The Economist INTELLIGENCE UNIT

Leaving the darkness, seeing the light:

A focus on people living with rare bone diseases

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About this briefing paper

Leaving the darkness, seeing the light: A focus on people living with rare bone diseases is an Economist Intelligence Unit briefing paper, sponsored by Ipsen, a global pharmaceutical company. This independent research covers rare bone diseases and the patient experience in the US and Europe with policy lessons for healthcare professionals and policymakers. Review of the evidence in the literature and interviews with representatives of clinical practice and patient organisations were undertaken to help inform our research and this report. Our thanks are due to the following for their time and insights (listed alphabetically):

- Inês Alves, founder and president, ANDO (National Patient Organization for Skeletal Dysplasia), patient expert and representative, European Reference Network for Rare Bone disorders (ERN BOND), EuRR-Bone registry member and chair of the European Rare Bone Forum, Portugal
- Natasha Appelman-Dijkstra, clinical scientist and head at the Center for Bone Quality, Leiden University Medical Centre, Netherlands
- Eric Rush, associate professor of paediatrics, University of Missouri-Kansas City School of Medicine; clinical geneticist, Children's Mercy Kansas City, US
- Laura Tosi, director, Bone Health Program at Children's National Hospital, Washington DC, US
- Charlene Waldman, director, Rare Bone Disease Alliance, US

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Executive summary

Approximately 5% of all rare diseases are rare bone diseases.[1,2] And while there are more than 460 officially recognised rare bone diseases, each with different manifestations, the majority of patients will ultimately need complex, multi-disciplinary care and lifelong management that can include therapies and surgeries.[3] For many of these, there is no known treatment.

In addition to the clinical complications, rare bone diseases are often plainly evident in the person's stature, appearance and mobility. The symptoms are often debilitating, distressing and painful. The impact of rare bone diseases therefore extends quite significantly into psychological, social, financial and economic areas.[4,5]

To bring light to the challenges faced by people living with rare bone diseases, their caregivers and the healthcare professionals that support them, The Economist Intelligence Unit embarked on a study to better understand the patient perspective and the factors that impact it.

Our research found there is much work to be done to improve the care pathways for people living with rare bone diseases and their caregivers. While there is diversity in symptoms and lifelong impact among rare bone diseases, there are common lessons for policymakers about the patient and caregiver experience in accessing appropriate healthcare and support.

Issues of note include:

- There are few clinical experts managing rare bone diseases, and access to specialist clinics can be challenging in the US and Europe.
- Education and support resources for clinicians, patients and their families are increasing, but more research needs to be undertaken, and lessons learned could increase patients' quality of life and care.
- Great advances are being made in understanding the pathogenesis of rare bone diseases and their treatments, but disseminating information to patients where needed is an ongoing challenge.
- Patient registries are numerous but disjointed. Strong efforts are being made in Europe to create a shared registry, while similar efforts under way in North America are so far less successful.
- There is a significant emphasis on paediatric research and clinical care, which is critically important. However, as patients eventually transition into adulthood they are often left without direction from experts managing their condition.
- There are currently no cures for rare bone diseases and very few have targeted treatments, however, there have been great therapeutic advances in recent years and more are on the horizon. This is underpinned by developments in genetic diagnosis and greater understanding of the mechanisms involved in bone function and development.

[1] Sabir AH, Cole T. The evolving therapeutic landscape of genetic skeletal disorders. Orphanet Journal of Rare Diseases. 2019;14(1):300. Published 2019 December 30th. doi:10.1186/s13023-019-1222-2

[2] Eekhoff EMW, Micha D, Forouzanfar T, et al. Collaboration Around Rare Bone Diseases Leads to the Unique Organizational Incentive of the Amsterdam Bone Center. *Front Endocrinol (Lausanne).* 2020;11:481. Published 2020 August 11th. doi:10.3389/fendo.2020.00481

[3] Tosi LL, Rajah EN, Stewart MH, Gillies AP, Hart TS, Lewiecki EM. The Rare Bone Disease TeleECHO Program: Leveraging Telehealth to Improve Rare Bone Disease Care. *Curr Osteoporos Rep.* 2020;18(4):344-349. doi:10.1007/s11914-020-00595-2

[4] Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development; Field MJ, Boat TF, editors. Rare Diseases and Orphan Products: Accelerating Research and Development. Washington (DC): National Academies Press (US); 2010. 2, Profile of Rare Diseases. Available from: https://www.ncbi.nlm.nih.gov/books/NBK56184/

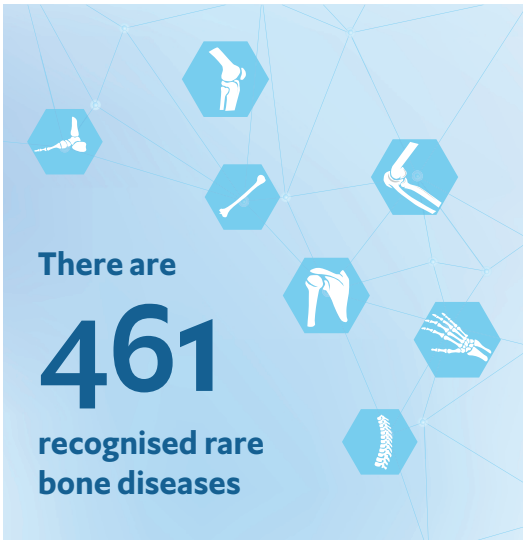
[5] Office of the Surgeon General (US). Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville (MD): Office of the Surgeon General (US); 2004. 5, The Burden of Bone Disease. Available from: https://www.ncbi.nlm.nih.gov/books/NBK45502/

Chapter 1: Falling through the gaps: challenges for patients and their caregivers

There are 461 recognised rare bone diseases that can affect cartilage and other soft tissues, bones and teeth.[6,7] Diagnosed individuals will present in different ways that can require complex and multidisciplinary care.

Different though the specific diseases may be, there are some common threads in the experience of patients and caregivers as they navigate their lives, their clinical care and lifelong management of their condition.

The Economist Intelligence Unit interviewed rare bone disease clinical experts and patient groups to better understand the underlying themes that can affect a patient's and family's experience. The results range from timely diagnosis—impacting the tailoring of appropriate care—to international co-operation of research groups in order to further progress the quality of treatment and care.



What is a rare disease?

- In the US, a rare disease is defined as one that affects fewer than 200,000 people in the US at any given time.[8]
- The EU defines rare diseases as conditions that affect fewer than 5 people per 10,000 people, but many are much rarer.[9]

[6] The Rare Bone Disease TeleECHO Program: Leveraging Telehealth to Improve Rare Bone Disease Care. https://link.springer.com/article/10.1007/s11914-020-00595-2

[7] Prado HV, Carneiro NCR, Perazzo MF et al. Assessing a possible vulnerability to dental caries in individuals with rare genetic diseases that affect the skeletal development. *Orphanet J Rare Dis* 14, 145 (2019). https://doi.org/10.1186/s13023-019-1114-5

[8] National Human Genome Research Project. https://www.genome.gov/FAQ/Rare-Diseases

[9] European Commission. https://ec.europa.eu/health/non_communicable_diseases/rare_diseases

Rare bone diseases at a glance

- About 5% of rare diseases are rare bone diseases—affecting millions of patients worldwide.[10]
- They fall into four general categories (see Appendix for examples).
- Incidence can vary from around 15.7 per 100,000 births for a "common" rare disease like skeletal dysplasias to "ultra-rare" disorders for which only a few known patients exist worldwide, such as spondylo-ocular syndrome.[11]
- One of the more common rare bone diseases is osteogenesis imperfecta (OI), which appears in about 1 in every 30,000 live births.[12] OI is a group of rare bone diseases that manifests clinically with increased fracture rate, bone fragility and a range of non-skeletal defects.
- Rare bone diseases have few personalised treatments.[13]

Diagnostic delays declining, but still too common

Rare diseases in general are notoriously difficult to diagnose.[14,15] Although some rare bone diseases can be apparent from birth, others begin to show signs over time, sometimes in early childhood and some as late as in the teenage years. In fact, some patients with a milder phenotype don't present until adulthood. Regardless, a later diagnosis can, in some cases, also delay appropriate care and treatment to avoid harm.[16]

The earliest diagnoses tend to come from within families with a known specific rare bone disease—the hereditary disease hypophosphatemic rickets, associated with muscle weakness, short stature, skeletal deformities and bone pain, is one example.[17] Families that have one or several members diagnosed with the disease are more likely to recognise the signs and symptoms immediately when the next affected child is born.

