Chapter 13

From Systems Understanding to Personalized Medicine: Lessons and Recommendations Based on a Multidisciplinary and Translational Analysis of COPD

Josep Roca, Isaac Cano, David Gomez-Cabrero, and Jesper Tegnér

Abstract

Systems medicine, using and adapting methods and approaches as developed within systems biology, promises to be essential in ongoing efforts of realizing and implementing personalized medicine in clinical practice and research. Here we review and critically assess these opportunities and challenges using our work on COPD as a case study. We find that there are significant unresolved biomedical challenges in how to unravel complex multifactorial components in disease initiation and progression producing different clinical phenotypes. Yet, while such a systems understanding of COPD is necessary, there are other auxiliary challenges that need to be addressed in concert with a systems analysis of COPD. These include information and communication technology (ICT)-related issues such as data harmonization, systematic handling of knowledge, computational modeling, and importantly their translation and support of clinical practice. For example, clinical decision-support systems need a seamless integration with new models and knowledge as systems analysis of COPD continues to develop. Our experience with clinical implementation of systems medicine targeting COPD highlights the need for a change of management including design of appropriate business models and adoption of ICT providing and supporting organizational interoperability among professional teams across healthcare tiers, working around the patient. In conclusion, in our hands the scope and efforts of systems medicine need to concurrently consider these aspects of clinical implementation, which inherently drives the selection of the most relevant and urgent issues and methods that need further development in a systems analysis of disease.

Key words Clinical decision support, Integrated care, Comorbidity, Disease modeling, Knowledge management

1 Introduction

The ultimate aim of personalized medicine [1] is to design and deliver healthcare interventions adjusted to the needs of the individual patient. In practice, this translates into the process followed to establish an individual longitudinal health plan with well-identified objectives for each patient. Such an approach aims at fostering optimization of health outcomes, preventing both useless and/or harmful effects provoked by some medical interventions,

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and enhancing healthcare value generation and cost containment provided that care delivery is done in the appropriate setting. It should be highlighted that generalization of the practice of personalized medicine remains a vision still far away from the characteristics of current healthcare practice.

A systems approach to health, understood as a holistic analysis of health determinants including multilevel integration of information and data analytics using computational modeling, constitutes a fundamental requirement to pave the way toward personalized medicine. But, systems medicine represents only a key methodological orientation needed to achieve a medical practice based on the principles that define personalized medicine as one of the components of a 4P medicine strategy (personalized, predictive, preventive, and participatory) [1]. Here we review challenges and opportunities within the area of systems medicine as well as issues related to the implementation of personalized medicine in the clinic based on a systems medicine approach.

1.1 Drivers of the Changing Landscape of Medicine and Clinical Practice

The interplay between three driving forces pushing toward a radical change in the health paradigm are major epidemiological changes [2], the urgent need for increasing healthcare efficiencies to ensure sustainability of current health systems [3–5], and a novel approach to practice based on a network medicine analysis facilitating an understanding of disease mechanisms for different subgroups of patients within and between comorbid diseases [6–8]. Overall, these three driving forces are significantly contributing to shape the concept of personalized medicine, as well as to the design of strategies to make that concept progressively a reality in specific medical areas.

Over the last years, the still-increasing epidemics of noncommunicable diseases (NCDs) [2] has been the principal triggering factor for a profound reshaping of the way we approach delivery of care for chronic patients [9, 10]. This has been so, mainly because of the interplay of two main factors: population aging and unhealthy lifestyles [2] leading to a high burden worldwide on both healthcare and societal aspects. Major disorders responsible for such a burden are cardiovascular conditions; cancer; chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD); type II diabetes mellitus; and mental illnesses [5].

Integrated care, following the chronic care model [9–11], is widely accepted as a conceptual approach to profoundly redesign future health systems to face the challenge generated by NCDs and to pave the way for personalized medicine for chronic patients. In this new scenario, conventional disease-oriented approaches, centered on the management of clinical episodes, are being and ought to be replaced by articulation of novel patient-centered integrated care services. Such a transition has proven successful in areas wherein one organization is providing care [12–14], but extensive

deployment of integrated care services in settings with heterogeneous healthcare providers remains a challenge [11].

The three major barriers for adoption of integrated care [11] are (1) change of management, (2) implementation of appropriate business models, and (3) adoption of information and communication technologies (ICT) providing organizational interoperability among professional teams across healthcare tiers, working around the patient. Different ongoing initiatives aiming at enforcing the transition toward adoption of the novel healthcare model, such as the EIP-AHA (European Innovation Partnership on Active and Healthy Ageing) [9] as well as the program currently being shaped by the European Institute of Technology for Health (EIT-Health), are generating and disseminating specific proposals to foster extensive deployment of integrated care.

It is currently well accepted that extensive deployment of ICT-supported integrated care services may contribute to enhance health outcomes without increasing overall costs of the health system. One of the main factors generating healthcare efficiencies is individualized health risk prediction and stratification fostering delivery of care in the most appropriate setting. Targeting stratification and thereby improving individualized predictions is therefore not only a major challenge in realizing personalized medicine but is also significant opportunity using new techniques for multidimensional data collection and analysis [15]. Cost savings are partly achieved by the transfer of service complexities from specialized to primary care. Moreover, it is generally hypothesized that the generation of health efficiencies can be markedly boosted by promoting a more active role of both citizens and patients allowing implementation of novel cost-effective preventive strategies aiming at modulating disease progress.

As alluded above, adoption of proper strategies for patient's health risk assessment and stratification constitute a key element for large-scale deployment of integrated care. However, current stratification tools [4] rely on population-based analyses [16–18] of past use of healthcare resources. They are useful to support interventions and/or to define health policies at group level, but show limitations for clinical applicability at patient level. It is of note that these predictive tools have proven potentially useful for case-finding purposes, that is, for detection of citizens showing high-risk occurrence of major undesired health events such as unplanned hospitalizations, fast functional decline, and/or risk of death. However, scalability of the existing predicting tools for case finding and their transferability into the clinical area still requires further developments. It is acknowledged that this level of stratification is currently not sufficiently sophisticated, and it is very far from the concept of personalized medicine. Current changes in the landscape of risk assessment are driven largely by the convergence of two trends: (1) phenomenal advances in molecular and

systems biology leading to a progressively mature network medicine [9, 19–21] and (2) ICT-supported integrated care facilitating novel scenarios for data analytics, including longitudinal analyses combining biological and nonbiological phenomena [22]. These two drivers are prompting adoption of the emerging methods in systems medicine as tools to inform risk assessment and decision-making in the clinical arena that, ultimately, should contribute to shape personalized medicine to its full extent.

