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A Systems Medicine Clinical Platform for Understanding and Managing Non-Communicable Diseases

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Abstract: Non-Communicable Diseases (NCDs) are among the most pressing global health problems of the twenty-first century. Their rising incidence and prevalence is linked to severe morbidity and mortality, and they are putting economic and managerial pressure on healthcare systems around the world. Moreover, NCDs are impeding healthy aging by negatively affecting the quality of life of a growing number of the global population. NCDs result from the interaction of various genetic, environmental and habitual factors, and cluster in complex ways, making the complex identification of resulting phenotypes not only difficult, but also a top research priority. The degree of complexity required to interpret large patient datasets generated by advanced high-throughput functional genomics assays has now increased to the point that novel computational biology approaches are essential to extract information that is relevant to the clinical decision-making process. Consequently, system-level models that interpret the interactions between extensive tissues, cellular and molecular measurements and clinical features are also being created to identify new disease phenotypes, so that disease definition and treatment are optimized, and novel therapeutic targets discovered. Likewise, Systems Medicine (SM) platforms applied to extensively-characterized patients provide a basis for more targeted clinical trials, and represent a promising tool to achieve better prevention and patient care, thereby promoting healthy aging globally. The present paper: (1) reviews the novel systems approaches to NCDs; (2) discusses how to move efficiently from Systems Biology to Systems Medicine; and (3) presents the scientific and clinical background of the San Raffaele Systems Medicine Platform.

Keywords: Systems medicine, non-communicable diseases, P4 medicine, systems biology.

1. NON-COMMUNICABLE DISEASES

Non-Communicable Diseases (NCDs), by definition, the diseases not transmitted from person to person [6]; and those that are of long duration and slow progression, are increasingly being regarded as a prominent, global health problem [1]. In fact, NCDs are mainly responsible for the burden of morbidity and mortality worldwide, affecting both developed and emerging countries, while posing intolerable management and socio-economic needs that are jeopardizing the sustainability of healthcare systems [2, 3]. NCDs impede healthy aging, thereby imposing a huge public health crisis around the world [4]. Healthy aging is the result of balanced gene-

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environment interactions over time; but this is perturbed in NCDs, leading to a less-adapted organism at risk of unstable or fatal imbalance (disease). Managing NCDs relies on the global evaluation of phenotypes based on mathematical and statistical modeling. Not only clinical features like co-morbidities and symptom severity should be considered, but also life-style, sociologic, prokaryotic and genomic parameters, together with the evolution of these conditions as diseases progress.

From this perspective, the concept of the *exposome*, that a set of exposures to which an individual is subjected over the course of his or her life [5], should be taken into account. Each exposome has a variety of different elements, which include one's metabolism, circulating hormones, gut microbiota (internal exposome), radiation exposures, infections, chemicals and pollutants, diet, tobacco, alcohol, drugs, occupation (a specific external exposome), urban versus rural living, climate, education, socio-economic status and psychological stress (a general external exposome) [6]. Multi-*omic* technologies can help in assessing the effects of various types of exposure, not only of ones already known, but also in an unbiased manner, discovering biomarkers not previously recognized as connected to specific environmental factors. Metabotypes resulting from the complex interplay between host genes, lifestyle and diet can be further used to stratify individuals, and they are highly dependent upon one's gut microbiome [7]. In this context, a disease is considered a dynamic perturbation of interconnected genetic, regulatory and metabolic networks, triggered by the interaction between intrinsic molecular components and external stimuli.

2. SYSTEMS APPROACHES TO NON-COMMUNICABLE DISEASES

Systems Biology (SB) is a relatively new research strategy, one that no longer focuses on individual cellular or molecular components, but rather on system properties. Biological organisms, thanks to billions of years of evolution, are essentially complex, self-organizing, non-linear, open, and intrinsically dynamic systems that should be regarded as "a network of interconnected and mutually dependent components that constitute a unified whole" [8]. Systems are hierarchically organized, with interactions occurring both within and between different levels. From this point of view, no element is replaceable or modifiable without perturbing the whole system, and the system's behavior may differ from the sum of the behaviors of its single components. A reductionist approach is therefore largely insufficient to address the system's description. Instead, an inclusive, non-reductionist, open-system perspective that stresses the study of relationships between components should be adopted.

An SB approach involves the analysis and reconstruction of biological networks at various levels of organization: from molecules, cells and tissues to organs, organisms, and groups of interacting organisms. At each of these levels, interactions with environmental components occur, influencing the normal or pathological behavior of the biological system [8,9,10]. An essential feature of biological systems is that all bodily systems interact with each other. However, thanks to homeostasis and to the observation that biological modules can be described and are reasonably self-contained, it is possible to develop and analyze models of a finite and usable size, without needing to model everything before anything can be deduced. These properties are also an important result of evolution, where bodily systems are added to each other and also evolve in complexity. A key characteristic of a system is the emergence of properties that cannot be explained by any of the elements that form the system alone. From this perspective, life, health and disease are emerging properties of a very complex system — the human body.

The complexity of such data systems is related to different characteristics that they possess: e.g., non-homogeneity; non-linear change, levels of equivalence and distinctness, multi-contextuality, relationships to possible fuzzy systems or multiple systems, the potential for multiple coherences and correlations, and various scale-free properties. Such complexity requires multiple levels of representation and multiple models: e.g., "macroscopic", using indexes; "mesoscopic", considering suitable clustering; and networks, using nodes and links and considering topological properties. In particular, collective systems and the related collective information should be used to represent their emergent properties.

