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Deliverable: D6.9 Report on ERACoSysMed/CASyM joint workshops

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WP: WP6
Task: 6.5
Lead beneficiary: MIZS
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1 INTRODUCTION

The task 6.5 – Collaboration with CASyM aims at fostering strong coherence and frequent communication with the Coordination Actions Systems Medicine, CASyM, providing benefits for both CASyM and ERACoSysMed. Therefore, the survey for contact persons from various stakeholders (clinics, patient organizations, industry, regulatory authorities), expanding upon the list of stakeholders identified by CASyM, and among universities and general stakeholders has represented an important starting point to reach this aim. The survey's main findings, based on data up to January 2017, are gathered in the Deliverable 6.8. – Report on survey results. However, they were updated with novel data obtained by June 2017 (see attached updated report).

The survey results provided topics for two workshops: 1) Implementation of Systems Medicine education in medical schools and 2) Integration of Systems Medicine into clinical practice and research.

Ministry of Education, Science and Sport, Slovenia (MIZS) and Faculty of Medicine, University of Ljubljana (UL), Slovenia, implemented the task 6.5 jointly.

2 IMPLEMENTATION

2.1. Update of the survey

As detailed in the Deliverable 6.8 – Report on the survey results, the online Systems Medicine survey remained open, after the initial cutting off phase at the end of January 2017. Namely, in the middle of January it was complemented with five questions about demographic information of participants and was sent once more to the list of 2400 recipients.[1] The received replies were re-evaluated, updated in the report (see attachment), and presented at the first workshop (see point 3.1.5.).

2.2. First workshop and awareness event

The first workshop was related with the awareness event (Task 6.3 - Additional activities to create awareness of Systems Medicine). MIZS and Faculty of Medicine formed organisational and scientific committees, which in agreement with ERACoSysMed coordinator and WP5 leader, developed the plan to join the two tasks into a two-day international event "Systems Medicine Conference in Slovenia", which took place on 8-9 June 2017 in Hotel Slon, Ljubljana, Slovenia. Report on the awareness event was included in Deliverable 6.4 – Report on annual awareness events.

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[1] Including people involved in Systems Medicine-related training (undergraduate, graduate or other levels) and general stakeholders: CASyM and EASyM partners; participants of the 1st EASyM conference that was held in October 2016 in Berlin, Germany; contacts provided from the Center for Functional Genomics and Biochips (Faculty of Medicine, UL); and to contacts provided by ERACoSysMed consortium partners, including evaluators and applicants from the first ERACoSysMed Joint Transnational Call (JTC) and those evaluators invited to participate in the second JTC.

2.3. Second workshop

MIZS and Faculty of Medicine formed organisational and scientific committees, which in agreement with ERACoSysMed coordinator and WP5 leader developed the plan to organise the workshop into a two-day international Symposium "Systems Medicine in Clinical Practice", 10-11 June 2019 in Ljubljana, Slovenia, hosted by the Faculty of Medicine.

3 SYSTEMS MEDICINE CONFERENCE, 8-9 June 2017, Ljubljana, Slovenia

The focus of the first day (8 June) was on raising awareness of Systems Medicine and opportunities in daily clinical practice and consequences for the patients. The first half of the second day (9 June) was dedicated to a scientific symposium hosted by the Centre for Functional Genomics and Biochips, Faculty of Medicine, whilst in the second half of the day the workshop "Systems Medicine Education in Medical Schools: How Far from the Pan-European Effort?," was organised, with invited representatives of national and international Medical Students' Associations. The conference brought together diverse stakeholders from academia, including teaching staff, medical students, patient representatives, clinicians and journalists.

3.1. Workshop "Systems Medicine Education in Medical Schools: How Far from the Pan-European Effort?"

The objective of the workshop was to gather different views on implementing Systems Medicine education in medical schools and to open a discussion about present and future training of medical doctors. The aim was to gather views from professors and students on how to implement Systems Medicine training into medical schools' curricula. University professors from Faculty of Medicine presented the extent to which training on Systems Medicine is available in the current curriculum. National and international student organization representatives (European Medical Students' Association, International Federation of Medical Students' Association and Slovenian Medical Students' Association) presented their views on implementing new courses to the medical students' training. Following the presentations, discussion ensued on how to motivate the clinicians to train in Systems Medicine. In conclusion, workshop's aim and objective were achieved, reaching also an expected result of the workshop – the establishment of a cooperation between the students and professors on implementing Systems Medicine lectures into curriculum.

3.1.1. The importance of integrating Systems Medicine into medical schools' curricula

Debates about what is the best approach to teach Systems Medicine and how to incorporate this in the running medical schools' curricula are vivid and continuous. Up to the present, there are only a few best Systems Medicine training practices, so there are still multiple opportunities for paving the path. The consortium of the Coordinating Actions Systems Medicine - CASyM established a European plan for education in Systems Medicine. This should be based on existing programmes and experiences gained from relevant training concepts, and should result in sustainable education programmes for Systems Medicine training of medical doctors and related scientists. Since it is not agreed what should be the best age/level to start with systems approaches in biomedical education, CASyM proposed several possibilities. One is to design tailored interdisciplinary programmes and implement training at the master's, doctoral and postdoctoral level, as well as specifically for clinicians at different stages of their careers. To achieve this, one needs to specify course modules relevant for Systems Medicine, which could be incorporated into curricula for medical and other biomedical fields. Whether this could result in a widely accepted independent "Systems Medicine" curriculum is still not clear. It is thus important that the Systems Medicine courses are accredited by the European Credit Transfer and Accumulation System in the path towards formalization of this

interdisciplinary education branch. Only early integration of Systems Medicine topics into medical schools' curricula can make a sufficiently large step forward, since young people are much more susceptible to accepting novel concepts compared to established specialists. However, to reach also the population of already established scientists and medical doctors with the degree, lifelong education possibilities can be offered, such as Systems Medicine meetings, expert guided workshops and summer schools, targeted lecture series, etc. Medical doctors can be attracted if the courses (online and face-to-face) are accredited to offer the CPD (Continuous Professional Development) credits, which for medical doctors mean the Continuous Medical Education (CME) credits that are in several European countries required for maintaining the practitioner license.

To introduce Systems Medicine topics into the medical schools' curricula, the scientific community needs to work hand-in-hand with AMSE (Association of Medical Schools in Europe), IFMSA (International Federation of Medical Students' Associations) and EMSA (European Medical Students' Association), since they have a voice to suggest modifications of the existing curricula.

3.1.2. Objectives of the workshop

The objective of the workshop was to gather representatives from national and international medical students' organizations and Faculties of Medicine to present their views on how to implement Systems Medicine education into medical schools' curricula and to open a discussion about the possibilities of present and future training of medical students.

3.1.3. Expected results of the workshop

An expected result of the workshop was to gather different views, both positive and negative, on integrating Systems Medicine into the medical schools' curricula. Student representatives welcomed the introduction of contemporary topics into the medical schools' curricula, such as Systems Medicine, but with some reservations. University professors are aware of the difficulties in changing the curriculum and acknowledged the student's reservations. The result of the workshop was achieved and potential problems in introducing Systems Medicine into medical training were identified as well as solutions proposed. In addition, another expected result was to open a discussion on how to implement new courses into curriculum between students and professors. This result was achieved as students are willing to participate in shaping new curricula and professors are willing to include students in the process of designing of new curricula.

3.1.4. Brief description of the program of the workshop

The chairpersons of the workshop were Prof. Dr. Ana Plemenitaš and Prof. Dr. Damjana Rozman, professors from the Faculty of Medicine, University of Ljubljana. The workshop started with short presentations from university professors, followed by an open discussion with national and international students' representatives.

Prof. Dr. Damjana Rozman presented results from the updated online Systems Medicine survey (as mentioned on page 3, point 2.2.) regarding education and training in Systems Medicine. Briefly, the survey showed that almost 35% of participants highlighted as the most critical step, the implementation of Systems Medicine into the clinics. They also pointed out that there is very little mathematics and informatics in medical students' training. Results from the survey are available in

the updated report (see appendix).

Prof. Dr. Ana Plemenitaš, a member of the Academic Affairs Commission of Faculty of Medicine, University of Ljubljana, presented an overview from the faculty's curriculum of several obligatory and elective courses, where medical students learn about Systems Medicine. Students can learn more about Systems Medicine also during their research work. However, she concluded that the knowledge about Systems Medicine is presented in a fragmented way during several diverse courses and there is no single Systems Medicine course currently part of the medical students' training at Faculty of Medicine in Ljubljana. She pointed out that the major problem is that students already have many obligatory courses and adding a new course would mean to exclude one of the old courses.

Dr. Tanja Carli, an assistant at the Faculty of Medicine in Ljubljana, commented from the audience that majority of medical students have limited mathematical knowledge. Many do not understand a simple graph or function in physiology even though they were selected among best students at enrolment at the Faculty. Professors and students agreed that there is not enough mathematical lectures available during training, which hinders understanding the mathematical side of Systems Medicine.