1.2 Convergent Strategies Toward Personalized Medicine

The adoption of the novel health paradigm involves convergence between adoption of the integrated care approach [10, 11] and a holistic (systems medicine) orientation aiming at generating knowledge on different dimensions (scales) in space and time influencing disease that cannot be achieved otherwise. It is currently accepted that only a small proportion of disease susceptibility (~10%) is explained by genetic variants identified to date [23]. As it has been noted [23], moving forward requires greater awareness and inclusion of what is referred to as the exposome paradigm. The concept of exposome, which consists of all of the internal and external exposures an individual incurs over a lifetime, is dynamic and variable and changes with age. The concept offers an expansive view of environmental exposures over the life course and is likely to contribute to clarify disease etiology and mechanisms. Efforts should be made to combine information from different levels (Fig. 1) in order to identify possible causal pathways and opportunities

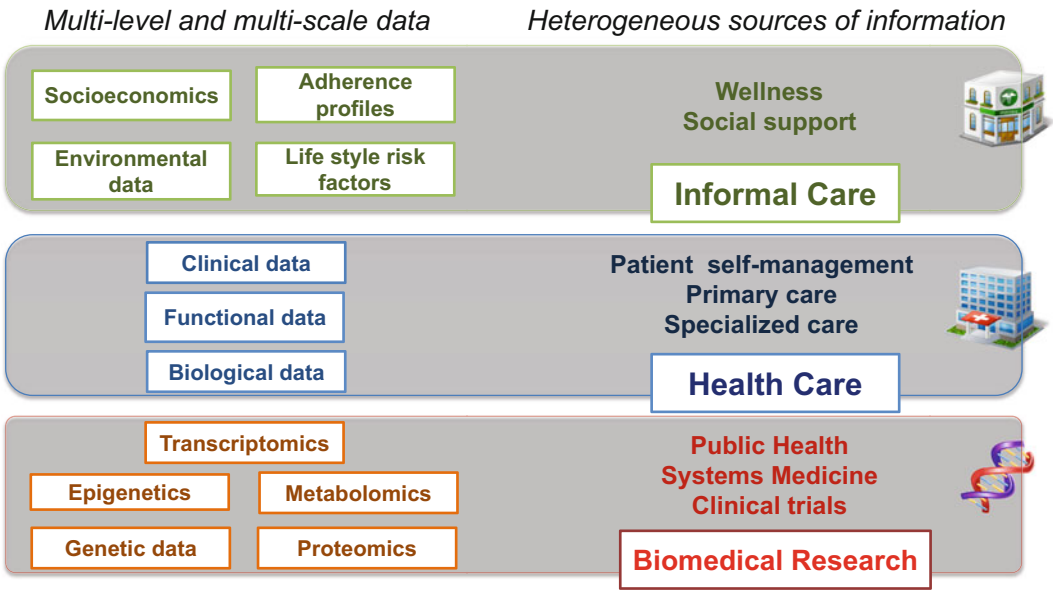

Fig. 1 Integration of heterogeneous multilevel and multi-scale data is needed to encompass all dimensions modulating patient health status. To this end, communication among informal care, healthcare, and biomedical research constitutes a key functional requirement that was addressed in the Synergy-COPD project through the concept of Digital Health Framework (DHF)

for intervention. Consequently, additional research is needed to clarify biological, as well as nonbiological, mechanisms and their causality in exposure-disease associations. It has become increasingly evident that such a program requires new methods and approaches enabling integrative bioinformatics to bridge between these different levels of description, ranging from molecules to clinical phenotypes [24]. Moreover, to dissect causal relationships operating at different scales, it is necessary to use different types of mathematical modeling facilitating an analysis of the causal effect of different types of interventions [15]. Ongoing collaborative efforts to decode the human epigenome [25] are likely to be key in combining different "omics" levels, as well as clinical data, with information about environmental exposures, behavioral profiles, and socioeconomic traits that individuals incur over a lifetime. Recently, emerging evidence suggests that the effect of environmental and lifestyle-related factors is mediated through the epigenome [26].

In this regard, the epigenome may serve as the bridge for traditional healthcare delivery (i.e., formal care) and informal care (e.g., patient self-management, wellness programs, social care) through adoption of citizen's (patient's) personal health records as management tools. In this new scenario, the appropriate articulation of patient gateways and mobile devices, also known as mHealth [27], is promising to empower for the first time an efficient channel enhancing accessibility to the health system, facilitating monitoring, and including patient's behavioral and environmental factors into health management. The ultimate goal of patient gateways is to support cost-effective preventive interventions to modulate the evolution of the disease, which might represent tremendous sources of efficiencies if in place.

1.3 COPD as an Instructive Use Case

Chronic obstructive pulmonary disease (COPD) is a prevalent chronic respiratory disease that is currently the fourth leading cause of mortality [2]. It is caused by inhalation of irritants, mainly tobacco smoking, in susceptible patients. However, only approximately 15–20% of all tobacco smokers are prone to develop the disease, and there is marked individual variability of both clinical manifestations and COPD progression [28–30] with relevant implications in terms of health risk assessment and patient management [31]. Moreover, COPD patients can also show systemic effects of the disease [31, 32] and comorbid conditions [33]. Highly prevalent chronic conditions such as cardiovascular disorders (CVD) and type 2 diabetes mellitus (T2DM)-metabolic syndrome (MS) and anxiety-depression often occur as a comorbidity cluster in COPD patients [31, 34]. Likewise, the risk of lung cancer is increased in these patients such that it can conceptually also be considered as a comorbidity of COPD [35]. There is evidence suggesting that systemic effects of the disease and comorbidity clustering are independently associated with poor prognosis [31].

Since COPD is a highly heterogeneous disorder and that comorbidities are one of the most relevant phenomena that modulates patient prognosis, the disease constitutes an optimal use case to address complexity of chronic conditions in general. There is a strong rationale for further research on subject-specific health risk prediction and stratification aiming at enhancing cost-effective management of COPD patients. The ability to better understand heterogeneity of COPD [36] should permit the development and implementation of therapeutic strategies that are specific for subgroups of patients, as well as the development of new therapies [37]. From the strategic standpoint, the approach will likely show transferability to other complex chronic conditions.

1.4 Synergy-COPD

Synergy-COPD (2011–2014) [38] was a European Union project, within the Virtual Physiological Human 7th Framework Program, conceived to explore the potential of systems medicine to generate knowledge on underlying mechanisms of chronic obstructive pulmonary disease (COPD) heterogeneities observed in the patients both in terms of clinical manifestations and disease progression [28, 31]. A core component of the project was the transfer of the acquired knowledge into the clinical arena with a twofold purpose. Firstly, analysis of the role of a systems approach to COPD heterogeneity to enhance individual health risk assessment and stratification leading to innovative patient management strategies. The second purpose was to identify novel modalities for the interplay between healthcare and biomedical research aiming at fostering deployment of 4P medicine for patients with chronic disorders [39–41]. Ultimately, Synergy-COPD was designed to generate outcomes in three different dimensions: (1) biomedical area, (2) information and communication technologies (ICT), and (3) transfer into healthcare.

