



**European  
Reference  
Network**

for rare or low prevalence  
complex diseases

 **Network**  
Bone Disorders (ERN BOND)

# ERN-BOND White Paper on Diagnosis of Osteogenesis Imperfecta: Synopsis





ERNs provide key EU-added value for patients living with rare diseases in the EU, breaking down geographical barriers to diagnosis, treatment and care, and allowing knowledge to be shared across borders. ERNs also have the capacity to build a fuller picture of each rare disease, and in this respect I commend ERN-BOND's initiative to conduct surveys into HCP's knowledge and patients' experiences, starting with Osteogenesis imperfecta. Such surveys help to give valuable insights into the challenges of diagnosing individual rare diseases. Identifying the obstacles is the first step towards reducing delays to diagnosis and finding the best solutions for patient. I hope that other ERNs will be inspired by this approach.



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## ERN-BOND mission and vision

European Reference Networks (ERNs) are virtual networks involving healthcare providers across Europe. They aim to tackle complex or rare diseases as well as conditions that require highly-specialised care and expertise<sup>1</sup>. The ERN-BOND is the European Reference Network for Rare Bone Disorders<sup>2</sup>. It brings together 38 highly specialised healthcare providers from 10 EU Member States (see figure 1).

Figure 1: ERN-BOND member countries



The main objective of the ERN-BOND is to foster holistic, multidisciplinary and patient-centred care so as to ensure excellent standards of support for people living with rare bone diseases (RBDs) across Europe. To meet this goal, the ERN-BOND connects the best healthcare professionals with the best researchers, in order to improve access to cross-border medical expertise in line with Directive 2011/24/EU<sup>3</sup>.

ERN-BOND embraces continuous improvement within a patient-centered care model. With the objective of improving the care provided to people living with RBDs, the network has selected one of the most common rare bone diseases, osteogenesis imperfecta, as an area of focus. ERN-BOND will conduct a survey among healthcare professionals and patients to explore and understand the common challenges in diagnosing rare bone diseases, and provide recommendations for improving referrals, reducing diagnostic errors and shortening diagnostic delays.

## Living with osteogenesis imperfecta (OI)

Osteogenesis imperfecta, (OI, also known as brittle bone disease) is a genetic disorder which affects mainly bones. It is caused by a qualitative or quantitative defect in type I collagen, which is sometimes associated with extreme bone fragility and an increased risk of fractures<sup>4</sup>. Additional symptoms may include limb deformity, disproportionate short stature, large head size (macrocephaly), hearing loss and hindered teeth development, as well as brain and lung complications.



OI's inheritance pattern is usually autosomal dominant (approximately 85% of cases); however, rare autosomal recessive forms of OI do exist (approximately 10% of cases). In the latter case, OI is inherited from two healthy parents who are mutation carriers of an OI allele<sup>5</sup>. In Europe the prevalence of being a carrier is estimated to be between 1 in 10,000 and 1 in 20,000 people<sup>6</sup>.

OI is a debilitating disease that usually causes pain and restricts daily functioning<sup>7,8</sup>. The fractures – which can occur in some children before birth – can cause acute or chronic pain, reduced quality of life and high mental-health distress, including depression<sup>9</sup>.

For individuals with a family history of OI, early detection may be easier, given that a routine prenatal screening by ultrasound may identify it in the unborn infant, while genetic testing can usually confirm the diagnosis. Where there is no family history of OI and if a genetic abnormality remains undetected, an OI diagnosis can be made on the basis of clinical features (such as the presence of fractures); however, this may prove more difficult. Given that the detection rate is very low with lack of family history or input from a specialist, this can therefore lead to missed diagnoses and/or

diagnostic error<sup>10</sup>. In addition, no evidence-based clinical guidelines currently exist for diagnosing the disease early.

There is no cure for OI. However, there are treatments available, which are tailored depending on the severity of the disease and the age of the patient, and which can be provided through a multi-disciplinary approach. These focus on preventing and managing symptoms in order to maximise a person's mobility, as well as support bone mass and muscle development. Surgical and dental procedures are often recommended for people with OI<sup>11</sup>, in addition to physical therapy.

Optimal OI care and management requires a multi-disciplinary team that connects primary care doctors with other specialists. The paediatrics and adult multi-disciplinary team may include geneticists, orthopaedics, endocrinologists, rheumatologists, pulmonologists, neurologists, surgeons, radiologists, physiotherapists, occupational therapists and pain specialists.

