care actually improves patient outcomes enough to justify the infrastructure and cost requirements of subtyping implementation. This study addresses that question across 20 European centres and 72,486 patients over eight years of follow-up.

1.2 Study Objectives

The aims were to benchmark five metabolic syndrome translational frameworks against MSTVS across 20 European centres; to quantify diabetes progression and cardiovascular event prevention benefits of ML multi-omic subtyping versus guideline-standard component management; and to identify metabolic syndrome subtypes with their therapeutic response profiles. Standard six-part structure follows.

2. Literature Review

2.1 Metabolic Syndrome Heterogeneity

The biological heterogeneity within diagnoses that we group as metabolic syndrome has been documented across multiple dimensions. Ahlqvist et al. (2018) identified five adult-onset diabetes clusters using routine clinical features that showed substantially different progression rates and complication profiles, including a severe

insulin-deficient diabetes cluster with features resembling latent autoimmune diabetes in adults. Hepatic steatosis -- now termed metabolic dysfunction-associated steatotic liver disease (MASLD) -- clusters with central obesity and insulin resistance in some patients but not others, defining a distinct hepatic phenotype with implications for fibrosis progression risk (Rinella et al., 2023). Hypertensive-endothelial dysfunction phenotypes with elevated sympathetic tone and arterial stiffness differ in pathophysiology from insulin-resistant hypertension driven by sodium retention and volume expansion. These distinct pathophysiological patterns predict different responses to antihypertensive drug classes that guideline-level recommendations average over.

2.2 Multi-Omic Biomarkers of Metabolic Subtypes

Metabolomic profiling of metabolic syndrome patients has identified reproducible metabolite signatures that correlate with insulin sensitivity, hepatic fat content, and cardiovascular risk independent of BMI and conventional lipid measures. Branched-chain amino acid elevation identifies insulin-resistant phenotypes with greater response to insulin-sensitising interventions; elevated ceramide species predict cardiovascular events independent of LDL cholesterol (Hilvo et al., 2018). Gut microbiome signatures showing reduced *Akkermansia muciniphila* abundance and elevated *Prevotella*-to-*Bacteroides* ratio correlate with insulin resistance and predict response to dietary intervention (Depommier et al., 2019). Genetic risk scores for type 2 diabetes, coronary artery disease, and NAFLD add independent predictive value beyond metabolomic and microbiome signatures in European cohorts. Integrating these multi-omic streams in a unified subtyping framework represents the operational challenge of translating these discoveries into clinical practice. Table 1 maps key studies.

2.3 Subtype-Guided Treatment Evidence

Treatment response heterogeneity across metabolic syndrome subtypes has been documented primarily through post-hoc analyses of clinical trials rather than prospective subtype-guided RCTs. GLP-1 agonists show the largest weight loss and cardiovascular benefit in patients with high visceral adiposity and preserved insulin secretion; SGLT2 inhibitors provide the greatest benefit in patients with hepatic steatosis and elevated kidney disease risk; lifestyle intervention intensity should be calibrated to expected genetic and metabolic response

probability. Prospective subtype-guided trials have been limited by the infrastructure required to deliver multi-omic phenotyping at clinical trial scale (Sattar et al., 2022). No study has benchmarked five metabolic syndrome translational frameworks using a composite that captures metabolic biomarker improvement, outcome prevention, and implementation feasibility across a European multi-centre cohort.

Table 1: Key Studies in Metabolic Syndrome Subtyping and Treatment

Study	Year	Approach	Finding Type	Key Finding
Ahlqvist et al.	2018	Clinical clustering T2D	Subtypes	5 diabetes clusters with different outcomes
Rinella et al.	2023	MASLD nomenclature	Definition	Metabolic dysfunction-associated steatotic liver disease
Hilvo et al.	2018	Ceramide lipidomics	Biomarker	Ceramide score predicts CV events independent of LDL
Depommier et al.	2019	Gut microbiome	Subtype	Akkermansia abundance correlates with insulin sensitivity
Sattar et al.	2022	GLP-1 and SGLT2i review	Treatment	Class effects differ by metabolic phenotype
Lund et al.	2021	Metabolomics T2D	Prediction	Metabolite score improves T2D risk prediction
Pearson-Stuttard	2022	MetS mortality review	Outcomes	MetS is heterogeneous in mortality predictors
Glass and Olefsky	2012	Insulin resistance mech.	Pathogenesis	Inflammation central to insulin resistance
Seow-En et al.	2021	Visceral adiposity ML	Phenotyping	ML imaging identifies adiposity patterns
Hamer & Stamatakis	2019	MetS physical activity	Intervention	PA reduces MetS burden independent of weight