When patients do not have a hereditary disease, or are first in the family to have it, a timely diagnosis can be more challenging. The first line of contact is often family physicians,

[10] Sabir AH, Cole T. The evolving therapeutic landscape of genetic skeletal disorders. *Orphanet Journal of Rare Diseases*. 2019;14(1):300. Published December 30th 2019. doi:10.1186/s13023-019-1222-2

[11] Eekhoff EMW, Micha D, Forouzanfar T, et al. Collaboration Around Rare Bone Diseases Leads to the Unique Organizational Incentive of the Amsterdam Bone Center. *Front Endocrinol (Lausanne)*. 2020;11:481. Published August 11th 2020. doi:10.3389/fendo.2020.00481

[12] NORD. Osteogenesis Imperfecta. https://rarediseases.org/rare-diseases/osteogenesis-imperfecta

[13] Sabir AH, Cole T. The evolving therapeutic landscape of genetic skeletal disorders. *Orphanet Journal of Rare Diseases*. 2019;14(1):300. Published December 30th 2019. doi:10.1186/s13023-019-1222-2

[14] Rare Disease UK. Rare Disease Impact Report: Insights from patients and the medical community. Published January 2016. https://globalgenes.org/wp-content/uploads/2013/04/ShireReport-1.pdf

[15] Świdrowska-Jaros J, Smolewska E. A complicated path to the CRMO diagnosis - case of a 9 year old girl whose story comes full circle. *BMC Musculoskelet Disord*. 2019;20(1):392. Published Aug 31st 2019. doi:10.1186/s12891-019-2776-9

[16] Skrabl-Baumgartner A, Singer P, Greimel T, Gorkiewicz G, Hermann J. Chronic non-bacterial osteomyelitis: a comparative study between children and adults. *Pediatric Rheumatology Online Journal*. 2019;17(1):49. Published July 23rd 2019. doi:10.1186/s12969-019-0353-2

[17] NORD. Familial Hypophosphatemia. https://rarediseases.org/rare-diseases/familial-hypophosphatemia.

Symptoms like swelling of the joints and fractures can be confused with other, more common diseases, and even misdiagnosed as child abuse

who are not trained in, or comfortable with, counselling patients in this area.[18] The patient's symptoms may also not be recognisable as a bone disease. Symptoms like swelling of the joints and fractures can be confused with other, more common diseases, and even misdiagnosed as child abuse.[19] In addition, systemic pain from the disease tends to underline the experience for many patients and their caregivers.[20]

Thus, rare bone diseases are often only correctly identified after a referral to a specialist centre. Even so, most specialists will not see many of the over 460 known rare bone diseases in their lifetime of practice. This makes it difficult for them to correctly diagnose a new bone disease when it is first encountered with a X-ray or magnetic resonance imaging (MRI). That's why many specialists use genetic testing to confirm a suspected diagnosis. Once a rare bone disease is correctly identified, the patient's care can be tailored.

According to Dr Laura Tosi, director of the Bone Health Program at Children's National Hospital in Washington DC, US, "if you can identify the genetic causes of a disorder, oftentimes you can have an extraordinary opportunity to change the individual's therapeutic course and outcome."

Unfortunately, genetic testing in some countries, such as the US, is not always easy to secure. According to Eric Rush, a clinical geneticist at Children's Mercy Kansas City in the US, "a lot of times rare disease diagnostic pathways can be a real bottleneck because there's over 300 million Americans, and less than 1,000 clinical geneticists are currently believed to practice in the US ." Furthermore, insurance companies don't like the cost, [21,22] although he argues that it's not that expensive and more cost-effective than combining the other tests needed to reach a diagnosis (eg, X-rays, MRIs), which often lead to genetic testing for confirmation anyway. "The best thing we can do is help open that doorway to [genetic] testing," he says.

Against this backdrop, clinicians say that they see a heterogeneous group of patients with an early or late diagnosis. Some of the more "common" forms of rare bone diseases like

[18] Lewiecki EM, Bilezikian JP, Bukata SV, et al. Proceedings of the 2016 Santa Fe Bone Symposium: New Concepts in the Management of Osteoporosis and Metabolic Bone Diseases. *Journal of Clinical Densitometry.* 2017;20(2):134-152. doi:10.1016/j.jocd.2017.01.001

[19] Paterson CR. Bone disease and fractures in early childhood. Child Abuse: Indicators, Psychological Impact and Prevention. 2012.

[20] Shore EM, Pacifici M. JBMRPlus: Special Issue on Rare Bone Diseases 2019. *JBMR Plus.* 2019;3(8):e10218. Published August 9th 2019. doi:10.1002/jbm4.10218

[21] Handfield R, Feldstein J. Insurance companies' perspectives on the orphan drug pipeline. American Health & Drug Benefits. 2013;6(9):589-598.

[22] Gong S, Jin S. Current progress in the management of rare diseases and orphan drugs in China. *Intractable & Rare Diseases Research.* 2012;1(2):45-52. doi:10.5582/irdr.2012.v1.2.45

osteogenesis imperfecta (OI), also known as brittle bone disease, where patients experience increased fractures, bone fragility and other non-skeletal issues, have an average diagnosis time of less than 6 months from the first symptom, according to the European Reference Network for Rare Bone disorders (ERN BOND). However, a fifth of people studied living with OI indicated that it took up to four years for a diagnosis—suggesting significant differences and inequalities between the patients' access to specialist care.[23]

Fortunately, late diagnosis, although still very much an issue, is less common than it used to be, according to interviewees. But when it does occur, it can hugely impede a patient's quality of life. Misdiagnosis could also lead directly to harmful procedures in some people living with rare bone diseases.

"We do occasionally see adult age patients with a new diagnosis, for instance, for osteogenesis imperfecta, because they have a milder form," explains Natasha Appelman-Dijkstra, head of the Center for Bone Quality at Leiden University Medical Centre in the Netherlands. "They usually thought, and everybody told them, that they were very active as a child and that's why they broke bones so often." However, she notes that by the time some patients are seen as adults, such as those with Fibrous Dysplasia or Mc Cune Albright syndrome, some physical deformities from their fractures cannot be easily repaired.

"Sometimes, even in adulthood, they come to us with a complication from a lesion and we have to tell them that they have lesions elsewhere. This is why we endeavour to reduce diagnostic delays." She adds that, once diagnosed, a follow-up is vital, as it will help patients to cope with their disease much better through targeted, customised treatment plans.

Uneven access to care

Access to specialised care can vary significantly by country, where people living with a rare bone disease can experience financial and geographic challenges.[24,25]

In the US, the type of insurance a patient holds (private or public) can impact the level of care afforded. And navigating different insurance approvals presents another series of hurdles, as some insured patients in the US can often

[23] European Reference Network. ERN-BOND White Paper on Diagnosis of Osteogenesis Imperfecta: Synopsis. 2019.

[24] Office of the Surgeon General (US). Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville (MD): Office of the Surgeon General (US); 2004.

[25] Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development; Field MJ, Boat TF, editors. Rare Diseases and Orphan Products: Accelerating Research and Development. Washington (DC): National Academies Press (US); 2010. 2, Profile of Rare Diseases. Available from: https://www.ncbi.nlm.nih.gov/books/NBK56184/

be covered for some treatments but not others.

Charlene Waldman, director of the Rare Bone Disease Alliance in the US, says that, in her experience, many patients deal with this on an ongoing basis. "If a patient runs into that problem, then they have to hope that their physician or another member of staff is willing to spend time on the phone with the insurance company to explain and campaign for the necessary treatments." She adds that patient organisations have also played an important role in contacting insurance companies on behalf of patients and progressing what treatments and testing can be more readily approved.

In Europe, populations can have diverse private health insurance plans, but public, national and universal healthcare systems are also widely available. This system helps contrast the US's funding issue around access to surgical or pharmacological therapies. Although access to certain therapies can also be an issue. For example, patient access to orphan medicines is highly varied across Europe.[26,27]

Yet geographic barriers more often arise as the main barrier to care. Inês Alves, founder and president of ANDO Portugal, the National Patient Organization for Skeletal Dysplasias says that "Europe has a huge and broad diversity of care and practices regarding care of patients with rare bone diseases." She explains that some European countries have several specialist centres with good infrastructure and high expertise to diagnose patients and provide follow up care and evaluation, while others do not.

Yet even where specialist centres exist, there is usually poor access to specialised emergency care. For example, a 2020 study found that children living with rare bone diseases, whether medically complex or not, raised multiple issues in emergency situations.[28] The study highlights that children with genetic diseases in general account for a significant number of paediatric hospital admissions, their stays tend to be longer and more expensive, and they are also more likely to be associated with a non-planned repeat visit within 30 days. It concludes that there is room for improvement in the healthcare provided by paediatric emergency centres.

