

RARE BONE DISEASES IN ARGENTINA: EPIDEMIOLOGIC PATTERNS AND REGISTRY GAPS

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Abstract

Introduction: Rare bone diseases (RBDs) encompass a heterogeneous group of disorders affecting bone, cartilage, or dentine, with an estimated prevalence of fewer than 1 in 2000 individuals. Despite advances in genetics and imaging, substantial gaps remain in diagnosis, molecular confirmation, and clinical management. In Argentina, epidemiological data on RBDs are limited to isolated reports and small institutional series.

The aim was to identify and characterize patients with RBDs evaluated at a national reference center in Buenos Aires, compare findings with other Argentinian and international registries, and highlight the need for a coordinated national network.

Materials and methods: A retrospective, cross-sectional study was conducted at Instituto de Diagnóstico e Investigaciones Metabólicas (IDIM). Medical records from 2012 to 2024 were reviewed to identify adult and pediatric patients with confirmed RBDs. Demographic and clinical data were analyzed descriptively.

Results: A total of 230 patients met inclusion criteria (95.7% adults, 4.3% children). The most frequent diagnosis was post-surgical hypoparathyroidism (58.8%), followed by tumor-induced osteomalacia (8.5%) and multiple myeloma (8.5%). Only 7.8% of patients with RBDs had a confirmed genetic diagnosis. Relative to European and North American registries (with 70% molecular confirmation), Argentinian data remain pri-

marily clinical, highlighting diagnostic inequity and structural barriers.

Conclusion: This study provides to our knowledge, the largest Argentinian cohort of RBDs to date. Findings reveal distinctive national patterns shaped by referral bias and limited genetic testing. Establishing a coordinated Argentinian Rare Bone Disease Network, integrated with EuRR-Bone and ERN-BOND, is urgently needed to standardize data collection, expand education, and bridge diagnostic and research gaps.

Key words: rare bone diseases, registry, hypoparathyroidism, tumor-induced osteomalacia, Argentina, epidemiology

Resumen

Enfermedades óseas raras en Argentina: patrones epidemiológicos y diferencias en los registros

Introducción: Las enfermedades óseas raras (EOR) abarcan un grupo heterogéneo de trastornos que afectan al hueso, cartílago o dentina, con una prevalencia en la población igual o inferior a 1 en 2000 personas. Existen importantes desafíos en el manejo clínico, la confirmación molecular y diagnóstico de estas enfermedades. En Argentina, los datos epidemiológicos sobre las EOR se limitan a reportes de casos y pequeñas series. El objetivo

fue identificar y caracterizar los pacientes con EOR de un centro de referencia nacional y comparar los resultados con los de otros centros nacionales e internacionales.

Materiales y métodos: Estudio transversal retrospectivo en Instituto de Diagnóstico e Investigaciones Metabólicas (IDIM). Se revisaron historias clínicas desde el 2012 al 2024 para identificar pacientes adultos y pediátricos con diagnóstico de EOR. Se analizaron descriptivamente los datos demográficos y clínicos.

Resultados: Un total de 230 pacientes fueron incluidos (95.7% adultos, 4.3% niños). El diagnóstico más frecuente fue hipoparatiroidismo post quirúrgico (58.8%), seguido de osteomalacia inducida por tumor (8.5%) y mieloma múltiple (8.5%). Solo el 7.8% de los pacientes tenía un diagnóstico genético confirmatorio. En comparación con los registros europeos y norteamericanos (con un 70% de confirmación molecular), los datos argentinos siguen siendo principalmente clínicos.

Conclusión: Este estudio describe, en nuestro conocimiento, el grupo más grande de pacientes con EOR en Argentina. Los resultados están condicionados por la limitación en el diagnóstico genético y los sesgos de derivación. Se hace imperiosa la necesidad de establecer un sistema nacional integrado de identificación de pacientes con EOR para mejorar el diagnóstico, acceso, tratamiento e investigación.

Palabras clave: enfermedades óseas raras, registro, hipoparatiroidismo, osteomalacia inducida por tumores, Argentina, epidemiología

PUNTOS CLAVE

Current knowledge

- Rare Bone Diseases encompass a heterogeneous group of disorders with an estimated prevalence of fewer than 1 in 2000 individuals. Despite advances in genetics and imaging, substantial gaps remain in diagnosis, molecular confirmation, and clinical management. In Argentina, epidemiological data on RBDs are limited to isolated reports and small institutional series.

