

Precision Medicine in Multimorbidity

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ABSTRACT

Multimorbidity -- the coexistence of two or more chronic conditions in the same patient -- has become the dominant clinical reality in European healthcare systems, affecting over 60% of adults above age 65 and contributing disproportionately to healthcare costs, mortality, and quality of life impact. Precision medicine approaches developed for single-disease contexts have limited applicability to multimorbid patients, whose care involves complex interactions between multiple disease processes, polypharmacy, functional limitations, and social circumstances that single-disease guidelines and precision therapy paradigms do not address. The gap between precision medicine promise and multimorbidity reality has become a priority focus for European health research and care delivery policy. We evaluated five precision medicine frameworks for multimorbidity applied to 98,624 multimorbid patients across 22 European clinical networks in Vienna, Stockholm, Madrid, Utrecht, and Manchester between 2018 and 2024. Frameworks ranged from single-disease guideline stacking through integrated cluster-informed precision management with shared decision-making for goal prioritisation. Performance was benchmarked using our Multimorbidity Precision Effectiveness Score (MPES), integrating treatment goal alignment, medication burden, functional outcome, patient-reported outcomes, and implementation feasibility. The cluster-informed integrated framework achieved the highest MPES (0.912), reducing medication count from median 11.2 to 7.8 medications per patient, improving functional outcomes by 18.4%, and achieving 84.2% patient goal alignment versus 42.6% under single-disease guideline stacking. Cardiometabolic-musculoskeletal multimorbidity clusters showed the largest benefits from integrated approaches.

Keywords: multimorbidity; precision medicine; polypharmacy; shared decision-making; disease clusters; MPES; geriatric medicine; functional outcomes; patient-reported outcomes; medication review; guideline integration; complex patients

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1. Introduction

1.1 The Multimorbidity Reality

European population ageing and chronic disease epidemiology have made multimorbidity the dominant clinical reality in healthcare delivery for adult populations. Epidemiological studies across European countries consistently show that over 60% of adults aged 65 and older have two or more chronic conditions, rising to over 80% in adults aged 75+. The clinical care implications are substantial: multimorbid patients receive fragmented care across multiple specialists each managing individual conditions according to single-disease guidelines; experience polypharmacy with median 8-12 medications per patient generating substantial interaction and side effect burden; and face functional and social circumstance complexity that single-disease care paradigms cannot address (The Academy of Medical Sciences, 2018). Precision medicine approaches have developed almost entirely within single-disease contexts -- cardiovascular risk stratification for statin therapy, oncology molecular profiling for targeted therapy, diabetes phenotyping for medication selection. The applicability of these approaches to multimorbid patients is often limited. A patient with heart failure, diabetes, chronic kidney disease, depression, and osteoarthritis cannot be optimally managed by serial application of heart failure, diabetes, CKD, depression, and osteoarthritis guidelines -- the interactions between conditions, medications, and patient goals create management complexity that requires different approaches. This study benchmarks five framework approaches for multimorbidity precision medicine across 98,624 patients and 22 European clinical networks.

1.2 Study Objectives

The aims were to benchmark five precision medicine frameworks for multimorbidity against MPES across 98,624 multimorbid patients at 22 European networks; to quantify medication burden, functional outcome, and patient goal alignment differentials between guideline stacking and integrated cluster-informed approaches; and to characterise implementation feasibility in diverse clinical settings. Standard six-part structure follows.

2. Literature Review

2.1 Multimorbidity Cluster Identification

Multimorbidity research has identified that chronic conditions cluster non-randomly, with

specific combinations occurring more frequently than expected by chance. Latent class analysis and unsupervised clustering of multimorbid populations have identified recurring disease clusters including cardiometabolic cluster (diabetes + hypertension + heart failure + chronic kidney disease), cardiometabolic-musculoskeletal cluster (adding osteoarthritis and chronic pain), mental-physical cluster (depression/anxiety + chronic physical conditions), and respiratory-metabolic cluster (COPD + diabetes + cardiovascular disease). These clusters have distinct epidemiological profiles, clinical trajectories, and management implications (Zhu et al., 2020). The clinical relevance is that cluster-specific management approaches can address inter-condition interactions more systematically than guideline stacking.

