Research Tracks for Intelligent Processing to Support Cardiovascular Disease Management in Personalized Healthcare: Results from LiNK Project

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Abstract. The goal of LiNK is to discover and define research tracks in the area of intelligent processing to support cardiovascular disease management in Personalized Healthcare (PHC). The strategy was based on a two-fold approach. First, using a status assessment of the current research on PHC and an international research forum. From this roadmap, specific innovative research tracks were developed by common workgroups. Knowledge transfer methodologies between partners by using a "learn by doing" approach increased the research excellence momentum. These research tracks supported concept definition activities that will be the basis for new project, network and PhD grant proposals, leading to a continuum of widening. Second, existing links to international leading organizations and key actors in PHC (academic, industrial and users) were exploited to launch a research and innovation forum in which the definition of a research agenda and curricula for advanced training was completed.

1 Introduction

Cardiovascular diseases (CVD) are the deadliest among chronic diseases, and with more people surviving their first cardiac event, CVD is becoming a chronic disease. It is estimated that they are responsible for 12 million disability adjusted life years lost annually1 and that nearly half of all deaths in Europe (48%) and in the EU (42%) are due to CVD. It is the main cause of the disease burden (illness and death) in Europe (23%). There is a multitude of etiologies for CVD such as ischemic heart disease, hypertension, valvular heart disease, infection and other primary and secondary myocardial diseases [1]. CVD has a major impact on health expenditure. Overall CVD is estimated to cost the EU27 €192 billion distributed between €109 billion of direct costs (10% of the EU expenditure) and about €83 billion in indirect costs (€41 billion of lost in productivity and €42 billion for informal care).

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In order to handle the challenges induced by the chronic disease burden, the EU health systems are undergoing a paradigm shift from reactive care to preventive care and from in-hospital to home care. Prevention systems support and motivate users in adopting healthy lifestyles (e.g., physical activity, nutrition, stress management) in order to prevent or delay manifestations of disabling chronic diseases. Disease management systems handle the care of patients with chronic disease, combining expertise from different areas, and integrating new technologies to offer the patient better and more cost effective care. In this context, personalizing health and care (PHC) systems have a central role in supporting the paradigm shift by assisting in the provision of continuous and personalised services to empower patients and professionals in managing their health. Although in the last decade there has been an intense and significant research on developing and deploying PHC services in CVD management (up to 50% of the PHC market products and 40% of research projects are related to CVD management2), there are still some major gaps that need to be addressed [2].

Today's PHC systems miss adequate integration of clinical evidence and knowledge from holistic clinical practice and biomedical research required to support truly holistic management of chronic diseases and their co-morbidities. Current PHC systems are designed using the "one fits all" principal lacking a truly personalization by capturing and adapting to the patients' phenotype (e.g., by linking systems medicine and the virtual physiological patient to tele-monitoring data) and individualized treatment or context needs. Data processing is at the core of PHS where acquired data is turned into meaning and action. In order to pave the way from personal to personalised systems, PHC require intelligent algorithms to treat and correct data obtained from uncontrolled conditions, to efficiently integrate multimodal and multi-scale data, to be self-adapting (moving from population-based to patient-specific adaptations) and interpretable, and to integrate clinical and biomedical evidence at their genesis.

In this chapter our goal is to outline the approach developed and implemented in the LiNK project and to provide an overview of the achieved results in identifying and creating a research ecosystem to address central scientific and technical challenges for PHC deployment. The methodology followed is fostering EU impact and leadership in intelligent processing for CVD management in PHC, led from Coimbra, Valencia and Milan.