<sup>1</sup> Available at: [https://ec.europa.eu/health/ern\\_en](https://ec.europa.eu/health/ern_en) (accessed 13 February 2018)

<sup>2</sup> Available at: [https://ec.europa.eu/health/sites/health/files/ern/docs/ernbond\\_factsheet\\_en.pdf](https://ec.europa.eu/health/sites/health/files/ern/docs/ernbond_factsheet_en.pdf) (accessed 13 February 2018)

<sup>3</sup> Available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:en:PDF> (accessed 13 February 2018)

<sup>4</sup> Available at: <https://www.oife.org/en/oi> (accessed 13 February 2018)

<sup>5</sup> Available at: <https://www.oife.org/en/oi> (accessed 13 February 2018)

<sup>6</sup> Available at: [http://www.orpha.net/consor/cgi-bin/Disease\\_Search.php?lng=EN&data\\_id=654&Disease\\_Disease\\_Search\\_diseaseGroup=osteogenesis-imperfecta&Disease\\_Disease\\_Search\\_diseaseType=Pat&Disease\(s\)/group%20of%20diseases=Osteogenesis-imperfecta&title=Osteogenesis-imperfecta&-search=Disease\\_Search\\_Simple](http://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=654&Disease_Disease_Search_diseaseGroup=osteogenesis-imperfecta&Disease_Disease_Search_diseaseType=Pat&Disease(s)/group%20of%20diseases=Osteogenesis-imperfecta&title=Osteogenesis-imperfecta&-search=Disease_Search_Simple) (accessed 13 February 2018)

<sup>7</sup> Available at: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2015/10/human\\_orphan\\_001626.jsp&mid=W-C0b01ac058001d12b](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2015/10/human_orphan_001626.jsp&mid=W-C0b01ac058001d12b) (accessed 13 February 2018)

<sup>8</sup> Forestier-Zhang L, Watts L, Turner A, et al (2016). Health-related quality of life and a cost-utility simulation of adults in the UK with osteogenesis imperfecta, X-linked hypophosphatemia and fibrous dysplasia. *Orphanet J Rare Dis*, 11(1):160.

<sup>9</sup> Available at: <https://icd.codes/icd10cm/Q780> (accessed 13 February 2018)

<sup>10</sup> Available at: <https://www.omicsonline.org/open-access/a-systematic-overview-of-osteogenesis-imperfecta-2168-9547-1000150.php?aid=65983> (accessed 13 February 2018)

<sup>11</sup> Alharbi SA (2016). A Systematic Overview of Osteogenesis Imperfecta. *Mol Biol*, 5:150.

# The ERN-BOND White Paper on Diagnosing Osteogenesis Imperfecta

The objective of the White Paper is to provide an overview of the current situation relating to diagnosing OI in the 10 Member States represented within the ERN-BOND. As collective experience points towards delays in detection, this paper's main aim is to identify the key challenges and potential solutions to further reduce these shortcomings, and improve the patient experience. Hence, information was collected from both patients and healthcare professionals (HCPs) through two separate questionnaires carried out between November 2017 and January 2018.

The questionnaire for HCPs was circulated among ERN-BOND members. For the dissemination of the questionnaires adapted for patients, each participating healthcare provider was asked to identify 3 patients affected with OI at differing stages of the diagnosis.

The questionnaire for HCPs included questions to:

- 1) Characterise patients
- 2) Understand the epidemiology of OI
- 3) Relay diagnostic processes
- 4) Estimate the time for a diagnosis
- 5) Identify barriers in order to make recommendations to improve the overall diagnostic pathway.

The questionnaire for patients was reviewed by the European Patient Advocacy Groups (ePAGs), nominated by the ERN-BOND, so as to ensure adequacy in language. In addition to the areas covered by the questionnaire for HCPs, it included qualitative questions on the patient's personal experience during the diagnostic process. To reach a wider patient community, the questionnaire was also translated into several European languages upon request.

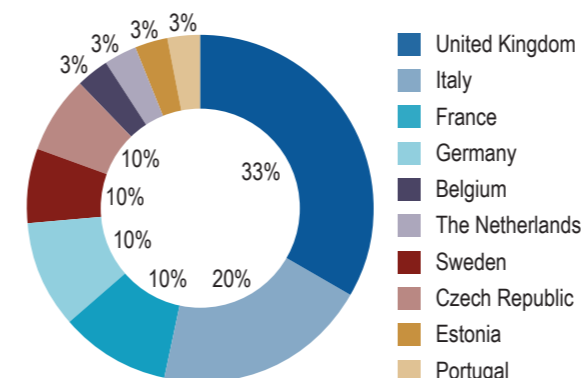
The collected data was analysed to identify key challenges in diagnosis, and compare access to the latter between and within the Member States represented by the ERN-BOND.

In line with the General Data Protection Regulation<sup>12</sup>, patients were asked to complete and return a consent form prior to having access to the questionnaire. To ensure anonymity of patient-reported data, no personal information was requested in the questionnaire.

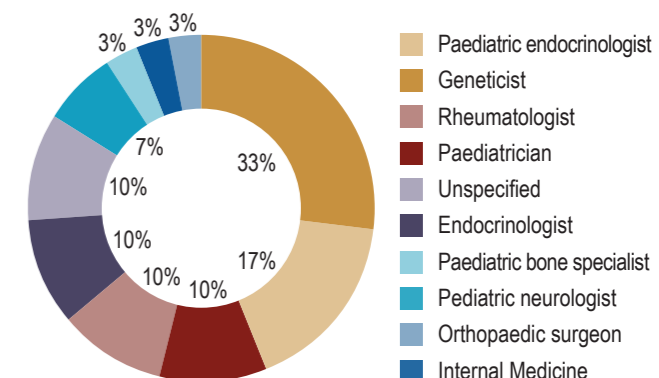
## The Sample: questionnaire for HCPs

Figure 2 shows the country affiliation of the 38 respondents who completed the questionnaire for HCPs: the majority come from the UK (33%), followed by Italy (20%), Germany (10%) and France (10%). Figure 3 denotes the area of specialty of said respondents, showing that almost half were either paediatric endocrinologists or geneticists.

