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Osteoporosis and Measurement of Bone Mass in Children and Adolescents

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The foundation for lifetime skeletal health is established during childhood and adolescence. Although there is controversy regarding the exact timing of peak bone mass, bone size and strength reach a maximum by early adulthood [1–3]. Failure to accrue optimal peak bone mass has been linked to an increased risk of osteoporosis [4]. The variables that contribute to optimal bone health have been delineated in studies of healthy youth [1–3]. An estimated 60% to 80% of the variability in risk for osteoporosis can be explained by heritable factors [1,2,5]. This genetic potential is reached, however, only if modifiable factors are optimal. Adequate weight-bearing physical activity, nutrition, body mass, and hormonal balance are essential to achieve optimal skeletal health.

Threats to pediatric bone health

Early bone health may be compromised by several genetic or acquired childhood disorders [6,7], as listed in Box 1. Bone fragility in most heritable disorders results from defects in the bone matrix that affect the entire skeleton. Osteogenesis imperfecta is the best example of these disorders, and, given the variable expressivity of these genetic defects, there is a range of skeletal effects. Some patients show only asymptomatic low bone mass, while others progress to chronic bone pain, recurrent fractures, and progressive skeletal deformity [8].

A growing list of chronic diseases has also been linked to low bone mass or fragility fractures [6,7,9–32]. Disorders causing rickets and osteomalacia are reviewed by Pettifor elsewhere in this issue. In some chronic conditions, a single factor (eg, immobilization or hypogonadism) accounts for the

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Box 1. Disorders associated with low bone mass or fractures in childhood

Genetic disorders [7,8]
- Ehlers-Danlos
- Fibrous dysplasia
- Homocystinuria
- Hypophosphatasia
- Idiopathic hypercalciuria
- Marfan's syndrome
- Menkes' kinky hair syndrome
- Osteogenesis imperfecta

Chronic disease
- Anorexia nervosa [9,10]
- Athletic amenorrhea [11]
- Celiac disease [12]
- Cystic fibrosis [13]
- Diabetes (type I) [14]
- Hematologic thalassemia, sickle-cell anemia [15]
- Inflammatory bowel disease [16]
- Malignancy [17–19]
- Post transplantation [20]
- Renal failure [21]
- Rheumatologic disorders [22]

Endocrine disorders
- Glucocorticoid excess [23]
- Growth hormone deficiency [24]
- Hyperparathyroidism [25]
- Hyperthyroidism [26]
- Sex steroid deficiency or resistance [27,28]

Immobilization
- Cerebral palsy [29]
- Muscular dystrophy [30]
- Paraplegia
- Spina bifida

Miscellaneous
- Idiopathic juvenile osteoporosis [31]
- Idiopathic scoliosis [32]

increased risk of low bone mass. In most of these disorders, however, skeletal health is threatened by a combination of risk factors including malnutrition, vitamin D insufficiency, malabsorption, deficiency or resistance to sex steroids or growth hormone, immobilization, and increased cytokine production. Medications that are used to treat these disorders, such as glucocorticoids, calcineurin inhibitors, and chemotherapeutic agents, also may contribute to bone loss [7]. The magnitude of effect that these disorders or medications will have on an individual patient varies, depending upon genetic factors, disease severity, activity, and other variables. For this reason, clinicians seek diagnostic tools to identify patients at greatest risk for bone fragility.

Assessing pediatric bone health

A bone fracture that occurs with minimal or no trauma is clinical evidence of bone fragility. Individuals with low bone mass, however, are typically asymptomatic until a fracture occurs. The goal of noninvasive skeletal testing is to identify children at risk for fracture before fractures occur. To do this requires an understanding of the factors that contribute to bone strength. Resistance of bone to fracture is determined not only by the mass of bone but by the geometry, quality, and material properties also [33,34]. Both the size and distribution of bone mineral within the bone influence strength. Given two bones of equal material properties, the larger bone will be less likely to fracture. Similarly, resistance of bone to torsion increases with the distance of bone mass from the center of the bone. Small increases in the diameter of bone will increase bone strength markedly [33]. Increased rates of bone turnover also contribute to bone fragility, at least in the elderly [34].

