IL "SAN MATTEO COMPLEXITY STUDY" (SMAC STUDY)

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AN INTRODUCTORY & SUBTLE TERMINOLOGICAL DIFFERENCE

Complexity, a new paradigm of clinical medicine

Complicated	***Complex***
↓	↓
complĭcatūm	**complexŭs**
↓	↓
compiegato, arrotolato difficile da capire	**abbracciato, intrecciato interconnesso**

BRINGING COMPLEXITY INTO CLINICAL PRACTICE

- in the last decades, ageing of the general population has favoured the occurrence of chronic diseases, which tend to accumulate over the time, generating multimorbidity
- multimorbidity has been considered for years the hallmark of CC, but recent studies have shown that CC is something more and different
- CC originates from the interaction between patient's own factors and other external, contextual factors → a *complex system* is a cluster of individual factors from whose dynamic interaction new properties of the system itself emerge
- as a consequence, the observable outcomes of a CS are more than the sum of its single parts
- CC is one of the most challenging issue of modern medicine, since current health systems are still focused on single diseases or organ pathologies

Eur J Intern Med 2019

COMPLEXITY IS A CHALLENGING ISSUE

J Whittle & H Bosworth

Studying complexity is complex

J Gen Intern Med 2007

BJ Turner & L Cuttler

The complexity of measuring clinical complexity

Ann Intern Med 2011

MM Safford

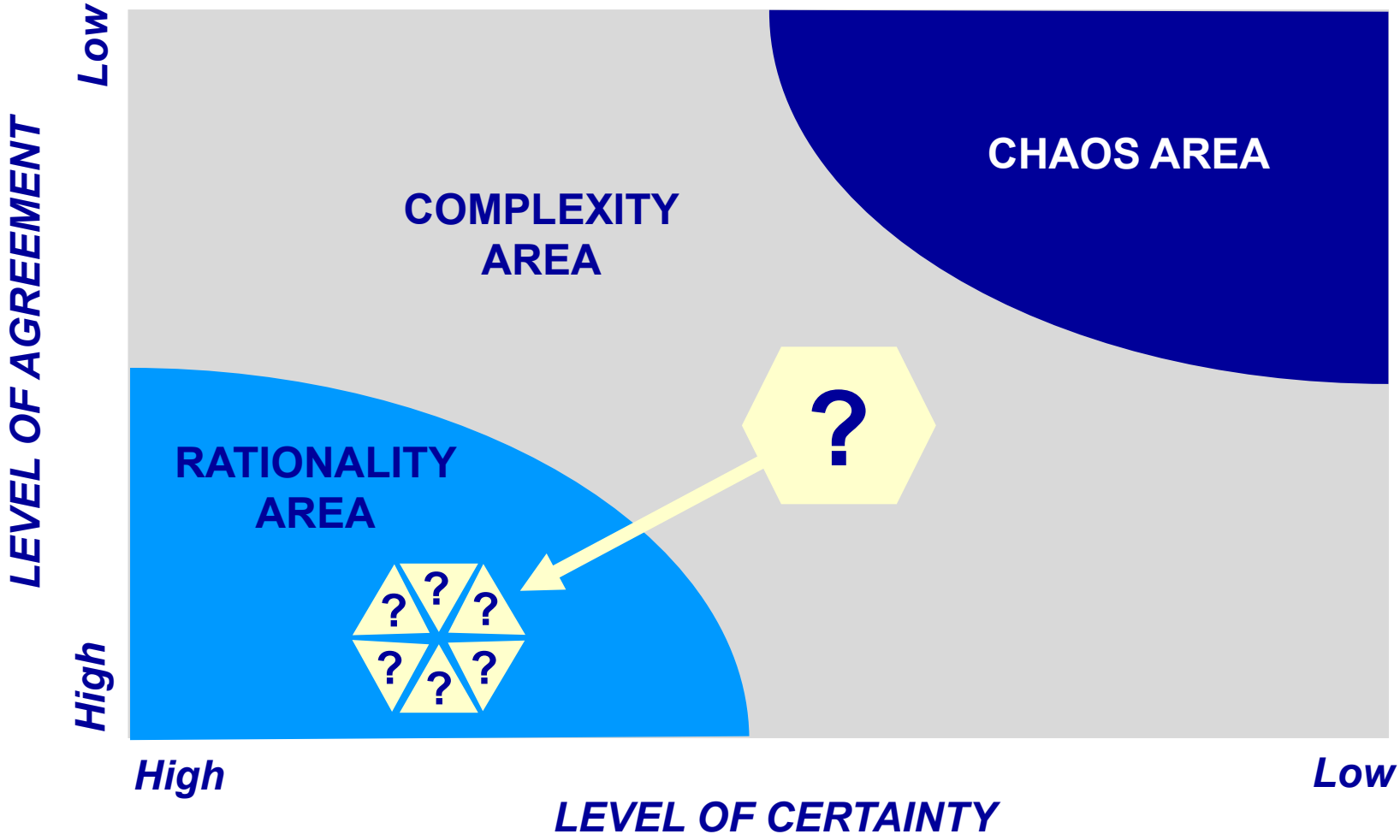
The complexity of complex patients

J Gen Intern Med 2015

THE INTRICATE FEATURES OF CSs

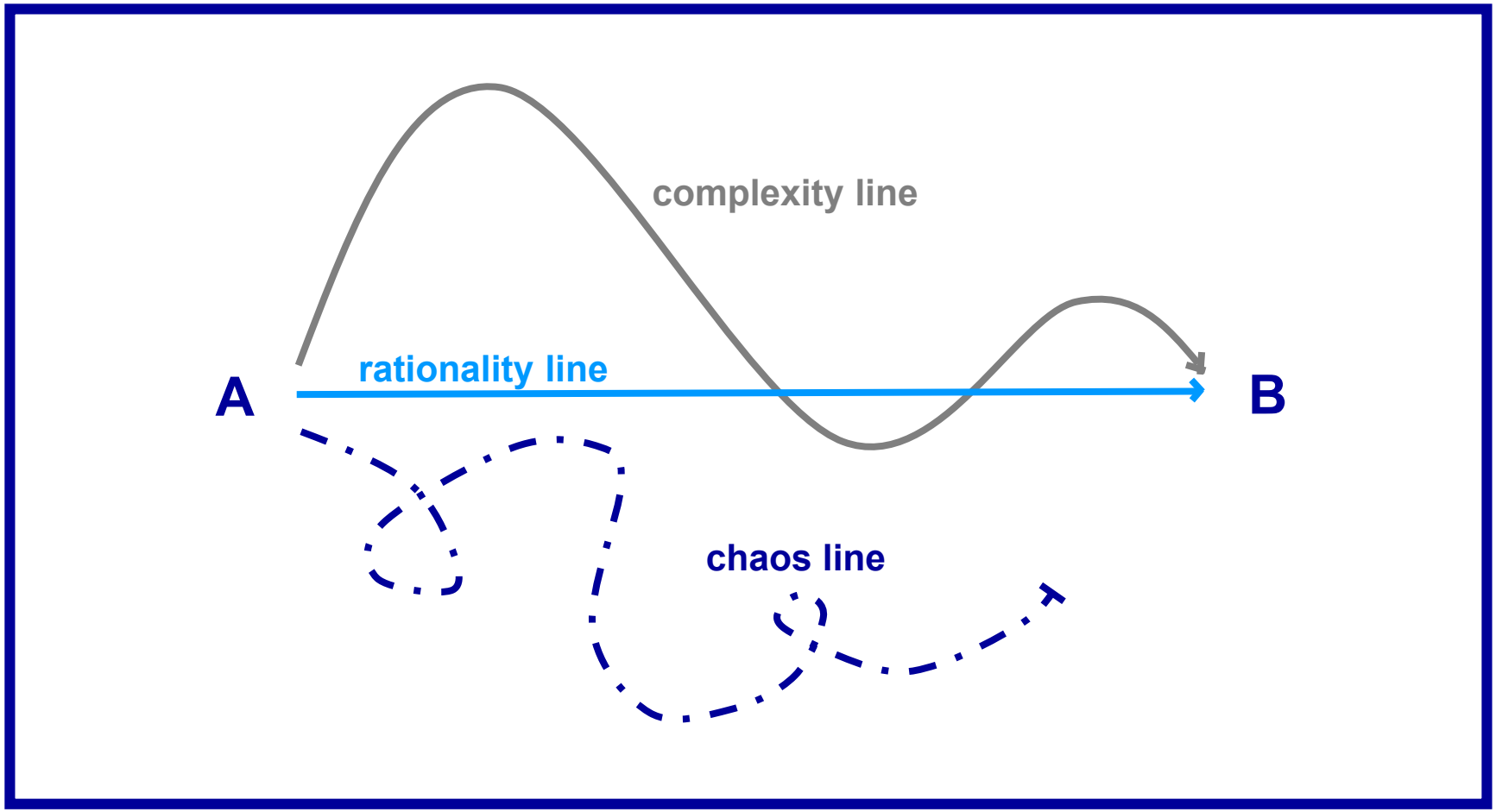
- ***co-evolution***: as CSs are embedded within other systems, the evolution of one system influences and is influenced by that of other systems
- ***adaptivity***: as individual components can change, a CS can adapt its behaviour over time
- ***non-linearity***: small changes in a single part of the CS may lead to huge changes in global outcomes
- ***unpredictability***: CSs are not governed by a simple cause/effect model

