European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

European Reference Networks

DELIVERABLE 4.5 ERN-EUROBLOODNET REPORT ON THE AVAILABILITY OF HIGHLY SPECIALIZED PROCEDURES FOR RARE HEMATOLOGICAL DISEASES 2

ERN-EuroBloodNet European Reference Network on Rare Hematological Diseases

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DOCUMENT INFORMATION

DELIVERABLE 4.5 ERN-EUROBLOODNET REPORT ON THE AVAILABILITY OF HIGHLY SPECIALIZED PROCEDURES FOR RARE HEMATOLOGICAL DISEASES 2

Report document

ERN: **ERN-EuroBloodNet (European Reference Network on Rare Hematological Diseases)**

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Short Description

Report on results from the different surveys conducted to assess the availability of specific procedures for diagnosis and/or treatment of rare hematological diseases considered as highly specialized procedures and expected to be involved in cross border health.

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1. INTRODUCTION

CROSS-BORDER HEALTH ON RARE DISEASES

Although the vast majority of health care is obtained from providers within the patient's country, this situation may change when highly specialized procedures (HSP) are required. Given the scarcity and heterogeneous distribution of expertise on certain pathologies and of the allocation of specialized services, it is relatively common for patients suffering from complex disorders that the most appropriate care is offered in another Member State (MS). This situation is commonly faced for the management of Rare Diseases (RDs), defined as those affecting less than 1 person in 2000.

The EU Council Recommendation on an action in the field of rare RDs already outlined these disorders in 2009 out as a unique domain of very high added value of action at Community level due to the limited number of patients and scarcity of relevant knowledge and expertise. This added value can be achieved by gathering national expertise on RDs, which is scattered throughout the MS and organising collaboration between centres of expertise, healthcare providers, laboratories, patients and individual experts within and between MS to offer optimal cross-border services to all EU citizens.

In this context, Directive 2011/24/EU of the European Parliament and of the Council on the application of patient rights in cross-border healthcare provides rules regarding access and reimbursement for healthcare received in another EU country in order to encourage cooperation between EU Member States in the field of health.

HIGHLY SPECIALIZED PROCEDURES IN THE CONTEXT OF RARE HEMATOLOGICAL DISEASES

As the basis for a cross-border health action, highly specialized procedures (HSP) are defined in the context of the network as those procedures that for a number of reasons i.e. economical, lack of expertise or awareness, are not available in all EU-MS, thus preventing the delivery of the best care for EU citizens suffering from a rare haematological disease (RHD) independently of their country of origin.

These HSP are classified as "under the scope" of the Directive 2011/24/EU if they are defined as standards of Care and/or included in the national basket of health services for patients or "out of the scope" in the cases that they are still performed on academic or experimental environment. In these cases, the European cooperation can be produced on the research field.

HSP involve both interventions for diagnosis and for treatment, and their complexity can rely on technological advances or expertise of multidisciplinary team, or both.

During the first and second year of ERN-EuroBloodNet implementation two surveys were conducted among ERN-EuroBloodNet members and non-members addressed to identify the European state of the art of Next generation sequencing (NGS) and Bone marrow transplantation (BMT) on non-oncological disorders as highly specialized procedures key for the diagnosis or treatment of many non-oncological RHD and presenting high inequalities for its access among MS. The two questionnaires were conducted among ERN-EuroBloodNet members with the gathering of 50 and 39 and responses received respectively. Answers allowed the identification of important gaps among the need and availability of a) NGS for rare anaemia disorders and b) BMT for Sickle cell disease **(Deliverable 3.2 State of the art of Bone marrow transplantation and Next generation sequencing for non-oncological rare haematological diseases in the context of ERN-EuroBloodNet, SGA2017, January 2019).**

This successful approach has now been expanded to the mapping of diagnostic procedures for Primary vitreo-retinal lymphomas.

PRIMARY VITREO-RETINAL LYMPHOMAS CHALLENGES

Intraocular lymphomas (IOL) include different types of lymphomas that could involve many parts of the eye (vitreous, retina, choroid, ciliary bodies…). Theses IOLs could correspond to primary or secondary disease and are characterized by different histological subtypes or overall prognosis.

This mapping only concerns primary vitreo-retinal lymphoma (PVRL) and VRL occurring in a context of primary central nervous system lymphoma (PCNSL). PVRLs are rare high-grade extranodular non-Hodgkin lymphomas affecting the vitreous, the retina or exceptionally the optic nerve. The vast majority of PVRLs are high-grade diffuse large B-cell lymphomas.