**Figure 2: HCPs questionnaire – distribution of respondents among participating countries**



**Figure 3: HCPs questionnaire – area of expertise of the respondents**

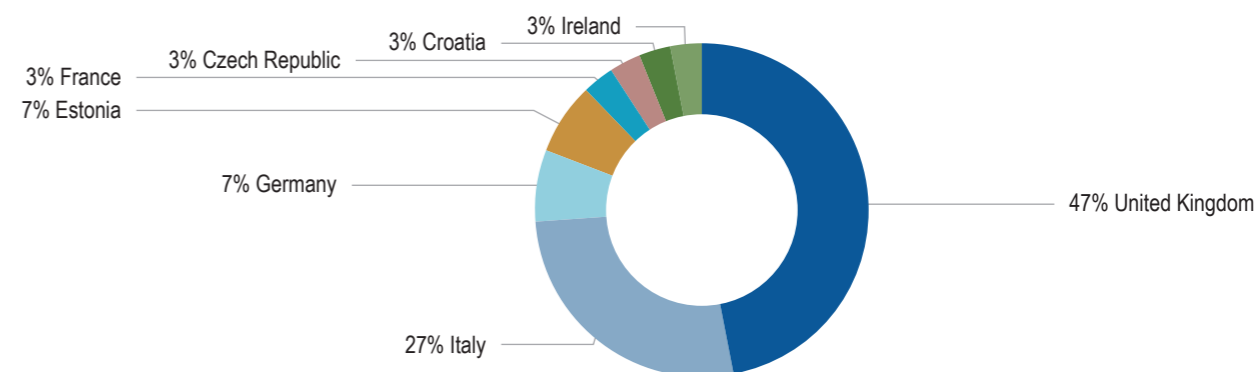


The majority of HCPs indicated that they were unaware of any incidence of OI in their country. When it comes to prevalence, respondents provided an accurate estimate (ca 0.9 in 10,000), which is slightly lower than the average European estimates (1-5 in 10,000<sup>13</sup>). However, more than 60% of HCPs suspected the presence of OI in undiagnosed patients<sup>14</sup> in their Excellence Centre. 61% of the HCPs also indicated that they confirmed the OI diagnosis in more than 50% of the cases referred.

## The Sample: questionnaire for patients

The patient questionnaire was filled in by a total of 30 individuals, of which 63% were patients and 37% were carers. As shown in Figure 4, the majority of the respondents come from the UK (47%), followed by Italy (27%), Estonia (7%) and Germany (7%).

**Figure 4: Patients questionnaire – geographical distribution of the respondents**



The age of the OI patients surveyed either directly or indirectly (via carers) varied greatly, ranging from new-borns to 71 years old. The majority of respondents (63%) said that they were not involved in a patient organisation. None of the carers indicated that they were members of an OI organisation.

<sup>12</sup> Available at: <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679&from=EN> (accessed 14 February 2018)

<sup>13</sup> Available at: [http://www.orpha.net/consor/cgi-bin/Disease\\_Search.php?lng=EN&data\\_id=654&Disease\\_Disease\\_Search\\_diseaseGroup=osteogenesis-imperfecta&Disease\\_Disease\\_Search\\_diseaseType=Pat&Disease\(s\)/group%20of%20diseases=Osteogenesis-imperfecta&title=Osteogenesis-imperfecta&search=Disease\\_Search\\_Simple](http://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=654&Disease_Disease_Search_diseaseGroup=osteogenesis-imperfecta&Disease_Disease_Search_diseaseType=Pat&Disease(s)/group%20of%20diseases=Osteogenesis-imperfecta&title=Osteogenesis-imperfecta&search=Disease_Search_Simple) (accessed 13 February 2018)

<sup>14</sup> Undiagnosed cases concern patients which are not molecularly diagnosed but suspected to have heritable bone fragility/osteogenesis imperfecta

