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European Reference Network
for rare or low prevalence complex diseases
Network Eye Diseases (ERN-EYE)

ERN-EYE WORKSHOP ON GENETIC TESTING

10th to 12th October 2018, Florence, Italy

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ERN-EYE WORKSHOP ON GENETIC TESTING

ERN-EYE Project Management Team 23/10/2018

Introduction

Workshop on Genetic Testing from October 10th – October 12th, 2018

After a first workshop devoted to ontology last year, ERN-EYE organized a second one on genetic testing from 10th to 12th October in Florence, Italy. The workshop gathered nearly 100 people from the HCPs of the 13 member states of the network, as well as invited speakers. The first day of the workshop was dedicated to the opening the debate on research in this field in in Europe.

This workshop was the opportunity to discuss the needs, challenges and issues of the network about genetic testing. As an introduction, Christina Fasser and Avril Daly, ePAG representatives, explained the present pathway to genetic diagnostic from the patient perspective.

A definition of the genetic testing needs in the ERN-EYE member countries will be set up, as well as the next issues for ERN-EYE in the coming months on this subject.

situation for genetic testing across the member states partners of ERN-EYE.

The second day was devoted to the clinical practice, the genomic diagnostic and the future issues for the genetic testing group in the ERN-EYE.

The last day made it possible to draw conclusions of the meeting is going to end with a final round table

Thanks to this workshop, a definition of the genetic testing needs in the ERN-EYE member countries will be set up, as well as the next issues for ERN-EYE in the coming months on this subject.

ERNs in brief

European Reference Networks (ERNs) are unique and innovative cross-border cooperation platforms between specialists for the diagnosis and treatment of rare or low prevalence complex diseases.

ERNs are virtual networks bringing together healthcare providers across Europe to tackle complex or rare medical conditions that require highly specialized treatment and a concentration of knowledge and resources. They are being set up under the EU Directive on Patients' Rights in Healthcare (2011/24/EU), which also makes it easier for patients to access information on healthcare and thus increase their treatment options.

The ERNs will be supported by European cross-border telemedicine tools, and can benefit from a range of EU funding mechanisms such as the "Health Program", the "Connecting Europe Facility" and the EU research program "Horizon 2020".

PLENARY OPENING SESSION

Welcome address – Inaugural welcome speeches

Hélène Dollfus, ERN-EYE coordinator & Andrea Sodi, ERN-EYE member, Florence, Italy, host of the meeting; Maria Teresa Mechi, Responsabile Qualità dei servizi e reti cliniche, Regione Toscana and Stanislao Rizzo, Chairman Dept. of Ophtalmology Azienda Ospedaliero - Universitaria Careggi

The workshop was opened by Hélène Dollfus, coordinator of ERN-EYE, Andrea Sodi, local host, representative of the Hospital Azienda Ospedaliero Universitaria Careggi in Florence, member of ERN-EYE, Maria Teresa Mechi, responsible Qualità dei Servizi e Reti cliniche, Regione Toscana and Prof. Stanislao Rizzo, Chairman of the Department of Ophtalmology of the Hospital Azienda Ospedaliero Universitaria Careggi.

All of them highlighted the fact that this workshop is the opportunity to discuss the needs, challenges and issues of the network about genetic testing.

Presentation of present pathway to genetic diagnostic from the patient perspective

Christina Fasser, e-pag representative

The patient associations represented by Christina Fasser, opened the first part of the meeting with the patient perspective regarding ERN-EYE.
Christina Fasser pointed out the importance for patients to have access to genetic testing and genetic counselling in their daily life. Now more and more is available, patients have waited for years for it but having access to it for everybody in Europe is still a challenge.

Avril Daly, EURORDIS Vice-president and CEO of Retina International

Avril Daly presented the study Eurordis conducted about genetic testing last year in order to understand the current status of genetic testing pathways for IRD patients. They asked Member organisations in different countries what their experiences were. The 9 respondents from both EU and non-EU countries (good panel of people) revealed disparities in test types availability, access and payment options. Moreover the study highlighted the problems of waiting time, turn-around time for getting results, shortage of key staff (genetic counsellors, clinical geneticists) noticeably.