The World Health Organization classification considers PVRL as a subtype of PCNSL, as booth are closely linked together. Indeed, 65 to 90% of PVRL patients ultimately develop central nervous system dissemination within 30 months, while 15 to 25% of PCNSL patients will present intraocular involvement. As CNS involvement is responsible of the ultimate death of the patient, PVRL prognosis is still poor, estimated to 60 months in published series.

PVRL is a complex disease. The first ocular symptoms and the clinical signs of PVRL could be easily confounded with chronic uveitis, leading to a delay of diagnosis of 1 year on average. The common ophthalmologic examination (slit lamp and fundus examination) but also more specific tests (fluorescein angiography, optical coherence tomography (OCT) of the retina…) could provide a high clinical suspicion of PVRL, which however need a cytologic evaluation of tumoral B-cells on ocular samples to confirm the diagnosis of PVRL. Ocular samples, mainly from vitreous, are provided by vitrectomy performed by ophthalmologist and give the opportunity

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to perform many more tests, as flow cytometry, immunohistochemistry, cytokine dosages (also on aqueous from anterior chamber tap) or molecular biology. However, all of these tests are not available in all care centers and the choice of ones from others depends on the practice of hematologist, neurologist and ophthalmologist.

The main goals of the treatment of PVRL are the management of the intraocular disease but also to prevent, if possible, the apparition of CNS involvement which is responsible of the bad prognosis of the pathology. However, precise guidelines are still lacking, and daily practice differs from team to team. While some teams prefer local treatment only (intraocular injection of methotrexate or, less frequently, rituximab), others teams use systemic treatment (high dose methotrexate …) and use intravitreal treatments only in case of specific situations. Well-design prospective studies are not yet available in the literature to determine which alternative for first-line treatment or for relapse management would be the best choice. Even the definition of clinical response to treatment or relapse differs between specialists (hematologists, neurologists, ophthalmologists) and between teams.

All in all, the creation of a European task force bringing together different specialists hematologists, neurologists and ophthalmologists could be could be the optimum approach to face this challenges.

In this context, a European mapping exercise was launched in the previous period of implementation in collaobration with the multidisciplinary team of Institut Curie. First results compiled were presented while the mapping action was still open for gathering answers in **Deliverable 4.4 ERN-EuroBloodNet report on the availability of highly specialized procedures for RHD, September 2020.**

2. OBJECTIVES

ERN-EuroBloodNet has conducted in collaboration with the multidisciplinary team of Institut Curie dealing with PVRL patients, a European mapping exercise to identify the state of the art of the management of PVRL across Europe and specifically to:

- Identify how these lymphomas are diagnosed, treated and monitored in “real life”
- Assess the necessity of the establishment of a European task force for epidemiological surveillance and the establishment of European guidelines

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3. METHODOLOGY

DEFINITION

For the conduction of the mapping exercise an online survey was designed in collaboration with the multidisciplinary team dealing with PVRL patients from ERN-EuroBloodNet member Institut Curie, including: Denis Malaise (MD, Ophthalmologist), Alexandre Matet (MD, PhD, Ophthalmologist), Nathalie Cassoux (MD, PhD, Ophthalmologist) and Carole Soussain (MD, PhD, Hematologist).

Survey is focused on addressing key parameters on the diagnostic procedures and clinical practice of the management of PVRL and ocular involvement of PCNSL for the identification of disparities between European countries.

A block of questions is dedicated to the diagnosis of PVRL, with a different approach depending on the specialists (hematologist/neurologist versus ophthalmologist). Precise questions are asked on the type of ophthalmologic examinations requested in case of suspicion of PVRL and which systemic work-out is performed to exclude concomitant CNS involvement. A specific question focusses on cytokine dosage on vitreous or aqueous sample, as it is a really interesting and low invasive (if aqueous) way to validate a high clinical suspicion of VRL.

The next section aims to determine which first-line treatment is mainly used and how follow-up is performed by ophthalmologists, hematologists and neurologists. Also on the treatment used in case of intraocular involvement and which screening is performed to exclude secondary ocular involvement in case of pure PCNSL at diagnosis.

Final section is related to gather participants' expectations from a future European taskforce on intraocular lymphoma.