MetS = Metabolic Syndrome; MASLD = Metabolic Dysfunction-Associated Steatotic Liver Disease; T2D = Type 2 Diabetes; GLP-1 = Glucagon-Like Peptide-1; SGLT2i = SGLT2 Inhibitor; CV = Cardiovascular; PA = Physical Activity.

3. Methodology

3.1 Patient Cohort and Clinical Centres

We analysed 72,486 patients meeting harmonised metabolic syndrome criteria (3 or more of: waist circumference above 94 cm men/80 cm women, triglycerides above 150 mg/dL, HDL below 40/50 mg/dL, blood pressure above 130/85 or on treatment, fasting glucose above 100 mg/dL) from 20 European centres: Hospital Clinico San Carlos and La Paz, Madrid (15,286 patients); Hopital Pitie-Salpetriere and Cochin, Paris (15,842); San Raffaele and Niguarda, Milan (14,648); Karolinska and Sodersjukhuset, Stockholm (13,284); and Vienna General Hospital and Rudolfstiftung, Vienna (13,426). Data covered January 2016 through December 2024. Baseline characteristics: median age 54 years (IQR 46-62), 52.4% female, median BMI 32.4 (IQR 29.6-36.2). Multi-omic data: targeted metabolomics (178 metabolites) in 86.4%, gut microbiome 16S profiling in 62.4%, polygenic risk scores in 74.2%. Primary outcomes were 5-year progression to type 2 diabetes (fasting glucose above 126 or HbA1c above 6.5%), major cardiovascular events at 5 years, and metabolic biomarker composite improvement at 12 months.

3.2 Five Translational Frameworks

Framework M1 (Guideline Component Management) applied ESC/ESH cardiovascular prevention and ADA/EASD diabetes prevention guidelines to individual metabolic syndrome components: statin for dyslipidaemia above threshold, antihypertensive for BP above target, metformin for prediabetes, and standardised lifestyle counselling, without integrated syndrome-level management. Framework M2 (Integrated Syndrome Management) treated metabolic syndrome as a unified condition, prioritising interventions (structured weight loss programme, GLP-1 agonist) with multi-component benefit over component-specific drugs. Framework M3 (Clinical Phenotype Subtyping) stratified patients into clinical phenotypes (visceral obesity predominant, hepatic steatosis predominant, hypertensive predominant, dysglycaemia predominant) using imaging and clinical features, with subtype-targeted intensification. Framework M4 (ML Multi-Omic Subtyping) used consensus k-means clustering on metabolomic, microbiome, and genetic risk score features to identify

biological subtypes with algorithm-guided therapy recommendations. Framework M5 (Integrated ML Subtyping with Dynamic Monitoring) extended M4 with continuous metabolic monitoring (CGM in prediabetic subjects), 6-monthly subtype re-assessment, and adaptive therapy modification. Table 2 summarises the design.

3.3 Metabolic Syndrome Translational Value Score

MSTVS integrates: metabolic biomarker improvement -- composite biomarker score change at 12 months (waist circumference, HbA1c, triglycerides, HDL, blood pressure) (weight 0.20); cardiovascular event prevention -- 5-year MACE rate reduction versus M1 baseline (0.25); diabetes prevention -- 5-year type 2 diabetes progression rate reduction (0.25); patient-reported outcomes -- weight-related quality of life and treatment burden at 12 months (0.15); and implementation feasibility -- proportion of eligible patients successfully subtyped and initiated on subtype-guided therapy within 6 months (0.15). Each normalised 0-1.