Danaja Plevel, head of the Slovenian Medical Students' Association, who explained that she did not know what Systems Medicine was until she attended this conference, initiated the open discussion. From fragmented knowledge received at several diverse courses during her training, she did not get a general idea about Systems Medicine. Also new approaches are usually presented at the end of courses and are not a part of the exam; therefore, the students do not learn them. She sees several problems in implementing Systems Medicine into the curriculum: Lack of standard procedures and proper literature in Slovenian language and lack of knowledge about Systems Medicine among clinicians.

Žiga Barbarič, Medical Education Director of European Medical Students' Association (EMSA), presented EMSA Policy on Introducing Contemporary Topics into Medicine Curriculum. He stated that EMSA agrees that contemporary topics are included into medical training; however, certain conditions have to be met beforehand. Firstly, the aim of the new course needs to be defined (is it only to inform the students about a topic or to train them to expert level?). Next, the new course has to be included into the curriculum at the proper time during the training. He also pointed out that there has to be proper literature available in native language. Further, medical training is already 6 years long; therefore, there is little room available for adding a new course, probably leading to exclude an old course. Additionally, the change in curriculum should be done on the EU level, so that it does not interfere with student exchange programme during training. In conclusion, the EMSA welcomes new topics in medical curriculum.

Andrej Martin Vujkovac, a Vice-President for Capacity Building at International Federation of Medical Students' Associations (IFMSA), presented the IFMSA Policy on Introducing Contemporary Topics into the Medicine Curriculum. He stated that IFMSA also welcomes changes to the medical schools' curricula; however, students want to be equal partners and want to contribute to the shaping of the

new curriculum and selection of new lectures.

In the general discussion, one of the first comments from the audience was that we should not limit only to medical schools' curricula, but instead medical doctors and clinicians should also receive training. Professors from Faculty of Medicine agreed with the comment, but pointed out that clinicians generally do not attend conferences except those, which are in the field of their specializations. The solution is that there would be lectures or workshops at these specialized medical conferences.

A professor from Bar Ilan University in Israel, Dr. Sol Efroni, explained that he teaches Systems Medicine to students and clinicians at his university. In his experience, clinicians wanted to be trained, when they see other clinicians use Systems Medicine tools in their work and see the benefits, such as better diagnostics and treatment of their patients.

A patient organisation representative, David Supple, pointed out that relationship between patient and its doctor is imperative, and with Systems Medicine there is additional complexity, which is difficult to include in the 5 minutes' period available to the clinician to explain to the patient the disease and the treatment.

All participants of the workshop agreed that clinicians need to fully understand the tools and concept of Systems Medicine to be able to explain the benefits to the patient.

As Prof. Dr. Dušan Šuput, General Secretary of Association of Medical Schools in Europe (AMSE), dean of Faculty of Medicine in Ljubljana, was not able to attend the workshop due to personal reasons, Prof. Dr. Damjana Rozman presented the AMSE Policy on Introducing Contemporary Topics into the Medicine Curriculum. She represented many declarations, which are binding for Medical Schools in Europe and concluded that AMSE supports inclusion of Systems Medicine into medical schools' curricula. The professors understand that they need students' cooperation to change the curricula and students' representatives were invited to participate in preparation of the statement about inclusion of Systems Medicine into medical training.

Workshop was concluded by Dr. Eva Batista from Ministry of Education, Science and Sport and Prof. Dr. Damjana Rozman from Faculty of Medicine, University of Ljubljana.

3.1.5. General findings of the updated survey

Since Systems Medicine is a developing field and striving for broader recognition, it is important to address the needs of different stakeholders and user communities that could be met by Systems Medicine in the way towards personalized medicine. This was the aim of the Systems Medicine online survey. Initially, the survey only contained questions about Systems Medicine, but in mid-January we added 5 general questions regarding the person's gender, country of residence, level of education, professional background and current position and institution. By January 23rd 2017, 111 answers were collected and by June 1st 2017 additional 64 answers (final number being 175).

Outcome of the survey showed that participants were mostly from Europe (more than 90%) and their

professional background was predominantly based in academy (68 %).

The lack of common understanding of Systems Medicine and translating Systems Medicine's insights into clinical practice are the biggest challenges for Systems Medicine community. Almost 35% of participants highlighted integration of Systems Medicine into clinic. Most (68%) think that Systems Medicine should be pushed forward to the clinic and share the opinion that it should bring together all the relevant fields and equally develop in all of them. Almost 30% of participants think that Systems Medicine would increase patient benefit and cost effectiveness in the healthcare setting. Most participants think that Systems Medicine needs wider recognition.

Survey results pointed out a lack of information about mathematical and informatical tools regarding big data, which have been used in the field of Systems Medicine and a lack of their integration in curricula.

The majority of participants propose that learning about basic understanding of terms/methods is necessary, such as biometry/statistics, computer science, systems theory, programming and understanding of how data science works.

3.1.6. Conclusions

All participants of the workshop acknowledged that contemporary courses, such as Systems Medicine, have to be implemented in medical schools' curricula. However, several issues were identified, which need to be addressed for successful implementation of Systems Medicine into medical doctor training:

- Already full curriculum with little space for introduction of new obligatory subjects, only at the expense of excluding old subjects;
- Limited mathematical knowledge and training of medical students, which hinders the potential to understand and use Systems Medicine;
- The aim of Systems Medicine course needs to be defined, courses need to be standardized and introduced at proper time during training, proper study literature needs to be available also in local language;
- Courses need to be implemented in EU wide medical schools' curricula; and
- Limited knowledge of clinicians about Systems Medicine hinders the transfer of Systems Medicine research and tools into practice and training of future clinicians.

3.1.7. Future objectives

A short-term objective is to produce a statement signed by representatives of EMSA, IFMSA and AMSE, about the need to include more mathematical principles in medical studies, which should be a start of organized discussions at the level of European medical schools and associations of medical students.

The medium-term objective aims to identify particular medical schools in Europe that would be interested to pilot a Systems Medicine course or topics, and to potentially locate financial resources to support these activities.

A longer-term goal is to broaden the vision about the importance of Systems Medicine approaches in the modern, post-genome medicine. Since there is currently no financial resources available for long-term activities, it is perhaps too optimistic to propose an establishment of a webpage for education and dissemination of Systems Medicine topics, results and best practices. However, this might eventually be possible in collaboration with some European research infrastructures, such as ELIXIR, where a large effort is placed on education and training platforms as well as their sustainability.

4 SYMPOSIUM "SYSTEMS MEDICINE IN CLINICAL PRACTICE", 10-11 June 2019, Ljubljana, Slovenia

The objective of the symposium was to present the use of Systems Medicine tools and approaches in clinical setting, their benefits for the patients and the ways in which this field contributes to the cost effectiveness in the healthcare setting. The symposium's aim was to tackle one of the problems exposed at the workshop organized in June 2017 and in the online survey, which is the lack of Systems Medicine training of clinicians and therefore integration of Systems Medicine into clinical practice and research. Established clinicians and researchers who already use Systems Medicine tools in their research and practice presented funded projects from the ERACoSysMed Joint Transnational Calls 2015 and 2017. Participants presented their work with posters and additional workshop on *Systems Medicine in clinical practice: ethical dilemmas and education* was organized. In conclusion, symposium's aim and objective were achieved and a Systems Medicine training was organized for the clinicians, researchers and students.

4.1. Description of the Symposium

In June 2017 a workshop titled *Systems Medicine Education in Medical Schools: How Far from the Pan-European Effort?* was organized as a part of a two day *Systems Medicine Conference in Slovenia.* The objective of the workshop was to gather different views on implementing Systems Medicine education in medical schools and to open a discussion about present and future training of medical doctors. One of the comments from the workshop audience was that we should not limit training only to medical schools' curricula, but expand it to the medical doctors, who are already active in the clinic. The overall experience was that clinicians want to gain this knowledge when they see other clinicians use Systems Medicine tools in their work and its benefits, such as better diagnostics and treatment of their patients. Additionally, the results of the 2017 general *Online survey about Systems Medicine* pointed out two major challenges for the Systems Medicine community: (1) Lack of common understanding of Systems Medicine and (2) Translation of Systems Medicine's insights into clinical practice. The overall conclusion of the event was that Systems Medicine training of established clinicians will promote integration of Systems Medicine into clinical practice and research. To achieve this, lifelong education possibilities have to be offered to clinicians, such as Systems Medicine meetings, expert guided workshops, summer schools, targeted lecture series, etc.

