Deliverable 4.3

Project ID	654241
Project Title	A comprehensive and standardised e-infrastructure for analysing medical metabolic phenotype data.
Project Acronym	PhenoMeNal
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Work Package Title	Interfacing with Biomedical European Infrastructures
Deliverable Title	D4.3 Consensus agreement document from the working groups
Delivery Date	M30
Work Package leader	CIRMMP
Contributing Partners	CIRMMP, UB
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Abstract: This deliverable report on the identification of an overlap between the themes developed by the working groups implemented in the first two years of the PhenoMeNal project. This overlap corresponds to the role of metabolomics in systems medicine, which reunites the systems biology focus of the first working group and the clinical application focus of the second group. A table of contents to develop a document on systems medicine has been agreed upon.

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1 EXECUTIVE SUMMARY

The activities of WP4 aim to foster the interactions of PhenoMeNal with other research centres (public or private), large infrastructures (such as ESFRIs) and national, regional or European initiatives that produce or consume metabolomics data as part of their routine work. In addition, the PhenoMeNal partnership is committed to proactively intercept current and future developments in the overall field of metabolomics in order to be aware of ongoing trends, and possibly evaluate suitable tools to address them. This is achieved through the implementation of working groups involving experts outside the present partnership. In the first half of the project, two such working groups[1] have been established:

- The first working group has a focus on the role of metabolomics in systems biology (SB), and the associated computational strategies.
- The second working group involves mainly clinicians, with the goal to develop a vision for metabolomics in clinical research/practice, focussing on the role of computational workflows such as those provided by PhenoMeNal.

The first working group has produced a document that is now in press in the journal Metabolomics (and will be Open Access). The second group is going to finalise a document (the target is February 2018), to be submitted for publication in a peer-reviewed journal.

Then, by comparing the activities and output of these two groups it became apparent that a relevant area of scientific overlap was that of the role of metabolomics in systems medicine. In a nutshell, systems medicine can be defined as the application of systems biology to human disease. It was thus decided to extend the work of the groups, and some of their members will analyse the perspective of metabolomics and the potential role of PhenoMeNal in this scientific context.

2 CONTRIBUTION TOWARDS PROJECT OBJECTIVES

The activities described in the present report contribute to the achievement of the following objectives:

Objective 4.3 Optimise synergies between projects by providing input and receiving feedback from working groups addressing activities of common interest.

More generally, they contribute towards the following overall objectives of the project:

[1] http://phenomenal-h2020.eu/home/outreach/work-groups/

- to establish technology for a water-tight audit trail for the processing of human metabolic phenotyping data from the raw data acquisition all the way to the generation of high-level biomedical insights (such as a medical diagnosis).
- **to foster the worldwide adoption of PhenoMeNal through a wide range of outreach, dissemination, networking and training activities.**

3 DETAILED REPORT OF THE DELIVERABLE

3.1 Background: Working Group on Metabolomics in Systems Biology

This working group produced a document entitled "*From correlation to causation: analysis of metabolomics data using systems biology approaches*", which was accepted for publication in Metabolomics (currently assigned DOI 10.1007/s11306-018-1335-y). This document started from the observation that metabolomics is a well-established tool in systems biology, especially in the top-down approach. A major limitation of the impact of metabolomics experiments is that they often result in discovery studies that provide intriguing biological hypotheses, but rarely offer mechanistic explanation of such findings. In this light, systems biology-enhanced analysis of data can provide insights into the molecular mechanisms that originated the observed metabolic profiles, enhancing the impact of metabolomics studies. The document thus provided an overview of computational methods used in system biology approaches, such as network analysis, metabolic modelling, and discussed how these methods can be and/or have been successfully deployed in metabolomics studies.

3.2 Background: Clinical Working Group

Metabolic Phenotyping examines in analytical detail the metabolites, from a diverse range of tissues and biofluids such as blood and urine, to gain insights into the metabolic network, the metabolome, and to link metabolism to health and disease. The metabolome is dynamic and sensitive to environmental and disease factors and is a valuable diagnostic and prognostic tool in stratified medicine, i.e. augmenting the classical 'signs and symptoms' etiology with a measurable evidence on the biochemical level. At the patient level, metabolomic phenotyping offers the realistic possibility of truly personalised medicine through individual profiling in the identification, treatment and prevention of disease. At a population level, it offers the ability to associate population metabolic traits with disease profiles provided by large epidemiological studies, thus delivering a paradigm shift in the understanding of disease incidence and spread on a global scale. The aim of the document by the Clinical Working Group of PhenoMeNal is to introduce and disseminate metabolic phenotyping in medical research and

healthcare. The document addresses also the limitations of the approach, its ethical, legal and security (ELSI) issues, and discusses the challenges facing the practical implementation of personalised medicine in today's healthcare system.

3.3 Consensus Document between the Working Groups

Representatives of the two working groups have discussed possible topics to bridge the themes addressed by the groups and agreed that the area of systems medicine is a logical overlap.

A tentative table of contents has been discussed:

Metabolomics in Systems Medicine: an overview of challenges in data analysis and model integration

1. Introduction to System medicine goals
2. Multi-omics approaches
    a. omics data Integration in predictive models for biomarkers and drug targets discovery
    b. databases where to found the different "omics" data
    c. 'Metabolomics' data integration into models
3. Metabolic models in systems biology: from metabolic pathways to genome scale mode
    a. kinetic models
    b. stoichiometric models (constraint based models)
    c. applications in systems medicine
4. Metabolomics data processing: towards FAIR workflows in the context of PhenoMeNal
5. Practical considerations

At present discussions have taken place by email or teleconference, also given the commitment of the groups to complete the other documents (described in the previous two sections). With the document of the first working group now accepted for publication, a first draft of the full text is being assembled by members of that group. This will be subsequently reviewed and extended by both groups together. A face-to-face meeting has been tentatively planned for the second half of April 2018.

4 WORK PLAN

4.1 Structure and Management of WP4 tasks

The aim of WP4 is to maximise the interaction of PhenoMeNal with European infrastructures and national or regional research centres with an interest in biomedical data generation and analysis. In this way, the present consortium can inform other infrastructures and research centres about the development of the PhenoMeNal e-infrastructure, remaining aligned with the progress in the field and the needs of PhenoMeNal potential users.

The present Deliverable is part of task T4.2

Task 4.2: **Establish and convene working groups** involving the PhenoMeNal consortium as well as participants in other biomedical infrastructure and research projects. (CIRMMP, ICL, UB, UOXF, EMBL-EBI, ISB, UL, UU) The working groups will discuss on the evolution of selected aspects of the biomedical and/or eScience fields that are relevant to metabolomics.

WP4 is led by CIRMMP who is responsible for planning and coordinating the work and the related deliverables. The planning was carried out in collaboration with ICL, UB, UOXF, UL, EMBL-EBI, and UU. CIRMMP led the implementation of the first working group; EMBL-EBI, UU, ICL and UB led the implementation of the second working group. CIRMMP and UB are leading the preparation of the consensus document.

5 DELIVERY AND SCHEDULE

The deliverable report on the initial work/planning for the preparation of the consensus document by the two working groups of PhenoMeNal. An advanced draft should be available by late April/mid May. This is due to the time still required to finalise the document by the clinical working group.

6 CONCLUSION

This report describes the conclusion of the activities of the two working groups involving the PhenoMeNal partnership as well as external experts in various fields that constitute areas of potential strategic development for metabolomics, as well as the plan and initial work to produce a consensus document addressing the role of metabolomics in

systems medicine. The latter field has been identified as the main area of scientific overlap between the themes addressed by the two groups.