Article's contribution to current knowledge

- This study provides the largest Argentinian cohort of RBDs to date. Findings reveal distinctive national patterns shaped by referral bias and limited genetic testing.

The current work provides an opportunity to increase awareness among clinicians and promote a national educational network.

RBDs comprise a wide and complex spectrum of skeletal disorders that affect bone, cartilage, or dentine, with an estimated prevalence of < 1 in 2,000 individuals^{1,2}. Most definitions consider disease prevalence as the principal criterion; however, there is no universal definition of rare diseases to date^{1,2}.

Although each condition is uncommon, together they represent a significant proportion of rare disorders, approximately 10% of all rare diseases worldwide¹. Advances in molecular genetics have improved the understanding of these disorders³, yet major disparities persist in diagnosis, treatment availability, and clinical follow-up between high-income and middle-income countries.

In Argentina, Law 26.689 (2011) legally defines a rare disease as one affecting ≤ 2000 people⁴. However, despite this legislative framework, epidemiological data remain fragmented^{5,6}. Until recently, information on RBDs in Argentina was limited to isolated case reports and small institutional series. Recently, Brance et al. from Rosario, reported 133 cases of skeletal rare diseases diagnosed over 12 years⁷. Their pioneering work underscored the heterogeneity of local presentations from complex regional pain syndrome and XLH to osteopetrosis and tumor-induced osteomalacia and called for a coordinated national effort.

IDIM is a reference center for metabolic bone and endocrine diseases, attending more than 90 000 consultations annually. Beyond describing clinical patterns and epidemiology, our goal is to increase awareness among healthcare professionals, highlight the educational and translational role of reference centers, and contribute to the foundation of a wide national RBD registry integrated into international networks such as European Registries for Rare Bone and Mineral Conditions (EuRR-Bone) and European Reference Network for Rare Bone Diseases (ERN-BOND).

Rare bone diseases can be systematically classified according to the taxonomy proposed by the Skeletal Rare Diseases Working Group of the International Osteoporosis Foundation (IOF),

which groups these disorders into four major categories based on their underlying metabolic pathogenesis: (1) disorders due to altered osteoclast, osteoblast, or osteocyte activity; (2) disorders due to altered bone matrix proteins; (3) disorders due to altered bone microenvironmental regulators; and (4) disorders due to altered calciotropic hormonal activity⁸. This framework, also referenced in the recent Argentinian registry from Rosario⁷, offers a clinically useful structure for the non-expert reader and is summarized in Table 1, together with the minimum clinical features and diagnostic approach for the entities identified in the present cohort.

The study aims to identify patients with RBD at IDIM, and to describe the types of RBD in adults and children, analyzing demographic data (age, sex) and clinical features (presence of genetic testing, family history, presence of affected relatives and presence of disability certification).

Materials and methods

A descriptive retrospective cross-sectional study was conducted. Data were obtained through a review of medical records from the *Instituto de Investigaciones Metabólicas* (IDIM) from May 2012 (when the electronic health record system was implemented) until March 2024. Inclusion criteria comprised adult and pediatric patients who had at least one consultation at the institution and a diagnosis of a RBD. Patients under the age of 16 were classified as pediatric. Patients with rare diseases not primarily involving the skeleton and with no confirmed diagnosis were excluded.

Patient identification was performed using two methods. First, a review of 509 diagnoses available in the electronic health record system was conducted. Diagnoses related to rare bone disease were selected following the 2023 revision of the *Nosology of Genetic Skeletal disorders*. These included: “McCune Albright”, “osteopetrosis”, “X-linked hypophosphatemia (XLH)”, “Camurati Englemann”, “hypophosphatasia”, “familial hypophosphatasia”, “melorheostosis”, “fibrodysplasia ossificans progressiva (FOP)”, “hypoparathyroidism”, “Achondroplasia”, “rickets”, “osteogenesis imperfecta”, “bone dysplasia”, “tumor-induced osteomalacia (TIO)”, “fibrous dysplasia”, “hypocalciuria”, “tubulopathies”, “multiple myeloma (MM)”, “systemic mastocytosis”, “rare genetic pediatric disease”, “rare bone diseases” (Table 1).

