Could clustering of comorbidities be useful for better defining the internal medicine patients' complexity?

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ABSTRACT

Internal medicine patients are mostly elderly with multiple comorbidities, usually chronic. The high prevalence of comorbidity and multimorbidity has a significant impact on both positive responses to treatment and the occurrence of adverse events. Clustering is the process of nosography grouping into meaningful associations with some index disease, so that the objects within a cluster have high similarity in comparison with one another. In the decision-making process it is imperative that, in addition to understanding the immediate clinical problems, we are able to explicit all the contextual factors that have to be taken into account for the best outcome of care. Cluster analysis could be leveraged in developing better interventions targeted to improve health outcomes in subgroups of patients.

Introduction

Multi-morbidity is like the universe. Diseases can combine infinitely, but some kinds of clusters are much more common than others[1]

Internal medicine patients are mostly elderly with multiple comorbidities, usually chronic. The high prevalence of comorbidity and multimorbidity has a significant impact on both positive responses to treatment and the occurrence of adverse events. The large majority of oldest old subjects have multimorbidity, such as hypertension, diabetes mellitus, dyslipidemia, ischemic cardiomyopathy, heart failure, stroke, chronic obstructive pulmonary disease, atrial fibrillation, peripheral arterial disease, Parkinson's disease, cancer, dementia, anemia, chronic kidney disease, visual impairment and deafness.[2] The current focusing on single diseases should be replaced with a holistic view and approach to the patterns of comorbidity and multimorbidity in the *real clinical care world* (Table 1).[3-5]

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Older adults with multimorbidity are heterogeneous: the complexity of measuring clinical complexity

Older adults with multimorbidity are heterogeneous in terms of illness severity, functional status, prognosis, personal priorities, and risk of adverse events.[6] Multimorbidity generally refers to the presence of multiple clinical conditions, but a multitude of patient-level factors independent of specific comorbid conditions may complicate care and affect outcomes. An important dimension of multimorbidity is the comorbidity interrelatedness, *i.e.* the degree to which conditions interact to affect clinical management and outcome.[7] By definition, for research on multimorbidity no index disease is used, whereas for comorbidity research an index disease is obligatory.[8] According to these views, we stated that

Comorbidity does not reflect complexity in internal medicine patients.[9] Many indices are now available for estimating a multimorbidity score by weighting a range of diseases (*e.g.*, Charlson Comorbidity Index[10] or Cumulative Illness Rating Scale).[11] Other applied multimorbidity measures are the Chronic Disease Score,[12] the RxRisk Model,[13] or the Duke Severity of Illness Checklist.[14] Safford *et al*. proposed a conceptual approach to complex patients involving interactions between biological, socioeconomic, cultural, environmental, and behavioral forces as health determinants.[15] Thus, the issue of better defining the complexity, its prognostic implications and to provide suitable assessment tools is compelling. *The complexity of measuring clinical complexity* was the title of an editorial published on the *Annals of Internal Medicine* in 2011.[16] Indeed the concept of complexity in Internal Medicine lacks a precise definition.[17] A Veterans Affairs working group defined complexity as requiring challenging clinical decision-making and care processes that are not routine or standard.[18] Complexity is the quality of being intricate and compound. It refers to the degree of complication of a system or of a system component, determined by such factors as the number and intricacy of interfaces, the number and intricacy of conditional branches, the degree of nesting, and the types of data structures.[19] According to these meanings, complexity in a patient involves the intricate entanglement of two or more systems (*e.g.,* body diseases, family socioeconomic

Table 1. What does *comorbidity* mean and which are the related implications?

Comorbidity means that more than one disease or condition is present in the same person at the same time.
Conditions described as comorbidities are often chronic or long-term conditions. Other ways to name comorbid conditions are coexisting or co-occurring conditions and sometimes also *multimorbidity* or *multiple chronic conditions*.
- *Comorbidity:* additional presence of a disease in relation to a specific clinically dominant *index* disease in an individual;
- *Multimorbidity:* presence of multiple diseases in an individual;
- *Clusters of diseases:* two or more co-occurring specific chronic diseases;
- *Burden of morbidity:* the overall impact of different diseases in an individual taking into account their severity.

