PERSONALISED MANAGEMENT IN COPD: BEYOND GOLD REDUCTIONISM

Emiel F.M. Wouters, MD, PhD, FERS

Lung Center CIRO+

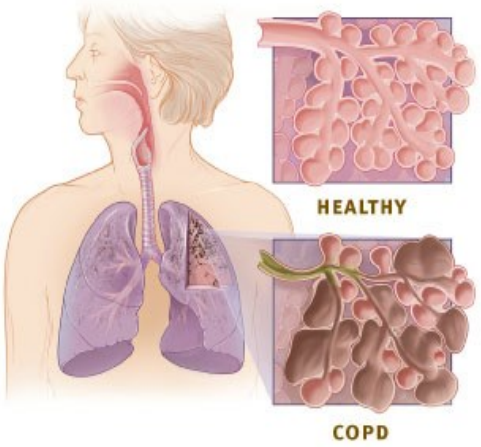
Dept. of Respiratory Medicine, Maastricht University Medical Center

The Netherlands

COPD: Definition

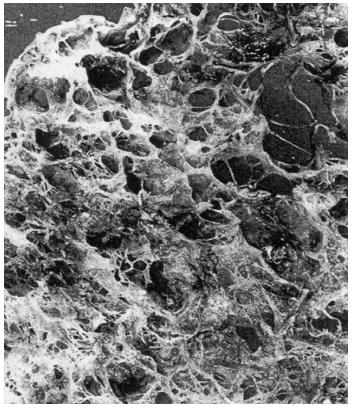
2001

- A disease state
- Airflow limitation is usually progressive
- Associated with an abnormal inflammatory response to the lungs



COPD

Small airway remodeling and obstruction



Alveolar destruction: loss of lung recoil

Airflow limitation

Decline in FEV1

Lung function trajectory

Tantucci & Modina, Int J COPD 2012

COPD definition: an organ centered approach

Reductionist approach

Illness is the resultant of a malfunction of its parts: airways

⇩

Knowable modification of known malfunctions result in linear, predictable results

⇩

Evidence based care

Wilson et al, BMJ 2001

COPD: Definition

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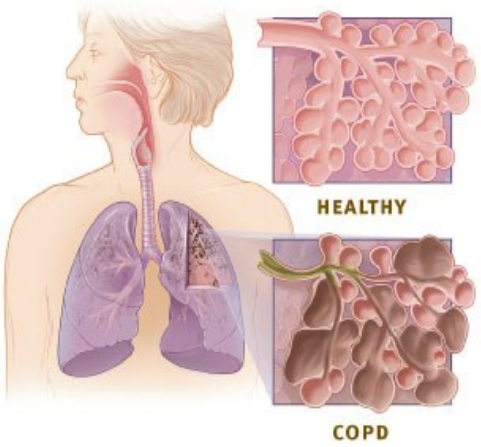
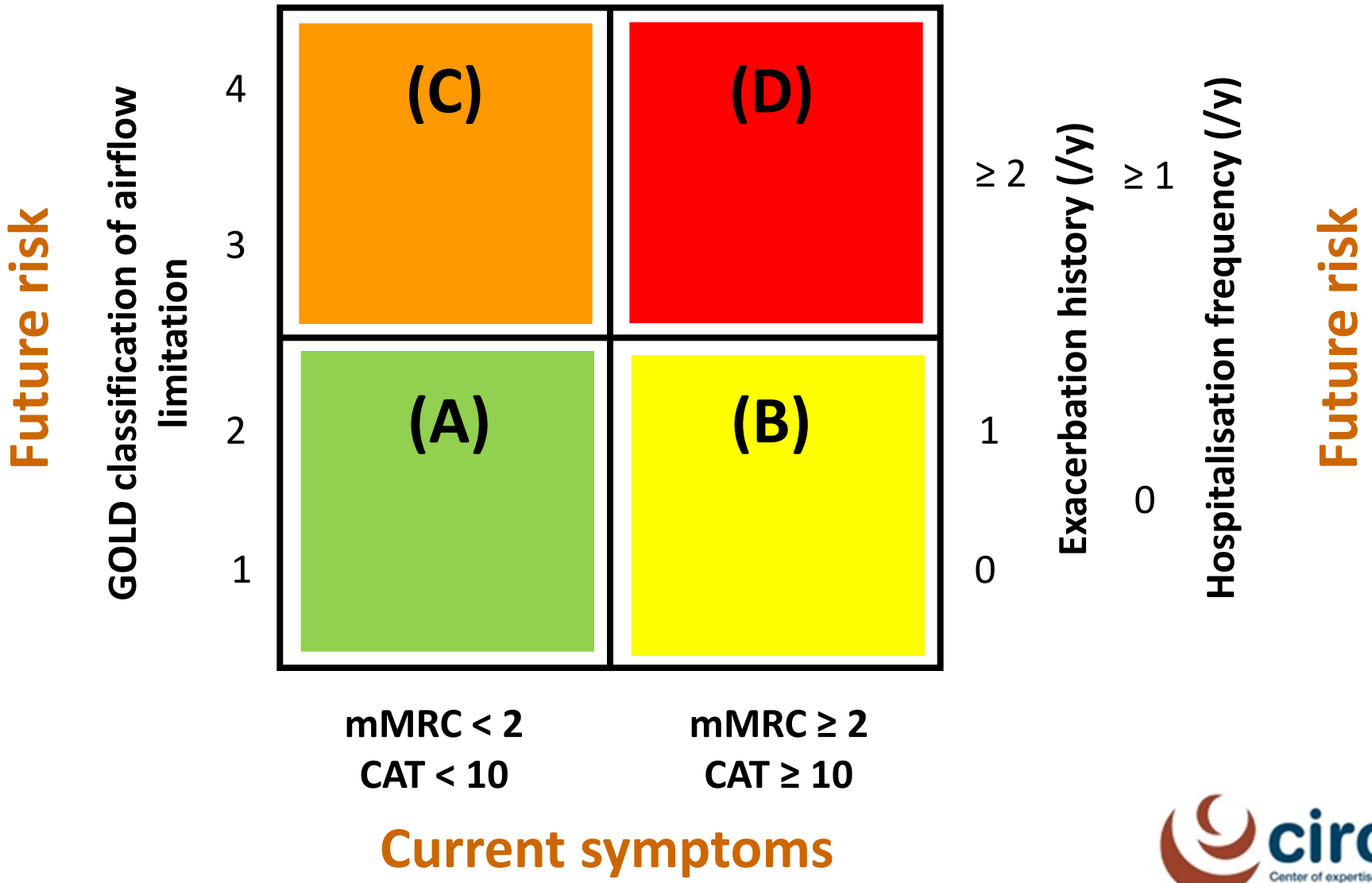


2015

- A common preventable and treatable disease
- Persistent airflow limitation that is usually progressive
- Associated with an enhanced chronic inflammatory response in the airways and the lung
- Exacerbations and comorbidities contribute to the overall severity in individual patients
- Added new knowledge

COPD GOLD classification: reductionist approach



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Problems with GOLD strategy

- Too simple: translates 3 dimensions into 4 categories
- Too complex: need a computer app to classify patients
- Lack of coherence: definitions of symptoms and exacerbations

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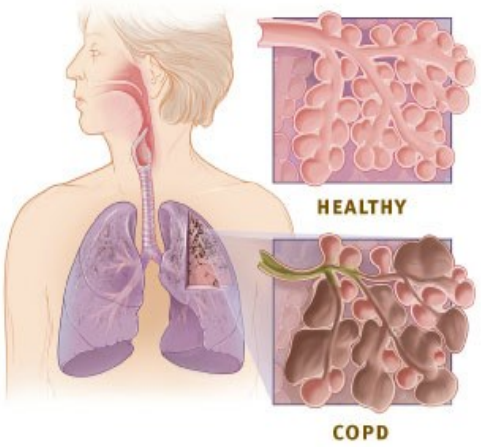

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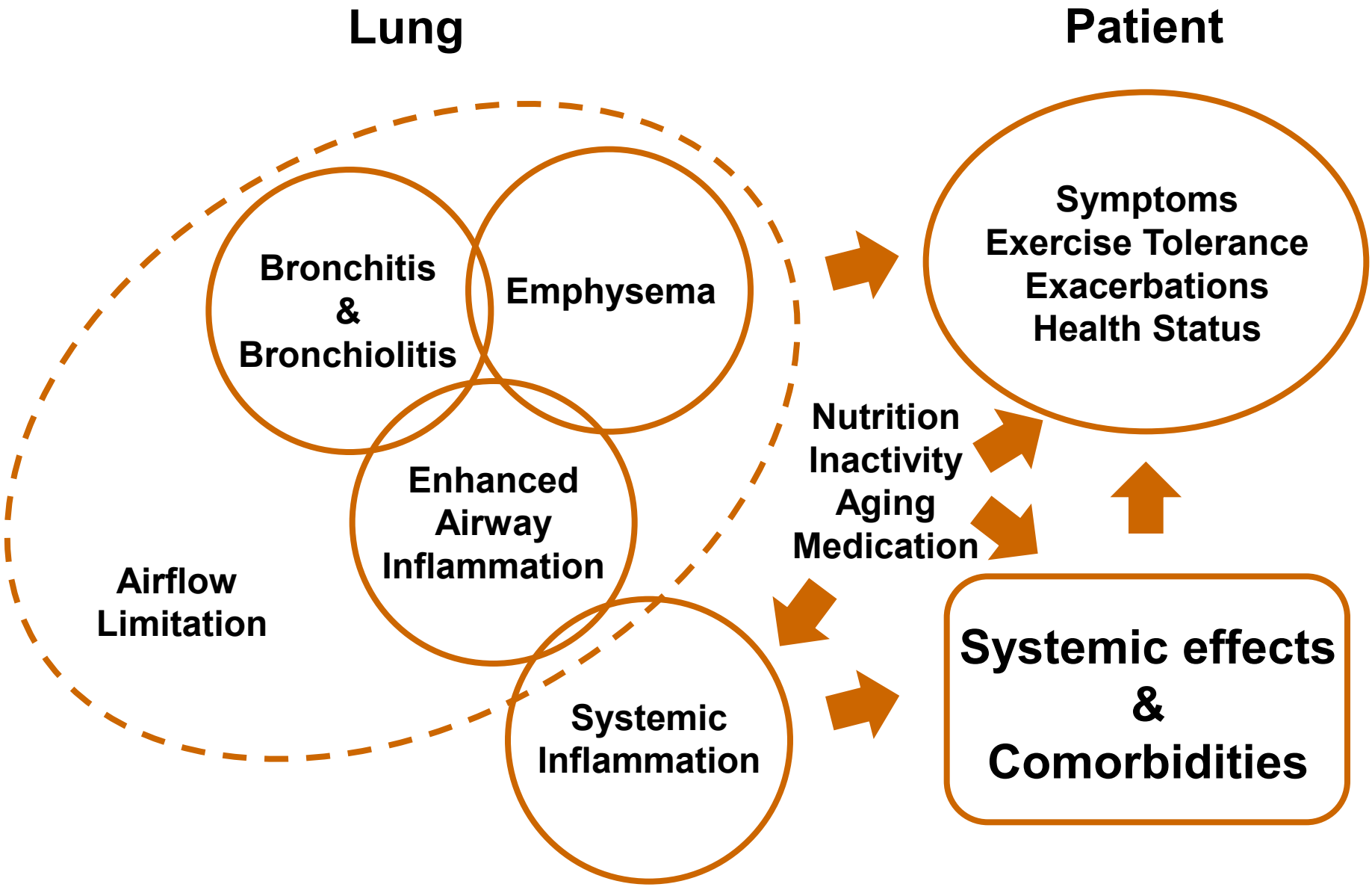
Treatable: an evidence-based approach