The second method was an interview by telephone or e-mail with all the medical doctors who worked at the

institution, asking whether they could recall any patients with RBD they had treated. To protect patient data and ensure privacy, a unique identification number was assigned to each patient.

Data were analyzed and summarized using descriptive statistics with the R software program, version 4.4.2. Patients were stratified by age group: adult and children (≤ 16 years old). Percentages were calculated based on the total number of patients in each group. For continuous variables, mean and median and standard deviation were reported. Results were presented using tables, bar charts, and pie charts.

This study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the *Instituto de Diagnóstico e Investigaciones Metabólicas* (IDIM) (Approval Number: IDIM-006-2023). Since a unique identification number was assigned to each patient to protect patient data and ensure privacy no informed consent was required.

Results

A total of 416 patients were initially identified, of whom 186 (44.7%) were excluded. Reasons for exclusion were: 181 patients with incorrect diagnoses, four suspected cases without accurate diagnosis, and one patient with a rare disease not primarily involving the skeleton. Consequently, 230 cases of RBD were included in the analysis (Figs. 1. Flowchart patient disposition).

Among these, 10 patients (4.3%) were children (pediatric group) and 220 (95.7%) were adults.

In the adult group, 178 (80.9%) were female and 42 (19.1%) were male, with a mean age of 49.7 ± 18.2 years. In the pediatric group, 7 patients (70%) were female and 3 (30%) male, with a mean age of 11.5 ± 4.9 years.

Hypoparathyroidism was the most frequent diagnosis among adults, accounting for 130 patients (58.8%), of whom, 118 (90.7%) were post-surgical cases. The second most common diagnosis in adults were tumor-induced osteomalacia (TIO) and multiple myeloma, each with 19 cases. In the pediatric group, pseudohypoparathyroidism was the most frequent diagnosis affecting 3 patients (Figs. 2-4).

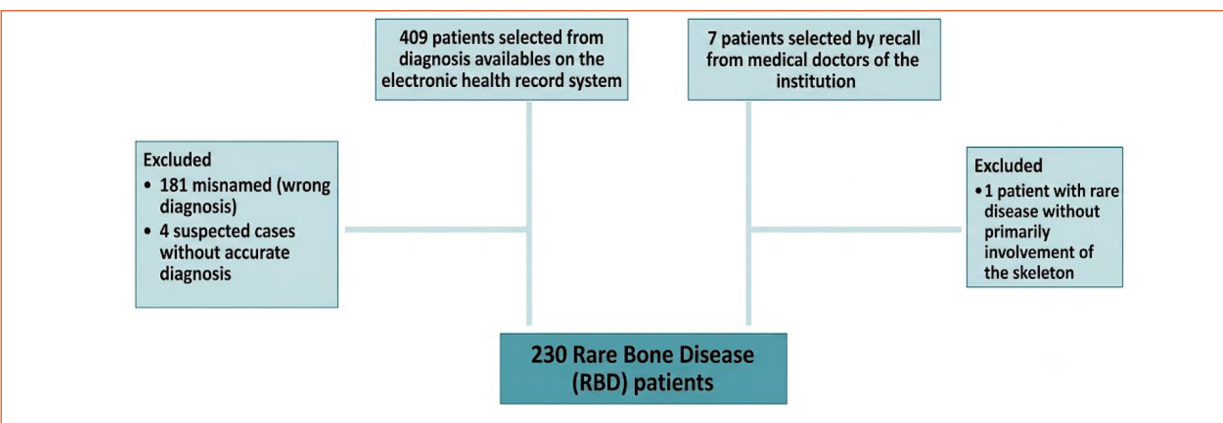
Eighteen patients had a confirmed genetic diagnosis (four DiGeorge syndrome, one familial hypocalciuric hypercalcemia, one hypoparathyroidism, one McCune Albright, one Osteogenesis imperfecta, two Osteopetrosis, three XLH, one TIO, one Leri Weill syndrome, one pseudo-