2 Methodology

LiNK project promotes the cooperation between the University of Coimbra, the Universitat Politècnica de València and the Politecnico di Milano in a long term sustainable way. The main goal of the project is to link competences in intelligent processing for CVD (cardiovascular diseases) management in PHC (Personal Health Care) with the aim of creating a research ecosystem to address two central scientific and technical challenges for PHC deployment: 1) Infusion of clinical evidence biomedical knowledge in PHC solutions and 2) Moving PHC solutions from personal to personalized services, i.e., services adapted to the specific user needs and characteristics. LiNK has established an innovation forum involving key international players as well as key regional players in the PHC area in order to identify gaps, industrial needs and best practices to

foster innovation culture in PHC. The main output of this forum is a research agenda to support international research in the field, but also to guide the consortium in its research strategy and approach, as well as its project proposals.
The LiNK project consists of three main phases (Fig. 1). The work was structured in four major Work Packages and in the project lifetime the definition of the research tracks is the major challenge and outcome, which is the focus of the present chapter.

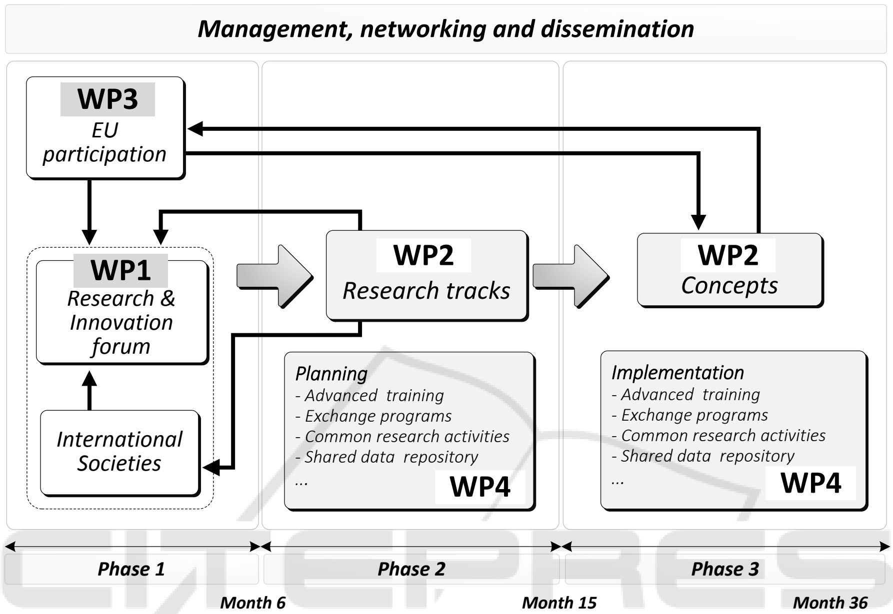

Fig. 1. LiNK phases and relationships between the Work Packages of the Project.

The research tracks are based on specific responses to selected specific research questions addressed by Academia, Industry and Healthcare professionals. These research questions are the result from the intersection of the inputs provided by the Research and Innovation Forum (RIF in WP1 – Fig. 1), key competences inside the consortium and shared research interests. This forum has supported the process of identifying the gaps in intelligent processing for PHC, to spot the relevant internal and external factors for innovation and high quality research in this field, and highlight innovation barriers and innovation best practices. The main output of this forum is a research agenda to support international research in the field, but also to guide the consortium in its research strategy and approach as well as project proposals. This key forum has also supported structuring curricula for advanced training in the area.

The first challenge was to create and select meaningful research questions to thereafter build inter-institutional teams for establishing the basement of the research tracks. Such activities included team building activities, training programs for knowledge transfer, researcher exchange and internships, as well as a set of PhD thesis and post-docs programs. During this phase knowledge transfer was implemented as well as the identification and setup of a common data repository and joint laboratories (activities to be coordinated by WP4- Dissemination and training in Fig. 1).

One of the major outcomes of research track activity was the Concepts definition (WP2 in Fig. 1), implemented in the third phase of the project, and managed in strait cooperation with WP3-EU inclusion, networking and transference. Concept definition/development aimed at identifying the scientific, technical, social and economic requirements of relevant project ideas. Such project concepts will be performed and leaded by LiNK consortium and other institutions in forthcoming years.

To achieve the definition of the research tracks, three main contributions were considered: 1) Outcomes provided by the RIF – research and innovation forum; 2) Key competences inside the consortium; and 3) Shared research interests.