[26] Zamora B, Maignen F, O'Neill P, Mestre-Ferrandiz J, Garau M. Comparing access to orphan medicinal products in Europe. *Orphanet Journal of Rare Diseases*. 2019;14(1):95. Published May 3rd 2019. doi:10.1186/s13023-019-1078-5
[27] Szegedi M, Zelei T, Arickx F, et al. The European challenges of funding orphan medicinal products. *Orphanet Journal of Rare Diseases*. 2018;13(1):184. Published November 6th 2018. doi:10.1186/s13023-018-0927-y
[28] Yang, D., Baujat, G., Neuraz, A. et al. Healthcare trajectory of children with rare bone disease attending pediatric emergency departments. *Orphanet J Rare Dis* 15, 2. Published January 3rd 2020. doi:10.1186/s13023-019-1284-1
https://ojrd.biomedcentral.com/articles/10.1186/s13023-019-1284-1

Even when medical care for patients living with a rare bone disease is good, it is often divorced from the psychological support that patients and their caregivers need

Emotional support gaps

Psychological and mental health support is another area needing attention. Even when medical care for patients living with a rare bone disease is good, it is often divorced from the psychological support that patients and their caregivers need.

Researchers have found that the quality of life of people living with rare bone diseases (children and adults) and their families is lower compared with the general population.[29,30,31] There is also a correlation between the lowest quality of life findings and patients living with more severe forms of rare bone diseases.

"It's really important to give psychological support to parents and close family because it's something that impacts them deeply. It's not just about rare bone diseases and the clinical care needs, it's all about quality of living and understanding the real life impact, because people do not expect or know how to manage it," says Ms Alves.

"Patients and families can feel really lonely," explains Ms Waldman. Indeed, research has found that rare chronic conditions have a substantial impact on caregivers.[32] "They feel like nobody knows what they're talking about because other family members and friends have never heard of the condition. They just don't understand." This is why patient support groups play an important role in their lives, as similar experiences can be shared with other families, which is "extremely important and helpful", she says.

Experts further agree that patients and families can greatly benefit from more information and resources that can help them take a more active role in their care. Patients often become their own advocates and specialists on their disease, and more information helps empower them. "We know that if people have active coping strategies, they perform way better than when they have passive coping strategies. So you need to improve coping and illness perceptions

[29] Witt S, Kolb B, Bloemeke J, et al. Quality of life of children with achondroplasia and their parents - a German cross-sectional study. *Orphanet Journal of Rare Diseases* 14(1). December 2019. doi: 10.1186/s13023-019-1171-9

[30] Majoor BCJ, Andela CD, Bruggemann J, et al. Determinants of impaired quality of life in patients with fibrous dysplasia. *Orphanet J Rare Dis*. 2017;12(1):80. Published April 27th 2017. doi:10.1186/s13023-017-0629-x

https://ojrd.biomedcentral.com/articles/10.1186/s13023-017-0629-x

[31] Rush ET, Moseley S, Petryk A. Burden of disease in pediatric patients with hypophosphatasia: results from the HPP Impact Patient Survey and the HPP Outcomes Study Telephone interview. *Orphanet J Rare Dis*. 2019;14(1):201. Published August 16th 2019. doi:10.1186/s13023-019-1167-5

[32] EURORDIS. Juggling care and daily life - The balancing act of the rare disease community - A Rare Barometer survey. May 2017.

... this will improve the quality of life of your patients," says Dr Appelman-Dijkstra.

Poor transition from paediatric to adult care

Another area overshadowing management of these diseases is the recognised challenge of transitioning from paediatric to adult care.[33] In fact, this is a recognised issue across most rare diseases.[34,35] And research suggests that poor (or a lack of) transition programmes can result in increased morbidity, increased hospitalisations, decreased hospital attendance and discontinuity of care.

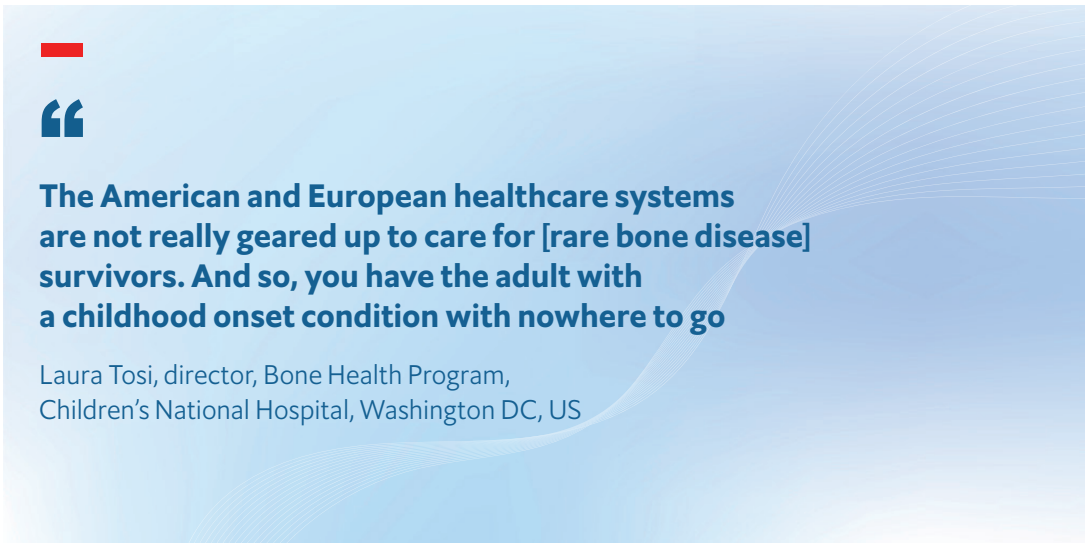
Rare bone diseases are no exception. Research, care and protocols all place significant emphasis on childhood, where paediatric patients can obtain quality care and regular monitoring. However, once children grow up there are very few dedicated centres that continue to provide continued, specialised care.[36,37]

Experts say good rare bone paediatric centres facilitate integrated care for patients, even including psychological and family support, but there are few such dedicated centres for adults. Patients are likely to become "lost in the system" and unable to find trained clinicians to help them manage their condition or face problems when they arise.

"It's like entering a void or a black hole," says Ms Alves. "They are not forgotten by the system, but they are not properly taken into account. Adults with rare bone diseases are seen as regular adults, not as adults with continuous special needs."

"The American and European healthcare systems are not really geared up to care for [rare bone disease] survivors. And so, you have the adult with a childhood onset condition with nowhere to go," adds Dr Tosi.

There are some reasons for this strong paediatric focus: rare bone diseases can



[33] Dogba MJ, Rauch F, Wong T, et al. From pediatric to adult care: strategic evaluation of a transition program for patients with osteogenesis imperfecta. *BMC Health Serv Res* 14, 489 (2014). https://doi.org/10.1186/s12913-014-0489-1
[34] De Castro M, Turner C, Kirmse B. Practical recommendations for the transition to adulthood for the adolescent with a genetic diagnosis. Special emphasis on inborn errors of metabolism. *Translational Science of Rare Diseases* 4 (2019) 159–168. Published April 13th 2020. doi: 10.3233/TRD-190042
[35] Rare Disease UK. Patient experiences of transition between care providers. https://www.raredisease.org.uk/media/1590/patient-experiences-of-transition-between-care-providers.pdf
[36] Dogba MJ, Rauch F, Wong T, et al. From pediatric to adult care: strategic evaluation of a transition program for patients with osteogenesis imperfecta. *BMC Health Serv Res* 14, 489 (2014). https://doi.org/10.1186/s12913-014-0489-1
[37] McDonagh JE, Robinson AJ. Growing up: the role of the Royal College of Physicians. Clin Med (Lond). 2012;12(3):197-199. doi:10.7861/clinmedicine.12-3-197

hinder growth and development, so children often need more regular, closer clinical monitoring and can suffer more complex situations as they grow.[38] The paediatric focus can also be explained by the natural history: as life expectancy of patients with rare bone diseases is now on the rise, some of these conditions are new to adult treaters.[39]

But demand for specialised care from adult patients themselves can sometimes be low and ad hoc, and therefore challenging to manage. "When they turn 18, they become responsible for making and keeping their own appointments, so it's easier for them not to show up," explains Dr Appelman-Dijkstra. Quite often, she says, adult patients don't see the point of attending follow-up appointments and undergoing additional tests, as healthcare professionals often just monitor the condition once they have stopped growing. "Besides all this, they are tired of being treated as a special patient and want to be normal."

Nevertheless, adult care is hugely important and deeply underserved: episodic needs arise and without management by a multidisciplinary team of clinicians (which can include surgeons and reproductive care experts and other specialists)[40,41] a lower standard of care could be inadvertently provided in primary care. Thanks to scientific progress and understanding of the disease, people with rare bone diseases are also living longer, meaning they are more likely to encounter health problems and chronic conditions that can be exacerbated by their underlying disease.

