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

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

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Short description: Report on mapping of availability of highly specialized procedures for diagnosis, next generation sequencing, and treatment, bone marrow transplantation, of non-oncological hematologic disorders in the context of ERN-EuroBloodNet

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1-Background and rationale

1.1. Crossborder 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.

1.2. Highly specialized procedures (HSP) in the context of rare hematological diseases (RHDs)

As the basis for a cross-border health action, we define highly specialized procedures (HSP) 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 (SOC) 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.

In the context of ERN-EuroBloodNet, two priority HSPs have been identified for an action on the field of non-oncological haematological diseases.

1.2.1. Bone Marrow Transplantation for non-oncological RHDs

Bone Marrow Transplantation is a HSP that is nowadays standard of care (SOC) for many hematologic conditions both oncological (i.e relapsed or high risk leukemias) and non oncological (i.e hemoglobinopathies). Nevertheless not all hematology reference centers in Europe have the capacity or the expertise to perform BMT for both oncological and non oncological conditions in the same center or in the same region or country.

Hemoglobinopathies, mainly sickle cell disorders (SCD) and thalassaemia disorders (THAL), are genetic disorders that, in their severe forms, are associated with chronic, life-impairing and -threatening conditions with inherent serious health sequelae that can lead to disability or even death.

Geographical distribution of SCD and THAL is heterogeneous and linked to the ethnic origin of the patient. In Europe, SCD is predominantly a disorder seen in immigrant and minority communities since the carrier state offers some protection against malaria infection hence it is most commonly seen in people originating from malarial endemic areas, and predominantly people of African origin. The gene however is seen in many other communities, it is present in many groups of Mediterranean, Middle Eastern origin; and Indian groups. Nevertheless in addition to immigrants within Europe, some indigenous Southern European people also carry the gene (i.e in Southern and North East Italy and in Greece and Albania). As a result of recent arrivals in Europe; there is increasing number of affected people especially in large urban centres leading to uneven distribution of SCD throughout Europe. THAL, in concrete beta thalassaemia, has a very variable prevalence since in the southern Mediterranean coastal area the thalassaemia genes are prevalent while in the northern countries they are rare in the indigenous populations. However, migrations have over the last few decades introduced the disease in most of the northern areas. In most European countries migrants now have reached around 10-12% of the population. These migrants originate not only from the southern states of Europe but also from Asia, the Middle East and Africa. In each country the migration

patterns are different, often related to the past or present relationships of host countries to the countries of origin and also to economic factors. Most migrations have been south to north and so from high prevalence areas to low prevalence areas. This has created a challenge for health care professionals for the delivery of best health care to patients affected by hemoglobinopathies.

Currently, the only curative treatment for both SCD and THAL is bone marrow transplantation, however experts teams on the management of these disorders are concentrated in those countries where higher prevalence of the disease are found. Some countries in Europe, such as Ireland, can offer the expertise and the capacity (in terms of adequate staff numbers and beds) that can cover only the BMT for patients with malignant conditions. Therefore, hematologists need to seek the BMT expertise elsewhere for those patients with non malignant conditions who are eligible for BMT.

Other non-oncological diseases requiring BMT include metabolism disorders leading to rare anaemia i.e. pyruvate kinase deficiency, inherited or acquired aplastic anemia and immune deficiencies.

It seems important to define across the European Reference Centers the magnitude of the problem and the availability of BMT for non malignant conditions.

1.2.2. Next generation sequencing for diagnosis of non-oncological RHDs

Diagnosis of most common rare anaemia disorders (RADs) i.e. hemoglobinopathies is usually easily performed based on routine laboratory. In contrast, for patients with more rare non-oncological RHDs, many of which are severe and life-threatening conditions, reaching a precise diagnosis is often extremely difficult and may be delayed for years. Clinical diagnosis of many non-oncological RHDs may be hampered by overlapping phenotypes leading to an important number of misdiagnosis cases. The phenotypic variability is related to a high genetic heterogeneity and probably to the presence of genetic variants acting as disease modulators.

With the exception of red cell membrane disorders, red cell morphology is often non-specific resulting on a lack of haematological and/or biochemical markers that correlate specifically with a pathological condition or with a causative gene. In these cases, diagnosis requires investigations that are expensive and restricted to laboratories in Centres of Expertise. Thus, it is unsurprising that many patients with non-oncological RHDs have no diagnosis, hampering effective patient management and genetic counselling.

Next generation sequencing is a powerful tool to improve the diagnosis of non-oncological RHDs, however, interpretation of resulting genetic variants is complex since there is scarce clinical evidence and existing information is fragmented.

Mapping of services available for NGS for non-oncological RHDs, as well as needs, will result on an European overview of centres of expertise on this HSP for both improving the diagnosis of patients living in countries where the service is not available and promote the European cooperation for enabling standardized procedures for referral and sample shipping, generating a common database of genetic variants increasing robustness of evidence, which turns on decreased number of undiagnosed and misdiagnosed cases.

2-Method

As previously commented, one of the major challenges faced in the promotion of the Cross-border access to highly specialized health care services is the inequalities of their availability in all countries. Accordingly, in order to assess the establishment of agreements between medical centres to provide the services to patients from other countries, it is essential to know the state of the art of the availability of such services at the European level.

2.1. Objective and design of the surveys

In agreement with the priorities identified in the RHD field for the establishment of cross-border agreements, two online surveys were identified to be conducted among ERN-EuroBloodNet members with focus on highly specialized procedures key for the diagnosis or treatment of many non-oncological RHD and presenting high inequalities for its access among MS: Bone marrow transplant and NGS for non-oncological disorders.

Surveys were first drafted by a Group of Experts within the ERN-EuroBloodNet non-oncological hub and circulated shared with the 24 members of the scientific and strategic board for comments. A pre-final version was produced and tested by a subgroup of experts. Fibal version of the questionnaires were released based on feedback from real testing by experts.

2.2. Survey on Bone marrow transplantation for non-oncological RHDs

Survey includes four main sections:

a) Responder data: name, surname, mail, institution, role, area of expertise

b) BMT need: To assess diseases for which the respondent consider the BMT for the correct management of the patients

c) BMT availability: To analyze for which non-malignant RHDs and patients' age the respondent's center offers the BMT. If BMT is not offered, reason is also requested for their assessment.

d) State of the art of BMT cross-border: To assess if referrals to other centers are ever considered when necessary and if a standardized procedure is in place in such cases. Problems experienced in the referral of patients are also requested for their analysis.

Full questionnaire in Annex I. Bone Marrow Transplantation questionnaire

2.3. Survey on Next Generation Sequencing and other Advanced technologies for non-oncological RHDs

Survey includes four main sections:

a) Responder data: name, surname, mail, institution, role, area of expertise

b) NGS/Advanced technologies need: To assess which advanced technologies and for which disorders the respondent consider necessary for the correct management of patients.

c) NGS/Advanced technologies availability: To analyze if responder's center performs NGS/Advanced technologies and for which non-malignant disorders. If these technologies are not offered, reason is also requested for their assessment.

d) State of the art of NGS/Advanced technologies cross-border: To assess if

- Referrals of samples to other centers are considered when necessary, with what objective and the procedure in place in such cases.
- Samples are received from other centers, with what objective and the procedure in place in such cases.