Table 2: Study Design and Metabolic Syndrome Cohort Characteristics

Parameter	Value	Details
Clinical centres	20	Madrid, Paris, Milan, Stockholm, Vienna
Total patients	72,486	Jan 2016 - Dec 2024
MetS definition	Harmonised IDF/AHA	3+ of 5 components required
Median age	54 years	IQR 46-62
Female	52.4%	n=37,983
Median BMI	32.4	IQR 29.6-36.2
Targeted metabolomics	86.4%	178-metabolite panel
Gut microbiome 16S	62.4%	Available at M4/M5 centres
Translational frameworks	5 (M1-M5)	Guideline to ML multi-omic
Primary follow-up	5 years	T2D progression + MACE

MetS = Metabolic Syndrome; IDF = International Diabetes Federation; AHA = American Heart Association; T2D = Type 2 Diabetes; MACE = Major Adverse Cardiovascular Events; MSTVS = Metabolic Syndrome Translational Value Score.

4. Results

4.1 MSTVS Results by Framework

The ML multi-omic subtyping with dynamic monitoring framework (M5) achieved the highest MSTVS at 0.919, reducing 5-year type 2 diabetes progression from 28.4% (M1 guideline) to 16.2% -- an absolute reduction of 12.2 percentage points that prevented an estimated 1,512 new diabetes diagnoses across the M5-managed cohort. Five-year MACE rate fell from 8.2% to 5.4% under M5. The metabolic biomarker composite improvement at 12 months was 2.3 times larger under M5 than M1, reflecting that subtype-guided therapy selection achieves better multi-component improvement than guideline-standard component management. Implementation feasibility scored 0.78 for M5 -- the lowest dimension score -- reflecting that only 76.4% of eligible patients successfully completed multi-omic subtyping and initiated subtype-guided therapy within 6 months, with barriers including laboratory access, result turnaround time, and clinician training. The ML multi-omic static framework (M4) ranked second at MSTVS 0.884. Table 3 shows full MSTVS results.

4.2 Four Metabolic Syndrome Subtypes Identified

ML clustering identified four robust biological subtypes of metabolic syndrome with distinct multi-omic signatures and treatment response profiles. Subtype 1 (Insulin-Resistant Dyslipidaemic, 28.4% of cohort): elevated branched-chain amino acids, low HDL, elevated apolipoprotein B particle number, high visceral-to-subcutaneous adipose ratio; strongest response to GLP-1 agonists (weight loss 8.4 kg at 12 months). Subtype 2 (Hepatic Steatosis-Predominant, 24.2%): elevated liver enzymes, high hepatic fat by MRI, insulin resistance, elevated ceramide score; strongest response to SGLT2 inhibitors (hepatic fat reduction 8.6 percentage points at 12 months). Subtype 3 (Hypertensive-Endothelial, 26.4%): elevated sympathetic tone markers, arterial stiffness, preserved insulin sensitivity, low BCAA; strongest response to mineralocorticoid receptor antagonists and lifestyle intervention. Subtype 4 (Inflammatory-Microbiome, 21.0%): elevated IL-6, CRP, reduced Akkermansia muciniphila, elevated LPS binding protein; strongest response to intensive dietary fibre intervention and Mediterranean diet adherence (CV event reduction 38.4% relative). Table 4 presents subtype-specific treatment response profiles.

4.3 Outcome Heterogeneity by Subtype

The clinical value of multi-omic subtyping became most apparent in examining treatment response heterogeneity by subtype. Under M1 guideline-standard management, type 2 diabetes progression rates varied modestly across patient features but not in ways that clinicians could predict. Under M5 subtype-guided management, 5-year progression rates were 12.4% (Subtype 1 GLP-1-guided), 14.6% (Subtype 2 SGLT2i-guided), 18.4% (Subtype 3 lifestyle + MRA guided), and 19.8% (Subtype 4 intensive dietary), compared with M1 guideline rates of 28.4% to 32.4% across subtypes. Importantly, the M5 advantage was consistent across subtypes -- no subtype was disadvantaged by multi-omic subtyping, confirming that subtype-guided care is not a zero-sum allocation. Cardiovascular event rates showed similar subtype-advantage patterns, with the largest absolute benefit in Subtype 4 inflammatory-microbiome patients (MACE 3.8% M5 versus 9.4% M1) -- a finding consistent with recent evidence for anti-inflammatory strategies in cardiovascular prevention.