The recent step-change in successful applications of this emerging field has been aided by the possibility of quantitatively capturing the complexity of organisms in health and disease through advances in measurement technologies and associated analysis tools. This advanced approach provides a novel perspective in medicine, complementary to the highly-successful reductionist approach of past decades. The availability of new computational methods and high-throughput platforms for multi-*omic* studies (e.g., genomics; epigenomics; transcriptomics of short and long, coding and non-coding RNAs; proteomics; and metabonomics) has triggered the recognition of SB as a discipline [11, 12]. Similarly, the application of SB in the clinical setting, the use of computational and advanced statistical tools, and the availability of high-dimensional datasets contributing to personalized risk assessment, have provided the basis for the development of *Systems Medicine* (SM) [13] (Fig. **1**).

Systems Medicine applies the perspective of SB to the study of disease mechanisms, with the aim of improving the diagnostic process, disease management, and outcomes [14]. The integration of data from various levels of biological organization with clinical and environmental information, using the power of modeling, drives the transition from evidence-based reactive medicine to new medicine that is Predictive, Preventive, Personalized and Participatory (P4 medicine) [15, 16]. P4, or proactive medicine, is targeted to health maintenance and well-being, rather than to the treatment of diseases. Further specific features are the use of large datasets of integrated information drawn from several sources — like clinical practice, epidemiology and biology (e.g., multi-*omics*) — and the individual-centered approach that permits personalized treatment for patient-specific phenotypes. New opportunities are provided for clinical research on rare phenotypes, and for the identification of new biomarkers of co-morbidity, as well as disease severity and progression.

Creating SM knowledge platforms allows one to approach NCDs in their complexity, by defining and dissecting unknown phenotypes and endophenotypes [17]. Reiterative cycles of model construction, experimental assays, and model refinement allow us to understand how NCDs cluster together, as they stem from the interaction of genetic and environmental factors. Identifying the resultant *composition* phenotypes constitutes the baseline knowledge required to comprehend the full characteristics of the *new ontology* to leverage and replace the *old ontologies* with different clinical features. Other factors, belonging to the socio-economical and psychological sphere of the individual, might have their influence; however, their relative impact on classical outcomes — like quality of life, hospitalization and re-hospitalization patterns, and disease-free survival — is not yet within the domain of contemporary medical knowledge. Modeling clusters of clinical significance in large SM datasets requires novel approaches to extract significant information to support the clinical decision-making process. Setting-up SM datasets needs clinical information to be as complete as possible, thereby requiring its coupling with extensive data generated by advanced *omic* techniques [18]. Systems Medicine is driving the change from classical phenotypes based on *a priori* ontologies and organ-oriented definitions of disease — e.g., cardiovascular disease, chronic obstructive pulmonary disease (COPD), and type 2 diabetes (T2D) — to new phenotypes generated through the modeling of clinical and molecular features of NCDs.

This requires specific predictive, preventative and personalized therapeutic strategies, including distinct rehabilitation paths [19, 20]. This approach will potentially enable researchers and clinicians

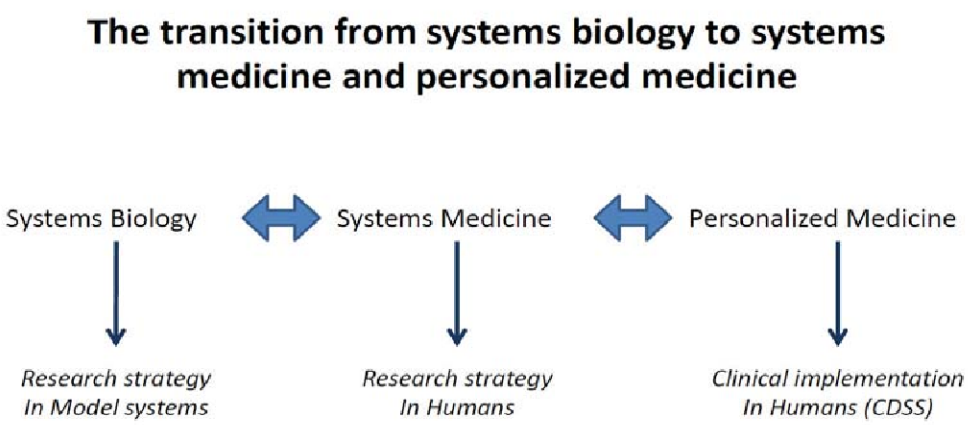

Fig. (1). Critical steps in the transition from Systems Biology to Personalized Medicine (*Alvar Agusti, personal communication).*

to develop efficient, automated and integrated workflows that predict the most suitable therapeutic strategy, not only at the population level but, most importantly, at the individual patient level [21].

3. FROM SYSTEMS BIOLOGY TO SYSTEMS MEDICINE

Unlike SB, which hinges on homogeneous datasets generated by experimental studies on controlled model organisms, SM must interpret connections between the precision of molecular and cellular mechanisms and the tremendous degree of heterogeneity that exists among data drawn from real clinical practice. The major challenge of this approach is to construct a multi-scale *systems-level model of the physiological alterations underlying the disorders* while *assimilating a large and often conflicting corpus of data* [22]. To achieve this goal, models should be developed by combining hypotheses-driven (*top-down*) and data-driven (*bottom-up*) approaches, integrating reliable sources of data like clinical networks. Interconnections between NCDs have been revealed by early investigations, suggesting that different diseases may share common genetic determinants [23,24]. For example, Alzheimer's disease (AD) exhibits connections with both metabolic [25] and cardiovascular diseases [26]; and certain genetic mutations, like those in *TP53* or *PAX6*, are associated with up to ten diseases [23]. A recent study [27] revealed that cellular senescence is strongly interconnected with aging, longevity and age-related diseases, including atherosclerosis, T2D, AD and cancer. These diseases share common genomic features, including the expression of regulator genes, post-transcriptional co-regulation through the same micro-RNAs (miRNAs), protein-protein interactions and, ultimately, common pathways. As an example, the dys-regulation of *miR21*, one of the most studied miRNAs, is shared between neurodegenerative disorders, cancer, T2D, atherosclerosis and AD [28].

