System Medicine Approaches for the Definition of Complex Phenotypes in Chronic Diseases and Ageing. From Concept to Implementation and Policies

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Abstract: Chronic diseases are diseases of long duration and slow progression. Major NCDs (cardiovascular diseases, cancer, chronic respiratory diseases, diabetes, rheumatologic diseases and mental health) represent the predominant health problem of the Century. The prevention and control of NCDs are the priority of the World Health Organization 2008 Action Plan, the United Nations 2010 Resolution and the European Union 2010 Council. The novel trend for the management of NCDs is evolving towards integrative, holistic approaches. NCDs are intertwined with ageing. The European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) has prioritised NCDs. To tackle them in their totality in order to reduce their burden and societal impact, it is proposed that NCDs could be considered as a single expression of disease with different risk factors and entities. An innovative integrated health system built around systems medicine and strategic partnerships is proposed to combat NCDs. It includes (i) understanding the social, economic, environmental, genetic determinants, molecular and cellular mechanisms underlying NCDs; (ii) primary care and practice-based interprofessional collaboration; (iii) carefully phenotyped patients; (iv) development of unbiased and accurate biomarkers for co-morbidities, severity and follow up of patients; (v) socio-economic science; (vi) development of guidelines; (vii) training; and (viii) policy decisions. The results could be applicable to all countries and adapted to local needs, economy and health systems. This paper reviews the complexity of NCDs intertwined with ageing. It gives an overview of the problem and proposes two practical examples of system medicine applied (MeDALL) to NCD co-morbidities (MACVIA-LR).

Keywords: Chronic disease, co-morbidities, health system, systems medicine, patient, active and healthy ageing, MeDALL, MACVIA-LR.

INTRODUCTION

Chronic diseases are diseases of long duration and generally slow progression. They include the four major Non-Communicable Diseases (NCDs) listed by WHO [1]: cardiovascular disease, cancer, chronic respiratory diseases and diabetes, and other NCDs such as mental disorders and disabilities such as skeletomuscular diseases [2]. As survival rates and durations have improved, chronic diseases also include communicable diseases such as HIV/AIDS and genetic disorders such as cystic fibrosis. In the present paper the term "chronic disease" will refer to NCDs [3 , 4-6] (Fig. **1**).

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NCDs represent the major global health problem of the 21st century [3]. They are the world's leading cause of disease burden and mortality [1] and are increasing [7]. NCDs are a major cause of poverty and hinder economic development [8, 9]. Prevention and management of NCDs are prioritised at the EU and UN levels.

NCDs share common risk and socio-economic factors and cluster in co-morbidities. They are intertwined with ageing.

Poor health today is largely shaped by the NCDs. The development of society, rich or poor, can be judged by the quality of its population's health, how fairly health is distributed across the social spectrum, and the degree of protection provided from disadvantage due to ill-health. Effective action against NCDs should include the understanding of the social and economic determinants [10]. One of

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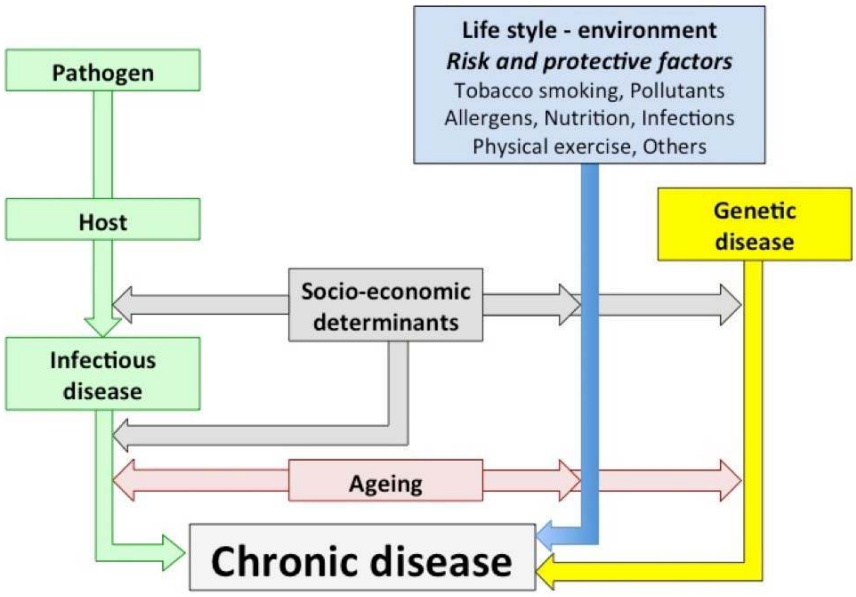

Fig. (1). Definition of chronic diseases.

the earliest approaches was the intervention study carried out very successfully in Karelia. This project emphasized the need for theory based sustained activity, within a national policy framework and lead to an increased health expectancy, reducing in particular the cardiovascular and cancer risks [11, 12]. Best practice interventions to reduce classic coronary risk factors could eliminate most of the socioeconomic differences in coronary heart disease mortality [13].

The challenge for NCDs in the 21st century is to deal with their complexity. One way is to view biology and medicine as informational sciences requiring holistic systems approaches using both hypothesis-driven and discovery-driven approaches. Systems medicine is the application of systems biology to medical research and medical practice. Its objective is to integrate a variety of data at all relevant levels of cellular organisation with clinical and patient-reported disease markers, using the power of computational and mathematical modelling, to enable the understanding of the mechanisms, prognosis, diagnosis and treatment of disease [14]. Medical informatics will play a key role to structure, integrate and provide access to the enormous amount of data generated [15].

Strategies for improving the care of patients with NCDs, considering the diseases in their totality with a focus on co-morbidities, have the potential to offer an efficient use of health service resources. An innovative cost-effective health system using interactions between systems medicine and integrated care should be proposed to combat NCDs. It should be centred on the patient, from primary care to science, training and policy making. This integrated approach should be applicable to all countries and adapted to local needs, economy and health systems.

The present paper reviews the complexity of NCDs intertwined with ageing. It gives an overview of the problem from mechanisms to a holistic and global approach of integrated care for NCDs. Finally, it proposes two practical examples of system medicine applied to NCD co-morbidities (in the frame of the European Innovation Partnership on Active and Healthy Ageing) and the understanding of the mechanisms of a complex series of related diseases (IgE-mediated allergy [16]). This paper follows and extends a previous one on systems medicine and integrated care for NCDs [17].

There are three important areas which need to be considered to combat NCDs : (1) the value of addressing social determinants of health, a primarily political agenda; (2) improved access to primary care, also primarily a political agenda; and (3) the use of systems biology tools to evaluate elderly patients with multiple chronic morbidities, to seek tools that help guide therapy, a research agenda.

1. NCDs REPRESENT THE PROTOTYPE OF COMPLEX DISEASES ASSOCIATED WITH GENE-ENVIRONMENT INTERACTIONS ACROSS THE LIFE CYCLE

NCDs are Multi-Factorial

NCDs often share the same environmental risk factors (e.g. tobacco, nutrition, microbiome, indoor and outdoor air pollution and sedentary lifestyle) [1], leading to sustained local and systemic inflammation [18]. Socio-economic determinants are vital for the generation, severity and management of NCDs [19 , 20]. Even in the high- and middle-income countries of Europe, the possibilities for surviving and living a healthy life are still closely related to the socio-economic background of individuals and families. These are reflected in substantial and even increasing social inequities in health within countries across Europe. These health inequities are unfair and avoidable, as they are caused by unhealthy public policies and lifestyles.

Biodiversity Loss Increases NCD Prevalence

The recent increase in immune and non-immune NCDs has been associated, at least in part, with biodiversity loss [21] and exposure to environmental risk factors (e.g. smoking, sedentarism, biomass fuel combustion and nutrition) [1].

Global health implications of biodiversity loss represent an international political issue closely linked with climate change. Health issues include dietary health and nutrition, infectious diseases, NCDs, medicinal resources, social and psychological health. There is a vicious circle between biodiversity loss, poverty, social inequities and health impact [22].

Foetal and Early Life Events in NCDs

It is increasingly recognized that the *in utero* environment is an important determinant of adult NCDs including diabetes [23], CVD [24], asthma [25], COPD [26] or neuro-degenerative diseases [27]. Links with conserved foetal genes [28] and/or epigenetic mechanisms [25, 29] have been proposed. The role of early life infections

in the development of chronic inflammatory diseases needs to be better understood [30 , 31]. The interest towards developmental determinants of NCDs in ageing has been reinforced during the Cyprus Presidency of the EU Council (2012). A better understanding of these links will make it possible to propose effective primary prevention strategies [32].

Nutrition, Cardiovascular Diseases and Diabetes

Nutrition is one of the key environmental factors determining health and disease. Our understanding of the underlying complexities of the metabolic responses, physiology and pathophysiology at a systems level is not sufficient. We urgently need a systems based approach to understand the influence of nutrition on NCDs and to identify the most suitable targets for disease prevention and modification through dietary means.