Experts say that most adult patients reach out to clinicians when they have become desperate, for example, when the pain becomes unbearable or they start seeing complications. Ms Alves explains "they may have worsening symptoms because many general clinicians do not know what to do with the patients, which can lead to flaws and

Most adult patients reach out to clinicians when they have become desperate, for example, when the pain becomes unbearable or they start seeing complications

[38] Children's National. Pediatric Skeletal Dysplasias. https://childrensnational.org/visit/conditions-and-treatments/bones-joints-orthopaedics/skeletal-dysplasias
[39] Innovation District. Giving voice to adult osteogenesis imperfecta patients. Published August 14th 2017. https://innovationdistrict.childrensnational.org/giving-voice-adult-osteogenesis-imperfecta-patients/
[40] Vivanti AJ, Cordier A-G, Baujat G, Benachi A. (2016). Abnormal pelvic morphology and high cervical length are responsible for high-risk pregnancies in women displaying achondroplasia. *Orphanet Journal of Rare Diseases*. 11, 166. Published May 27th 2020. doi:10.1186/s13023-016-0529-5.
[41] Zhytnik L, Simm K, Salumets A, et al. Reproductive options for families at risk of Osteogenesis Imperfecta: a review. *Orphanet Journal of Rare Diseases*. 15, 128. Published May 27th 2020. doi: 10.1186/s13023-020-01404-w
https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01404-w

poor outcomes. When they finally see the healthcare provider, they may be so advanced with their chronic disease or a complication related to their rare bone disease, that it may be too late."

Resource allocations for rare bone diseases

In terms of resources dedicated towards rare bone diseases—research, therapies, clinical centres, protocols, education, integrated services—the consensus seems to be that significant progress has been noted in the past decade and led to notable improvements in patient wellbeing.[42] But there is much more to do.

Limited treatments and cures

To date, only a handful of rare bone diseases have a specific medical treatment, while surgery may be required for many conditions.

Nevertheless, in the past decade there has been significant progress on the therapeutic front that has coincided with advances in the understanding of the genetic and molecular influences of rare bone diseases.[43] This has led to the conclusion that the mechanism of many rare bone diseases may be modified with pharmaceutical or other interventions.[44,45]

According to Dr Tosi, "in terms of sheer numbers, OI is the disorder that has seen some of the most significant improvements in quality of life over the last two decades.

Specifically, bisphosphonates combined with expanding metal rods that can be inserted into long bones have reduced fracture rates and allowed children to walk who have some of the most severe forms of disease." Other novel and developing therapies are showing promise for targeting rare bone diseases as well.[46]

For example, fibrodysplasia ossificans progressiva (FOP) is an ultra-rare, life-shortening and painful bone disease caused by a mutation in the gene's receptors signalling abnormal messages that cause excess bone formation.[47] Although there is no cure in sight, thanks to the identification of the gene responsible research efforts are continuing.[48]

The potential to effectively treat rare bone diseases[49] creates interest among life sciences companies and draws funding.

However, according to the International Rare Diseases Research Consortium, about 1% of rare disease research projects by medical domain cover rare bone diseases.[50]

Despite an increasing interest in rare bone diseases, the reality is that only a small

[42] Sabir AH, Cole T. The evolving therapeutic landscape of genetic skeletal disorders. *Orphanet Journal of Rare Diseases*. 2019;14(1):300. Published December 30th 2020. doi:10.1186/s13023-019-1222-2

[43] Bacon S, Crowley R. Developments in rare bone diseases and mineral disorders. *Therapeutic Advances in Chronic Disease*.

2018;9(1):51-60. doi:10.1177/2040622317739538

[44] Sabir AH, Cole T. The evolving therapeutic landscape of genetic skeletal disorders. *Orphanet Journal of Rare Diseases*. 2019;14(1):300. Published December 30th 2019. doi:10.1186/s13023-019-1222-2

[45] Cappato S, Giacopelli F, Ravazzolo R, Bocciardi R. The Horizon of a Therapy for Rare Genetic Diseases: A "Druggable" Future for Fibrodysplasia Ossificans Progressiva. *International Journal of Molecular Sciences*. 2018;19(4):989. Published March 26th 2018. doi:10.3390/ijms19040989

[46] Sabir AH, Cole T. The evolving therapeutic landscape of genetic skeletal disorders. Orphanet Journal of Rare Diseases. 2019;14(1):300. Published December 30th 2019. doi:10.1186/s13023-019-1222-2

[47] Ibid

[48] Cappato S, Giacopelli F, Ravazzolo R, Bocciardi R. The Horizon of a Therapy for Rare Genetic Diseases: A "Druggable" Future for Fibrodysplasia Ossificans Progressiva. International Journal of Molecular Sciences. 2018;19(4):989. Published March 26th 2018. doi

[49] Kwon D. The Scientist. How Orphan Drugs Became a Highly Profitable Industry. 2018 April 30. https://www.the-scientist.com/features/how-orphan-drugs-became-a-highly-profitable-industry-64278

[50] International Rare Diseases Research Consortium. State of Play of Research in the Field of Rare Diseases: 2015-2018. https://irdirc.org/wp-content/uploads/2019/09/IRDiRC_State-of-Play-2018_Final.pdf

percentage of such disorders have available targeted therapeutics, explains Dr Rush.

Additionally, experts interviewed say ongoing pharmaceutical research seems to be largely centred on paediatrics. There could be a few reasons for this: growth and development are most profoundly impacted by bone health during childhood, and treatment in this stage can change natural history and, in some cases, early treatment can ease challenges later in adulthood.[51,52]

Osteogenesis imperfecta (OI)

Often referred to as brittle bone disease, OI is the most common category of rare bone disease. It is a disorder that largely impacts the bone's connective tissue and its symptoms generally include low bone mass, increased bone fragility, bone deformity and growth deficiency. OI has a prevalence of 1 per 20,000 live births. Currently, intravenous and orally administered bisphosphonates are the main form of treatment.[53,54]

Fibrodysplasia ossificans progressiva (FOP)

FOP is ultra rare and sometimes called the most catastrophic bone disorder. It transforms soft tissue to bone and joints become locked into place over the course of a person's life. This ultimately limits movement and can lead to a person being trapped in a position (often, a person's jaw bones become locked up causing trouble with eating and speaking).

It affects an estimated 1-2 per million people, making it exceptionally difficult for doctors, researchers and patient groups to find and connect with patients.[55]

However, the FOP international registry now tracks over 300 people across 64 countries.[56,57] While there is no cure, drugs are currently used to relieve pain and swelling associated with flare-ups.[58]

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[51] Haffner D, Emma F, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nature Reviews Nephrology.* 2019;15(7):435-455. doi:10.1038/s41581-019-0152-5

[52] Overview of Bone Disorders in Children. Oct 2020. https://www.msdmanuals.com/home/children-s-health-issues/bone-disorders-in-children/overview-of-bone-disorders-in-children

[53] Bacon S, Crowley R. Developments in rare bone diseases and mineral disorders. *Therapeutic Advances in Chronic Disease.*

2018;9(1):51-60. doi:10.1177/2040622317739538

[54] NHS. Great Ormond Street Hospital for Children. Osteogenesis imperfecta. https://www.gosh.nhs.uk/conditions-and-treatments/conditions-we-treat/osteogenesis-imperfecta

[55] Sabir AH, Cole T. The evolving therapeutic landscape of genetic skeletal disorders. *Orphanet Journal of Rare Diseases*. 2019;14(1):300. Published December 30th 2019. doi:10.1186/s13023-019-1222-2

[56] Ibid

[57] 2019 FOP Registry Annual Report.

[58] NORD. Fibrodysplasia Ossificans Progressiva. https://rarediseases.org/rare-diseases/fibrodysplasia-ossificans-progressiva/

Registries need standardisation

With 461 identified rare bone diseases, or skeletal dysplasias, the need for registries is important to support better understanding of the natural progression of these conditions.

Experts say the knowledge gap is particularly true for patients as they age, even for conditions where there is good understanding. "A lot of our knowledge is really geared towards the paediatrics side of things. And as it turns out, most of us will spend the majority of our lives as adults," says Dr Rush.

Thus it becomes even more important to understand the adult manifestations of these conditions and other aspects of the ageing process. For example, some ageing patients with certain rare bone diseases may develop severe arthritis or bone density changes, increasing their risk of fractures.[59,60]

Registries also help with understanding the impact of therapies over time. "We need to be able to share information about natural histories with one another," explains Dr Rush. "We want to know what happens to a patient with a brittle bone disease that's been receiving medication for 18 years. What do they look like when they're 40? We can guess but that's not a good way to do things, that's why we really need those registries."