The central biomedical hypothesis of the project was that heterogeneities observed in COPD patients cannot be explained by the activity of pulmonary disease only, as suggested by an organ-centric vision of the disease [42]. Alternatively, it is hypothesized that abnormalities in co-regulation of core metabolic pathways (bioenergetics, inflammation, tissue remodeling) at systemic level seem to play a central role on both systemic effects of COPD and comorbidity clustering often seen in these patients. In this scenario, overlap among certain modules of the interactome could be expected in complex COPD patients [6]. Moreover, there is evidence that oxidative stress is a characteristic feature of the disease [43] likely playing a central causal role in complex COPD. To this end, relationships among cell oxygenation, bioenergetics, and abnormal reactive oxygen species (ROS) generation were analyzed as a relevant part of the project.

The current chapter describes how a systems-oriented research on COPD heterogeneity generated novel knowledge, not achievable

through classical methods. It indicates the elevated potential for generalization of the research findings to other prevalent chronic disorders. Moreover, it describes relevant bottlenecks encountered during the project's development as well as recommends effective strategies to overcome the barriers to pave the way for a stepwise implementation of personalized medicine for chronic patients.

2 Project Outcomes

Lessons learned during the Synergy-COPD life span are grouped in three main fields: (1) biomedical outcomes, (2) ICT-related achievements, and (3) strategies for transfer of the project results into healthcare. Under the current subheading, description of project outcomes combines analysis of well-defined achievements with identification of bottlenecks that precluded further progress during the EU project.

2.1 Biomedical Challenges

The biomedical rationale of the entire project was based on the results of an unbiased clustering analysis of clinically stable COPD patients, the PAC_COPD (*phenotypic characterization and course of COPD patients*) study [44], assessed after their first hospitalization and followed up during a 5-year period. The study identified and prospectively validated three COPD subtypes: (1) *group I*, severe respiratory COPD; (2) *group II*, moderate respiratory COPD patients in whom the most distinctive trait was a dissociation between severe emphysema score together with mild to moderate airway remodeling leading and moderate airflow limitation, as expressed by forced expiratory volume during the first second (FEV_1); and (3) *group III*, including COPD patients in whom the most characteristic trait was comorbidity clustering, mainly cardiovascular disorders (CVD) and type II diabetes mellitus (T2D) often accompanied by metabolic syndrome (MS). It is of note that skeletal muscle dysfunction was a transversal characteristic with patients distributed in all three PAC_COPD groups [45]. The findings of the PAC_COPD study prompted the need for tackling COPD heterogeneity with a systems approach and prompted the four main biomedical challenges described below.

2.1.1 Abnormal Regulation of Relevant Skeletal Muscle Biological Pathways

Integrative multilevel analyses of skeletal muscle of healthy subjects and COPD patients [46] including different "omics" layers (transcriptomics, epigenetics, proteomics, and metabolomics), physiological characteristics, and clinical information generated strong evidence of abnormal regulation of muscle bioenergetics both at baseline and after the perturbation of the biological system by a standard endurance training protocol. Abnormal training-induced adaptations were observed at several different levels of the mitochondrial respiratory chain, but also in the interplay between

oxidative and glycolytic pathways, as well as in fatty acid metabolism. Network analysis of metabolic pathways indicated abnormalities in key mechanisms governing skeletal muscle bioenergetics and ribosome biogenesis [8], such as mTOR and its interplay with the insulin signaling pathway. Interestingly, the different analyses carried out in COPD patients consistently showed abnormal relationships between cytokines and tissue remodeling at baseline and after training. These results were supported by experimental animal studies in guinea pigs and mice wherein it was shown that combined effects of tobacco smoking and cellular hypoxia may generate abnormal inflammatory responses [47].

Acknowledged limitations for the multilevel analysis of the interactome in the skeletal muscle in COPD patients with and without systemic effects and in healthy subjects, studied before and after endurance training, were both the reduced sample size and the unbalanced number of subjects in each study group.

2.1.2 Increased Risk of Comorbid Conditions in COPD Patients

Using 13 million health records from US Medicare [48, 49], the project identified 27 disease groups (DG) with significantly elevated risk to co-occur with COPD; in all cases, the risk increased with aging. These groups included both well-established associations like CVD or lung cancer, but also unexpected ones, like digestive track disorders, that could be interesting candidates for more focused follow-up investigations. For each DG, we constructed a comprehensive list of known associated genes from the literature, and by performing a pathway enrichment analysis, a number of pathways that are shared between different disease groups were identified, suggesting that the observed comorbidities are indeed rooted in shared molecular mechanisms. By further inspecting the characteristics of the interactome, the project was able to identify a number of genes with the potential to characterize COPD comorbidities. Ongoing analyses on potential biomarkers predicting the level of comorbidity remain to be validated in further studies.

2.1.3 Identification of COPD Candidates for Lung Cancer Case Finding

An ancillary aim of the project was the analysis of group II of the PAC_COPD study [44] using the mechanistic model of spatial pulmonary heterogeneities as described in [50] in order to generate rules for identification of this subset of COPD patients in primary care. The rationale behind this approach is that this subset of COPD patients could be a candidate for screening programs for early diagnosis of lung cancer, which is one of the priorities in respiratory medicine. The literature appears to indicate that dissociation between high emphysema score and mild airway remodeling is associated with a higher probability of developing lung cancer [35]. Unfortunately, the maturity of the modeling development did not allow completion of the analyses as initially planned.

2.1.4 Computational Modeling for Better Understanding Biological Mechanisms of Disease

The project combined several system-based modeling approaches, probabilistic and mechanistic [51], to further explore underlying responsible mechanisms of the three biomedical areas alluded above, namely, (1) skeletal muscle dysfunction, (2) comorbidity clustering, as well as (3) group II from the PAC_COPD study [44]. Moreover, a novel application of existing modeling techniques, Bayesian analyses [52] and Thomas network formalism [53], assessing the interplay between probabilistic and mechanistic modeling, was used aiming at expanding the potential of future systems-oriented analyses of biological phenomena, as explained in detail in [51].

Overall, both the modeling developments and the strategies adopted showed to be useful to explore the biomedical challenges of the project and to identify potential biomarkers. Moreover, the interplay between the two main modeling strategies indicated the potential of probabilistic modeling approaches to contribute to parameter refinement in mechanistic modeling (e.g., enhanced parameter estimation for mitochondrial function in the integrated model).

Overall, the biomedical results seem to support the central hypothesis of the project indicating that abnormal regulation of pivotal pathways at systemic level can contribute to both comorbidity clustering and systemic effects in COPD patients. Moreover, the analyses support a causal role for nitroso-redox disequilibrium [54] as contributor to the abnormal pathway regulations observed in COPD. Accordingly, individual susceptibility to deregulation of metabolic pathways, together with epigenetic mechanisms, may play a role modulating both systemic effects and comorbidity clustering in these patients, beyond well-known risk disease factors, such as tobacco smoking. Despite that the results from different animal experiments carried out during the project lifetime seem to provide support to our interpretations, we fully acknowledge that further validation of the current speculations is required before we move to transfer of knowledge into the clinical scenario, as discussed in the following sections of the current chapter.