Challenges for food and biodiversity loss encompass food production, smallholder income generation, access to health care, harmful child care practices, and tackling the coexistence of undernutrition and caloric over-nutrition [3, 33]. Issues of food-biodiversity interactions are the problems of micronutrient and vitamin deficiencies and coexisting obesity and related chronic and degenerative diseases. They constitute a formidable challenge for the future [34]. Recommendations towards healthy diet adoption are needed globally to prevent the onset and control of NCDs [35]. However, changing life style is a major challenge in public health efforts, and an interdisciplinary approach including social, behavioural and communication sciences is urgently needed.

Tobacco and Biomass Fuel Combustion

Other important risk factors of NCDs include inhaled risk factors such as tobacco [36, 37] and biomass fuel combustion [38]. These risk factors may already act *in utero* and in early life [39]. Any study in the prevention and control of NCDs should consider these risk factors. Translational epidemiology is key to explore the role of these risk factors for use in practice to guide interventions [40]. As for nutrition, tobacco cessation is changing lifestyle and requires a similar multidisciplinary approach.

The main challenge for NCDs in the 21st century is to understand their complexity [17]. This requires an integrated systems medicine approach that leverages from extensively characterized patients, integration of clinical and biological data into NCD phenotypes using multi-level/multi-layer datasets and the development of appropriate medical informatics infrastructure bridging ICT management and e-Health.

The current management strategy using clinical and biological criteria categorising each NCD separately is insufficient for the control of NCDs. The trend for NCD management is towards holistic multi-modal integrated care, and multi-scale, multi-level systems approaches. Recent advances in systems biology and network analysis have opened new avenues to understanding the mechanisms of co-morbidities of multi-factorial NCDs and their clustering [17].

Gender Differences

The rapid rise in NCDs affects women's health directly and impacts their socio-cultural and economic roles. The rapid rise in NCDs not only affects women's health directly, but it can also severely impact their role as unpaid carers and the sick [41]. In general, women live longer with NCDs than men, although they are in poor health [42]. The ten leading causes of death in females have been estimated by WHO. In the world, ischaemic heart diseases, stroke and COPD are ranking among the five first causes of deaths in women [43]. . Diabetes [44] and hypertension are among the first 10. These death estimates are consistent in high and middle-income countries and with some variation in low-income countries. Despite recent considerable progress, gender inequities represent a major dimension and challenge of NCDs and the consequences of their risk factors. This burden is an underappreciated cause of poverty and hinders the economic development of many countries. Gender differences exist in NCD risk factor responsiveness, co-morbidities, phenotypes and prognosis but they have not been integrated into the NCD complexity.

Co-morbidities

NCDs cluster in co-morbidities [19]. Co-morbidity (multimorbidity) is the presence of one or more diseases in addition to a primary disease. Although NCDs are considered individually in most patients, many different NCDs are frequently seen in the same patient [8]). Co-morbidiy number and severity increase with age. NCD co-morbidities are associated with worse health outcomes, complex pharmacological interventions and clinical management strategies, and increased costs [45 , 46].

Complexity of NCDs

Besides environmental factors and increased life expectancy, intrinsic host responses, such as local and systemic inflammation, immune response and remodeling [47, 48 , 49 , 50], are key aspects for the initiation and persistence of diseases and co-morbidities. The "Chronic disease complex phenotype" is the core concept of NCDs which represent the expression of a continuum or a common group of diseases with intertwined gene-environment interactions, and co-morbidities leading to complex phenotypes [17]. Similar and different pathways of local and systemic inflammation [51], bioenergetics [52] repair, remodelling and senescence [53], among others, lead to individual-specific complex biological and clinical phenotypes [17]. Given the functional interdependencies between molecular components, a disease reflects complex network perturbations that link molecules, cells, tissues and organs [54] (Fig. **2**). These interactions lead to highly complex systems.

2. ACTIVE AND HEALTHY AGEING IS CLOSELY RELATED TO NCDs

NCDs affect all age groups but particularly old-age patients. Functioning and physical health declines with advancing age and/or NCD and co-morbidity [55]. Ageing increases the likelihood of NCDs and co-morbidities, thereby confounding their effects on health and well-being. As the general population ages, the number of patients with NCDs is growing. There may be gender differences [56]. The magnitude of the effect of NCDs on ageing is greater in developing countries [57].

Active and Healthy Ageing (AHA) is a major societal challenge common to all European countries, to all populations. Ageing is intertwined with socioeconomic inequalities, is an underappreciated cause of poverty and hinder economic development, particular in undeserved populations and women. AHA should be promoted very early in life.

In the EU, several initiatives are responding to this challenge and consider NCD co-morbidities as key. European Innovation Partnerships (EIP) aim to enhance EU competitiveness and tackle societal challenges through research and innovation. They will address weaknesses in the EU research and innovation (e.g. underinvestment, fragmentation and duplication), which considerably complicate the discovery or exploitation of knowledge and may ultimately prevent the entry of innovations into the market place and the health systems.

The pilot EIP on AHA will pursue a triple win for Europe (http://ec.europa.eu/research/innovation-union/index_en.cfm?section=active-healthy-ageing&pg=implementation-plan):

- Enabling EU citizens to lead healthy, active and independent lives while ageing.
- Improving the sustainability and efficiency of social and health care systems.

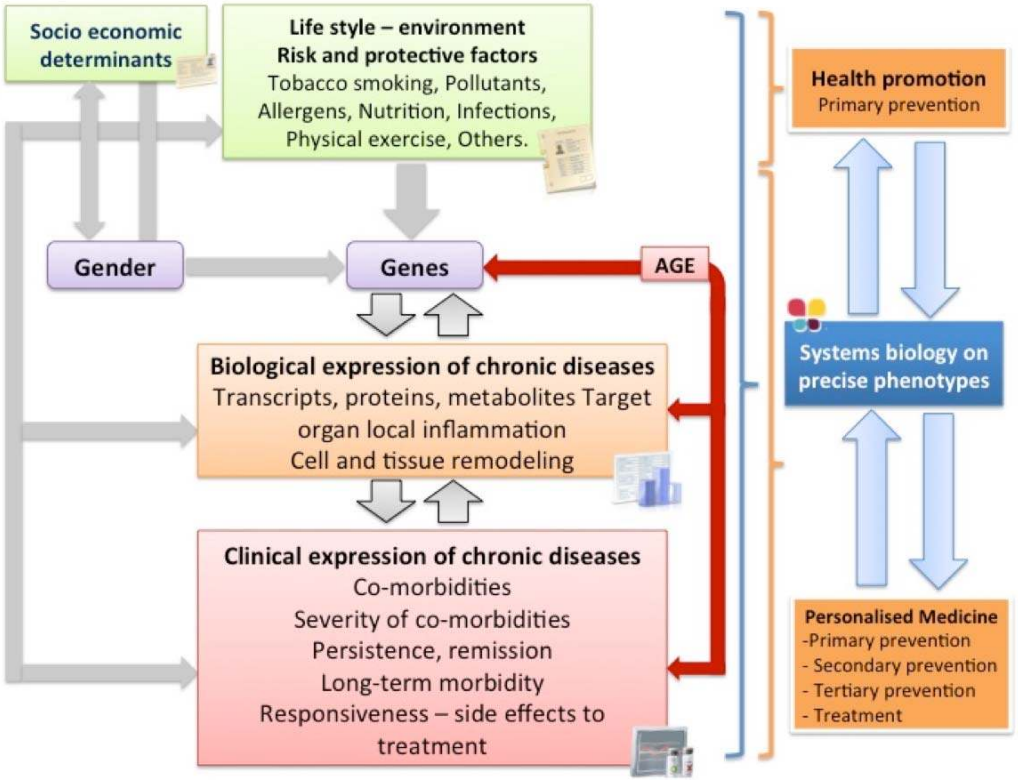

Fig. (2). Complex interplay in NCDs *(from Bousquet et al* [17]*).*

- Boosting and improving the competitiveness of the markets for innovative products and services, responding to the ageing challenge at both EU and global level, thus creating new opportunities for businesses and development.

The EIP on AHA will be deployed in 3 areas (Table **1**).

Table I. Action groups of the EIP on AHA

• Action Group A1: Prescription and adherence action at regional level
• Action Group A2: Personalised health management: Falls prevention
• Action Group A3: Prevention of functional decline and frailty
• Action Group B3: Integrated care for chronic diseases, including remote monitoring at regional level
• Action Group C2: Interoperable independent living solutions
• Action Group D4: Age friendly buildings, cities and environments

(https://webgate.ec.europa.eu/eipaha/actiongroup/index/what)

The overarching target of this partnership will be to increase the average healthy lifespan by two years by 2020 (measured by Healthy Life Years, HLY by 2 years) [58]. Other indicators will include unavoidable hospitalizations for NCDs in the elderly.