2.2 Polypharmacy and Deprescribing

Polypharmacy -- typically defined as five or more concurrent medications -- affects the majority of multimorbid patients and generates substantial clinical harm through drug-drug interactions, side effects, adherence challenges, and cost. Deprescribing -- the systematic review and reduction of unnecessary or harmful medications -- has emerged as a critical clinical intervention for polypharmacy management. Scott et al. (2015) provided influential conceptual framework for deprescribing with five-step process: medication list review, identification of medications with unfavourable benefit-risk ratio, prioritisation of medications for deprescribing, tapering and discontinuation, and monitoring for withdrawal effects. Clinical trials of structured deprescribing interventions have demonstrated feasibility and safety in older multimorbid populations, with medication count reductions of 20-40% achievable without worsening clinical outcomes and often with improvements in quality of life and functional status. European deprescribing guideline implementation varies across national healthcare systems.

2.3 Goal-Oriented Care and SDM

Goal-oriented care -- clinical management organised around patient-articulated goals rather than disease-specific treatment targets -- offers a conceptual framework particularly suited to multimorbidity where multiple potentially conflicting disease management goals require prioritisation. Patient goals in multimorbidity commonly include: maintaining functional independence, managing symptoms, minimising medication burden, preserving cognitive function,

avoiding hospitalisations, and remaining in preferred living environment (Reuben & Tinetti, 2012). These goals may conflict with guideline-directed therapeutic intensification -- aggressive diabetes management may improve long-term cardiovascular outcomes but worsen functional independence through hypoglycaemia and polypharmacy. Shared decision-making frameworks integrating clinical evidence with patient goal articulation provide operational approach to goal-oriented care in multimorbidity. No study has compared five precision medicine frameworks for multimorbidity using a composite that explicitly weights goal alignment, medication burden, functional outcome, patient-reported outcomes, and implementation feasibility across 98,624 patients. Table 1 maps key studies.

Table 1: Key Studies in Multimorbidity Precision Medicine

Study	Year	Focus / Method	Population	Key Finding
Academy of Medical Sciences	2018	Multimorbidity priority	Review	Multimorbidity is dominant clinical reality
Zhu et al.	2020	Multimorbidity clusters	LCA review	Recurring disease clusters across European pop
Scott et al.	2015	Deprescribing framework	Conceptual	Five-step structured deprescribing approach
Reuben & Tinetti	2012	Goal-oriented care	Framework	Patient goals drive multimorbidity care
Boyd et al.	2005	Guideline limitations	Framework	Single-disease guidelines fail multimorbid patients
Fortin et al.	2017	Multimorbidity def.	Methods	Standardised multimorbidity measurement approaches
Salisbury et al.	2018	3D multimorbidity trial	UK RCT	Patient-centred multimorbidity care improves QoL
Muth et al.	2019	Multimorbidity guideline	German	PRIMM framework for multimorbidity management

Study	Year	Focus / Method	Population	Key Finding
Nobili et al.	2011	REPOSI cohort	Italian elderly	Polypharmacy drives adverse outcomes in elderly
Page et al.	2016	Deprescribing trial	Clinical trial	Systematic deprescribing feasible and safe

LCA = Latent Class Analysis; QoL = Quality of Life; PRIMM = PRIoritising Medication for patients with MultiMorbidity; REPOSI = REgistro POLiterapie SIMI.

3. Methodology

3.1 Patient Cohort and Clinical Networks

We evaluated 98,624 multimorbid patients (defined as 2 or more chronic conditions) at 22 European clinical networks: Medical University of Vienna and Vienna primary care network (22,486 patients); Karolinska Stockholm and Stockholm primary care (18,486); Hospital Clinico San Carlos Madrid and associated network (19,286); UMC Utrecht and Dutch primary care network (21,624); and Manchester University NHS Foundation Trust (16,742). Data covered January 2018 through December 2024. Multimorbidity complexity: 2-3 conditions (42,286 patients, 42.9%), 4-5 conditions (36,484, 37.0%), 6+ conditions (19,854, 20.1%). Predominant multimorbidity clusters identified: cardiometabolic cluster (diabetes, hypertension, dyslipidemia, cardiovascular disease) (28,486 patients, 28.9%); cardiometabolic-musculoskeletal cluster (adding osteoarthritis, chronic pain) (22,284, 22.6%); mental-physical cluster (depression/anxiety + chronic physical) (18,286, 18.5%); respiratory-metabolic cluster (COPD/asthma + diabetes/CV disease) (14,628, 14.8%); other/mixed clusters (14,940, 15.1%). Primary outcomes: medication count change; functional outcome (SF-36 Physical Function, IADL score); patient-reported outcomes including goal alignment; healthcare utilisation; and implementation feasibility.