Furthermore, in two recent epidemiological studies performed on very large populations ($\simeq$400,000 and $\simeq$900,000 people), it was demonstrated that COPD is significantly associated with obesity, regardless of smoking status, and with cardiovascular diseases (CVDs), suggesting potential mechanistic links between adipose tissue mass, systemic inflammation, and CVDs in patients suffering from COPD [29, 30].

Integrated SM approaches to individual diseases, like specific types of cancer [31], are making considerable progress; and, indeed, this framework can be extended to co-morbidities.

The recent emergence of sophisticated systems to record and store clinical data has increased the potential for research on multimorbidity and disease networks remarkably. This has fuelled research aimed at identifying unexplored associations between diseases, grounded either in a common pattern of genomic changes or in phenotypic similarities. A convincing example has emerged in the study of COPD, where the prospective collection of 13 co-morbidities based on validated objective measurements resulted in five clinically-relevant clusters [32]. Moreover, in this setting, publicly-available datasets like Online Mendelian Inheritance in Man (OMIM, www.ncbi.nlm.nih.gov/omim) represent a powerful tool with which to investigate relationships between pathologies, by integrating gene-disease associations with additional information; for example, protein-protein interactions from large-scale proteomic studies. Connecting information from repositories of disease-associated genes and proteins to clinical data extracted from patient record systems, offers privileged insights into causative mechanisms of disease and associations between phenotypes and genotypes [23, 33, 34], via high-performance computer platforms' analysis, and the integration, modeling and simulation of complex biological, clinical and multi-*omic* datasets.

Mathematical Syntax

The conceptualization of biological networks and the rapid growth of databases for protein-protein interactions, genetic regulations, and biochemical reactions have fostered the development of novel algorithms and network analysis methods designed to extract meaningful biological information from large datasets. Historically, the quantitative models of biochemical networks with ordinary differential equations (ODEs) have been the most established analytical approach (reviewed in Chaouiya, 2007) [35]. Complex systems (signaling pathways and genetic circuits) are represented as a system of ODEs that can be solved by numerical integration methods. In these systems, quantitative approaches are complemented by qualitative approaches that are more suitable to model dynamic properties of complex biological systems, especially in cases of sparse kinetic data availability. Graphical and mathematical formalism suitable for the modeling and analysis of concurrent, asynchronous, distributed systems, like Petri nets-based models, have largely been used for this purpose [36]. In addition to modeling approaches, numerous studies focusing on the structural and topological properties of biological networks, degree of distribution [37], characteristic path length [38], clustering [39] and centrality [40, 41] have been published.

A valuable tool for the interpretation of a broad range of data characterizing cellular systems under different conditions or in different states of a disease is sub-network enrichment analysis (SNEA) algorithm [42], which is an extension of the original enrichment algorithm [43] that uses a modified Kolmogorov-Smirnov test to evaluate the significance of differences between the distributions of all expression values and of those within a group (*gene set*). Other approaches include the *causal reasoning algorithm* [44], which uses causal knowledge to predict *drivers* of observed large-

scale transcriptional changes; and *network reconstruction methods*, which attempt to infer or extend biological regulatory networks directly from experimental data, primarily from time series [45,46].

Generating actionable knowledge (i.e., extracting predictive patterns from multiple types of information by statistical or mathematical models) requires strategies for data handling and their integration into prior biomedical knowledge. Currently, disjoint containers for individual scales of structured data (e.g., 1,400 public databases on molecular biology-related information [47]) exist next to unstructured knowledge in scientific literature, including high-content imaging, physiological, biochemical and clinical data. To bridge multiple sources and scales of knowledge, semantic models have recently been developed [48,49,50]. Well-defined vocabularies and standards exist to represent molecular and biochemical processes [51], whereas the technical infrastructure required to provide an adaptive architecture and the ability to develop and add concepts is still needed [52]. Text mining provides an initial step towards being able to extract entities and their associations from unstructured literature; however, it currently fails to detect complex relationships, specific mechanisms or quantities [53]. Correspondingly, the knowledge management infrastructure needs to support processes for knowledge extraction from human experts, such as the DataSHaPER process for integration of data from different clinical studies [54].

"Phenotyping" Platforms

Phenotypes are relatively stable, but not invariable over time [55]. Hence, temporal fluctuation analysis of complex biomarkers, like interacting network components, is likely to add key information to the description of health and disease [56]. Platforms providing the framework for SM studies have already been implemented for some specific human diseases. For instance, Bousquet and colleagues [57] published the results of a long-term birth cohort study designed to generate a novel definition of allergies based on complex phenotypes; and Madhavan *et al*. (2011) [12] have developed a web platform integrating high-throughput research with data on the characteristics and clinical outcomes of cancer patients. For respiratory diseases, Maier *et al*. (2011) [58] have created a knowledge portal that integrates formalized knowledge on COPD with computational COPD modeling, clinical data of COPD patients and *omics* data. Other examples come from psychiatric diseases, which represent a suitable area for systems approaches, due to their multifaceted pathogenesis and clinical complexity [59, 60]. Roque *et al*. (2011) [34], using medical records for phenotypic descriptions of psychiatric inpatients, identified new patient clusters based on clinical features and co-morbidities, thereby providing critical information which could be subsequently mapped on SB frameworks.