THE ZONE OF COMPLEXITY

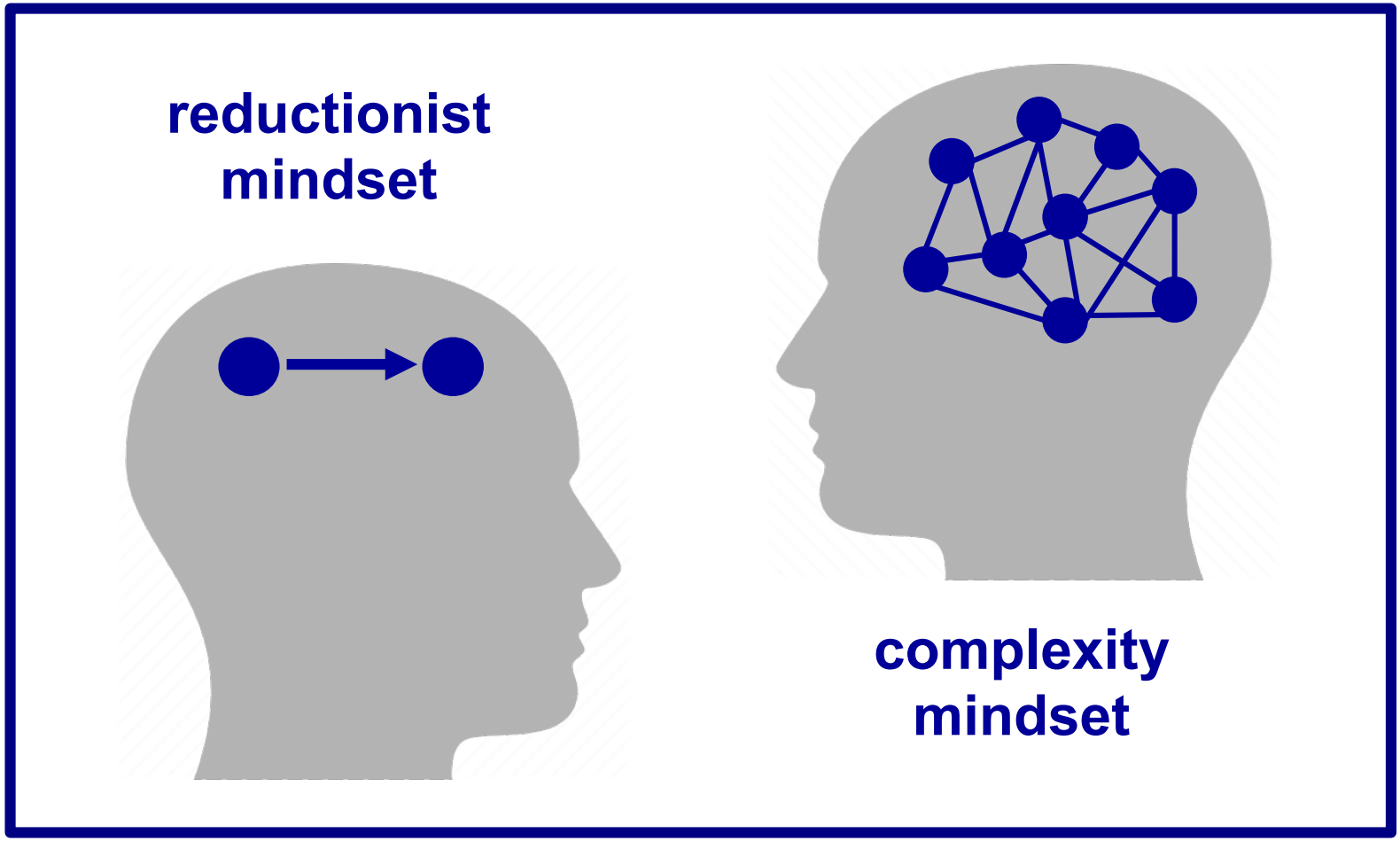


Stacey, *Financial Times 1999*

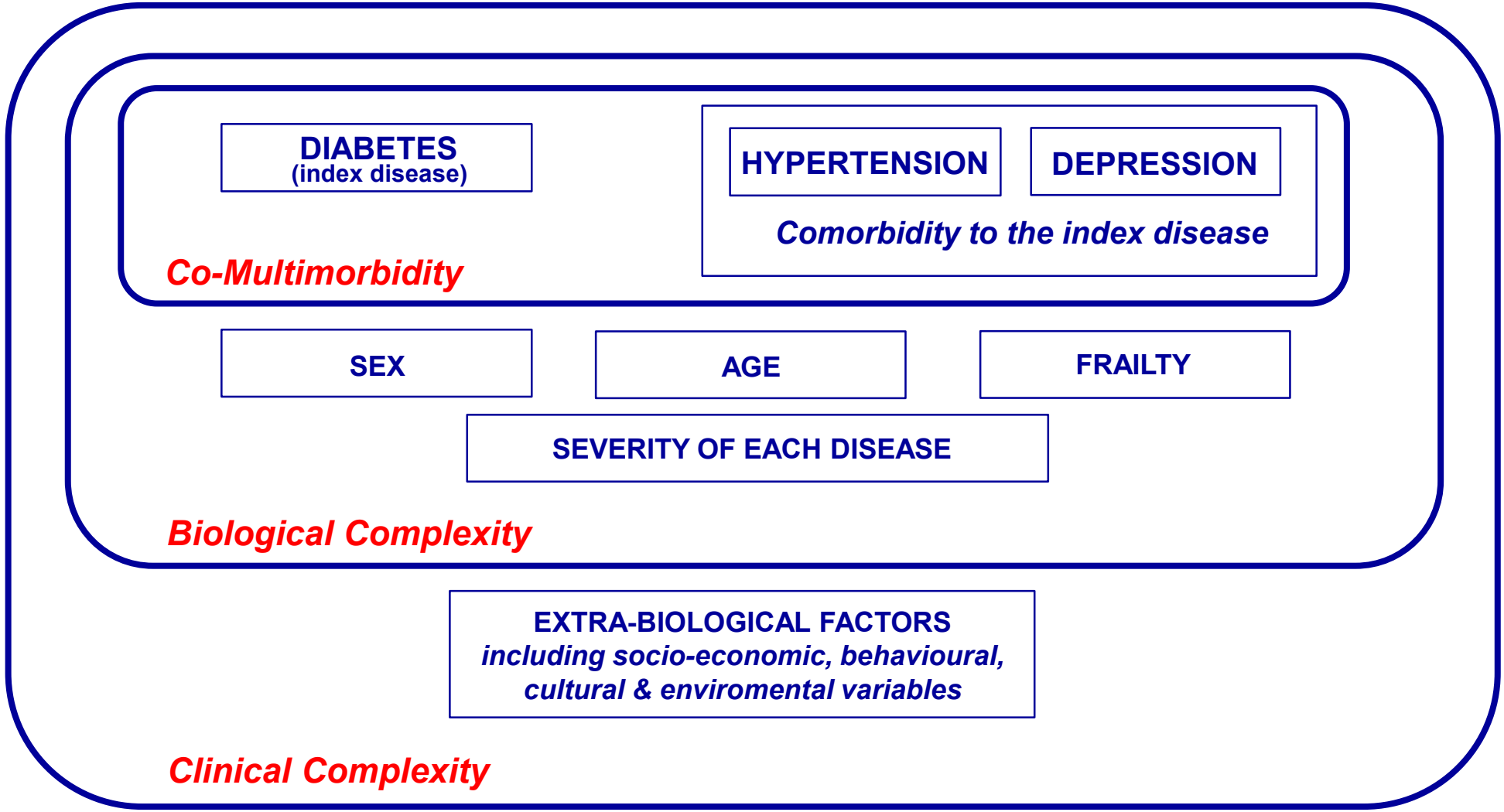
CSs HAVE NON-LINEAR AND UNPREDICTABLE BEHAVIOUR



