

**Deliverable 4.2**

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<b>Project Acronym</b>	PhenoMeNal
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<b>Work Package Number</b>	4
<b>Work Package Title</b>	Interfacing with Biomedical European Infrastructures
<b>Deliverable Title</b>	D4.2 Report describing the activity and output of working groups
<b>Delivery Date</b>	M18
<b>Work Package leader</b>	CIRMMP
<b>Contributing Partners</b>	CIRMMP, ICL, UB, UOXF, EMBL-EBI, UL
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**Abstract:** This deliverable reports on the implementation and activities of the working groups established as part of the work of the PhenoMeNal consortium and involving also participants in other biomedical infrastructures and research projects. During the period covered by the present deliverable, two working groups have been established. One WG focuses on metabolomics in systems biology; the second WG addresses the application of metabolomics in clinical practice. Both WG's have been working towards the preparation of position papers to be publicly released.



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## 1. EXECUTIVE SUMMARY

The activities of WP4 aim to foster the interactions of PhenoMeNal with other research centers (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. The rationale is that such centers and infrastructures constitute a relevant part of the potential user basis of PhenoMeNal. Therefore, it is important to raise awareness of the activities of PhenoMeNal already at an early stage of the project development. This allows the aforementioned stakeholders to convey their needs to the PhenoMeNal partnership as well as to avoid potential duplications of effort.

The partnership is also 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. At present, two such working groups<sup>1</sup> have been established:

- The first working group has a focus on the role of metabolomics in systems biology (SB). In particular, the dual aspect of metabolomics as a data source for the construction of SB models and of SB as a framework for the mechanistic interpretation of metabolomics data is addressed.
- The second working group involves mainly clinicians. It was established as part of the outcome of the clinical workshop in Barcelona in May 2016<sup>2</sup>. The overall goal of this working group is to develop a vision for metabolomics in clinical research/practice, focussing on the role of computational workflows such as those provided by Phenomenal.

Both working groups are committed to making their outputs publicly available in the form of position papers on public repositories, such as Zenodo<sup>3</sup>, or reviews published in peer-reviewed scientific journals (open access). As part of the future work, we will monitor opportunities to implement a third working group. One option is to seek interactions with other e-Science initiatives (VREs, EGI competence centers ...), also based on the mapping of e-infrastructures carried out previously.

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<sup>1</sup> <http://phenomenal-h2020.eu/home/outreach/work-groups/>

<sup>2</sup> <http://phenomenal-h2020.eu/home/outreach/workshops-training/2/>

<sup>3</sup> <https://zenodo.org/>



## 2. CONTRIBUTION TOWARDS PROJECT OBJECTIVES

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

**Objective 4.2** Align PhenoMeNal activities to the requirements of large-scale EU biomedical infrastructures and national and regional research centers, and their users.

**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:

- 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.**
- to develop a model to ensure sustainability of the PhenoMeNal network.

## 3. DETAILED REPORT OF THE DELIVERABLE

### Working group on Metabolomics in Systems Biology

Systems biology is a scientific domain that links straightforwardly to metabolomics. The latter provides a direct view on biochemical reaction occurring with cells or whole organs and thus provide invaluable experimental information that can be used to set up or validate quantitative models. Conversely, networks derived within systems biology studies provide a broad framework for the interpretation of metabolomics data, especially in the case of untargeted analyses, providing the opportunity to attach a mechanistic interpretation to the novel biological hypotheses that metabolomics studies often raise. Thus, it appeared natural to implement the first working group to address these aspects.

This working group was kick-started on the occasion of a scouting action at the Systems and Synthetic Biology laboratory of Wageningen University<sup>4</sup>, which took place in September 2016. This action leveraged the contacts with the node of the ISBE<sup>5</sup>

<sup>4</sup> <http://www.wur.nl/en/Expertise-Services/Chair-groups/Agrotechnology-and-Food-Sciences/Laboratory-of-Systems-and-Synthetic-Biology.htm>

<sup>5</sup> <http://project.isbe.eu>



(Infrastructure for Systems Biology Europe) ESFRI infrastructure located at the University of Wageningen initiated on the occasion of the stakeholders meeting at the first general meeting of PhenoMeNal. In line with what mentioned in the preceding paragraph, the initial discussion focused on two different aspects of the relationship between the discipline of systems biology (SB) and metabolomics:

- Metabolomics data can be used to inform systems modelling, which is a core aspect of SB
- Systems-level view of cell functioning should provide a framework to understand the metabolic response of the organism under investigation to stimuli

The latter aspect appeared of particular interest, as a systems approach to the interpretation of metabolomics data is not routinely performed within metabolomics labs and initiatives. However, it would provide, at least in principle, a framework to rationalize the evidence provided by changes in metabolomic profiles as a function of external stimuli, disease/healthy state, etc. The local SB team has relevant expertise in related applications, such as to develop network representations of metabolic phenotypes.