3. P4 MEDICINE IN NCDs

Health and health care depend on a complex fabric of systems that are constantly interacting and shaping human health, particularly in patients with NCDs. P4 medicine (predictive, preventive, personalised and participatory) was proposed a few years ago to take into account the contribution of genomics [59]. Systems biology approaches have extended this concept to medicine in general [60]. P4 medicine represents by itself a revolution that extends far beyond what is usually covered by the term personalized medicine [61, 62]. P4 medicine is likely to be the foundation of global health in the future. The key benefits of P4 medicine, for the patient and for the healthcare system, include:

To prevent the occurrence of NCDs by implementing effective action at societal and individual levels:

- To detect disease at an early stage, when it can be controlled effectively.
- To stratify patients into groups, enabling the selection of optimal therapy.
- To reduce adverse drug reactions through the early assessment of individual drug responses.
- To improve the selection of new biochemical targets for drug discovery.
- To reduce the time, cost, and failure rate of clinical trials for new therapies.
- To shift the emphasis in medicine from reaction to prevention and from disease to wellness.

Moreover, in addition, it is of importance to consider and include patients' and populations' preferences for interventions and health states.

However, "P4 medicine" may not transform health care or population health, except to the extent that it encompasses actions already recommended related to the social determinants of health and primary care services.

4. INTEGRATED CARE MODEL FOR THE CONTROL OF NCDs

A worldwide debate on the efficiency of primary health care attempts to re-orientate health systems in developed and developing countries, optimising costs [63]. Health care is often provided using

a model that focuses on single diseases, advanced technology and specialist care, health being considered as the result of biomedical interventions. Primary health care provides the means of organising a complete range of care, from home to hospital, investing resources rationally in the different levels of health. NCDs require an integrated care model using multidisciplinary and teamwork approaches in which primary care is on the front line in order to provide optimal care on a basis of adequate public health strategies [64, 65].

Information-Communication Technology (ICT)

ICT is needed in the implementation of integrated care in a systems medicine approach. Although home telemonitoring appears to be a promising approach to patient management, designers of ICT could consider ways to make this technology more effective as well as controlling possible mediating variables, and to consider diseases in their totality. Continuous and precise monitoring makes the clinical history of each patient a valuable source of comprehensive information. More user-friendly and efficient ICT platforms are needed to understand and tackle NCDs in their totality for several years using precise constructs which need to be validated [45, 66]. The effectiveness of interventions to promote ICT adoption in healthcare settings remains uncertain [67] probably since co-morbidities are not included in most plans.

Shared Decision Making (SDM)

SDM, the process by which a healthcare choice is made jointly by the practitioner and the patient, is an essential objective for patient-centred care in an integrated ICT system [68]. An innovative patient management programme combines ICT and SDM in a multidisciplinary approach. Patients' values and preferences should dominate decision making [69].

A personalised patient education plan could be included and proposed to all patients that allows a clear evaluation and integration of patients' values and preferences in the decision making process. Content, acceptance and effectiveness of such approaches in NCDs could be tested.

An innovative patient management programme could combine ICT, SDM, personalised patient education and an interaction between primary, secondary, and tertiary care levels when available and appropriate. However, for most patients it is hoped that primary care will have sufficient tools to monitor and manage most patients who have a controlled disease. This model will enable a perfect follow-up of patients.

Optimizing Primary Care Practice on Co-Morbid Multi-Factorial NCDs

In May 2009, the 62st WHO World Health Assembly recommended re-orienting health systems globally to promote primary health care as the most cost-effective strategy [63]. Health care often focuses on single diseases, advanced technology, biomedical interventions and specialist care. Most health care takes place in primary care settings [70], with its emphasis on providing a complete range of care, from home to hospital, and on investing resources rationally. Fragmenting care can cause primary care clinicians to lose essential skills and reduce their ability to ensure that a patient's care is comprehensive, integrated, holistic, and coordinated [71]. One considerable challenge in primary care is deciding whether a person has a significant NCD or temporary symptoms, given that nearly 3 out of 4 presenting complaints are self-limited [72].

Practice-based Inter-Professional Collaboration (IPC)

IPC interventions can improve healthcare processes and outcomes. However, rigorous, cluster randomised studies, with an explicit focus on IPC and its measurement, are needed to provide better evidence of the impact of practice-based IPC interventions on professional practice and healthcare outcomes [73]. Any study should include qualitative methods to provide insight into how the interventions affect collaboration and how improved collaboration contributes to changes in outcomes.

Interactions between Primary Care and Research: Community-Based Participatory Research

New approaches to supplement existing methods are needed to take research from bench to bedside and from bedside to practice. Community-based participatory research is an emerging model that enhances ongoing clinical research by involving key stakeholders, including community members and patients. The missions of this model are: (i) to investigate questions related to NCDs; (ii) to improve the quality of primary care; and (iii) to carry out the widespread dissemination and adoption of new information which will positively impact overall health at both a local and national level.

5. DEFINITION OF NCD PHENOTYPES

From Individual NCDs to Complex NCDs with Co-Morbidities

The current management strategy using clinical and biological criteria categorising each NCD separately is insufficient for the control of NCDs. NCD definitions usually follow the international standards/guidelines for each disease (hypothesis-driven approach: **classical phenotypes**). The novel concept of "chronic disease complex phenotypes" (discovery-driven approach: **novel phenotypes**) centred on patient (co-morbidities, risk factors, socio-economic determinants, gender and age) as defined in the MeDALL project [16] is favored by comparison to **classical phenotypes** based on disease ontologies (CAD, COPD, DM2) for a comprehensive definition of co-morbid NCD clustering of clinical usefulness (Fig. **3**).

Classical phenotypes (CAD only, COPD only, DM2 only, CAD+COPD, CAD+DM2, COPD+DM2, CAD+COPD+DM2) can be described with respect to risk factors, socio-demographic, clinical and functional characteristics. Clustering of risk factors can be assessed and contribute to the overlap of classical phenotypes estimated. Special attention should be given to factors that may add complexity to NCDs clinical decision-making, such as medications, socioeconomic factors, health status, and other NCDs.

Novel phenotypes can be identified using a hypothesis-free approach that can allow identifying the clustering of NCDs in patient populations (cross-sectional studies or cohorts) by measuring the distances between variables which include those used for NCDs definition and severity. Several statistical models can be used: first, diseases will be considered as discrete entities (yes/no) using latent class analysis; then continuous processes for the diseases (e.g., glucose tolerance for diabetes, carotid intima media thickness for CVD, and pulmonary function for COPD) will be considered using cluster analysis. Several stopping rules, such as Calinski-Harabasz [74] or CritCF, for the number of clusters (new potential phenotypes) can be applied and their differences (if any) be tested and quantified. The resulting groups should be described with respect to risk factors, sociodemographic, clinical and functional characteristics. These new entities should then be validated for their clinical meaning against potential risk factors of NCDs (e.g., lifestyle, environmental and socioeconomic risk factors) and outcomes (e.g., drug response) as well as follow-up using previous experiences in EU projects *MeDALL, Synergy-COPD* and *Biobridge*. The identification of novel phenotypes is important for a better understanding of NCDs and co-morbidities and can, at present only be approached in research. However, in the future it can make a promessing clustering of NCDs of clinical value.

Concepts of Disease Severity, Activity, Control and Responsiveness to Treatment

- **Severity:** loss of function in the target(s) organs induced by disease [75]. It is important to highlight that severity may vary overtime and needs to be regularly re-evaluated, in particular

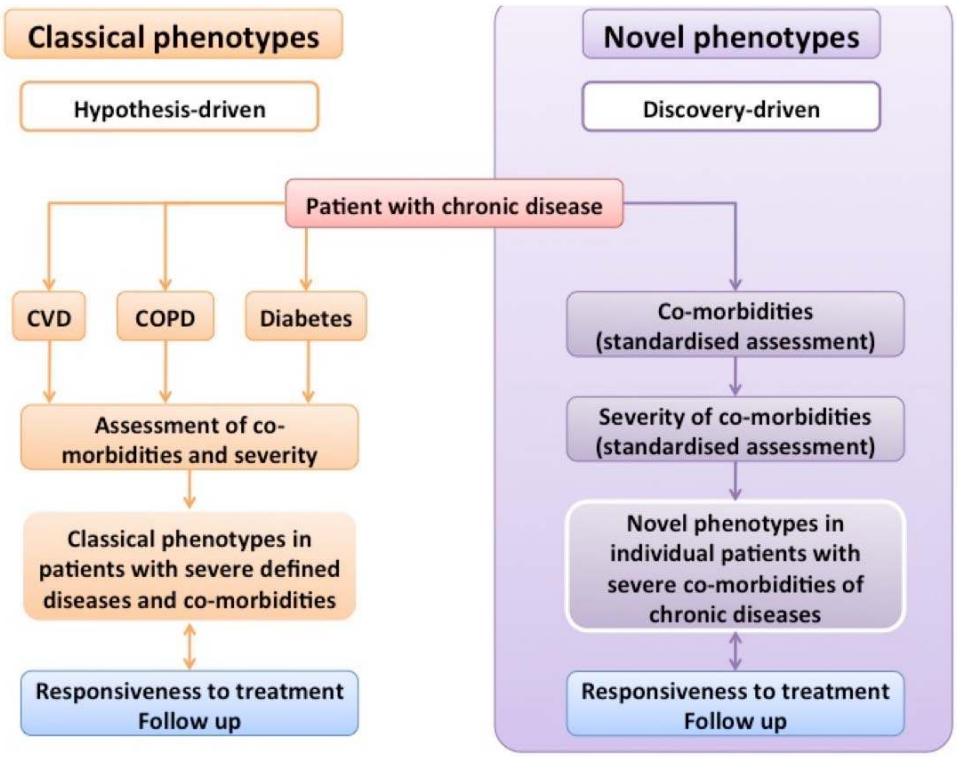

Fig. (3). Classical (hypothesis-driven) and novel (discovery-driven) phenotypes of NCDs *(from Bousquet et al* [17]).

since the population is ageing [76]. Notably, temporal fluctuations of disease markers may provide a diagnostic or phenotypic signal by themselves [77, 78].