Table 1 | Classification of rare bone diseases identified in the cohort, according to the IOF taxonomy

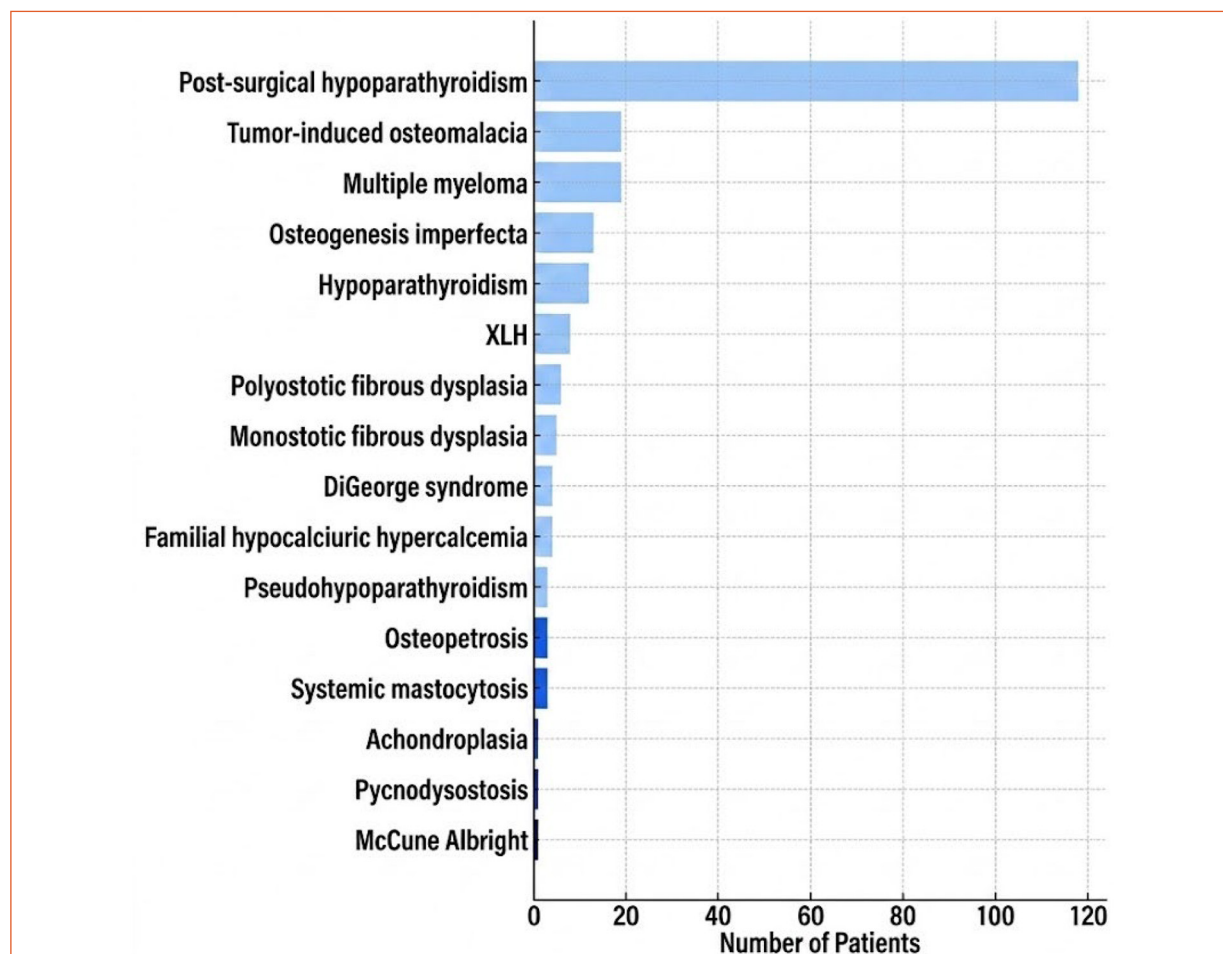
Category (IOF taxonomy)	Diseases in this cohort	Minimum clinical features	Diagnostic approach
1. Altered osteoclast, osteoblast, or osteocyte activity	Osteopetrosis; Camurati–Engelmann disease; melorheostosis	Increased or decreased bone density; sclerotic long-bone diaphyses; bone pain and deformity	Skeletal radiographs / CT; targeted genetic testing (e.g., CLCN7, TCIRG1, TGFβ1)
2. Altered bone matrix proteins	Osteogenesis imperfecta; fibrous dysplasia / McCune–Albright syndrome	Bone fragility with recurrent fractures and deformity; fibrous replacement of bone, café-au-lait macules, endocrinopathies	Clinical and radiologic criteria; COL1A1/COL1A2 or GNAS genetic testing
3. Altered bone microenvironmental regulators	Tumor-induced osteomalacia; multiple myeloma; systemic mastocytosis	Hypophosphatemic osteomalacia and bone pain; lytic lesions; diffuse osteosclerosis/osteopenia	Serum FGF23 and functional imaging for TIO; serum/urine protein electrophoresis and bone marrow biopsy for MM; serum tryptase and bone marrow biopsy for mastocytosis
4. Altered calciotropic hormonal activity	Hypoparathyroidism / pseudohypoparathyroidism; X-linked hypophosphatemia; familial hypocalciuric hypercalcemia; rickets; renal tubulopathies	Hypocalcemia or hypophosphatemia with abnormal PTH, vitamin D, or FGF23 axis	Serum calcium, phosphate, PTH, 25(OH)D, FGF23; genetic testing (PHEX, CASR) as indicated