Established clinicians and researchers, who already use Systems Medicine tools in their research, were invited as speakers. These success stories were presented to the interested audience of clinicians, researchers and students, who would like to use Systems Medicine tools. Symposium's target audience were medical doctors of all specialty and seniority as Systems Medicine is a field applicable to all specialities, especially to those with complex multifactorial disorders. The idea was to bring together the whole community, provide it with ideas, and empower clinicians to use Systems Medicine tools to improve diagnostics and treat patients more precisely and cost effectively. Besides success stories from basic and clinical research, the symposium also offered discussion about ethical aspects, patients' perspectives, education of future generations of medical doctors, interactive lectures, poster presentation sessions, etc. The symposium was accredited by the European Accreditation Council for Continuing Medical Education (EACCME®) with 6 European CME credits

(ECMEC®s) (LEE19-00523).

The symposium started on afternoon of June 10th 2019 with welcome speeches of official representatives from the Ministry and University of Ljubljana. The opening lecture, given by an EASYM member, Dr. Isaac Cano, was followed by project presentations from ERACoSysMed Joint Transnational Call 2015. Afterwards, a patient organisation representative and a researcher, who is also an EASYM member, presented different perspectives on Systems Medicine. The first day finished with the poster session. The second day started with project presentations from ERACoSysMed Joint Transnational Call 2017, followed by a workshop titled *Systems Medicine in clinical practice: ethical dilemmas and education*. The symposium finished by mid-day.

4.2. Results and conclusions

73 participants attended the symposium, coming from Europe, America and Asia, and 21 posters were presented during the poster session. 26 evaluation forms were collected for the EACCME certificates and 10 EACCME certificates were awarded. Evaluation forms about the symposium were available on paper and online. Summary of the results calculated by analysing evaluation forms is presented in Table 1.

Table 1: Results from the evaluation forms (max 4.0 - min 1.0).

Category	Mean score[*]
Quality of the event	3.3
Relevance of the event	3.6
Suitability of formats used during the event	3.9
Ways the event affected the participant's practice	3.0

[*]*The score system for each category was score value:*
- *Quality: extremely useful (4), useful (3), fairly useful (2), not useful (1)*
- *Relevance: very much (4), somewhat (3), not much (2), not at all (1)*
- *Suitability of formats: yes, always (4), yes, sometimes (3), only rarely (2), never (1)*
- *Effect on clinical practice: very much (4), somewhat (3), not much (2), not at all (1)*

The evaluation form was predesigned by EACMME and the scoring system was based on selecting an answer as described in the footnotes of Table 1. These answers were translated to numerical scores as described in the footnote of Table 1 and the mean score was calculated. According to the answers received from one third of the participants, the workshop was well acknowledged. The participants were satisfied with the quality of the event (3.3 out of 4), which they considered as generally relevant (3.6 out of 4). Almost all of the participants appreciated the format of the workshop (3.9 out of 4), which turned out to be somewhat useful for their work in clinical practice (3 out of 4).

In conclusion, the objective, aim and expected result of the symposium were achieved.

5 APPENDIX

5.1. Systems Medicine Conference in Slovenia – agenda

SYSTEMS MEDICINE CONFERENCE IN SLOVENIA, 8-9 June 2017

June 8th 2017 - DAY 1: National Awareness Event

8.30-9.00	Registration

INTRODUCTION TO THE AWARENESS EVENT

Chairperson: Dr. Eva Batista, Ministry of Education, Science and Sport, Slovenia

9.00-9.15	Welcome speeches: Dr. Goran Turk, Vice-rector of University of Ljubljana, Slovenia Dr. Tomaž Boh, State Secretary of Ministry of Education, Science and Sport, Slovenia
9.15-9.30	Dr. Marc Kirschner, Project Management Jülich, Germany: Presentation of CASyM – The Coordinating Action Systems Medicine
9.30-9.50	Dr. Sylvia Krobitsch, Project Management Jülich, Germany: ERACoSysMed: Implementation of Systems Medicine in Europe

SUCCESS STORIES FROM ERACOSYSMED JOINT TRANSATIONAL CALL 2015

Chairperson: Dr. Tadeja Režen, University of Ljubljana, Slovenia

9.50-10.10	Dr. Jochen Hampe, MD University Clinic Dresden, Project coordinator of Dynaflow: Towards Personalized Treatment of Primary Sclerosing Cholangitis
10.10-10.30	Dr. Edward Vigmond, University of Bordeaux, Project coordinator of PUSHCART: Personalized Cardiac Resynchronization Therapy
10.30-10.50	Dr. Martin Kuiper, Norwegian University of Science and Technology, Project coordinator of COLOSYS: The Logical Way to Tackle Cancer
10.50-11.10	Dr. Mario Gorenjak, University of Maribor, Slovenia: Presentation of project SysPharmPedia: Systems Pharmacology Approach to Difficult-to-Treat Pediatric Asthma
11.10-11.40	Coffee break

EUROPEAN INITIATIVES IN SYSTEMS MEDICINE

Chairperson: Dr. Nataša Debeljak, University of Ljubljana, Slovenia

11.40-12.00	Dr. Timothy Radstake, University of Utrecht: Presentation of EASyM - European Association of Systems Medicine
12.00-12.20	Dr. Harald Schmidt, Maastricht University: Systems Medicine for Mechanistic Disease Redefinition and Omics-based Drug Repurposing for Rapid Proof of Concept and Patient Relevant Impact – Presentation of COST - OpenMultiMed
12.20-12.40	Dr. Martin Kuiper, Norwegian University of Science and Technology: Setting the Stage for the Gene Regulation Knowledge Commons – Presentation of GREEK COST
12.40-14.00	Lunch

ROUNDTABLE DISCUSSION: HOW SYSTEMS MEDICINE CAN HELP YOU?

Chairpersons: Dr. Timothy Radstake and David Supple, representatives of European Association of Systems Medicine

	Presentations from Patient Representatives and Clinicians
14.00-14.20	Dr. Tanja Španić, president of Europa Donna – Slovenian Association for Battle Against Breast Cancer Dr. Simona Borštnar, Institute of Oncology, Slovenia
14.20-14.40	Stefanija Zlobec, patient representative from Spominčica – Slovenian Association for Help with Dementia Dr. Milica Kramberger, University Medical Centre Ljubljana, Slovenia
14.40-15.00	David Supple, chair of the U-BIOPRED patient platform at the European Lung Foundation Guiseppe de Carlo, project manager at European Federation of Allergy and Airways Diseases Patients' Associations Dr. Timothy Radstake, University Medical Centre Utrecht, Netherlands Director of European Society of Preventative Medicine & Vice-Chair of European Association of Systems Medicine
15.00-16.30	Discussion
16.30-17.00	Coffee break

CLOSING LECTURE

17.00-17.45	Dr. Timothy Radstake, University of Utrecht: Molecular Re-classification of immune mediated inflammatory disease; are we beyond fiction?
18.00-20.00	Networking dinner

June 9th 2017 - DAY 2: 12th CFGBC Symposium and Workshop "Systems Medicine Education in Medical Schools: How Far from the Pan-European Effort?"

8.30-9.00	Registration

12th CFGBC SYMPOSIUM

Chairpersons: Dr. Tanja Kunej, University of Ljubljana, Slovenia and Dr. Sol Efroni, Bar Ilan University, Israel

9.00-9.05	Welcome speech
9.05-10.00	Opening lecture dame Dr. Janet Thornton, EMBL-EBI, Hinxton: Exploring Human Variation and Its Impact on Proteins and in the Clinic
10.00-10.20	Dr. Sol Efroni, Bar Ilan University, Ramat-Gan, Israel: The T Cell Repertoire as a Metric for Breast Cancer Status
10.20-10.40	Dr. Sendi Montanič and Dr. Blanka Vidan Jeras, Institute for Transfusion Medicine of Republic Slovenia: Immunogenetics in Transplantation of Haematopoietic Stem Cells
10.40-11.10	Coffee break
11.10-11.30	Dr. Tadeja Dovč Drnovšek, Institute for Transfusion Medicine of Republic Slovenia: Molecular-biological Investigations for Determining Blood Groups
11.30-11.50	Dr. Nataša Debeljak, University of Ljubljana: Familial Erythrocytosis: From Mutation Analysis to Clinical Application
11.50-12.10	Dr. Jernej Jakše, University of Ljubljana: In-depth Sequencing of RNA as an Efficient Pathogen Discovery Tool: The Case of New Hop Viroid
12.10-12.30	Dr. Mojca Milavec , National Institute of Biology: Metrology for Quantitative Molecular Biology: Accurate and Reproducible Nucleic Acid Measurements
12.30-12.50	Dr. Brane Leskošek, University of Ljubljana: Telepharmacology and ELIXIR-SI Data Services
12.50-15.00	Lunch /Poster presentation

WORKSHOP: Systems Medicine Education in Medical Schools: How Far from the Pan-European Effort?