2.2 ICT Challenges: Digital Health Framework

The formulation of the concept, detailed characteristics [41], and road map for deployment of a Digital Health Framework (DHF) was one of the most relevant achievements of the project (Fig. 2). The DHF aims to embrace the emerging requirements—data and tools—for applying systems medicine into healthcare with a three-tier strategy articulating formal healthcare, informal care, and biomedical research. Accordingly, it has been constructed based on three key building blocks, namely, novel integrated care services with the support of information and communication technologies, a personal health folder (PHF), and a biomedical research environment (DHF-research). Details on the functional requirements and necessary components of the DHF-research were extensively

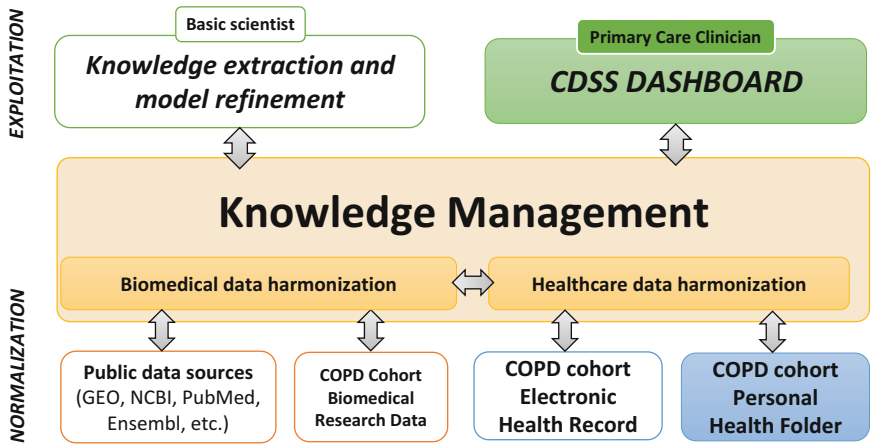

Fig. 2 Diagram describing the core elements of a Digital Health Framework fostering communication among: (1) informal care, (2) healthcare, and (3) biomedical research. The color-filled areas are the areas prioritized for development in the DHF deployment road map

presented in [41]. The specifics of the building block strategy for deployment of the DHF and the steps toward adoption are analyzed during the project lifetime, and recommendations for implementation at local level have been formulated. The proposed architectural solutions and implementation steps constitute a pivotal strategy to foster and enable 4P medicine (predictive, preventive, personalized, and participatory) in practice and should provide a head start to any community and institution currently considering to implement a biomedical research platform.

2.2.1 Data Harmonization, Data Analytics, and Knowledge Generation

The COPD knowledge base (COPDKB) developed [55] in Synergy-COPD provides interoperability and integration between multiple data sources and tools commonly used in biomedical research. The COPDKB is based on the concept of "knowledge as network" and bridges multiple sources and scales of knowledge by abstracting commonly used concepts to communicate disease-specific knowledge into objects and their relations. Structuring explicit and implicit knowledge into these formal concepts enables the use of existing, well-defined vocabularies (e.g., GO [56], ICD10 [57]) and standards (e.g., SBML [58], HL7 [59]) to represent molecular, biochemical, and clinical processes. The COPDKB plays a key role facilitating the interplay with public datasets for omics analyses, as displayed Table 1.

The use of computation models in biomedical research poses the challenge of the integration of models at different scales as well as the mapping to corresponding clinical, physiological, or molecular data. We defined standard operating procedures for model documentation and developed a concept of orthogonal ontology use to create semantic descriptions for models, model parameters, and clinical parameters. These included standards for the definition of spatiotemporal compartments to allow ontology-based

Table 1
List of public datasets for omics analyses included in the COPDKB

Bioassays	DrugBank	ICD-9/10	miRBase	Prosite
BIND	EMBL	ITFP	miRTarBase	Pubchem
BioGrid	Ensembl	IntAct	miRWalk	Reactome
BRENDA	Enzyme	IPI	OMIM	REBASE
CATH	EPD	KEGG	PDB	RefSeq
ChEBI	FASTA	LIGAND	PDQ clinical trials	SBML
CHEMBL	GenBank	LIPID maps	Pfam	SCOP
ChemIDplus	GEO	Medline	PharmGKB	SMART
ClinicalTrials.gov	GenPept	MEROPS	PLACE	Taxonomy
COG	GOA	MeSH	Plant-QTL	TransFac
COSMIC	Gramene	MiMI	Prints	TransPath
CTD comparative	HSSP	MINT	ProDom	Unigene
dbSNP	Human metabolome	MGI Phen	Prolink	UniProt

model-model and model-data connection. The orthogonal ontology use allows generating semantic descriptions of complex statements such as "partial arterial oxygen pressure" which are not represented in any current ontology.

A network search enables the use of interconnecting information and the generation of disease-specific subnetworks from general knowledge. Integration with a clinical decision-support system allows delivery into clinical practice.

The COPDKB is the only publicly available knowledge resource dedicated to COPD and combining genetic information with molecular, physiological, and clinical data as well as mathematical modeling. Its integrated analysis functions provide overviews about clinical trends and connections, while its semantically mapped content enables complex analysis approaches. The COPDKB is freely available after registration at www.copdknowledgebase.eu.

2.2.2 *User Profiled Interfaces*

Figure 2 identifies two well-defined user profiles: (1) practicing clinician and (2) scientist performing basic and/or translational research. Practicing physicians, as described below, will require clinical decision-support systems (CDSS) with an adaptive visualization interface responsible for presenting a meaningful view of all relevant patient-specific data as well as dynamic predictions and recommendations generated by the reasoning systems component of the CDSS. It is of note, however, that beyond formulation of the two basic user profiles, no further progress was done within the project life span.

Table 2
Clinical decision-support systems (CDSS) for COPD management in an integrated care scenario

1. Early diagnosis—COPD case-finding program The suite of CDSS supports the regional deployment of a program of early COPD diagnosis targeting citizens at risk examined in pharmacy offices and non-diagnosed patients studied in primary care. Additional objectives of the program are to ensure high-quality forced spirometry accessible across healthcare tiers, as well as prevention of overdiagnosis of COPD in the elderly (73)
2. Enhanced stratification of COPD patients It should include three families of CDSS with well-differentiated objectives: (1) enhance applicability of the 2011 GOLD Update criteria for COPD staging; (2) facilitate offline comparisons with other COPD staging criteria, namely, BODE, DOSE, ADO, etc.; and (3) enhanced patient-based health risk assessment and stratification
3. Community-based integrated care program The suite of CDSS aims at supporting different integrated care services fostering the transfer of complexity from specialized care to the community with an active role of patients. The two programs being deployed are (1) sustainability of training-induced effects and promotion of physical activity in clinically stable moderate to severe COPD and (2) management of patients under long-term oxygen therapy (LTOT). The two programs were assessed within NEXES [69], as part of the deployment of integrated care services in the health district of Hospital Clinic

2.3 Transfer to Healthcare

As part of the strategies for transferring novel biomedical knowledge into the clinical arena, the three families of clinical decision-support systems (Table 2) were conceived to be embedded into the clinical processes at primary care level using an ICT platform supporting integrated care services [60]. The three CDSS families displayed in Table 2 show heterogeneous degrees of deployment: (1) early COPD diagnosis is ready for deployment at regional level in Catalonia (ES) within 2015–2016; (2) enhanced COPD stratification was only formulated conceptually without real deployment so far; and (3) community-based COPD management encompasses two programs being prepared for deployment at healthcare sector level (urban area of 540,000 inhabitants in Barcelona).