And some other definitions:[3]
- *Trans-syndromal comorbidity*: represents the coexistence of two or more syndromes pathogenetically related to each other;
- *Trans-nosological comorbidity*: denotes the coexistence of two or more nosological units pathogenetically related to each other.

Classification
- *Counts* (a merely count of number/sum of diseases)
- *Concordant or Discordant**:[5]
- Concordant comorbidities:
- referred to diseases as parts of the same pathophysiologic risk profile and more likely to share the same management and are more likely to be the focus of the same disease management plan (for example, the triad of hypertension, diabetes and coronary artery disease)
- sharing common etiological factors
- if improvements in one risk area is likely to reduce risks elsewhere.
- Discordant comorbidities:
- referred to diseases that are not directly related in either pathogenesis or management and do not share an underlying predisposing factor, *e.g.* type 2 diabetes mellitus and asthma or diabetes and prostate cancer);
- on average we develop one new long-term condition (LCT) every 5 years from the age of 55
- treatment for one LTC may have no impact on other comorbidities
- in some cases, treatment options conflict *e.g.* the use of L-DOPA for Parkinsonism with history of psychosis

Evidence to describe multimorbidity is often incomplete
- Pressure for simplicity in data collection
- Time consuming tools
- Specificity/sensibility of assessment tools not optimal

Significance
- Clinical aspects, such as: interpreting symptoms, symptomatic *versus* asymptomatic chronic comorbidities/finding underlying/not overt/*iceberg* diseases
- Inappropriate performance/outcome metrics
- Modified risks of mortality
- Risk of poor mobility and health status
- Burden on resource utilization, on caregivers
- Multidimensional assessment need
- Need to know context to inform patient-centered care

Comorbidities and co-treatment may be critical in optimizing or worsening outcomes
- Comorbidities are never considered as a confounding factor in the evaluation of the outcomes in most of the clinical trials
- Decreased relevance of evidence-based medicine and clinical guidelines, with some implications in clinical accountability
- Judicious use and appropriate selection of medication therapies by the competent Internal Medicine doctor has to ensure safety in managing comorbidities, preventing exacerbations, and minimizing poly-pharmacy adverse drug reactions and drug-drug related interactions

Modified from Alexander, 2016.[4] *The nature and direction of the observed associations not always are fully explained by the concordant-discordant model.[5]

status, therapies) and how a disease may influence multiple systems.[20] In complexity, the interaction of multiple different factors in the same patient (social, medical, family, therapy, *etc*.) and its consequences have to be assessed in a multidimensional approach. Patient complexity cannot adequately be captured in measures focusing only on comorbid conditions,[21] but considering all potential interactions between several factors, such as between illnesses, multiple medications and treatments, multiple providers and tension between therapeutic goals. Several factors may contribute to the final quality of care.

The clustering disease tool

There has been very little research to date exploring the prevalence of particular combinations or clusters of chronic conditions. Almost all studies examining specific comorbidities do so from the perspective of a specific index disease rather than examining all co-occurring chronic conditions.[22,23] Most clinical guidelines address single diseases, often missing treatment of patients with multimorbidity and co-occurrence of multiple (chronic) diseases within one person. Clustering is the process of nosography grouping into meaningful associations with some index disease, so that the objects within a cluster have high similarity in comparison to one another, but are dissimilar to objects in other clusters.[24] The *disease clusters approach* could serve as a first priority setting towards the development of new multimorbidity guidelines, with the most frequently occurring diseases and combinations.[25] In elderly patients some associations are useful in identifying groups of those at risk of in-hospital adverse clinical events and death, according to disease clustering[26] (Table 2).

An example: the chronic heart failure

A paradigmatic example of some potential interactions between several medical conditions is specifically referred to chronic heart failure, one of the most prevalent disease in Internal Medicine wards.[27] This process has to consider all pharmacologic and managing options in a multidimensional assessment context[28] (Figure 1).