- **Activity:** level of biological process activation that drives disease progression [79]. This is a fundamental concept that needs to be clearly separated from "severity" because treatment strategies are different. Hence, whereas treatment of disease activity aims at stopping and/or reducing the progression of the disease, thus eventually avoiding the occurrence of severe disease, treatment of severity aims at palliating the impact of the disease on patient's health status. Current management of NCDs focuses on treatment of severity but neglects treatment of activity because of the lack of validated activity biomarkers.
- **Control:** degree to which therapy goals are currently met [76]) such as glycemic control in diabetes [80]. The lack of validated biomarkers of disease activity limits their use in most NCDs.
- **Responsiveness**: ease with which control is achieved by therapy [75]. Adherence to therapy is a key component of responsiveness and should also be monitored.

These concepts are linked (Fig. **4**).

The uniform definition of severe asthma presented to WHO used this approach [82]. It has been proposed for allergic diseases (Fig. **5**) and may be extended to assess the severity of NCDs (Table **2**) [83].

6. MACVIA-LR: THE MULTIDISCIPLINARY APPROACH OF THE LANGUEDOC ROUSSILLON REGION ON NCD CO-MORBIDITIES AND AGEING

Most patients with chronic diseases have more than one disease. At 70 yrs of age most patients suffer at least from 2-3 comorbidities. However, these comorbidities are not identified and, as an example, many elderly diabetics are hospitalized for non-diabetes

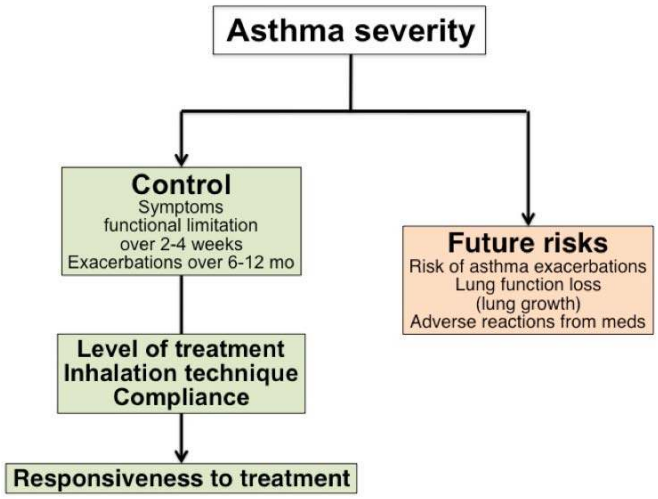

Fig. (4). Complex interplay between severity, control, responsiveness to treatment and risk in asthma (from Busse *et al*, [81]).

conditions although mostly linked to comorbidities. The detection of comorbidities and their management will reduce unavoidable hospitalizations as this has already been demonstrated for diabetes [84]. A similar tend is expected for other NCDs.

In most NCD patients a screening of comorbidities is never done although a large part of the morbidity, mortality, hospitalization and resources are caused by severe comorbidities [85]. Moreover, the current NCD management is characterized by the addition of interventions and recommendations coming from the various medical specialists involved. Minimal interactions between them and limited information to the general practitioner lead to a fragmented health approach, non-concerted prescriptions, a scattered follow-up and a high cost-effectiveness ratio [63]. It is therefore of

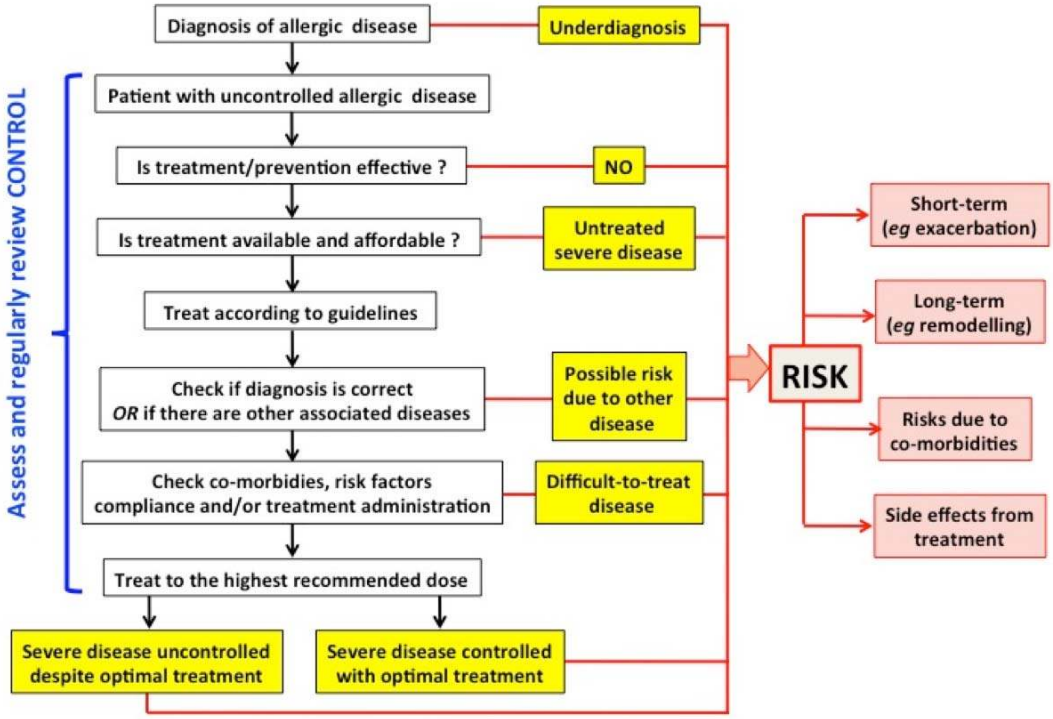

Fig. (5). Uniform severity of allergic diseases (from Bousquet *et al* [83]).

Table 2. Uniform severity in asthma and type-2 diabetes.

	Asthma	Diabetes
Underdiagnosis	Risk of acute exacerbation	Risk of coma and death
Effective treatment	ICS, ß2 agonists	Insulin, oral drugs
No treatment available/ affordable	Risk of acute exacerbation	Risk of coma and death
Incorrect diagnosis	COPD (adults) CF (children)	Weight loss diagnosis
Difficult-to-treat disease	Compliance Inhaler misuse Risk factors	Compliance Complications Risk factors
Controlled treatment dependent disease	Risk of exacerbation when treatment stopped	Risk of death when treatment stopped
Uncontrolled treatment resistant disease	Treatment resistant asthma: Risks	Insulin-resistant diabetes Risks

paramount importance to assess major comorbidities in NCD patients using a simple multidisciplinary approach. MACVIA-LR (Fighting Chronic Diseases for Active and Helathy Ageing) is the initiative lead by the Région Languedoc Roussillon, the University of Montpellier 1, the teaching university hospitals of Montpellier and Nîmes (France) with private and public stakeholders to tackle NCD co-morbidities and ageing.

A one-day chronic disease clinic can assess if (i) major NCD comorbidities and their risk factors can be screened, (ii) an overall assessment of severity of all co-morbidities can be performed (iii) a risk assessment can be made in order to predict and prevent acute events and long-term prognosis. In this clinic, a patient is admitted and discharged on the same day.

Investigated criteria include questionnaires, physical examination, other exams and biologic tests on peripheral blood and urine. They were selected using a systematic approach presented in this paper.

Selection of Criteria used to Develop a One-Day Chronic Disease Clinic

The list of criteria to be investigated in the one-day chronic disease clinic was evidence-based depending on the major NCD co-morbidities. Since there was no defined list of criteria, a proposal was developed by methodologists and clinicians. It includes the criteria for (i) the screening of comorbidities of CVD, COPD or D2M, (ii) the prediction of their exacerbations and (iii) the overall appreciation of severity (Fig. **6**).