Full questionnaire in Annex II. NGS/Advanced technologies questionnaire

2.4. Conduction of the surveys

Online Surveys were performed through Google forms. They were launched by e-mail on December 2018 with an introductory message of the activity and the link to complete the surveys.

The questionnaire were sent to the 66 ERN-EuroBloodNet members already recognized at the European level as centres of expertise in rare hematological diseases. From which, 56

Healthcare providers have been recognized as centers of expertise in non-malignant RHD, and specifically:

- 37 Healthcare providers are recognized as part of the Rare Red blood cell defects subnetwork
- 22 Healthcare providers are recognized as part of the Bone marrow failure and hematopoietic disorders subnetwork
- 35 Healthcare providers are recognized as part of the Rare bleeding-coagulation disorders and related diseases subnetwork
- 16 Healthcare providers are recognized as part of the Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis subnetwork

3-Results and discussion

3.1 Bone Marrow Transplantation for non-oncological RHDs

A total of 27 centres from 13 member states (MS) answered the survey so far, accounting for the 48,2% of ERN-EuroBloodNet members belonging to any of the non-oncological subnetworks. Distribution of responders by subnetwork and by member State (MS) are shown in Table 1 and 2, respectively.

BMT	Members EuroBloodNet	Responders	%
Non oncological	**56**	**27**	**48,2%**
RBC	37	17	45,9%
BMF	22	14	63,6%
Bleeding coagulation	35	5	14,3%
HH-Iron	16	9	56,3%

Table 1 – Total number of responders and distribution by subnetwork

BMT	Responders by Member State
BE	1
BG	1
CY	1
CZ	1
DE	2
ES	1
FR	3
IE	1
IT	12
NL	1
PT	1
SE	1
UK	1

Table 2 – Distribution of responders by Member State

To the question: “Do you consider Bone marrow transplantation for your patients as a treatment option?”, 8 of the 27 centres (30%) always consider BMT for your patients as a treatment option, 15 (55%) sometimes and 4 (15%) never consider it as a treatment option. Figure 1.

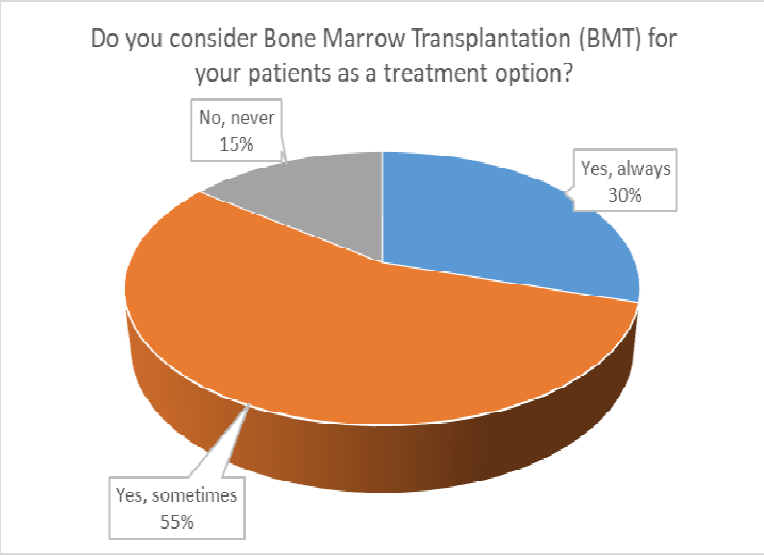

Figure 1. Distribution of answer (%) to the question “Do you consider Bone marrow transplantation for your patients as a treatment option?”

The 4 centres never considering BMT as a treatment option belong to rare bleeding-coagulation disorders and related diseases or Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis.

When coming to specific diseases, BMT was found to be more considered as a treatament option for Inherited or acquired aplastic anemia 77.8%, followed by Thalassaemia syndromes 74.1% and Sickle cell disorders 70.4%. For Immune Deficiencies and Metabolic Disorders, BMT was considered as a treatment option in 51.9% and 48.1% of the centres respectively. In addition, Congenital neutropenia, Congenital Dyserythropoietic anaemia, and other transfusion dependent rare anaemia disorders were declared by one centre each as disorders for which BMT was considered also as a treatment option. Figure 2.

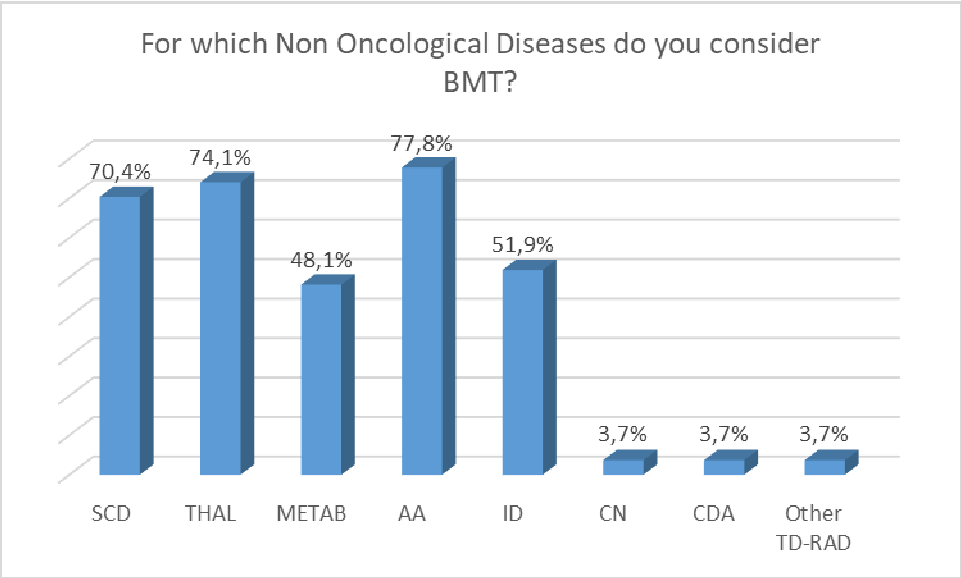

Figure 2. Distribution of answer (%) to the question "For which non oncological diseases do you consider BMT?"
SCD: Sickle cell disorders, THAL: Thalassaemia syndromes, METAB: Metabolic Disorders, AA: Inherited or acquired aplastic anemia, ID: Immune Deficiencies, CN: congenital neutropenia, CDA: Congenital Dyserythropoietic anaemia, Other TD-RAD: Other transfusion dependent rare anaemia disorders

Regarding BMT performance in the centres, thus availability of the procedure, 4 out of the 27 centres (14.8%) declared not to perform BMT. 80.8% of the centres perfom BMT for oncological diseases, however when coming to non-onological disorders, only 65,4% of the centres declared to perform BMT. 66.7% of the centres cover pediatrics and 52,4% adults, and only 38,1% of the centres cover both pediatrics and adults. Figure 3.