Survey was implemented in Google drive and tested among the Institut Curie team. Final version of the questionnaire was released based on feedback from real testing by experts. Full questionnaire is available in **Annex I. ERN-EuroBloodNet European mapping of highly specialized procedures for primary vitreo-retinal lymphoma.**

CONDUCTION

The mapping exercise was launched July 2020 with an introductory letter of the exercise explaining the main objectives and including the link to the survey to ERN-EuroBloodNet members representatives, substitutes and experts from their multidisciplinary teams, scientific societies of hematology, neurology and ophthalmology, and ERNs coordination teams of ERN-RITA and ERN-EYE.

The exercise was opened in a first stage for one month. An expansion of the deadline until November 2020 was agreed with the objective to achieve further responses after summer period.

New waves of dissemination were launched accordingly, including the diffusion through dedicated pieces of news for ERN-EuroBloodNet website and distributed through ERN-EuroBloodNet monthly and dedicated Newsletter and communication channels (Twitter, Linkedin) (Fig 1)

Fig 1. Dissemination of the mapping

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4. RESULTS

A total of 86 responses were gathered from 18 countries. 70% of answers gathered were obtained from Ophthalmologists, 28% from Hematologists and 2% Neurologists (Fig 2).

Regarding the type of institutions participating in the mapping, 81% of the participants belonged to a Public hospital or tertiary referential center, and 19% to a Private clinic (Fig. 3).

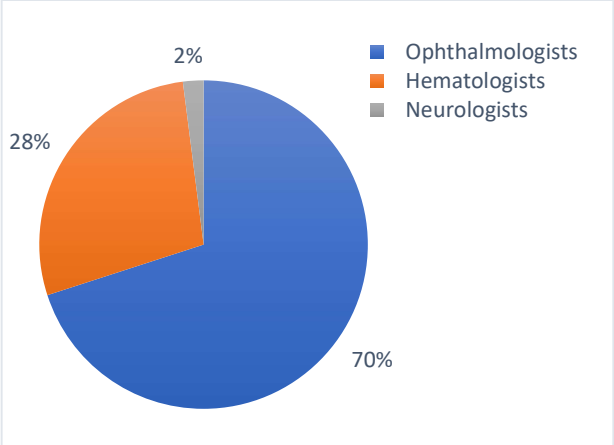

Fig 2. Participants' clinical area

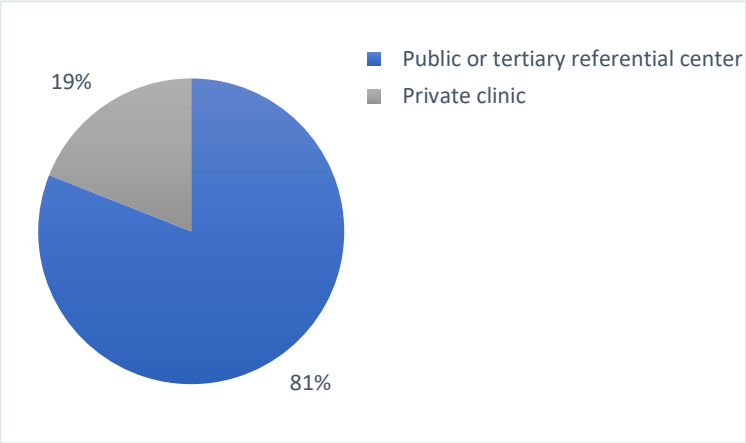

Fig 3. Participants' institutions

75% of the ophthalmologists participating stated to have diagnosed or treated a primary intraocular lymphoma, while this number increased up to 85% of the hematologists and neurologists participating. From these results, some interesting answers were provided.

According to the answers compiled, most of ophthalmologists perform slit-lamb and fundus examination or angiography as intraocular diagnostic procedure followed by vitrectomy and IL-10 and IL-6 levels in anterior chamber (AC), while hematologists and neurooncologists mostly uses the slit-lamp and fundus examination or vitrectomy (Fig 4).