CAPACITY TO COPE WITH COMPLEXITY CANNOT BE INFERRED FROM TEXTBOOKS



THE CONCENTRIC COMPONENTS OF CC



Valderas et al, *Ann Fam Med 2009*
Grant et al, *Ann Intern Med 2011*
Eur J Intern Med 2019

TREATMENT BASED ON CPG FOR A HYPOTHETICAL 80yr-OLD WOMAN WITH MULTIMORBIDITY

Time	MEDICATIONS	Time	MEDICATIONS
7:00 am	Ipatropium md inhaler Alendronate 70 mg/wk	1:00 pm	Ipatropium md inhaler Calcium 500 mg Vitamin D 200 IU
8:00 am	Calcium 500 mg Vitamin D 200 IU Hydrochlorothiazide 12,5 mg Lisinopril 40 mg Glyburide 10 mg Aspirin 81 mg Metformin 850 mg Naproxen 250 mg Omeprazole 20 mg	7:00 pm	Ipatropium md inhaler Metformin 850 mg Calcium 500 mg Vitamin D 200 IU Lovastatin 40 mg Naproxen 250 mg
		11:00 pm	Ipatropium md inhaler

20 doses, 12 separate medications, 5 times/day

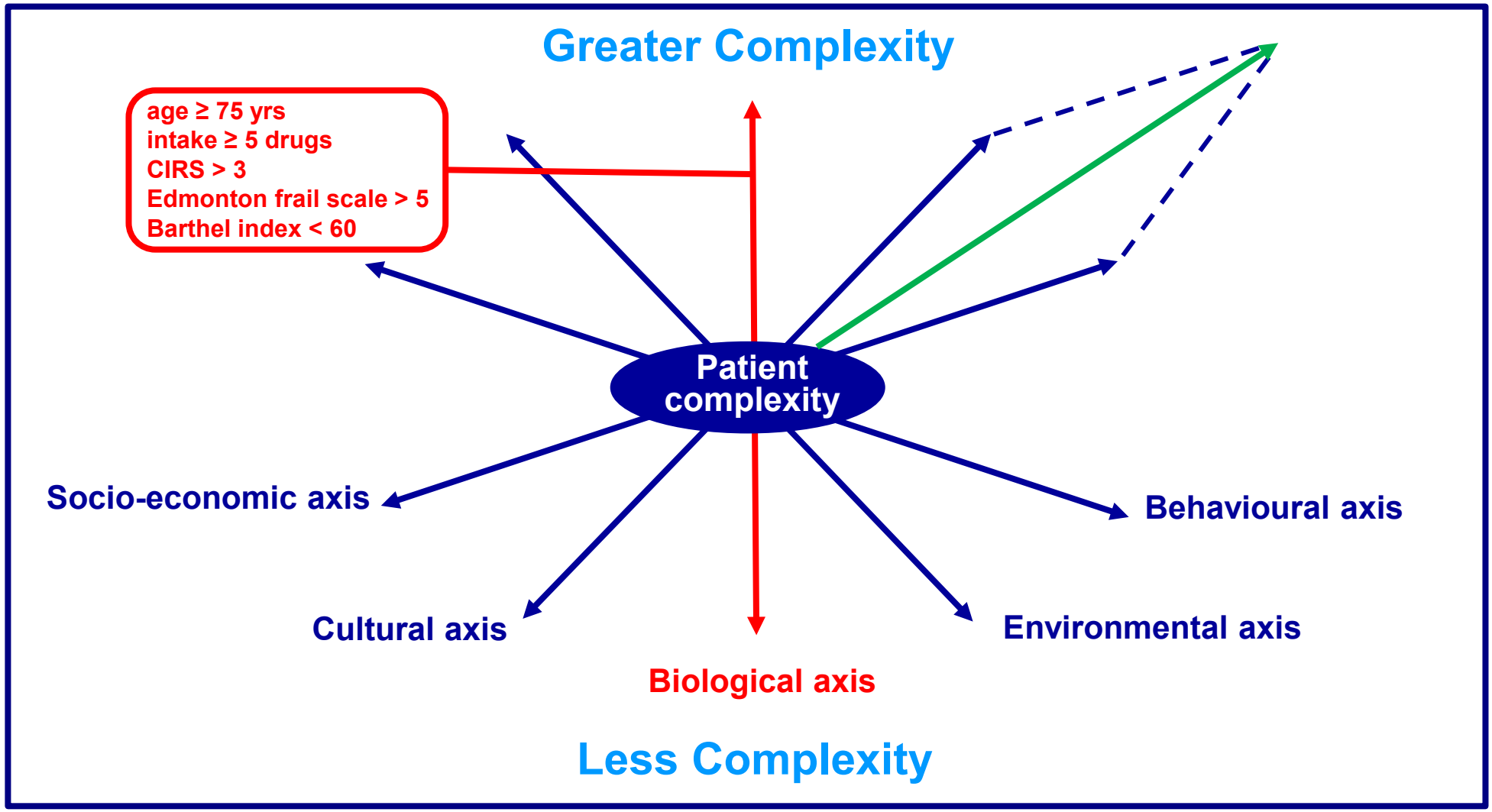
Boyd et al, *JAMA 2005*

THE "SMAC" STUDY

- *1451 consecutive pts* enrolled over a 2-yr period (Nov 2017 – Nov 2019)
- *power of the study* 1000 pts will allow to show an increase in R from 0.80 to 0.84 with power 90% & alpha 1% 2-sided for the correlation of the complexity index and length of stay
- *primary end-point* length of stay of the index hospitalisation
- *secondary end-points* hospital readmission within 1 mo, # of readmission in the first yr, # of ER accesses in the first yr, # of drugs prescribed in the first yr, mortality at 1 and 5 yrs, hospital reimbursement according to the regional DRG system
- *follow-up* at mo 4-8-12, then at yrs 2-3-4-5
- *source* for a number of sub-projects