LINEARITY

- proportionality: output changes have a straight line relationship with input
- superposition: effects of combined action of different inputs can be figured out and predicted by dissecting the input-output relationships of the individual components

Jayasinghe S, 2011

COPD as a heterogenous and multi-component disease



Heterogeneity of COPD

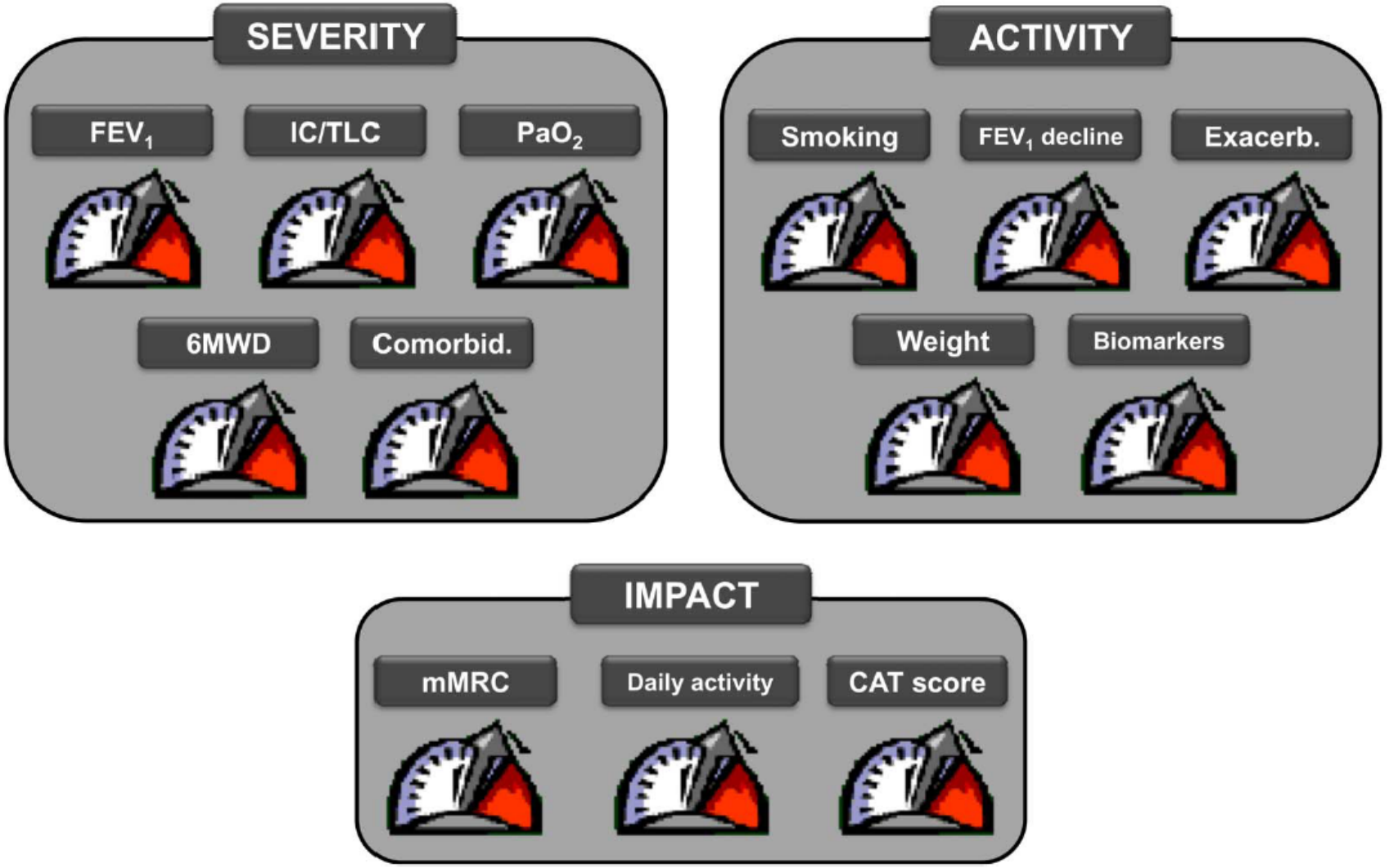
$$COPD \overset{?}{=} \sum_{n=1} (COPD_n)$$

- Diagnostic labels are affixed onto non-specific symptoms and signs and some physiological abnormalities

- New knowledge is “added” to the original disease definition

NO RISKS
WELCOME TO THE BORING CONTROL FREAK SHOW
SMART PHONE ATTACHED TO HAND!
HE CONTROLS EVERY THING
ALIVE
ELIMINATES ALL UNCERNTAINTIES!

COPD control panel: towards personalised medicine



Agusti & MacNee, Thorax 2012

COPD control panel: towards personalised medicine

Agusti & MacNee, Thorax 2012

ISAAC NEWTON
Father of the clockwork universe

P4 Medicine

PREDICT PREVENT PERSONALIZE PARTICIPATE

'A medicine that focuses on the integrated diagnosis, and treatment and prevention of disease in individual patients'

Hwang et al, Mol Syst Biol 2009

Hood et al, Science 2004

Precision medicine

"Treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations"

Precision, personalised and individualised medicine are ofter used interchangeably

Jameson & Longo, NEJM 2015

Precision medicine

Patients

- clearer understanding of their disease,
  its prognosis and the most effective treatment

Physicians and health systems

- share interest of patients
- balance individual patient needs with management
  of overall health care utilisation

Payers

- new diagnostic tests and drugs will drive up health
  care expenditures

Pharmaceutical industry

- new drug opportunities

Jameson & Longo, NEJM 2015

From organ to a patient centered approach

Reductionist approach

Illness is the resultant of a malfunction of its parts

↓

Knowable modification of known malfunctions result in linear, predictable results

↓

Evidence base care

Complex adaptive systems

Illness is the result from complex, dynamic and unique interactions between different components of the overall system

↓

Holistic or *integrated* approach

↓

Acceptance of unpredictibility

Wilson et al, BMJ 2001

Moving out of the comfort zone

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Chronic Obstructive Pulmonary Disease Phenotypes

The Future of COPD

MeiLan K. Han[1], Alvar Agusti[3], Peter M. Calverley[4], Bartolome R. Celli[5], Gerard Criner[6], Jeffrey L. Curtis[1,7], Leonardo M. Fabbri[8], Jonathan G. Goldin[9], Paul W. Jones[10], William MacNee[11], Barry J. Make[12], Klaus F. Rabe[13], Stephen I. Rennard[14], Frank C. Sciurba[15], Edwin K. Silverman[5,16], Jørgen Vestbo[17], George R. Washko[5], Emiel F. M. Wouters[18], and Fernando J. Martinez[2]

- Classification of patients into distinct subgroups that provide prognostic information and allow us to better determine appropriate therapy that alters clinically meaningful outcomes.
- Selection of a uniform group of patients and assess the most important outcome measures in that group for therapeutic clinical trials.

→ Robust disease classification

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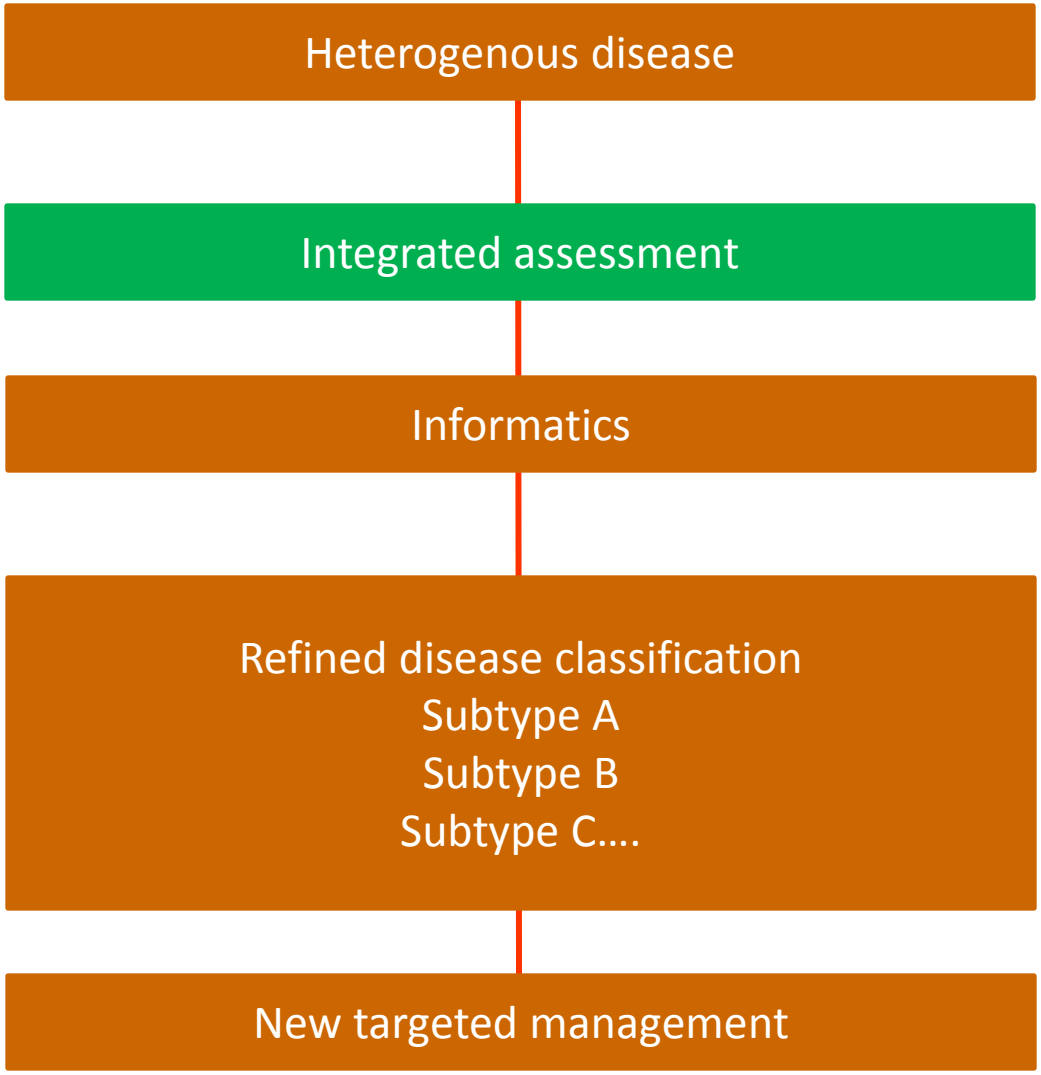
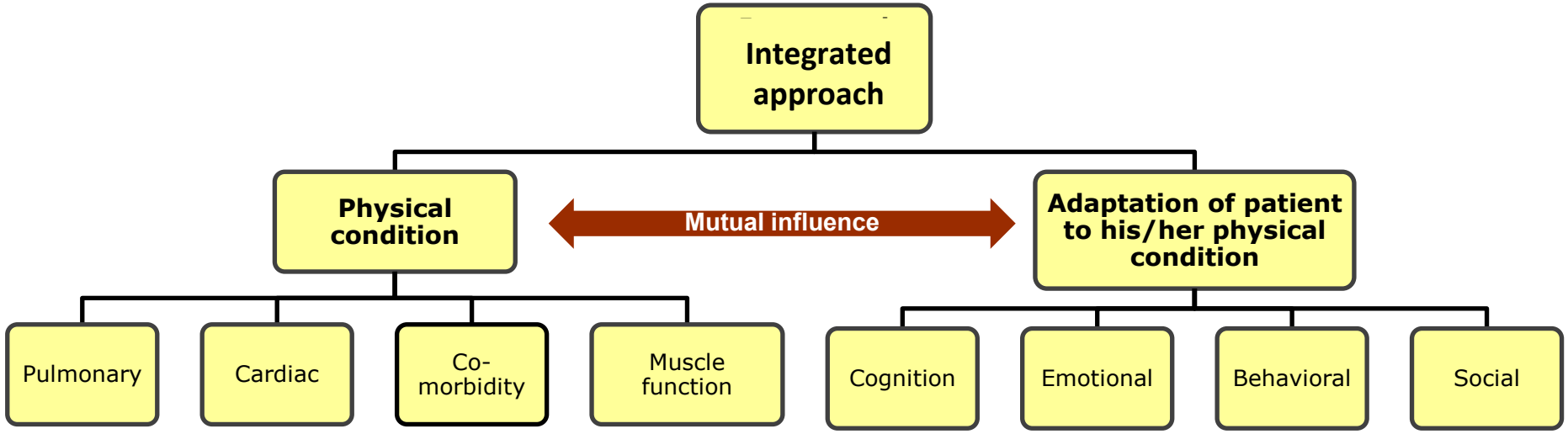
Scope of personalised medicine