Chairpersons: Dr. Ana Plemenitaš and Dr. Damjana Rozman, University of Ljubljana

15.00-15.45	Dr. Damjana Rozman, University of Ljubljana: Results from the International Online Questionnaire regarding Education and Training in Systems Medicine Followed by Open Discussion
15.45-16.00	Dr. Ana Plemenitaš, Member of the Academic Affairs Commission of Faculty of Medicine, University of Ljubljana: Systems Medicine Topics at Faculty of Medicine University of Ljubljana; Current Status and Future Directions
16.00-16.15	Danaja Plevel, Head of Slovenian Medical Students' Association: Systems Medicine Topics at Faculty of Medicine, University of Ljubljana: A Student Perspective
16.15-16.30	Žiga Barbarič, Medical Education Director, European Medical Students' Association (EMSA): EMSA Policy on Introducing Contemporary Topics into Medicine Curriculum
16.30-16.45	Andrej Martin Vujkovac, Vice-President for Capacity Building, International Federation of Medical Students' Associations (IFMSA): IFMSA Policy on Introducing Contemporary Topics into the Medicine Curriculum
16.45-17.00	Coffee break
17.00-17.15	Dr. Dušan Šuput, General Secretary, Association of Medical Schools in Europe

	(AMSE), dean of Faculty of Medicine, University of Ljubljana: AMSE Policy on Introducing Contemporary Topics into the Medicine Curriculum
17.15-17.45	General discussion
17.45-18.00	Dr. Eva Batista, Ministry of Education, Science and Sport Slovenia and Dr. Damjana Rozman, Faculty of Medicine, University of Ljubljana: Summary of the Workshop and Concluding Remarks

5.2. Symposium »Systems Medicine in Clinical Practice« - agenda

Symposium "Systems Medicine in Clinical Practice", 10th - 11th June 2019

Monday, June 10th 2019

12.30-13.00	Registration

OPENING OF THE SYMPOSIUM

Chairperson: Dr. Damjana Rozman, University of Ljubljana, Faculty of Medicine, Slovenia

13.00-13.15	Welcome speeches: Prof. Dr. Igor Švab, Dean of Faculty of Medicine, University of Ljubljana, Slovenia Prof. Dr. Igor Papič, Rector of University of Ljubljana, Slovenia Dr. Tomaž Boh, Director General of Science Directorate, Ministry of Education, Science and Sport, Slovenia
13.15-14.00	Dr. Isaac Cano, IDIBAPS, University of Barcelona, Spain Paradigm changes for diagnosis: using big data for prediction

SUCCESS STORIES FROM ERACOSYSMED JOINT TRANSNATIONAL CALL 2015

Chairpersons: Dr. Pablo Villoslada, IDIBAPS, University of Barcelona, Spain & Prof. Dr. Damjana Rozman, University of Ljubljana, Faculty of Medicine, Slovenia

14.00-14.30	Prof. Dr. Friedrich Feuerhake, Hannover Medical School, Germany SysMIFTA: A Systems Medicine approach to minimize macrophage-associated interstitial fibrosis and tubular atrophy in renal allograft rejection
14.30-15.00	Prof. Dr. Cormac Taylor, University College Dublin, Ireland OxyUC: The impact of hypoxia on inflammation and tumorigenesis in ulcerative colitis
15.00-15.20	Coffee break
15.20-15.50	Dr. Pablo Villoslada, IDIBAPS, University of Barcelona, Spain Sys4MS: Using computational tools to design personalized healthcare for Multiple Sclerosis
15.50-16.20	Prof. Dr. Thomas Hoefer, German Cancer Research Centre, Germany

	OPTIMIZE-NB: Optimizing first-line therapy for aggressive neuroblastoma by Systems Medicine
16:20-16:30	Discussion time

DIFFERENT PERSPECTIVES ON SYSTEMS MEDICINE

Chairperson: Assist. Prof. Dr. Tadeja Režen, University of Ljubljana, Faculty of Medicine, Slovenia

16.30-17:00	Marko Korenjak, European Liver Patients' Association, Belgium Systems Medicine and liver diseases: a patients' perspective
17:00-17:30	Prof. Dr. Damjana Rozman, University of Ljubljana, Faculty of Medicine, Slovenia Systems Medicine research towards novel liver disease stratification strategies
17.30-19.30	Poster session with welcome reception

Tuesday, June 11th 2019

8.30-9.00	Registration

SUCCESS STORIES FROM ERACOSYSMED JOINT TRANSNATIONAL CALL 2017

Chairpersons: Prof. Dr. Wilfried Gwinner, Medizinische Hochschule Hannover, Germany & Dr. Mirjana Liović, University of Ljubljana, Faculty of Medicine, Slovenia

09:00-09.30	Dr. Mirjana Liović, University of Ljubljana, Faculty of Medicine, Slovenia 4D Healing: Data-Driven Drug Discovery for Wound Healing
09.30-10.00	Prof. Dr. Wilfried Gwinner, Medizinische Hochschule Hannover, Germany ROCKET: Systems Medicine based improvement of diagnosis and prediction in kidney transplant patients: Reclassification using OmiCs integration in Kidney Transplantation
10:00-10:30	Prof. Dr. Jean-Cristophe Corvol, INSERM, Clinical Research Centre for Neurosciences, France PD-Strat: Multi-dimensional stratification of Parkinson's disease patients for personalised interventions
10:30-11.00	Coffee break

WORKSHOP "SYSTEMS MEDICINE IN CLINICAL PRACTICE: ETHICAL DILEMMAS AND EDUCATION"

Chairpersons: Prof. Dr. Sona Vasudevan, University of Georgetown, Medical Faculty, USA & Prof. Dr. Igor Švab, University of Ljubljana, Faculty of Medicine, Slovenia

11.00-11.20	Prof. Dr. Igor Švab, University of Ljubljana, Faculty of Medicine, Slovenia Family medicine, genomics and ethics
11.20-11.40	Sebastian Schleidgen, M.A., University of Philosophy and Theology Vallendar, Germany Ethical aspects in Systems Medicine
11:40-12.00	Prof. Dr. Sona Vasudevan, University of Georgetown, Medical Faculty, USA Do we need Systems Medicine specialists?
12:00-13.00	Dr. Jernej Kovač, University Clinical Center Ljubljana, Slovenia Interactive tutorial: Whole genome sequencing in clinical practice
13.00-13.05	Closing of symposium

Project Acronym: ERACoSysMed

Project title: Collaboration on systems medicine funding to promote the implementation of systems biology approaches in clinical research and medical practice

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<p style="text-align:center;">**-updated September 2019-**</p>

WP: WP6

Lead beneficiary: MIZS

Contact: Dr. Eva Batista (eva.batista@gov.si)

Dissemination level: Public

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1 INTRODUCTION

The task 6.5 aims at fostering strong coherence and frequent communication with the Coordination Actions Systems Medicine, CASyM, providing benefits for both CASyM and ERACoSysMed. Therefore, the survey for contact persons from various stakeholders (clinics, universities, patient organizations, industry, regulatory authorities), expanding upon the list of stakeholders identified by CASyM, and among universities represents an important starting point to reach this aim. Furthermore, the survey results and the input gathered on the national level will provide topics for workshops organized by ERACoSysMed, which may be related to training activities and to priority issues, research areas and industrial needs arising from the final update of the CASyM roadmap.

By implementing this task, the objective of the ERACoSysMed projects is reached, namely to provide a platform for the implementation of the actions recommended by the CASyM road map. The central goal of this process is the formation of a coherent European approach for Systems Medicine, which is driven by clinical needs. ERACoSysMed will greatly benefit from the work already performed by the CASyM consortium and in the same way ERACoSysMed is the consistent next step for the practical implementation of Systems Medicine based on the CASyM roadmap.

The specificities brought about by Systems Medicine involve the use of dedicated mathematical, bioinformatic and statistical tools that are necessary to address properly the critical issues of integrating across multiple scales, the dynamics of disease processes and treatment efficacy, as well as their modulation by genetic, epigenetic, lifestyle determinants of the person, and environmental factors.

Key for successful interdisciplinary approaches, relevant not only for training and educational issues, are close interactions among the relevant people and groups. Different cultures in preclinical and clinical research require activities to promote closer interactions in order for both parties to understand the value of each other's expertise and thereby reach mutual respect. Good examples are translational research centres, where preclinical and clinical researchers work together „in the same room". This cultural problem should not be underestimated and demands major structural changes at different levels starting with education (medicine, biology, biomedicine etc.), including both under- and graduate levels.

Since Systems Medicine is a developing field and striving for broader recognition, it is important to address the needs of different stakeholders and user communities that could be met by Systems Medicine on the path towards the personalized medicine. This was the general aim of the survey, which was according to the agreement for implementation of the task 6.5 between the Ministry of Education, Science and Sport, Slovenia (MIZS) and Faculty of Medicine, University of Ljubljana (UL), Slovenia prepared and conducted by the latter. The analytical findings of the collected survey answers, presented in this report, will serve as the basis to determine the priority theme, which will be addressed at the workshop, organised together with the Awareness event, in June 2017 in Ljubljana, Slovenia.