INTRODUCTION OF THE WORKSHOP

Setting the scene & objectives of the workshop

Hélène Dollfus, ERN-EYE coordinator and Graeme Black, Chair of TWG6 for genetic testing, Manchester, UK

Hélène Dollfus and Graeme Black introduced the meeting with the objectives of the workshop.
Genetic testing is a hot topic nowadays with more and more technical possibilities, and a lot of hope.
Important questions will be asked during the workshop: What is the state of genomics in ophthalmology? What is the ideal nature of genomics in ophthalmology? What are the priorities? How to use our knowledge and expertise? The key words to illustrate the debate could be costs, archivism, advocacy… This workshop aims to write a position paper.

Results of the SURVEY: Overview genomic testing across ERN-EYE members

Dorothée Leroux, ERN Project manager, Strasbourg, France

Dorothée Leroux presented the results of the survey about genetic testing across ERN-EYE members launched in July to open the debate.

21 HCP representatives answered from 11 countries. It appears that the genetic testing is in majority delivered in national and regional accredited laboratories, ordered by ophthalmologists and clinical geneticists and the results are delivered by ophthalmologists and clinical geneticists.

SESSION 1: SITUATION FOR GENETIC TESTING ACROSS THE MEMBER STATES PARTNERS OF ERN-EYE (Chair: Hélène Dollfus)

CPMS state of the art and recent improvements, from the provider's side.

Situation of each member state for ERN -EYE (by one delegate for each member state)

Caroline Van Cauwenbergh (Belgium), Petra Liskova (Czech Republic), Karen Grønskov (Denmark), Artur Klett (Estonia), Hélène Dollfus (France), Susanne Kohl (Germany), Andrea Sodi (Italy), Sandra Valeina (Latvia), Marius Sukys (Lithuania), Lonneke Haer-Wigman (Netherlands), Katarzyna Nowomiejska (Poland), João Pedro Marques (Portugal), Graeme Black (United Kingdom), Adela Chirita-Emandi (Romania), Anna Tracewska (Poland)

A representative of each member state presented the situation in his or her country for genetic testing. It appears that in some country, there is very few genetic testing and in some others there are already national plans to develop genetic testing and facilitate the access to it. In addition to them, Adela Chirita-Emandi, from the University of Medicine Timisoara, was invited to present the challenges of genetic testing in Romania as well as Anna Tracewska from Wroclaw research centre EIT in Poland.

GENOMIC TESTING IN EVERY DAY CLINICAL PRACTICE: HOW IS IT ORGANIZED TODAY AND HOW DOES THIS HELP PATIENTS AND FAMILIES? (Chair: Graeme Black)

The concept of clinical utility in genomics

Panagiotis Sergouniotis, Manchester, UK

Panagiotis Segouniotis talked about clinical utility in genomics. For him, there is a set of conditions in which there is scope for the ophthalmologist to be offer and request genetic testing. A key reason has to do with the distinction between a phenotype (a sign or a combination of signs, a symptom, an imaging finding) and a diagnosis. Cataract, ectopia lentis or retinal dystrophy are phenotypes/appearances and not final diagnoses and it needs to be asked if this is an isolated or part of a multisystem disorder.

The role of the clinical laboratory

Caroline Van Cauwenbergh, Ghent, Belgium

Caroline Van Cauwenbergh presented the clinical laboratory; the goal is to raise credibility, to assure quality, to minimise errors, to consistently deliver valid and reproducible results in acceptable turnaround time and to have every step of the process being traceable.

The role of the genetic counsellor and the importance of multidisciplinary working

Georgina Hall, Manchester, UK

Georgina Hall presented the role of the genetic counsellor. In UK, there are 280 genetic counsellors and 20 specialised in ophthalmology. Genomic diagnosis, communication of uncertain, complex or evolving results and test families should increase. Multidisciplinary working is a success, because the team shares the same goals.

Genomics in everyday Rare Eye Diseases practice in Strasbourg (CARGO) PANELS WES WGS

Hélène Dollfus, Strasbourg, France

Hélène Dollfus shared her experience in genetic testing. For her, tomorrow WGS will be a « routine ».
Compare to 5 years ago, genetic testing is much more prescribed.

Now more than 50% of cases are solved by genetic testing.
She concluded: “Keep in mind clinical presentation and basic genetics, stay opened minded and never give up!”

A transatlantic perspective of genomic in every day practice

Elise Héon, Hospital for Sick Children, Toronto, Canada

Elise Héon spoke about the situation for genetic testing in Canada. She explained that it is a big country with only a few specialists. There is no national strategy for genetic testing and regulations are provincial. Consents are institution based: for all tests made, it needs consents. Tests are ordered by ophthalmic genetics expert with GC or clinical geneticist. The same people do the counselling after weekly result review at multidisciplinary meetings. They really work as a team also with social workers.