Jameson & Longo, NEJM 2015

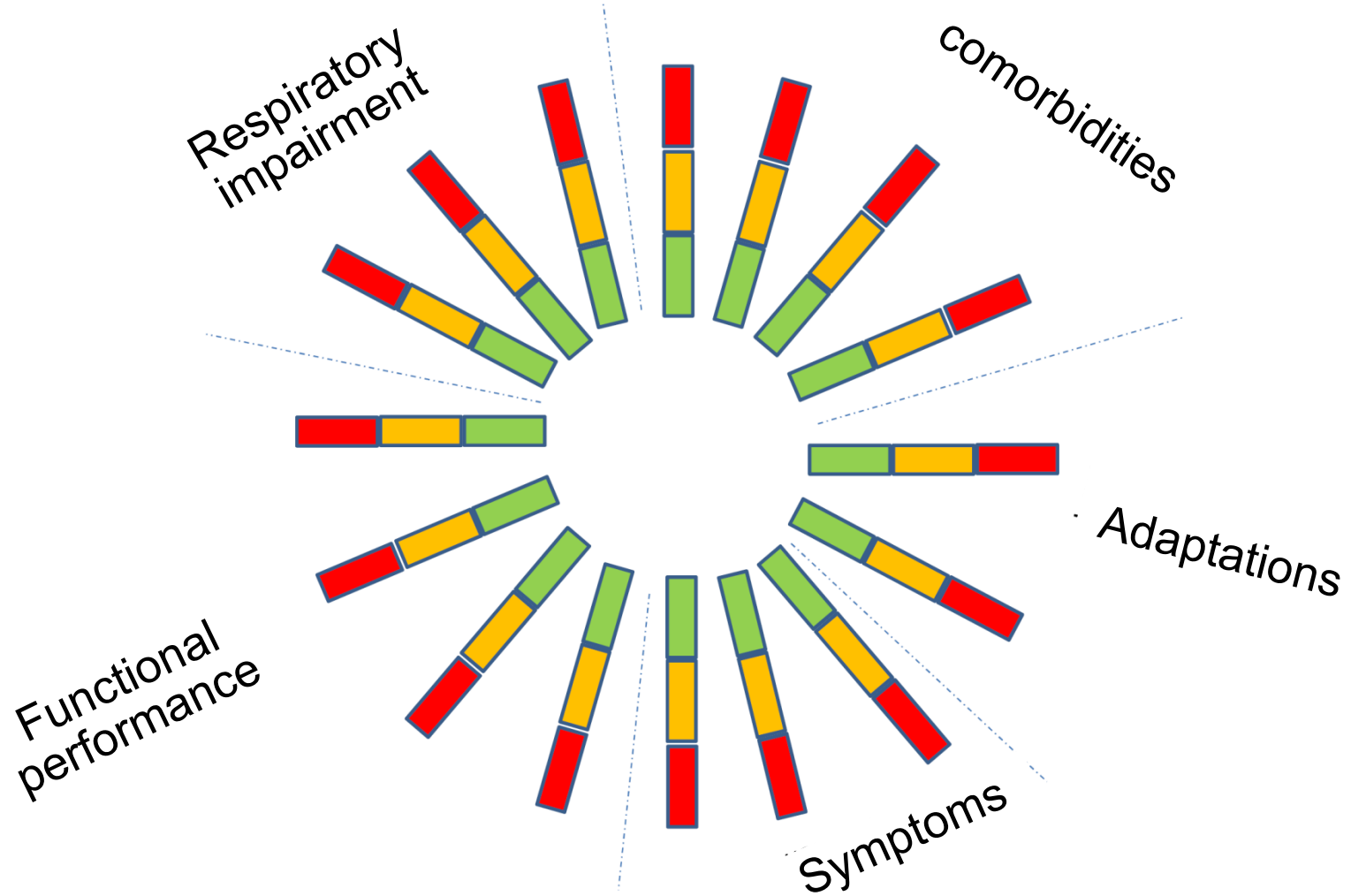
hoofdingang

Mapping COPD characteristics



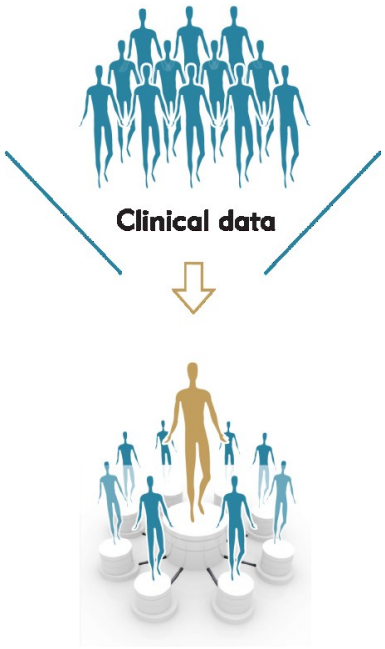
Augustin et al, Clinical Research in Pulmonology, 2015

Integrated assessment

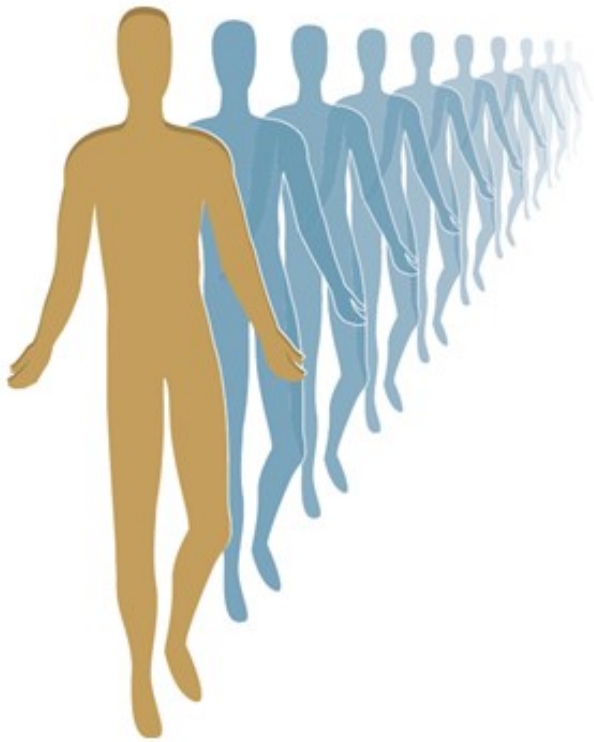


Augustin et al, Clinical Research in Pulmonology, 2015

From an organ to a patient centered approach



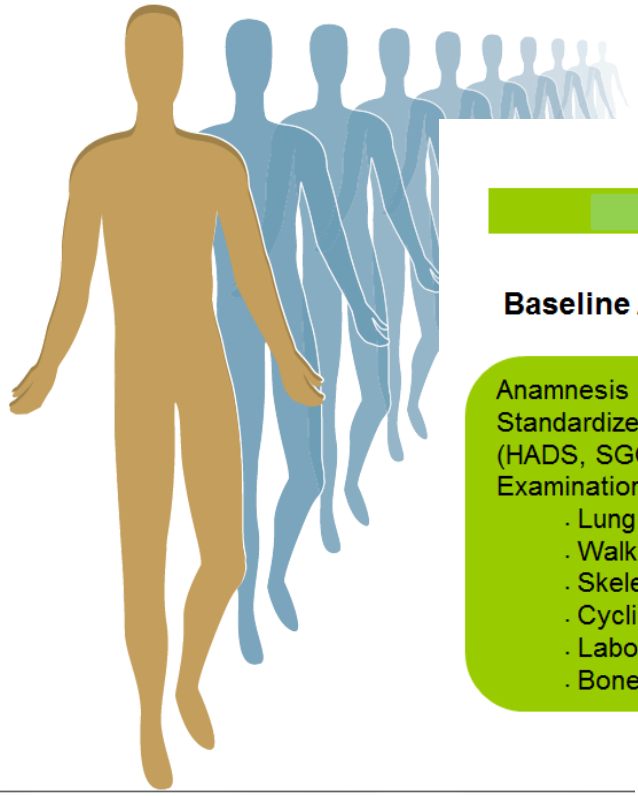
- Improve patient care



TREAT THE INDIVIDUAL WITH THE KNOWLEDGE OF ALL

Rational of the CIRO+ Integrated Knowledge System (IKS)

