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I. Executive Summary

The international course "Training on strategies to foster solutions of undiagnosed rare disease cases" has been organised, as foreseen by the Grant Agreement of the European Joint Programme on Rare Diseases (EJP RD) in 4 editions from 2020 to 2023. One additional edition has been carried out in 2024. The 2024 edition has been performed in the framework of the eight-month extension of the EJP RD, motivated by the high request to attend the Course.

Among the tasks of Work Package (WP) 14 there has been the objective to address strategies to foster solutions of undiagnosed rare disease cases with dedicated training courses.

For the organisation of the five editions of the training course Istituto Superiore di Sanità (ISS), leader of this specific Task, has carried out a strong collaboration with Task Partners, "Solve-RD", and the "Undiagnosed Diseases Network International" (UDNI).

Through the training courses participants have been provided with newly developed strategies and tools based on phenotypic and molecular analysis to foster solutions for undiagnosed rare disease cases.

The training, originally foreseen as 3-day residential course, had to be adapted to an online version for its first three editions (2020, 2021, 2022), given the emergency situation linked to the outbreak of the Covid-19 pandemic. Despite this unforeseen adaptation all three editions saw large participation of attendants from many EU countries and registered good feedback from the participants. The fourth and additional fifth edition have been delivered in presence, hosted at ISS.

For the in-person editions of the training course, 4 fellowships have been assigned yearly to participants living and working in a EU-13 Country, and in Turkey.

The audience of the training has been represented by the research community, by clinicians and medical specialists, interested in rare diseases.

The training has been characterised, overall, by high interactivity and stimulated the establishment of international networks.

Some editions of the training courses dedicated to foster solutions of undiagnosed rare disease cases have received the endorsement of the International Collaboration on Rare Diseases and Orphan Drugs (ICORD).

II. Introduction and Objective

This document is a report on the training activities on the strategies to foster solutions to undiagnosed RD cases that represent a specific Task of Work Package (WP) 14, "Training on data management and quality", led by ISS.

The organisation of the course titled "Training on strategies to foster solutions of undiagnosed rare disease cases" has been carried out yearly by ISS starting from year 2 of the project, in close collaboration with Task (T) 14.3 Partners. Task 14.3 Partners are EKUT, LBG (LBI-RUD), ACU/ACURARE, ISCIII, INSERM (AMU), FTELE, UMCG, IMAGINE, CNAG-CRG, IPCZD (CMHI). Deliverable (D) 14.5 "First Report on International course on undiagnosed diseases", consultable at the following LINK, describes the premises and aims of this specific training course.

The outcomes of each of the 5 editions of the "Training on strategies to foster solutions of undiagnosed rare disease cases" organised by ISS in collaboration with Task 14.3 Partners as online and residential trainings have been outlined and summarised.

To this purpose, the following points have been analysed for each year of the training:

- the number of registrations
- the number of selected attendants
- the effective number of participants
- the countries represented by the effective participants
- the number of awarded fellowships
- the number of participants belonging to a project/programme related to undiagnosed diseases
- the number of speakers and their affiliation, as well as their country of employment/residence
- the percentage results of the scoring from the satisfaction surveys for each training module and some highlights from the free comments

III. Results

1. Summary of the first edition of the Training on strategies to foster solutions of undiagnosed rare disease cases

The registration to the course has been carried out through the LisyLime Platform of INSERM. 60 applicants filled the form correctly and completely, of which 23 asked for a travel and accommodation fellowship for participants living and working in a EU-13 Country. 37 instead of the foreseen 30 applicants have been admitted attending the training, including 4 applicants that have been awarded with a travel and accommodation fellowship.

The participants awarded with the fellowships lived and worked in the following countries: Hungary, Poland, Bulgaria, and Romania.
Overall, 28 participants accepted their seat.