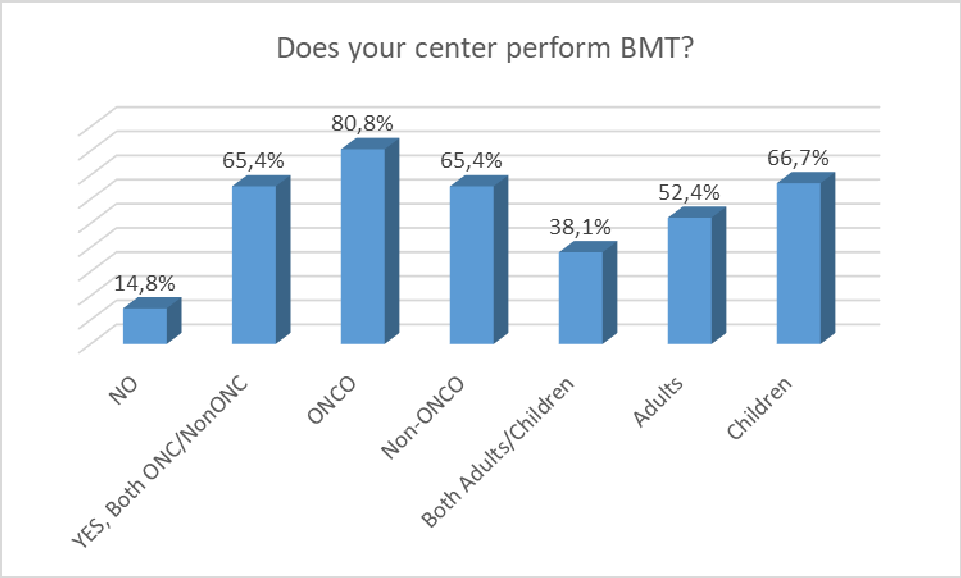

Figure 3. Distribution of answer (%) to the question "Does your centre perform BMT?"

However, the availability of the procedure for the different diseases included in the non-oncological subnetworks is not equal distributed. BMT is available for Inherited or acquired aplastic anemia in 74.1% of the centres, for Thalassaemia syndromes and Immune Deficiencies in 59.3% of the centres, for Sickle cell disorders in 48.1% of the centres and for Metabolic Disorders in 44.4% of the centres. Figure 4.

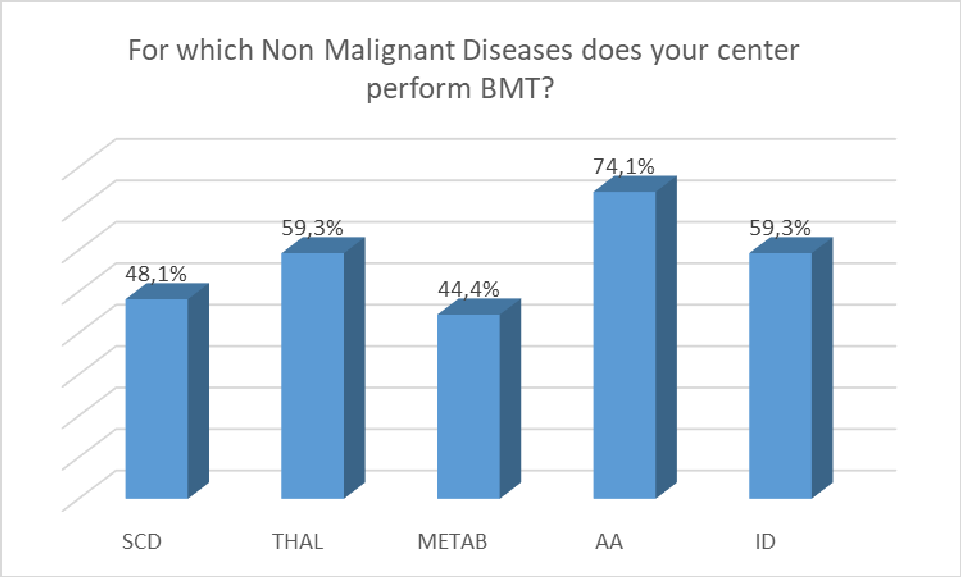

Figure 4. Distribution of answer (%) to the question "For which non malignant diseases does your centre perform BMT?"
SCD: Sickle cell disorders, THAL: Thalassaemia syndromes, METAB: Metabolic Disorders, AA: Inherited or acquired aplastic anemia, ID: Immune Deficiencies

Comparison between need for BMT per disease declared by the centres (figure 2) and availabilty of BMT (Figure 4) is shown in Table 3.

Comparison BMT need / BMT availability			
	Need	**Availability**	**Difference**
SCD	70,4%	48,1%	22,2
THAL	74,1%	59,3%	14,8
METAB	48,1%	44,4%	3,7
AA	77,8%	74,1%	3,7
ID	51,9%	59,3%	-7,4

Table 3. Comparison between need for BMT per disease declared by the centres and availabilty of BMT
SCD: Sickle cell disorders, THAL: Thalassaemia syndromes, METAB: Metabolic Disorders, AA: Inherited or acquired aplastic anemia, ID: Immune Deficiencies

SCD is the condition for which the availability of BMT (48,1%) is the lowest, 22,2 points below the need (70,4%), followed by Thalassaemia syndromes in which availability of BMT (59.3%) is 14,8 points below the need (74.1%). In 7 centres which consider BMT for SCD patients, the procedure is not available, 5 of them belonging to the red blood cell subnetwork. From the 7 centres, 6 confirmed that they refer patients to another centre, 5 in the same country and one abroad. However, only 2 have a standardised procedure for referral of patients, being one of the two the centre referring patients abroad.

To the question: "If you consider BMT for your Non oncologic patients but DO NOT have possibility to transplant them at your center, do you refer them to another center?" From the 27 centres, 15 declared that in the cases that BMT is not available in their centres and they consider it as a treatment option for a patient, the patient is referred to another centre; 25.0% of the centres refer the patient to a centre in the same regional area, 75,0% in the same country and 18.8% abroad. Only one centre (6,3%) declared not to refer the patient to any centre for performing BMT. Figure 5.