ClinicalTrials.gov NCT03439410

THE VECTOR MODEL OF PATIENT COMPLEXITY



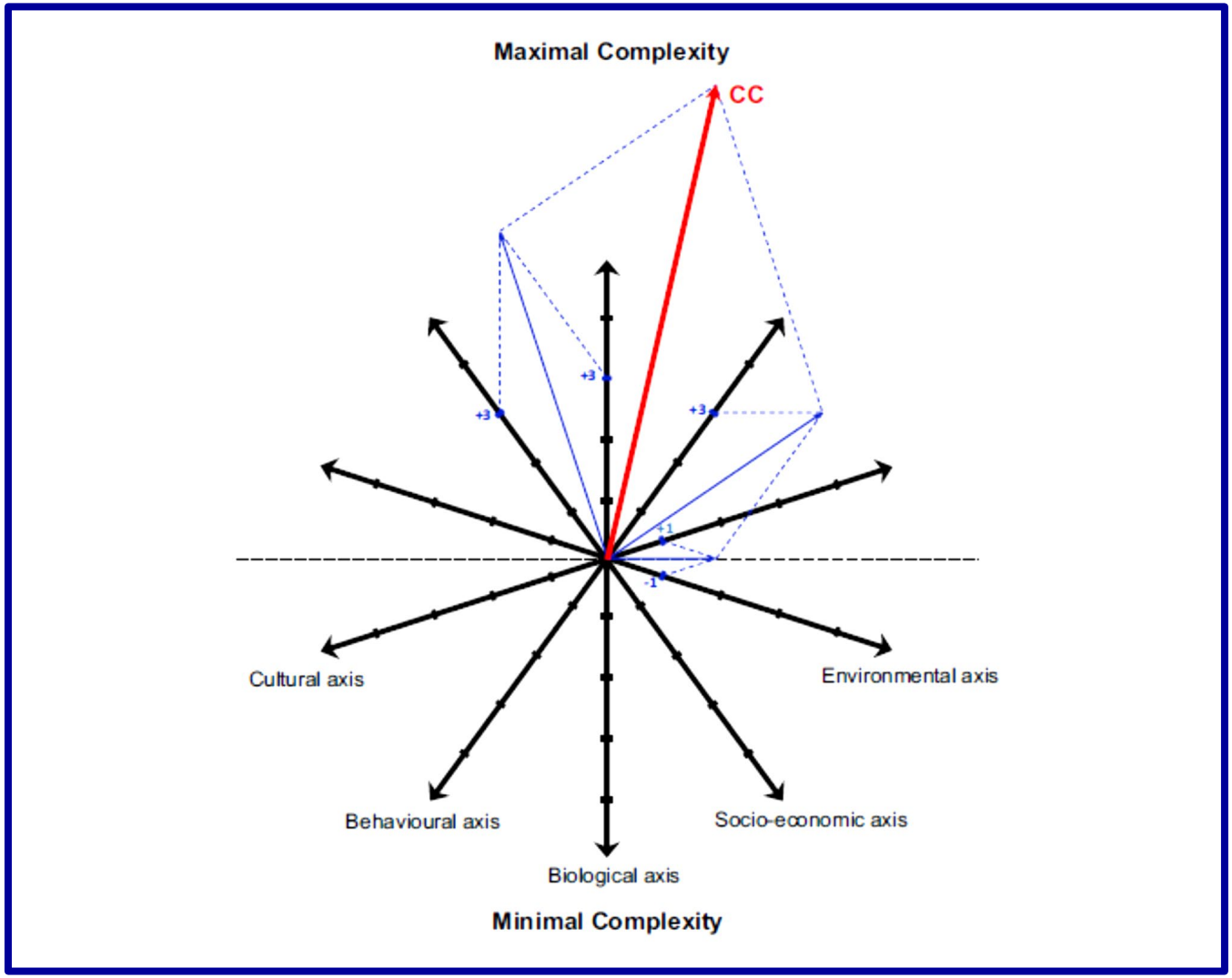
Safford et al, *J Gen Intern Med 2007*
Intern Emerg Med 2017

CC DOMAINS & RELATED VARIABLES. RESULTS OF A CONSENSUS MEETING

BIOLOGICAL DOMAIN		
Age > 75 years	yes☐	no☐
Intake ≥ 5 medications	yes☐	no☐
CIRS > 3 and/or CIRS severity >3	yes☐	no☐
↑ frailty (Edmonton Frail Scale > 5)	yes☐	no☐
↓ mobilization (Barthel<60)	yes☐	no☐
SOCIO-ECONOMIC DOMAIN		
Living alone	yes☐	no☐
Income < 1000 €/month	yes☐	no☐
Unemployment/precarious work	yes☐	no☐
Dependent/disabled family member	yes☐	no☐
Need for a caregiver	yes☐	no☐
BEHAVIORAL DOMAIN		
Inadequate adherence to medications	yes☐	no☐
Active smoking of at least 4 cigarettes/day	yes☐	no☐
Alcohol (>3 Alcohol Units/day) and/or drug abuse (current or past)	yes☐	no☐
Inappropriate diet	yes☐	no☐
Cognitive impairment (Short Blessed Test > 9)	yes☐	no☐
ENVIRONMENTAL DOMAIN		
Institutionalization	yes☐	no☐
Difficult access to healthcare	yes☐	no☐
Presence of home architectural barriers	yes☐	no☐
Occupational exposure to toxins	yes☐	no☐
Air pollution	yes☐	no☐
CULTURAL DOMAIN		
Schooling < 8 years	yes☐	no☐
Insufficient access to information	yes☐	no☐
Lack of adherence to health screening programs	yes☐	no☐
Language barriers	yes☐	no☐
Perceived discrimination	yes☐	no☐

Intern Emerg Med 2017

SMAC STUDY. CLINICAL COMPLEXITY OF A LONELY, UNWEALTHY, 85yr-OLD MAN ADMITTED FOR ACUTE HEART FAILURE



Intern Emerg Med 2017

EVALUATED INDEXES

Author, year	Tool name	N. Items	Variables included	Strength and limitations
Linn et al., 1968	Cumulative illness rating scale (CIRS)	13, 5-point scale (0-4)	Cardiovascular-respiratory system, gastrointestinal system, genitourinary system, musculo-skeletal-integumentary system, neuropsychiatric system, general system	Biologic measure of aging; designated better than did chronological age the individual along his life span and with regard to his capacity for survival
Shah et al., 1989	Barthel Index	10, ADL functions rated on a scale with different scores	Personal hygiene, bathing self, feeding, toilet, star climbing, dressing, bowel control, bladder control, ambulation, wheelchair*, chair/bed transfers	It is reliable and highly repeatable
Rolfson el al., 2006	Edmonton Frail Scale (EFS)	9, each rated on a 3- point scale (0-2)	Cognition, health status, functional dependence, social support, medication use, nutrition, mood, continence, functional performance	Easily available questionnaire to measure frailty in the elderly, both in a hospital and in an outpatient setting
Katzman et al., 1983	Short Blessed test (SBT)	6, each rated with different scores	Time orientation, ability to count backwards from 20 to 1, ability to say the months of the year in reverse order, and ability to repeat a memory phrase	Tool for detecting mild dementia and it is sensitive to subthreshold impairments; adversely affected by age and education
Connor et al., 2003	Connor-Davidson Resilience Scale (CD-RISC)	25, each rated on a 5-point scale (0-4)	Personal competence, high standards, and tenancy (a); trust in one's instincts, tolerance of negative affect, and strengthening effects of stress (b); positive acceptance of change and secure relationships (c); control (d); and spiritual influences (e)	The scale does not assess the resiliency process or provide information about the theory of resilience, it also has not been validated against an objective measure, or against biological measures of resilience
Morisky et al., 1986	MMAS-4 Morisky Medication Adherence Scale	4, each positive answer has a score of 0 and each negative of 1	Do you ever forget to take your medicine (a); Are you careless at time about taking your medicine? (b); Sometimes if you feel better when you take the medicine do you stop taking it?; Sometimes if you feel worse when you take the medicine do you stop taking it?	This questionnaire provides a measure of therapeutic adherence self-referred structured in four elements, it can also be complete independently by the user