Registries for rare bone diseases exist in both Europe and the US, but at varying degrees of maturity and usefulness. In the EU, the European rare bone registry was set up in 2019 and formally started in 2020.[61] It's EU funded and many European countries are contributing data. It also allows patients to submit data on their natural history of living with the disease.

"Registries are much more popular nowadays. And it's much easier to build them from a technical point of view," says Dr Appelman-Dijkstra, who helps run the European registry for rare bone conditions.

Europe's registry is expected to be increasingly helpful in supporting research into rare bone diseases. "With registries, it's easier to do observational studies and prospective cohort studies," says Dr Appelman-Dijkstra.

In the US, however, there has been less progress, and the country does not have a good national registry for rare bone diseases. Instead, there are many small proprietary registries, some of which are better funded and more robust than others—making it difficult to combine data for research. "They're very different," confirms Ms Waldman. "Some you could say are more scientific. Some are just like a big database. But if an organisation uses its registry properly it can be extremely helpful."

Efforts are under way in the US to support the development of disease-specific registries. In 2019, the US's National Institutes of Health (NIH) set up a website with tools to help advocacy organisations to set up and maintain registries.[62,63,64] "These are good programmes,

[59] Masi L, Agnusdei D, Bilezikian, J et al. Taxonomy of rare genetic metabolic bone disorders. International Osteoporosis Foundation (IOF). 2015.https://www.iofbonehealth.org/osteoporosis-musculoskeletal-disorders/skeletal-rare-disorders

[60] Mickute G, Staley K, Delaney H. et al. Rare musculoskeletal diseases in adults: a research priority setting partnership with the James Lind Alliance. *Orphanet Journal of Rare Diseases*. 15, 117. Published May 19th 2020. doi:10.1186/s13023-020-01398-5

[61] Launch of EuRR-Bone. https://oife.org/2020/06/10/launch-of-eurr-bone/

[62] Agency Unveils RaDaR to Help Patient Groups Develop Rare Disease Registries. https://fragilexnewstoday.com/2019/05/28/radar-help-patient-groups-develop-rare-disease-registries/

[63] RaDaR Rare Disease Registry Programme. https://registries.ncats.nih.gov/

[64] Rare Diseases Registry Programme (RaDaR). https://ncats.nih.gov/radar

but they will need years to produce compelling data," says Dr Tosi.

Where possible, clinicians also say they want single global registries rather than many small ones that each capture only a few patients. One good example is the global registry by the International FOP Association.[65] This has led to broad consensus on methods for FOP's diagnosis, interventions, the prevention of flare-ups and family-centred care. However, as one study concludes, regional preferences still exist, as does regional access to recommended care pathways.[66]

Guidelines and protocols are works in progress

It should not come as a surprise that, given the lack of knowledge of the natural histories of rare bone diseases, guidelines and protocols are also sparse, especially for adult patients.[67,68]

Protocols and guidelines, our experts say, are fairly good for managing patients diagnosed young and monitored through childhood. But when the diagnosis comes later, and certainly when patients reach adulthood, then management might be difficult. Often there are zero protocols, and the few that do exist are fragmented and not detailed.

Dr Rush explains that the US's lack of formal protocols is largely a by-product of not having a formal national healthcare system like European countries typically have. This lack of consistency could lead to uneven quality of care, but he notes that impromptu collaborations have nevertheless aligned best practices.

"If you want to write treatment guidelines for a rare bone disease, you find experts that you've worked with before and build these ad hoc networks to create the guidelines. You publish them and hope that people will adopt them and hopefully they are useful for patients. It's not ideal. But it's kind of how we do it."

Another underlying problem is that guidelines need to be updated to keep up with the pace of change. Treatments are changing and, as people are reaching an older age, so are the diseases' natural histories.

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[65] FOP Registry. https://www.ifopa.org/fopregistry

[66] Di Rocco M, Baujat G, Bertamino M, et al. International physician survey on management of FOP: a modified Delphi study. *Orphanet Journal of Rare Diseases*. 2017;12(1):110. Published June 12th 2017. doi:10.1186/s13023-017-0659-4

[67] White KK, Bober MB, Cho TJ, et al. Best practice guidelines for management of spinal disorders in skeletal dysplasia. *Orphanet Journal of Rare Diseases*. 2020;15(1):161. Published June 24th 2020. doi:10.1186/s13023-020-01415-7

[68] Tosi LL, Oetgen ME, Floor MK, et al. Initial report of the osteogenesis imperfecta adult natural history initiative. ***Orphanet Journal of Rare Diseases***. 2015;10:146. Published November 14th 2015. doi:10.1186/s13023-015-0362-2

Chapter 2: Progress in the patient and caregiver experience

Healthcare professionals and rare bone disease advocates are trying to find ways to improve the quality of care of people living with these conditions through improved genetic testing, faster diagnosis, digital tools, and a leap in knowledge and education.

Progress is not universal, but in some areas, and in some medical centres, observers can see positive trends taking root. In this chapter, we highlight progress in the way that patients, caregivers and clinicians learn and practice in order to tackle the challenges laid out in the previous chapter.

Multidisciplinary care recommendations

In the field of rare bone diseases, multidisciplinary clinical care and research efforts are increasingly being called for.[69, 70, 71]

While a person living with a rare bone disease may be often be medically viewed through the lens of bone health, their care will ultimately involve other clinical experts. Having an extensive, collaborative network of specialists and researchers helps clinicians keep abreast of various advances in specific fields that can support a patient's management and care.

To illustrate the complexity of these conditions, in some cases a patient's care requires extensive networking and integrated care with experts in a number of other clinical specialities, including: plastic, orthopaedic and thoracic surgery; traumatology; urology; ear, nose and throat surgery; audiology; ophthalmology; dietetics; cardiology; pulmonology; neurology; neurosurgery; dermatology; radiotherapy; gastroenterology; endocrinology; rheumatology; dentistry; rehabilitation; and psychiatric and social support.[72]

Networks of specialist physicians and researchers are rare. One such example is the Amsterdam Bone Center, which created a "collaborative organisational model" in 2016. A 2020 report on the centre's progress says it has led to many research advances including the development of new clinical trials, innovative diagnostics and improved patient care.[73]

In Switzerland, an interdisciplinary consultation team was set up in 2012 to support the management of patients and families with OI. So far it has proved useful in improving physical activity and mental health, continuity of care, and families' understanding of patients' health.[74]

Multidisciplinary centres can also address other access to care issues that adult patients often face. Dr Tosi says: "Many patients need special equipment just to get physically

[69] Rush ET, Childhood hypophosphatasia: to treat or not to treat. *Orphanet Journal of Rare Diseases*. 2018;13(1):116. Published July 16th 2018. doi:10.1186/s13023-018-0866-7

[70] Tosi LL, Rajah EN, Stewart MH, Gillies AP, Hart TS, Lewiecki EM. The Rare Bone Disease TeleECHO Program: Leveraging Telehealth to Improve Rare Bone Disease Care. Curr Osteoporos Rep. 2020;18(4):344-349. doi:10.1007/s11914-020-00595-2

[71] Eekhoff EMW, Micha D, Forouzanfar T, et al. Collaboration Around Rare Bone Diseases Leads to the Unique Organizational Incentive of the Amsterdam Bone Center. *Front Endocrinol* (Lausanne). 2020;11:481. Published August 11th 2020. doi:10.3389/fendo.2020.00481

[72] Ibid

[73] Ibid

[74] Aubry-Rozier B, Richard C, Unger S, et al. Osteogenesis imperfecta: towards an individualised interdisciplinary care strategy to improve physical activity and quality of life. Swiss Medical Weekly. 2020;150:w20285. Published July 6th 2020. doi:10.4414/smw.2020.20285

into the office. Some women may need special examination tables if they're going to have appropriate gynaecological exams, and so forth." While it is unlikely that a multidisciplinary care centre or team can provide all of the services that adults need, they can serve as a trusted resource that directs patients to appropriate, safe care for their condition.

In the US there are some examples of strong multidisciplinary models, such as the Mayo Clinic's Children's Center.[75] But Dr Rush would like to see more. He imagines a gold standard for care of patients with rare bone diseases that would be akin to the US's cancer care programmes, which are more holistic and less challenging for patients and families to navigate.

Bridging the transition from paediatric to adult care

Clinicians are well aware of the problem that patients with chronic diseases face when transitioning from paediatrics to adulthood.[76] In fact, all clinicians we spoke with are taking younger and older patients to help bridge the gap, although each acknowledge they are bending the rules to do so.

Dr Appelman-Dijkstra, for example, is a clinician who cares for adult patients but is increasingly seeing younger patients especially in the years of and just prior to adult transition. "In some cases, they start to see me from the age of 12 with the pediatrician. This helps because before they grow up they already know me, so it's really easy for them to then come to my [adult] outpatient clinic alone."