PATIENT STRATIFICATION
TREAT THE INDIVIDUAL WITH THE KNOWLEDGE OF ALL



Leveraging the CIRO+ Clinical Process

Start → 3-4 months → **End**

Baseline Assessment

Anamnesis
Standardized questionaries (HADS, SGQRT)
Examinations/Tests
- Lung function
- Walking test
- Skeletal muscle function
- Cycling tests
- Laboratory
- Bone density (DEXA)

Rehabilitation

Treatment plan

Outcome Assessment

Standardized questionaries (HADS, SGQRT)
Examinations/Tests
- Lung function
- Walking test
- Skeletal muscle function
- Cycling tests
- Laboratory
- Bone density (DEXA)

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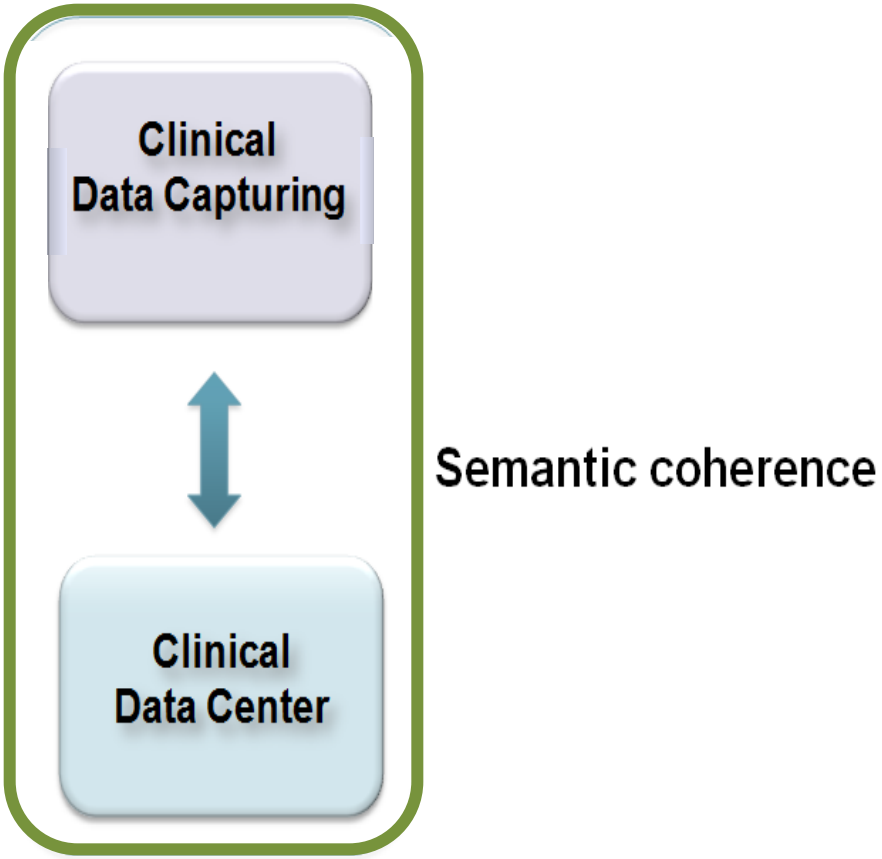
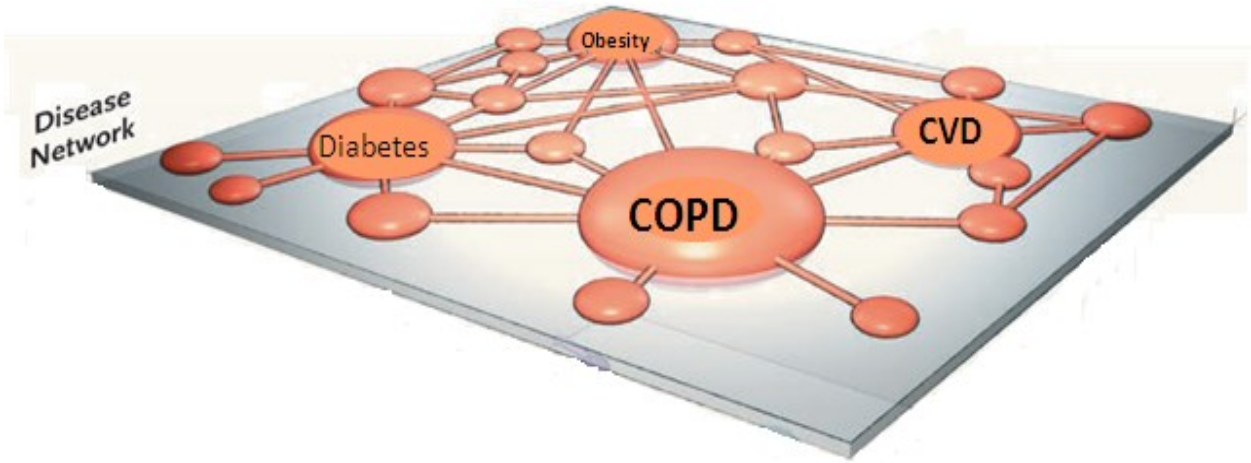
CIRO+
Integrated Knowledge System (IKS)



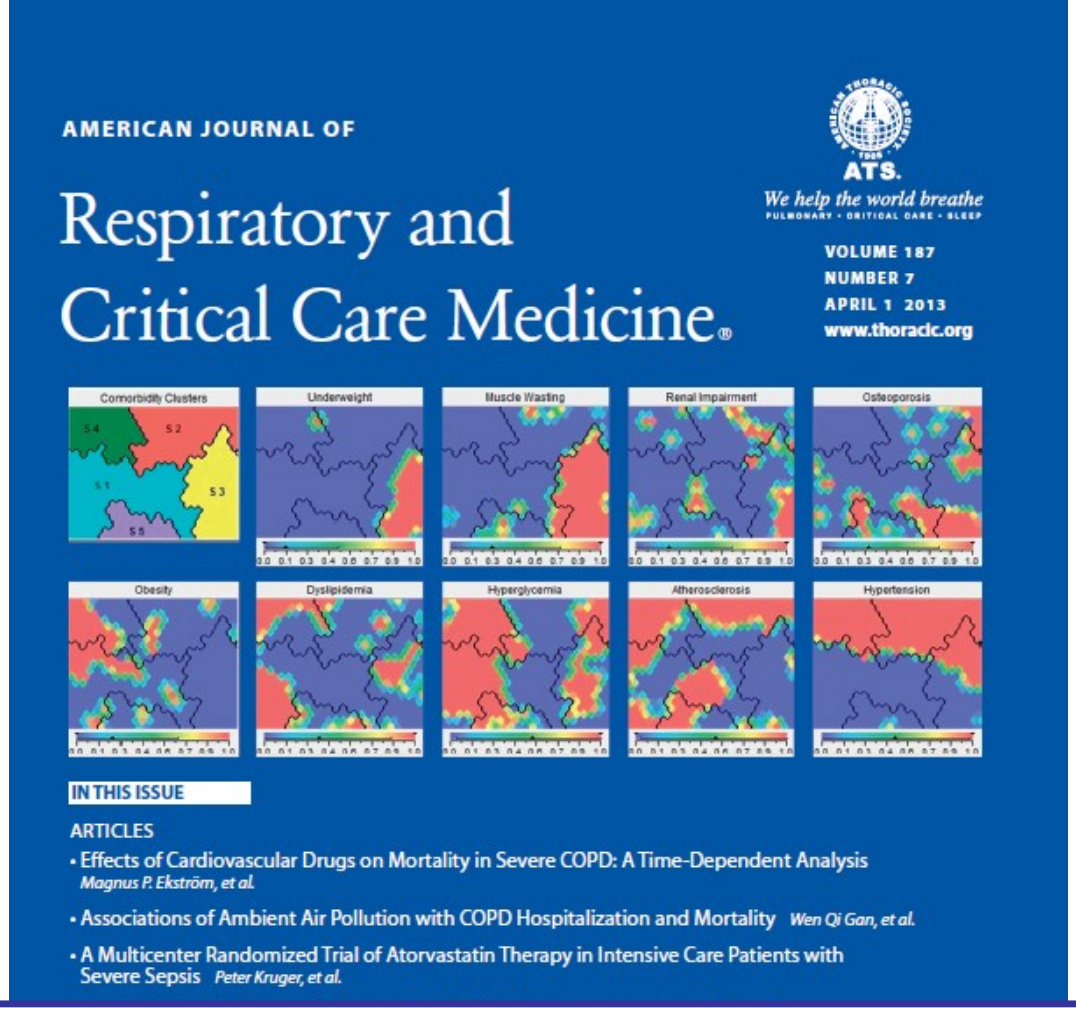
Data Center and Capturing – CIRO+ IKS core

Network medicine



- Chronic disease
- Comorbidities
- Extra-pulmonary features

Adapted from: Barabasi et al, New Engl J Med 2007



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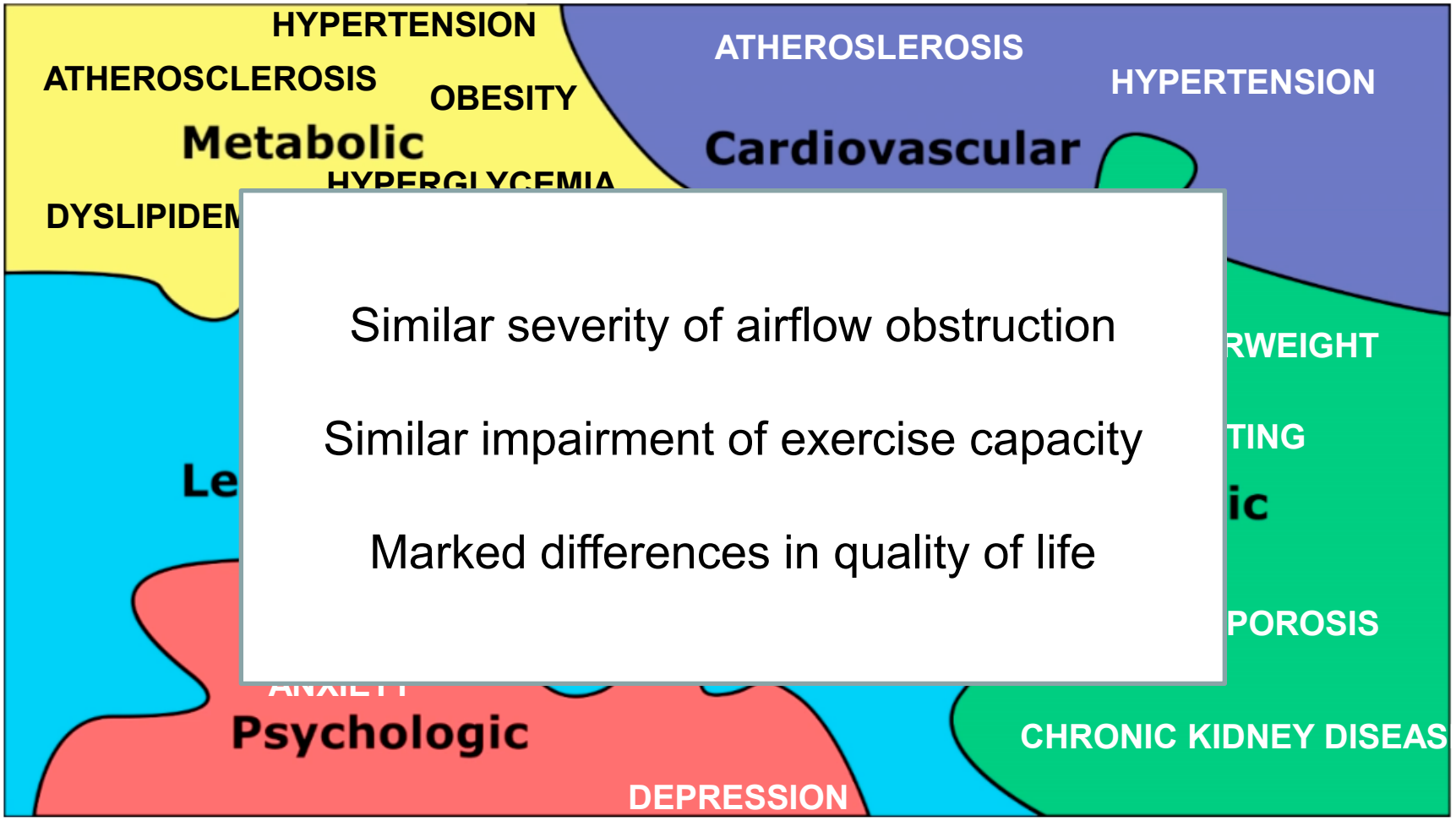
Clusters of Comorbidities Based on Validated Objective Measurements and Systemic Inflammation in Patients with Chronic Obstructive Pulmonary Disease