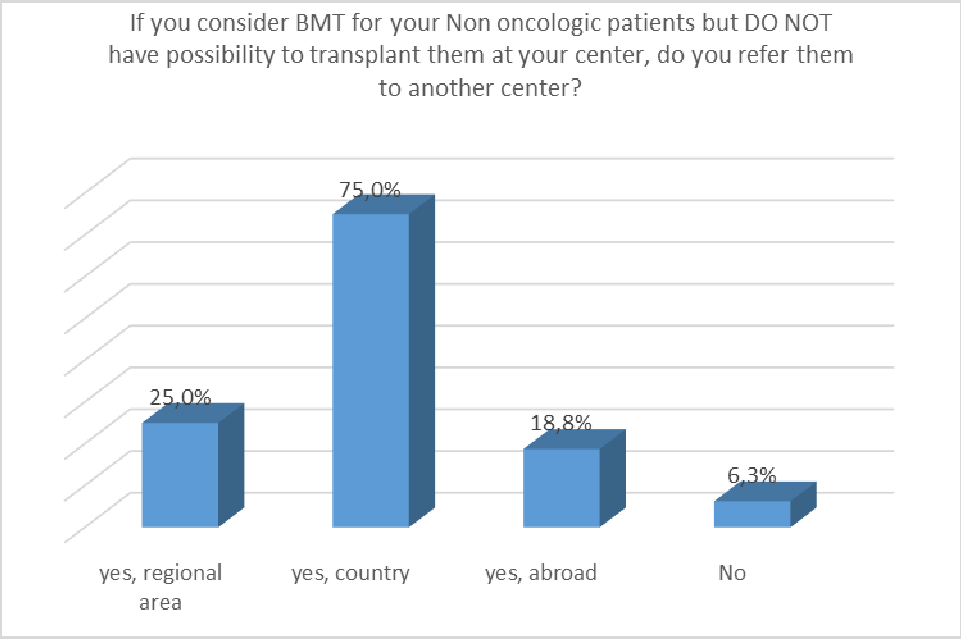

Figure 5. Distribution of answer (%) to the question "If you consider BMT for your Non oncologic patients but DO NOT have possibility to transplant them at your center, do you refer them to another center?"

In addition, 12 of the centres confirmed that in case of referral, they follow a standardized procedure.

To the question: “Does the referral to another center need your institution’s approval?” From 18 answers received, 8 declared that no Institutional approval is required, 1 requires financial approval and 3 both financial and medical approval, 2 only endorsement letter and 3 declared that approval was required by but other regulatory body. One centre was not aware on the type of approval required since they never considered it. Figure 6.

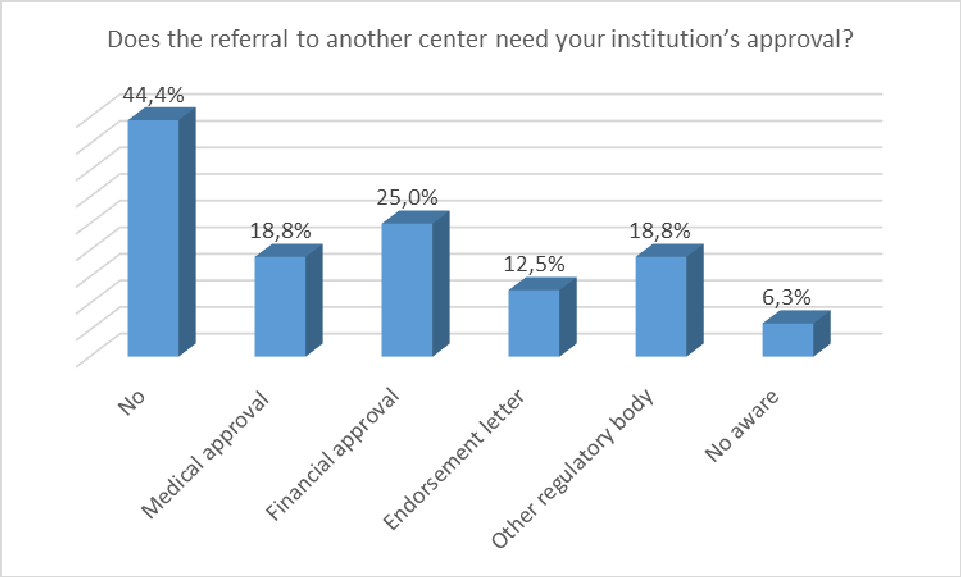

Figure 6. Distribution of answer (%) to the question “Does the referral to another center need your institution’s approval

It is important to highlight that the 3 centres referring patients abroad, two of them declared to follow a standardized procedure requiring both medical and financial approval. Meanwhile, the third one declared not to follow a standardized procedure but confirmed the requirement of approval by other regulatory body different from its institution.

3.2. Next Generation sequencing for non-oncological RHDs

A total of 38 centres from 12 member states (MS) answered the survey, accounting for the 67.9% of ERN-EuroBloodNet members belonging to any of the non-oncological subnetworks. Distribution of responders by subnetwork and by member State (MS) are shown in Table 4 and 5, respectively.

NGS	Members EuroBloodNet	Responders	%
Non oncological	**56**	**38**	**67,9%**
RBC	37	24	64,9%
BMF	22	12	54,5%
Bleeding coagulation	35	13	37,1%
HH-Iron	16	12	75,0%

Table 4 – Total number of responders and distribution by subnetwork

NGS	Responders by Member State
BE	2
BG	1
CY	1
CZ	1
DE	1
ES	1
FR	5
IE	1
IT	17
NL	4
SE	1
UK	3

Table 5 – Distribution of responders by Member State

To the question: “For which Non Oncological Diseases do you request NGS/Advances technologies?”, 75% of the centres declared that they request the service for rare anemia disorders, followed by 52,8% of the centres requesting the service for bone marrow failure syndromes, 41,7% for inherited or acquired aplastic anaemia, 33.3% for immune deficiencies and 8.3% for other conditions, including red blood cell pre-implantation genetic disorders, hereditary hemochromatosis, hereditary disorders of iron metabolism and Inherited thrombocytopenia. Figure 7.

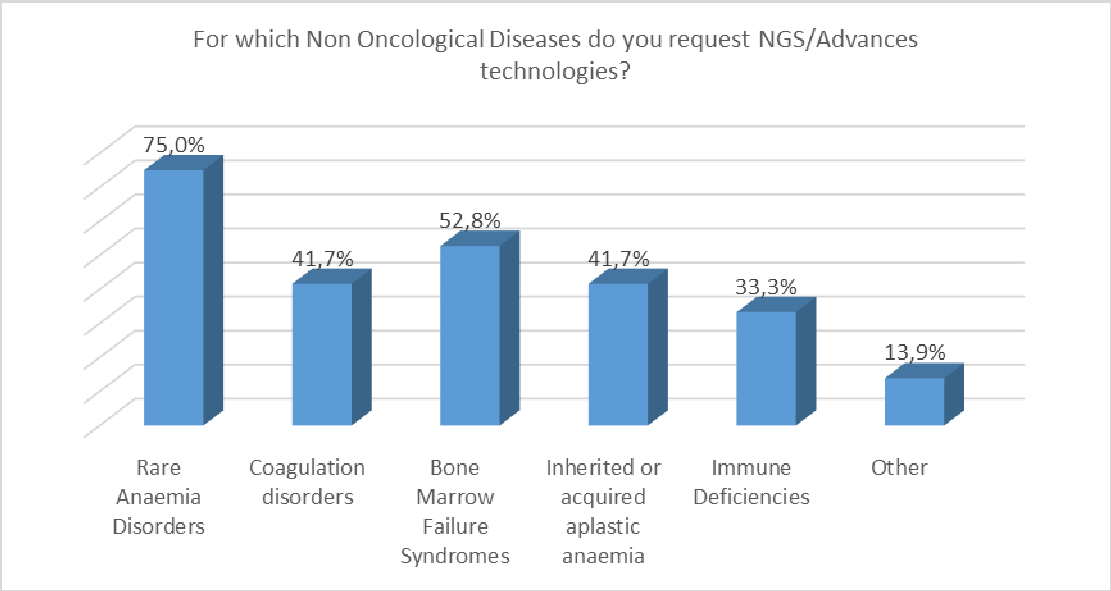

Figure 7. Distribution of answer (%) to the question “For which Non Oncological Diseases do you request NGS/Advances technologies?
Other includes red blood cell pre-implantation genetic disorders and Inherited thrombocytopenia.