SB/SM centers have been established in various countries, among them the National Phenome Centre in the United Kingdom (MRC-NIHR, www1.imperial.ac.uk/phenomecentre/); the Centre for Chronic Diseases at Maastricht University Medical Centre (http: //www.mumc.nl/) and the Centre of Expertise for Chronic Organ Failure CIRO+ (www.ciro-horn.nl.) in the Netherlands; the European Institute for System Biology and Medicine in France (www.eisbm.org/); and the Luxembourg Centre for Systems Biomedicine in Luxembourg (http: //wwwen.uni.lu/lcsb). Last, but not least, projects aimed at modeling outcomes of specific diseases in an SM environment have been established. These include Unbiased BIOmarkers for the Prediction of REspiratory Diseases outcomes (U-BIOPRED, http: //www.ubiopred.european-lung-foundation.org/16005-the-project.htm); Synergy-COPD (http: //www.synergy-copd.eu/); and Airway Disease Predicting Outcomes through Patient Specific Computational Modeling (AirPROM, http: //www.airprom.european-lung-foundation.org/). Consortia also have been established as European Translational Information and Knowledge Management Services (eTRIKS, http: //www.etriks.org/).

Contrary to all these "disease-oriented/based" structures, we have envisaged the creation of a multi-disease/multi-level clinical platform that, albeit hinging on a "classical diagnosis" framework, would have, by design, the potential to go beyond categorical classifications.

4. THE SAN RAFFAELE SYSTEMS MEDICINE NETWORK AND PLATFORM FOR NON-COMMUNICABLE DISEASES

The Clinical Platform

From a practical viewpoint, an SM approach requires an infrastructure that allows one to develop tools for the analysis and interpretation of complex datasets. The availability of structured clinical platforms represents the basic condition needed to address current priorities in medicine, such as personalizing treatment and improving outcomes, implementing clinical trials tailored to newly-defined phenotypes and, ultimately, bringing P4 medicine into clinical practice, while assuring the sustainability of this approach within national health systems.

The San Raffaele Group manages a network of integrated services that include rehabilitation, nursing homes, and both long-term and palliative care. The group counts eight rehabilitation facilities (for inpatients and outpatients) acting in the fields of internal medicine, as well as respiratory, neuromotor, psychiatric, cardiac, and pediatric rehabilitation; four outpatient clinics; and sixteen nursing homes. All are located in Central and Southern Italy. All scientific activities are coordinated by the IRCCS San Raffaele Pisana in Rome, a Centre of Excellence in biomedical research, management and health care organization, which creates and manages scientific collaborations with networks of other clinical and research institutions that treat endocrine, psychiatric, neurological, respiratory and metabolic diseases.

A critical step in the process of integrating multi-dimensional data and their interpretation within a functional framework is the initial adoption of a data-driven approach for the collection and storage of clinical features. This is, by far, the most efficient way to integrate biological and clinical complexity, and has the potential to change the traditional hypothesis-driven approach, making it possible to convert standard clinical taxonomy into new complex phenotypes.

The multi-level San Raffaele platform for NCDs (SR-NCDs), launched in January 2013, collects and archives clinical information and biological samples obtained from all patients with chronic diseases admitted for physical rehabilitation at either of the San Raffaele facilities in Rome or other regional clinical facilities and university hospitals participating in the SR-NCDs (Table **1**). The SM approach is currently offered to in-patients only, although a protocol dedicated to outpatients is under evaluation (with the potential to multiply the number of participating subjects three to five-fold).

Patients are initially selected for inclusion according to classical phenotypes that have determined their hospital admission. After expressing their consent to contribute their data to SR-NCDs, this classification is discarded and patients receive an unbiased clinical and biological evaluation. The most common diseases that warrant admission to the San Raffaele facilities or the other centers participating in SR-NCDs are: chronic respiratory diseases (COPD, interstitial lung diseases, respiratory failure, tracheotomy, undergoing mechanical ventilation), cancer (lung cancer), CVDs (heart failure, ischemic heart disease), type 2 diabetes, neurological and psychiatric disorders (headache or pain, Alzheimer's disease, Parkinson's disease, schizophrenia, and affective psychoses). Table **1** provides a more detailed description of participating centers. All patients who give their informed consent to participate in the study are characterized extensively according to several parameters: psychosocial (e.g., socio-economic status, quality of life, coping styles, life events), behavioral (e.g., tobacco, diet and alcohol habits, physical exercise, lifestyle) and clinical (e.g., screening for multi-morbidity,

Table 1. Hospital and Universities contributing patients to the San Raffaele Non Communicable Diseases Platform (SR-NCDs) in 2012.

Institution (Department)		Number of patients
San Raffaele Pisana, Roma	*Respiratory rehabilitation "Guglielmo Cardaci" (inpatients)*	436
	Cardiovascular rehabilitation (inpatients/outpatients)	389/76
	Parkinson's Disease Unit (inpatients and outpatients)	756
	Headache and Pain Unit (outpatients)	728
San Raffaele Montecompatri, Montecompatri (RM)	*Respiratory rehabilitation (inpatients)*	312
	Psychiatry (inpatients)	104
San Raffaele Cassino, Cassino (FR)	*Respiratory rehabilitation (inpatients)*	122
Università Cattolica del Sacro Cuore, Roma	*Alzheimer's Disease Unit (outpatients)*	89
Università Cattolica del Sacro Cuore, Roma	*Thoracic Surgery (lung cancer inpatients)*	102
Mental Health Department Roma E, Roma	*Psychiatric Intensive Care Unit, San Filippo Neri Hospital, Roma (inpatients)*	267
Policlinico Tor Vergata, Roma	*Diabetes Unit (outpatients and inpatients)*	489/92
Ospedale Mazzini, Pescara	*Thoracic Surgery (lung cancer inpatients)*	102
Centro Oncologico Sesto Fiorentino, Sesto Fiorentino (Firenze)	*Thoracic Surgery (lung cancer inpatients)*	34

personal medical history, clinical and instrumental assessment). In addition, biological samples (whole blood, serum, plasma and urine) are collected and stored in a clinically-annotated biorepository.