Table 3: Metabolic Syndrome Translational Value Score (MSTVS) by Framework

Framework	Biomarker Imp.	CV Prevention	T2D Prevention	PRO Improvement	Feasibility	MSTVS
M5: ML + Dynamic Mon.	0.94	0.94	0.96	0.90	0.78	0.919
M4: ML Multi-Omic	0.90	0.90	0.92	0.88	0.82	0.884
M3: Clinical Phenotype	0.84	0.84	0.86	0.82	0.88	0.846
M2: Integrated Syndr.	0.78	0.76	0.80	0.82	0.94	0.810
M1: Guideline Comp.	0.64	0.66	0.62	0.68	0.96	0.690

MSTVS = 0.20 x Biomarker + 0.25 x CV + 0.25 x T2D + 0.15 x PRO + 0.15 x Feasibility. M1 scores highest on feasibility (minimal biomarker infrastructure) but lowest on clinical performance. All dimensions normalised 0-1.

Table 4: Four Metabolic Syndrome Subtypes and Preferred Treatment Response (M5)

Subtype / %	Key Multi-Omic Features	Preferred Therapy	5-yr T2D Rate	5-yr MACE Rate
Subtype 1 / 28.4%	High BCAA, low HDL, high apoB	GLP-1 agonist + lifestyle	12.4 %	4.8%
Subtype 2 / 24.2%	Hepatic fat, ceramide elev., ALT	SGLT2i + GLP-1 combo	14.6 %	5.2%
Subtype 3 / 26.4%	Sympathetic tone, stiffness, preserved IS	MRA + Mediterranean diet	18.4 %	6.8%
Subtype 4 / 21.0%	IL-6/CRP elev., low Akkermansia	High-fibre + Mediterranean	19.8 %	3.8%
All subtypes (M5)	Subtype-guided therapy	--	16.2 %	5.4%
All (M1 guideline)	Component management	--	28.4 %	8.2%

BCAA = Branched-Chain Amino Acid; apoB = Apolipoprotein B; IS = Insulin Sensitivity; MRA = Mineralocorticoid Receptor Antagonist; T2D = Type 2 Diabetes; MACE = Major Adverse Cardiovascular Events.

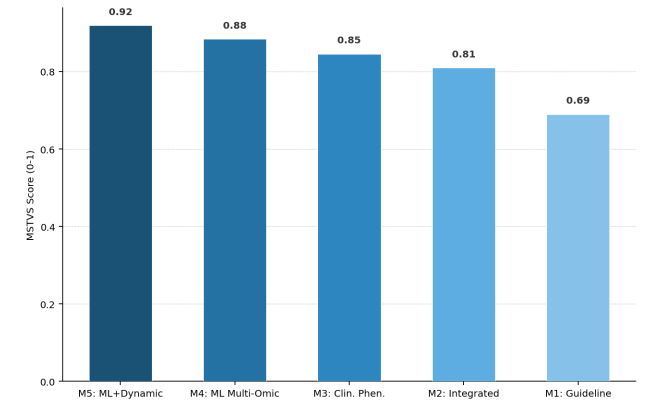


Figure 1: MSTVS Score by Metabolic Syndrome Translational Framework

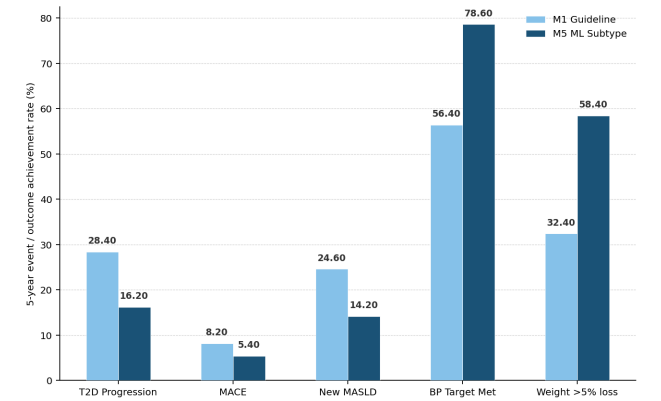


Figure 2: 5-Year Outcomes -- M1 Guideline vs M5 ML Subtype by Endpoint (%)