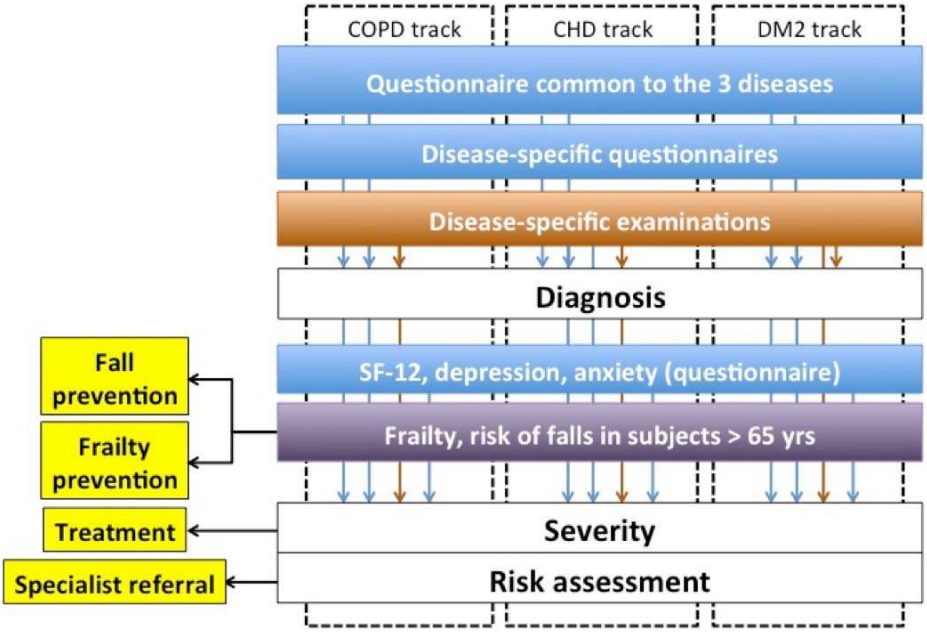

Fig. (6). Chronic disease clinic to assess NCD co-morbidities.

1. Criteria

a. Questionnaire on disease, comorbidities, overall severity and risk factors (less than 1 hr).

b. Physical examination

c. Biomarkers on peripheral blood and/or urine.

d. Exams.

2. Selection of criteria

a. Item included in guidelines and/or recommendations.

b. Item not included in guidelines and/or recommendations:

i Sensitivity to screen or diagnose the chronic disease (not severity).

ii Specificity to screen or diagnose the chronic disease (not severity).

iii Safety and side effects.

c. Cost.

d. Duration.

e. Integration in the chronic disease clinic.

f. Patient's views

i Results of the item (including long-term psychological effects of a diagnosis, e.g. discovery by chest CT scan of a nodule).

ii Patient's acceptance of each individual criteria and of the chronic diseases clinic.

3. Criteria considered

The list of criteria included in the one-day clinic has been established using a Delphi process. It is an iterative approach to seeking agreement from an expert panel using a validated consensus-development methodology that enables a group of experts to deal with a complex problem via a structured group communication process [86]. The method is based on the assumption that group judgments are more valid than individual judgments. It uses an iterative process of questioning and, after each round of questions, an independent facilitator provides an anonymous summary of the experts' views from the previous round.

The current list is proposed as a common list which will be used for all patients referred to the clinic. However, there will be some age-specific criteria (frailty and falls in the elderly). In the future, it is possible that depending on a pre-screening the list will be based on patient's characteristics before assessment in the clinic. When available, the recommendations of the French Authority of health (Haute Autorité de Santé, HAS) were used.

Electronic Co-Morbidity Clinic Investigating COPD, Coronary Heart Disease (CAD) and Type 2 Diabetes (D2M)

1. Co-morbidity screening

The following comorbidities are currently tested:

- Cardiovascular.
- Diabetes.
- Metabolism/obesity.
- Chronic respiratory diseasess.
- Chronic kidney disease.

The list will be optimized with time depending on new evidence, new technologies, integration of the different criteria in the one day clinic, shorten duration of any test, decreased costs…..

2. Assessment of Risk Factors

- Tobacco is the most common risk factor for death.
- Diet and alcohol:
- Physical exercise.
- Socio-economic status
- Outdoor air pollutants increase respiratory and CV morbidity [87] but will not be studied because of the length of the questionnaire.

3. Global Assessment of a Patient with an NCD

- **Cognitive function:** Cognitive impairment may increase the risk of cardiovascular events [88] and participate to patient's literacy, an essential component of treatment adherence.
- **Depression:** Depression is common in NCDs [89]. NCDs can increase the risk of depression which, in turn, can intensify

NCD severity, impact on health service and worsen overall prognosis [90].

- **Mood and anxiety:** Anxiety, although as common as depression, has received less attention and is often undetected and undertreated. A 2-item screening test may enhance detection [91].
- **Quality of life:** The presence of multiple chronic conditions is associated with lower health related quality of life (HRQOL). Disease severity also influences HRQOL [92].
- **Frailty:** Functional decline is a major health problem, particularly in ageing countries. The prevalence of disabilities increases dramatically with age. While the great majority of elderly people consider themselves to be in good health and lead independent lives, a significant proportion, 10-20% depending on the definition, would be classified as frail [93]. NCDs increase frailty. The EIP on AHA has proposed a specific action (A3) concerning frailty [94].
- **Adherence to treatment:** Non-compliance and limited health literacy (user-friendly information) are major barriers to the benefits of evidence-based treatments [95] accompanied with increased health services utilisation, and expenditures.

4. Prediction of risk (acute events or long-term outcome of individual NCD and co-morbidities)

- **The Charlson co-morbidity index** predicts the ten-year mortality for a patient with a screening of 22 co-morbid conditions [96]. Other co-morbidity indexes include the Cumulative Illness Rating Scale (CIRS), that takes into account disease severity [97], the Index of Coexisting Disease (ICED) [98] or the Kaplan-Feinstein Classification [99]. The Charlson Index has excellent reliability and the others have acceptable reliability [99].
- **Falls in the elderly:** Approximately 30% of people over 65 years of age fall each year and one third of them are repeated fallers. Approximately 30% of falls result in an injury that requires medical attention, with fractures occurring in approximately 10%. Falls are the third leading cause of years living with disability and are also one of the leading causes for hospitalization leading to high costs [100]. Falls can also have psychological consequences: fear of falling and loss of confidence that can result in self-restricted activity levels resulting in reduction in physical function and social interactions. There is a large body of evidence on the effectiveness of fall prevention interventions [101-103]. The EIP on AHA has proposed a specific action (A2) concerning a fall prevention initiative [94].
- **Cardiovascular risk (including risk charts):** Cardiovascular risk (CV) charts have been proposed for a long time. Electronic health record data can be used to automatically perform CVD risk stratification and identify patients in need of risk-lowering interventions [104]. This could improve detection of high-risk patients of whom physicians would otherwise be unaware. The CV risk model based on classic risk factors (e.g. cholesterol, blood pressure) may be refined if it included biomarkers (C-reactive protein, N-terminal pro-B-type natriuretic peptide, troponin I) [105].
- **Respiratory risk:** Many instruments including the BODE-index (Body mass index, Obstruction, Dyspnea, Exercise capacity) [106] and the HADO-score (Health, Activity, Dyspnea, Obstruction) have made the prediction of mortality among COPD patients. Comorbidities are frequent in COPD and 12 of them negatively influence survival. The BODE index was combined with the Charlson index to obtain a co-morbditiy risk in COPD [107]. Some biomarkers may improve the risk determination in COPD [108, 109].

Integrated Care, CDSS and ICT

"Integrated care is a concept bringing together inputs, delivery, management and organization of services related to diagnosis, treatment, care, rehabilitation and health promotion. Integration is a means to improve services in relation to access, quality, user satisfaction and efficiency" [110]. Integrated care is of importance to service provision to the elderly, as elderly patients often are chronically ill and present several co-morbidities.

Clinical Decision Support Systems CDSS (Linkcare®), an interactive decision support system (DSS) Computer Software specific to the co-morbidity clinic will assist physicians and other health professionals with decisions for diagnosis and management of patients. It will also be linked with the *Dossier Pharmaceutique*® and, for the CHU of Montpellier, IP-Soins® (Fig. **7**). The *Dossier Pharmaceutique*® (pharmaceutical dossier, *article L.1111-23 Code de la santé publique*) aims at the electronic monitoring of patient's prescriptions by the pharmacists. 15,000/22,000 pharmacists in France are using the system which makes it possible to follow the prescription of medications (*article L. 4211-1*).

This integrated systems will make it possible continuity of care which is often subdivided in 3 components: (i) Continuity of information (though shared records), (ii) continuity across the secondary-primary care interface (discharge planning from specialist to primary care), (iii) provider continuity (seeing the same professional each time with value added if there is a therapeutic, trusting relationship).