## Epidemiology of patients with OI

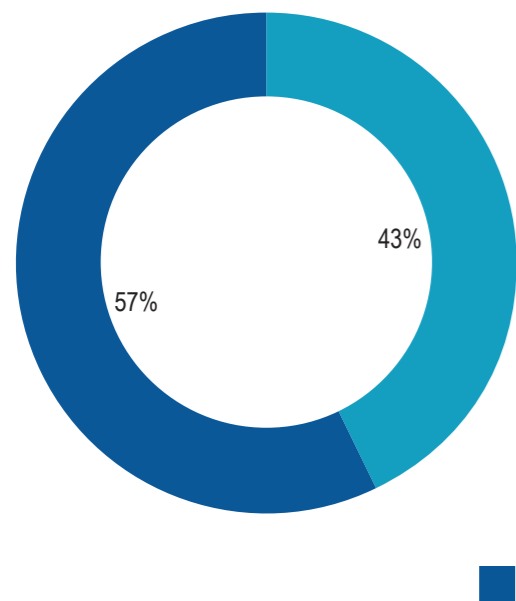
A large variety of data has been collected via the HCP questionnaire, and significant discrepancies between countries were identified. As an example, a high disparity was reported among respondents in the number of new and follow-up patients. Similarly, the number of patients with a family history of OI varied considerably, ranging from 0% to 100%. The answers also revealed that there is significantly limited knowledge of the number of newly-diagnosed patients per country. Notably, respondents from the same country showed different levels of awareness of the existence of a patient registry and provided contradictory answers. With regards to the time taken to complete the diagnosis, the average stood at under a year.



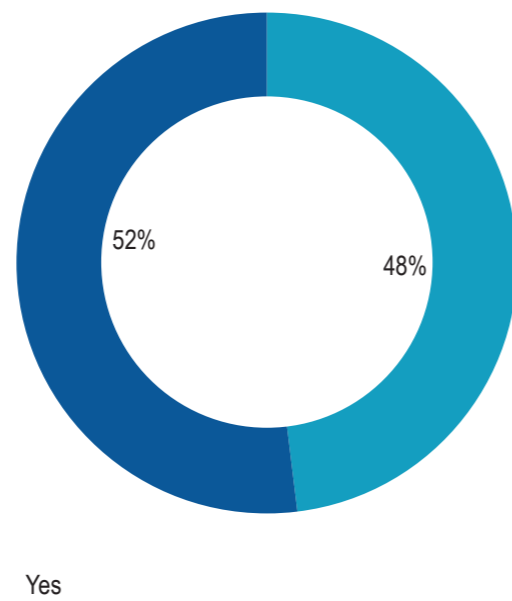
## Diagnostic tests

Healthcare professionals reported a high proportion (43%) of patients with a family history of OI (figure 5). For comparison, almost half of the patient respondents (48%) reported to have a family history of OI (figure 6).

**Figure 5: HCPs questionnaire – family history of OI**



**Figure 6: Patients questionnaire – family history of OI**

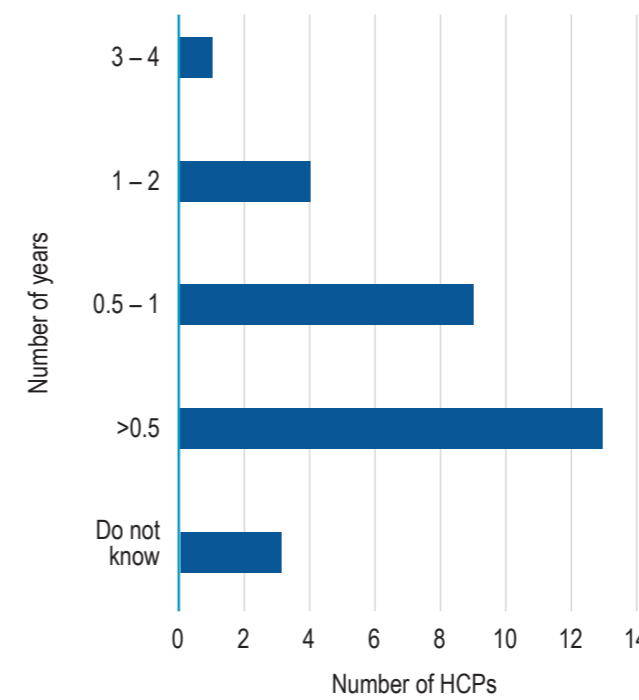


60% of patients reported that a genetic test was performed to confirm the diagnosis; they also reported that when the genetic test was not performed, it was either because it was not available in that centre or because the responsible professionals were reluctant to use it. On the HCPs side, almost half of the specialists stated that genetic testing had contributed to accelerating diagnosis. The questionnaire for HCPs also showed a high level of heterogeneity in the diagnostic and testing procedures used by the different centres across the various countries.