The training course, foreseen to be held at ISS on 27-29 April 2020, had to be rapidly adapted to an on online version given the outspread early in the year of the COVID-19 pandemic and the consequent limitations set by the health authorities to limit the outspread of the virus. The selected participants have been informed by email of the replacement of the mode of delivery of the course. The assigned fellowships could not be availed.

The need for the online adaptation entailed an intensive work between Task Partners. It has been decided to replace the Problem Based Learning Methodology by 30 minutes to one hour question and answer session that followed the presentations of the experts, to allow in depth discussions between participants and speakers.

A total of 26 participants connected to the online training sessions, delivered through the Zoom Platform. The participants lived and worked in the following countries:

- EU Countries Spain (3), Italy (9), UK (1), Austria (1)
- EU-13 Countries: Bulgaria (3), Romania (3)
- Other Countries: Turkey (1), North Macedonia (1), Ukraine (1), Georgia (3).

12 of the attendants belonged to an ERN, more in detail:

- ERN ITHACA (3 participants)
- ERN CRANIO (1 participant)
- ERN EuroBloodNet (1 participant)
- MetabERN (1 participant)
- ERN-RND (1 participant)
- ERN GUARD-HEART (2 participants)
- ERN EURO-NMD (1 participant)
- ERN RITA (1 participant)
- ERKNet (1 participant)

Moreover, 4 participants were involved in national and/or international RD programmes and projects related to unsolved rare disease cases, namely UDNI (2 participants), ICORD (1 participant) and CIBERER (1 participant).

The Speakers were from the following institutions, representing 6 different countries:

- National Institutes of Health (USA)
- Centre Nacional d'Anàlisi Genòmica (Spain)
- University of Toronto (Canada)
- Casa Sollievo della Sofferenza (Italy)
- Istituto Superiore di Sanità (Itay)
- University of Turin (Italy)
- The Hospital for Sick Children (Canada)
- Eberhard Karls Universität Tübingen (Germany)
- Institute of Rare Diseases Research & CIBERER, ISCIII (Spain)
- Tigem and University of Napoli (Italy)
- Institute IMAGINE, Institute of Genetic Diseases (France)

During the first two training days, presentations and use-cases have been proposed by the experts, and question and answers followed each session. On the third day hands-on exercises and tool demonstrations have been carried out.

The results of the satisfaction survey filled by the participants at the end of the training evidenced a high level of appreciation of the training. 100% of the participants that filled the satisfaction questionnaire answered agree/strongly agree to the item "The course increased my knowledge".

Below a table showing the percentage of the participants answering "agree/strongly agree" to the other items of the satisfaction questionnaire

The contents were appropriate for my level of knowledge	81%
The objectives were clearly defined	76%
The teaching method was effective	95%
Time dedicated to individual/group exercises is sufficient	57%
The learning materials were sufficient and of good quality	95%
The number of speakers/teachers was sufficient	100%
The speakers/teachers were competent and prepared	100%
The course is well organized	100%

The free comments highlighted the quality and up to date of the contents provided in the training, the friendly, interactive and international context, the successful combination of clinical and management issues, the bright spectrum of clinical cases, the possibility of networking and link with experts, the high scientific content.
Positive comments were shared also on the social media.

2. Summary of the second edition of the Training on strategies to foster solutions of undiagnosed rare disease cases

The second edition of the training has been held on 12-14 April 2021. This second edition too had to be adapted to an online format, due to the persistence of the Covid-19 pandemic.

The registration to the course has been carried out through the Microsoft Forms of the EJP RD, and 83 attendants applied to be selected.
Fellowships could not be launched for this online edition.
The selection committee identified 36 applicants to be admitted to the training.
Of these, 29 connected to the training sessions, that have been provided on the Microsoft Videoconferencing Platform of the EJP RD.

The 29 attendants represented the countries listed below:

- EU Countries: Germany (3), Greece, Italy (6), Portugal (2), Luxembourg (2)
- EU-13 Countries/Turkey: Cyprus, Czech Republic, Latvia, Romania, Poland, Slovenia, Turkey (3)
- Other Countries: Mali (3), Singapore (2), Ukraine.