2 IMPLEMENTATION

Faculty of Medicine (UL) prepared the survey questions over the course of several phases. Firstly, a 7-question survey draft was prepared and tested among 20 participants of the 1st EASyM conference held in October 2016 in Berlin. The draft and the general findings of this test survey were forwarded by MIZS to the ERACoSysMed consortium partners and furthermore complemented with their input. The first version of the survey was prepared with collaborating efforts from MIZS and Faculty of Medicine (UL), including 9 questions:

1. How often does your daily work routine involve or relate to Systems Medicine?
2. When did you hear about Systems Medicine for the first time?
3. What is the biggest/most critical challenge, obstacle, issue or question in Systems Medicine?
4. How would you propose to address this?
5. In which direction should Systems Medicine develop in the future?
6. Why should society invest in Systems Medicine? What would be the main helpful driver? (We do not want this to be an academic exercise.)
7. Do you think that Systems Medicine lacks wider recognition?

Two questions were added only for people involved in Systems Medicine related training (undergraduate, graduate or other levels):

1. How are mathematic and informatic themes, including big data, covered in the biomedical curricula you are taking part in?
2. What do you think is required for successful Systems Medicine training?

The online 9-question survey was prepared using Google Forms application (see Figure 1.) and sent to approximately 2400 recipients[1] at the end of December 2016.[2]

In mid-January 2017, 5 general questions were added about demographic information of respondents (including gender, affiliation, country of residence, level of education and professional background/affiliation). The 14-question survey was resent to the abovementioned list of 2400 recipients and remained open until June 2017. Altogether, 175 replies to the survey were received. However, because responding to all questions was not mandatory, there are different numbers of answers reported for each question.

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[1] Including people involved in Systems Medicine related training (undergraduate, graduate or other levels) and general stakeholders: CASyM and EASyM partners, respondents of the 1st EASyM conference that was held in October 2016 in Berlin, Germany, contacts provided from the Center for Functional Genomics and Biochips (Faculty of Medicine, UL) and to contacts provided by ERACoSysMed consortium partners, including evaluators and applicants from the first ERACoSysMed Joint Transnational Call (JTC) and those evaluators invited to participate in the second JTC. The survey was not sent exclusively to universities with medical schools.

[2] Available at the following link: https://goo.gl/forms/pBxSLGiTOLTaAKfa2
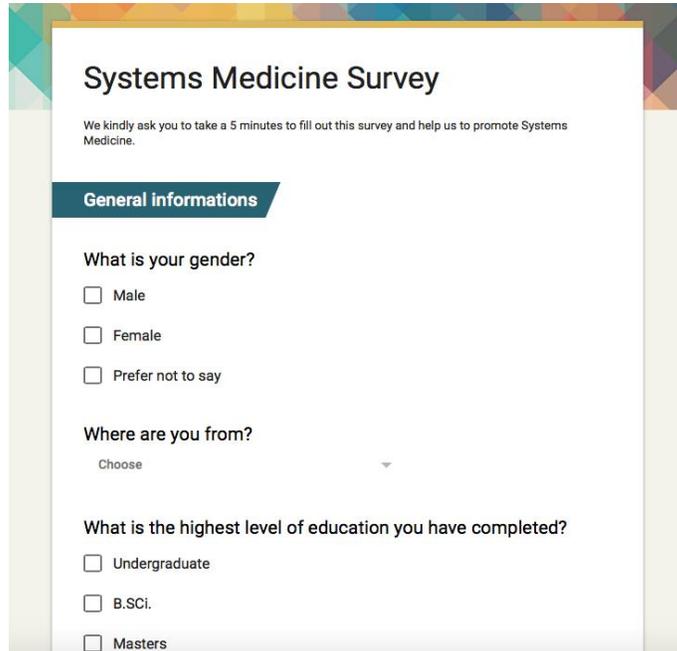
Figure 1: A screenshot of the online survey about Systems Medicine

3 SURVEY OUTCOME

In this section, the summarized results from the analysis of the collected 175 survey replies are presented, including the outcomes and overall evaluation. All of the questions were reviewed manually.

3.1. QUESTION: What is your gender?

From 79 replies, two thirds of respondents were male and the remaining third were female.
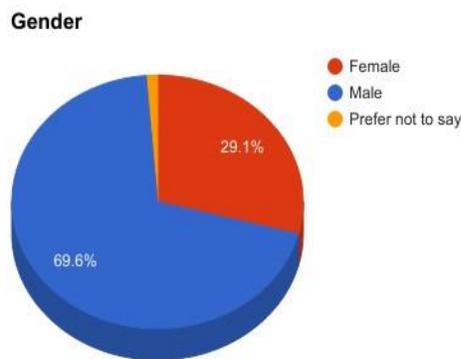
Figure 2: Gender distribution

3.2. QUESTION: Where are you from?

Among 65 replies, respondents can be distributed among three regions, North America, Europe and India.
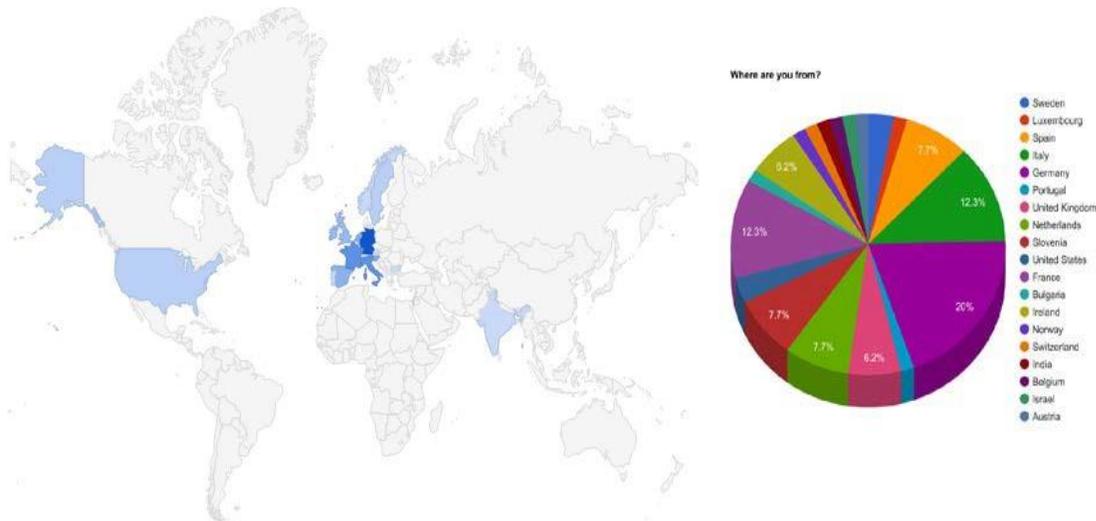
Figure 3: Geolocalization of respondents

3.3. QUESTION: What is the highest level of education you have completed?

Almost 90% of survey respondents' highest education was PhD.
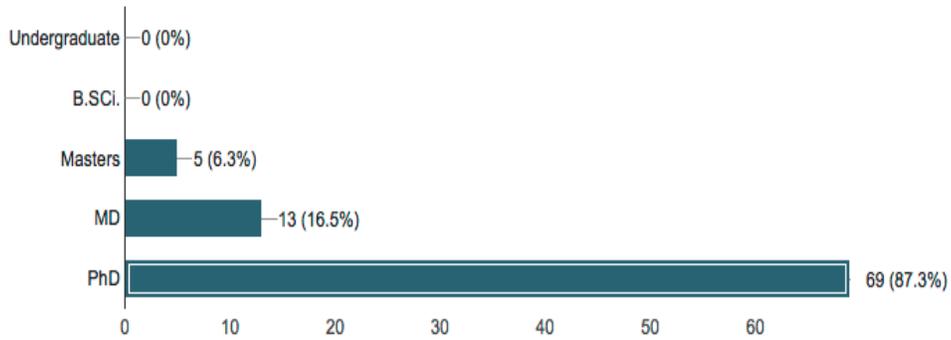

Figure 4: Level of education

3.4. QUESTION: Your professional background?

Majority of respondents' professional background was academia (68.3%), followed by clinical practice (11.1%).
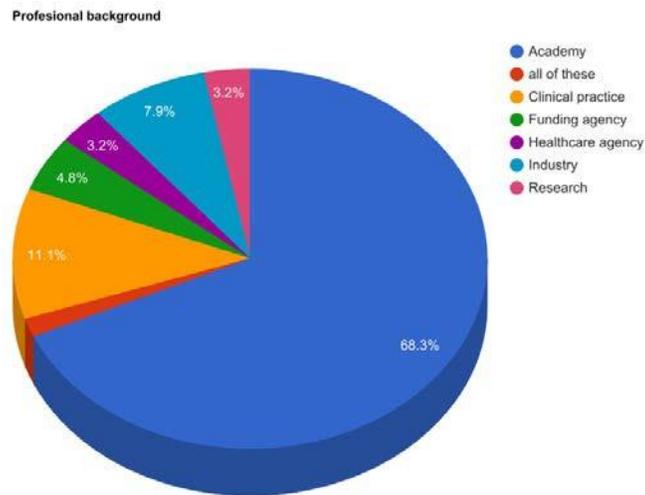
**Figure 5:** Professional background

3.5. QUESTION: Your current position and institution?

62 survey respondents replied to this question in different depth. Some of them indicated their specific affiliation, whilst others replied in a more general way; therefore, the analysis of these replies is not conclusive.