To the question: “Which diagnostic tool do you consider?”, all centres declared to consider targeted NGS panels and 62.9% consider whole exome sequencing. However, when it comes to wide genome sequencing or proteomics, only 17.1% and 11.4% of the centres respectively declared to consider it. Figure 8.

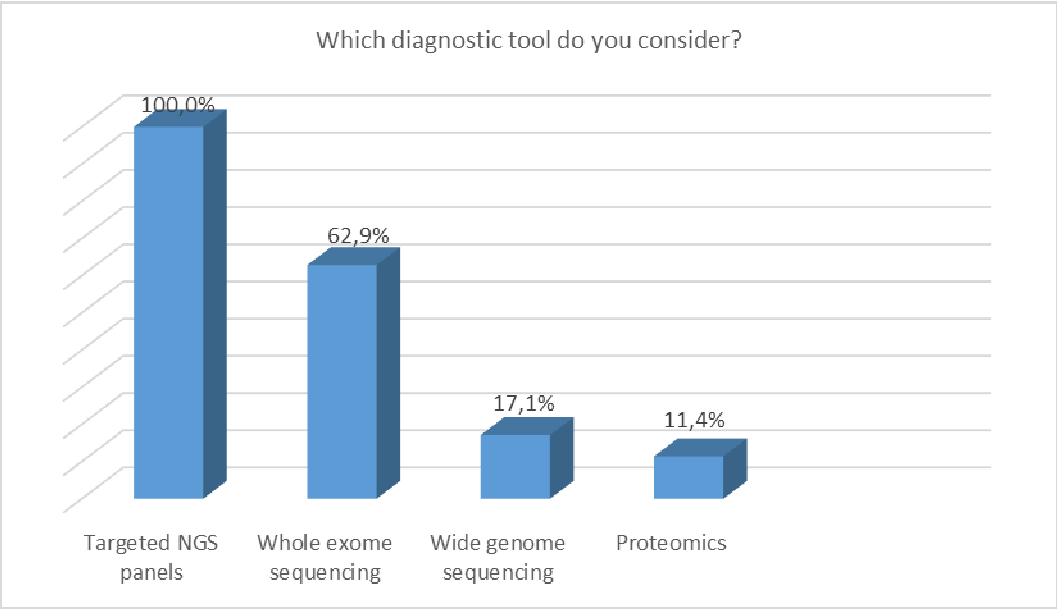

Figure 8. Distribution of answer (%) to the question "Which diagnostic tool do you consider?"

Regarding availability of NGS/Advanced technologies in the centres, 78.9% of the centres declared to perform targeted NGS panels in their own centres. However, only 39.5% of the centres declared to perform whole exome sequencing. Wide genome sequencing was performed only in 13.2% of the centres and none centre declared to perform proteomics. Finally, 15.8% of the centres declared not to perform any NGS/Advanced technologies for diagnosis of non oncological RHDs. Figure 9.

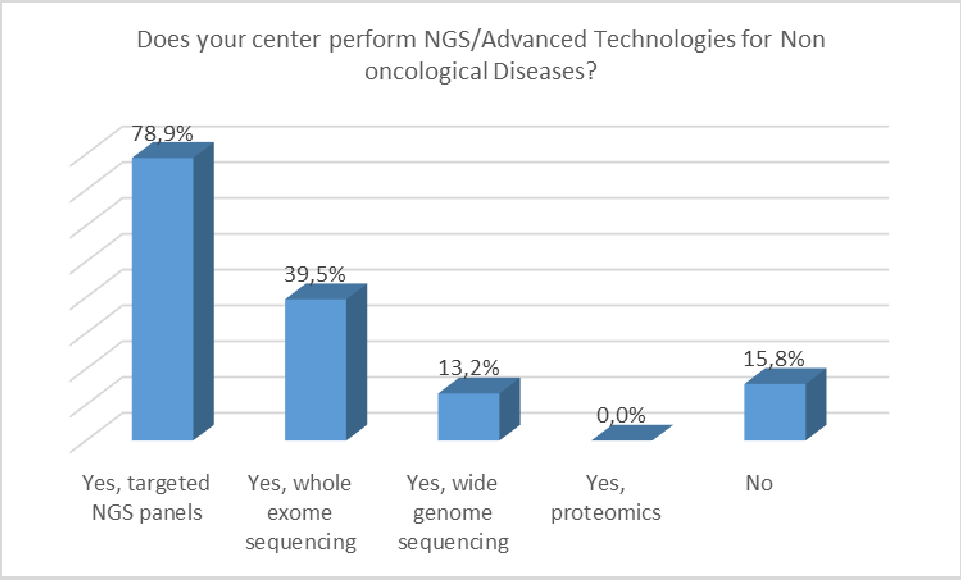

Figure 9. Distribution of answer (%) to the question "Does your center perform NGS/Advanced technologies for non oncological diseases?"

Comparison between need for NGS/Advanced technologies declared by the centres (figure 8) and their availabilty (Figure 9) is shown in Table 6.

Comparison NGS need / NGS availability			
Options	**Need**	**Availability**	**Difference**
Targeted NGS panels	100,0%	78,9%	21,1
Whole exome sequencing	62,9%	39,5%	23,4
Wide genome sequencing	17,1%	13,2%	4,0
Proteomics	11,4%	0,0%	11,4

Table 6. Comparison between need for NGS/Advanced technologies declared by the centres and their availabilty

The availability of the two HSP considered as more needed by centres, targeted NGS panels (78.9%) and whole exome sequencing (39.5%) respectively, is more than 20 points below the need, 21.1 for targeted NGS panels and 23.4 for whole exome sequencing. Less difference is resulting for wide genome sequencing, only 4 points below the need, showing that most of the centres considering it are those performing it. It is important to highligh that none centre perform proteomics.

Regarding diseases for which the centres perfrom NGS/advanced tecnologies, 62.5% of the centres perform them for rare anaemia disorders, followed by 50% of the centres performing them for bone marrow failure syndormes, 40.6% for coagulation disorders, 37.5% for inherited or acquired aplastic anaemia and 34.4% for immune deficiencies. In adition, 12.5% of the centres declared to perform NGS/advanced technologies for other disorders including hereditary hemochromatosis, hereditary disorders of iron metabolism and inherited thrombocytopenia. Figure 10.