Public-Private Partnership

Hospital Based Clinic and Links with Primary Care

The CHU of Montpellier has set up the clinic and use IP-Soins® as an ICT tool. Patients with NCDs (WHO 2008 [1] and DG Sanco 2012 [111] definitions) will be referred to the chronic disease clinic of the hospital by a primary care physician. After co-morbidity evaluation, the patient will be followed up in primary care.

Mobile Chronic Disease Clinic

A mobile chronic disease clinic has been set up using the same examinations in order to screen co-morbidities in remote areas of rural counties of the Region. Pilot studies will be carried out in the *maisons médicales pluridisciplinaires* by the project DeProPASS (*Dépistage des Pathologies associées aux maladies chroniques*).

7. SYSTEMS BIOLOGY ITERATING CLINICAL AND BIOLOGICAL DATA

A biomarker, or biological marker, is an indicator of a biological state, or the past or present existence of a particular type of organism. It is not necessarily a genomic or post-genomic one. Blood lipids are a risk factor for cardiovascular disease [112]. However, for many diseases (including chronic respiratory diseases), biomarkers do not exist and need more sophisticated approaches. Although this has not been confirmed, it is proposed in this paper that systems biology may help to discover new pathways for disease prediction, monitoring and prevention. Biomarkers of pharmacogenomics will also be of interest.

Understanding Co-Morbidities Using Network Analysis

Biological information on gene and environment is connected to NCD complex phenotypes by biological networks/circuits that capture, integrate and transmit information to molecular machines (often proteins) that perform the biological function. Network medicine provides a new conceptual framework using biological networks to describe and model disease complexity [54, 113]. Network analysis can explore systematically the molecular complexity of NCDs, leading to the identification of disease modules and pathways, and the molecular relationships among apparently distinct pathophenotypes. Potential novel genes are those that interact with the largest number of known disease genes, and such a prop-

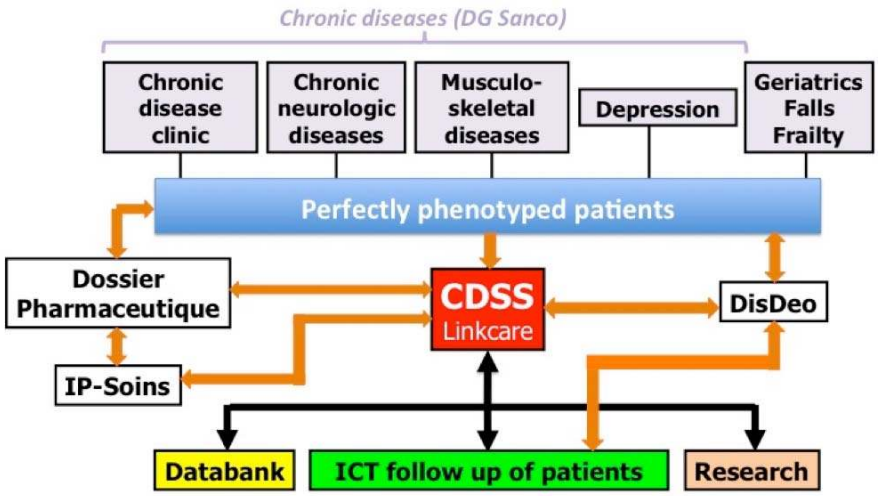

Fig. (7). Integrated care for NCDs.

erty suggests a high likelihood that the gene belongs to the disease cluster [113]. Furthermore, the susceptible candidate genes could be implicated in several disease modules suggesting that different disease modules can overlap [54]. Comorbidity of chronic diseases has been studied [114] and significant correlations were found between the underlying structure of cellular networks and disease comorbidity patterns. This study suggests that a combination of population-level data and cellular network information could help build novel hypotheses about disease mechanisms. Complementary approaches using computational models extended from existing models derived from the Physiome project [115] and statistical modelling can be used to further define phenotypes and develop predictive models within the framework of a fully integrated knowledge management systems [116].

Systems Biology to Identify Unbiased Novel Biomarkers and Mechanisms

Medical informatics play a key role to structure, integrate and provide access to the enormous amount of data generated [15]. Modelling biological systems is one of the most challenging and fastest growing research areas in applied mathematics and physics which are used with support of computer sciences and infrastructures to describe biology at different levels: genes, proteins, cells and populations. As an example, stochastic modelling may be used since it is suited to cell biology [117] and immunology [118] at many scales of biodiversity impact. In addition, non-parametric modelling of the temporal behaviour of disease read-outs at short [78] or long time [77] intervals has shown to be successful in identifying NCDs and their sub-phenotypes. It is however of paramount importance to perform system biology approaches on precisely defined clinically phenotyped subjects.

The development of biomarkers is a bottleneck in the discovery and development of new medicines as identified by the Innovative Medicines Initiative (IMI). In most NCDs, finding a single biomarker is probably insufficient and a panel of biomarkers is required. Biomakers improve the understanding of molecular mechanisms of diseases, identify possible new disease pathways, predict models of complex diseases, determine the level of biological activity of the disease, refine disease phenotypes and guide treatment responses, and possibly lead to personalised medicine.

Novel phenotypes of co-morbidities and NCD complexity can be defined and further tested using iterative cycles of modelling and experimental testing (Fig. **8**). Attempts to find unbiased novel biomarkers of disease development, severity, activity, control, progression and prognosis by combining clinical data with genomics, epigenetics, proteomics, transcriptomics, metagenomics and metabolomics, integrated in a systems biology approach are of great potential. Data analysis, integration and modelling require strict statistical procedures in order to avoid false discoveries [119]. Some of these methods are currently used to assess the mechanisms of the development of allergy (MeDALL [16, 120]). Such an approach may be used to model NCDs [121]. These biomarkers need to be validated and replicated in independent case control or prospective patient cohort studies [122, 123]. Based on studies in non-medical complex ecosystems, "early warning signals" that predict the state of disease progression and the occurrence of abrupt phase transitions may be found [124].

Functional genomics and systems biology approaches in peripheral blood, fluid samples or tissues will generate NCD phenotypes extending knowledge on key mechanisms of NCD comorbidities, and identify and validate novel network perturbations.

The MeDALL Approach for Allergic Diseases

The origin of the epidemic of IgE-associated (allergic) diseases is unclear. The project "*Mechanisms of the Development of ALergy* (MeDALL)" [16], an FP7 project, aims to generate novel knowledge on the mechanisms of initiation of allergy and to propose early diagnosis, prevention, and targets for therapy. A novel phenotype definition and an integrative translational approach are needed to understand how a network of molecular and environmental factors can lead to complex allergic diseases.

MeDALL proposes a novel, stepwise, large-scale and integrative approach leaded by experts in allergy, epidemiology, allergen biochemistry, immunology, molecular biology, epigenetics and genomics, functional genomics, bioinformatics, computational and systems biology, combining the strengths of previous and ongoing EU projects. A feasible and achievable project links epidemiological and clinical research with experimental and animal models.

MeDALL follows the following strategy:

1. **Definition of classical and novel phenotypes of IgE-associated allergic diseases**: Single phenotypes like asthma, rhinitis and atopic dermatitis are complex and heterogeneous. Clustering of single phenotypes in subjects and populations is not yet understood. Classical (expert based) and novel phenotypes (obtained by hypothesis free statistical models using latent class and cluster analysis) in existing birth cohorts will be compared [120]. The novel phenotypes will be extensively characterised by running IgE and IgG arrays in 2,000 existing samples of birth cohorts. This will also make it possible to

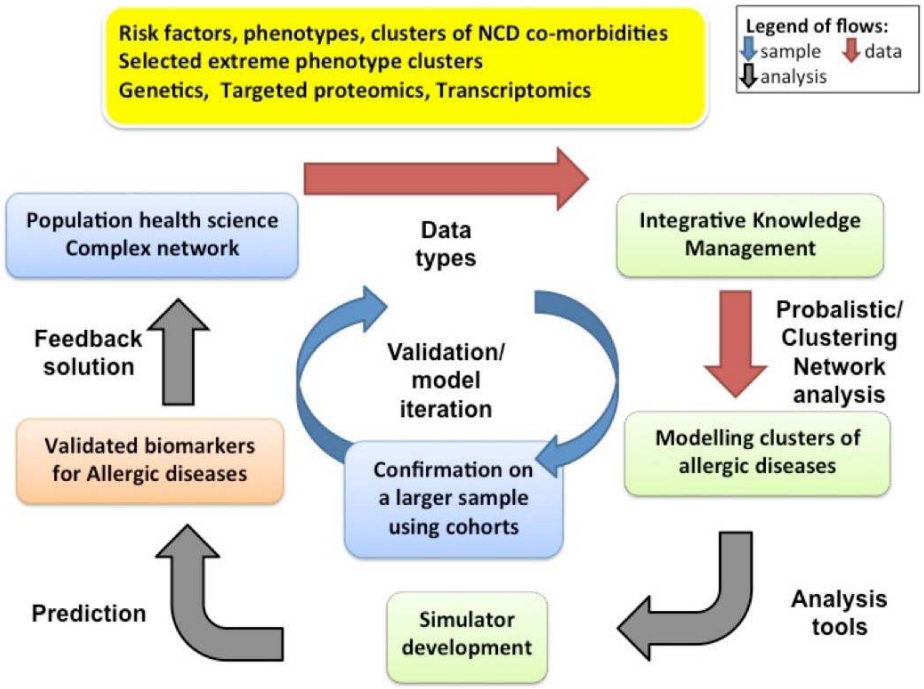

Fig. (8). Workflow of systems biology for NCDs *(from Bousquet et al* [17]).

characterize potential inhalant and food allergens across Europe.