14 of the attendants belonged to an ERN, more in detail:

- ERN LUNG (2 participants)
- ERN GENTURIS
- EURO-NMD
- ERN ITHACA (4 participants)
- ERN BOND
- MetabERN (2 participants)
- ERN RITA
- EURACAN

Moreover, 15 participants were involved in national and/or international RD programmes and projects related to unsolved rare disease cases, namely UDNI (5 participants), Solve-RD (5 participants) and other programmes/projects (5 participants).

The Speakers were from the following institutions, representing 7 different countries:

- Acibadem Mehmet Ali Aydinlar University, Rare Disease and Orphan Drug Research and Application Center and School of Medicine, ACU/ACURARE (Turkey)
- Centre Nacional d'Anàlisi Genòmica (Spain)
- Human Genetics of Aix-Marseille University (France)
- National Centre for Rare Diseases (Italy)
- Radboud University Medical Centre (The Netherlands)
- Instytut Pomnik- Centrum Zdrowia Dziecka (Poland)
- Institute of Medical Genetics and Genomics, Sir Ganga Ram Hospital (India)
- Genetics and Rare Diseases Research Division, Ospedale Pediatrico
- Bambino Gesù (Italy)

The programme of the course alternated presentations of the speakers and question and answers sessions. Large space has been dedicated to the presentation of use-cases and to hands-on sessions.

90% of the participants filled the satisfaction questionnaire and 85% of these answered agree/strongly agree to the item "The course increased my knowledge".

Below a table showing the percentage of the participants answering "agree/strongly agree" to the other items of the satisfaction questionnaire

The contents were appropriate for my level of knowledge	81%
The objectives were clearly defined	93%
The teaching method was effective	96%
Time dedicated to discussion was adequate	93%
The displayed materials were explanatory and of good quality	96%
The number of speakers/teachers was sufficient	94%
The speakers/teachers were competent and prepared	93%
The course is well organized	100%

Furthermore, 94% declared that the connection to the event was easy, and 85% that the quality of the transmission was good.

The free comments reported, among others, the satisfaction on the afforded topics (from bioinformatics to patient cases), the accessibility of the provided information for all backgrounds, the possibility to concretely apply what has been learned to the

clinical routine and the high level and excellence of the course with excellent speakers and organisers.

Summary of the third edition of the Training on strategies to foster solutions of undiagnosed rare disease cases

The third edition of the training took place on 11-13 April 2022. The online format has been adopted for this third edition, too, as some countries continued to adopt travel restrictions and limitations for in-person events.

The registration to the course has been carried out through the Microsoft Forms of the EJP RD, and 139 applications have been submitted.
Fellowships could not be awarded for the online training.

40 applicants have been selected, and 26 joined the online training sessions.

As for the previous edition, the Microsoft Videoconferencing Platform of the EJP RD has been used.

The 26 attendants represented the countries listed below:

- EU Countries: France, Portugal (2), Spain, Italy (4), Greece, Germany
- EU-13 Countries/Turkey: Bulgaria, Slovenia, Poland, Malta, Latvia, Lithuania
- Other Countries: Australia, Chile, Mexico, Israel (2), Georgia, North Macedonia, Serbia, Ukraine, UK

12 of the attendants belonged to an ERN, more in detail:

- EURO-NMD (2)
- MetabERN
- ERN EYE
- ERN-RND
- ERKNet
- ERN RARE-LIVER
- ERN EpiCare
- ERN RITA
- ERKNet
- ERN ITHACA
- ERN BOND

Moreover, 15 participants were involved in national and/or international RD projects dedicated to unsolved cases, namely UDNI (5 participants), Solve-RD (6 participants) and other programmes/projects (4 participants).