Data collection from participating individuals has been designed as a multidimensional assessment system, based on two tools. Both an extensive epidemiologic and patho-physiological questionnaire (Table **2**) and an electronic chart specifically designed for the SR-NCDs exist, including established diagnostic/prognostic scales for the most common diseases, allowing us to store the results of medical and instrumental examinations. This chart is split into a common module that accommodates parameters of general interest (e.g., clinical scales, physical examination, blood and urine tests, cognitive status, drug therapy) and a symptoms-oriented section to be used only if a patient screens positive for one of a selected group of conditions (i.e., respiratory or cardiovascular failure, AD, PD, psychiatric disorder, headache and pain, lung cancer, T2D, or metabolic disease). The disease-specific assessment is based on rating scales, cognitive tests, and clinical and instrumental exams. Cognitive tests and rating scales were chosen according to medical and practical criteria. They allow for a comprehensive symptomatic assessment of classical phenotypes and are self-administered whenever possible. In addition, the time necessary to administer the scales is compatible with a regular clinical assessment.

Patients screened according to the common module are evaluated by means of 10 rating scales/tests. In addition, physical examination data, blood and urine tests, ECG, pulse oximetry and actual drug prescriptions are recorded, together with the use of medical devices. The Modified Cumulative Illness Rating Scale (MCIRS) [61, 62], a 14-item scale used to assess multi-morbidity by rating impairment across 14 different organs/systems, is used as a quantitative index of co-morbidity.

To assess general cognitive status, patients are administered: 1) the Mini Mental State Examination (MMSE) [63], a 30-point scale composed of a series of questions and tests that evaluates different mental abilities, including memory, attention and language; 2) the Montreal Cognitive Assessment (MoCA) [64], a 30-point tool that assesses various cognitive domains, including short-term memory, visuo-spatial abilities, executive functions, attention, language and orientation; and 3) the Rey-Osterrieth Complex Figure test (ROCF) [65], an instrument designed to evaluate visuo-spatial abilities, memory, attention, planning and executive functions.

Psychological symptomatology is assessed via: 1) the Centers for Epidemiologic Studies Depression Scale (CES-D) [66], a 20-item questionnaire specifically developed to screen for depression in the general population; 2) the Zung Self-Rating Anxiety Scale (SAS) [67], a 20-item questionnaire that measures anxiety levels across different groups of manifestations (e.g., cognitive, autonomic, motor); and 3) the Brief COPE [68], a 28-item questionnaire that assesses coping skills, specifically psychological mechanisms used to *cope with* personal and interpersonal problems.

Well-being and daily living autonomy are evaluated using: 1) the Short Form (36) Health Survey (SF-36) [69], a 36-item health survey that provides an 8-scale profile of functional health and well-being; 2) Activities of Daily Living (ADL) [70], a 6-item scale that assess the patient's ability to independently perform activities of daily living (e.g., bathing, dressing, feeding oneself); and 3) Instrumental Activities of Daily Living (IADL) [71], an 8-item scale that assesses a person's ability to perform tasks, such as using a telephone, preparing food or doing laundry.

After this initial screening, patients with additional symptoms or with a positive history for other diseases receive a further assessment based upon specific modules.

In the respiratory and cardiovascular module, data from the instrumental examination (echocardiogram, cardiopulmonary test, 24-hour ECG monitoring, blood gases analysis, spirometry, expectorate exam, nocturnal oximetry, bronchoscopy and bronchoalveolar lavage) are collected from clinical records and seven rating scales/tests are administered: 1) the St. George Respiratory Ques-

Table 2. Description of clinical and epidemiological items collected from each patient enrolled in the San Raffaele Non Communicable Diseases Platform (SR-NCDs).

Field of information	Number of items	Domains
Demographic data	16	Hospital, ward, date of admission, age, gender, education, residence
Occupational history	12	Current and past professions, duties, workplaces
Smoking habits	21	Age of onset, type and amount of smoking, age of quitting, cohabitation with smokers
Alcohol intake	6	Type of beverage and quantity
Diet	7	Intake of fresh food and supplements
Leisure-time activities	5	Amount of spare time, type of activities
Social relationships	6	Presence of relatives/friends, amount of time spent with them
Stressful life events in the previous six months	3	Type of events
Personal medical history	302	Heart diseases, vascular diseases, blood and lymphatic system diseases, respiratory diseases, gastrointestinal diseases, liver diseases, genito-urinary diseases, musculoskeletal system diseases, endocrine and metabolic diseases, psychiatric diseases, neurological diseases, other diseases.
Family medical history	166	Smoking habits, cardiovascular diseases, respiratory diseases, psychiatric diseases, headache and pain, diabetes, memory impairment, Parkinson's disease, Alzheimer's disease, other diseases.

tionnaire (SGRQ) [72, 73], a 51-item questionnaire, that assesses respiratory symptomatology and how patient's daily physical activity and psycho-social function are affected; 2) the Maugeri Foundation Respiratory Failure Questionnaire (MRF- 26) [74, 75], a 26-item questionnaire assessing everyday life, cognitive function and invalidity in patients with chronic respiratory failure; 3) the Modified Medical Research Council Dyspnoea Scale (MMRC) [76], a 5-item grading system assessing the patient's level of dyspnoea/shortness of breath; 4) the 6-Minute Walking test (6MWT) [77], which assesses functional capacity by measuring the distance that a patient can walk quickly on a flat, hard surface over a period of six minutes; 5) the Bode Index for COPD, [78] a multidimensional grading system for COPD that predicts survival, based on one-second forced expiratory volume (FEV1) (% of predicted), distance walked in six minutes, MMRC score, and body mass index (BMI); 6) the Modified Borg Dyspnoea Scale [79], a 0 to10-rated scale evaluating the patient's subjective rating of dyspnoea; and 7) the Barthel Index [80], a 10-item tool that measures a patient's level of daily functioning.