2.3.1 Early Diagnosis of COPD

The program has a twofold aim: (1) achievement of high-quality spirometry in primary care and (2) COPD case-finding program in both primary care [61] and pharmacy offices [62]. It encompasses different aspects: (1) remote support to automatic assessment of quality of forced spirometry in the community including offline support of specialized professionals if needed [63], (2) standardization of forced spirometry information and accessibility to testing across levels of care and providers, and (3) enhanced communication and support to coordination between informal care (pharmacy offices) and formal care (primary care and specialists). Accomplishment of regional deployment of the program should generate the following outcomes: (1) enhanced quality of testing;

Table 3
Risk classification of COPD patients according to the 2011 Gold Update

Risk GOLD classification					Risk exacerbation history
	3–4	(C) High risk, less symptoms	(D) High risk, more symptoms	≥2	
	1–2	(A) Low risk, less symptoms	(B) Low risk, more symptoms	0–1	
mMRC 0–1 CAT < 10			mMRC ≥ 2 CAT ≥ 10		

The *2011 COPD Update* [28] defines four risk categories for COPD patients (A to D) depending upon: (1) *symptoms* (modified dyspnea score from the Medical Research Council, mMRC) or CAT questionnaire; (2) *spirometric classification*: GOLD I: $FEV_1 \geq 80\%$ pred; GOLD II: $50\% \leq FEV_1 < 80\%$ pred; GOLD III: $30\% \leq FEV_1 < 50\%$ pred; and GOLD IV: $FEV_1 < 30\%$ and/or $PaO_2 < 60$ mmHg breathing F_IO_2 0.21); and (3) *frequency of exacerbations per year*. Recent reports have assessed the predictive value of this classification

(2) early COPD diagnosis, (3) enhanced case management, and (4) open new avenues for early detection of patients with abnormally fast lung function decline and/or those with abnormal biological variability of testing suggesting bronchial hyperresponsiveness.

2.3.2 Enhanced Stratification of COPD Patients

Patient-based health risk assessment and stratification for COPD patients is an unmet need. Appropriate patient stratification including various aspects of COPD heterogeneity, namely, (1) pulmonary disease severity, (2) disease activity, (3) systemic effects, and (4) comorbidities, is still a challenge for COPD patients. The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) (Table 3) has represented one step forward in terms of assessment of expert-based knowledge in the field, but the proposed approach based on (1) lung function impairment, (2) symptoms, and (3) exacerbations has not yet been fully validated [64]. Moreover, several composite indices of COPD severity with proven prognostic accuracy have been developed in single studies (i.e., various BODE indices: ADO, DOSE, CODEX [65–68]), but no comprehensive comparisons are available to support evidence-based strategies for patient-based stratification in COPD. A better understanding of COPD heterogeneity should permit the development and implementation of both therapeutic strategies for subgroups of patients aiming at generating cost-effective preventive interventions fostering synergies between pharmacological and non-pharmacological approaches. Yet, Synergy-COPD was not able to develop a consistent strategy to approach the problem, as discussed below.

Future developments should be likely based on CDSS combining expert-based knowledge and outcomes from patient-based risk prediction modeling taking into account holistic approaches that consider all the elements included in Fig. 1. Unfortunately, refined strategies to achieve this goal are not in place yet.

2.3.3 Community-Based Integrated Care Management of COPD Patients

Deployment experiences of integrated care services [69] developed in parallel with Synergy-COPD have demonstrated positive health outcomes together with cost containment through the transfer of healthcare complexity from specialized care to the community fostering an active and participatory role of both citizens at risk, patients and carers. In this scenario, the use of CDSS to support health professionals for chronic care management appears as an effective approach to transfer novel biomedical knowledge into healthcare. Such an approach was successfully addressed through qualitative assessment approaches in the validation work package of the project. Moreover, the parallel deployment experiences [69] carried out during the lifetime of the project identified the high potential of the personal health folder (PHF) [70] for transferring different types of nonmedical patient information, namely, lifestyles, social frailty, adherence profile, etc., into formal healthcare, as detailed in [41].

2.3.4 CDSS Design

Key factors that contribute to successful CDSS outcomes in terms of impact in healthcare are (1) decision support integrated into the clinical workflow, (2) decision support delivered at the time and place of decision-making, and (3) actionable recommendations [71]. Thus, one of the important aspects that should be taken into account in the design of the CDSS is the ability to interface to existing health information systems that are already used by the intended target users of the CDSS. The implementation challenge is to design a modular CDSS framework that is portable enough to be deployed in various site clinical environments and be able to enhance the day-to-day workflow of the target clinical user with minimal impact on additional overhead.

Major factors to be taken into account in the design and implementation of CDSS are (1) the need to interface to existing health information systems in place in each of the sites, (2) a modular CDSS framework that is flexible enough to be deployed in various pilot clinical environments, and, finally, (3) the capacity to enhance the day-to-day workflow of the target clinical users. CDSS should comprise three main components: (1) an adaptive visualization interface responsible for presenting a meaningful view of all relevant patient-specific data as well as dynamic predictions and recommendations generated by the reasoning systems component, (2) a reasoning system operating on clinical rules from expert knowledge-based models and health risk predictive modeling tools, and (3) a patient data exchange module that should implement one or more interoperable clinical information standards (such as HL7, EN/ISO 13606) for receiving and uploading patient-specific data to the existing health information system.

2.3.5 Logistics for 4P Medicine

The accepted limitations in terms of subject-specific predictive modeling did not preclude other relevant technological and organizational outcomes such as the described developments of

CDSS [71], as well as formulation of the Digital Health Framework (DHF) [41]. We believe that the deployment of these tools within an integrated care scenario paves the way toward predictive, preventive, participatory, and personalized (4P) medicine for these patients preventing fragmentation of care. It is important to note that the entire DHF still requires a proof-of-concept validation before considering specific strategies for its scale-up.