The respondents belong to different phases in their scientific careers, including student (1 respondent), researcher (7 respondents), post-doc (3 respondents), senior researcher (2 respondents), junior group leader at university (1 respondent), group leader at university (5 respondents), research assistant (1 respondent), assistant professor (4 respondents), scientific officer (3 respondents), professor (13 respondents), emeritus professor (2 respondents) and others.

3.6. QUESTION: How often does your daily work routine involve or relate to Systems Medicine?

Among the 175 respondents, 58.3% replied that their daily work routine often involves Systems Medicine approaches. 30.3% of respondents use Systems Medicine only sometimes and 9.1% rarely. 2 interviewees use Systems Medicine constantly or almost always. In one case Systems Medicine was indirectly related with the person's work.
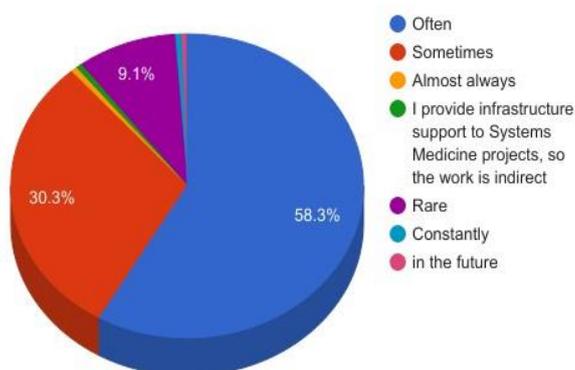
Figure 6: Involvement of Systems Medicine in a person's daily work routine.

3.7. QUESTION: When did you hear about Systems Medicine for the first time?

Almost half of the survey respondents (43.1%) have heard of Systems Medicine only a few years ago and only 19.5% a long time ago. 23% was involved in Systems Medicine even before the terminology was defined. 11.5% of respondents got in contact with Systems Medicine when the community started to get organized. A small percentage (2.9 %) got in contact with Systems Medicine very recently.
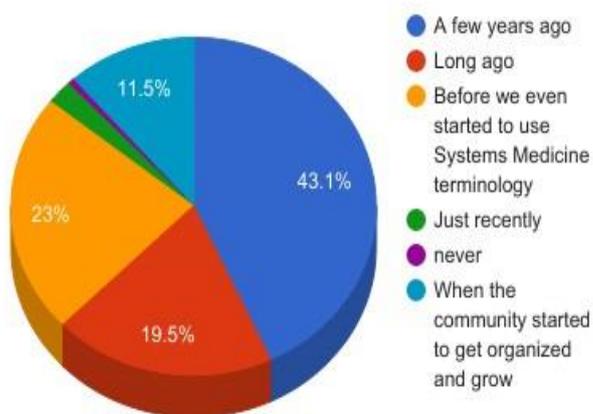
Figure 7: First contact with Systems Medicine

3.8. QUESTION: What is the biggest/most critical challenge, obstacle, issue or question in Systems Medicine?

The lack of common understanding of Systems Medicine and translating Systems Medicine's insights into clinical practice are the biggest challenges for Systems Medicine community. Almost 35% of respondents highlighted integration of Systems Medicine to clinic.

Here are some of the more interesting answers regarding the biggest challenges of Systems Medicine:

- To integrate omics data and transfer them to clinical practice and diagnostic reports;
- Education of physicians;
- Algorithmic thinking and communication in the medical community;
- Ignorance from the rest of the medical profession;
- Interaction between clinicians and wet/dry lab researchers. Everyone's expertise is required in order for this to work;
- Acceptance by and involvement of clinicians;
- The iterative and reciprocal feedback between clinical investigations with computational, statistical and mathematical multiscale analysis and modelling is far from being applied in clinical practice.

As discussed above, integration of big data to clinical meaningful implementation is the next big step for Systems Medicine community. The current status shows large amounts of data being produced and too few information getting extracted from it. Data interpretation is a common problem, stemming from the conflict between small numbers (associated with single patients) and large numbers (which are necessary for good statistics, reproducibility and predictability). Standardization is another crucial issue, where we come to the question of how to standardize data analyses, taking into account the ethical and privacy (legal) issues. Everyone is aware of the problem, but none of the interviewees was able to offer a solution. Some other problems linked with big data are:

- Lack of tools available to perform the meaningful analyses on a systems level;
- Multiscale data integration;
- Correlation of genetic, epigenetic, transcriptomic, metabolomic data into pathways;
- Management of huge amounts of data;
- Data quality (there is always an issue with the clinical data).

After managing the big data, the next step would be multi scale modelling to address diseases in transition from physiology to pathophysiology and the relevant hierarchical levels of pathogenesis (molecules, cells, tissues or higher). Access to biological samples from the clinic would contribute to having robust models that could be applied outside of the laboratory. Correct data interpretation from systems models and reproducible results that allow replicable predictions would help to apply them to clinical research/treatment. If basic researchers in combination with computational modelling would demonstrate success, i.e. dynamic changes in molecular networks during disease evolution and

resolution, maybe clinicians would more easily adopt Systems Medicine approaches. The main problems related with big data and modelling are:

- Access to, exploitation and sharing of existing data;
- Systematic collection of quantitative data and information;
- Multi-model management;
- Asset curation for quality data;
- Sustainability and funding models for asset (data, models, samples) infrastructure.

Systems Medicine community needs to put a bigger effort into personalized treatments of patients. The variability of diseases and phenotypes is huge, therefore identifying clinically relevant phenotypes of patients and finding suitable treatments for their specific condition would be a real benefit for them, also taking into account the sustainability of the health systems. This would be a win-win position for the patient, medical doctors and health organizations. Some of the answers, which are presented here, highlight Systems Medicine's aim for personalization:

- Since for many people it is unclear, what it really covers, clarification of the scope of the field is required, specifically how it relates to P4/P5 medicine and what is the role of technologies it involves, as compared to re-organizational issues on medical systems;
- Broader recognition that Systems Medicine is a tool aiming towards personalized medicine and its appreciation by medical doctors;
- Stakeholders' Consensus within the Systems Medicine community (modelling - biological sciences - clinical sciences) and among communities in the domains of Personalized - Precision Medicine.

It is necessary to cross a gap between basic academic research and clinical practice and to form interaction between different areas. Multidisciplinary trainings, education, international cooperation and changing our mindsets would be a big contribution to a number of experts. It is necessary to show and explain the importance of Systems Medicine, transform it in a reality beyond the hype and to attract bright people really involved in the discipline itself. Some other challenges, obstacles, issues or questions in Systems Medicine are:

- Social: Institutional support, willingness to alter stiff institutional structures. Expensive drug schemes and rigid and non-productive clinical testing schemes. If the question rather implies the scientific aspects, then systematic harvesting of results from the "search space" of drug combinations and molecular marker combinations is critical;
- Peer acceptance of the utility of Systems Medicine;
- To convince scientific Community that a Systems Medicine Approach would help scientists to identify novel and more useful tools in research, diagnostics, clinics;
- Systems Medicine requires multidisciplinary knowledge according to Humboldt's style of education. Current educational paradigms contradict to that by focusing on efficiency in time, money, resources, etc.;
- Finding the best application areas and proving that SM is superior to conventional approaches;

- Different mindsets/philosophies/languages in informatics vs. biology vs. medicine; lack of mutual understanding of the disciplines and way of work; gap especially between basic academic research and clinical practice; (bio)informatics is seen only as a helper-discipline;

- Crossing the chasm from early adopters to widespread impact, through tangible PoCs and regulatory science maturation regarding Medicine & Science;

- Financial issues;

- Complexity / "new buzzword" syndrome.