Dr Tosi, a paediatric orthopaedic surgeon, follows her patients orthopaedic needs into adulthood when asked. "Even though technically we're a paediatric hospital and you can't come in after you're 22 years of age, our age policy allows us to still see long-term patients into adulthood, although primarily for outpatient services. I know of only few places where this is common practice but I think this is a good way to do it."

She adds: "I can help patients stay independent by insuring help with wheelchairs, braces, physical therapy orders, and more. I also serve as a resource to assist in finding more specialised, truly adult services when needed."

And Dr Rush makes it a point to see both children and adults. "It's a particular training path that's not common in other countries, and there's not a ton of us in the US either. But I did this training very consciously because I knew I wanted to take care of patients across their lifespan, because I didn't really like that idea of having to give up those patients at some point in the future … It's a nice thing for me, and I don't have to sneak patients in very much."

All agree that this is part of a much wider trend. And, collectively, these admissions signal the start of a movement towards better integration and collaboration between specialised caretakers.

[75] Mayo Clinic. Pediatric Metabolic Bone Disorders Clinic. https://www.mayoclinic.org/departments-centers/childrens-center/overview/specialty-groups/pediatric-metabolic-bone-disorders-clinic

[76] Dogba MJ, Rauch F, Wong T, Ruck J, Glorieux FH, Bedos C. From pediatric to adult care: strategic evaluation of a transition program for patients with osteogenesis imperfecta. *BMC Health Services Research*. 2014;14:489. Published October 31st 2014. doi:10.1186/s12913-014-0489-1

Faster diagnosis with genetic testing

Patient advocates argue that if doctors spent additional time learning about bone diseases in medical schools then patient outcomes and quality of life would improve through faster referral to specialists and ultimately to faster diagnosis.

This is not to suggest that already overburdened primary care physicians should have detailed knowledge on rare bone diseases and how to diagnose them. Rather, as Dr Appelman-Dijkstra puts it, it would be helpful if all doctors in medical school were educated to a level where they could detect when something is "off" about their patients' bones.

"Ideally, I think that doctors need to have more knowledge about calcium and phosphate and bone metabolism. Because when they know what's normal, you don't need to know exactly what the name is of the abnormal thing that you're observing," she says. "They can be taught to think about bone health in a broader sense."

And once an abnormality is suspected, patients and family physicians both agree that rapid referral to specialists is needed for more timely diagnosis and improved care. Too often, patients go from specialist to specialist before a diagnosis is reached.[77]

Delays in genetic testing continue to hinder the last mile to diagnosis, but there are signs of change. Dr Rush says his hospital is one of several in the US that is working to expand access and reduce genetic testing delays from several years to under one year. "We're looking to bend the curve by not only bringing expertise in the right place at the right time, but also bringing comprehensive genetic testing to the right place at the right time."

Expanding patient education resources

Another important area that needs addressing is the role of patient groups in the rare bone disease space. Patient groups often are experts on a given disease and can help drive research and understanding of the patient perspective. Their networks also help improve the availability of information that patients and caregivers can use to understand and manage their condition.

In opposition to the US, there are numerous languages spoken in Europe and patient groups play an important role in providing information at the national level and in different languages. This way, patients and their caregivers, regardless of where they live, can be empowered with knowledge about their condition. A good starting point for

[77] European Reference Network. ERN-BOND White Paper on Diagnosis of Osteogenesis Imperfecta: Synopsis. 2019.

patient information is Orphanet,[78] a France-based website supported by the European Commission, which provides information about orphan drugs and rare diseases for patients and physicians in multiple languages. But Ms Alves says many patients want more detailed information about their condition, and for that they need access to relevant scientific journals and publications. This, she says, helps patients and caregivers to feel more empowered and engaged, boosting literacy around their condition.[79]

"Many patient organisations also collect relevant scientific and medical information, do summaries and translate it for patient information into different languages," says Ms Alves. "Yet, the majority of scientific publications are not open access which limits information. Also, there are several studies on rare bone diseases being conducted by different entities, that are not compliant with the FAIR principles, where data is Findable, Accessible, Interoperable and Reusable," she says, adding that this could avoid having patient's information and data duplicated in different studies or small registries or in none at all.

Educational leaps among specialists

When asked what patients' clinicians can do to better improve their quality of life, there was a clear consensus: "Education, education, education," says Ms Waldman. "It's a big, broad answer, and it's what those of us in this field have been working on for many years."

Because rare bone disease research is moving quickly—medicines are advancing, natural histories changing, and new best practices constantly being explored—it can be a challenge to keep up. Specialists acknowledge that constant education is central to progression in this field.

Dr Rush says he tries to keep up with the literature. "I'm always trying to read. I try to get through at least one journal every day. I don't always get there but I try because, honestly, that's the only way I found that I can really keep up with my specialty."

And all interviewees agree that digital tech has helped revolutionise access to clinical education on rare bone diseases. Dr Tosi says "Zoom has changed our opportunities to educate people who are eager to learn. Online sessions are expanding at a rapid pace."

For example, during the covid-19 pandemic, online attendance to meetings and conferences exploded. The American Society for Bone and Mineral Research annual meeting, which usually sees around 200 live attendees, saw many more unique users when the 2020 meeting switched to digital due to covid-19.

The Rare Bone Disease TeleECHO programme, launched in 2019 and described as a monthly video teleconference that "fosters a collegial community of practice and opportunities for active learning through interactive case-based learning", also saw high attendance.[80]

Dr Tosi, who is also involved in TeleECHO, says "it's clear that there's a growing, shared belief that we should strive to be sure that all patients get the best possible and most up-

[78] Orphanet. https://www.orpha.net/consor/cgi-bin/index.php

[79] COST Action BM1105, Badiu C, Bonomi M, et al. Developing and evaluating rare disease educational materials co-created by expert clinicians and patients: the paradigm of congenital hypogonadotropic hypogonadism. *Orphanet Journal of Rare Diseases.* 2017;12(1):57. Published March 20th 2017. doi:10.1186/s13023-017-0608-2

[80] Tosi LL, Rajah EN, Stewart MH, Gillies AP, Hart TS, Lewiecki EM. The Rare Bone Disease TeleECHO Program: Leveraging Telehealth to Improve Rare Bone Disease Care. *Curr Osteoporos Rep.* 2020;18(4):344-349. doi:10.1007/s11914-020-00595-2

to-date care. No matter where you live, your doctor should be able to be as well trained and as tuned in as someone at the world's leading universities."

Additionally, during the covid-19 outbreak, the European Reference Network on Rare Bone Diseases (ERN BOND) co-ordinated with 78 experts on rare bone diseases, representing 38 specialised centres and four European Patient Advocacy Groups from ten European states, to create the COVID-19 Helpline for Rare Bone Diseases. This hotline is intended to provide expert information remotely to patients and healthcare professionals.[81] Patients (and their families) make up 80% of logged calls and their questions centre more around drug treatments, while clinician calls (which make up the remaining 20%) are often about invasive procedures and abnormal anatomy due to bone deformities.

Digital transformation and patient care

Many people living with a rare bone disease have compromised immune systems, and can be more susceptible to covid-19.[82, 83] Thus, many have been hesitant to make in-person doctor appointments and risk exposure. Specialists, who are also working from home when feasible, have therefore largely switched to telephone or online appointments where possible.

"A large part of the disabled community has not left their home since March 2020," says Dr Tosi. "Such extreme isolation can be demoralising. Luckily many advocacy groups and others have stepped up and leveraged Zoom and other social media platforms to help bring people together virtually. Virtual platforms have allowed an explosion of

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Laura Tosi, director, Bone Health Program, Children's National Hospital, Washington DC, US

[81] Brizola E, Adami G, Baroncelli GI, et al. Providing high-quality care remotely to patients with rare bone diseases during COVID-19 pandemic. *Orphanet Journal of Rare Diseases*. 2020;15(1). 228. https://doi.org/10.1186/s13023-020-01513-6 https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01513-6

[82] Algaecal. The Role of the Immune System in Bone Loss. 2020. https://www.algaecal.com/expert-insights/immune-system-and-bone-loss/

[83] Mori G, D'Amelio P, Faccio R, Brunetti G. The Interplay between the bone and the immune system. *Clinical and Developmental Immunology*. 2013;2013:720504. doi:10.1155/2013/720504

education, sharing, and support opportunities for individuals who feel cut off."

Videoconferencing has indeed changed the way specialists are engaging with patients. Dr Appelman-Dijkstra, for instance, has largely switched to remote care during the pandemic. She says some of advantages include seeing how a patient's home is set up to give insight on how they may be coping with their illness. It also makes it easier to include a family member or caregiver in the conversation. Videoconferencing can act as a complementary service to existing face-to-face consultations or with patients known to the clinician. However, for new patients "it's hard to do remote care if you've never seen them."