2. **Building discovery using cross-sectional analysis of Karelian children** [125, 126] **and European birth cohorts**. These studies will be carried out on children with IgE-associated diseases, asthma, atopic dermatitis and food allergy. They will capitalise on existing and expanding clinical tests, information on health, disease and exposures, biobanks from longitudinal population studies (birth cohorts and Karelia cross-sectional studies). Pooled databases will include all children from the birth cohorts on allergic diseases, environmental exposures, outcomes, biomarkers and genes.

3. **Building discovery using longitudinal analysis in European birth cohorts**. Within MeDALL, several European birth cohorts on asthma and allergy which previously collaborated in GA²LEN [127, 128] and ENRIECO [129] are performing a harmonized follow-up assessment with identical questionnaires and clinical methods. Their study participants will be in preschool and early school-age (4-10 years) and in adolescence (14-18 years). Previously collected (historical) data and new follow-up data using a harmonized questionnaire will be included in a common database in order to perform pooled pan-European data analyses. The primary aims of these analyses will be the examination of early childhood predictors for allergy and asthma later in life as well as gender differences in the natural course of the disease. Unsupervised statistical analysis will be carried out to compare novel phenotypes (data-driven) to classical phenotypes (hypothesis-driven) [120]. These cross-sectional and longitudinal studies will make it feasible:

- To use a large number of possibilities for experimental studies: epigenetics (DNA samples) [130], expression profiling (mRNA), systems biology, IgE and IgG_4 serology (component resolved diagnosis), serum biomarkers.
- To analyse the data for environmental protection/susceptibility factors in both the classical and the novel phenotypes taking into account a wide range of mechanistic data.

4. **Classical approach for phenotype definition and predictive biomarkers**

- The classical phenotypes will be sampled according to both informative and power criteria.
- Blood samples will be tested against a large range of biomarkers to obtain a limited range of candidate biomarkers.
- The predictive validity of biomarkers will then be assessed on the new phenotypic information provided by the birth cohorts follow-up.

5. **Novel approach for phenotype definition and predictive biomarkers**

- From the existing data of birth cohorts, novel phenotypes will be segregated through appropriate statistical modelling.
- Targeted proteomics, transcriptomics, and epigenetics will be performed in groups of samples to determine candidate biomarkers (novel fingerprints). In a further step, the results of the latter assays will be integrated by mathematical modelling into novel phenotypes handprints.
- Fingerprints and *phenotype* handprints will be extensively validated in birth cohorts. Systems biology will be carried out on nested case samples of these cohorts to characterize biomarkers. A stepwise approach will be proposed. Fingerprints of clinical data, IgE, epigenetics, targeted proteomics and transcriptomics data will be identified in order to select some expected and novel pathways. These will be further studied in a larger number of samples from birth cohorts (confirmation in samples already available and replication on samples obtained in the follow up study). Finally, all fingerprints will be combined into phenotype handprints to identify biomarkers.
- Confirmatory studies in SCID (severe combined immunodeficiency (severe combined immunodeficiency) mouse and other animal models will be used to confirm novel phenotypes.
- *In vitro* human studies will be used to investigate the effect of environment on T and B regulatory and effector cells.

- In the novel approach, iterative improvement of mathematical modelling will be used.

The Following Studies have been Completed

- Definitions of the classical phenotypes of allergic diseases were based on an initial literature review and agreed upon by experts in a MeDALL meeting organized in June 2011. A protocol for the review of classical phenotypes was drafted and an initial literature mining has been performed including 219 original studies and 129 ad-hoc studies. This protocol can be applicable to systematic reviews for other complex and convoluted chronic diseases.
- A harmonized questionnaire for prospective birth cohorts has been designed and is available as a web-based version in 4 languages. This questionnaire allows the comparison of prospective data across all participating birth cohorts.
- A pooled database of recent ongoing longitudinal birth cohorts on allergy-related phenotypes (atopic dermatitis, rhinitis and asthma) has been built. It is using historical data from the 14 birth cohorts participating in MeDALL, which are spread across Europe, making this study unique in terms of geographical variability. The data of over 44,000 children have been included: 22,417 aged around 4-6 years and 18,975 aged around 8-10 years.
- Based on the pooled database, the prevalence of the classical phenotypes of allergic diseases using the MeDALL-agreed definitions was analysed per age period (4-6 year, 8-10 year) in the pooled data and also per cohort, and according to availability of specific antibodies against allergens in serum samples.

8. NOVEL HEALTH CARE SYSTEM BASED ON NCD CO-MORBIDITIES

Integrated care for NCD co-morbidities should not only include the phenotypic characterisation of the patients using clinical and biologic methods but shoud integrate all components of health care including patient's views, health and social care and all stakeholders involved in the process.

Patient Empowerment

The patient should be at the centre of the system using an optimal multidisciplinary approach when needed. Any study should be built around carefully phenotyped patients and follow high methodological standards. A challenge will be to develop automated and integrated workflows that predict the most suitable therapeutic strategy not only at the population level but for an individual patient. Patients should be involved during the entire cycle of decisions for an integrated care programme. The goal and rationale of patient involvement in medical decisions is patient empowerment. Empowered patient knows their disease, have the skills and motivation to take good care in their everyday life, adjust treatment and be prepared in new or potentially exacerbating situations, detect side-effects, take contact with healthcare professional when needed and adhere to treatment regime. Many tools support empowerment, shared decision making models and patient education. Patient empowerment should be included in healthcare professionals' curriculum. International guidelines in allergy and asthma recognize the need for patient involvement and empowerment. Another key aspect of patient involvement in medical decisions is the patient representatives' involvement in the healthcare policy and organization in practice [131]. Among the many questions, 3 could be carefully evaluated:

- Acceptance of NCDs by the patient.
- Engagement of patients in decisions regarding management [132], research and clinical trials [61].
- Improvement of quality-of-life with the proposed management.

Political Commitment Closing the Gaps in Public Health Issues

A leading priority of the European Union is to reduce health inequalities across European societies, and, within its framework to improve prevention and control of NCDs, in particular in the elderly. A strong political commitment has been achieved by the EIP on AHA. It is vital for the deployment and implementation of successful integrated care programmes for NCDs.

Population Health Science Leading to a Novel Health Care System for Patients with NCDs

There is a need for population health sciences to integrate personalized medicine in public health interventions in order to prevent and manage NCDs in a cost-effective manner. Support for this approach is for example an important element of the UK Medical Research Council strategy "Research Changing Lives" (http://www.mrc.ac.uk/ StrategicPlan2009-2014).

NCDs can disconnect populations from their usual milieu, with negative implications for physical and mental well-being. In the social domain, there is mounting evidence that those who have fewer resources are more vulnerable to NCDs. It is vital for the success of policies that they distribute the burdens equitably and that impacts on jobs and on the life of underserved groups are taken into account. The social dimension of the consequences of NCDs needs to be pursued in the social and employment fields, and all social partners need to be involved. Issues like gender and age need to be integrated into the systems based decision paths for prevention and therapy.

Moving beyond the disease-by-disease approach to tackle NCDs overall demands a better understanding of their common causes. The common causes are more likely to be upstream social and environmental factors rather than specific individual exposures. Research should be oriented to identify these determinants and to develop effective actions. The 2008 WHO Commission on Social Determinants of Health recently urged that gaps in health due to political social and economic factors be closed in a generation [133]. Achieving this goal requires a social determinants approach to create public health systems that translate efficacy documented by research into effectiveness in the community [134].

In order to understand, preserve and improve the health of human populations and individuals, an integrated proposal could include:

Medico-Economic Studies Assessing Cost-Effectiveness

Direct and indirect costs incurred by uncontrolled NCDs are substantial for the patient, the family and the society, especially in undeserved population [135]. P4 medicine should be put in the context of health economics to show that expensive strategies are cost-effective [61].

Micro and Macro-Economic Perspectives

NCDs place a considerable economic burden on the society and increase inequities. People who have fewer resources are more vulnerable. The social dimension of NCDs to be pursued in the economic and employment fields, and all stakeholders need to be involved. The net social benefit of improving medical and social care related to NCDs should take co-benefits into account.

Health costs for NCDs should be balanced with health benefits, wealth creation and economic development.

The management of NCDs involves the necessary coordination of stakeholders in the public and private sectors within a governance framework that includes networks of care.