The transition toward a novel biomedical research scenario fostering 4P medicine has two major biomedical research goals, namely, (1) to speed up the transfer of biomedical knowledge, including novel therapies, into healthcare and (2) to generate operational feedback from healthcare and informal care into biomedical research. The last step shall produce two main benefits. Firstly, biological knowledge will be enriched with information on different dimensions of the patient (adherence profile, frailty, lifestyles, socioeconomic and environmental factors, etc.), and secondly, it will facilitate an iterative process that shall result in progressive refinement of subject-specific predictive modeling. In this regard, the interoperability among the PHF, the healthcare through ICT-supported services [60], and the novel biomedical research platform proposed in [41], within the concept of the DHF, constitute a major achievement of the project toward the consolidation of innovative biomedical research scenario that overcomes current limitations due to fragmentation of the information.

3 Discussion

The Synergy-COPD project has demonstrated that embracing a systems-oriented research targeting COPD heterogeneity generated novel knowledge, not achievable through classical methods. In the project, COPD was chosen as a use case because of the high prevalence and impact of the disease, as well as the relevance of COPD heterogeneity for subject-based health risk assessment and stratification in the clinical arena. Several of the biomedical and ICT-related challenges are in our hands generic to several other chronic conditions. Hence, COPD provides an opportunity to address these core challenges while also having an elevated potential for generalization of the research findings to other prevalent chronic disorders.

The concept of Digital Health Framework developed in the project and the road map for its implementation involves an overall strategy for the transition from current healthcare practice to a novel scenario fostering cross talk between informal care, healthcare, and systems-oriented biomedical research that shall facilitate implementation of 4P medicine for chronic patients.

3.1 Priorities Beyond Synergy-COPD

Both the outcomes of the project and the limitations faced during the project life span are key pieces to delineate the priorities beyond Synergy-COPD, as discussed below.

3.1.1 Datasets Availability to Facilitate Patient-Based Health Risk Predictive Modeling

Despite the current exponential generation of large amounts of biomedical data of different natures, several factors associated to availability of appropriate datasets have determined two major limitations of Synergy-COPD outcomes. Firstly, the project has generated insufficient consolidation of knowledge on underlying mechanisms of systemic effects of COPD and comorbidity clustering to bring the new knowledge closer to clinical application. A second limitation is availability of data to adequately generate clinically applicable patient-based health risk predictive modeling.

The following limiting aspects were identified: (1) the fragmented nature of the available datasets, (2) insufficient context-specific information, and (3) the lack of large datasets with proper experimental designs including multilevel "omics" information and clinically driven hypotheses.

Additional problems encountered throughout the project lifetime have been: (1) insufficient harmonization of medical coding across countries and within large longitudinal datasets, (2) gaps in semantic interoperability with large variations in disease definitions and coding, (3) publicly available information biased toward well-established and expected diseases and their underlying mechanisms, (4) lack of multilevel "omics" information bridging between GWAS information and phenotypic characterization, and (5) lack of accompanying nonclinical information (environmental, lifestyle, socioeconomic factors) in biobanking data. In summary, the characteristics of the available datasets had a negative impact on the project precluding the generation of subject-specific predictive modeling. However, they also constituted a limitation to validate the explored novel modeling approaches (e.g., Bayesian analysis and Thomas formalism) that should facilitate the interplay between probabilistic and mechanistic modeling for further characterization of complex biological processes. In this regard, policies promoting data sharing are highly recommended. In addition, generation of smart strategies linking population-based health risk assessment and subject-specific predictive modeling to enhance patient stratification and to generate real progress toward predictive and personalized medicine for chronic patients is needed.

3.1.2 Maturity of the Field

Mechanistic modeling techniques have shown usefulness to characterize biological mechanisms and to provide quantitative assessment of the phenomena analyzed, but they have serious limitations to address complex biological phenomena. In contrast, network medicine approaches based on statistical models seem suitable to address complex biomedical phenomena when large amount of data are available. Moreover, high-throughput analysis shows that canonical analysis of biological pathways is too simplistic not reflecting the real complexity of interconnectedness of biological networks [72]. It is of note, however, that the high expectations generated by emerging high-throughput methods are not yet balanced by a sufficient degree of applications in the clinical field.

3.1.3 Societal Changes

The project clearly identified that major organizational and technological changes are required to pave the way for a credible transition toward 4P medicine. Some of the key requirements for such a transition are described in [41] within the concept of Digital Health Framework. But, cultural factors such as (1) workforce preparation, (2) evolving concepts in terms of ethical factors relative to privacy of information transfer and information sharing, and (3) development of novel business environments fulfilling the requirements of the novel scenario are relevant elements to be taken into account in the definition of strategies leading to a successful implementation of the change. It must be emphasized that the identification of the limiting elements alluded above does not define at all a negative landscape for systems-oriented research in the biomedical area. On the contrary, one of the most important outcomes of Synergy-COPD has been the identification of the challenges to be faced and the definition of innovative strategies to adequately overcome the limiting factors alluded above that should lead to unprecedented developments in the medical practice.

3.2 Opportunities Identified During the Project Lifetime

The profound change in the health paradigm is leading to major healthcare transformations. Overall, the emerging scenario is exceedingly favorable for the convergence between integrated care and systems medicine as an efficient way to accelerate a mature deployment of 4P medicine for chronic patients. The outcomes of the Synergy-COPD project clearly reinforce such an orientation for future developments in the field.

The acknowledgment of the complexities faced during the project lifespan delineates the need for planning a building-block strategy in future endeavors designed to achieve further progress in the area. Moreover, the concept of Digital Health Framework provides the rationale for prioritization of the ICT developments, as identified in the proposed road map for the deployment.

It is currently well accepted that the chronic care model through deployment of integrated care services supported by information and communication technologies can contribute to enhance health outcomes without increasing overall costs of the health system. Such a generation of healthcare efficiencies is partly achieved by the transfer of complexities from specialized to primary care and to the community. It is reasonable to hypothesize that the generation of health efficiencies can be markedly boosted by: (1) promoting a more active role of citizens, patients, and carers in self-management and codesign of the services and (2) fostering cost-effective preventive strategies aiming at modulating disease progress. These two strategic proposals require adoption of the novel health paradigm that involves bridging traditional healthcare delivery (i.e., formal care) and informal care (e.g., patient self-management, wellness programs, social care, etc.) through adoption of citizen's (patient's) personal health records as

management tools. In this new scenario, the correct articulation of patient gateways and mobile devices (mHealth) [27] is promising to empower, for the first time, an efficient channel enhancing accessibility to the health system, facilitating monitoring, and including patient's behavioral and environmental factors into health management. The ultimate goal of patient gateways is to support cost-effective preventive interventions to modulate the evolution of the disease, which might represent tremendous sources of efficiencies if in place.

Moreover, the analysis of the lessons learned during the Synergy-COPD project facilitates the identification of specific challenge-driven opportunities in all the areas described above. A proper prioritization of future actions following the general recommendations generated by the project should contribute to make 4P medicine for chronic patients a successful reality.