The *comorbidome* concept

Comorbidities influence not only the severity of the symptoms and the quality of life of individual patients, but also their prognosis, as risk of hospitalization and death. Adding comorbidity tools in the assessment of some index disease, for instance chronic obstructive pulmonary disease (COPD), is very useful for significantly improved outcome prediction.[29-32] Comorbidities are frequent in COPD and some of them could negatively influence survival. The *comorbidome* concepts was introduced as a useful representation of the prevalence and impact of comorbidities in hospitalized COPD patients: it is a graphic representation of the prevalence and strength of association to mortality constructed on the bases of a multivariate analysis of all the comorbidities that increase mortality.[33,34] Thus we have to consider that management of the complexity of multimorbidity could be useful in achieving a better quality of life and prognosis for patients.[35-37]

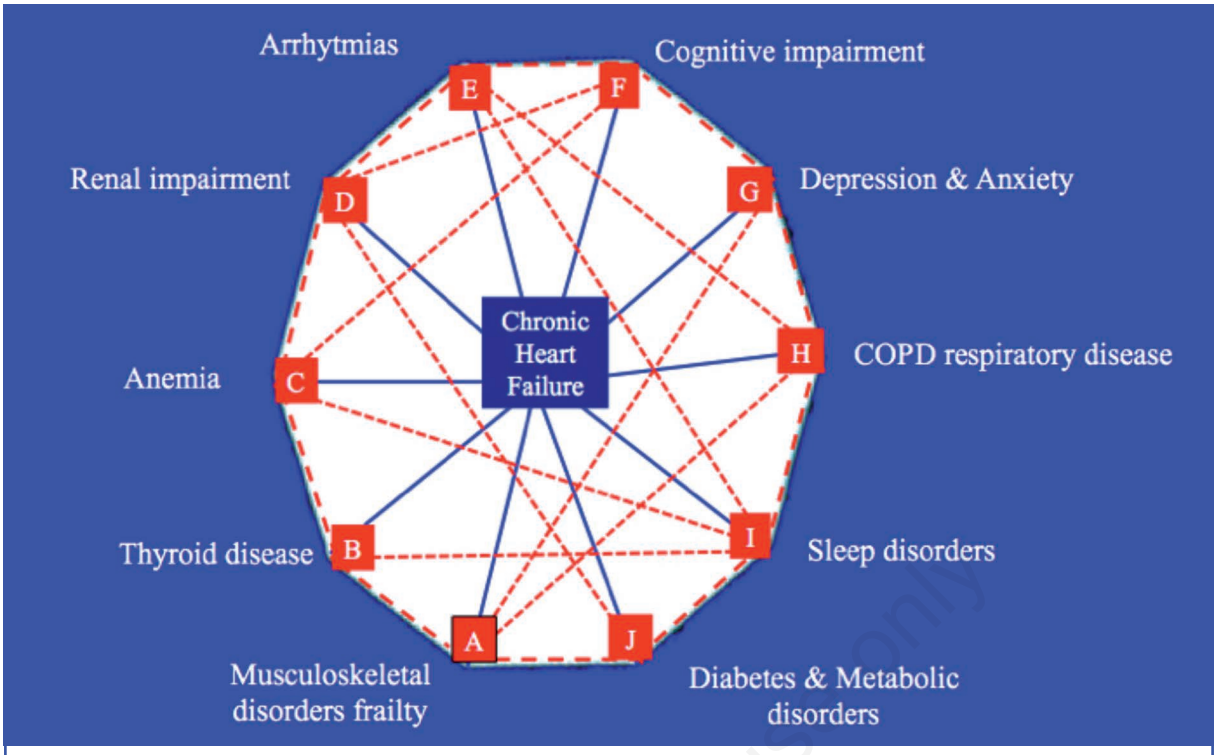
Frailty as a further factor for complexity

Frailty is a further factor that contributes to increasing complexity, with poor outcomes. In the REPOSI registry, enrolling 2841 patients aged 65 or older admitted to internal medicine and geriatric wards, four clusters were identified: i) the healthiest; ii) those with multimorbidity; iii) the functionally independent women with osteoporosis and arthritis; and iv) the functionally dependent oldest old patients with cognitive impairment. A significantly higher in-hospital mortality was found in Cluster II [odds ratio (OR)=2.27, 95% confidence interval (CI)=1.15-4.46] and Cluster IV (OR=5.15, 95% CI=2.58-10.26) and a higher 3-month mortality in Cluster II (OR=1.66, 95%

Table 2. Associations between pair of diseases and in-hospital outcome.