In the psychiatric module, seven rating scales are used to assess a patient's clinical condition: 1) the Operational Criteria Checklist for psychotic and affective illness (OPCRIT) [81], a 90-item checklist that encompasses symptoms of major psychoses; 2) the 18-item version of the Brief Psychiatric Rating Scale (BPRS-18) [82], a tool that assesses different domains of psychopathology, like anxiety, depression, hallucinations, and grandiosity; 3) the Hamilton Rating Scale for Depression (HRSD) [83], a 21-item scale that allows for a quantitative assessment of depression; 4) the Young Mania Rating Scale [84], an 11-item scale that explores the key symptoms of mania; 5) the Hamilton Anxiety Scale [85], a 14-item scale for the quantitative evaluation of anxiety; and 6) the Positive and Negative Syndrome Scale (PANSS) [86], a 30-item scale that evaluates the current pattern of symptoms in schizophrenia patients.

In the headache and pain module, four rating scales are used: 1) the Migraine Disability Assessment [87, 88], a 7-item questionnaire used to determine how severely migraines are affecting a patient's life; 2) the 6-item Headache Impact Test questionnaire (HIT-6) [89], a 6-item tool that measures the impact of headaches on different life domains; 3) a 10-point Visual Analogue Scale [90] on which patients rate their headache pain severity; and 4) the Neuropathic Pain Scale [91], a 10-item tool to measure and analyze pain caused by lesions in the nervous system.

In the Alzheimer's disease module, the following scales are administered to patients with a positive history: 1) the Mental Deterioration Battery [92], a battery of neuropsychological tests to detect the effect of deterioration in different cognitive areas; and 2) the Neuropsychiatric Inventory (NPI) [93], a tool to obtain information from the patient's caregiver regarding behavioral disturbances. The latter investigates the frequency and severity of delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, aberrant motor activity, and sleep and appetite disturbances. The NPI also is administered to Parkinson's disease patients.

Further scales are used in the Parkinson's Disease module to assess patients: 1) the Unified Parkinson's Disease Rating Scale (UPDRS) [94], a rating scale used to follow the longitudinal course of Parkinson's disease (this scale has three sections that evaluate the key areas of disability, together with a fourth section that evaluates any complications of treatment, accompanied by two further scales: the Hoehn and Yahr staging scale and the Schwab and England Activities of Daily Living scale); 2) the Parkinson's Disease Sleep Scale (PDSS) [95], a visual analog scale that assesses 15 PD-related symptoms relating to nocturnal disability; 3) the Epworth Sleepiness Scale (ESS) [96], a short questionnaire that measures daytime sleepiness; 4) the Abnormal Involuntary Movement Scale (mAIMS) [97], a 6-item scale used to assess the severity of abnormal involuntary movements in the oro-facial area, extremities and trunk; 5) the Unified Diskinesia Rating Scale (UDysRS) [98], developed to evaluate involuntary movements often associated with treated Parkinson's disease (this scale is composed of two primary sections: Historical [Part 1 (On-Dyskinesia) and Part 2 (Off-Dystonia)], and Objective [Part 3 (Impairment) and Part 4 (Disability)]; 6) the Minnesota Impulsive Disorders Interview (MIDI) [99], a 36-item semi-structured interview that includes separate screening modules to

diagnose pathological gambling, trichotillomania, kleptomania, pyromania, intermittent explosive disorder, compulsive buying, and compulsive sexual behaviors; 7) the Progressive Supranuclear Palsy (PSP) Rating Scale [100], that estimates level of disability in people with PSP (this scale includes 28 items across six categories — daily activities by history, behavior, bulbar, ocular motor, limb motor, and gait/midline — with the total maximum score of 100 reflecting the highest level of impairment; 8) the Non-Motor Symptoms Questionnaire (NMSQuest) [101], a questionnaire of 30 items that is a screening tool for the presence of NMS; 9) the Non-Motor Symptoms Scale (NMSS) [102], a 30-item scale for the assessment of NMS across nine dimensions — cardiovascular, sleep/fatigue, mood/cognition, perceptual problems, attention/memory, gastrointestinal, urinary, sexual function, and miscellaneous; 10) the Wearing Off Questionnaire (WOQ 19) [103], a self-rated 19-item questionnaire that is a screening tool for wearing-off, that is the re-emergence of motor and non-motor symptoms before the administration of the next dose of drug) in patients with Parkinson's disease; 11) the Unified Multiple System Atrophy Rating Scale (UMSARS) [104], which quantifies disease severity and includes four parts (Part I, historical, with 12 items that primarily assess for disease-related impairments; Part II, a motor examination with 14 items; Part III, an autonomic examination; and Part IV, a global disability scale; 12) the Parkinson's Disease-Cognitive Rating Scale (PD-CRS) [105], a scale that investigates fronto-subcortical and cortical cognitive functions, aiming to capture the whole spectrum of cognitive functions impaired over the course of PD; 13) the Beck Depression Inventory (BDI) [106], a 21-item rating inventory that measures the characteristics, attitudes and symptoms of depression; and 14) the Parkinson's Disease Questionnaire (PDQ-39) [107, 108], a questionnaire with 39 questions covering eight components of quality of life, that is used as a Parkinson's disease-specific measure of health status.