3.9. QUESTION: How would you propose to address this?

Some interviewees pointed out that it is not possible to answer to this question in one line, since it is a complicated and a long-term process. The primary emphasis should be on collaboration. Joint work, meetings, conferences, integrating additional clinical groups into research institutes and vice versa, stronger integration of industry and health systems, and other forms of collaboration should increase the communication and the success of Systems Medicine. For this purpose, large-scale dialogue platform with all stakeholders (including policy - funding agencies) is required. Some suggestions of aims for that kind of platform are:

- Further research proposals worldwide with the Systems Medicine term;
- Large, international collaborative studies with better data sharing;
- Start with 2 or 3 chronic diseases and talk to patients on what it does to their life and body as a whole system and over time. Look at what medication etc. they are taking and look at where the system is not treated sufficiently;
- Pushing the implementation of multidisciplinary groups, including bioinformatics;
- A common terminology and definition used and repeated each time the term is used by actors and institutions; involving actors in the health systems more and not only researchers;
- Precisely define, what is to be achieved and what 'translation' should be involved;
- Fostering exchange between stakeholders, scientists and relevant medical problems.

In relation to this, respondents also mentioned some of the platforms, such as AETIONOMY, ELIXIR, ERA-NET and GA4GH.

Systems Medicine community needs to raise the awareness of clinicians and health providers and to involve medical doctors into clinician-scientist collaborations. With improvements in education, people would understand the limitations and be able to correctly apply Systems Medicine approaches. Systems Medicine community needs to provide not only more teaching courses in bioinformatics at the university level, but also more specific programs, interdisciplinary trainings and workshops, encourage contacts with foreign disciplines early in education (e.g. courses for undergraduates from different fields in both programming and molecular biology techniques could be used to integrate Systems Medicine principles in a regular curricula of numerous scientists). Long story short, training of new generation of scientists paves the way for implementation of Systems Medicine approaches in clinical practice.

Systems Medicine needs a "common language" among different scientists involved in research. Standardization of models (SBML) and available data and/or protocols represent a step to integrations of data diversity. Research data must be freely available. If we cannot rely solely on data collections, it is mandatory to try to understand the regulatory principles and combine data-driven research with hypothesis-driven approach in combination with the usage and development of more advanced computational biology tools and closer work between biologists and bioinformaticians. Researchers need to be focused and dedicated, enforced through publication and public repositories. Computational backing lies in using large sample sizes, avoiding overfitting, more strategic development of analysis

methods and state-of-the-art biobanks to streamline the technological platforms. Conclusive thoughts on this issue are well defined in an answer by one of the survey respondents: "Integrate modelling and data and validate, validate, validate."

The biggest aim of Systems Medicine is to find a way to integrate real world data across the world and to derive meaningful and simple standards. Following with evaluating single technologies just as other technologies and development and usage of appropriate evaluation designs for comprehensive approaches of Systems Medicine. It is necessary to underline that the amount of money spent on systems approaches is probably less than the amount spent on a few drug deliveries. Almost 10% of survey respondents said that there are strong reasons to increase the financing of Systems Medicine projects and to sustain grant application targeting this issue.

To conclude, Systems Medicine community needs to take all relevant players on board as soon as possible, and set the priorities: Specific calls as demonstrator projects, standardized approaches, guidelines, dissemination, identification of action areas for implementation of Systems Medicine and build Systems Medicine approaches not generically but specifically. In this way, it would provide good examples that its usage can make a difference.

3.10. QUESTION: In which direction should Systems Medicine develop in the future?

Among the 175 survey respondents, 67.6% think that Systems Medicine needs to be pushed forward to the clinic, 11.9% said that it would do better by being developed in academic/theoretical fields. Almost 17.1% of respondents share the opinion that Systems Medicine needs to bring together all of the relevant areas and equally develop all of them. Only 3.4% of respondents believe that industry is the true way for Systems Medicine development in the future, whilst 4 respondents want Systems Medicine to bridge the gap between academic/theoretical and clinical practice.

In which direction should Systems Medicine develop in the future?

All
17,1%

Academic /
theoretical
11.9%

Buisness (industry)
3,4%

Clinical pratice
67,6%
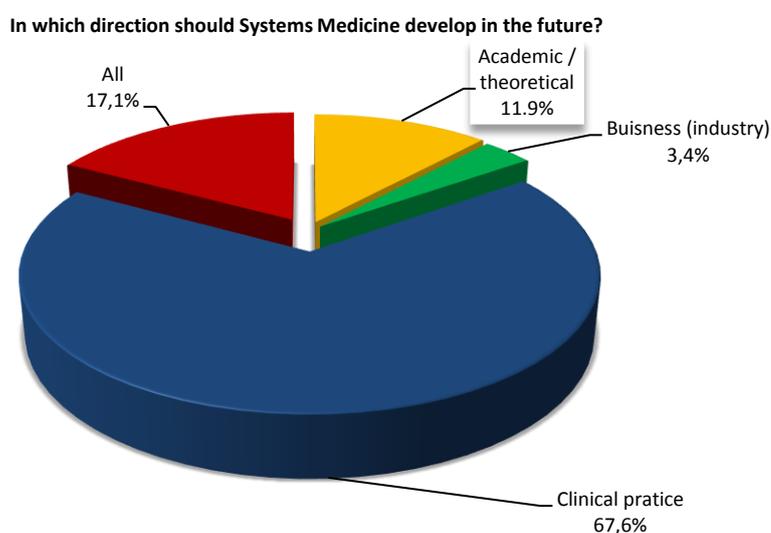
Figure 8: Direction for Systems Medicine development

3.11. QUESTION: Why should society invest in Systems Medicine? What would be the main helpful driver? (We do not want this to be an academic exercise.)

There are some opinions that present-day medicine represents just the tip of the iceberg and that traditional medicine needs to develop faster and accelerate the transfer of theories to clinical practice. Integration among different disciplines can be precious. Systems Medicine would bring together knowledge and capacities from different scientific fields and sectors in finding solutions for health challenges. Systems Medicine solutions will in the longer run:

- Decrease the cost of healthcare (i.e. better prevention) and lead to a higher quality of life of European citizens;
- Provide better insights and solutions for societal challenges including underzed health, an ageing population and sustainable bio-based economy;
- Improve patient survival and reduce experimental costs;
- Provide more cost efficient treatments for patients;
- Show reflections on health and industry (once it will be working);
- Improve healthcare and quality of health services,
- Improve therapeutic innovation, optimizing clinical development strategies, evidence-based new drug value demonstration;
- Avoid spending money on inefficient treatments, because a tailored medicine would avoid deaths due to side effects;
- Find new potentials for prediction, prevention, diagnosis and therapy of complex disorders;
- Eliminate the trial and error approach to medicine;
- Contribute to sustainable Public Health Policies and Services, local, national and worldwide.

Almost 30% of survey respondents find that Systems Medicine would increase patient benefit and cost effectiveness in the healthcare setting, having in mind to develop cost-effective therapeutic strategies.

It is impressive that approximately half of the respondents find that Systems Medicine will contribute to understanding and treating complex diseases. Better understanding of the complexity of diseases would aid in developing drugs that are more efficient (pathophysiology and therapeutic decision-making). Curing complex diseases requires a paradigm shift, from evidence-based medicine to hypothesis-based medicine. It could transform medical treatment in the future and help identify therapeutic targets in current "untreatable" diseases. Not only that, but Systems Medicine could reduce the costs and even make the personalized/stratified medicine part of reality (approximately 20% of respondents share this opinion). Focusing on one disease is no longer an option. There is much co-morbidity and extra challenges to everyday life and taking good care of ourselves. The hope of curing severe diseases as diabetes and asthma with Systems Medicine approaches is higher than with traditional medicine. Computational approaches could offer a new data-driven view of what constitutes a disease and how to best handle treatments. It could potentially be a good way to reduce animal testing.

One respondent explained that the single molecule/single target paradigm, which is now around for more than fifty years, has to be replaced by network thinking, resp. network-directed medications. Not only change in thinking, but better data quality, longitudinal data on both clinical and molecular level, better collaboration between disciplines and better understanding of each-other's work and possibilities, could prove to be the perfect combination for integration of scientific results in clinical practice and the implementation of personalized medicine.

Some of the respondents expressed opinions, which were not completely in line with the above-mentioned general viewpoints:

- „In my opinion, the investment will be huge and the general benefits will be quite small."

- „I see the two recently hot themes of personalized and preventative healthcare as immensely more difficult to apply in a believable manner as curative medicine. Personalized reduces to a sample size of one or at best "one's like this one", and preventative requires treatment and interventions need to be based and evaluated in light of changes which are now considered sub-clinical. Both are unrealistic without a robust and ideally rigorous foundation for interpreting the subtle, multifaceted interactions and appreciating the important and subsidiary components of inter-individual variety. Systems Medicine can play an important role in both these areas by addressing complexity and providing testable bases for evaluation."

- „It is already impacting clinical practice within cancer. It is hampered by a lack of structural support mechanisms both within society and within the hospital system."

- „We have too few trained and skilled professionals that are able to define and carry out SM projects for the benefit of the patient."