The first contribution included a set of stakeholders, composed by experts from different countries (US, Italy, Spain, Portugal, Belgium, etc.) with different profiles (clinician, decision maker, multinational company, researcher, entrepreneur, patients' associations). During the first months of the project, a questionnaires and interviews were performed in a Delphi study, helping the consortium to identify the top research questions and challenges with a global perspective.

Based on these questionnaires, it was possible to identify hot challenges to face from the research perspective in the PHC for CVD field. These challenges were also prioritized on the basis of the following statements: i) Analysis of the state of the art and future trends in pHealth solutions for integrated CVD management; ii) Identification of open research problems and opportunities in algorithms for pHealth solutions for integrated CVD management to support these concepts; and iii) Identification of opportunities for Concept development in pHealth solutions for integrated CVD management.

The last two contributions (key competences inside the consortium and shared research interests) were addressed through a state-of-the-art revision and a systematic discussion inside the consortium. These discussions were focused around four main perspectives: data sets, research interests/gaps, health outcomes and CVD applications.

2.1 Setup of the Research and Innovation Forum

Strategic Research Agenda definition should be a heuristic and unbiased process that provides a privileged view of which are the most and least important topics for next years. Even though a systematic review or a review of the later 10 years research directions could provide a picture of the current status and a brush on the future directions, the aim of LiNK was to extract opinions from key stakeholders. Such key persons were already identified and engaged through the Research and Innovation Forum (RIF), accounting of high performance professionals riding and conducting clinical, research and commercial actions in the field of CVD. To this extent, the methodology used to prioritize concepts was the consensus analysis throughout a Delphi interview study.

Among the decision making process, one of the most common methodologies used in projects design and management is the Delphi technique. This approach has been adopted in several fields from 90s and even though is a well-known world-wide used technique, still little guidance exists to conduct a rigorous method of data collection.

Nevertheless, the literature gathers many proposition and lessons learned papers on which are the mandatory areas that should be tackled for preparing a Delphi survey.

Table 1. Areas for designing the Delphi survey.

Research problem	-Research Agenda for CVD
Rationale	-State of Art and future trends related to PHC -Opportunities for integrated management -Open research problems related to other concepts
Methodology	
Data Collection	-Structured online form and email request with periodic reminders
Sample	-Research and Innovation Forum panel of experts
Data Analysis	-Number of responders and response rate. -Statistical distributions for priorities and quantitative answers -Qualitative analysis of open answers

Delphi methodology is appropriate to investigate specific problems with careful considerations and assumptions. The rationale for the study was categorized in three parts, with a set of statements for each case:

Part 1. Analysis of the State of the Art (SoA) and future trends in pHealth solutions for integrated CVD management, composed of 13 items (Table 2).

Table 2. Statements for the analysis of the State of the Art in future trends for CVD management.

ID	Statement
1	Success of PHC for CVD is fully dependent on data availability
2	Physical robots will act as main catalysers for PHC services either at home or at the hospital
3	New algorithms are needed to infer knowledge from data in order to practice evidence based medicine
4	Quality of data is a dimension not to be missed when researchers are inferring knowledge from heterogeneous databases
5	New data infrastructures, mostly cloud based, are needed to support PHC services
6	Pervasive telemonitoring is key to manage PHC services in an efficient way
7	It is crucial to have real time telemonitoring to provide PHC services, being possible thanks to mobile services
8	Feature selection and patient stratification are key elements for PHC
9	Ethical issues need to be addressed in order to guarantee a successful provision of PHC services
10	Legal issues need to be addressed in order to guarantee a successful provision of PHC services

11	Clinical process management needs to be technology based to improve use of clinical resources.
12	The creation of individualized behavioural models will allow personalised medicine and patient empowerment
13	It is key to address and model the Patient context for a proper PHC management.

Part 2. Identification of open research problems and opportunities in algorithms for pHealth solutions for integrated CVD management to support these concepts, composed of 11 elements (Table 3).

Table 3. Open research problems and opportunities.