The Speakers were from the following institutions, representing 9 different countries:

- National Institutes of Health (USA)
- Centre Nacional d'Anàlisi Genòmica (Spain)

- Instituto de Investigación de Enfermedades Raras, ISCIII - Instituto de Salud Carlos III (Spain)
- Human Genetics of Aix-Marseille University (France)
- Department of Genetics, School of Medicine, Yale University (USA)
- IRCCS Santa Lucia Foundation, Department of Clinical and Behavioral Neurology (Italy)
- National Centre for Rare Diseases (Italy)
- Wilhelm Foundation (Sweden)
- Department of Medical Genetics, The Children's Memorial Health Institute (Poland)
- Department of Medical Sciences, University of Turin (Italy)
- Department of Informatics, Technical University of Munich (Germany)
- Laboratory of Genomic Medicine, UILDM, Fondazione
- Santa Lucia (Italy)
- Institute of Medical Genetics and Applied Genomics, University of Tübingen (Germany)
- Department of Human Genetics, Radboud University Medical Centre (The Netherlands)
- Vilnius University Hospital Santaros Klinikos (Lithuania)

As for the previous editions, presentations from experts and sessions dedicated to questions and answers, as well as hands-on exercises were part of the programme.

81% of the participants filled the satisfaction questionnaire and 100% of these answered agree/strongly agree to the item "The course increased my knowledge".

Below a table showing the percentage of the participants answering "agree/strongly agree" to the other items of the satisfaction questionnaire.

The contents were appropriate for my level of knowledge	91%
The objectives were clearly defined	96%
The teaching method was effective	86%
Time dedicated to discussion was adequate	91%
The displayed materials were explanatory and of good quality	91%
The number of speakers/teachers was sufficient	96%
The speakers/teachers were competent and prepared	95%

The course is well organized	100%

Furthermore, 100% declared that the connection to the event was easy, and 95% that the quality of the transmission was good.

When asked for free comments the participants referred to have appreciated the possibility of trying different sites for data analysis, the relevance of the afforded topics, the high level of the speakers and the good overall organisation of the course.

3. Summary of the fourth edition of the Training on strategies to foster solutions of undiagnosed rare disease cases

The fourth edition of the training took place on 3-5 April 2023. The training course has been delivered as face-to face event at ISS, as the restrictions linked to the Covid 19 pandemic ceased.

The Microsoft Forms of the EJP RD has been used to collect the online registrations, and 70 applications have been submitted.

4 Fellowships were reserved to participants living and working in a EU-13 Country or in Turkey and 6 applicants asked to receive such facility.

33 applicants have been selected to attend, and 23 joined the training at ISS. All four fellowships have been awarded. The fellowship winners lived and worked in Hungary, Malta, Romania and Slovenia.
The remaining participants, that attended without fellowships, lived and worked in the following countries:

- EU Countries: Spain (4), Italy (13), Germany
- EU-13 Countries/Turkey (without fellowship): Slovenia
- Other Countries: -

12 of the attendants belonged to an ERN, more in detail:

- MetabERN
- ERN-RND (3)
- ERN RITA
- ERN ITHACA (3)
- ERN BOND
- ERN TransplantChild
- ERN EuroBloodNet (2)

9 participants were involved in national and/or international RD projects dedicated to unsolved cases. 2 participants were involved in Solve-RD and 7 participants in other programmes/projects.

The Speakers were from the following institutions, representing 6 different countries:

- Centre Nacional d'Anàlisi Genòmica (Spain)
- Instituto de Investigación de Enfermedades Raras, ISCIII - Instituto de Salud Carlos III (Spain)
- Human Genetics of Aix-Marseille University (France)
- National Centre for Rare Diseases (Italy)
- Wilhelm Foundation (Sweden)
- Department of Medical Genetics, The Children's Memorial Health Institute (Poland)
- University of L'Aquila (Italy)
- Institute of Neurogenetics, University of Lübeck (Germany)
- Centre Nacional d'Anàlisi Genòmica (Spain)
- Hôpital Necker Enfants malades, Université Paris Descartes, Institut Imagine (France)
- Tigem and University of Napoli (Italy)
- Hôpital Necker Enfants malades, Université Paris Descartes, Institut Imagine (France)
- University of Tor Vergata (Italy)
- Sapienza University, San Camillo-Forlanini Hospital (Italy)

Use cases, hands-on sessions and presentations with dedicated question and answer slots were part of the programme, as for the previous editions.