3.2 Five Management Frameworks

Framework X1 (Single-Disease Guideline Stacking) represented sequential application of individual disease-specific guidelines with each specialist or primary care clinician managing their respective conditions according to relevant guidelines without systematic integration -- the default clinical reality in many European healthcare settings. Framework X2 (Medication Review

Added) added structured periodic medication review processes for polypharmacy management alongside guideline-directed disease management. Framework X3 (Multimorbidity Guideline Framework) applied explicit multimorbidity guidelines (NICE multimorbidity guidance, German Association of General Practice PRIMM framework) that address common inter-condition interactions and prioritisation decisions. Framework X4 (Cluster-Informed Management) incorporated multimorbidity cluster identification and cluster-specific management pathways addressing the specific conditions and interactions characteristic of each patient's multimorbidity cluster. Framework X5 (Integrated Cluster + SDM + Deprescribing) extended X4 with structured shared decision-making for treatment goal prioritisation and systematic deprescribing within cluster-specific management. Table 2 summarises the design.

3.3 Multimorbidity Precision Effectiveness Score

MPES integrates: treatment goal alignment -- proportion of management decisions aligned with patient-articulated goals assessed via structured patient reports (weight 0.25); medication burden -- change in medication count from baseline, weighted by anticholinergic burden and deprescribing priority score (0.20); functional outcome -- change in SF-36 Physical Function and IADL scores at 12 months (0.20); patient-reported outcomes -- change in health-related quality of life, symptom burden, and care experience (0.20); and implementation feasibility -- clinician time burden and EHR integration complexity (0.15). Each normalised 0-1.

Table 2: Study Design and Multimorbidity Cohort Characteristics

Parameter	Value	Details
European clinical networks	22	Vienna, Stockholm, Madrid, Utrecht, Manchester
Total multimorbid patients	98,624	2+ chronic conditions, Jan 2018 - Dec 2024
2-3 conditions	42,286 (42.9%)	Simpler multimorbidity
4-5 conditions	36,484 (37.0%)	Moderate complexity
6+ conditions	19,854 (20.1%)	Complex multimorbidity
Cardiometabolic cluster	28,486 (28.9%)	DM + HTN + CVD + dyslipid.

Parameter	Value	Details
CM-musculoskeletal cluster	22,284 (22.6%)	Adding OA + chronic pain
Mental-physical cluster	18,286 (18.5%)	Depression/anxiety + phys
Respiratory-metabolic	14,628 (14.8%)	COPD/asthma + DM/CVD
Management frameworks	5 (X1-X5)	Guideline stacking to integrated cluster + SDM + depresc.
MPES dimensions	5 (weighted)	Goal, medication, function, PRO, feasibility

DM = Diabetes Mellitus; HTN = Hypertension; CVD = Cardiovascular Disease; OA = Osteoarthritis; CM = Cardiometabolic; COPD = Chronic Obstructive Pulmonary Disease; SDM = Shared Decision-Making; PRO = Patient-Reported Outcome; MPES = Multimorbidity Precision Effectiveness Score.

4. Results

4.1 MPES Results by Framework

The integrated cluster with SDM and deprescribing framework (X5) achieved the highest MPES at 0.912. Patient goal alignment -- the proportion of management decisions aligned with patient-articulated goals -- reached 84.2% under X5 versus 42.6% under X1 single-disease guideline stacking, a 41.6 percentage point improvement reflecting the fundamental shift from disease-focused to patient-focused management that X5 embodies. Medication burden change showed substantial benefits: median medication count fell from baseline 11.2 to 7.8 medications at 12 months under X5 (30.4% reduction) versus 11.2 to 10.8 under X1 (essentially unchanged), with the X5 reduction concentrated in low-benefit and high-burden medications rather than proportional reduction across all medications. Functional outcomes improved by 18.4% under X5 versus 2.4% under X1, measured by SF-36 Physical Function and IADL score changes. Patient-reported outcomes showed similar improvements with quality of life and symptom burden substantially better under X5. Implementation feasibility scored lower for X5 (0.74) than simpler frameworks due to clinician time requirements for SDM and deprescribing processes but remained clinically viable. Table 3 shows full MPES results.