ID	Statement
1	How can different sources of information be integrated, especially on large data-bases?
2	Based on data exploitation, how will new associations be discovered? How will new therapeutic strategies be suggested?
3	How will mobile technologies improve continuous monitoring?
4	Which techniques will be used for pervasive monitoring?
5	Which indicators are the key ones for CVD risk assessment?
6	What are the best strategies to combine data and knowledge-driven learning and modelling approaches?
7	What are the key stones in interpretable models for DSS?
8	How can the assessment of cardiovascular functions and status using wearable technologies can be improved?
9	How can multi modal and multi scale data fusion for robust biosignal processing be improved?
10	How to personalize models for diagnosis and prognosis?
11	How to support the integration, discovery and use of clinical knowledge in daily clinical practice?

Part 3. Identification of opportunities for Concept development in pHealth solutions for integrated CVD management (Table 4)

Table 4. Concept development opportunities in integrated CVD management.

ID	Statement
1	Coronary artery disease (CAD) e.g. physiological models
2	Heart Failure (HF) – keeping patients diagnosed in a secure path
3	Sleep – e.g. sleep patterns and correlation with CVD
4	Stress
5	Diabetes

Experts were asked to prioritize the top five elements for each part in a 5 item Likert Scale: Low Priority, Low to Medium Priority, Medium Priority, Medium to High Priority and High Priority. The questionnaire included open answer questions, in which experts could add new statements from their own opinion and expertise, and the justification for the statement selected in each priority level.

2.2 Research Tracks Definition

The approach to accomplish the definition of the Research Tracks followed a strategy based on three different inputs: 1) Experts discussions - where the key competences inside the consortium and shared research interests were identified; 2) Analysis of the state of the art and future trends in pHealth solutions for integrated CVD management; and 3) Outcomes provided by the RIF – research and innovation forum.

The first two actions (internal discussions and state of the art) started during the kick-off of the Project (Jan 2016), and have been maintained regularly during the progress of the project through conference calls and face to face meetings. RIF priorities, aiming to help the consortium in the identification of the top research questions and challenges, were available at month 7 (July 2016). These inputs were used to complement as well as to validate the definition of the Research Tracks.

Part 1. Internal Discussions. Aligned with the main goals of LiNK, four main perspectives have been considered in the discussions (Fig. 2).

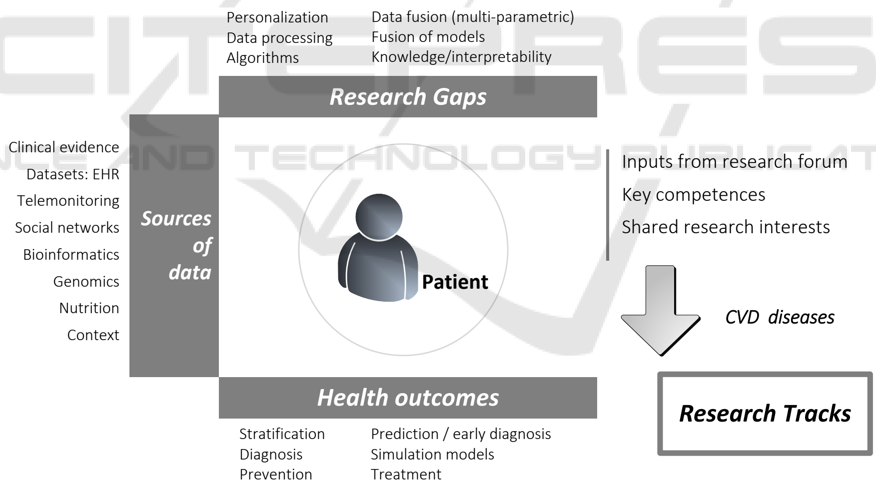

Fig. 2. Perspectives considered in the definition of the research tracks.

Available Datasets: The identification of possible sources of data, and related available data sets, was considered by the consortium as a decisive requirement. These include physiological signals, clinical evidence, bioinformatics, electronic health records, etc. In fact, all the research, implementation and validation work to be carried out depends decisively of the existence of useful data sets.