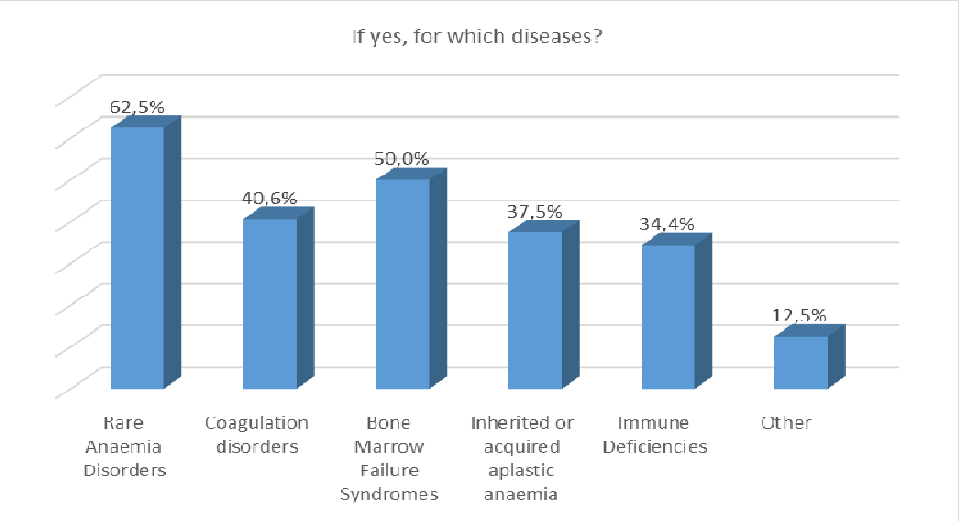

Figure 10. Distribution of answer (%) to the question "For which diseases does your center perform NGS/Advanced technologies for non oncological diseases?"

Comparison between need for NGS/Advanced technologies declared by the centres (figure 7) and their availabilty (Figure 10) by disease is shown in Table 7.

Comparison NGS need / NGS availability by disease			
Options	**Need**	**Availability**	**Difference**
Rare Anaemia Disorders	75,0%	62,5%	12,5
Coagulation disorders	41,7%	40,6%	1,0
Bone Marrow Failure Syndromes	52,8%	50,0%	2,8
Inherited or acquired aplastic anaemia	41,7%	37,5%	4,2
Immune Deficiencies	33,3%	34,4%	-1,0
Other	13,9%	12,5%	1,4

Table 7. Comparison between need for NGS/Advanced technologies declared by the centres and their availability by disease

Differences are observed mainly for rare anaemia disorders, for which availability (62.5%) is 12.5 points below need (75.0%). Differences in the other groups are less of 5 points, indicating that most of the experts on those conditions have access to NGS/advanced technologies in their own centres.

To the question: “If not available in your centre, do you send the samples to another center where these techniques are available?”, most of the centres 72% send the samples to another centre in their own country, 32% on their own regional area and 32% to another centre abroad. 4.0% of the centres refer the patient to another centre for diagnosis or the patient has to go by him/herself to another centre. In the 8% of the centres neither the samples nor the patient is referred to another centre for diagnosis.

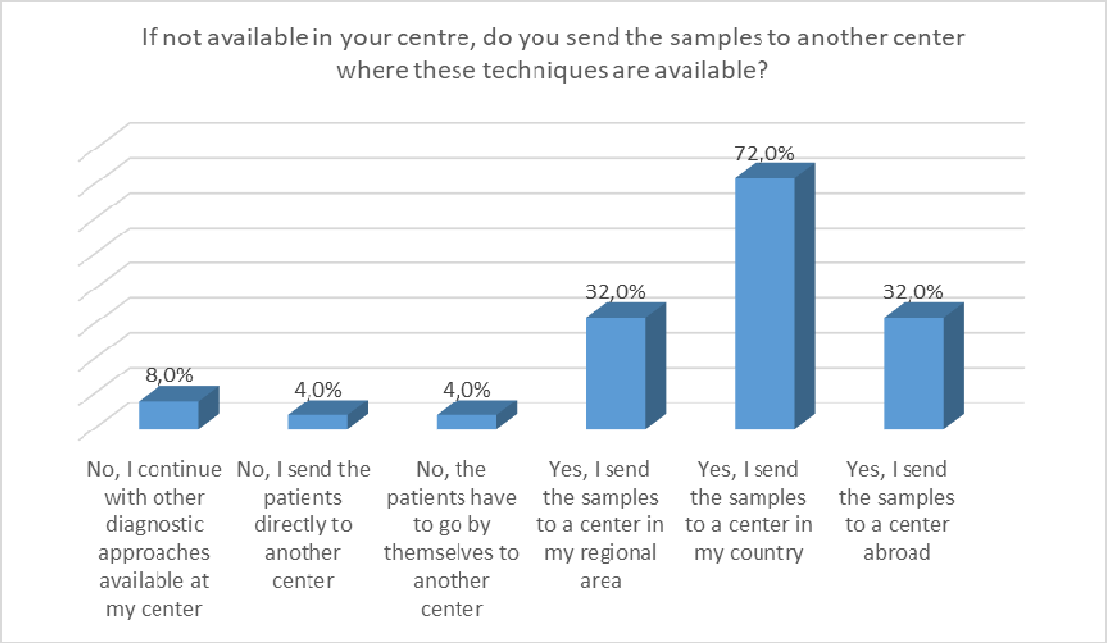

Figure 11. Distribution of answer (%) to the question "If not available in your centre, do you send the samples to another center where these techniques are available?"

In addition, 72.7% of the centres referring samples to another centre confirmed that they used a standardized procedure. Meanwhile, 42,4% of the centres declared not to require any institution's approval for the referral, 33.3% of the centres require financial approval, 9.1% medical approval and 12,1% ethical approval. 15.2% of the centres only require endorsement letter by the institution, and 3.0% of the centres require approval by other regulatory body. Figure 12.