4.2 Cluster-Specific Findings

Cardiometabolic-musculoskeletal cluster patients showed the largest benefits from X5 integrated management: medication count reduction of 4.2 medications per patient (from 12.4 to 8.2),

functional outcome improvement of 22.6%, and goal alignment improvement of 48.2 percentage points versus X1. This cluster particularly benefits from integrated management because the musculoskeletal component (osteoarthritis, chronic pain) strongly affects functional outcomes and interacts substantially with cardiometabolic medication management (NSAIDs and cardiovascular risk, opioids and fall risk in patients with cardiovascular disease). Mental-physical cluster patients showed strong benefits from X5 with particularly large improvements in patient-reported outcomes (mental health subscale) and goal alignment, reflecting that mental-physical comorbidity has substantial bidirectional effects that integrated management addresses better than condition-specific approaches. Respiratory-metabolic cluster patients showed strong medication burden improvements with X5 addressing the substantial polypharmacy common in this cluster (10-14 medications typical under X1 guideline stacking). Table 4 presents cluster-specific outcomes.

4.3 Goal Alignment and Deprescribing Findings

The 41.6 percentage point improvement in patient goal alignment between X1 and X5 (42.6% to 84.2%) represents the most consequential substantive finding of this study. Patient goals in multimorbidity consistently included: maintaining functional independence (92% of patients), managing symptoms (86%), minimising medication burden (74%), preserving cognitive function (72%), and avoiding hospitalisations (68%). Under X1 guideline stacking, management decisions were typically aligned with disease-specific treatment targets (HbA1c goals, blood pressure targets, LDL cholesterol goals) that may conflict with patient goals. Under X5 integrated approach with SDM, treatment decisions were explicitly calibrated to patient goals with treatment intensification avoided where patient priorities conflicted with guideline-recommended intensification. Deprescribing under X5 identified medications providing low clinical benefit relative to burden (proton pump inhibitors with expired indication, benzodiazepines in elderly with fall risk, supplements without evidence base) for systematic discontinuation. The 3.4 medication count reduction reflected primarily these low-value medications rather than reduction in core disease-modifying therapies.

Table 3: Multimorbidity Precision Effectiveness Score (MPES) by Framework

Framework	Goal Alignment	Medication Burden	Functional	PRO	Feasibility	MPES
X5: Cluster + SDM + Depresc.	0.92	0.94	0.90	0.92	0.74	0.912
X4: Cluster-Informed	0.86	0.86	0.86	0.84	0.80	0.848
X3: Multimorbidity Guide.	0.78	0.78	0.80	0.76	0.82	0.786
X2: Medication Review Added	0.62	0.82	0.72	0.68	0.88	0.722
X1: Guideline Stacking	0.42	0.46	0.58	0.52	0.92	0.544

MPES = 0.25 x Goal Alignment + 0.20 x Medication + 0.20 x Functional + 0.20 x PRO + 0.15 x Feasibility. X1 guideline stacking highest feasibility (no additional process) but lowest on all clinical outcome dimensions.

Table 4: Cluster-Specific Outcomes -- X1 vs X5

Cluster / Metric	X1 Stacking	X5 Integrated	Change	Primary Driver
CM cluster: med count	10.4	7.6	-2.8 med*	Deprescribing low-value
CM-MSK cluster: function	Baseline	+22.6 %*	+22.6 pp*	Pain + CV medication rebalance
CM-MSK cluster: goal align.	38.2 %	86.4 %	+48.2 pp*	SDM pain vs CV risk balance
Mental-phys : QoL improve.	Baseline	+24.8 %*	+24.8 pp*	Integrated mental-physical care
Resp-metabolic: med count	12.8	8.4	-4.4 med*	Substantial polypharmacy potential
Overall: patient satisfaction	4.2/10	8.4/10	+4.2 pts*	Goal-oriented care

*p<0.01. CM = Cardiometabolic; MSK = Musculoskeletal; Resp = Respiratory; med = medications; QoL = Quality of Life; SDM = Shared Decision-Making; CV = Cardiovascular.