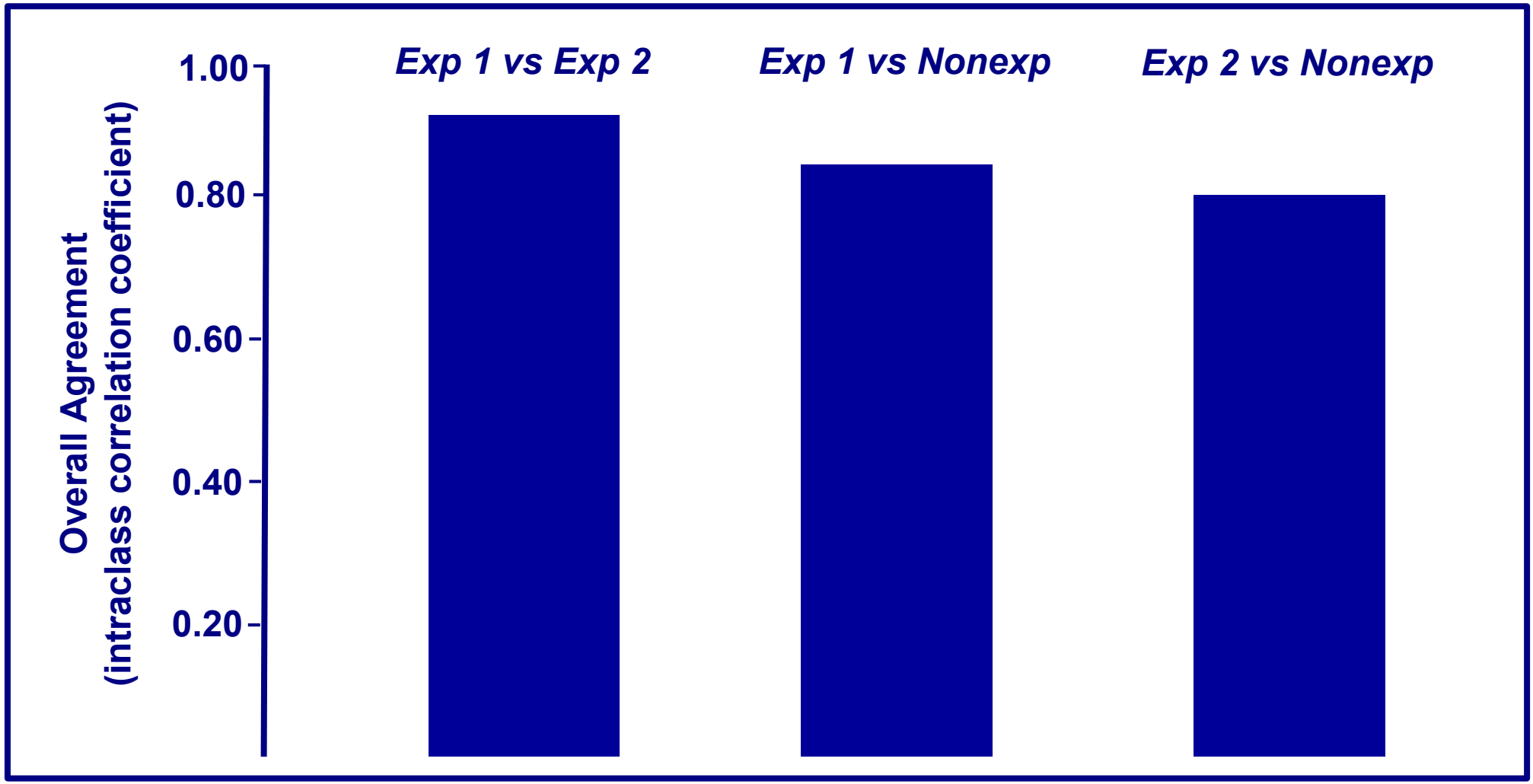
CAPTURE-RECAPTURE TECHNIQUE

- if a patient was lost to follow-up, the capture-recapture technique was applied
- GP or other available phone numbers were the first means of recapture
- if the above did not work, we ascertained the vital status from the last known municipality of residence
- death certificates were obtained from the local mortality registry; the cause of death was classified according to the 9th International Classification of diseases

Corrao, Corazza et al., *Lancet 2001*

REPRODUCIBILITY IN THE ASSESSMENT OF CC

30 consecutive pts - 3 healthcare professionals



J Gen Intern Med, 2019

HOW DOES THE DECEMBER HOLIDAY PERIOD AFFECT CC?

***106 cases* (15 DEC-15 JAN) / *121 controls* (16 JAN-16 FEB)**

	Cases	*Controls*	*p*
Age (yrs)	**79.4**	**74.3**	**0.014**
CCI	**17.7**	**15.2**	**0.001**
Biological domain	7.8	7.1	NS
Socioeconomic domain	**3.5**	**2.9**	**0.012**
Behavioral domain	**2.4**	**1.9**	**0.017**
Environmental domain	1.3	1.0	NS
Cultural domain	2.7	2.2	NS
CIRS	3.7	3.5	NS
Length of stay (days)	**15.5**	**11.0**	**0.001**

CCI, age, & low income independently correlated with cases

PLOSOne 2020

ADMINISTRATIVE DATA FOR EXPLORING MULTIMORBIDITY

	Administrative data	Clinical data
Time required to gather data	Short, computer-aided	Long, time-consuming
Costs required to gather data	Low	High, a skilled research physician is needed
Amount of data	High	Usually low
Patient-reported outcomes	Not assessable	Easily assessable and comparable to physician-reported outcomes
Risk factors analysis	Can only be inferred or assumed from the records, no causal relation with disease	Can be directly assessed and patients can be stratified according to the risk factors
Retrospective vs prospective design	Retrospective may promptly analyse large amount of data, especially the costs of a specific intervention	Prospective collects clinically meaningful exposure data
Reproducibility	Potentially high if a standardised method is used (e.g., ICD codes); may be low due to misclassification and may vary in different healthcare systems	Potentially high when samples are age-, gender-, and ethnicity-matched; may be low due to other contextual variables; large sample size is needed
Clinical transferability	Poor	High
Policymaker transferability	High	Poor

Intern Emerg Med 2020

HETEROGENEITY BETWEEN COMORBIDITY & MULTIMORBIDITY FRAMEWORKS

MCC recently reclassified into 2 ≠ MeSH

- *Comorbidity additional conditions to a single disease under study*
- *Multimorbidity co-occurrence of multiple diseases in which no single one holds priority*

n. 1394	*Comorbidity*	*Multimorbidity*	*p value*
Pts (%)	20.5	75.7	
CIRS (median)	2.97	4.09	<0.001
EFS >5 (%)	8.2	19.2	<0.001
Intake ≥5 medications (%)	50.9	78.7	<0.001
Median age (yrs)	71	82	<0.001
Age groups (%)			
18-64	36.7	11.0	
65-74	20.6	13.5	
75-84	28.3	37.7	
≥85	14.4	37.8	