3.3 Conclusions

The chapter summarizes main outcomes and lessons learned from the Synergy-COPD project. The characteristics of the disease (COPD), the inherent challenges, and our actions toward mitigating the gap between research and clinical practice on the one hand and personalized medicine on the other reinforce the high potential for generalization of the results to other chronic conditions. Overall, the project showed that convergence between a systems medicine approach and integrated care may generate substantial healthcare efficiencies for the management of complex chronic patients.

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References

1. Auffray C, Charron D, Hood L (2010) Predictive, preventive, personalized and participatory medicine: back to the future. Genome Med 2(8):57
2. Murray C, Lopez A (2013) Measuring the global burden of disease. New Engl J Med 369:448–457
3. WHO (2002) Innovative care for chronic conditions: building blocks for action. World Health Organization (WHO/MNC/CCH/02.01), Geneva, http://www.who.int/chp/knowledge/publications/icccreport/en/
4. EU C (2010) Innovative approaches for chronic diseases in public health and healthcare systems. Council of the EU 3053rd Employment, social policy health and consumer affairs
5. WHO (2008) 2008–2013 Action plan for the global strategy for the prevention and control of noncommunicable diseases. http://www.who.int/nmh/publications/9789241597418/en/
6. Menche J, Sharma A, Kitsak M, Ghiassian SD, Vidal M, Loscalzo J et al (2015) Disease networks. Uncovering disease-disease relationships through the incomplete interactome. Science 347(6224):1257601

7. Jensen AB, Moseley PL, Oprea TI, Ellesøe SG, Eriksson R, Schmock H et al (2014) Temporal disease trajectories condensed from population-wide registry data covering 6.2 million patients. Nat Commun 5:4022
8. Roca J, Vargas C, Cano I, Selivanov V, Barreiro E, Maier D et al (2014) Chronic obstructive pulmonary disease heterogeneity: challenges for health risk assessment, stratification and management. J Transl Med 12(Suppl 2):S3
9. EIP-AHA (2014) European scaling-up strategy in active and healthy ageing. http://ec.europa.eu/research/innovation-union/pdf/active-healthy-ageing/scaling_up_strategy.pdf
10. ACT (2015) The Advancing Care Coordination & Telehealth Deployment (ACT) Programme. http://www.act-programme.eu/
11. Hernandez C, Alonso A, Garcia-Aymerich J, Grimsmo A, Vontetsianos T, García Cuyàs F et al (2015) Integrated care services: lessons learned from the deployment of the NEXES project. Int J Integr Care 15:e006
12. Atkins D, Kupersmith J, Eisen S (2010) The veterans affairs experience: comparative effectiveness research in a large health system. Health Affair 29(10):1906–1912
13. McCreary L (2010) Kaiser Permanente's innovation on the front lines. Hardvard Bus Rev 88(9):92, 4–7, 126
14. True G, Butler AE, Lamparska BG, Lempa ML, Shea JA, Asch DA et al (2013) Open access in the patient-centered medical home: lessons from the Veterans Health Administration. J Gen Intern Med 28(4):539–545
15. Tegner JN, Compte A, Auffray C, An G, Cedersund G, Clermont G et al (2009) Computational disease modeling – fact or fiction? BMC Syst Biol 3:56
16. Wharam JF, Weiner JP (2012) The promise and peril of healthcare forecasting. Am J Manag Care 18(3):e82–e85
17. Kansagara D, Englander H, Salanitro A, Kagen D, Theobald C, Freeman M et al (2011) Risk prediction models for hospital readmission: a systematic review. JAMA 306(15):1688–1698
18. Moharra M, Vela E et al (2015) Comparison of predictive risk modeling among 5 European regions in the ACT project. International Foundation for Integrated Care (IFIC), 25 Març, Edinburg (abstract)
19. Loscalzo J, Barabasi AL (2011) Systems biology and the future of medicine. Wiley Interdiscip Rev Syst Biol Med 3(6):619–627
20. Gomez-Cabrero D, Lluch-Ariet M, Tegner J, Cascante M, Miralles F, Roca J et al (2014) Synergy-COPD: a systems approach for understanding and managing chronic diseases. J Transl Med 12(Suppl 2):S2
21. Topol EJ (2014) Individualized medicine from prewomb to tomb. Cell 157(1):241–253
22. Abugessaisa I, Saevarsdottir S, Tsipras G, Lindblad S, Sandin C, Nikamo P et al (2014) Accelerating translational research by clinically driven development of an informatics platform – a case study. PloS One 9(9):e104382
23. Coughlin SS (2014) Toward a road map for global -omics: a primer on -omic technologies. Am J Epidemiol 180(12):1188–1195
24. Tegner J, Abugessaisa I (2013) Pediatric systems medicine: evaluating needs and opportunities using congenital heart block as a case study. Pediatr Res 73(4 Pt 2):508–513
25. Bernstein BE, Stamatoyannopoulos JA, Costello JF, Ren B, Milosavljevic A, Meissner A et al (2010) The NIH Roadmap Epigenomics Mapping Consortium. Nat Biotech 28(10):1045–1048
26. Liu Y, Aryee MJ, Padyukov L, Fallin MD, Hesselberg E, Runarsson A et al (2013) Epigenome-wide association data implicate DNA methylation as an intermediary of genetic risk in rheumatoid arthritis. Nat Biotech 31(2):142–147
27. EU C (2014) eHealth Action Plan 2012-2020. Green Paper on mobile health ("mHealth"). https://ec.europa.eu/digital-agenda/en/news/green-paper-mobile-health-mhealth
28. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A et al (2013) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 187(4):347–365
29. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA et al (2010) Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res 11:122
30. Casanova C, de Torres JP, Aguirre-Jaime A, Pinto-Plata V, Marin JM, Cordoba E et al (2011) The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. Am J Respir Crit Care Med 184(9):1015–1021
31. Vestbo J, Agusti A, Wouters EF, Bakke P, Calverley PM, Celli B et al (2014) Should we view chronic obstructive pulmonary disease differently after ECLIPSE? A clinical perspective from the study team. Am J Respir Crit Care Med 189(9):1022–1030
32. Maltais F, Decramer M, Casaburi R, Barreiro E, Burelle Y, Debigare R et al (2014) An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 189(9):e15–e62

33. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V et al (2012) Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 186(2):155–161
34. Van Hoyweghen I, Horstman K (2008) European practices of genetic information and insurance: lessons for the Genetic Information Nondiscrimination Act. JAMA 300(3):326–327
35. Celli BR, Decramer M, Wedzicha JA, Wilson KC, Agusti A, Criner GJ et al (2015) An official American Thoracic Society/European Respiratory Society statement: research questions in COPD. Eur Respir J 45(4):879–905
36. Rennard SI (2011) COPD heterogeneity: what this will mean in practice. Respir Care 56(8):1181–1187
37. Chen X, Xu X, Xiao F (2013) Heterogeneity of chronic obstructive pulmonary disease: from phenotype to genotype. Front Med 7(4): 425–432
38. Synergy-COPD (2011/2013) Modelling and simulation environment for systems medicine: chronic obstructive pulmonary disease (COPD) as a use case. FP7-ICT-270086
39. Bousquet J, Anto J, Sterk P, Adcock I, Chung K, Roca J et al (2011) Systems medicine and integrated care to combat chronic noncommunicable diseases. Genome Med 3(7):43
40. Hood L, Auffray C (2013) Participatory medicine: a driving force for revolutionizing healthcare. Genome Med 5(12):110
41. Cano I, Lluch-Ariet M, Gomez-Cabrero D, Maier D, Kalko S, Cascante M et al (2014) Biomedical research in a digital health framework. J Transl Med 12(Suppl 2):S10
42. Barnes PJ, Celli BR (2009) Systemic manifestations and comorbidities of COPD. Eur Respir J 33(5):1165–1185
43. Barnes PJ (2015) Mechanisms of development of multimorbidity in the elderly. Eur Respir J 45(3):790–806
44. Garcia-Aymerich J, Gómez FP, Antó JM (2009) Phenotypic characterization and course of chronic obstructive pulmonary disease in the PAC-COPD study: design and methods. Arch Bronconeumol (English Version) 45(01):4–11
45. Garcia-Aymerich J, Gomez FP, Benet M, Farrero E, Basagana X, Gayete A et al (2011) Identification and prospective validation of clinically relevant chronic obstructive pulmonary disease (COPD) subtypes. Thorax 66(5):430–437
46. Turan N, Kalko S, Stincone A, Clarke K, Sabah A, Howlett K et al (2011) A systems biology approach identifies molecular networks defining skeletal muscle abnormalities in chronic obstructive pulmonary disease. PLoS Comput Biol 7:e1002129
47. Davidsen PK, Herbert JM, Antczak P, Clarke K, Ferrer E, Peinado VI et al (2014) A systems biology approach reveals a link between systemic cytokines and skeletal muscle energy metabolism in a rodent smoking model and human COPD. Genome Med 6(8):59
48. Barabasi A, Gulbahce N, Loscalzo J (2011) Network medicine: a network-based approach to human disease. Nat Rev Genet 12:56–68
49. Lee D, Park J, Kay K, Christakis N, Oltvai Z, Barabasi A (2008) The implications of human metabolic network topology for disease comorbidity. Proc Natl Acad Sci U S A 105: 9880–9885
50. Burrowes KSD, Brightling C (2014) Computational modeling of the obstructive lung diseases asthma and COPD. J Transl Med 12(Suppl 2):S5
51. Gomez-Cabrero DM, Cano I, Abugessaisa I, Huertas-Miguelanez M, Tenyi A, Marin de Mas I et al (2014) Systems medicine: from molecular features and models to the clinic in COPD. J Transl Med 12(Suppl 2):S4
52. Needham CJ, Bradford JR, Bulpitt AJ, Westhead DR (2007) A primer on learning in Bayesian networks for computational biology. PLoS Comput Biol 3(8):e129
53. Thomas R, Kaufman M (2001) Multistationarity, the basis of cell differentiation and memory. I. Structural conditions of multistationarity and other nontrivial behavior. Chaos 11(1):170–179
54. Poole D, Hirai D, Copp S, Musch T (2012) Muscle oxygen transport and utilization in heart failure: implications for exercise (in)tolerance. Am J Physiol Heart Circ Physiol 302:H1050–H1063
55. Cano I, Tenyi A, Schueller C, Wolff M, Huertas Miguelanez MM, Gomez-Cabrero D et al (2014) The COPD knowledge base: enabling data analysis and computational simulation in translational COPD research. J Transl Med 12(Suppl 2):S6
56. Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM et al (2000) Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. Nat Genet 25(1):25–29
57. WHO (1992) World Health Organisation. International statistical classification of diseases and related health problems, 10th Revision (ICD-10), Geneva
58. Hucka M, Finney A, Sauro H, Bolouri H, Doyle J, Kitano H et al (2003) The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models. Bioinformatics 19:524–531

59. Van Hentenryck K (1997) Health level seven. Shedding light on HL7's version 2.3 standard. Healthc Inform 14(3):74
60. Cano I, Alonso A, Hernandez C, Burgos F, Barberan-Garcia A, Roldan J et al (2015) An adaptive case management system to support integrated care services: lessons learned from the NEXES project. J Biomed Inform 55:11–22
61. Burgos F, Disdier C, de Santamaria EL, Galdiz B, Roger N, Rivera ML et al (2012) Telemedicine enhances quality of forced spirometry in primary care. Eur Respir J 39(6):1313–1318
62. Castillo D, Burgos F, Guayta R, Giner J, Soriano JB, Lozano P et al (2012) Effect of a Community Pharmacy COPD case finding program: a novel approach to reduce COPD underdiagnosis. Congreso Nacional SEPAR, Oviedo 2011. Arch Bronconeumol 47:91
63. Burgos F, Melia U (2014) Clinical decision support system to enhance quality control of spirometry using information and communication technologies. JMIR Med Inform 2(2):e29
64. Calverley P (2013) The ABCD of GOLD made clear. Eur Respir J 42:1163–1165
65. Puhan M, Garcia-Aymerich J, Frey M, ter Riet G, Anto J, Agusti A et al (2009) Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. Lancet 374:704–711
66. Puhan M, Hansel N, Sobradillo P, Enright P, Lange P, Hickson D et al (2012) Large-scale international validation of the ADO index in subjects with COPD: an individual subject data analysis of 10 cohorts. BMJ Open 2:e002152. doi:10.1136/bmjopen-2012-002152
67. Jones R, Donaldson G, Chavannes N, Kida K, Dickson-Spillmann M, Harding S et al (2009) Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: the DOSE Index. Am J Respir Crit Care Med 180:1189–1195
68. Motegi T, Jones R, Ishii T, Hattori K, Kusunoki Y, Furutate R et al (2013) A comparison of three multidimensional indices of COPD severity as predictors of future exacerbations. Int J Chron Obstruct Pulmon Dis 8:259–271
69. Roca JGH, Grimsmo A, Meya M, Alonso A, Gorman J et al (2013) NEXES: supporting healthier and independent living for chronic patients and elderly: final report. http://www.nexeshealth.eu/media/pdf/nexes_final_report.pdf
70. Barberan-Garcia A, Vogiatzis I, Solberg HS, Vilaro J, Rodriguez DA, Garasen HM et al (2014) Effects and barriers to deployment of telehealth wellness programs for chronic patients across 3 European countries. Resp Med 108(4):628–637
71. Velickovski F, Roca J, Burgos F, Galdiz J, Nueria M, Lluch Ariet M (2014) Clinical decision support systems (CDSS) for preventive management of COPD patients. J Transl Med 12(Suppl 2):S9
72. Silverman EK, Loscalzo J (2012) Network medicine approaches to the genetics of complex diseases. Discov Med 14(75):143–152