Research Interests/Gaps: Moreover, the research tracks should be aligned with the current research gaps, recognized as pertinent and relevant by the scientific community, as well as in line with the research interests of each partner. Examples of such gaps are: personalized algorithms, predictive decision tools and multi-modal and multi-scale models.

Health Outcomes: Another relevant perspective is oriented towards the specific problems to be addressed. In other works, the clinical relevance of each RT should be clearly defined. Examples of such health outcomes are diagnosis, prognosis, and stratification.

CVD applications: Finally, between the several possible CVD applications, the specific domain of application has to be identified. Examples of such CVD applications are related with cardiovascular status, heart failure, and sleep comorbidities.

In a first phase these four perspectives were discussed independently. Then, in a second phase, the different perspectives were combined in a multi-input matrix (Figure 3), enabling the systematization of the different perspectives, and the identification of the RTs and a set of associated activities. Basically, the process was guided by the following principle: "Each RTs addresses a particular health outcome (3), and is composed of several activities, each one addressing a specific research gap (2), for a particular CVD application (4.), using a suitable data set (1)".

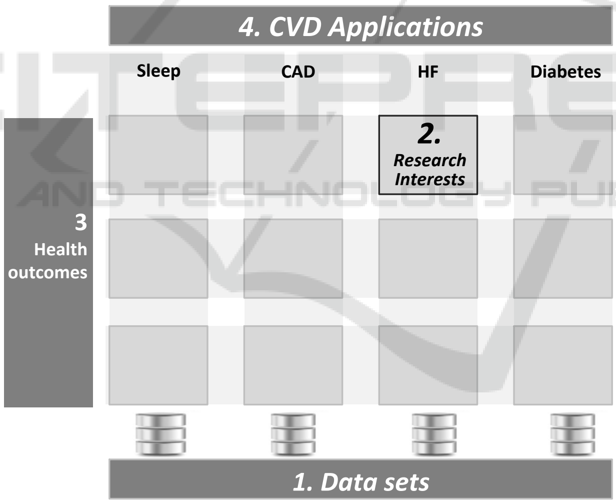

Fig. 3. Matrix used in the RTs definition combining the different perspectives: sources of data, health outcomes, research interests and CVD applications.

3 Results

3.1 Outcomes from the Research and Innovation Forum

24 members of the Research and Innovation Forum (RIF) participated in the Delphi study during the month of July 2016. Participation into the RIF was approved upon application acceptance (Table 5)

Table 5. Concept development opportunities in integrated CVD management.

Academic Profile		**N**		**N**
	Eng	1	PhD	17
	M Sc	1	Professor	5
Type of Entity		**N**		**N**
	Corporate	2	Research Institute	3
	Hospital	3	Scientific Society	3
	Patient Associations	1	SME	7
	Policy Maker	2	University	3
Area/Continent		**N**		**N**
	Central Europe	5	North Europe	1
	East Europe	2	South Europe	13
	North America	3		

Part 1. Analysis of the State of the Art (SoA) and future trends in pHealth solutions for integrated CVD management. Two analyses were done for the inputs provided by experts dealing with the state of the art, considering the priorities they gave (allocating from 5 to 1 points to the different options) or just considering equal the 5 top priorities (allocating 1 point to all the priorities selected by each expert) as some experts expressed that for them, there were a set of 4-5 statements with the highest top priority.

Based on answers from experts, it can be inferred especially from **Error! Reference source not found.** that there are three big blocks of statements: Top priority statements (between 37 and 16 points); Middle priority statements (between 11 to 7 points) and Low priority statements (between 4 and 3 points)

Table 6. Top priority statements in future trends of pHealth Solutions for CVD Management.