Intern Emerg Med, 2022

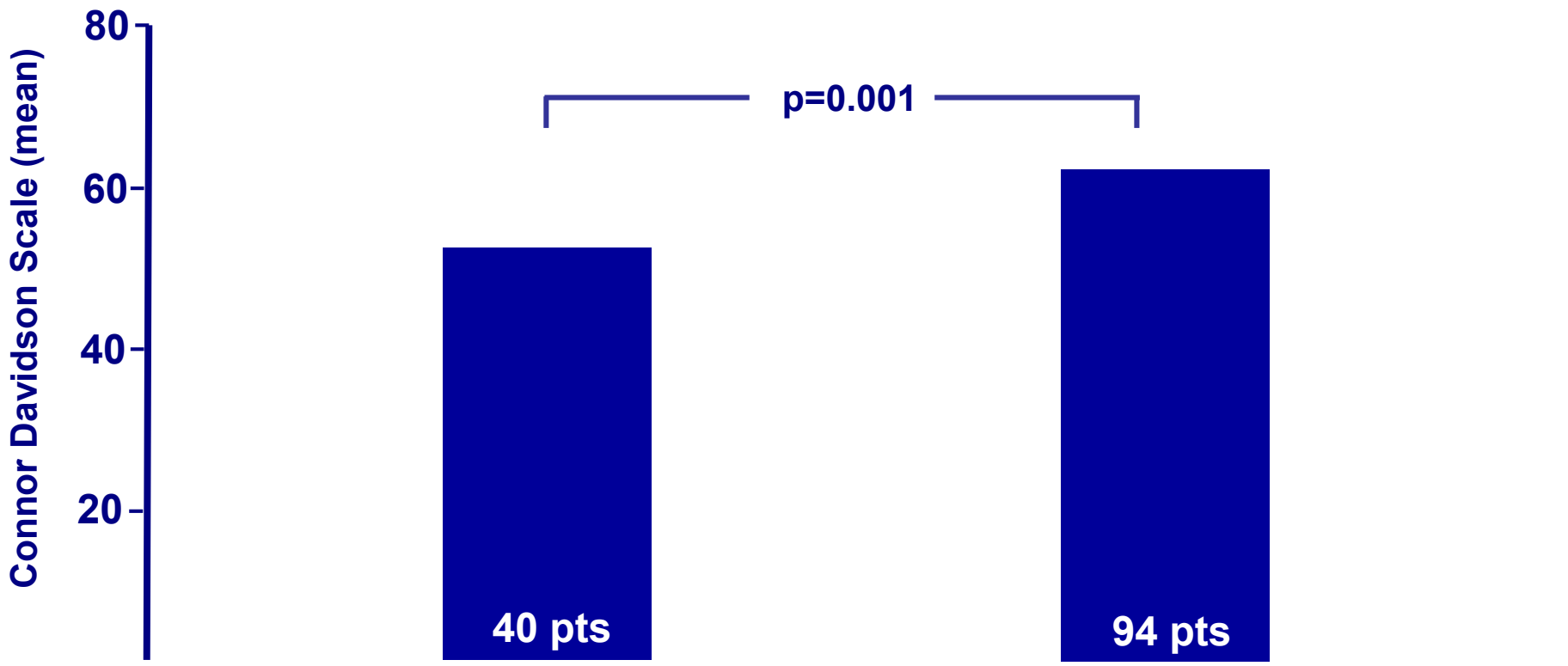
HETEROGENEITY BETWEEN COMORBIDITY & MULTIMORBIDITY FRAMEWORKS (II)

Multivariable analysis for the clinical outcomes

	Hospital mortality	30d Mortality	30d Readmission
Comorbidity (OR)	0.60 ns	1.34 ns	0.97 ns
Multimorbidity (OR)	0.32 ns	0.73 ns	0.86 ns
Age ≥75 yrs (OR)	4.82 p=0.002	3.42 p<0.001	2.17 p=0.037

Intern Emerg Med, 2022

RESILIENCE, FRAILTY & AGEING IN HOSPITALISED PTS (n. 143)



at multivariable analysis, RES significantly related to FRA (p=0.022) in adults (<65 yrs) and to DEPENDENCY (p=0.031) in older patients (≥65 yrs)

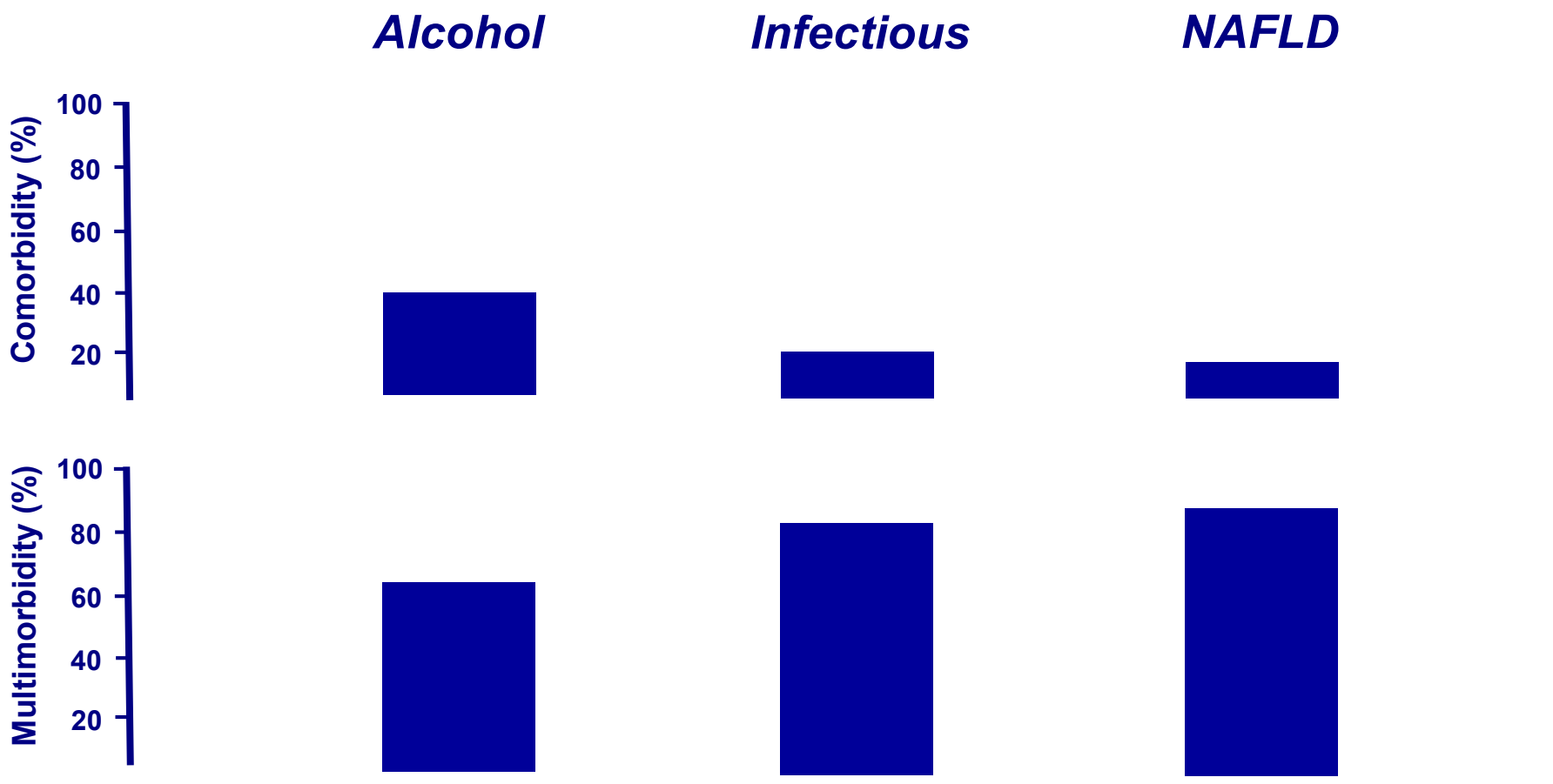
BMC Geriatrics 2022

RATE & RISK FACTORS FOR EARLY MORTALITY IN HOSPITALISED PTS (n. 1451)