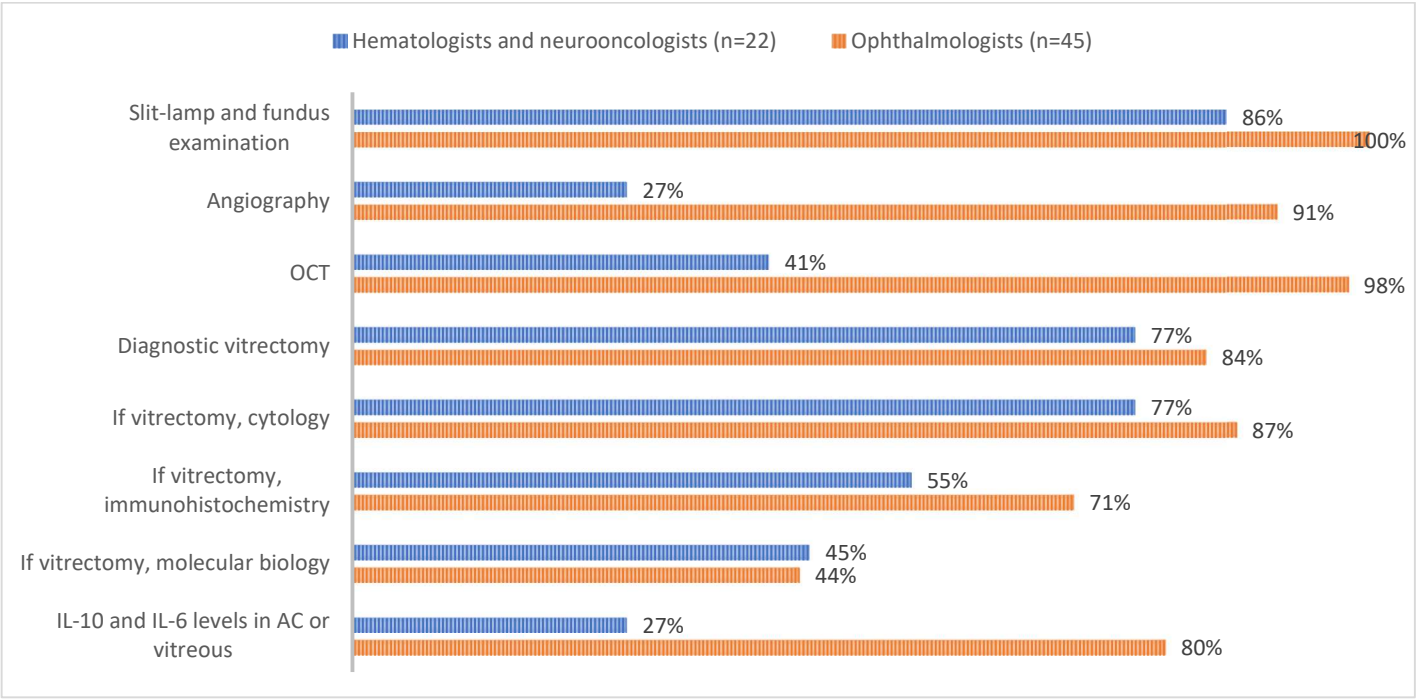

Fig 4. Intraocular diagnostic procedures

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The initial systemic workup was found to be delegated to haematologists/neurooncologists by 50% of ophthalmologists. The haematologists/neurooncologists perform this initial workup by cerebral MRI, CSF examination and body CT or body TEP-scan.

Regarding the cooperation between specialists, 77% of haematologists/neurooncologists requests multidisciplinary team discussion, versus remarkably, the 93% of ophthalmologists request them, being only present at the 45% of the discussions.

In the area of provision of treatment "local, systemic, both", great disparities are found between responders where no real trend is identified (Fig 5), while great disparities are found among responders on the duration of the follow up, ranging from 3 months to life long. Similarly, nearly all specialists perform a systematic surveillance using brain MRI but no specific schedule could be determined.