Lowie E. G. W. Vanfleteren[1,2], Martijn A. Spruit[1], Miriam Groenen[1], Swetlana Gaffron[3], Vanessa P. M. van Empel[1,4], Piet L. B. Bruijnzeel[5], Erica P. A. Rutten[1], Jos Op 't Roodt[6], Emiel F. M. Wouters[1,2], and Frits M. E. Franssen[1,2]

Identification of five clusters of comorbidities



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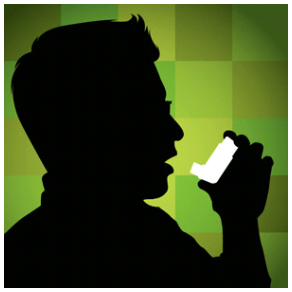
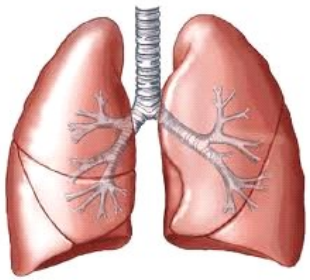
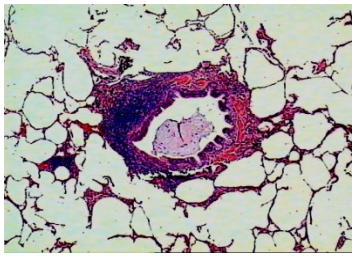
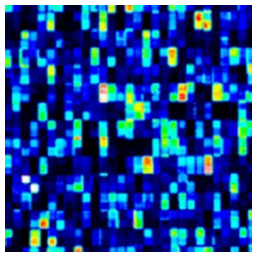





The patient

Lung function

Airway histology

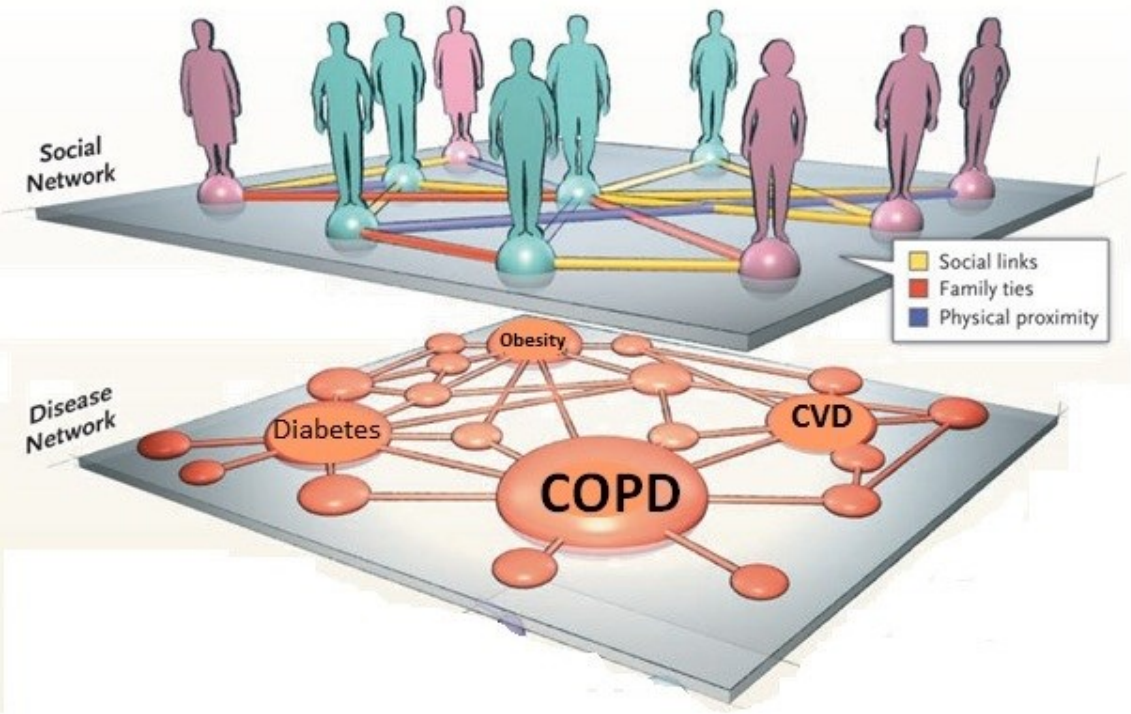
Gene expression

Genes

respiratory disease phenotyping

Quality of life
Co-morbidity
Symptoms
Obstruction
BHR
Remodeling
Inflammation
Immunity
Microbiome
Metabolome
Proteome
Transcriptome
Epigenetics
Genetics

Wheelock et al, and U-BIOPRED Study. Eur Respir J 2013



- Psychological aspects
- Healthy life style (activity)
- Autonomy and participation
- Social networks

- Chronic disease
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Precision medicine

Patients

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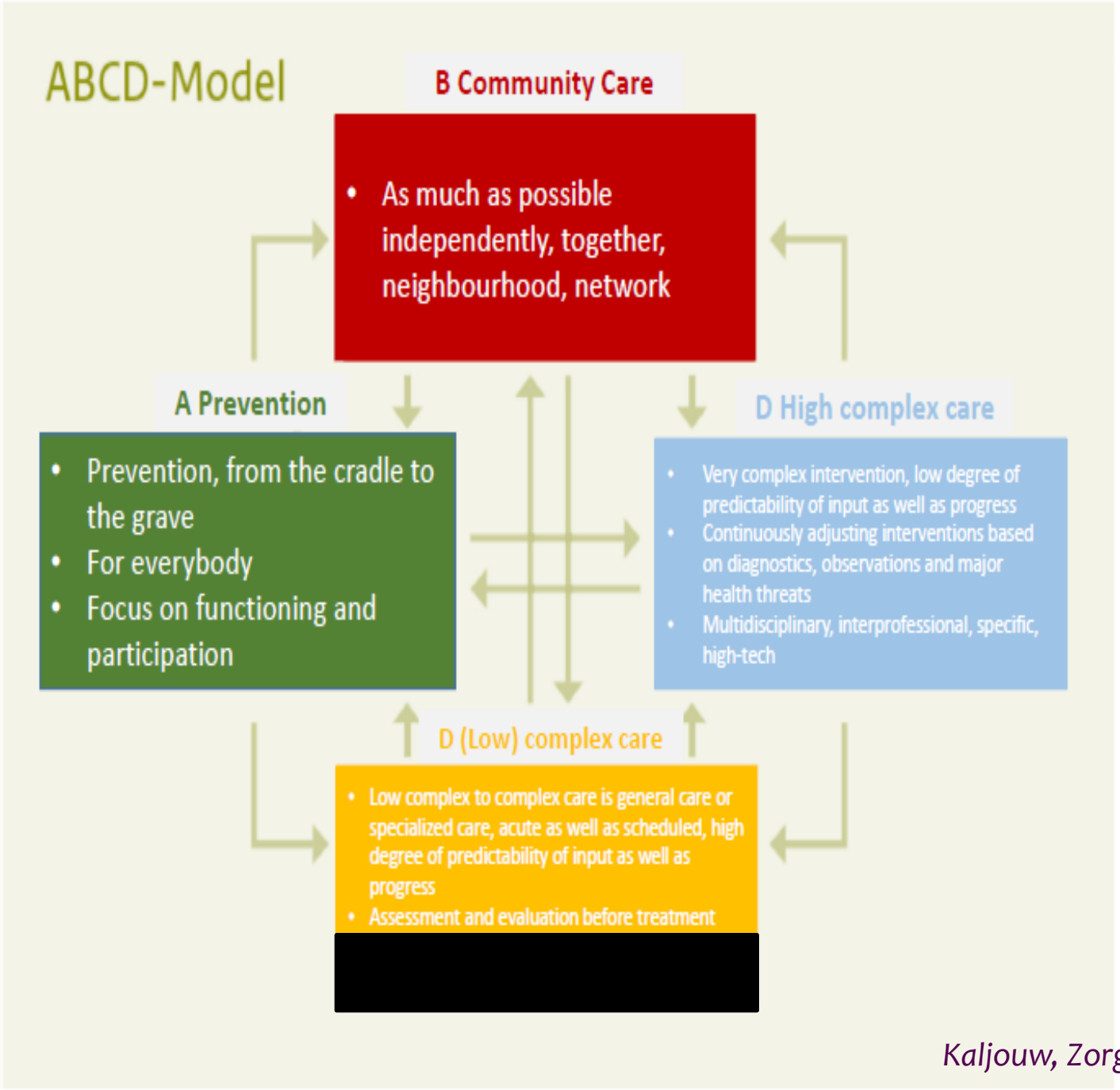
Payers

- new diagnostic tests and drugs will drive up health care expenditures

Pharmaceutical industry

- new drug opportunities

Jameson & Longo, NEJM 2015



Kaljouw, Zorginstituut 2015

16TLRM0191_Wouters
S2213-2600(16)30045-5
Linked to DOI:10.1016/S2213-2600(15)00524-X

COPD health-care delivery: a holistic and dynamic approach needed

In the *Lancet Respiratory Medicine*, Alvar Agusti proposed that patients with chronic obstructive pulmonary disease (COPD) can be divided into two categories: simple versus complex COPD.[2] The author expressed hope that this proposal will stimulate further discussion about how to best organise health-care delivery for this highly prevalent disease.