GENOMIC DIAGNOSTIC: STATE OF THE ART AND NEEDS FOR THE ERN-EYE WORKING GROUPS

WG1 - RETINAL RARE EYE DISEASES (Chair: Michael Larsen)

Retinal dystrophies and genetic testing, the current status and the current needs for genomic diagnostic everyday IRD practice

Bart Leroy, Ghent, Belgium

Bart Leroy presented the needs for genomic diagnostic in the IRD practice. For him, the needs for genotyping are enormous but doable; there are serious issues that remain across EU and USA (and in the rest of the World).

Genotyping is a right for every patient with inherited disease and there is a need for natural history studies. The logistics requirements in centres are also enormous.

Targeted (gene panel) RED diagnostics using WES; from syndromes to isolated RP. Comparison with other rare diseases and phenotype-genotype correlations

Lonneke Haer-Wigman, Nijmegen, Netherland

Lonneke Haer-Wigman showed the situation for RED diagnostic using WES in her centre in the Netherlands. She presented the cases of retinal dystrophies, cataract and optic neuropathies.

Achromatopsia and related disorders: what genetic testing has taught us?

Susanne Kohl, Tübingen, Germany

Susanne Kohl explained the symptoms of achromatopsia and the ophthalmic examination. She presented the ATF6 gene and the cohort of Tübingen. Finally, she showed the diagnostic strategy and discussed cost efficiency of the strategy given the frequency and the size of the gene.

CSNB : what has genetic testing told us?

Christina Zeitz, Paris, France

Christina Zeitz explained that precise clinical diagnosis in Congenital Stationary Night Blindness (CSNB) targets to specific gene defects. In these cases, Sanger sequencing remains a gold standard: it also covers GC-rich regions poorly covered by NGS-approaches. It needs strong genotype-phenotype correlations in CSNB that could allow to use candidate genes approaches or WES/WGS.

WG2 - NEURO- OPHTHALMOLOGY RARE DISEASES (Chair: Steffen Hamann)

What are the clinician's needs for RED in neuro-ophthalmology?

Axel Petzold, London, by video

Axel Petzold explained that WG2 is a small, but active WG. It is focused on 2 projects. There will be a meeting in Amsterdam on 1-2 March 2019. They need to join forces with WG specific patient organisations and EU collaborators.

Optic neuropathies in the genetic laboratories

Patrick Yu Wai Man, Moorfields Eye Hospital, London, UK

Patrick Yu Wai Man talked about the challenges of the diagnostic of optic neuropathies. For him, it needs access to more specialised genetic testing (e.g. whole mtDNA sequencing). The other challenges are the cost-related issues (geographical disparity), the variable turnaround time for results (increasing service pressures) and the data interpretation in the era of next-generation sequencing (variants of unknown significance).

Genomic testing in a busy paediatric setting

Jane Ashworth, Chair of WG3, Manchester

Jane Ashworth explained the reasons why we need to integrate genomic testing into care in paediatric ophthalmology. The clearly illustrated major reasons that were presented are that it helps to get a precise diagnosis, to reduce time to diagnosis, investigations, and number of appointments.

Microphthalmia, aniridia

Patrick Calvas, CHU Toulouse, France

Patrick Calvas detailed the microphthalmia and aniridia symptoms, as well as all the different concerned genes. He described the panels available and their resolving rate. For those pathologies, he recommends doing genetic testing; keeping in mind that WES is not the solution at this stage.

LCA: how the clinical background enlightens the genetic testing and vice-versa

Jean-Michel Rozet, Paris, France

Jean-Michel Rozet presented the state of the art for Leber Congenital Amaurosis patients and the links between genetic testing results and the clinical symptoms. He paid particular attention to the importance of the molecular diagnostic, the genetic counselling, the prenatal diagnosis and the inclusion in developing therapeutic trials. He also underlined the importance of differential diagnosis, the visual prognosis and extra-ocular prognosis for patient care.

WG4 - ANTERIOR SEGMENT (Chair: Artur Klett)

The clinician's need in genetic anterior segment diseases: from cornea to lens

Petra Liskova, Prague, Czech Republic

Petra Liskova explained that most patients with anterior segment disorders do not get referred to ophthalmic genetic clinic. There is a need for involvement of corneal specialists. The diagnostic genetic yield for monogenic corneal disorders is high (over 90%) and the diagnostic yield for anterior segment dysgenesis disorder is low (around 30%).