Patients affected by diabetes (T2D) are subjected to a fundoscopic examination, Doppler ultrasound of carotid and neck vessels, as well as of the lower limbs, Computed Tomography Angiography (CTA) of the legs, an assessment to detect any signs of autonomic or peripheral neuropathy and diabetic foot screening.

Similar to the diabetes module, lung cancer patients are assessed for the presence of tumor markers, genetic mutations, and both radiological and histopathological characteristics of the tumor.

For all modules, when a new pathologic assessment is impossible, patients and/or caregivers are requested to bring recent clinical/instrumental exams.

A synthetic description of items selected for the common module and for each symptoms-oriented module is presented in Table **3**.

All collected data are organized into a customized relational database. The SR-NCDs data repository is intended to store multiple types of information for each patient, gathering demographic data, clinical outcomes, laboratory and instrumental examinations, together with quantitative measurements of the disease-specific phenotype and genomic, epigenomic, proteomic, and metabolomic profiles.

Patient data are inserted into the SR-NCDs via web-based input, through a safe system specifically designed to ensure both data security and privacy. Standard operating procedures (SOPs) have been established to standardize all steps concerning data collection, input, storage and quality control. Procedures also are available for the collection, transport, processing, fractioning, storage and quality control of biological specimens, and for personnel training. Detailed procedures for the development and management of scientific collaborations based on data and samples from the SR-NCDs platform have been defined, including rules for participation in multicentre studies, data sharing, sample shipment, and the dissemination of results.

A pilot study on a restricted case-mix of patients recruited from different wards is currently ongoing to evaluate the feasibility of the system before beginning the systematic enrollment of patients from clinical facilities participating in the SR-NCDs.

Statistical and Epidemiological Analysis

The identification of correlations and associations between the various types of data for each patient and across all patients represents the next step, once the dataset has been developed. Application of numerical tools implies digitization of all data. Even a '1' or '0' classification is a start. There is, of course, a wide range of data, including biomarkers (e.g., glycaemia), physiological parameters (e.g., body temperature), responses to questionnaires (e.g., a deranged mental state), physician observations (e.g., he/she looks ill), and imaging and biopsy data. Each type of data suggests different modeling approaches; and the more the modeling increases in complexity, the more cross correlations can be performed.

Therefore, the first step must entail clearly organizing all the scales used to classify patients; for example, biomarker ranges, clusters of symptoms, imaging records and interpretation. Next, all attempts to detect cross correlations and co-morbidities via indicators should be cataloged. This would constitute a useful database in itself, and would point the way towards developing systems medicine computational modules by identifying dominant elements that could and should be incorporated into models.

Although some data are non-quantitative and collected only once for a given patient, other data may be collected as time series; for example, multiple biomarkers from blood or excreted samples, biopsies and imaging. These data may be treated discretely, or fit by functions in order to compare data taken at different time points and cross correlations can be calculated between these data functions.

In modeling data for multiple patients, much better results might be obtained by stratifying large groups of patients into smaller groups that share similarities. New multiple disease phenotypes and their single or multiple combinations of biomarkers, each with variable "danger" levels according to the new phenotype, will continually emerge from this new and extensive means of analysis.

5. ETHICAL CONSIDERATIONS

The exploratory nature of this study, in which data from routine clinical examinations and experimental procedures are compiled, makes a careful consideration of ethical issues a priority. During the admission procedure, all eligible subjects are requested to sign an informed consent form prior to being enrolled in the platform project, and to allow both the current and future use of biological samples, including the potential for unforeseen applications based upon newly-defined questions or novel technologies. A trained physician collects each patient's consent, after explaining the aim of the study, the need to monitor participants for further hospitalizations and mortality information, and the fact that participation in the study will involve only indirect benefits to them, in terms of a better understanding of complex diseases. Patients who agree to participate are then informed about their right to withdraw their consent at any time.

All ethically-relevant procedures have been planned in agreement with international guidelines for bio-repositories [109, 110, 111]. The project pursues the implementation of Good Clinical Practice in the conduct of clinical trials on human volunteers, as recommended by the European Directive 2001/20/EC [112] and 2005/28/EC [113]. Individual data included in the SR-NCDs are treated in accordance with Italian privacy regulations (DL 196/2003) [114].

The SR-NCDs platform is intended as a tool for the implementation of SM and molecular epidemiology translational studies. External scientific collaborations are actively pursued and applications to access stored specimens and epidemiological/clinical data

Table 3. Description of clinical and instrumental information collected from all patients enrolled in the San Raffaele Non Communicable Diseases Platform (SR-NCDs) (common module) and for patients with positive anamnesis or symptoms of specific diseases.