In Agusti's algorithm, patients with simple COPD would be in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) A group, and all other patients (GOLD B–D) would be labelled complex. This classification refers to the latest GOLD revision, and that illnesses arise from dynamic interaction within and between these systems. In this recognition, health can be re-established through a holistic approach that builds on subtle emergent forces within the overall system[3]. In this personalised approach, interdisciplinary management programmes need to address the physical, emotional, and social functioning of the patient. As such, complexity is not a static condition and is non-linear; differential responses can be obtained attenuating the level of individual complexity[4] and allowing the patient to control their own wellbeing.

For health care in general and chronic diseases particularly, a document of the National Health Care Institute in the Netherlands proposed a so-called ABCD model comprised of prevention (A), community care (B),

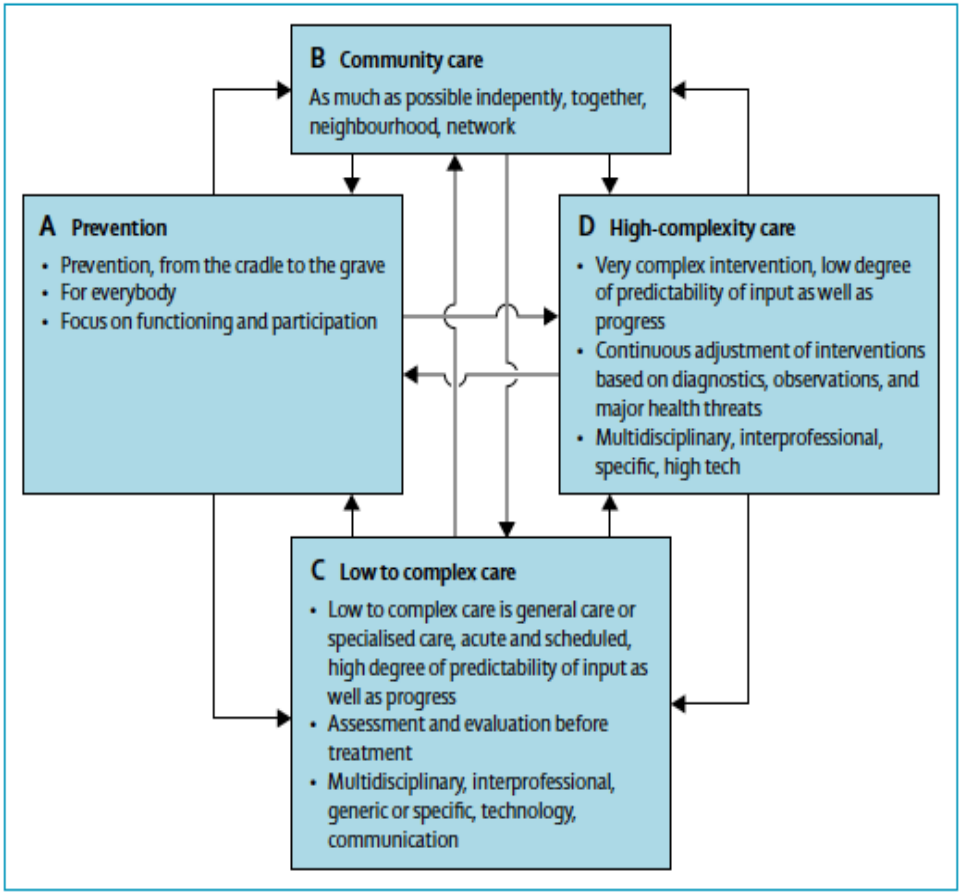
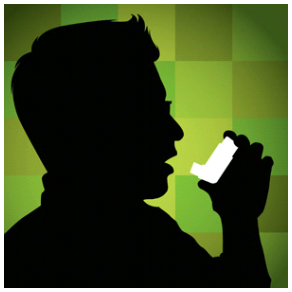
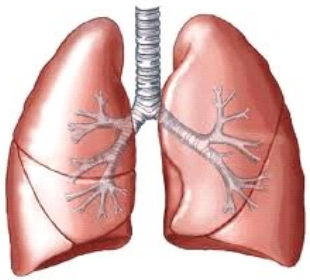
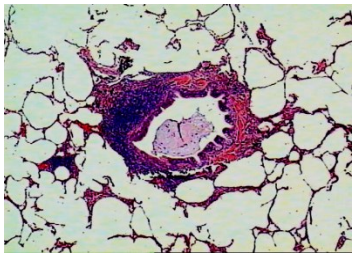
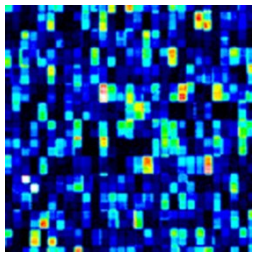


Figure: **ABCD model for patient categorisation**
Reproduced by permission of the Care Institute Netherlands/(Dutch) National Healthcare Institute.

*Emiel F M Wouters, Ingrid M L Augustin

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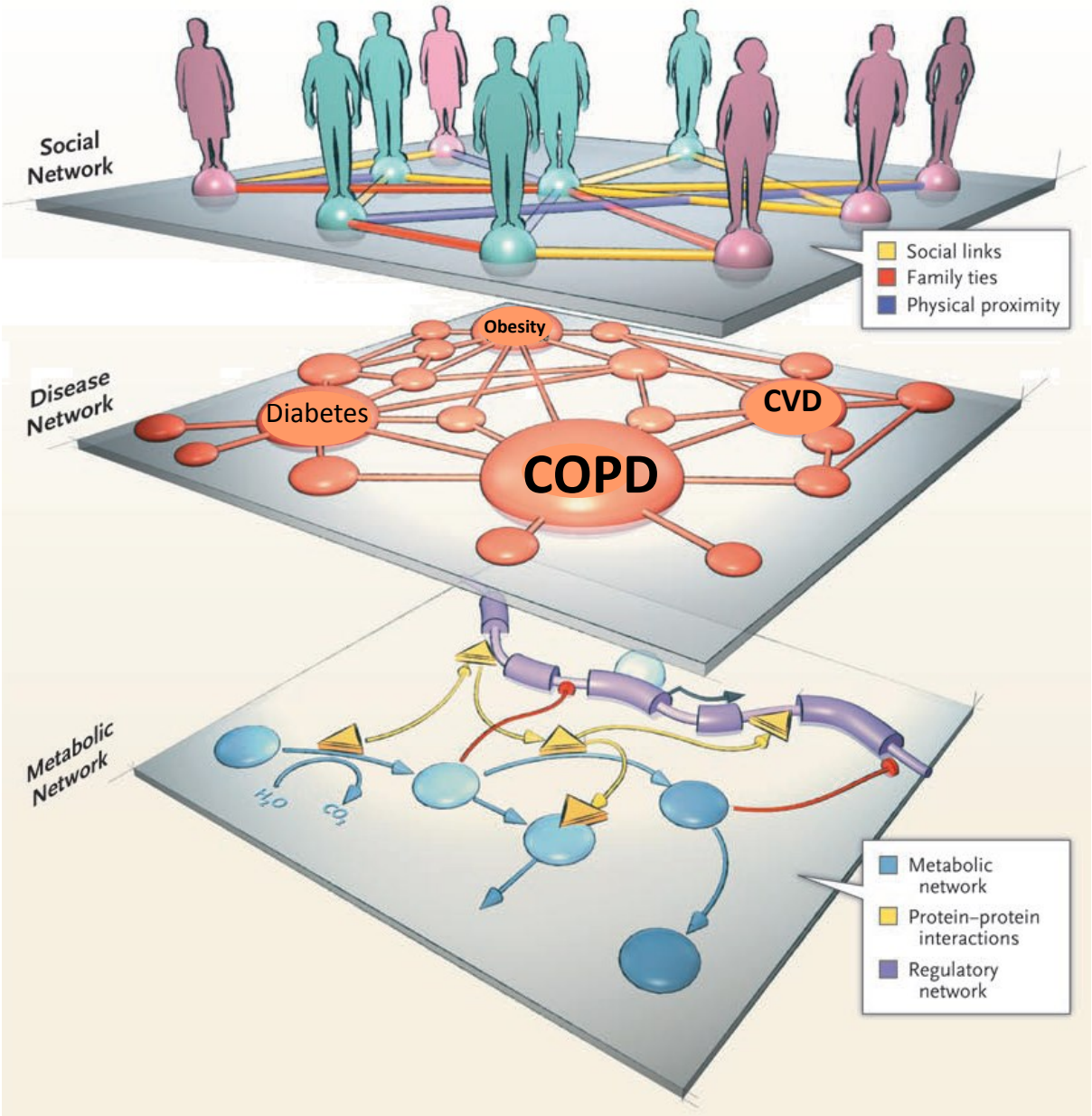

- Psychological aspects
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- Social networks

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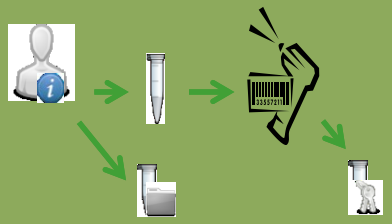
- Inflammation
- Oxidant/anti-oxidant imbalance
- Ageing
- Metabolic changes
- Immunology