74% of the participants filled the satisfaction questionnaire and 100% of these answered agree/strongly agree to the item "The course increased my knowledge".

Below a table showing the percentage of the participants answering "agree/strongly agree" to the other items of the satisfaction questionnaire.

The contents were appropriate for my level of knowledge	76%
The objectives were clearly defined	88%
The teaching method was effective	77%
Time dedicated to discussion was adequate	88%
The displayed materials were explanatory and of good quality	94%

The number of speakers/teachers was sufficient	94%
The speakers/teachers were	100%

competent and prepared	
The course is well organized	100%

The free comments revealed positive feedback regarding the friendly atmosphere, the networking efforts, the excellent balance between the presented topics, the time dedicated to discussions and to use cases, the opportunity to learn new tools for the diagnosis of rare diseases.

4. Summary of the additional fifth edition of the Training on strategies to foster solutions of undiagnosed rare disease cases

The trainings dedicated to foster the solutions of undiagnosed RD cases were foreseen by Grant to be held as face-to-face trainings until year 5 of the EJP RD, in four editions. The online adaptations motivated by the outbreak of the Covid 19 pandemic, entailed that only one edition was held in presence. The additional in-presence edition of the training has been envisaged thanks to the 8 months extension of the EJP RD and has been accepted to allow a second in-person editions of the course.

The Microsoft Forms of the EJP RD has been used to collect the online registrations, and 66 applications have been submitted.

4 Fellowships were reserved to participants living and working in a EU-13 Country or in Turkey and 21 applicants asked to receive the fellowship.

31 applicants have been selected to attend, and 18 participated in the training at ISS. Two fellowships have been awarded to participants that lived and worked in Cyprus and Romania.
The remaining participants, that attended without fellowships, lived and worked in the following countries:

- EU Countries: Italy (4), Portugal, Austria, Spain (5)
- EU-13 Countries: Romania(2), Turkey (2), Malta (1)
- Other Countries: -

3 of the attendants belonged to an ERN, more in detail:

- ERN EYE
- ERN GENTURIUS (2)

8 participants were involved in national and/or international RD projects dedicated to unsolved cases. 1 participants were involved in Solve-RD and 1 participants in other programmes/projects.

The Speakers were from the following institutions, representing 7 different countries:

- Acibadem University (Türkiye)
- National Centre for Rare Diseases, ISS (Italy)
- Wilhelm Foundation (Sweden)
- University of Tübingen (Germany)
- Fondazione Policlinico Universitario A. Gemelli IRCCS (Italy)
- Instituto de Salud Carlos III (Spain)
- The Children's Memorial Health Institute (Poland)
- University of Groningen (The Netherlands)

Use cases, hands-on sessions and presentations with dedicated question and answer slots were part of the programme.

78% of the participants filled the satisfaction questionnaire

Below a table showing the percentage of the participants answering "agree/strongly agree" to the other items of the satisfaction questionnaire.

The contents were appropriate for my level of knowledge	79%
The objectives were clearly defined	86%
The teaching method was effective	86%
The course increased my knowledge	93%
Time dedicated to discussion was adequate	86%
The displayed materials were explanatory and of good quality	93%
The number of speakers/teachers was sufficient	93%
The speakers/teachers were competent and prepared	93%
The course is well organized	93%

IV. Conclusion and Next actions

The course has received interest since the first edition, as proved by the several requests that led to the organization of a further edition.

The feedback, on the content and organization of the course was very positive, due to the cooperation and availability of task partners and speakers who were also able, for example, to adapt the course to an online format in an emergency situation such as the one that occurred for the COVID 19 pandemic. The experience and observations gathered from these editions of the course will be useful in planning and organizing future courses.