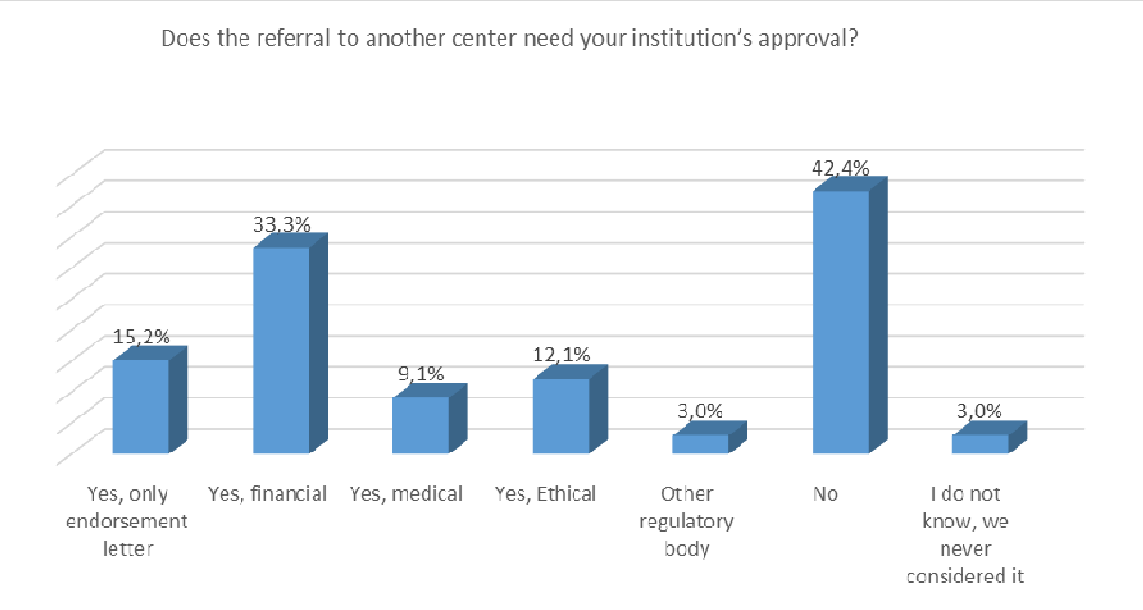

Figure 12. Distribution of answer (%) to the question "Does the referral to another center need yout institution's approval?"

In addition, 97.3% of the centres referring samples declared that the analysis is performed for diagnosis, meanwhile in 40.5% of the cases it is performed on research basis.

According to the results, the cost is covered mainly by the sending centre and/or through the national health system, 45,2% and 51.6% of the centres respectively. In 6.5% of the cases, it is covered by the receiving institution or directly by the patient, and in 3.2% other funding sources as charitable non-profit organization are used. None centre declared to have a cross-border agreement in place, although 32,0% of the centres declared to send the samples abroad. Figure 13.

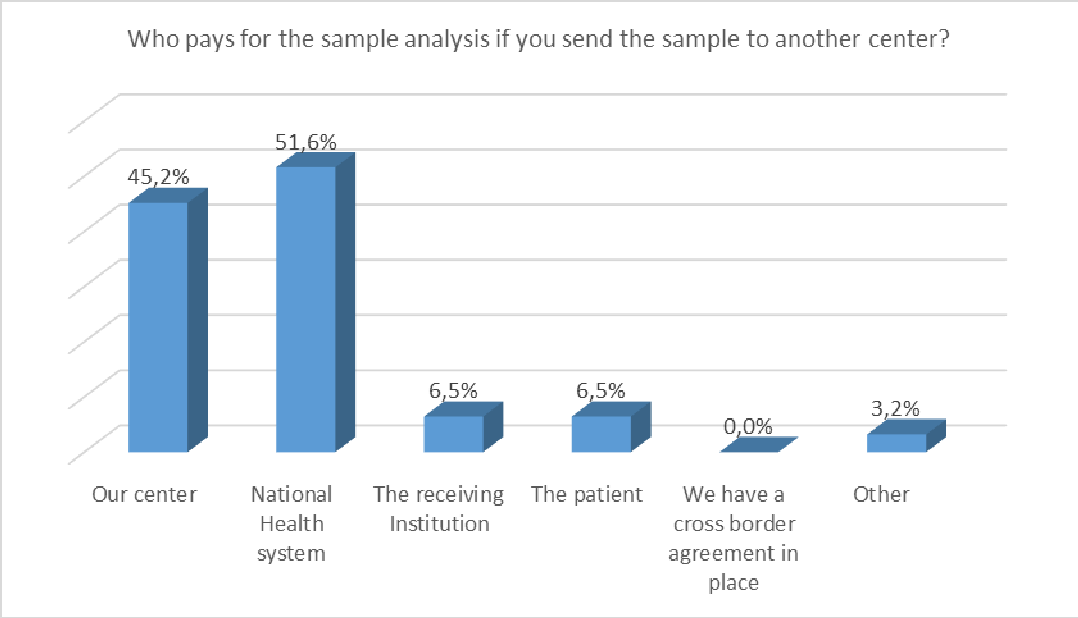

Figure 13. Distribution of answer (%) to the question "Who pays for the sample analysis if you send the sample to another centre?"

In case that NGS is performed in the Centre, a high number of centres declared to receive samples from the same country, 66,7% from other national centres and 51,5% from other regional centres. In addition, there is also a high % of centres receiving samples from abroad, 30,3% from other European centres and 39,4% from other worldwide centres. Figure 14.

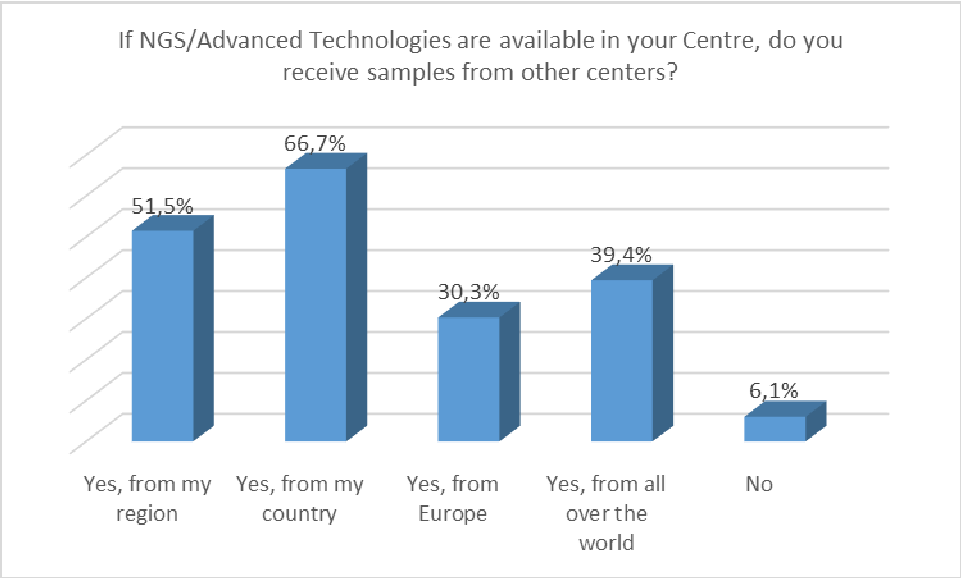

Figure 14. Distribution of answer (%) to the question "If NGS/Advanced Technologies are available in your Centre, do you receive samples from other centers?"

Mostly of samples received have diagnostics objectives (90,6%) and a high number are received on research basis (53,1%). It is higlhighted that the costs encountered when samples are received are mostly concerning to the analysis and reagents used for the procedure.

Most of the costs are covered by the receiving institutions through the research funding or with reimbursement procedures (50% and 53,1% respectively). Only one center has a cross border agreement in place for receiving samples from abroad.