The ideal densitometer would measure all these parameters of bone health with speed, precision, low cost, and little to no exposure to ionizing radiation. A large set of normative values from a representative population of healthy youth would be available for comparison. Finally, densitometry results would be predictive of clinical outcome such as low trauma fracture. Because none of the currently available techniques fit this tall order, the choice of methodology will depend upon the clinical or research question to be addressed.

Bone densitometry methods

Several noninvasive methods are available to assess the peripheral, central, or total body bone mass [35]. Each is more sensitive than conventional radiography for detecting deficits in bone mineral. The methods vary in cost, speed of measurement, exposure to ionizing radiation, and regions of the skeleton that can be scanned (Table 1). These techniques also vary in accuracy (the difference between bone measurement and ash weight) and precision (the reproducibility of repeated measurements). For clinical purposes, precision is of greater importance than accuracy.

Table 1
Bone densitometry methods

Method	CV precision (%)	Skeletal sites	(microSv) Skin (entrance) dose	(microSv) Effective dose
DXA	0.7–1.7	PA spine	35	0.12–0.5
	0.7	Total body	18	4.6
	1.3–2.6	Proximal femur	60	0.14–1.4
QCT	1.5	Spine	3000	30
	0.6–1.5	Femur	1500	3
PQCT (forearm)	0.8–1.5	Radius	300	10
	—	Tibia	—	—
QUS	0.8–2.5	Heel	0	0
	0.5–1.1	Finger	—	—
	0.2–0.7	Tibia	—	—
	0.4–0.8	Radius	—	—
	1.5	Patella	—	—
Chest radiograph	—	—	500	50
Background radiation	—	—	—	2400/y

Abbreviations: CV, coefficient of variation; PA, posteranterior.

Data from Mora S, Bachrach L, Gilsanz V. Noninvasive techniques for bone mass measurement. In: Glorieux FH, Pettifor JM, Juppner H, editors. Pediatric bone: biology and diseases. San Diego (CA): Academic Press; 2003. p. 303–24.

Although all have been used successfully in children, there are varying amounts of pediatric reference data for each method. The choice of densitometry study will depend upon these factors and the availability of equipment.

Dual-energy x-ray absorptiometry (DXA) is viewed widely as the preferred method for clinical use in children because of its speed, precision, safety, and widespread availability. The radiation exposure is comparable to that received during a round trip transcontinental airplane flight. Pediatric reference data for lumbar spine, whole body, and proximal femur have been published (Table 2). DXA has several important limitations, however [33–35]. The technique does not provide a measure of volumetric bone mineral density or of bone geometry nor does it distinguish between cortical and trabecular bone. Although bone size and geometry can be adjusted for mathematically, these are only estimates of these parameters.

The other densitometry methods offer both advantages and limitations for clinical use. Quantitative ultrasound (QUS) is portable, inexpensive, and has no associated ionizing radiation [35,36]. The technique is less precise than DXA, however, and it can be used only in the peripheral skeleton. There are fewer pediatric reference data for QUS than for DXA, and the normative values vary by manufacturer [37,38]. Ultrasound results are reported as bone ultrasound attenuation (which is thought to reflect the microarchitecture of bone) and speed of sound (proposed to reflect bone mass) [36]. The properties of bone captured by QUS are not identical to