Pair of diseases		Adjusted (for age, gender and education) OR (95% CI)
Hypertension	Diabetes	1.7 (1.3-2.2)
	CVD	2.0 (1.4-2.7)
	Dyslipidemia	4.5 (2.9-6.8)
Chronic heart failure	AF	4.6 (3.1-7.0)
	COPD	2.2 (1.5-3.5)
	CRF	2.4 (1.5-3.9)
Coronary heart disease	COPD	1.7 (1.2-2.2)
Diabetes	CHD	2.5 (1.9-3.3)
	CVD	1.7 (1.2-2.3)
	Dyslipidemia	2.0 (1.4-2.9)
	CRF	2.3 (1.6-3.3)
Liver cirrhosis	Anemia	2.9 (1.7-4.2)
	Malignancy	2.9 (1.8-4.7)
Thyroid dysfunction	AF	2.5 (1.6-3.8)
Chronic renal failure	Anemia	2.6 (1.7-4.1)
Gastric diseases	Intestinal diseases	3.1 (1.9-5.0)

OR, odds ratio; CI, confidence interval; CVD, cerebrovascular disease; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CHD coronary heart disease; CRF, chronic renal failure.



Note: Ten most common conditions were identified as several combinations. There are multiple points of interaction between these factors that inevitably lead to high levels of patient complexity, with subsequent prognostic implications and premature mortality without therapeutic intervention. The blue lines indicate the direct and concordant relationship between CHF and single comorbidities; the dotted red lines indicate the relations between CHF and some discordant co-morbidities.

Figure legend:

A: Musculoskeletal system diseases, frailty
Muscle wasting reduces exercise capacity and muscle strength, and a reduced skeletal muscle mass is greatly associated with advanced chronic HF.
In patients with HF, the presence of frailty is associated with significantly worse outcomes. The lack of physiologic reserve in frail patients allows acute stressors to cause rapid functional deterioration and debility. In addition to a two-fold increase in mortality risk, frail HF patients experience greater rates of hospitalization, endure longer lengths of stay, have increased risk of rehospitalization.

B: Thyroid disorders
Both hyperthyroidism and hypothyroidism can be primary or contributory causes of HF.

C: Anemia
There are potential beneficial effects of anemia treatment with erythropoietic agents on exercise capacity and quality of life in CHF patients. Further studies are needed to determine the optimal threshold for initiation of treatment and target hemoglobin during therapy.

D: Acute/chronic kidney dysfunction
A loss of glomerular filtration rate, as in acute kidney injury (AKI) or chronic kidney disease (CKD), independently predicts mortality and accelerates the overall progression of cardiovascular disease and HF.
The coexistence of heart failure and renal dysfunction constitutes the *cardiorenal syndrome* which is increasingly recognized as a marker of poor prognosis.

E: Atrial and ventricular arrhythmias
Both atrial and ventricular arrhythmias are common in patients with heart failure (HF) and cardiomyopathy, regardless of underlying etiology. They can cause symptoms, morbidity (such as stroke due to embolization with atrial fibrillation) and may be responsible for sudden cardiac death (SCD).

F: Cognitive dysfunction/dementia
It may be important to carry out a screening for cognitive dysfunction as it may influence HF patients' prognosis and their ability to perform self-care, *e.g.* make lifestyle changes, adhere to medical treatment and monitor, evaluate and treat symptoms of deterioration.

G: Anxiety/depression
The prevalence of depression and anxiety is high in both chronic obstructive pulmonary disease (8-80% depression; 6-74% anxiety) and chronic heart failure (10-60% depression; 11-45% anxiety).

H: COPD and pulmonary diseases
Chronic obstructive pulmonary disease (COPD) and heart failure are different conditions. But both can make you short of breath when you do something physical, like exercise, climbing stairs, or walking for a long distance.

I: Sleep disorders
Sleep-disordered breathing, short sleep time, and low sleep quality are frequently reported by patients with heart failure (HF). Sleep-disordered breathing, which includes obstructive sleep apnea (OSA) and central sleep apnea (CSA), is common in patients with HF.

J: Diabetes mellitus, metabolic syndrome and dyslipidemia
Diabetes not only increases the risk of HF, but also accelerates its occurrence. The prognosis for patients with heart failure is worse in those with diabetes than in those without diabetes.
Metabolic syndrome [insulin resistance, hypertension (high blood pressure), cholesterol abnormalities, and augmented risk of clotting] increases the risk of heart failure burden being an important risk factor.

Figure 1. Chronic heart failure and some of its potential interactions with and between several conditions.