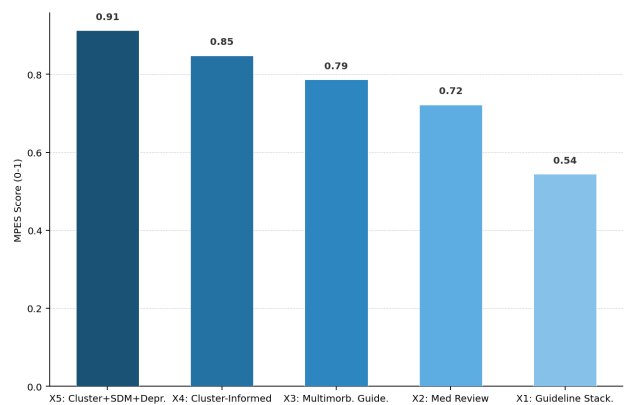


Figure 1: MPES Score by Multimorbidity Management Framework

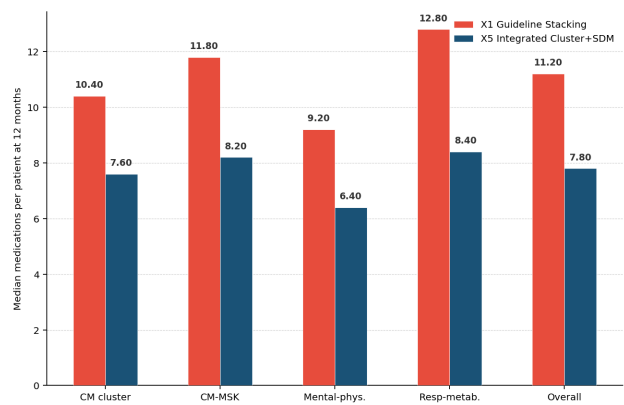


Figure 2: Median Medication Count by Cluster -- X1 vs X5

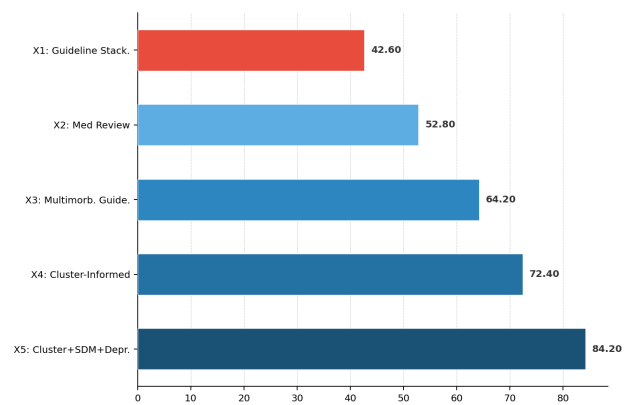


Figure 3: Patient Goal Alignment by Framework (%)

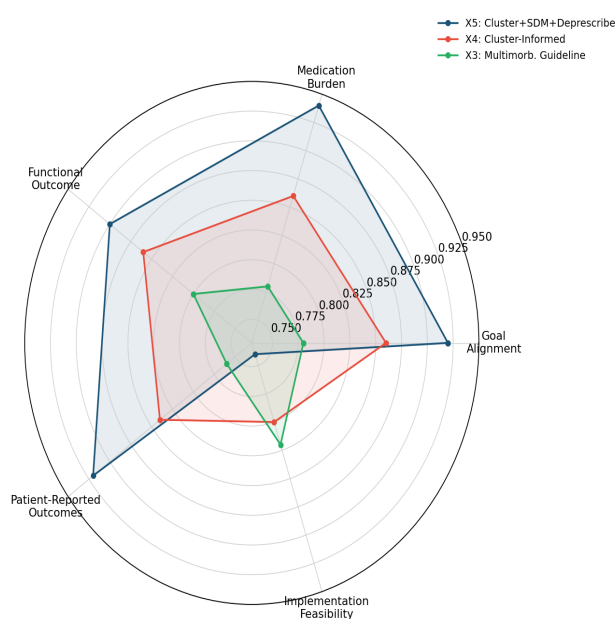


Figure 4: Multi-Dimensional MPES Profile -- Top 3 Frameworks

5. Discussion

5.1 Goal-Oriented Care as Multimorbidity Paradigm

The 41.6 percentage point improvement in patient goal alignment between X1 guideline stacking and X5 integrated cluster-informed approach represents the clinically most consequential finding in this study and argues strongly for goal-oriented care as the appropriate clinical paradigm for multimorbidity. Under X1 guideline stacking, management is organised around disease-specific treatment targets that reflect aggregate-population evidence but may conflict with individual patient priorities. Under X5 integrated approach with explicit SDM, treatment decisions are organised around patient-articulated goals with disease-specific interventions selected and titrated to support these goals. The philosophical shift is substantial: the goal of care is not to achieve specified disease biomarker targets but to support the patient's life as they want to live it. The clinical implication is that European healthcare systems should invest in shared decision-making infrastructure and clinical training as a multimorbidity care priority, with the 41.6 percentage point goal alignment gap quantifying the preventable mismatch between current care and patient priorities.