Table 2
Pediatric reference data for dual-energy x-ray absorptiometry

Equipment [Ref.]	No. of patients	Age (y)	Ethnicity/race	Spine[a]	Other site
Hologic 1000 [60]	218	1–19	White/African-American	L_{1-4}	—
Hologic 1000 [61]	207	9–18	White (Switzerland)	L_{2-4}	Fem neck
Hologic 2000 [62]	>234[b]	8–17	White (Canada)	L_{1-4}	Fem neck
Hologic 1000W [63]	423[b]	9–25	White, African-American, Asian, Hispanic	L_{2-4}	Whole body, fem neck, and total hip
Hologic 2000 [64]	982	5–18	White, African-American, Hispanic	—	Whole body
Hologic 2000 [57]	94	2–9	White, African-American	—	Whole body
GE Lunar [65]	444[b]	4–23	White (Netherlands)	L_{1-4}	Whole body
GE Lunar [66]	209	5–27	White (Australia)	L_{1-4}	Fem neck and shaft
GE Lunar [67]	148[b]	8–18	White	—	Whole body
GE Lunar [68]	459	3–30	White (Australia)	—	Whole body
Norland [69]	433	2–20	White female (Argentina)	L_{2-4}	—
Norland [70]	778	2–20	White (Argentina)	—	Whole body

[a] Lumbar vertebrae 1–4 and 2–4.
[b] Number of scans included in these databases exceeds the number of subjects because individuals were scanned repeatedly in these longitudinal studies.

those measured by DXA. Heel ultrasound parameters correlate only modestly ($r = 0.2$ to 0.6) with DXA measurements of BMD measurements at hip, spine, and whole body in children and young adults [38–40]. In adults, QUS measurement predicts hip fracture as well as DXA, suggesting that the technique captures aspects of bone quality independent of bone mass [41]. Preliminary data from chronically ill children also suggest that heel ultrasound parameters may be comparable to DXA in identifying those with fractures [39].

Quantitative computed tomography (QCT) measures true volumetric bone density, distinguishes between cortical and trabecular bone, and can be used to assess the central and peripheral skeleton [35,42]. Unfortunately, QCT is generally less available for clinical use, costs more, and requires a radiation exposure approximately 10 times that of DXA. Pediatric reference norms are also more limited than for DXA [42]. Peripheral CT (pQCT) offers the advantages of QCT for measuring volumetric BMD and bone geometry and differentiating between cortical and trabecular compartments [43]. This technique can be used to measure the tibia or radius with far less radiation and cost than QCT of the spine. pQCT is not available for routine clinical use, but this methodology holds considerable promise if problems of imprecision and lack of pediatric norms can be resolved.

MRI has been used successfully to examine the geometry and mass of bone in children but remains a research tool because of cost and lack of availability of equipment and normative data [44].

Indications for bone densitometry: who warrants bone density testing?

The list of pediatric conditions linked to low bone mass without or with fractures continues to grow. To some degree, this reflects new groups of high risk-patients such as long-term survivors of childhood cancers or organ transplantation [17–20]. In addition, it reflects the increased use of bone densitometry in pediatric research. Studies using DXA in children have mushroomed in the past decades, going from fewer than 25 publications annually in the 1970s to more than 220 in 2003. Despite this increase, current understanding of prevalence, severity, or natural history of bone fragility in childhood remains incomplete. Current knowledge is derived largely from cross-sectional observations in small convenience samples of patients. Longitudinal data from larger cohorts representing a spectrum of disease severity are needed to fully understand the long-term risk for fracture and the potential for recovery of bone mass with treatment.

It may be dangerous to extrapolate the risk of bone fragility in children from adult data. For example, chronic glucocorticoid therapy causes bone loss in older adults often enough to warrant trials of bisphosphonate as a preventive measure when steroid treatment in begun [45]. Bone loss may not be as common in all children on similar chronic high-dose corticosteroid regimens. A recent study found that children with steroid-responsive nephrotic syndrome who had received chronic, high-dose glucocorticoids had bone mineral that was comparable to that of healthy controls after adjusting for bone size [46]. The authors concluded that the bone loss seen in many chronic disorders is caused by disease-related malabsorption, inflammation, or other risk factors rather than to glucocorticoids. Findings such as these underscore the need to assess bone health in pediatric patients before treating.