CI=1.13-2.44) and Cluster IV (OR=1.86, 95% CI=1.15-3.00) than in Cluster I. Some quantified most prevalent medical conditions, as cluster analysis according to main anchoring conditions in the elderly, are reported in Table 3. In this series, frailty of the elderly is mostly associated with mental health conditions, diabetes, obesity, stroke, cardiac disease, kidney disease, skin ulcers and dementia.[38]

In a complex patient the clinical decision-making is very complex

In complex patients, health professionals are required to make decisions with multiple foci, such as diagnosis, intervention, interaction and evaluation, in several setting of care and in dynamic contexts, with different skills between professionals decision makers, with multiple variables involved, often in situations of uncertainty, reduced relevance of clinical guidelines and lack of evidence. Patterns from overall multimorbidity analyses have potential implications for clinical decision-making and patient management, such as drug-disease, disease-disease, and drug-drug interactions, and in clinical practice and research.[39] Socioeconomic factors may contribute to the outcome of chronic diseases and quality of life[40] (Figure 2).

Conclusions

In order to redesign our health care systems to more effectively care for complex patients, we need a better handle on exactly who they are.[21]

Simply counting the number of comorbid conditions does not really capture whether a patient is complex.[9,17,21] In patients with multimorbidity, there is a co-occurrence of diseases beyond chance, which clinicians have to take into account in their daily practice.[41] In complex patients a multidimensional approach in identifying and addressing the best care is needed[6] (Table 4).

Different multimorbidity patterns share some diagnosis groups, influence each other and overlap in a large part of the population. In recognizing the full complexity of multimorbidity we might improve our

Table 3. Subgroups of elderly complex patients identified through cluster analysis.

Anchoring conditions	Most prevalent medical conditions in cluster (%)
Chronic pain with mental conditions	Chronic pain (99.8) Mental health conditions (69.2) Obesity (47.2)
Diabetes with obesity and mental health conditions	Diabetes (100) Obesity (86) Mental health conditions (44)
Kidney disease with diabetes and obesity	Kidney disease (99.9) Diabetes (51.2) Obesity (50.9)
Frailty related in the elderly	Mental health conditions (45.4) Diabetes (39.7) Obesity (37.7) Stroke (35.2) Cardiac disease (30.7) Kidney disease (26.7) Skin ulcers (26.4) Dementia (25.8)
Cardiac disease and obesity	Cardiac disease (100) Obesity (54.2) Diabetes (39.4)
COPD with obesity and mental health conditions	COPD (100) Obesity (60.4) Mental health conditions (55.4)
Gastrointestinal bleeding with obesity and mental health conditions	Gastrointestinal bleeding (100) Obesity (42.1) Mental health disorders (34.9)
Abdominal and orthopedic surgeries with obesity	Abdominal surgery (66.7) Obesity (60.8) Orthopedic surgery (48.0)
Cancer with obesity and mental health conditions	Cancer (100) Obesity (47.7) Mental health disorders (33.9)

COPD, chronic obstructive pulmonary disease.

ability to predict needs and achieve possible benefits for elderly patients who suffer from multimorbidity.[42] Knowledge of the pathophysiologic interactions between comorbidities increases the understanding of their development and contributes to strategies for prevention or improved treatment.[43] To study the multimorbidity pattern can be useful to improve clinical management of each specific subgroup of patients showing a particular multimorbidity pattern.[44] Higher prevalence in older adults of specific combinations of diseases could help us in the development of clinical practice guidelines (CPGs) that account for the simultaneous presence of multiple chronic conditions. In order to assure CPGs more *patient centered* rather than *disease driven*, guideline developers should include information on elderly patients with comorbidities and their interrelatedness.[45] Studying disease combinations could serve as a first priority setting towards the development of multimorbidity guidelines,[46] starting with the diseases with the highest observed prevalence rates and those with potential interacting treatment plans.[47] In the decision-making process it is imperative that, in addition to understanding the immediate clinical problems, we are able to explicit all the contextual factors that have to be taken into account for the best outcome of care. Cluster clinical analysis methods are appropriate to detect subgroups of entities, but many problems are associated with

Table 4. Strategies to address comorbidity among Internal Medicine patients.