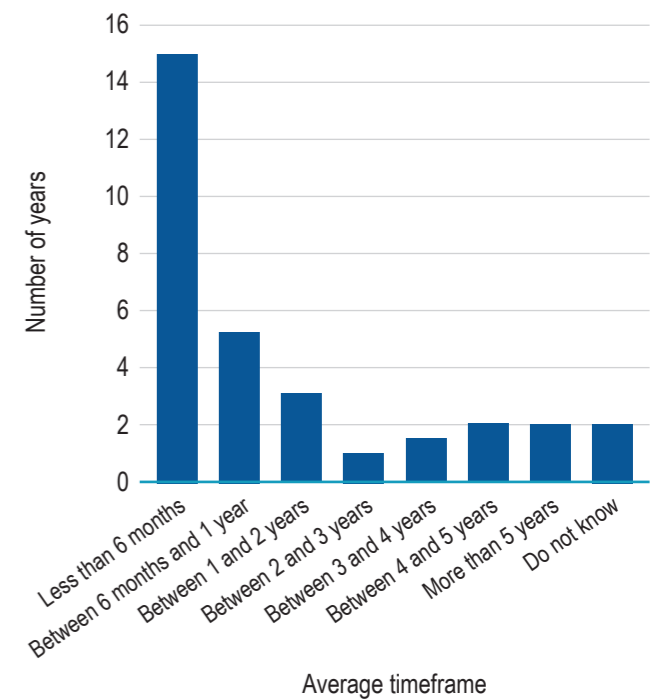
## OI diagnostic pathway

From the time of the disease's first symptoms emerging to obtaining an accurate diagnosis, the majority of both HCPs and patients indicated an average period of less than 6 months (figures 7 and 8) to confirm the diagnosis. This corresponds to less than 5 visits between primary and specialised care (figure 9). OI patients reported consulting an average of two different healthcare providers before a diagnosis was made. This denotes that, within this sample, the time taken for diagnosing OI is not as long as for other rare diseases where the process might take up to 4.8 years<sup>15</sup>. However, despite the 6-month average, a fifth of overall respondents indicated that the procedure could take up to 4 years. This lays bare the significant differences and inequalities between catchment areas and countries.

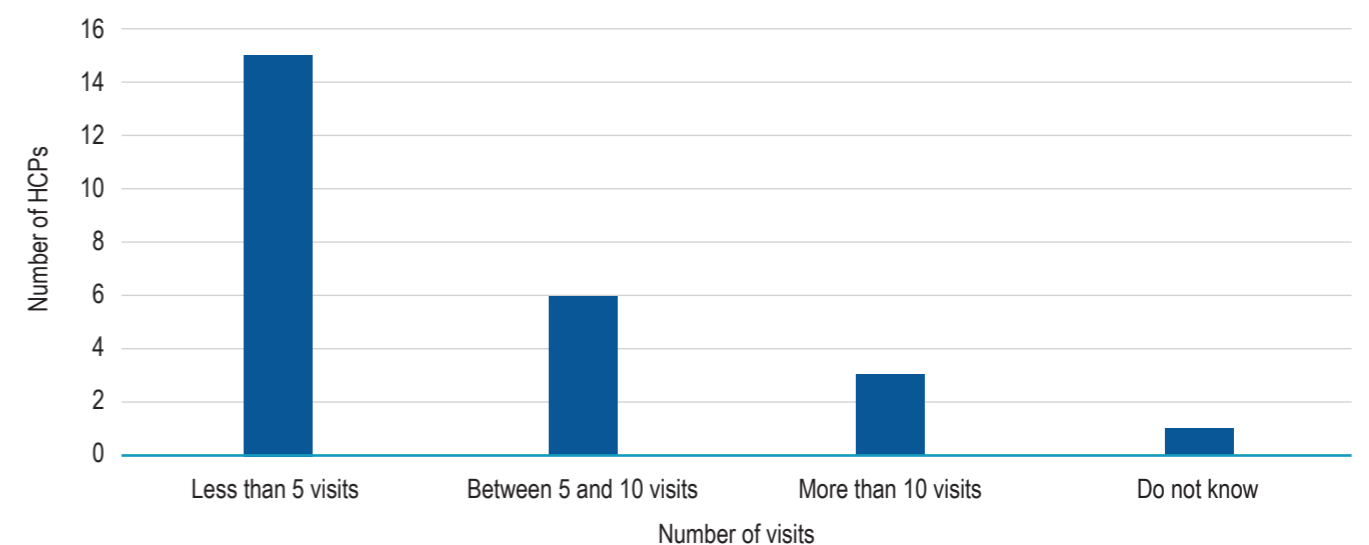
**Figure 7: HCPs questionnaire – estimated time to confirm diagnosis (in years)**



**Figure 8: Patients questionnaire – average timeframe to receive diagnosis (in years)**



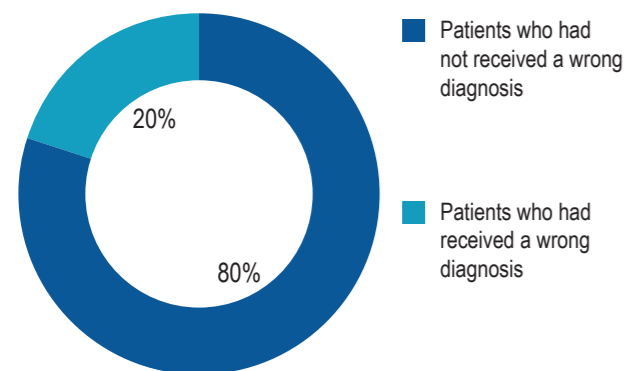
**Figure 9: Patients questionnaire – number of visits to the family doctor or emergency room before a confirmed diagnosis**