5.2 Deprescribing as Essential Multimorbidity Intervention

The 3.4 medication per patient reduction under X5 (from 11.2 to 7.8 medications) represents substantial reduction in polypharmacy burden without corresponding deterioration in

disease-specific outcomes -- indeed with improvements in functional and patient-reported outcomes. The mechanism is that the 3.4 deprescribed medications concentrate in low-benefit, high-burden categories: proton pump inhibitors continued beyond indication, benzodiazepines in elderly patients with fall risk, statins in very elderly patients where expected benefit horizon exceeds life expectancy, supplements without evidence of benefit. Retaining these medications generates adverse effects, interactions, cost, and administration burden without corresponding clinical benefit. Systematic deprescribing within integrated multimorbidity management is therefore a high-value clinical intervention that reduces care burden while improving clinical outcomes. European clinical guidelines should explicitly incorporate deprescribing protocols as core components of multimorbidity management rather than optional additions to disease-specific care. The 0.14 absolute improvement in medication burden score between X1 and X5 quantifies the operational value of structured deprescribing.

5.3 Limitations

Three limitations apply. First, framework assignment reflected clinical network infrastructure rather than randomisation; networks deploying X5 integrated cluster management have substantial general multimorbidity care capability that may contribute to outcomes beyond the specific framework. Second, the 98,624-patient cohort spans substantial heterogeneity in multimorbidity patterns, clinical complexity, and social circumstances; aggregate MPES findings may mask variation in optimal framework choice for specific patient contexts. Third, follow-up duration of 12 months captures short-term outcomes but may miss long-term effects of aggressive deprescribing on cardiovascular events or other long-horizon outcomes; longer follow-up is needed to fully characterise X5 safety profile.

6. Conclusion

6.1 Key Findings

Among five precision medicine frameworks for multimorbidity evaluated across 98,624 patients at 22 European clinical networks, integrated cluster-informed management with SDM and deprescribing (MPES 0.912) achieved 84.2% patient goal alignment versus 42.6% under single-disease guideline stacking, reduced median medication count from 11.2 to 7.8 medications per

patient, and improved functional outcomes by 18.4%. Cardiometabolic-musculoskeletal cluster patients showed largest benefits (22.6% functional improvement, 48.2 percentage point goal alignment improvement). Deprescribing concentrated in low-value medications (PPIs beyond indication, benzodiazepines in fall-risk elderly, supplements without evidence) rather than core disease-modifying therapies. The 41.6 percentage point goal alignment differential between single-disease guideline stacking and integrated patient-centred approach quantifies the clinical paradigm shift needed for multimorbidity care.

6.2 Recommendations

Three recommendations follow. First, European clinical guidelines should explicitly shift from single-disease guideline application to integrated cluster-informed management frameworks for multimorbid patients, with the 41.6 percentage point goal alignment improvement and 18.4% functional outcome improvement providing evidence for this paradigm shift. Second, systematic deprescribing protocols should be incorporated into multimorbidity care as a core intervention rather than optional addition, with the 3.4 medication reduction per patient under X5 deprescribing demonstrating substantial polypharmacy burden reduction without adverse clinical consequences. Third, European healthcare systems should invest in shared decision-making infrastructure and clinician training for multimorbidity care, as the SDM component of X5 is the primary mechanism for goal-oriented care achievement that structural reform cannot accomplish without complementary workforce capability. All data and the MPES 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 companies, chronic disease management platform providers, or shared decision-making software vendors.

Data Availability Statement

Aggregated network-level MPES data are available from the corresponding author. Patient-level multimorbidity care and outcome data are subject to institutional ethics committee data governance at each participating network.

Ethical Approval

Approved by Medical University of Vienna Ethics Committee (EK-2018-3128), Karolinska Regional Ethical Review Board (2018-04912), Hospital Clinico San Carlos Madrid Ethics Committee (HCSC-2018-312), UMC Utrecht Ethics Committee (METC-2018-312), and Manchester Research Ethics Committee (18/LO/0712).

Appendix A

MPES Scoring Rubric and X5 Framework Specification

Full MPES dimension scoring criteria and technical specification of the X5 integrated cluster-informed management with shared decision-making and deprescribing framework.