IOF: International Osteoporosis Foundation; TIO: tumor-induced osteomalacia; MM: multiple myeloma; PTH: parathyroid hormone; FGF23: fibroblast growth factor 23

Figure 1 | Flowchart: Patient disposition



RBD: rare bone disease patients

Figure 2 | Diagnostic distribution of rare disease in adults (n=220)

XLH: X-linked hypophosphatemia

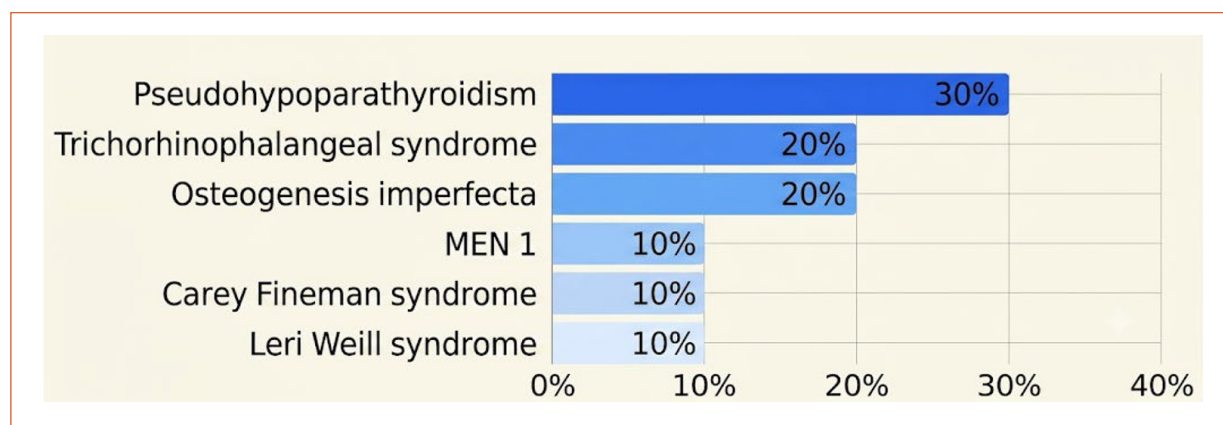
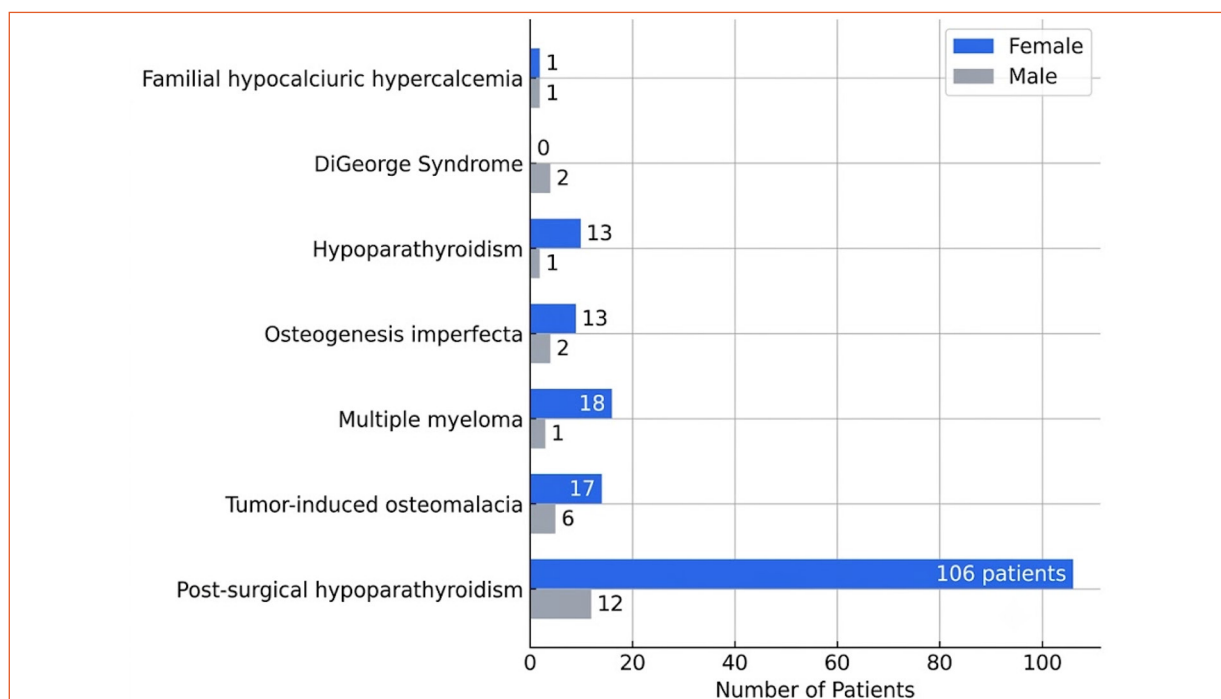
Figure 3 | Rare bone diseases in children (n=10) (syndrome, patients, sin mayúsculas)