During the scouting action, an initial analysis of the scientific literature was performed to identify possible previous work in the above direction. A few publications supported the overall concept but did not address consistently the use of SB to provide an interpretation framework of metabolomics. It thus appeared that there was an opportunity to make a meaningful contribution by reviewing existing literature within the perspective outlined in this section. A possible abstract has been prepared (Annex 1) and circulated to the PhenoMeNal partnership.

Building upon the favorable reaction of the consortium, a working group was implemented with the main aim to work on an overview of the use and applications of metabolomics in systems biology. The working group involves the group of Vítor Martins dos Santos (Wageningen University) and Marta Cascante (University of Barcelona) as members of the ISBE consortium; the group of José Camacho (University of Granada); and various PhenoMeNal partners (at present mainly CIRMMP, EBI, and INRA. The University of Barcelona is also a partner of PhenoMeNal. An initial draft of this document was assembled and collectively edited under the coordination of Dr. Edoardo Saccenti, one of the members of the Wageningen node, and will be circulated to all PhenoMeNal partners. A tentative title is “From correlation to causation: analysis of metabolomics data using systems biology approaches”. The current table of contents is

## I. Analysis of metabolomics data using network approaches

### A. Association networks



## B. Weighted co-expression networks

### 1. Possible limitations of the WCGNA approach

## C. Approaches from functional genomics

## D. Other approaches

## II. Pathway analysis

After positive feedback by the consortium, the document will be submitted in the form of a review to a peer-reviewed scientific journal in the field, as an open access publication. The document will highlight opportunities for PhenoMeNal to develop services that (could) encounter also some needs of the systems biology community, i.e. making PhenoMeNal the supplier of services for the the analysis of metabolomics data toward exploitation of that information for systems biology. At the same time it will identify frameworks of analysis that take into account pre-existing network information to support interpretation of metabolomics data. Such frameworks could be included in the PhenoMeNal platform.

### **Clinicians Working group**

A second stakeholder working group<sup>6</sup> was established, involving clinicians. The group was established as part of the outcome of the clinical workshop in Barcelona in May 2016 and had its first online meeting on November 24th, 2016. The one-day workshop focused on metabolic phenotyping in clinical practice, and involved about 25 participants of which several active in clinics and clinical research. The workshop addressed various topics, including identification of biomarkers, metabolomics for precision medicine, quantitative and reproducible phenotyping of patient samples, electronic health records, ethical aspects of metabolomics, clinical decision support, application scenarios. The outlined critical points included the reproducibility of analyses, the needs in terms of underlying IT and bioinformatics infrastructure, the identification of areas and applications with the highest (potential) benefit/cost ratio, how to reach out to policy makers and obtain support also for the necessary communication and training within the clinical community.

Based on the above experience and input, the present working group set the following priorities for its work:

- Represent clinical metabolomics practitioners as target users of Phenomenal. Initially these will primarily be clinical research scientists, with the expectation

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<sup>6</sup> <http://phenomenal-h2020.eu/home/outreach/work-groups/>



that those involved in translating metabolomics technologies to routine clinical practice will join.

- Advise what functions are required in Phenomenal tools and workflows by clinical users. This may involve defining specific use cases/scenarios.
- If tools that address the functionalities of point 2 are implemented in PhenoMeNal, participate in user testing.
- Work towards a manuscript or report which describes a vision for metabolomics in clinical research/practice, focussing on the role of computational workflows such as those provided by Phenomenal.

The coordinator of the working group is Dr. Hutan Ashrafian, a bariatric surgeon based at Imperial College London. So far, the working group has been meeting online on approximately a bi-monthly basis. The third meeting will take place on March 31st, 2017. As a first action, a small survey was carried out involving about 20 experts with 17 responses asking:

Perspective of metabolomics in clinical practice/science?