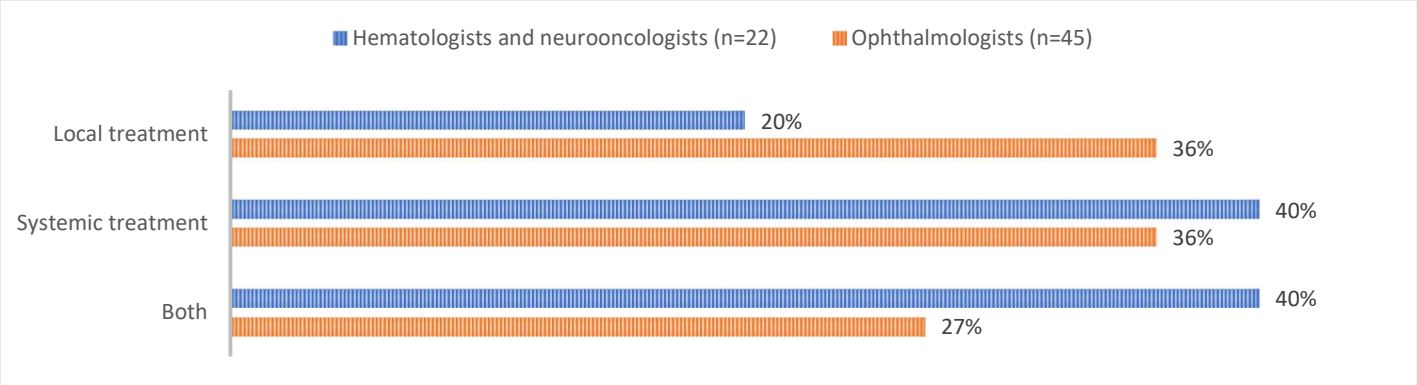

Fig 5. Prefered first line treatment

Regarding the routine ophthalmological follow up in case of PVRL (Fig 6) most of ophthalmologists and haematologists/neurooncologists perform slit-lamp and fundus examination, followed by surveillance for secondary brain involvement. Big differences can be observed among OCT (89% vs 18%), angiography (49% vs 0%) and IL-10 and IL-6 levels in anterior chamber (38% vs 9%).

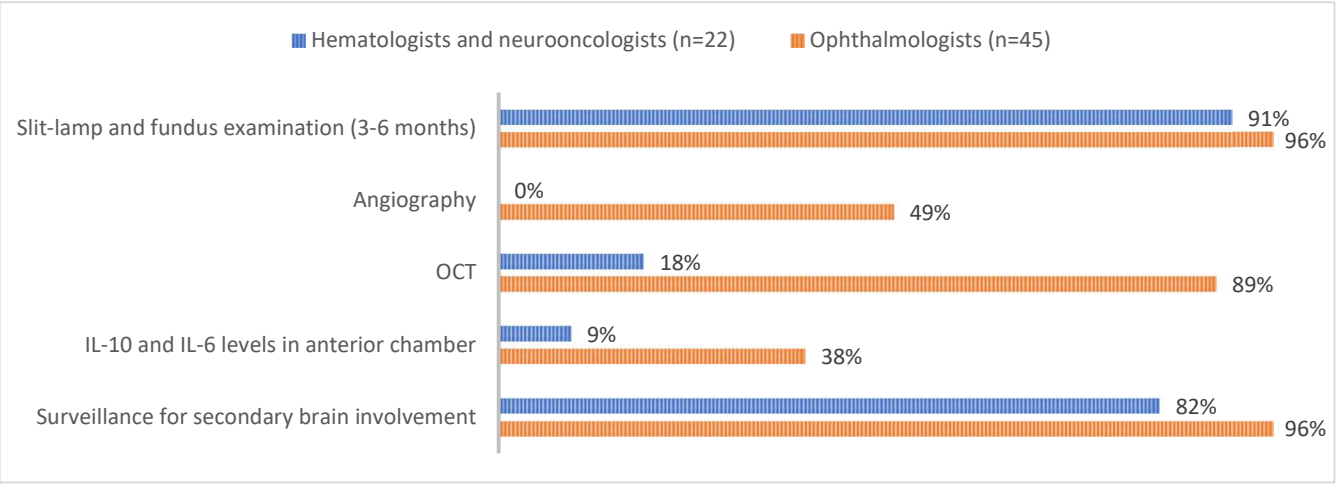

Fig 6. Response assessment and follow up in case of PVRL

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For PCNSL with intraocular involvement, 10/22 Hematologists /neurooncologists (45%) recommend a local treatment in addition to the systemic treatment, versus the 22/45 (49%) of the ophthalmologists. Regarding the intraocular monitoring after the end of the treatment (Fig 7), most of ophthalmologists and haematologists/neurooncologists perform slit-lamp and fundus examination, while big differences can be found on OCT (67% vs 14%) and agiography (47% vs 5%).The duration of the follow up is not homogeneous, ranging from 5-years to long life.