Module	Clinical and instrumental exams, rating scales
Common	Physical examination Blood tests Urine tests ECG Pulse Oximetry Drug therapy Presence of medical devices (oxygen, mechanical ventilation) 1) The modified Cumulative Illness Rating Scale (MCIRS) [61,62] 2) Mini Mental State Examination (MMSE) [63] 3) Rey-Osterrieth Complex Figure Test (ROCF) [65] 4) Montreal Cognitive Assessment (MoCA) [64] 5) Brief COPE [68] 6) Centre for Epidemiologic Studies for Depression Scale (CES-D) [66] 7) Zung Self-Rating Anxiety Scale (SAS) [67] 8) The Short Form (36) Health Survey (SF-36) [69] 9) Activities Of Daily Living (ADL) [70] 10) Instrumental Activities Of Daily Living (IADL) [71]
Respiratory/ Cardiovascular	Echocardiogram Cardiopulmonary Test 24 hours ECG monitoring Blood gases analysis Spirometry Expectorate Nocturnal Oximetry Bronchoscopy and bronchoalveolar lavage St.George Respiratory Questionnaire (SGRQ) [72,73] Maugeri Foundation Respiratory Failure Questionnaire (MRF26) [75] Modified Medical Research Council Dyspnoea Scale (MRC) [76] 6 Minute Walking Test (6MWT) [77] Bode Index for COPD [78] Modified Borg Dyspnoea Scale [79] Barthel Index [80]
Lung cancer	Tumoral Markers (Cyfra 21-1, CEA, Enolasi) and miRNA Radiological Findings (tumor size, H.U. value and morphological characteristics) Pathological Findings (histotype, grade, mitotic index, expression of bcl-2 and p53, immunohistochemical positivity for TTF-1) Genetic mutations on the surgical specimen (EGFR, ALK, K-RAS)
Psychiatric	Operational Criteria Checklist for psychotic and affective illness (OPCRIT) [81] Brief Psychiatric Rating Scale (BPRS) [82] Hamilton Rating Scale for Depression (HRSD) [83] Young Mania Rating Scale (YMRS) [84] Hamilton Anxiety Scale (HAM-A) [85] Positive and Negative Syndrome Scale (PANSS) [86]

(Table 3) Contd….

Module	Clinical and instrumental exams, rating scales
Headache and pain	The Migraine Disability Assessment Questionnaire (MIDAS) [87] Headache Impact Test (HIT-6 ™) [89] Visual Analogue Scale (VAS) [90] Neuropathic Pain Scale [91]
Alzheimer's Disease	Neuropsychiatric Inventory (NPI) [93] Assessment of focal deficits (strength, somatic sense, visive field) MDB (Mental Deterioration Battery) [92]: • Rey's Auditory Verbal Learning Test (RAVLT immediate and delayed recall) • RAVLT Recognition • Copy of figures with and without landmarks, • Digit Span Forward and Backward • Stroop Test • Phonological and Semantic Verbal Fluency • Multiple Features Targets Cancellation • Oral naming of nouns and action • Raven's Colored Progressive Matrices
Parkinson's Disease	Unified Parkinson's Disease Rating Scale (UPDRS) [94] Parkinson's Disease Sleep Scale (PDSS) [95] The Epworth Sleepiness Scale (ESS) [96] Abnormal Involuntary Movement Scale (mAIMS) [97] Unified Diskinesia Rating Scale (UDysRS) [98] MIDI Minnesota Impulsive Disorders Interview (MIDI) [99] Progressive supranuclear Palsy Rating Scale [100] Non Motor Symptoms scale and questionnaire (NMS) [101] Wearing Off Questionnaire (WOQ 19) [103] Parkinson's Disease-Cognitive Rating Scale *(PD-CRS)* [105] Unified Multiple System Atrophy Rating Scale (UMSARS) [104] Beck Depression Inventory (BDI) [106] Parkinson's Disease Questionnaire (PDQ-39) [107,108] Neuropsychiatric Inventory (NPI) [93]
Diabetes type 2	Fundus oculi examination Doppler ultrasound of carotid and neck vessels, and of lower limbs Computer Tomography Angiography (CTA) legs Assessment of autonomy and peripheral neuropathy Diabetic foot screening

from research groups interested in NCDs are encouraged. Dedicated procedures have been developed to protect the basic ethical rights of enrolled patients. A steering committee composed of the coordinators of the platform, as well as a member of each unit involved in the network, including the epidemiology and laboratory teams, reviews all requests. Applications are evaluated according to the scientific interest of the proposal, the qualification of proponents, the absence of ethical concerns, and the availability of aliquots for requested samples. If the steering committee authorizes the collaboration, the researcher who will receive samples or clinical data from the SR-NCDs platform is asked to sign a Material Transfer Agreement form before sample shipment is completed, so as to ensure that research fairness and compliance with all rules for the ethical conduct of biomedical research activities are respected.

6. CONCLUDING REMARKS

NCDs are among the most serious global health problems in the twenty-first century, mostly generated by disturbed gene-environment interaction networks over time. Global unbiased approaches, also taking into account parameters not strictly related to clinical practice — like the socio-economical and psychological sphere of the individual, as well as bringing into play extensive genomic, cellular and molecular global measurements — offer the potential for more effective and individualized diagnosis, prognosis, and treatment options [115].

This innovative approach, which started with Systems Biology, has the goal of recreating, within a virtual space, the complexity of disease pathways and interaction networks, allowing for a novel and quantitative understanding of the underlying non-linear biology. This is implemented via Systems Medicine, which brings into the study design the highly heterogeneous data collected in real clinical practice. System-level models of the interactions between biological and clinical features are constructed both to identify new ontologies and to improve disease recognition and treatment.

Despite the extensive literature addressing the transition from SB to SM and the core characteristics of SM for specific clinical phenotypes, little information is available on multi-scale model building, or on the validation of tools for implementing system modeling of disease. Most authors consider the implementation of disease and multi-disease platforms as the best way to support an SM approach [13, 15, 16, 21], as the strength of multi-disease clinical platforms lies in the unbiased manner in which studies on multimorbidity can be conducted. A standardized, multidimensional assessment is provided for all patients enrolled in the SR-NCDs platform, regardless of their initial diagnosis at the time of hospital admission. A multi-disease clinical platform with extensively characterized patients might support molecular and cellular biology studies on intermediate and novel phenotypes (identified via the integration of high-dimensional multi-omic datasets) and provide a basis for more targeted clinical trials.

Finally, when incorporated into a network of clinical facilities focused on rehabilitation, such as the San Raffaele network, multi-disease clinical platforms will enable us to estimate how an SM approach to disease treatment and prognosis may impact the escalating costs of healthcare.

CONFLICT OF INTEREST

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

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