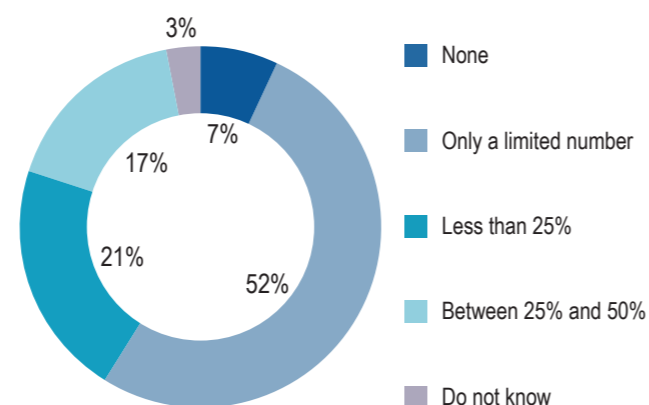
<sup>15</sup> Engel PA, Bagal S, Broback M, et al (2013). Physician and patient perceptions regarding physician training in rare diseases: the need for stronger educational initiatives for physicians. *Journal of Rare Disorders*, 1(2):1-15.

When patients were asked whether they had ever received a wrong diagnosis, 20% of them said that this was initially the case (figure 10). The majority of HCPs estimated that only a limited number of their patients had received a wrong diagnosis before being referred to their Excellence Centre (figure 11). Yet HCPs identified child abuse and osteoporosis as the most common reasons for a misdiagnosis (figure 12).

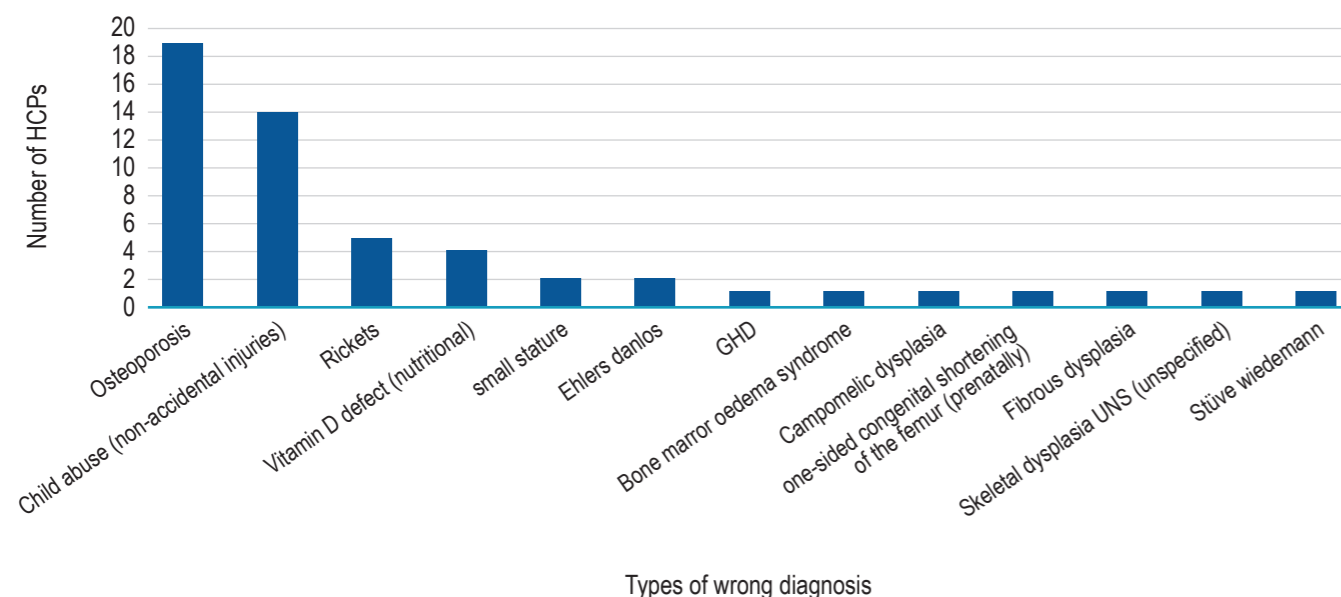
**Figure 10: Patients questionnaire – patients receiving a wrong diagnosis**



**Figure 11: HCPs questionnaire – patients with a wrong diagnosis**

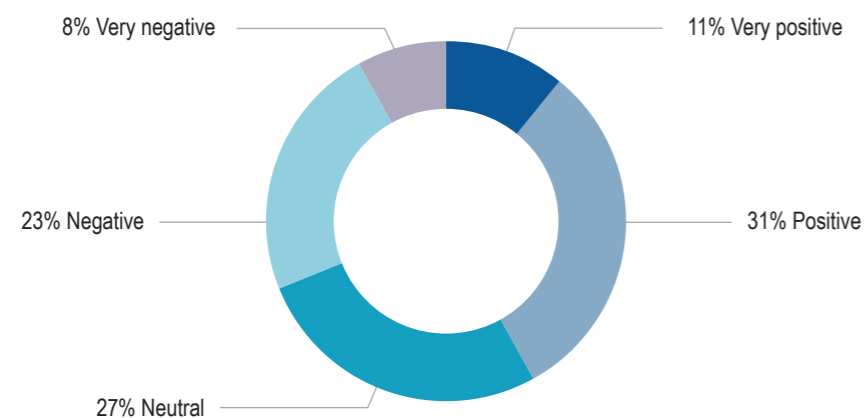


**Figure 12: HCPs questionnaire – types of wrong diagnosis**



With regards to the patient questionnaire, as shown in figure 13, the majority of respondents considered their overall experience of having OI diagnosed as either positive (42%) or neutral (27%). However, almost a third of the respondents reported a negative experience (31%).