ID	**Statement**	**Priority Points**
3	New algorithms are needed to infer knowledge from data in order to practice evidence-based medicine	37
4	Quality of data is a dimension not to be missed when researchers are inferring knowledge from heterogeneous databases	26
1	Success of PHC for CVD is fully dependent on data availability	20
7	It is crucial to have real time telemonitoring to provide PHC services, being possible thanks to mobile services	16

To avoid biasing due to high scores given by a single expert, the analysis was also done considering just 1 point for all the selections of each expert (Fig. 4)

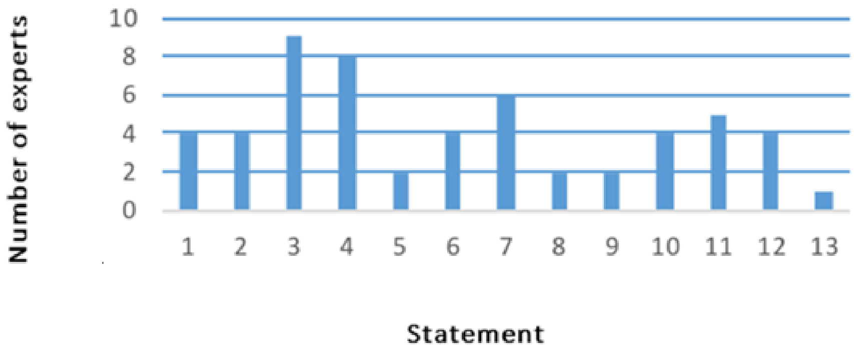

Fig. 4. Statement selection in the priorities of State of the Art.

Part 2. Identification of open research problems and opportunities in algorithms for pHealth solutions for integrated CVD management to support these concepts. Two analyses have been done for the inputs provided by experts dealing with the opportunities for development of new concepts around integrated CVD management, considering the priorities they gave (allocating from 5 to 1 points to the different options) or just considering equal the 5 top priorities (allocating 1 point to all the priorities selected by each expert) as some experts expressed that for them, there were a set of 4-5 statements with the highest top priority. Based on answers from experts, it can be inferred three big blocks of statements: Top priority statements (between 26 and 19 points); Middle priority statements (between 16 to 10 points) and Low priority statements (between 6 and 4 points).

Being the top priority statements concerning the new research questions to be addressed for PHC in CVD management the ones listed in Table 7.

Table 7. Top priority research problems and opportunities in algorithms for pHealth Solutions for CVD Management.

ID	Statement	Priority Points
11	How to support the integration, discovery and use of clinical knowledge in daily clinical practice?	27
10	How to personalize models for diagnosis and prognosis?	27
5	Which indicators are the key ones for CVD risk assessment?	26
6	What are the best strategies to combine data and knowledge driven learning and modelling approaches?	19

On the other side, if we just consider the amount of experts that selected each statement as it is reflected in Figure 5, the groups of research questions are almost the same with the difference of statement 6, which moved to middle priorities.

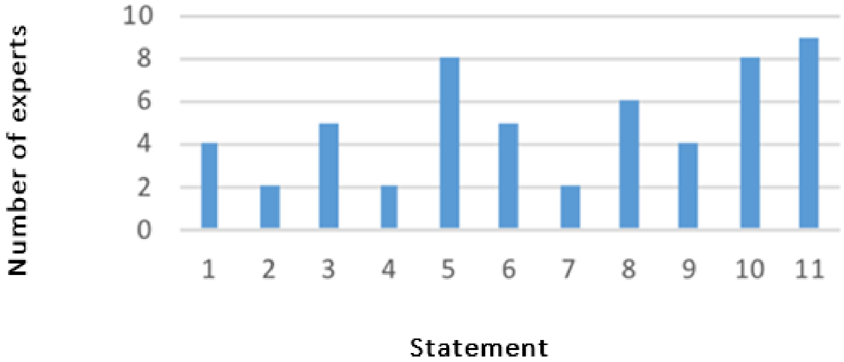

Fig. 5. Statement selection in the priorities of research problems and opportunities.

Part 3. Identification of opportunities for Concept development in pHealth solutions for integrated CVD management. Last part of the survey was focused on the development of concepts that engage transversally different research questions and problems previously raised with a direct focus on the society. In this case, as there were five themes, the analysis has been performed on the priority levels assigned by each expert. Figure 5 show graphically the results where Heart Failure (HF), namely, to keep diagnosed patients in a safe track and Coronary Artery Diseases (CAD) are the top opportunities identified. That is logical as they are strictly based on heart problems whereas the rest of options address the issue from a comorbidity point of view. At this stage, all experts prioritize diabetes versus stress and sleep.