- Diagnostics 31%
- Mechanisms 59%
- Population screening 0%
- All of the above 10%

Methods of communication of metabolomics information

- 34% stats
- 66% visual

The working group is currently in the process of collecting different user stories as the background material of their position paper. A suggested title for their latter is “Metabolomics: the stethoscope of the 21st century”. In addition, a tentative possible Table of Contents has been drafted:

- I. Introduction
- II. Bedside solutions and needs (includes user interface)
- III. Actual examples and usage
- IV. Research solutions & needs
- V. Computational needs
- VI. Conclusions & future strategies



The position paper will be released as open access. It has the ambition to define the landscape for a more extended role of metabolomics in clinical research/practice and thus to be useful to make the case for clinicians adopting metabolomics as well as policy makers and funding agencies supporting this. It will therefore contribute greatly to the visibility and sustainability of PhenoMeNal, as the project will be a major provider of the needed computational tools.

## 4. WORK PLAN

### Structure and Management of WP4 tasks

The aim of WP4 is to maximize the interaction of PhenoMeNal with European infrastructures and national or regional research centers with an interest in biomedical data generation and analysis. In this way, the present consortium can inform other infrastructures and research centers 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.

The following objectives are targeted:

**Objective 4.2** Align PhenoMeNal activities to the requirements of large-scale EU biomedical infrastructures and national and regional research centers, and their users.

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

These activities contribute also, indirectly, to Objective 4.4: Establish communication channels and participate in meetings with other European and world-wide biomedical and e-infrastructures. To this end the following events have been planned:

**March 2017:** Presentation of PhenoMeNal to the BBMRI-ERIC WG4 on metabolomics



**May 2017:** Participation in a round table co-organized by INSTRUMENT, involving various biomedical ESFRI's (such as ECRIN, ELIXIR, EuOpenScreen, InfraFrontier, INSTRUMENT, ...) and other H2020 projects.

The latter round table aims to discuss actions implemented to reach out systematically to potential new users/user communities and specifically to plan possible joint initiatives in this direction. This includes the provision of combined services. This will be an occasion to leverage the transversal nature of the PhenoMeNal infrastructure to explore the possibility of using it as a basis for computational services in other disciplines of the biomedical sciences.

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; ICL and UB led the implementation of the second working group.

*Utilization of resources:*

Total person month (PM) allotted: 10

Contribution from partners in terms of total PM utilized:

CIRMMP	ICL	UB	UL	UOXF	UU
3	2	1.5	2	1	0.5



## 5. DELIVERY AND SCHEDULE

The deliverable was submitted on time.

## 6. CONCLUSION

This report describes the implementation of two working groups involving the PhenoMeNal partnership as well as external experts in various fields that constitute areas of potential strategic development for metabolomics, and, consequently, are of interest to the present project also in terms of future collaborations and applications, and for sustainability of the e-infrastructure.

The two working groups link metabolomics to systems biology on one side and to clinical practice on the other one. The output of the groups will be made openly available either as position papers (via the project website and on Zenodo) or open access reviews providing hints for the foreseeable usage of metabolomics data in the future, with a close perspective on methods for data analysis and computational tools.

The future activities of this WP will include monitoring for opportunities to implement a third working group. In this respect, one option is to liaise with ELIXIR and other e-infrastructure/VRE initiatives in order to identify synergies and common bottlenecks as well as to disseminate and foster re-use of the technical solutions developed in this project. In parallel, we will maintain and expand our communication channels toward experimental biomedical infrastructures and large centers, also to explore the possibility that they use the PhenoMeNal infrastructure, wholly or in part, as a basis for their computational services.



## 7. APPENDIX

### **Appendix I. Abstract for a position paper on “metabolomics and systems biology”**

Metabolomics is a well-established tool in systems biology, especially in the top-down approach. Metabolomics studies often results in discovery studies that produce results that turn into intriguing biological hypotheses but rarely offer mechanistic explanation of such findings. In this light, the interpretation of metabolomics data can be boosted by deploying systems biology approaches. 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. This review aims to i) provide an overview of system biology approaches, such as network inference and analysis, metabolic modelling, and large scale integration of heterogenous data ii) discuss how these methods have been successfully deployed in metabolomics studies and iii) discuss current limitations and possible future direction for a synergistic integration of metabolomics and system biology.