**Figure 13: Patients questionnaire – general experience with the diagnosis**

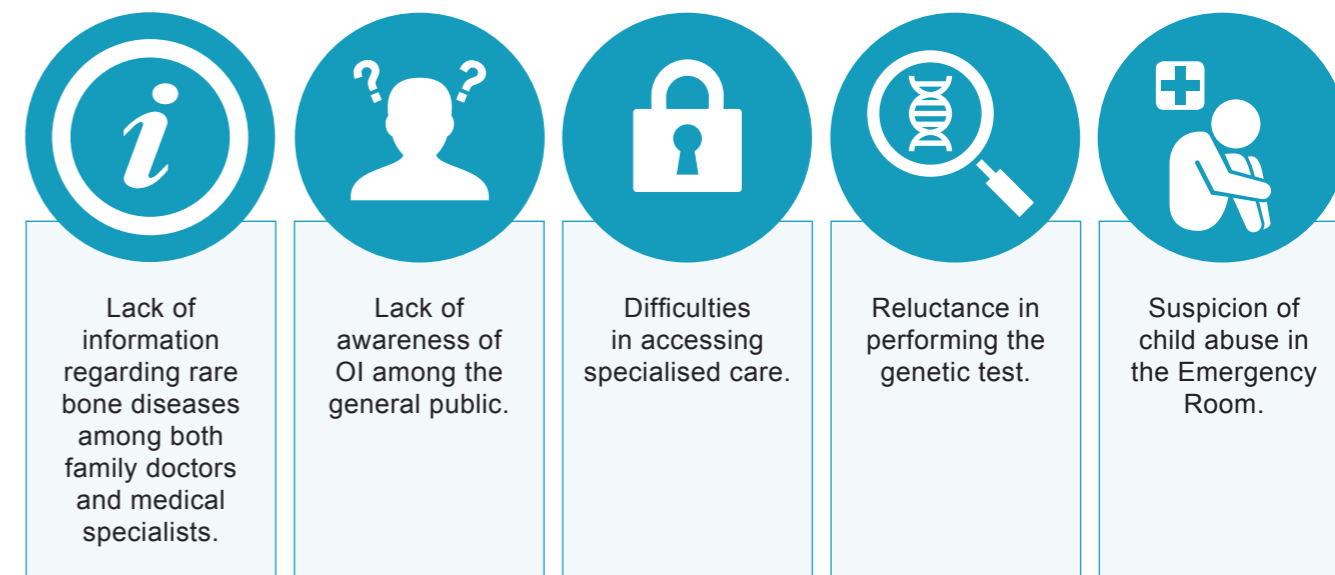


## Barriers and success factors

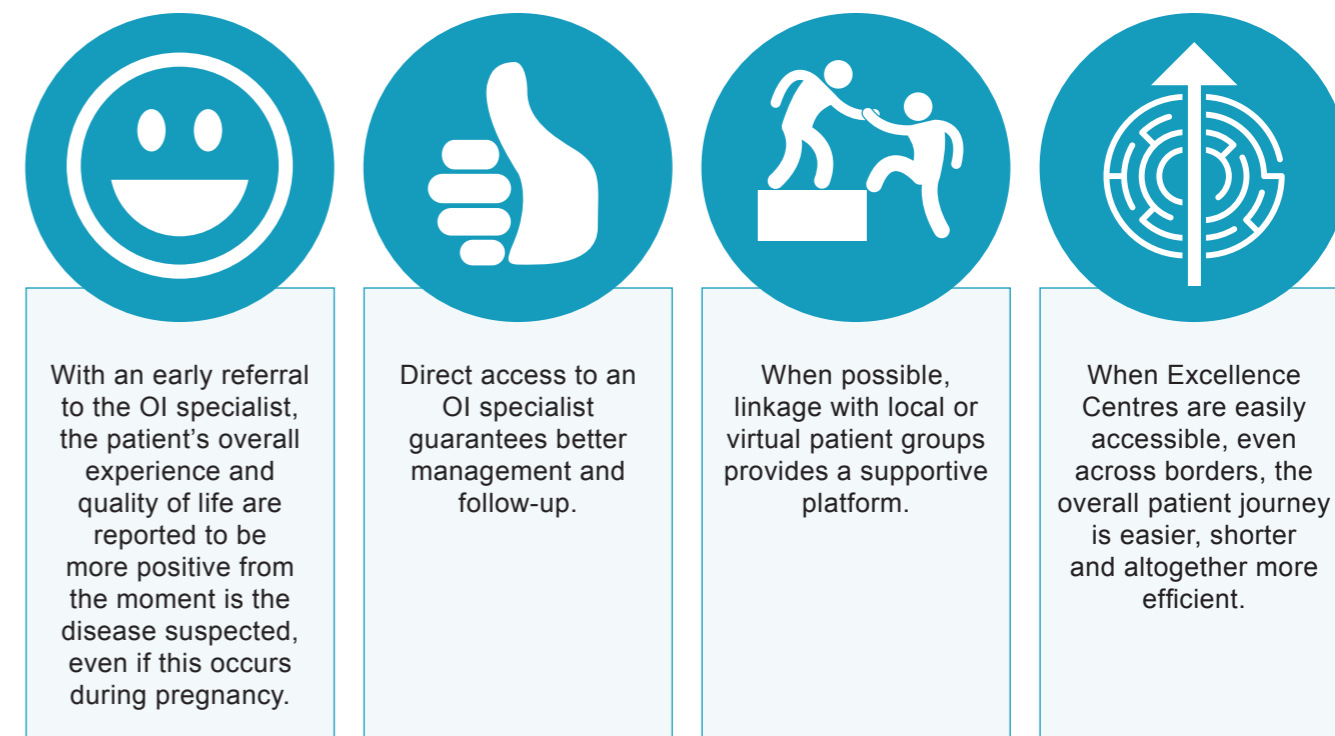


The surveys showed that patients and families, as well as physicians had limited awareness of OI. Symptoms are sometimes confused with those of child abuse, given that they are not always evident to doctors, nurses or emergency personnel who are not trained in the recognising the disease. The challenges in diagnosing OI directly impacts patients as delays can lead to inappropriate or delayed management, or even unnecessary interventions.

The barriers identified by HCPs and patients were similar:



Most of the best practice examples and success factors identified were the same for both groups, notably:

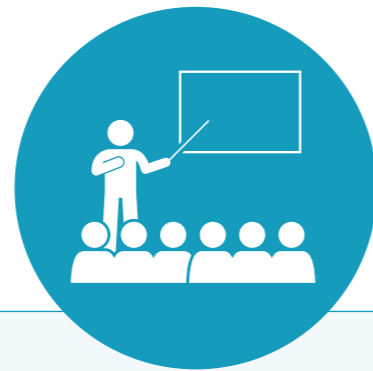


## Potential solutions

The data collected with this survey reveals that both physicians and patients agree on a need for **rapid referral to the specialised centre**, so as to ensure a **timely diagnosis of OI** and to improve care.



Since OI is often confused with other, more common diseases, including osteoporosis and child abuse, both groups underlined the importance of raising OI's awareness, especially among family doctors and emergency department healthcare professionals.



Continuous professional education for these groups, as well as for the members of the multi-disciplinary team was also identified as essential for avoiding delays in diagnosis.



Given the high heterogeneity in diagnostic procedures and testing, the majority of HCPs acknowledged that devising 'best clinical practice guidelines' for diagnosing OI could help standardise processes and address existing inequalities.



As OI is a genetic disease, performing a genetic test can help confirm the presence of the disease in the early stages of life. This would contribute towards ensuring an early diagnosis, and providing a better quality of life for patients with rare bone diseases.