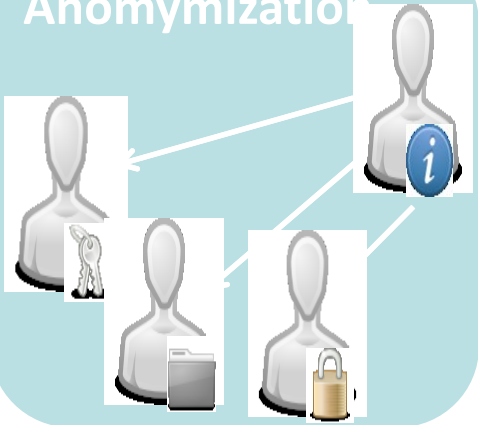
Barabasi et al, New Engl J Med 2007

CIRO+ Clinic



Full data capture

Anomymization

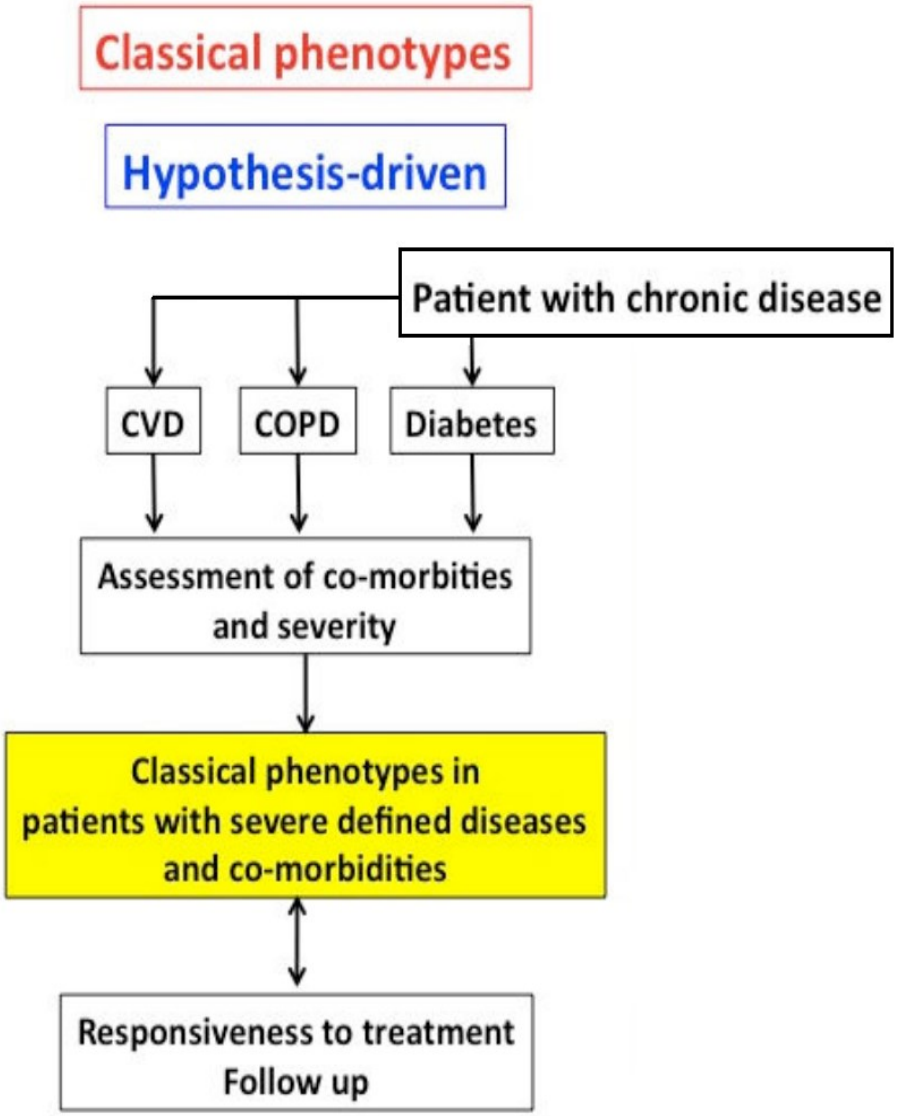


Data Center

IKS core

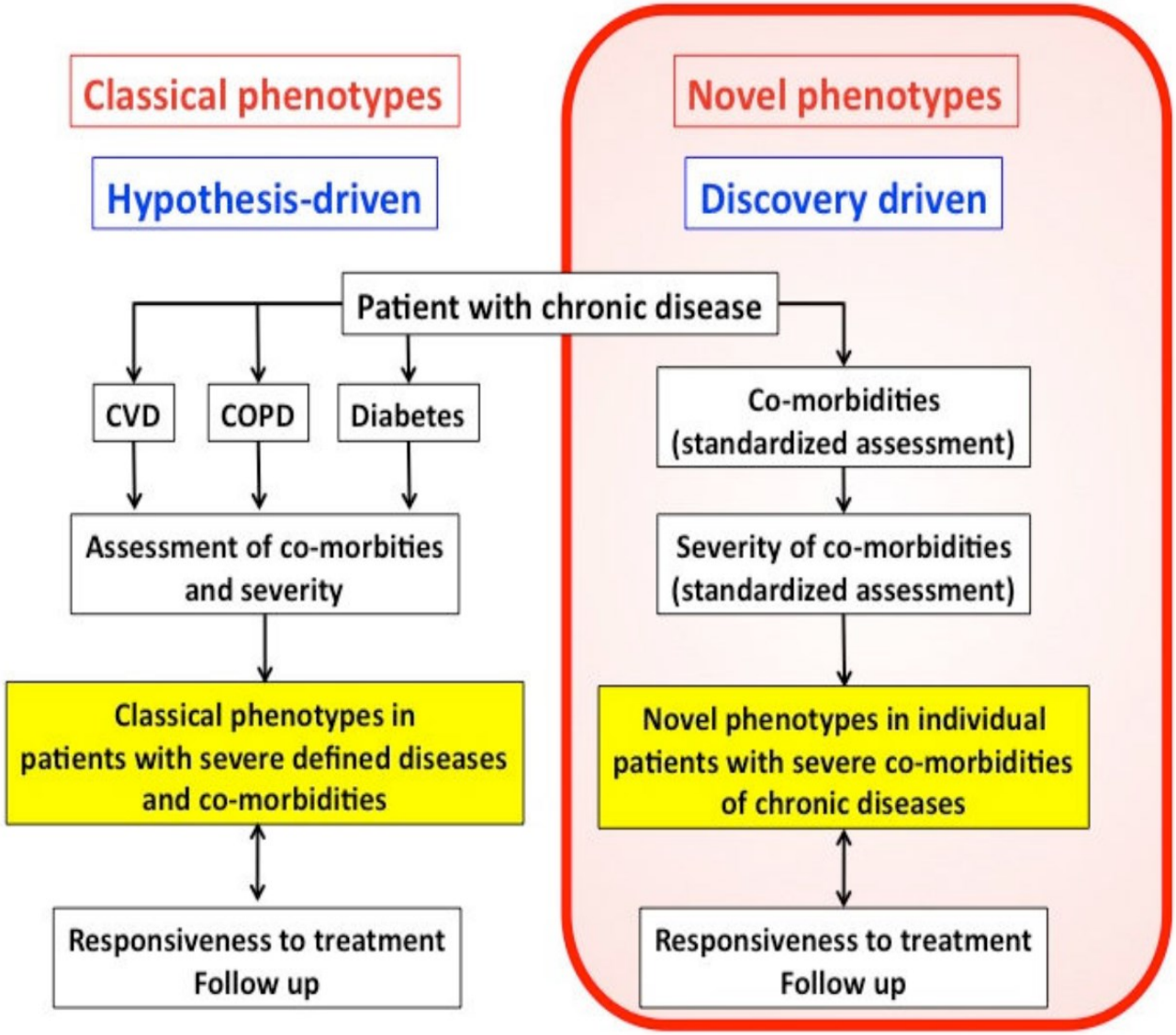
External Biobank

Addressing the complexity of chronic diseases



Bousquet et al, Genome Med 2011

Addressing the complexity of chronic diseases



Bousquet et al, Genome Med 2011

Patient stratification

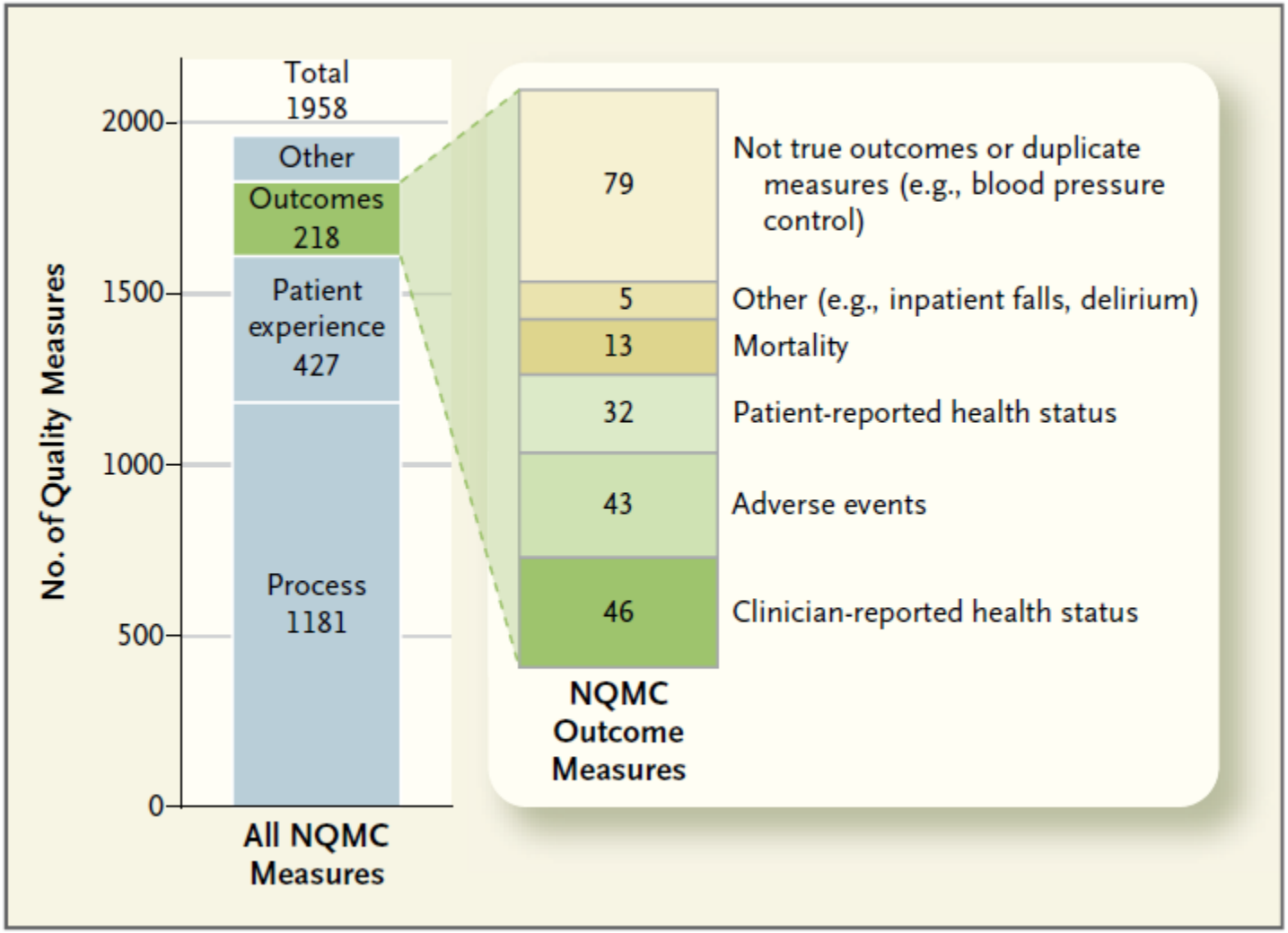
The Right Management

For The Right Patient

At The Right Time

For The Right Outcome

Categories of quality measures NQMC



Porter et al, NEJM 2016

ICHOM standardized outcome sets

- In health care “quality” is defined as compliance with evidence-based practice guidelines.
- Limited outcomes measurement has been led by specialty societies and does not encompass the whole cycle of care.
- Efforts at outcomes measurement have overwhelmingly focused on clinical status and left out functional status.
- Outcomes measurement has been slowed dramatically by the “let a thousand flowers bloom” approach.