Thus, future medical advances are much dependent on Systems Medicine. The goal of Systems Medicine is to foster more healthy life and offer the patient a proactive/precision medicine. But it is also important to keep in mind that two dimensions are relevant: The first one at the individual level, focused on preserving people's health and well-being; and the second one at the population level, focused on achieving sustainability of public health services.

3.12. QUESTION: Do you think that Systems Medicine lacks wider recognition?

Among the 175 respondents, 78.9% find that Systems Medicine needs wider recognition, while 14.9% find that it is recognized well enough. 6.2% of respondents were undecided.
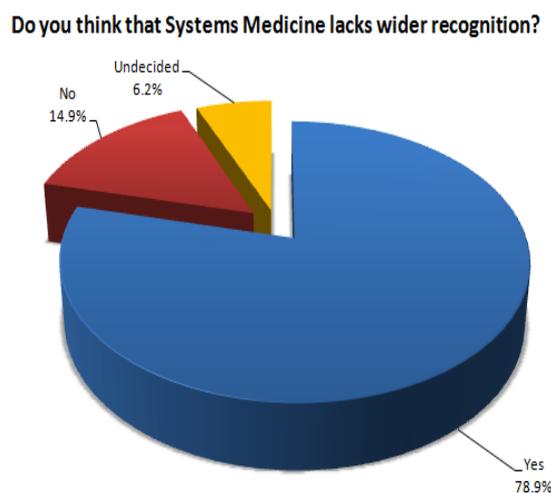
Figure 9: Systems Medicine wider recognition

Respondents, who think that Systems Medicine would deserve a wider recognition, commented that Systems Medicine:

- Is starting to get more recognized and implemented now in the field of biomedical research;
- Only specialists are aware of the term;
- Is a relatively new discipline;
- Becomes something concrete, when you have in mind a specific pathology;
- Needs success stories and leaders that can create a bridge between clinical and computational communities;
- Is still in its infancy and has not provided a great success yet;
- Is still lacking recognition by majority of medical doctors;
- Its potential is not yet realized or fully understood in society and within clinical practice;
- Is much less recognized in comparison to personalized medicine;
- Is still considered too complicated, expensive and not really useful;
- Is the ultimate mansion of systems biology and pharmacology.

One respondent pointed out that Systems Medicine is less well known than the "big data for health": „This big data bubble will eventually burst and this could have extremely detrimental spillover effects on Systems Medicine, if the wider pharma ecosystem does not understand by then the differences between data-driven and mechanistic modelling approaches."

Respondents defined the following reasons for Systems Medicine lacking wider recognition:

- It suffers from buzzy/marketing difficulties;
- It could further improve in connection with the aforementioned problems;
- It is not always clear, how it differs from systems biology;
- It lacks the understanding that a lot of basic research is still required to fulfill the promises;
- It needs a more fair/realistic presentation to be perceived more appropriately;
- Recognition will grow, if scientists demonstrate its usefulness;
- It needs to be presented as effective for patients;
- Many of the ideas are more widely known, but not as Systems Medicine.

3.13. QUESTION: How are mathematic and informatic themes, including big data, covered in the biomedical curricula you are taking part in?

101 respondents replied to this question.

Almost half of the respondents said that information regarding mathematic and informatic tools, including big data are limited or not at all covered in their curricula, especially in the field of medicine. Some try to integrate them in lectures and modelling practices.

Only 10% of respondents have covered mathematic and informatic tools including big data very well in their curricula. Some universities obviously have courses in Systems Medicine, Statistics and Computational biology, where the students can become familiar with programming, data analysis and statistical methods. Some students even get more insight to networks analysis, multilayer networks controllability and localization of interacting nodes in multilayer networks (nodes-genes, miRNA, proteins), ODEs- PDEs, Population Balance Modelling techniques, proteomics, metaproteomics, metagenomics.

Some approaches are included, but are mostly elective and not obligatory subjects, therefore being presented only to a limited number of students. One of the well-recognized problems is how to reach the students because of their lack of interest.

3.14. QUESTION: What do you think is required for successful Systems Medicine training?

108 respondents replied to this question.

The majority of respondents propose that learning about basic understanding of terms/methods is necessary, such as biometry/statistics, computer science, systems theory, programming, understanding of how data science works, understanding of types of information in different data types and about bias in different fields. With handling, the terminology, interaction of clinicians/experimentalists and theoreticians would become possible. Interviewees proposed workshops/courses, which would involve medical doctors, bioinformaticians and molecular biologists. However, it is necessary to offer better training materials at all levels of education and better trained interdisciplinary teachers. By addressing the question on how to raise curiosity of medical students for other fields and new ways of thinking, these suggestions were given:

- "Systems Biomedicine" summer schools for MDs;

- More involvement from physicians and more collaborations;

- Obligatory main stream courses rather than choice courses;

- Overlapping courses during masters programs (medical training for biologists and informaticians; biology and informatics training for medical students); practical courses (overlapping as mentioned above); common projects; positions for biologists and informaticians within medicine;

- Powerful use cases in different areas of medicine;

- Some training in formal methods should be given to every student of medicine;

- Start training PhDs with co-mentorships (medicine/biology + math/info/physics);

- The steps would include: (I) Creating an elective course in Systems Medicine; (II) Identification of clinicians with a quantitative bent-of-mind; (III) Inspiring them to create a change in medicine; (IV) Introducing Systems Medicine as a compulsory subject in medical schools in the near future;

- To start as early as possible and expose young people to mathematical principles that can help them later in their medical practice to solve questions or to form interdisciplinary groups between biomedical and mathematical - information technologies scientists;

- Topics, concepts and techniques chosen from the point of view of application (e.g. pathophysiology) and not from a computer science or mathematics curriculum.

4 CONCLUSIVE FINDINGS AND FUTURE RECOMMENDATIONS

Data generation and handling:

- The need for standardization;
- Securing personal data;
- Common protocols for data analysis;
- Data availability (standardized formats, public databases).

Establishment of a head organization that would:

- Provide a general platform for the Systems Medicine community;
- Define principles and regulations in the field;
- Educate an interdisciplinary group of experts that would aid in project development and provide support for the next generation of scientists;
- Define the principle directions, where Systems Medicine could show its benefits for solving complex diseases; this would convince traditional medicine to adopt these novel approaches into standard clinical practice;
- Organize events, that would bring together scientists from different fields and give them the opportunity to form collaborations;
- Provide funding for Systems Medicine projects that would help to further establish the field;
- Cooperate with other agencies (industry, national, private etc.) to provide sustainable funding schemes for Systems Medicine projects, education and publicity.

Education:

- Promote Systems Medicine approaches in daily medical curricula;
- Integrate basic Systems Medicine courses into undergraduate and graduate education programs, especially for medical students; this would contribute to better interdisciplinary communication;
- Increase awareness of Systems Medicine among students from different fields to grab their attention.

Promotion:

- Encourage the interest of general public, health organizations and clinic for Systems Medicine and provide attention to its potential benefits for better treatment outcomes, diagnostics and quality of lifestyle;
- Promote the financial benefits of using Systems Medicine from the point of view of personalized therapeutic approaches.

5 APPENDIX

5.1. Survey

SYSTEMS MEDICINE SURVEY

We kindly ask you to take a 5 minutes to fill out this survey and help us to promote Systems Medicine.

GENERAL INFORMATION

What is your gender?
- Male
- Female
- Prefer not to say

Where are you from?
- List of all countries

What is the highest level of education you have completed?
- Undergraduate
- B.SCi.
- Masters
- MD
- PhD

You are coming from:
- Academy
- Clinical practice
- Industry
- Healthcare agency
- Other

Your current position and institution:

_____

QUESTIONNAIRE

1.) How often does your daily work routine involve or relate to Systems Medicine?

- Often
- Sometimes
- Rare
- Other:

2.) When did you hear about Systems Medicine for the first time?

- Long ago
- Before we even started to use Systems Medicine terminology
- A few years ago
- When the community started to get organized and grow
- Just recently
- Other:

3.) What is the biggest/most critical challenge, obstacle, issue or question in Systems Medicine?

_____

4.) How would you propose to address this?

_____

5.) In which direction should Systems Medicine develop in the future?

- Academic / theoretical
- Clinical practice
- Business (Industry)
- Other:

6.) Why should society invest in Systems Medicine? What would be the main helpful driver? (We do not want this to be an academic exercise.)

_____

7.) Do you think that Systems Medicine lacks wider recognition?

_____

IF YOU ARE INVOLVED IN SYSTEMS MEDICINE RELATED TRAINING (UNDERGRADUATE, GRADUATE OR OTHER LEVELS), PLEASE ANSWER THE FOLLOWING QUESTIONS:

8.) How are mathematic and informatic themes, including big data, covered in the biomedical curricula you are taking part in?

_____

9.) What do you think is required for successful Systems Medicine training?

_____

We appreciate your effort. Thank you!