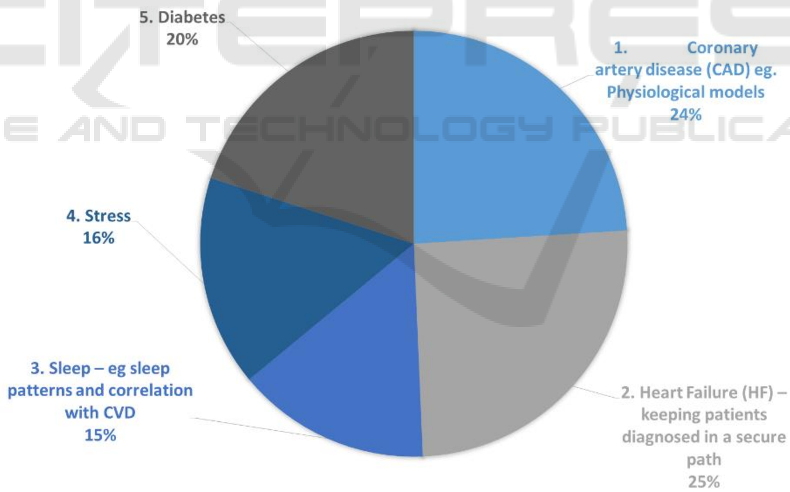

Fig. 6. Opportunities for concept development in pHealth solutions for integrated CVD management.

3.2 Definition of the Research Tracks for CVD in Personalized Healthcare

RT1 - Stratification and Diagnosis. The first research track proposed to design and develop models to assess CVD patients in three categories: CVD Status, Cardiorespiratory Assessment and Cycling Alternating Pattern (CAP) during sleep. Given that (i) CVDs are the most prevalent chronic diseases, (ii) which have a very significant impact both in patient's quality of life as well as in the financial sustainability of health provision systems, it is observed that research and development of new methodologies capable of a continuous and non-invasive assessment of the cardiovascular status of patients is of crucial importance to implement effective personal health care systems for adequate and preventive cardiovascular diseases (CVD) management. Being blood pressure (BP) a critical risk factor of CVD onset and progression, it is seen that the continuous and cuff-less monitoring of blood pressure is one critical research topic that has been intensively pursued by researchers during the last decade. Continuous hemodynamic assessment using BP, is still one of the major open research questions for CVD status assessment.

RT2 – Personalized Predictions. Cardiovascular diseases are a major public health concern, and a cause of considerable morbidity and mortality. As a consequence, the prediction of severe events is of great importance for professionals, since it provides the adequate tools to diagnose. The main goal of this work is the development of algorithms the early detection of critical events, using multi-parametric approaches that combine physiological measurements (e.g. ECG, blood pressure, weight) and other sources of information (e.g. medication).

Two main scientific challenges will be addressed: prediction methods and information fusion schemes, based on computational intelligence methodologies. The main hypothesis is that physiological time series with similar progression have prognostic value in future clinical states. Possible applications are the prediction of hypertension or decompensation episodes for heart failure patients.

RT3 – Integrated Care and Process Mining. The application of process mining techniques is highly influenced by the quality of the event logs that are used to discover models. Since this field of research is relatively new, there are no standardized ways to create process logs. Additionally, some of the logs used come from direct observation and manual annotation (especially in healthcare), what can introduce errors in the data which invalidates the models inferred. Therefore, some efforts are required to standardize the way data is collected and pre-processed to avoid bias in process mining algorithms outcomes. The aim of this research track is the creation of mechanisms that allow to collect, share and evaluate the data available from patients to ensure the creation of proper models using process mining techniques.

Currently, there are a big amount of available data coming from very different and heterogeneous sources and with different qualities. The homogenization of these data is crucial for the creation of accurate and reliable models. For any data analysis technique, the quality of the underlying data is important. Otherwise, the data processing will risk drawing the wrong conclusions.