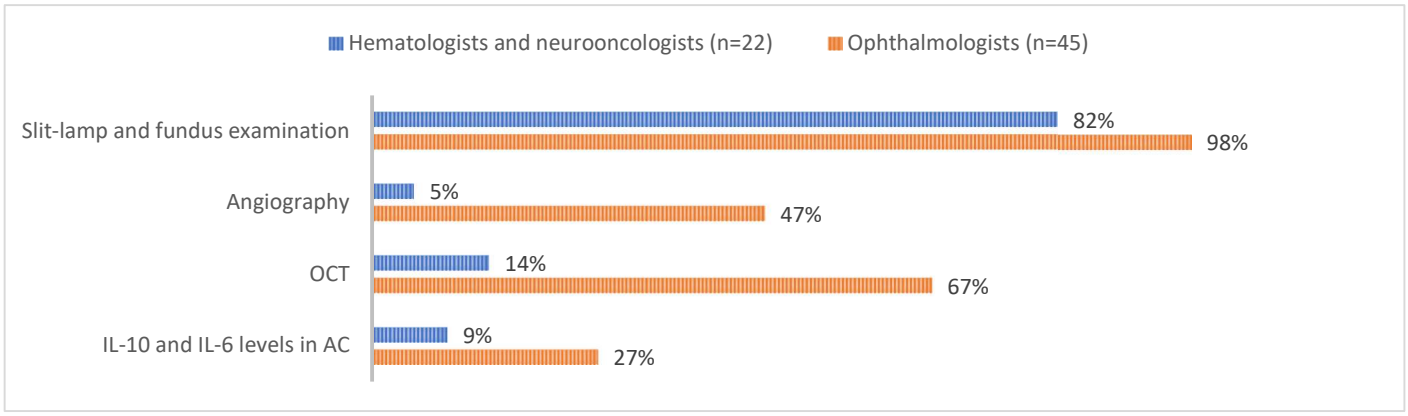

Fig 7. Intraocular monitoring after the end of the treatment for PCNSL with ocular involvement

For the PCNSL without intraocular involvement, ocular examination during the follow-up of the patient is recommended by 38/45 ophthalmologists (84%) versus 8/22 haematologists/neurooncologists (31%). The frequency is also variable ranging from only in case of ocular symptoms, annually or for the majority 5 years.

Finally, attending to the expectations of the health professionals from the creation of a European network for primary intraocular lymphoma (Fig 8), the highest need identified for both groups of health professionals is the creation of Guidelines and discussions about work out, treatment and follow up. This expectation is closed to the medical information about these disorders for both groups of professionals.

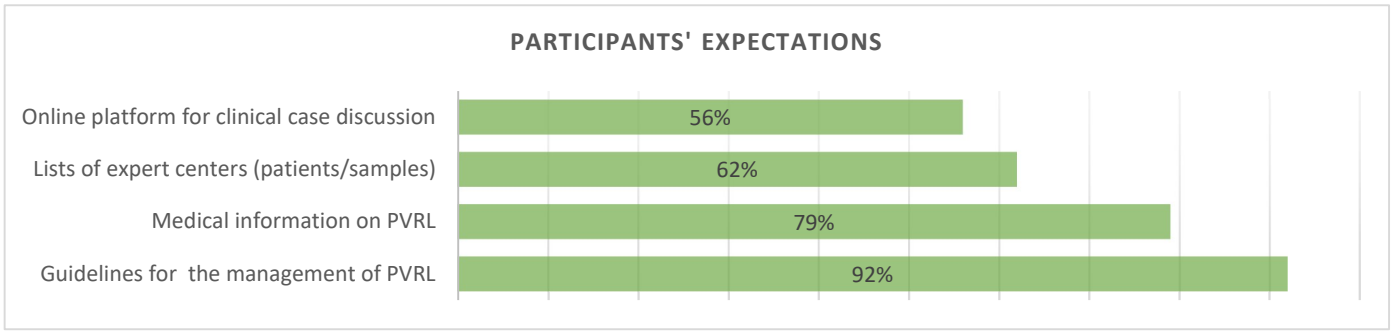

Fig 8. Expectations from the creation of a European Network for primary intraocular lymphomas

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PEER REVIEW PUBLICATION AND DISSEMINATION OF RESULTS

The paper "Primary vitreoretinal lymphoma: short review of the literature, results of a European survey and French guidelines of the LOC network for diagnosis, treatment and follow-up" was published in Current opinion in oncology in September 2021 with the acknowledgement of ERN-EuroBloodNet.

A dedicated piece of news was published at ERN-EuroBloodNet website and disseminated among the community through newsletter and communication channels (Twitter and Linkedin).

Fig 9. Peer review publication and piece of news

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5. CONCLUSIONS & NEXT STEPS

Diagnosis and management of PVRL is still a challenge, and the assessment of a European mapping on clinical experience about this pathology is an interesting opportunity to better determine what are the clinical practice of different European teams, which diagnostic techniques are used and why others are not, how they used to treat and follow patients, what are the main difficulties in the global management of PVRL and how a European taskforce could try to provide answers. Beside this major part of the mapping concerning PVRL, we would also determine how patients affected by PCNSL are screened for ocular involvement, as it could be an early sign of lymphoma relapse.