For invasive medical tasks such as blood tests, they rely on a local GP to perform these. "When we get the blood tests, we have a specific feature with our videoconferencing where we can share the screen and go over it with them," says Dr Appelman-Dijkstra. She also uses slides to educate patients on hereditary factors of the disease and what they need to know to ensure their medication is working. "It just makes you more flexible."

Clinicians agree that this has been a successful trial. After covid-19 concerns cease, rare bone disease clinicians interviewed—ranging from surgical specialists to clinical genetics specialists—say they and their peers will probably continue to see their known patients online when possible.

Patients drive priorities for unmet research needs

With so little relative research in the rare bone disease space, and so many unanswered questions, there has been a move to try and align research priorities with patient priorities.[84]

A prime example of this is the UK's James Lind Alliance (JLA), which set out to identify the top ten research priorities for rare bone diseases in adulthood in 2018. The priorities were identified and developed jointly by patients, caregivers and healthcare professionals. The goal, according to the JLA report, is to

With so little relative research in the rare bone disease space, and so many unanswered questions, there has been a move to try and align research priorities with patient priorities

[84] Swezey T, Reeve BB, Hart TS, et al. Incorporating the patient perspective in the study of rare bone disease: insights from the osteogenesis imperfecta community. *Osteoporosis International*. 2019;30(2):507-511. doi:10.1007/s00198-018-4690-7

encourage researchers, funding bodies and other stakeholders to use these priorities in guiding future research for those affected by rare musculoskeletal disorders.[85]

The results of JLA's research are laid out in Figure 1. They show an overarching need to better understand the progression, treatment and management of these diseases in adulthood. Many of the questions appear almost simplistic, shedding a light on some obvious gaps in research.

In general, clinicians are very positive about patient-driven research programmes and agendas. "All of my good research questions have resulted from me not knowing the answer to a question asked by a patient," says Dr Rush. "I'll ask my network and if they don't know either, it becomes a point of research. So the patients will almost inherently drive clinical research based on questions that we can't answer."

Dr Appelman-Dijkstra agrees. "In the end, the patient is the one with the disease. So we have to make sure that everything we do research on will ultimately benefit the patient. I'm absolutely in favour of these kinds of developments."

Figure 1: Rare bone diseases in adults: patient research priorities
Based on a survey of 198 patients with rare bone disease, their caregivers, health and social care professionals, and representatives of patient organisations.[86]

1. Treatment What is considered a good outcome of treatment in rare bone metabolic disorders? How can this be measured in studies of new treatments?	**6. Treatment** What are the best forms of surgery to treat bones and joints in people with rare metabolic bone disorders?
2. Prognosis What is the cause of pain in people with rare metabolic bone disorders?	**7. Treatment** What are the benefits and side effects of drug treatment for people with rare metabolic bone disorders in the short and long term? What is the optimal length of treatment?
3. Support and care What is the psychological impact of having a rare bone disorder and how can patients and their families be best supported?	**8. Prognosis** How do rare metabolic bone disorders progress as people grow older and how is this different from normal ageing?
4. Prevention What can be done to prevent rare metabolic bone disorders in the first place or stop them from getting worse?	**9. Self-management** How are other parts of the body affected by rare metabolic bone disorders to cause other symptoms?
5. Treatment What are the best ways to manage the fatigue linked to rare metabolic bone disorders?	**10. Prognosis** What are the best ways to prevent dental problems in people with rare metabolic bone disorders? Tied with: How and why do people with rare metabolic bone disorders have different symptoms, even when they have the same genetic mutation?

[85] James Lind Alliance Priority Setting Partnership. Rare musculoskeletal diseases in adulthood. Priority Setting Partnership. 2018. https://www.jla.nihr.ac.uk/priority-setting-partnerships/rare-musculoskeletal-diseases-in-adulthood/Downloads/MSK-PSP-Report-FINAL.pdf

[86] Ibid

From the patient organisation side, optimism about greater patient-driven research is more subdued. According to Ms Alves, it's more talk than action. "Now, more companies approach patient advocates and organisations to request joint collaborations to improve patient driven research and outcomes. But due to internal barriers and confidentiality aspects, the sharing of results with patients as participants in studies and trials is still a work in progress. This is not the same as being part of the broader clinical and research community."

Some organisations that are making patient-driven research central to their process include ERN BOND, which calls for patient groups to be involved in the network's decision- and opinion-making structures.[87] There's also the European Medicines Agency, which is asking for patient experts to be involved in the evaluation process for drug approvals.

"But," she adds, "at the end of the day, many researchers are not used to having patients as partners." They shouldn't be so dismissive, she says. "These experts need to widen their perspectives as many patients and their families have become extremely well educated on rare bone diseases, from the genetics to study design. Several parents and patients are even spearheading research, co-leading research initiatives."

In the US, Ms Waldman mirrors similar sentiments about true patient involvement. Federal government programmes have made small moves in this direction. For example, the Patient-Centered Outcomes Research Institute[88] helps patient groups set research priorities. "This has made a big impact," she says.

But she adds that patient-driven research will continue to be hampered—or aided—by the quality of registry services. "Many research organisations have their own registry and their scientists can evaluate the information in their registry, but if they are willing to make that information available to the scientific community, and they should, then it can be an even better tool for research."

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Charlene Waldman, director, Rare Bone Disease Alliance, US

[87] European Reference Network. Network agreement regarding the rules for the European patient advocacy groups (EPAGs). 2019.

[88] Patient-Centered Outcomes Research Institute (PCORI). https://www.pcori.org/

An inspiring patient-driven research story: Jansen's Syndrome

Jansen's Syndrome is an ultra-rare bone disease, affecting fewer than 100 people globally. It is often painful, impacting a person's ability to process calcium in the body. Surgical interventions and intense physical therapy are the only known ways to realign bones and reduce pain.

As a testament to its rarity, the founder of the Jansen's Syndrome Foundation, Neena Nizar, who has the disease, was not diagnosed until the age of 32, at which point she had two sons who also share the condition. Doctors simply did not know what she had.

Once diagnosed, she found that there was limited research into her disease and her future was filled with unknowns. Determined to build a better future for herself, her sons and others, she started to build a research network. Through her determination and collaboration, the foundation now has a potential therapy that is promising in animal models with plans for human testing.

Despite the extreme rarity of the condition, she was able to move the bar in treating it. Her story stands as an inspiration to many in the rare bone disease world, especially those with ultra-rare conditions who fear for their future.

Conclusion

People living with rare bone diseases and their families have many challenges to contend with in their personal lives and healthcare journeys. Both are strongly intertwined. Far too many patients face unknown future progressions of their disease. The majority of gatekeeping healthcare professionals remain unaware of many of the characteristics, natural history and optimal clinical follow-up for rare bone diseases, which reflects late diagnosis. Thus, in many cases, people living with a rare bone disease need the support of expert clinicians in specialised centres.

Despite this, progress is under way both in terms of research and systematic change that can improve the patients' quality of life and care pathways. Some of these steps are official and built into the care infrastructure, but many are not. And in all cases, there's more work to be done to help provide the best care:

- **Registry co-ordination and standardisation:** Disjointed registries remain widespread, especially in the US. Further incentives may be needed to consolidate and nationalise efforts. Scientific research should be more freely permitted across registries to halt private pockets of information to the detriment of the overall pursuit of care.
- **Transitional care structures:** Adult patients and soon-to-be adult patients shouldn't have to worry about their next steps in care. Finding a clinician who may see them throughout their transitional years seems possible if such a clinician is willing to "sneak" them past age restrictions. But this is stressful and burdensome to all parties. Instead, this should be an encouraged practice at specialised research and care centres. Furthermore, adult care infrastructures should be more findable and available to patients.
- **Integrated mental health services for patients and families:** A patient's psychological quality of life should not be kept apart from clinical care. More psychological support should be integrated into paediatric centres for patients and families, and these services should also be built into adult care networks.
- **Access to therapy:** People living with rare bone diseases can experience financial and geographic challenges when accessing specialised care. Access to orphan medicines and educational materials can also be variable across Europe. More efforts can be made to ensure people living with these conditions have sufficient support.
- **Truly patient-driven research:** While rare bone research and medical organisations have stated that they are using patient-driven research to guide their priorities and involve patients in their work, patient advocacy groups still have concerns whether all players will act on this. Working closely with patients in studies and clinical trials means research questions that are important to patients and their families are met.