	In-hospital mortality (6.4%)		*4-mo mortality (15.9%)*	
	OR	p value	HR	p value
Age	1.04	0.001	1.04	0.001
BMI <18.5	0.39	ns	2.13	0.001
Barthel index <60	2.60	0.001	1.65	0.002
CIRS >3	1.13	ns	0.80	ns
Drug intake >5	1.24	ns	1.25	ns
Length of stay	na	na	1.59	0.001

Clin Med 2023

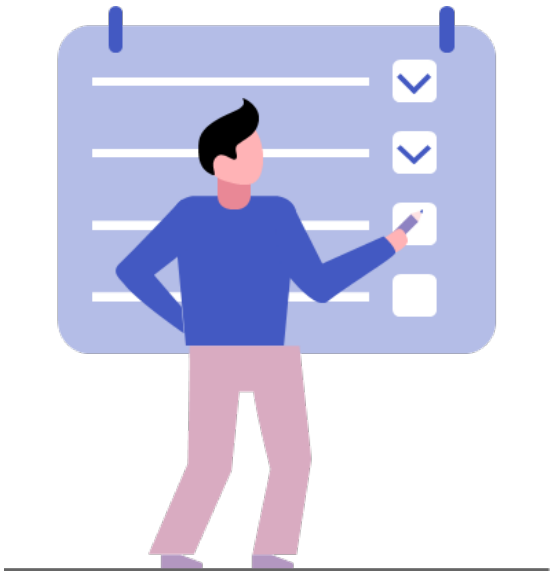
CO-MULTIMORBIDITY IN HOSPITALISED CIRRHOTIC PTS ACCORDING TO THE AETIOLOGY (n. 187)



at a multivariable analysis looking at factors affecting the risk of multimorbidity, admission related to cirrhosis was significantly and inversely correlated with this outcome

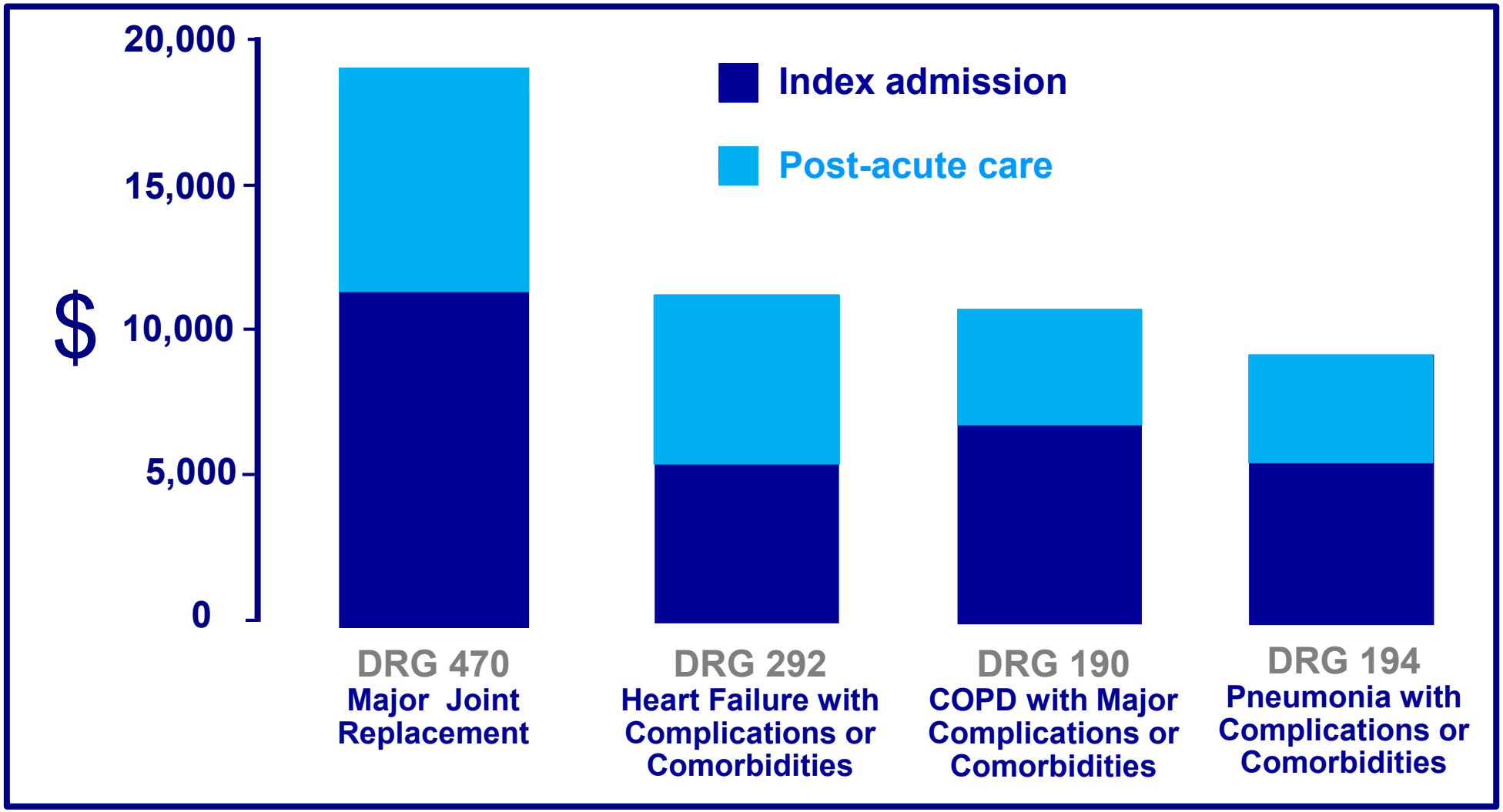
Submitted

NEW SUBPROJECTS 2022-23



1. Determinants of multimorbidity in young adults (age 18-35) vs middle-aged adults (age 35-60)
2. Polypharmacy and drug overprescription at discharge in an internal medicine setting
3. Sociodemographic and clinical characteristics of oncological patients admitted to an internal medicine ward
4. Underlying factors of end-of-life in an internal medicine setting
5. Impact of physical exercise in frail individuals. A narrative review