The launch of the European mapping exercise has allowed the gathering of 86 answers from 18 countries, allowing the identification of important disparities in clinical practice between physicians on diagnosis, treatment and assessment of treatment response and follow up, and therefore the high need for development of a Clinical Practice Guideline on the area that could be addressed by the ERN-EuroBloodNet Guidelines working group in the next period of network implementation.

Moreover, taking into consideration the existing Clinical Patient Management System (CPMS), as the online platform for sharing rare complex cases among health professionals members and non-members of ERNs, the creation of a group for specifically discussing these disorders within the platform is one of the potential outcomes from this network.

Lastly, communication between specialists (hematologists, neurologists and ophthalmologists) is not a clear evidence, and this mapping is a first step to create a taskforce bringing together all implicated physicians in the management of this rare and complex disease through a closer cooperation between specialists ("ophthalmologists are the eyes of hematologists/neurooncologists").

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ANNEX I

ERN-EUROBLOODNET EUROPEAN MAPPING OF HIGHLY SPECIALIZED PROCEDURES FOR PRIMARY VITREO-RETINAL LYMPHOMA

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Dear Colleagues,

Primary vitreo-retinal lymphomas (PVRL) is a rare subgroup of primary central nervous system lymphomas (PCNSL). The intraocular compartment of the eye can also be affected either at diagnosis or during the course of the PCNSL. The diagnosis, treatment and monitoring of intraocular lymphoma can be very challenging.

We aim to conduct a European mapping exercise to better know the prevalence of PVRL and intraocular involvement of PCNSL, and how these lymphomas are diagnosed, treated and monitored in “real life”. These data will allow to assess, within the European Reference Network on Rare Hematological Diseases (ERN-EuroBloodNet), the necessity of the establishment of a European task force for epidemiological surveillance and the establishment of European guidelines, bringing together different specialists: hematologists, neurologists and ophthalmologists.

As starting point, we have prepared a European mapping exercise to identify the state of the art of the management of these disorders across Europe.

If you are willing to be updated on the results of the analysis and on other related activities on the field, please provide your contact details, alternatively you can answer anonymously.

We would really appreciate that you collaborate to this European mapping and forward it to your colleagues implicated in the management of intraocular lymphomas, within or outside your center, it only will take you few minutes!

Thank you for your precious collaboration.

Sincerely yours,

Denis MALAISE, MD, Ophthalmologist
Alexandre MATET, MD, PhD, Ophthalmologist
Nathalie CASSOUX, MD, PhD, Ophthalmologist
Carole SOUSSAIN, MD, PhD, Hematologist

Institut Curie, Paris, France
*Required

1. Name and surname of responder (optional)

2. Mail address (optional)

_____

3. Are you ERN-EuroBloodNet member? *

Tick all that apply.

- [ ] Yes
- [ ] No, but member of other ERN
- [ ] Not member of any ERN
- [ ] Other: _____

4. If you are member of other ERN/s, which one/s?

_____

5. Country of work *

_____

6. Region of work

_____

7. Name of your institution (optional)

_____

8. In which type of institution do you work? *

Mark only one oval.

- ◯ Private clinic
- ◯ Private hospital
- ◯ Public hospital
- ◯ Tertiary referential center
- ◯ Other: _____

9. Health professional role of the responder *

Mark only one oval.

- ◯ Hematologist *Skip to question 16*
- ◯ Neurologist *Skip to question 16*
- ◯ Ophthalmologist

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Ophthalmologists

10. 1. Have you ever diagnosed or treated a primary intraocular lymphoma (PIOL)? *

Mark only one oval.

- ◯ Yes *Skip to question 11*
- ◯ No *Skip to question 39*

2. What work out could be performed in your care center in case of a suspicion of PIOL and which one do you recommend, if necessary?

11. 2.1 Intraocular work-out *

Tick all that apply.

- [ ] i. Slit lamp + fundus examination
- [ ] ii. Angiography
- [ ] iii. Optical Coherence Tomography (OCT) of the retinal lesion
- [ ] iv. Anterior chamber tap for cytokine dosage
- [ ] v. Vitrectomy
- [ ] vi. Retinal biopsy

Other: [ ] _____

12. If selected v. Vitrectomy, please specify

Tick all that apply.