4 Conclusions

One of the main goals of the LiNK project was to identify with a very solid perspective what are the right questions and challenges to be solved from a research perspective, to therefore define the current opportunities in the form of research tracks.

To engage representatives from the different stakeholders in the PHC for CVD field, that will help us to prioritize the key hot topics. Through the creation of a preliminary research agenda that will enhance S&T excellence of LINK institutions, but also for the entire community in systems for pHealth solutions for CVD management.

The RIF's community has been created with 24 participants from Europe and America, with different backgrounds and types of entities. RIF members have actively participated in the discussion, prioritising and providing comments about the suggested statements.

Therefore, based on existing literature and an analysis a set of topics have been identified, helping us to draft the preliminary research agenda. Concerning the State of the Art (SoA) and future trends in pHealth solutions for integrated CVD management, the top priorities identified by experts are dealing with new algorithms to infer knowledge from data, quality of data when data is coming from heterogeneous sources and the need for real time telemonitoring for PHC services using mobile technologies. Being these ones the top ones, there are also a set of trends that have been raised at least by half of the experts about data availability, robots, pervasive telemonitoring, legal issues, ICT based clinical management and creation of individualized behavioural models.

About the identification of the open research questions for phealth solutions for integrated CVD management to support these concepts, the three identified main questions to be addressed were: How to support the integration, discovery and use of clinical knowledge in daily clinical practice? ; How to personalize models for diagnosis and prognosis? And , which indicators are the key ones for CVD risk assessment?

Whereas being not top priority, experts recommend not to forget issues as the integration of different information sources on large databases, the assessment of cardiovascular functions and status using wearable technologies, the improvement of multimodal and multi-scale data fusion for robust biosignal processing be improved, the continuous monitoring through mobile technologies and the selection of strategies to combine data and knowledge driven learning and modelling approaches?

Finally, concerning the identification of opportunities for concept development in phealth solutions for integrated CVD management, Heart Failure (HF), that is, to keep diagnosed patients in a safe track and Coronary Artery Diseases (CAD) are the top opportunities identified. That is logical as they are strictly based on heart problems whereas the rest of options address the issue from a comorbidity point of view. At this stage, all experts prioritize also diabetes versus stress and sleep.

Research tracks were defined on the basis of RIF's priority challenges, key competences inside the LiNK consortium ad shared research interests. As result of this strategy, three main research tracks have been identified: RT1 – Stratification and diagnosis; RT2 - Personalized predictions and RT3 - Integrated care and process mining.

Additionally, each one of these RT is composed of several activities, each one addressing a specific research gap, for a particular CVD application, using a specific data set. Basically, the first research track, stratification and diagnosis, addresses the development of intelligent algorithms and models for stratification and diagnosis, providing an effective support to the decision making of professionals. The major data analysis functionalities include advanced tools for the personalization, integration, analysis and interpretation of the different sources of clinical information. The second research tack, personalized predictions, is linked with the concept of clinical prognosis, aiming to predict the future of a specific variable, a clinical condition or, ultimately, the health status of a patient. Moreover, predictive methods can be applied to help the planning and adjusting of treatments, by forecasting the effectiveness of the therapy in the future. Finally, the third research track, Integrated care and process mining, focus on the development of algorithms and tools to facilitate and support the application of the newest clinical evidence to clinical daily practice, mainly through interactive pattern recognition techniques.

The lack of patient-specific predictive algorithms with the capacity of estimating the evolution of the disease and, therefore, to pave the way for optimal, patient specific and coordinated treatment actions are major gaps to increase PHC solutions' robustness and acceptance by professionals and patients. The infusion of clinical evidence and existing biomedical knowledge while addressing these gaps will play a decisive role in improving accuracy, quality, personalization and, ultimately, acceptability by patients and professionals.

LiNK project has contributed to close these gaps by defining and implementing research tracks involving some of these key issues or others that might be identified inside the RIF. Research questions identified in these research tracks shall be used as contexts for shared advanced training such as in PhD thesis development or post-doc programs.

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