- Improving the *evidence-based care* to make treatment and management decision for those with comorbidity, by implementing further clinical trials in the *real world* including complex patients
- Improving the *measurement* of comorbidity
- Improving *integration* and *coordination* of care
- Preventing the occurrence of *new comorbidities* and limiting *exacerbations* of existing conditions
- Developing *better tools* to be used by clinicians for the prognosis
- Facilitating *skill development* for clinicians
- Building further *research* collaborations

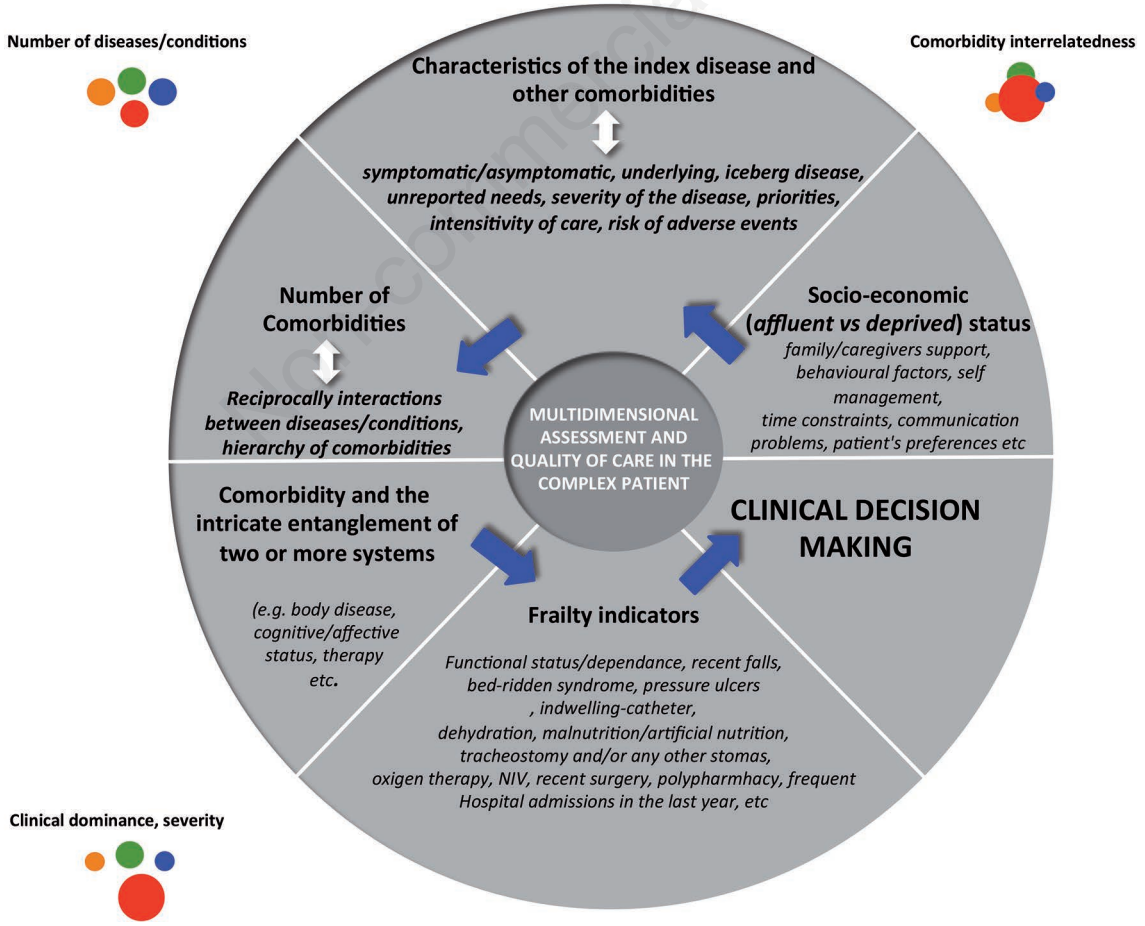


Figure 2. In a complex patient the clinical decision-making is very difficult.

clustering techniques, *e.g.*, the scaling of variables, the choice of clustering method, or the testing of the validity of the clusters found.[48] Cluster clinical analysis could be leveraged in developing better interventions targeted to improve health outcomes in subgroups of patients whose optimal care management is less well defined.[49] Further studies and research are needed in this area.[50]

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