Figure 4 | Sex distribution by diagnosis

hypoparathyroidism, one trichorhinophalangeal syndrome, one multiple endocrine neoplasia). Moreover, 15 patients reported having a relative affected by the same disease, and five patients held a disability certificate.

Discussion

This study identified 230 patients with rare bone diseases, representing, to our knowledge, the largest single-center Argentinian cohort reported to date. Post-surgical hypoparathyroidism was by far the most frequent condition, followed by TIO and multiple myeloma. The predominance of hypoparathyroidism differs markedly from data from the Rosario registry⁷, which documented 133 RBD cases, where complex regional pain syndrome (41.3%), XLH, and fibrous dysplasia predominated. This contrast likely reflects differences in referral profiles: IDIM serves as an endocrine center, while the Rosario cohort –mostly rheumatologists– was derived from musculoskeletal and oncologic services. Together, these two Argentinian experiences provide complementary perspectives on the national epidemiology of RBDs.

Our diagnostic distribution diverges from that reported by the ERN-BOND and the EuRR-Bone, in which osteogenesis imperfecta (OI) and fibrous dysplasia/McCune-Albright syndrome are the most common⁹⁻¹². Also, in these registries, up to 70-80% of cases possess molecular confirmation, compared with 7.8% in our series¹³. Sadly, similar patterns were described in Latin American cohorts, including Brazilian experiences with hypophosphatasia and hypoparathyroidism^{14,15}. These data underscore the urgent need for equitable access to genetic testing and national referral pathways in Latin America and Argentina.