## Conclusions and policy recommendations

This paper provides an overview of the state of play of OI diagnosis in the centres that participated in the survey. Even though the results do not reflect the situation in the whole of Europe, they provide important insights into existing inequalities and challenges in OI diagnosis between countries, which require further investigation.

The survey identifies areas for improvement that need a multi-stakeholder approach to increase standards and accelerate OI diagnosis, as well as accelerate the diagnosis of other rare bone diseases across Europe. Political will and support at all governance levels (local, national, European/regional and international) are seen as crucial for prioritising the following activities:



**Awareness-raising activities of rare bone diseases** among primary and emergency care practitioners, through training to identify the signs and symptoms of rare bone disorders for healthcare professionals, family doctors and emergency care practitioners, in order to improve referrals to the reference centres.



**Supporting the creation of national clinical networks connected to the Excellence Centres** in order to provide accurate diagnosis and clinical support for patients and families.



**Developing European guidelines for OI diagnosis** to facilitate rapid and accurate diagnosis through standardised procedures, and to reduce the differences between centres and countries.



**Empowering patients and their carers through strategies** to support the development of local support groups to provide them with high quality information.

## Acknowledgment of survey limitations

For the purposes of this White Paper, no differentiation was made between the types of OI, nor the degree of severity (moderate, mild and severe cases). The sample of the study presents an inherent bias since it was limited to the ERN-BOND members, who are primarily based in Western European countries. Perceptions from healthcare professionals and patients located in countries not represented by the ERN-BOND are not covered by this paper.

## Disclaimer

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*Funded by the European Union's Health Programme (2014-2020).*





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