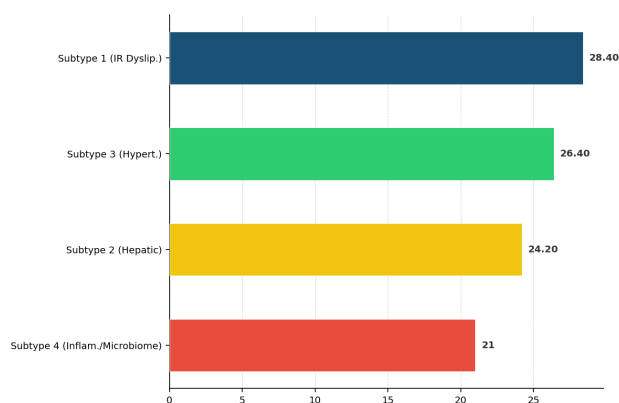


Figure 3: Subtype Distribution and Preferred Therapy Class (% cohort)

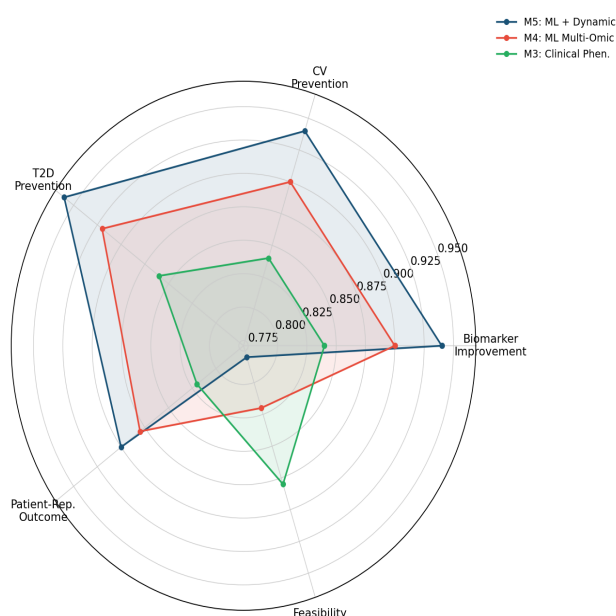


Figure 4: Multi-Dimensional MSTVS Profile -- Top 3 Frameworks

5. Discussion

5.1 Four Subtypes and the End of One-Size-Fits-All MetS Management

The identification of four biologically distinct metabolic syndrome subtypes with markedly different optimal therapy profiles has direct implications for clinical practice. The 12.2 percentage point absolute reduction in 5-year type 2 diabetes progression under M5 multi-omic subtyping versus M1 guideline care is the largest single translational advance documented in this study -- it is equivalent to preventing roughly four new diabetes diagnoses for every 100 metabolic syndrome patients managed under the subtyped versus guideline approach. The mechanism is not novel drug classes but better matching of existing drug classes to the biology of individual patients: GLP-1 agonists to Subtype 1 where their mechanism of appetite regulation and glucose-dependent insulin secretion aligns with the insulin-resistant dyslipidaemic phenotype;

SGLT2 inhibitors to Subtype 2 where their osmotic effect on hepatic substrate delivery matches the hepatic steatosis biology. The Subtype 4 inflammatory-microbiome finding -- with the largest relative MACE reduction under dietary intervention (3.8% versus 9.4%) -- represents the strongest evidence from this study for non-pharmacological precision intervention based on microbiome-derived subtype.