Across North America, Europe, Asia, and Russia, the prevalence and demographic distribution of rare bone diseases show substantial regional variation (Table 2). Reported frequencies differ widely by disorder from fractions per million for fibrodysplasia ossificans progressiva to several per ten thousand for osteogenesis imperfecta and craniofacial bone disorders. Age and sex patterns also vary, with some diseases restricted to adults (e.g., Paget's) and others primarily pediatric (e.g., fibrodysplasia, craniofacial

Table 2 | Rare bone disease comparison

Feature	Argentina (IDIM + Rosario)	Europe (ERN-BOND / EuRR-Bone)	North America	Asia / Other Regions
Sample size	230 (IDIM) + 133 (Rosario)	>5000 combined cases	~2000 (US- Canada)	Hundreds to thousands
Most common RBDs	Post-surgical hypoparathyroidism, TIO, MM, CRPS	OI, FD/MAS	OI, HPP, Paget	Paget, OI, FOP
Genetic testing access	Limited (<10%)	Extensive (70–80%)	Broad (80–90%)	Moderate (40–60%)
Registry integration	No national registry	National + supranational (EuRR-Bone)	NIH RDCRN, NORD	Regional or partial
Pediatric inclusion	Low (4%)	Moderate	High	Variable
Educational initiatives	Emerging (IDIM, AAMM)	ERN-BOND Academy	TeleECHO, RDCRN	Limited
Unique patterns	High post-surgical hypoparathyroidism; low genetic confirmation	OI predominance, strong biobanks	Paget decline; genetic diversity	High FOP in S. America; rural clustering
Main gaps	Awareness, registry, and genetics	Data harmonization	Minority representation	Access, diagnostic delays

IDIM: Instituto de Diagnóstico e Investigaciones Metabólicas; ERN-BOND: European Reference Network on Rare Bone Disorders; EuRR-Bone: European Registries for Rare Bone and Mineral Conditions

syndromes). Urban concentration of specialized care, as observed in Paris and Quebec, and rural clustering in certain regions highlight how geography shapes disease detection and reporting^{16–23}. Overall, these trends emphasize marked international heterogeneity and the critical importance of regional registries to capture local epidemiologic realities. Compared with these international series, the Argentinian cohorts (IDIM and Rosario) show distinctive signatures driven by referral bias, healthcare structure, and limited molecular testing. Whereas European and North American registries maintain high molecular confirmation rates and standardized biobanks, Argentinian data remain primarily clinical and descriptive, illustrating the critical need for infrastructure to bridge these scientific and diagnostic gaps.

Limited access to molecular and biochemical diagnostics remains a critical challenge across Latin America. In Argentina, testing is centralized in a few urban laboratories and seldom covered by insurance. Geographic disparities, spe-

cialist shortages, and heterogeneous electronic health records hinder systematic data collection. As noted in European registries, our dataset lacked details such as disease onset, complications, and longitudinal outcomes, underscoring the need for a national registry aligned with the 16 core data elements of the EU RD Platform^{9–12}. Establishing such a framework would enable interoperability with EuRR-Bone and facilitate multinational research.

The current work provides an opportunity to increase awareness among clinicians and promote a national educational network under the National Bone Society. The Rosario registry emphasized interdisciplinary management and education; our findings reinforce that vision. Systematic reporting enhances visibility, facilitates earlier diagnosis of conditions like TIO or pseudohypoparathyroidism, and strengthens continuing medical education. International models such as the Rare Bone Disease TeleECHO Program have shown that virtual case-based learning

can expand diagnostic capacity in resource-limited settings²⁴. IDIM intends to adapt this framework nationwide, combining training with registry data collection to achieve sustainable impact.

These experiences demonstrate that, even with limited resources, robust clinical and epidemiologic insights can be generated through collaboration. The logical next step is the creation of an Argentinian Rare Bone Disease Network, integrating reference centers, pediatric and adult services, and academic societies. Such a network would align with international initiatives like ERN-BOND and EuRR-Bone, enabling genetic research, standardized care, and policy advocacy. IDIM's high-volume practice and edu-

cational commitment make it a natural sentinel site for this mission.

The retrospective design and variable record quality limited clinical granularity. Pediatric cases were under-represented due to IDIM's adult focus. Also, many patients are probably underregistered because their diagnoses are not accurately documented in the digital history or because their doctors do not recall them when asked.

Future multicenter efforts should standardize data entry, include biobanking and patient-reported outcomes, and connect to international registries to enhance translational research and visibility.

Conflicts of Interest: None to declare

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