4-Next steps

- Surveys were launched on 19th December 2018 and results were gathered until 10th January 2019. Accordingly, this report present preliminary results based on a first analysis of answers and number of responders. A second wave of results is expected when sharing it with the members of the non-oncological subnetworks.
- Results will be critically discussed by members in order to agree on concrete recommendations for the MS to improve access to this two HSP.
- Information gathered will provide the evidence required for facilitating shaping public health policies addressing disease specific needs in the diagnosis and/or clinical management of the patient at the national level while shedding light into the current EU status of highly specialized procedures identified of added value for the establishment of a cross-border referral system.
- Moreover, individual results will be compiled in internal document to be shared between members/responders in order to assess potential cross border agreements between medical centres for specific diseases, e.g. bone marrow transplantation for adult SCD patients.
- In this sense, a pilot project between Italy and Ireland in the framework of cross border health care to allow access to BMT for Irish patients with Sickle Cel Disease and a sibling donor was established and is soon to start patient enrolment.

Annexes

Annex I Bone Marrow Transplantation questionnaire

ERN-EuroBloodNet Questionnaire - TFA Cross Border Health Care
Non Malignant Disorders

THERAPEUTIC PROCEDURE: Bone Marrow Transplantation

Name, surname and email of the responder

Health professional role of the responder
Laboratory specialist ☐
Haematologist ☐
Paediatrician ☐
Other _____

Health professional role of the responder (list of ERN-EuroBloodNet members)

Subnetwork of expertise of the responder
Rare Red blood cell defects ☐
Bone marrow failure and hematopoietic disorders ☐
Rare bleeding-coagulation disorders and related diseases ☐
Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis ☐
Other _____

1. Do you consider Bone Marrow Transplantation (BMT) for your patients as a treatment option?
Yes, always☐ Yes, sometimes☐ No, never☐

2. For which Non Malignant Diseases do you consider BMT?
Sickle Cell Disease ☐ Inherited or acquired aplastic anemia ☐
Thalassemia ☐ Immune Deficiencies ☐
Metabolic Disorders ☐ Other ☐ _____

3. Does Your Center perform BMT?
No ☐
Yes, but only for malignant diseases ☐
Yes, but only for non malignant diseases ☐
Yes, for both malignant and non malignant diseases ☐
Yes, Adults ☐
Yes, Children ☐

3.1 If number 3 is "No", please explain
_____

4. For which Non Malignant Diseases does your center perform BMT?
Sickle Cell Disease ☐ Inherited or acquired aplastic anemia ☐
Thalassemia ☐ Immune Deficiencies ☐
Metabolic Disorders ☐ Other ☐ _____
None ☐

5.If you consider BMT for your Non Malignant patients but DO NOT have possibility to transplant them at your Center, do you refer them to another Center?

Yes, in my Regional Area	☐	No, the patients have to go by themselves to another center	☐
Yes, in my country	☐	No, I continue with other treatments at my center	☐
Yes, abroad	☐		

6.In case of referral, do you have a standardized procedure?

Yes ☐ No ☐ Not yet, but working on it ☐

7.Does the referral to another center need your institution's approval?

Yes, only endorsement letter	☐	No	☐
Yes, financial	☐	Not from my Institution but other regulatory body	☐
Yes, medical	☐	I do not know, we never considered it	☐
Yes, Ethical	☐		

8.If you had to refer a patient, weather in your country or abroad, can you briefly describe the procedure/problems that you encountered?

_____

_____

_____

Annex II. NGS/Advanced technologies questionnaire

ERN-EuroBloodNet Questionnaire - TFA Cross Border Health Care
Non Malignant Disorders

DIAGNOSTIC PROCEDURE: Next Generation Sequencing and other Advanced technologies

Name, surname and email of the responder

Health professional role of the responder
Laboratory specialist ☐
Haematologist ☐
Paediatrician ☐
Other _____

Health professional role of the responder (list of ERN-EuroBloodNet members)

Subnetwork of expertise of the responder
Rare Red blood cell defects ☐
Bone marrow failure and hematopoietic disorders ☐
Rare bleeding-coagulation disorders and related diseases ☐
Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis ☐
Other _____

1. For which Non Malignant Diseases do you request NGS/Advances technologies?
Rare Anemias ☐
Coagulation Disorders ☐
Bone Marrow Failure Syndromes ☐
Other ☐ _____
Inherited or acquired aplastic anemia ☐
Immune Deficiencies ☐

2. Which diagnostic tool do you consider?
Targeted NGS panels ☐
Whole exome sequencing ☐
Wide genome sequencing ☐
Proteomics ☐
Others ☐ _____

3. Does your center perform NGS/Advanced Technologies for Non Malignant Diseases?
No ☐
Yes, Targeted NGS panels ☐
Yes, Whole exome sequencing ☐
Yes, Wide genome sequencing ☐
Yes, Proteomics ☐
Others

3.1 If 3. yes, for which diseases?

Rare Anemias ☐
Coagulation Disorders ☐
Bone Marrow Failure Syndromes ☐
Inherited or acquired aplastic anemia ☐
Immune Deficiencies ☐
Other_____ ☐

3.2 If 3. is No, please explain why

_____

4. If not available in your Centre, do you send the samples to another Center where these techniques are available ?

No, I continue with other diagnostic approaches available at my center ☐
No, I send the patients directly to another center ☐
No, the patients have to go by themselves to another center ☐
Yes, I send the samples to a Center in my Regional Area ☐
Yes, I send the samples to a Center in my country ☐
Yes, I send the samples to a Center abroad ☐

5. In case of referral of samples, do you have a standardized procedure?

Yes ☐ No ☐
Not yet, but working on it ☐ Other_____ ☐

6. Does the referral to another center need your institution's approval?

Yes, only endorsement letter ☐ No ☐
Yes, financial ☐ Not from my Institution but other regulatory body ☐
Yes, medical ☐ (i.e.patient's local health authority)
Yes, Ethical ☐ I do not know, we never considered it ☐

7. Who pays for the sample analysis if you send the sample to another center?

Our center ☐ The patient ☐
The receiving Institution ☐ We have a cross border agreement in place ☐
National Health system ☐ Other _____ ☐

8.The analysis is performed:

For diagnosis ☐
On research basis ☐

9. If you had to refer a sample/ patient, weather in your country or abroad, can you briefly describe the procedure/problems that you encountered?

_____

_____

_____

10. If NGS/Advanced Technologies are available in your Centre, do you receive samples from other centers?

Yes, from my region ☐
Yes, from my country ☐
Yes, from Europe ☐
Yes, from all over the world ☐
No ☐

11.The analysis is performed:

For diagnosis ☐
On research basis ☐

12. If you receive samples for another centers, which costs are encountered?

Custom ☐ Sample analysis/reagents ☐ Other ☐_____

13. Who pays for these costs?

Our receiving institution with research funding ☐
Our receiving institution with reimbursement procedures ☐
The patient ☐
We have a cross border agreement in place ☐
Other ☐ _____

Annex III Contributors to Bone Marrow Transplantation questionnaire

MS	Name and surname of responder	Health professional role of the responder	Healthcare provider
BE	Yves Beguin	Haematologist	University Hospital Liège
BG	Valeria Kaleva	Haematologist	Varna Expert Center of coagulopathies and rare anemias
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FR	Mariane de Montalembert	Paediatrician	Assistance Publique-Hôpitaux de Paris, Hôpital Necker-Enfants Malades
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Annex IV Contributors to NGS/Advanced technologies questionnaire

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