- **Education for primary care physicians to recognise bone health:** Bone health is arguably underrepresented in undergraduate medical education and largely centred on fractures, and experts think a wider understanding of bone abnormalities could help with earlier identification and diagnosis.
- **Wider access to genetic testing:** Barriers to conclusive genetic testing, including cost, long queues and limited resources, need to be addressed. Delayed diagnosis compounds patient health issues and delays meaningful conversations between patients and clinicians about management and long-term care. Should a doctor suspect bone abnormality, genetic testing should be one of the first available options for confirmation.
- **Greater adoption of digital learning for clinicians:** Clinicians can also benefit from easier access to educational materials to help with patient care. Covid-19 has transformed many destination conferences to online meetings and the result is often a significant rise in attendance. This should be kept in mind going forward, and more informational sessions held digitally to increase access.
- **Greater adoption of digital engagement with patients:** Patients have also benefited from the convenience of digital appointments, as have their caregivers. While some elements of care obviously must be undertaken in person, digital appointments should be encouraged when possible to complement face-to-face care.

Appendix

Rare bone diseases fall into four categories
Categories are also linked with 86 affected genes related to bone and mineral homeostasis.[89] Detailed prevalence and incidence data for rare bone diseases were published in January 2020 with co-funding by the EU.[90]

Altered osteoclast/osteoblast or osteocyte activity[91]

What this means
Throughout a person's lifetime, healthy bone activity includes a constant balance of bone resorption (the removal of old or damaged bone by osteoclasts) and bone formation (the subsequent replacement of new bone formed by osteoblasts).[92]

Bone diseases in this category show alterations of the specific genes encoding proteins for these processes. The result is in an increase or decrease in bone formation or bone resorption.

Patient impact
Many are familiar with osteoporosis, a common disease of this category associated with reduced bone mass and strength in older age.[93]

But in more rare and extreme cases this can lead to a mix of patient outcomes including—but certainly not limited to—a significant change in bone density, bone deformities, high fracture rates, short stature, mental retardation, pain, muscular atrophy and loss of sight and/or hearing.

Examples of rare bone diseases that fall into this category include:

- **Cystic angiomatosis of bone/Gorham-Stout disease** is an inherited osteolysis disorder characterised by destruction and resorption of affected bones with subsequent skeletal deformities and functional impairment.
- **Familial expansile osteolysis,** which can present with deafness, focal skeletal changes, severe, painful, disabling deformity and a tendency to pathologic fracture.
- **Hajdu-Cheney syndrome,** for which patients typically have short stature, coarse and dysmorphic facies, bowing of long bones, vertebral anomalies, small mouth with dental anomalies, low-set ears, and a short neck.
- **Camurati-Engelmann disease** can cause leg pain, muscular atrophy and cortical bone thickening. The most severely affected individuals have progression of mild skull hyperostosis to severe skull thickening and cranial nerve compression.

The numbers
At least 38 rare phenotypes (observable genetic characteristics) fall into this category.

[89] Masi L, Agnusdei D, Bilezikian, J et al. Taxonomy of rare genetic metabolic bone disorders. International Osteoporosis Foundation (IOF). 2015.https://www.iofbonehealth.org/osteoporosis-musculoskeletal-disorders/skeletal-rare-disorders

[90] Orphanet Report Series, Rare Diseases collection. Prevalence of rare diseases: Bibliographic data. January 2020. http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf

[91] Ibid

[92] Feng X, McDonald JM. Disorders of Bone Remodeling. *Annual review of pathology*. 2011;6:121-145. doi:10.1146/annurev-pathol-011110-130203

[93] Ibid

Altered bone matrix proteins

What this means

Bones have a complex matrix framework that provides structure and regulates its health.

The matrix's structure is primarily comprised of collagen, which helps the bone balance its flexibility and stiffness requirements. Many rare bone diseases in this category are due to defective or insufficient quantities of collagen molecules in the bone.

Other bone diseases in this category show disorders of alkaline phosphates, which help regulate bone metabolism.

Patient impact

Osteogenesis imperfecta (OI), also known as brittle bone disease, falls into this category. It is associated with bone fragility.

Overall, this category primarily affects bone density, which can lead to fractures, stiffness, pain, misshapen bones and mental retardation.

Rare forms of this disease in this category include:

- **Nondeforming with blue sclerae (OI type I)** is the mildest form of OI. Patients show a 50% reduction of the amount of collagen, hearing loss (onset usually around 20 years), mitral valve prolapse, thin skin, increased fracture rate throughout childhood (which then increases after menopause and in men aged 60-80 years) and a biconcave flattened vertebra.
- **Perinatally lethal (OI type II)** is the most severe form of OI. It presents with neonatal lethality, as patients are born prematurely and small for gestational age. Patients can present with multiple neonatal fractures and shortening and bowing of long bones leading to crumpled bones.
- **Progressively deforming (OI type III)** is a severe form. Patients are usually born prematurely and small for gestational age. Progression is marked by impairment of linear growth, deformity of long bones and spine, severe bone dysplasia, and severe osteoporosis with multiple fractures and bone deformities.
- **Hypophosphatasia (HPP)** is caused by various defects in tissue-nonspecific alkaline phosphatase. Problems occur at all ages and stages in growth. In adults, patients can experience premature loss of primary and secondary teeth, severe dental problems and recurrent fractures.

The numbers

To date, 28 rare phenotypes (observable genetic characteristics) have been identified in this category.

Mutated bone microenvironment regulators

What this means

Bone is a living material and the term "bone microenvironment" refers to the complex biological and structural system within that manages growth and function.

Mutations in this category stem from an alteration or mutation of the microenvironment, specifically the gene encoding protein involved in the regulation of bone turnover (regeneration).

Patient impact

Diseases in this category are often associated with symptoms that include muscular weakness, changes in bone density, osteoporosis, misshapen and fragile bones, increased bone formation and destruction, short stature, mild involvement of cranial bones, deafness, retinal degeneration, mental retardation, seizures, and more.

Examples of rare diseases in this category include:

- **Hyperphosphatasia with mental retardation syndrome 1 (HPMRS1)** is also categorised as an altered bone matrix protein disease because it is due to an error of bone and mineral metabolism caused by various defects in tissue-nonspecific alkaline phosphatase. Its signs are mental retardation, various neurologic abnormalities such as seizures and hypotonia, facial dysmorphism, and variable degrees of brachytelephalangy.
- **Fibrodysplasia ossificans progressiva (FOP)** is a devastating disease that presents with sporadic episodes of painful soft tissue swellings ("flare-ups"), hearing loss, widely spaced teeth, intermittently progressive ectopic ossification and malformed big toes.
- **Juvenile Paget's disease** is also categorised as an altered osteoclast, osteoblast or osteocyte activity. It is characterised by high bone resorption. Patients present with retinal degeneration (in some individuals), muscular weakness, deafness in infancy, osteoporosis, expanded long bones, bowed long bones, fragile bones, increased bone formation and destruction, progressive skeletal deformity, short stature, mild involvement of cranial bones, and islands of increased skull bone density.
- **Van Buchem disease type 2, autosomal dominant (VBCH2)** is also categorised as an altered osteoclast, osteoblast or osteocyte activity. It is due to high bone formation and can present in increased bone density. It is mostly asymptomatic, associated with osteosclerosis of the skull, enlarged and squared jaw (decreased gonial angle), cranial nerve compression, and sensorineural hearing loss.

The numbers

At least 13 rare phenotypes (observable genetic characteristics) fall into this category.

Deranged calciotropic hormonal activity

What this means

Calciotropic hormones are a general term for any hormones that play a major role in bone growth and bone remodelling.

Diseases in this category are due to alterations of the function of those hormones, which can affect normal function of the bone.

Patient impact

Symptoms of diseases in this category vary but children often present with progressive deformities and/or short stature, pain, and arthritis.

Diseases in this category are often associated with symptoms that include growth retardation, muscle weakness, skeletal deformities, bone pain, bowing of lower extremities, dental abnormalities and rickets.

Examples of rare diseases in this category include:

- **Hypoparathyroidism** shows systemic signs of increased neuromuscular irritability (cramping, tetany, seizures), soft tissue calcifications. Bone-specific signs include an increase in cancellous bone volume and cortical thickness.
- **Kenny-Caffey syndrome type 1 (KCS1)** symptoms include dental abnormalities, medullary stenosis of long bones, short stature, osteosclerosis, cortical thickening of the long bones and delayed closure of the anterior fontanel.
- **X-linked, dominant, hypophosphatemic rickets (XLHR)** presents with late dentition, tooth abscesses, bowing of lower extremities, enlarged costochondral junctions of the ribs, and metaphyseal flaring of the wrists or ankles.
- **Autosomal recessive hypophosphatemic rickets type 1 (ARHR1)** can present in ways that include short stature, limited movement of the spine and hip, calcification of the ligaments at the bony insertions sites, high bone density at the base of skull, and clavicle and rib anomalies.

The numbers

There are 54 rare phenotypes (observable genetic characteristics) that fall into this description.

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