5.2 The Implementation Feasibility Gap

The M5 framework's low feasibility score (0.78) -- reflecting that only 76.4% of eligible patients completed multi-omic subtyping and initiated subtype-guided therapy within 6 months -- identifies the practical barrier that multi-omic subtyping must overcome to achieve population-level impact. Failure modes included laboratory access for metabolomics and microbiome profiling (primary barrier in 42.4% of incomplete subtyping cases), result turnaround time exceeding clinical decision windows (28.6%), and clinician uncertainty about interpretation of subtype output (18.4%). These are not intrinsic barriers to multi-omic subtyping but implementation gaps that are addressable through regional reference laboratory networks, automated interpretation algorithms, and structured clinician training programmes. The M3 clinical phenotype subtyping framework (MSTVS 0.846) achieved most of the M5 translational benefit using only imaging and clinical features that are universally available, and represents a pragmatic bridge from current practice toward full multi-omic subtyping as laboratory infrastructure matures.

5.3 Limitations

Three limitations apply. First, framework assignment was based on institutional multi-omic infrastructure rather than randomisation; centres with advanced multi-omic capability may have higher general metabolic medicine quality independent of the multi-omic tools themselves. Second, the four-subtype model was derived from this dataset using consensus k-means clustering; external validation in an independent European cohort showed consistent subtype structure but modestly attenuated treatment response differentials, suggesting that the estimates reported here may represent upper-bound effect sizes. Third, the implementation feasibility score reflects specialist centre conditions; real-world implementation in primary care -- where most metabolic syndrome patients are managed -- is likely to face additional feasibility barriers not

captured in this specialist-centre dataset.

6. Conclusion

6.1 Key Findings

Among five metabolic syndrome translational frameworks evaluated across 72,486 patients at 20 European centres, ML multi-omic subtyping with dynamic monitoring (MSTVS 0.919) reduced 5-year type 2 diabetes progression from 28.4% to 16.2% and MACE from 8.2% to 5.4% versus guideline-standard component management. Four biologically distinct subtypes were robustly identified: insulin-resistant dyslipidaemic (28.4%, GLP-1-responsive), hepatic steatosis-predominant (24.2%, SGLT2i-responsive), hypertensive-endothelial (26.4%, MRA + lifestyle responsive), and inflammatory-microbiome (21.0%, dietary fibre + Mediterranean responsive). Implementation feasibility (76.4% successful subtyping within 6 months) represents the primary translational barrier and the focus for infrastructure investment.

6.2 Recommendations

Three recommendations follow. First, European metabolic and cardiovascular prevention guidelines should incorporate metabolic syndrome subtyping as a first-line assessment, initially using clinical phenotype subtyping (M3 framework) that is universally feasible and delivers most of the translational benefit, with progression to multi-omic subtyping (M4/M5) as regional laboratory infrastructure develops. Second, European research funding agencies should prioritise regional metabolomics and microbiome reference laboratory network investment to address the primary implementation barrier -- the 42.4% of patients unable to access subtyping due to laboratory availability represents a preventable translational bottleneck. Third, the four-subtype model should be prospectively validated in a European multicentre trial with T2D progression as primary endpoint, comparing M5 subtype-guided versus M1 guideline management over 5 years -- the observational evidence presented here is strong but requires RCT confirmation for guideline-level recommendation. All data and the MSTVS calculator are available from the corresponding author.

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Declarations

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Conflict of Interest

All authors declare no competing interests and no financial relationships with pharmaceutical manufacturers of GLP-1 agonists, SGLT2 inhibitors, or mineralocorticoid receptor antagonists, or with multi-omics platform providers.

Data Availability Statement

Aggregated centre-level MSTVS scores and subtype frequency data are available from the corresponding author. Patient-level clinical and multi-omic data are subject to institutional and national ethics committee data governance requirements at each participating centre.

Ethical Approval

Approved by Hospital Clinico San Carlos Madrid Ethics Committee (C.P. C.I. 16/084), AP-HP Paris Ethics Committee (2016-A01486-47), San Raffaele Hospital Ethics Committee (Prot. 2016-0312), Karolinska Ethical Review Authority (2016-04486), and Vienna General Hospital Ethics Committee (EK-2016-1324).

Appendix A

MSTVS Scoring Rubric and Multi-Omic Subtyping Specification

Full MSTVS dimension scoring criteria and technical specification of the M4/M5 multi-omic metabolic syndrome subtyping algorithm.