- [ ] Cytology
- [ ] Immunohistochemistry
- [ ] Cytokine dosage
- [ ] Molecular biology

13. Comments on the 2.1 Intraocular work-out?

_____

14. 2.2 Systemic work-out *

Tick all that apply.

- [ ] vii. CSF examination
- [ ] viii. Body CT scan or body TEP-scan
- [ ] ix. Cerebral MRI
- [ ] x. Not performed by the ophthalmologist

Other: [ ] _____

15. Comments on the 2.2 Systemic work-out?

Skip to question 22

Hematologist and Neurologists

16. 1. Have you ever diagnosed or treated a primary intraocular lymphoma (PIOL)? *

Mark only one oval.

- Yes *Skip to question 17*
- No *Skip to question 37*

2. What work out could be performed in your care center in case of a suspicion of PIOL and which one do you recommend, if necessary?

17. 2.1 Systemic work-out *

Tick all that apply.

- i. CSF examination
- ii. Body CT scan or body TEP-scan
- iii. Cerebral MRI
- Other:

18. Comments on 2.1 Systemic work-out?

19. 2.2 Intraocular work-out *

Tick all that apply.

- [ ] iv. Slit lamp + fundus examination
- [ ] v. Angiography
- [ ] vi. Optical Coherence Tomography (OCT) of the retinal lesion
- [ ] vii. Anterior chamber tap for cytokine dosage
- [ ] viii. Vitrectomy (if selected, sub-questions)
- [ ] ix. Retinal biopsy
- [ ] x. Other/Comments (empty box for comments)

Other: ☐ _____

20. If selected viii. Vitrectomy, please specify

Tick all that apply.

- [ ] Cytology
- [ ] Immunohistochemistry
- [ ] Cytokine dosage
- [ ] Molecular biology

21. Comments on 2.2 Intraocular work-out?

_____

_____

_____

_____

_____

Skip to question 22

22. 3. Can you perform a cytokine dosage in the anterior chamber or the vitreous as a routine procedure? *

Mark only one oval.

- ◯ Yes
- ◯ No

23. Any comment?

_____

4. For a patient with a primary vitreo-retinal lymphoma:

24. 4.1 What is you first treatment option (why and which treatment)? *

Mark only one oval.

- ◯ Local treatment
- ◯ Systemic treatment
- ◯ Both

25. Please specify

_____

26. 4.2 Is the case discussed in a multidisciplinary staff meeting? *

Mark only one oval.

- ◯ No
- ◯ Yes

27. If yes, which specialists are in this group?

_____

28. 4.3 What is your routine work out for the follow-up? *

Tick all that apply.

- [ ] Funduscopy with slit lamp examination every 3/6 months
- [ ] Cytokine dosage in the anterior chamber of the eye
- [ ] Angiography
- [ ] OCT
- [ ] Other: _____

29. Any comment?

_____

_____

_____

_____

_____

30. 4.4 What is the duration of the follow up?

_____

31. 4.5 Is a systemic evaluation for secondary brain involvement performed during the follow up? *

Mark only one oval.

- ◯ No
- ◯ Yes

32. If yes, how and when?

_____

5. For a patient with a primary central nervous system lymphomas (PCNSL) WITH intraocular involvement:

33. 5.1 Do you recommend a local treatment in addition to the systemic treatment? *

Mark only one oval.

- ◯ No
- ◯ Yes

34. If yes, which one?

_____

35. 5.2 What are the modalities and duration of the intraocular monitoring after the end of the treatment for the PCNSL? *

Tick all that apply.

- ☐ Funduscopy with slit lamp examination every 3/6 months
- ☐ Cytokine dosage in the anterior chamber of the eye
- ☐ Angiography
- ☐ OCT

Other: ☐ _____

36. Duration of the monitoring? any comment?

_____

6. For a patient with a primary central nervous system lymphomas (PCNSL) WITHOUT intraocular involvement:

37. Do you recommend an ocular examination during the follow up? *

Mark only one oval.

- ◯ No
- ◯ Yes

38. If yes, which one and when?

39. 7. What would you expect from a European network for primary intraocular lymphomas? *

Tick all that apply.

- [ ] Medical information about (intra)ocular lymphomas
- [ ] Guidelines and discussions about work out, treatment and follow up
- [ ] Information about referral centers where I can address a patient or a sample (aqueous humor, vitreous, retina, …)
- [ ] An online platform for clinical case discussion
- [ ] Other (empty box for answer)

Other: ☐ _____

40. Would you like to make any comment?

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