Unfortunately there are few established practice guidelines for the use of DXAs in pediatric patients [47]. Consensus statements recommend that baseline DXA studies be performed in patients with cystic fibrosis and survivors of childhood cancer by age 18, with earlier screening in those deemed to be at increased risk for poor bone health [48,49]. For the remainder of childhood disorders linked to poor bone health, the clinician must rely on clinical judgment to decide who warrants bone densitometry. Factors such as disease severity, dose and duration of exposure to potentially harmful medication, bone pain, and a history of fracture after minimal trauma are useful parameters for selecting candidates for DXA. Bone densitometry also may be warranted for children with recurrent or low-impact fractures. The number of fractures meeting the criterion of recurrent is not set, and it is not always simple to determine the force of

impact at the time of fracture. By definition, a low-impact fracture is one occurring from standing height or less, but forces during sports such as soccer may be significant [50]. A DXA study also may be warranted in those patients diagnosed with osteopenia on a plain film.

Before ordering a DXA, the clinician should consider how the information will influence clinical management [47]. In adults, bone densitometry is performed to predict fracture, to decide which patients warrant treatment, and to monitor response to therapy. The rationale for bone density testing is potentially the same in children as in adults. The performance and interpretation of densitometry are far more challenging in the younger patient, however. In particular, the diagnosis of osteoporosis in a child or adolescent cannot be made on the basis of BMD findings alone [51]. Factors other than bone mass (as measured by densitometry) influence bone strength. Bone size, geometry, material properties, and the nature of the trauma contribute to determining whether a bone will break [34].

This is not to say that low bone mass is not associated with an increased risk of fracture. Studies in generally healthy children have found that those who sustain a forearm fracture have a lower mean bone density than peers without a history of fracture [52,53]. Similarly, studies in children with chronic illness have observed both low bone mass and an increased incidence of fractures [7,40]. The studies linking bone mass and childhood fracture, however, are not sufficiently large to establish criteria for a pediatric fracture threshold.

Given these limitations, how can bone densitometry contribute to management of a patient at risk for bone fragility? Finding evidence of low bone density for age should prompt clinicians to address all skeletal risk factors by optimizing calcium intake, ensuring adequate vitamin D stores, replacing sex steroid deficiencies, or ensuring as much weight-bearing activity as possible. Children and their parents who are informed their bone density is low may be more compliant in adhering to these measures, as has been shown in adults [54]. As discussed previously, low bone density alone is not a sufficient criterion for treatment with the various drugs used to treat osteoporosis in adults. The safety and efficacy of bisphosphonates have not been established for children and adolescents, and none are approved by the Food and Drug Administration (FDA) for pediatric use. Until further pediatric studies are available, pediatric bone experts have recommended that bisphosphonate use be restricted to children enrolled in research trials or to those who have sustained fragility fractures [55].

A final consideration before ordering a DXA is the likelihood that the study will be performed and interpreted appropriately with minimal risk to the patient. Can the child cooperate and lie still for the study without sedation? Are there metal clips or pins in the region of interest that would invalidate the study? Are there contractures or scoliosis that would prevent proper positioning for an accurate study of the region(s) of interest? Are age-appropriate reference data available for the skeletal site(s) studied? Most

importantly, is the center performing the DXA familiar with the challenges of pediatric subjects [47]? The potential for erroneous interpretation of DXA is great, resulting in misdiagnoses, false alarms and inappropriate use of drug therapy. In recruiting subjects for a study of childhood osteoporosis, Gafni et al found that 88% of the DXA scans of the patients referred had at least one error in interpretation [56]. The mistake in 62% was the use of adult reference data rather than pediatric norms, which resulted in the inappropriate labeling of children as osteoporotic. After correcting for the errors, only 26% of the subjects were found to have low BMD.