Porter et al, NEJM 2016

An Official ATS/ERS Statement: Key concepts and advances in PR

Health status
- *SGRQ*
- *CRQ*
- *CAT*
- *NCSI*
- *SOLQ*
- *MRF-28*
- *SF-36*
- *EQ-5D*

Depression/anxiety
- *HADS*
- *CES-D*

Dyspnea
- *mMRC*
- *BDI*
- *SOBQ*

Exercise performance
- *6MWT*
- *ISWT/ESWT*
- *CPET*
- *CWRT*

Physical activity
- *Diaries / questionnaires*
- *Step counters*
- *Accelerometers*

Muscle strength
- *Lower-imb muscle strength*
- *Respiratory muscle strength*

Fatigue
- *FACIT fatigue*
- *MFI*
- *CIS*

Problematic ADL
- *MRADL Scale*
- *PFSDQ*
- *LCADL*
- *COPM*

Self-efficacy
- CSES

COPD knowledge
- *LINQ*
- *BCKQ*

Others
- *Comorbidities*
- *Body composition*
- *Exacerbation*
- *Readmission*
- *Survival*

Spruit et al, AJRCCM 2013

An Official ATS/ERS Statement: Key concepts and advances in PR

Health status
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- *CRQ*
- *CAT*
- *NCSI*
- *SOLQ*
- *MRF-28*
- *SF-36*
- *EQ-5D*

Depression/anxiety
- *HADS*
- *CES-D*

Dyspnea
- *mMRC*
- *BDI*
- *SOBQ*

Exercise performance
- *6MWT*
- *ISWT/ESWT*
- *CPET*
- *CWRT*

Physical activity
- *Diaries / questionnaires*
- *Step counters*
- *Accelerometers*

Muscle strength
- *Lower-imb muscle strength*
- *Respiratory muscle strength*

Fatigue
- *FACIT fatigue*
- *MFI*
- *CIS*

Problematic ADL
- *MRADL Scale*
- *PFSDQ*
- *LCADL*
- *COPM*

Self-efficacy
- CSES

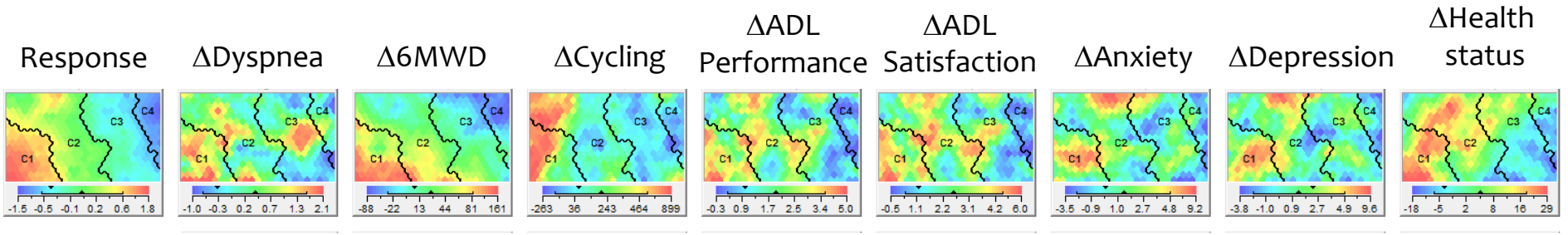
COPD knowledge
- *LINQ*
- *BCKQ*

Others
- *Comorbidities*
- *Body composition*
- *Exacerbation*
- *Readmission*
- *Survival*

Spruit et al, AJRCCM 2013

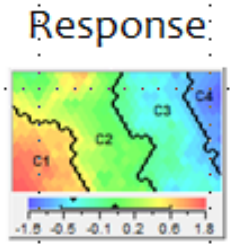
Response profiling

N=2068 patients with COPD



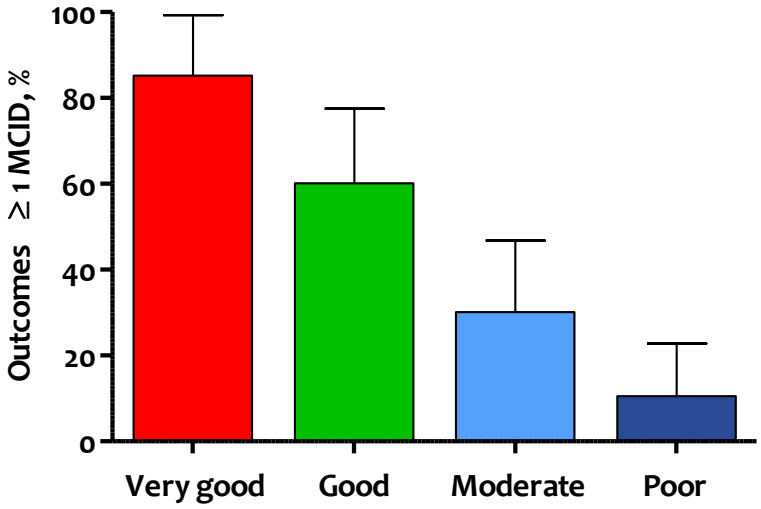
1. Differential response
2. Multidimensional outcome
3. Identification of clusters very good, good, moderate and poor responders

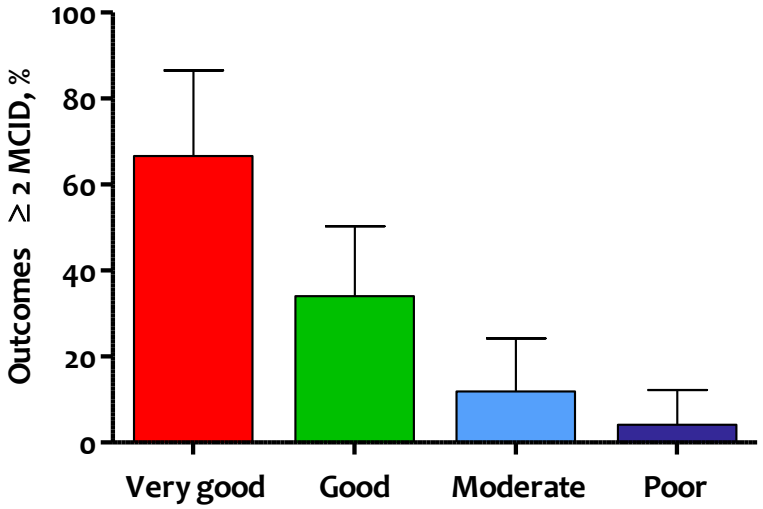
Spruit et al, ERJ 2015



Response profiling

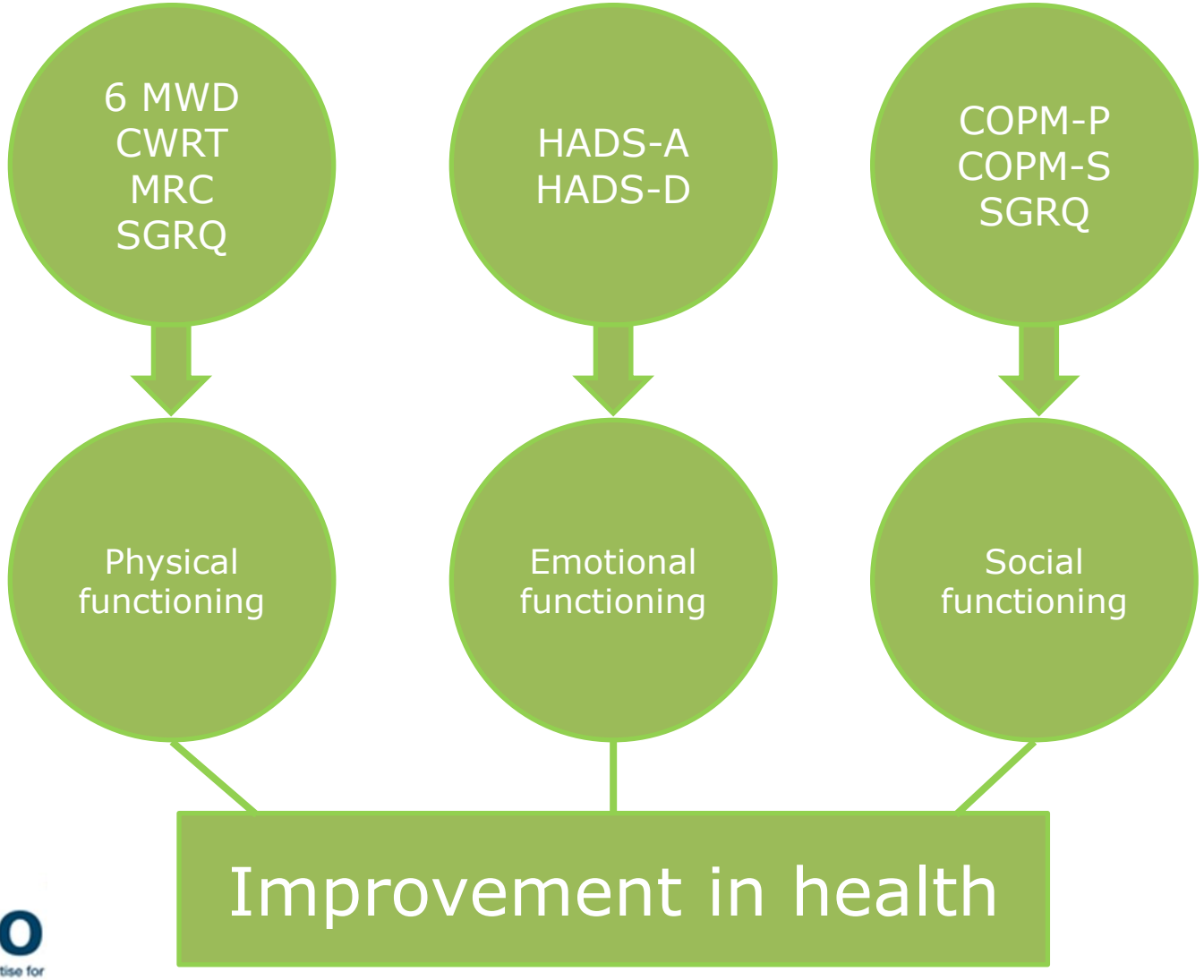
N=2068 patients with COPD





Spruit et al, ERJ 2015

Differential response to pulmonary rehabilitation



ciro
Center of expertise for chronic organ failure

Spruit et al, ERJ 2015

Conclusions

1. Current classification of human diseases as COPD is still based on Oslerian diagnostic labels.
2. Personalised medicine: moving from a reductionist approach to illness as the result of complex, dynamic and unique interactions.
3. CIRO+ Integrated Knowledge System (IKS): treat the individual with the knowledge of all:

   - comorbidity clusters

   - patient profiles: balancing individual patient needs with management of overall health care utilization.
4. CIRO+ IKS: systematic outcomes measurement as the sine qua non of value improvement

chronic
asthma
health
healthcare
lungs
concept
coughing
medical
male
disease
smoker
death
medicine

disease
copd
pulmonary
bronchitis
cancer
coughing
obstructive
cell
oxygen
chronic
illness
medical

respiratory
breathing
smoking
respiration
smoker
disease
death
bronchitis
cancer
medicine

illness
infection
lungs
medicine
oxygen
emphysema
health
pulmonary
respiratory
cancer
breathing
male
medical
chronic