MEDICARE ACUTE AND POST-ACUTE CARE PAYMENTS FOR 30-DAY EPISODES THAT BEGAN WITH HOSPITALIZATION

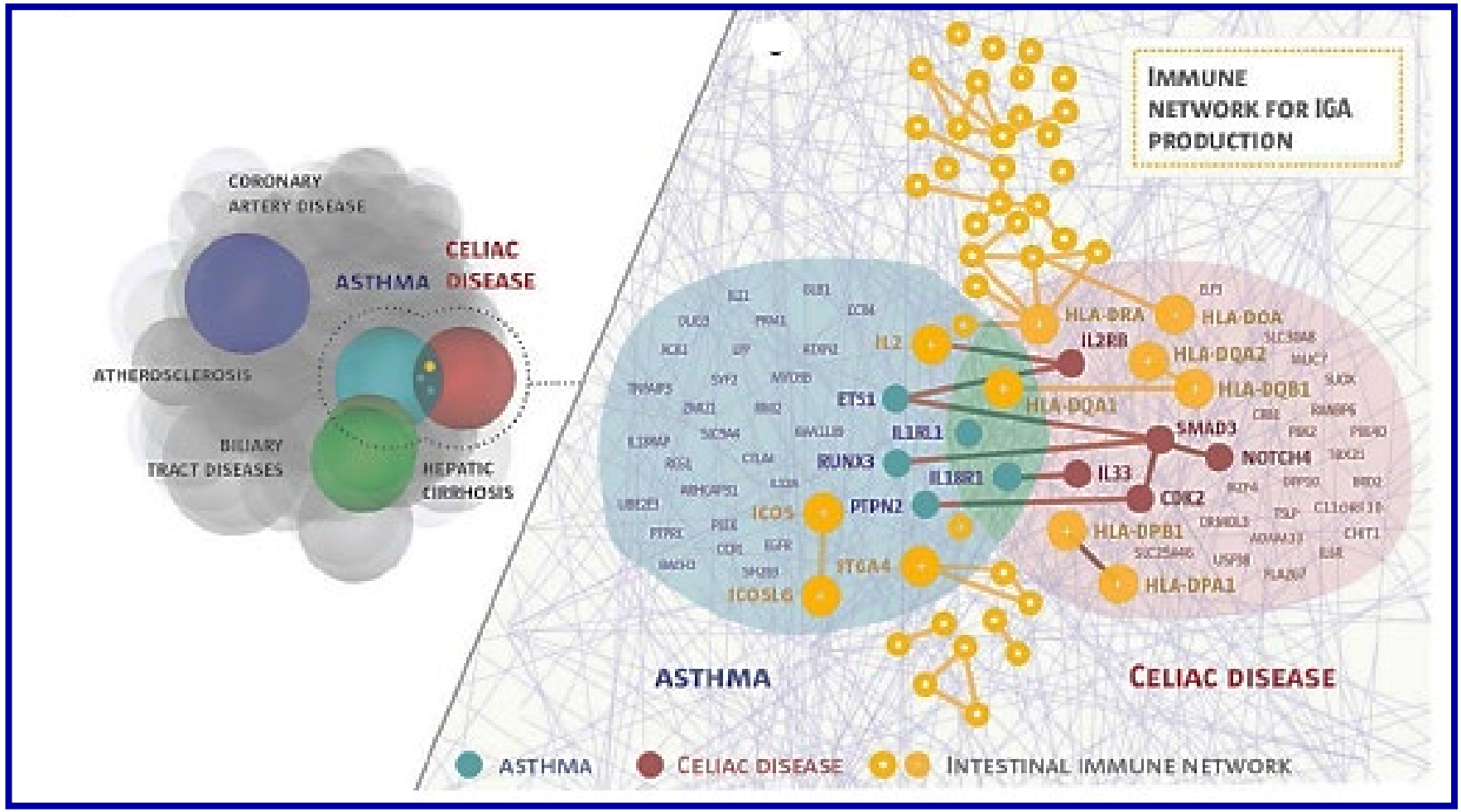


Mechanic, *New Engl J Med 2014*

THE WORTHINESS OF INTERNAL MEDICINE. A HISTORICAL PERSPECTIVE

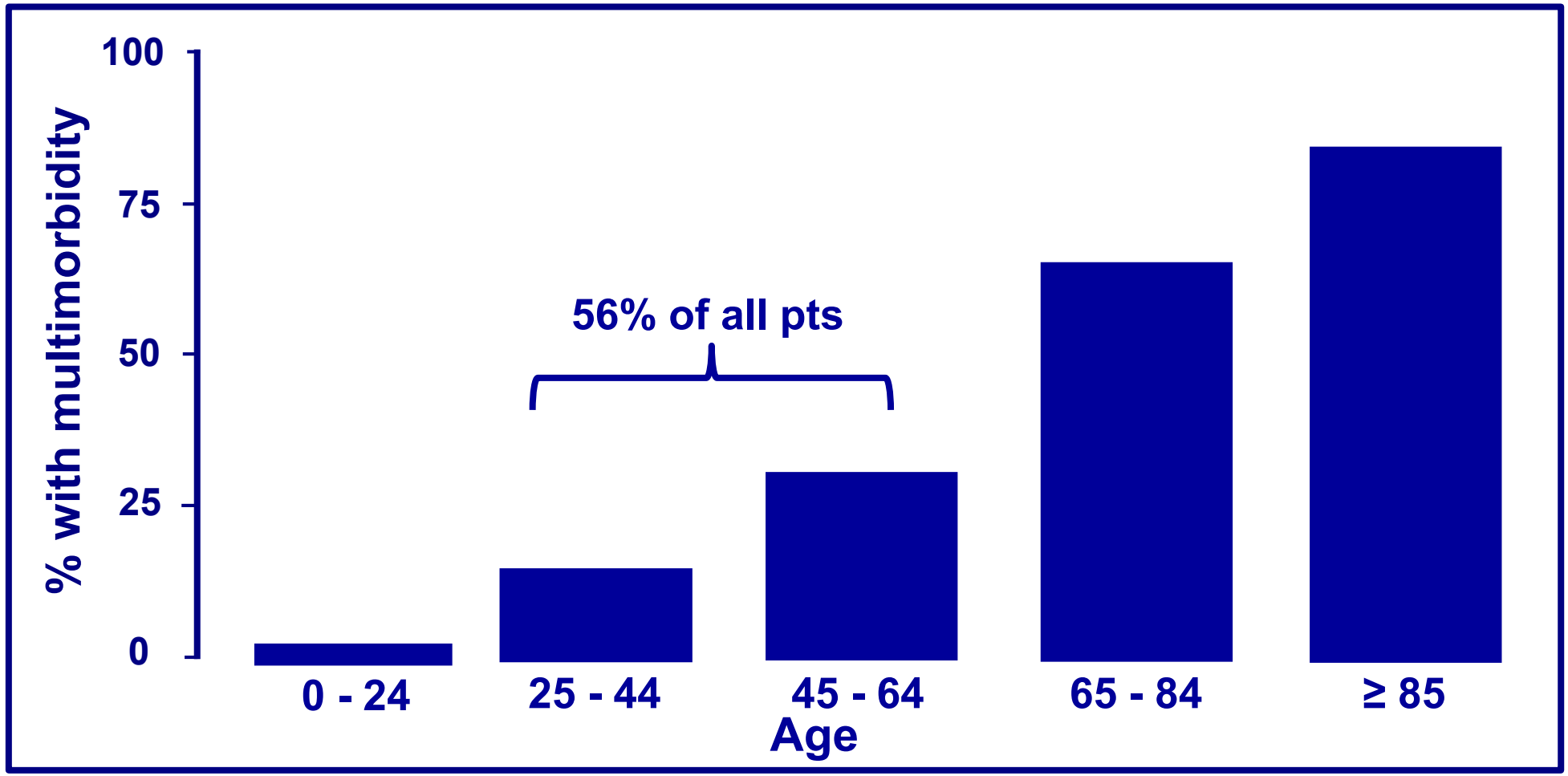
- clinical reasoning >> technical skill
- flexibility from primary to tertiary care
- capacity to shift through vast changes of medicine
- ability to relate with other specialties
- best suited for the application of cost-effective strategies

UNCOVERING DISEASE-DISEASE RELATIONSHIPS THROUGH THE "INTERACTOME"



Menche et al, *Science 2015*

DISTRIBUTION OF MULTIMORBIDITY IN RELATION TO AGE. A PRIMARY CARE DATABASE ON 1751841 SCOTTISH PTS



Barnett et al, *Lancet 2012*

? multimorbidity = complexity ?

FUTURE PERSPECTIVES ON CC

- both biological and clinical complexity are on increase
- stakeholders should update training programmes and reimbursement systems
- reinforcement of general medical care is an absolute need to achieve coordinated care and reorganise in a more efficient way the bidirectional flows between territory and hospital