Anterior segment and genetic diagnosis

Jane Sowden, University College, London, UK

Jane Sowden explained that reaching a molecular diagnosis in childhood ocular developmental conditions needs to address the large number of genes involved. Overlapping, complex or ambiguous phenotypes and comprehensive screening of genes affect the development of the eye and interrogation of virtual panels increased diagnosis. Networks and partnerships are needed for the interpretation of VUS. The 100'000 Genomes project has paved the way for the introduction of genomic medicine in the UK.

Challenges and Future issues for the genetic testing group in the ERN-EYE (Chair: Hélène Dollfus)

Different rules and practices in EU member states for genetic testing: cross border and economical aspects

Helena Kaariainen, National Institute for Health and Welfare, Helsinki, Finland

Helena Kaariainen presented the results of a Eucerd survey and put it in perspective with the previous presentations. In some countries, most tests are available within the country and in other countries; a lot of testing had to be bought from abroad. The choices are based on various reasons: sometimes it's just easier and non-bureaucratic. On the contrary, in some EU member states, the logistics and rules for sending DNA made cross-border testing was nearly impossible; in some other countries, very little was available in the own country and the test performed abroad had to be paid by the patient. A reflexion from the ground on good practices to adopt and share followed her talk.

Ethical EU aspects on genetic testing

Anne Cambon Thomsen, Toulouse, France

Anne Cambon Thomsen spoke about the numerous ethical EU aspects on genetic testing in regard to the quick evolution of the technology, IT system and data treatment. She explained that implementation is happening now and there is a necessity of studies embedded in pilot projects to be able to know and take into account stakeholders views .The ethical and legal frame has to be (re) considered for certain aspects. Databases are important as well as the circle between research and clinics.

Ethical EU aspects on genetic testing and consent

Davit Chokoshvili, Leuven, Belgium

Davit Chokoshvili presented the ethical aspects on genetic testing and especially the consent. For him, the current Informed Consent (IC) practices in genetic testing are deficient, but they can be improved. It needs to treat IC as a process, to tailor IC to a patient's needs and to allow for meaningful decision-making.

The patient perspective: what does genetic testing mean?

Christina Fasser, ePag representative

Christina Fasser spoke about the patient perspective in genetic testing regarding the technology available, the expertise available and the human rights. She thinks that economically, it makes sense to treat people in regard of the millions spend to create these tests. Moreover the human right is the right to health. People haven't to be discarded because of money. It needs good care, best possible access for all people in Europe. At present, the patient knows that he/she can go abroad if diagnosis is not available in Europe, so we have to make them available for all in more locally.

ADDITIONAL INFORMATION

New proposed legislation for harmonised Health Technology Assessment in Europe

Russel Wheeler, ePag representative

Russell Wheeler presented the Health Technology Assessment (HTA). He explained that HTA is important to patients and it is important to professionals. It can only get it right if the best people are involved. With new and costly technologies (gene therapy) the problem is likely to get much worse. The time for action is now. The current legislative proposal is likely to have a rocky path in Parliament and will be subject to substantial amendment or may even fail to be passed within the short remaining lifetime of this parliament.

Development and research around genetic testing in the EU (Chair: Frans Cremers)

Follow-up research explorations ('open-the-exome') of WES data sets for REDs and first results WGS of 'WES-negative' samples

Susanne Roosing, Radbound University Medical Center, Nijmegen, Netherlands

Susanne Roosing presented the development of genetic testing in the EU. The main points of her presentations were that open-the-exome procedure yields few novel genes, data sharing has become increasingly important, first cases are being genetically explained by WGS and knowledge remains to be gain.

Results from large cohort WGS studies in IRD: promises and challenges

Gavin Arno, University College, London, UK

Gavin Arno presented the results from large cohort WGS studies in Inherited Retinal Diseases. He explained that WGS enables full characterization of the variant landscape across the genome. It is important to have confidence in causality by exclusion. Expert variant interrogation is essential (clinician/scientist MDT).

General conclusion

All participants

During the general conclusion that ended the meeting, the main point that was mentioned is the fact that ERN-EYE needs to have/develop guidelines on Genetic Testing and maybe also a common consent form on this topic. It was also decided to write a position paper on all what was discussed during the workshop.

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