Development of Guidelines and Policies

Using data obtained from all components of research, guidelines on NCDs applicable to primary care could be developed using up-to-date methodology [136]. A major problem of current guidelines is that they focus only on one disease. Yet, co-morbidity is a key problem for basically all NCDs and management of a single disease in the context of some others may be difficult, may require a different approach/understanding and certainly has the potential to harm [137]. Then, policies for implementation could be proposed to translate the concept and management of NCDs into practice.

Adherence to Interventions and Health Literacy

Guidelines should be implemented and applied by physicians and patients. Patient-centredness is a core component of cost-effective high-quality care [138]. Non-adherence is accompanied with increased impaired health outcomes, services utilisation and costs. The *ABC* FP7 project [95] developed strategies for policy-makers to change the behaviour of patients and healthcare professionals, in order to enhance patient adherence. One specific issue in co-morbidities is poly-pharmacy, which is related to low adherence and medication safety. Well-informed patients can make more informed choices and decisions, leading to earlier diagnosis and recovery. Conversely, low health literacy is associated with poorer health outcomes and poorer use of health care services [139]. Health literacy interventions are cost-effective in increasing adherence. Within a holistic, multi-morbidity approach it would be sensible to include non-medication "prescriptions" such as those for lifestyle advice – since adherence to lifestyle advice is even lower than to medications.

Links with the Industry Through SMEs and Large Enterprises

One key mission of any integrated care programme for NCDs will be to ensure the successful transfer of innovation to the private sector. A business plan should actively seek patent protection and encourage the negotiation of licensing agreements aimed at bringing the most promising technologies to market and to the patient's bedside, also taking into account justice issues.

SMEs and large enterprises (pharmaceutical industry, ICT, others) should participate to provide technical grounds on which novel knowledge is generated and rapidly transformed in market-grade products to fulfil the needs of the EIP on AHA for the benefit of patients.

On 26 May 2012, the World Health Assembly adopted a resolution that could mark the beginning of a needed change in the current model of pharmaceutical R&D (Research and Development), and may lead to a novel global research and development agreement [140]. If this model is implemented in the future it twill be of paramount importance to align research for NCDs with the recommendations.

Embedding Public Health Actions in Ethical Frameworks

Strategies that consider NCDs in their totality with a focus on co-morbidities to improve the efficacy of care delivered to patients, can offer an efficient use of health service resources [141]. These organisational aspects include an essential ethical dimension of health care.

Values are at the basis of most actions in health sectors as well as of economic models. However they often are not made explicit. Changing paradigms and approaches for NCDs may challenge fundamental societal values and professional habits [142, 143]. With the multiplication of active stakeholders, their respective weight in the priority setting must be made clear. Transparency and proportionality may be prominent key features. Governance systems are key elements to set up in order to assure an optimal translation of modern biology into health applications while considering as well their societal dimension in a world where ethical values are strongly culturally embedded.

Training

Training is an essential component to educate all stakeholders on the approach, research and management of patients with NCDs using innovative training programmes (e.g. ICT).

Moreover, all stakeholders could have the right to be educated in a transversal manner to better understand NCDs in their totality. Education will address the question of how to teach and how people learn. Rather than seeing education as a process of transmission and transaction, training will include frames of reference for everyone involved in the combat against NCDs. This includes points of view, habits of mind, and all the information requested for the needs of the strategy. This programme needs to carry out educational ecosystems to help participants think differently about NCDs. A module of this programme should be developed with patients to help them engaging in all aspects of NCDs including research.

Working in interdisciplinary teams is a challenge in itself which needs to be in future training initiatives, otherwise the success of the programme is endangered.

9. IMPACT ON POLICIES

Reduction of Inequalities (Including Gender)

One particular concern is that NCD patients with low socioeconomic status bear a disproportionate burden of diseases. The European Commission has addressed NCDs a key priority from different angles. There is a specific policy focus on reducing health inequalities in NCDs through the 2009 European Commission Communication on reducing health inequalities in the EU (20 October 2009, http://ec.europa.eu/health). These policies tie in with active Commission support for the current United Nations Process to address NCDs and related socio-economic and environmental determinants. Even in the high- and middle-income countries of Europe, the possibilities for surviving and living a healthy life are still closely related to the socioeconomic background of individuals and families. These are reflected in substantial and even increasing social inequities in health within countries across Europe. These health inequities are unfair and avoidable, as they are caused by unhealthy public policies and lifestyles.

Equality between women and men is a fundamental right and a common principle of the EU. The EU can be considered as one of the main actors in this field. Since the 1970s, the EU has adopted an extensive body of equal treatment legislation and 13 directives addressing this domain. However, understanding gender differences in complex chronic disease phenotypes will help the European Commission's commitment to gender equality outlined in the *Roadmap for equality between women and men 2006-2010* with the adoption of a follow-up strategy.

European Innovation Partnership on Active and Healthy Ageing

Ageing raises important challenges for the 21st century: meet the higher demand for healthcare; adapt health systems to the needs of an ageing population while keeping them sustainable in societies with smaller workforce. Targeting NCDs, their co-morbidities, risk factors and socio-economic determinants will have a direct effect on healthy ageing by early diagnosis, prevention and treatment of hidden co-morbidities to increase healthy life years and reduce hospitalisations.

The objective of EIP on AHA is to foster innovation in products, processes and services, and in parallel facilitate the innovation chain and reduce the time to market for innovative solutions. Ultimately this will produce benefits for innovation's final users – the older people and care providers.

Global Fight Against NCDs

Most patients with NCDs live in developing countries where medications and services are often unavailable or inaccessible. Not only effective medications should be available for all patients such as inhaled corticosteroids for asthma [144] or insulin for diabetes [145], but there should be a global cost-effective application of P4 medicine in the world. Genomics are now widely used in developing countries and ICT will rapidly become available to many developing countries at a relatively cheap expenditure.

In addition, new private-public strategic partnerships, such as the pre-competitive Innovative Medicines Initiative, a joint undertaking of the European Union and the European Federation of Pharmaceutical Industry Associations (www.imi.europa.eu), and the Program on Public-Private Partnerships of the United States National Institutes of Health Roadmap [http://nihroadmap.nih.gov/] are required to overcome the bottlenecks towards the development of novel treatment strategies [146].

WHO actively supports capacity building, especially in developing countries, fosters partnerships around the world, and works to narrow the gap in healthcare inequities through the access of innovative approaches taking into account different health systems, economic and cultural aspects. Despite the growing consensus for the need for health system strengthening, there is little agreement on strategies for its implementation [147]. Widely accepted guiding principles should be developed with a common language for strategy development and communication in the global community in general [148] and in NCDs in particular.

CONCLUSIONS

The novel trend for the management of NCDs is evolving towards integrative, holistic approaches. To tackle them globally and in their totality in order to reduce their burden and societal impact, it is proposed that NCDs could be considered as a single expression of disease with different risk factors and entities.

P4 medicine for NCDs can have a strong societal impact and, ultimately, could lead to reduction of inequities around the world. Expected results include the structuring of translational research in a global approach of chronic disease, the development of prevention and treatment, a better support for patients through the elaboration of health care systems and follow up at home in improved conditions, a slowing down of the increase in health expenditure, a contribution to novel training courses for new skills and the application of this novel knowledge to all people in the world.

Integrated care for NCD patients, in particular the elderly will reduce inequities while boosting the economy of all countries in the world.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

AHA	=	Active and healthy ageing
BODE-index	=	Body mass index, Obstruction, Dyspnea, Exercise capacity
CAD	=	Coronary Heart Disease
CDSS	=	Clincial decision support system
CHU	=	Centre hospitalier universitaire (University teaching hospital)
COPD	=	Chronic obstructive pulmonary diseases
CHD	=	Coronary heart disease
CT	=	Computed tomography
CVD	=	Cardiovascular disease
D2M	=	Type-2 diabetes
DG	=	Directorate General
EIP	=	European Innovation Partnership
EU	=	European Union
MACVIA-LR	=	Fighting Chronic diseases for active and healthy ageing
FP7	=	Framework Programme 7 (EU)
HADO score	=	Health, Activity, Dyspnea, Obstruction
HRQOL	=	health related quality of life
ICT	=	Information Communication Technology
IPC	=	Practice-based interprofessional collaboration
MACVIA-LR	=	Contre les Maladies Chroniques pour un Vieillissement Actif
MeDALL	=	Mechanisms of the Development of ALLergy (FP7)
NAEPP-EPR3	=	National Asthma Education and Prevention Program, Expert Report 3
NCD	=	Non communicable disease
P4 medicine	=	predictive, preventive, personalised and participatory
Sanco	=	Santé et Consommateurs
SMD	=	Shared decision making
SMEs	=	Small and medium entreprises
U-BIOPRED	=	Unbiased BIOmarkers in PREDiction of respiratory disease outcomes (FP7)
UN	=	United Nations
WHO	=	World Health Organization

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