Ordering a dual-energy x-ray scan

The selection of skeletal site(s) to study by DXA depends upon the clinical concern being addressed. For example, glucocorticoid excess and sex steroid deficiency typically cause greater losses in trabecular than in cortical bone [23,27,28]. Scanning sites rich in trabecular bone such as spine and hip are appropriate. Conversely, growth hormone deficiency or hyperparathyroidism predisposes to greater losses of cortical bone, which may be detected better on whole body scans [24,25]. Other considerations in ordering site(s) for DXA include the time required to complete the examination (longer for whole body than for spine), the need to reposition the subject, and the availability of normative data. For most children, the posteroanterior spine (lumbar vertebrae 1–4 or 2–4) is the preferred site, because precision, speed, and normative data are best for this region. Lateral vertebral scans generally are reserved for research studies because of problems of poorer precision, interference from the ribs, the need for repositioning, prolonged scanning time, increased radiation exposure, and paucity of pediatric reference data [35].

Whole body scans are also a preferred site in children because precision is good and normative data are available. In children under the age of 10, the head contributes a considerable amount to the whole body measurement, thus reducing sensitivity for detecting age-related gains in bone mass or deficits due to illness [57]. Since pediatric norms for whole body BMD minus without the cranium are limited [57], however, many clinicians continue to include the head in the analysis.

The total hip, femoral neck and other regions of the proximal femur are the least useful sites for clinical studies in children because of the poorer precision, difficulty in identifying boney landmarks, and a paucity of normative data [58].

Contents of the dual-energy x-ray report

Bone mass as measured by DXA is reported in terms of bone mineral content (g) and bone mineral density (g/cm^2), which corrects bone mass for the

area of bone studied. DXA software programs then report a BMD T score, which is the number of standard deviations of that BMD from the mean for healthy adults. T scores should not be used in subjects younger than 20 years, because they have not reached peak bone mass yet [51]. To employ a T score in a younger subject is as inappropriate as using adult height standards to determine if a child is short. Instead, BMD data from children and adolescents should be expressed in terms of a Z score, the standard deviation from the mean for age- and gender-matched controls. If Z scores are not provided by the DXA software, published pediatric reference data can be used to calculate them. Unfortunately, there are no standardized pediatric norms, and calculated Z scores will vary depending upon the normative data used to calculate the standard deviation from the mean [59]. For this reason, the reference data used should be cited on the DXA report. Table 2 summarizes several larger DXA studies providing normative data from healthy youth [57,60–70]. All studies cited except that by Southard et al [60] provide appropriate gender-specific norms. Failure to calculate Z scores by both gender and age can lead to the overdiagnosis of low bone mass in males, particularly during the adolescent years, because females experience earlier peak height and bone mineral acquisition than males [59,61,71]. When selecting reference data, it is essential to use norms collected on DXA equipment from the same manufacturer because of the systematic differences between the devices. Ideally, data also should be collected using the same software version as used for the patient. Pediatric reference values from studies using the latest DXA software programs are available elsewhere [72,73].

Challenges of interpreting pediatric dual-energy x-ray

Interpreting bone mineral measurements is far more complex in children than in adults and goes beyond calculating a Z score [33,35,74,75]. Unlike the adult whose bone dimensions are stable with time, children and adolescents are moving targets whose bone size, geometry, and mineral content are changing. These processes evolve at varying rates in different regions of the skeleton, with appendicular growth preceding spinal mineral acquisition [75]. Furthermore, within a given region of interest, trabecular and cortical compartments respond variably to sex steroids, calcium intake, and mechanical loading. The tempo of mineral accrual is linked more closely to pubertal and skeletal maturation than to chronologic age, and these processes vary with gender and ethnicity [61,63,71,74,75]. For this reason, the influence of bone size and maturation must be considered in evaluating DXA results.

Young patients often have delayed growth and puberty and altered body composition; these must be considered in interpreting BMC and BMD. For children with delayed growth and maturation, it is reasonable to adjust for pubertal stage rather than for chronological age. Unfortunately, only a few studies have reported normative data by pubertal stage [65,69,76].

Alternatively, a bone age can be obtained and BMD data compared with norms for the patient's skeletal rather than chronological age.

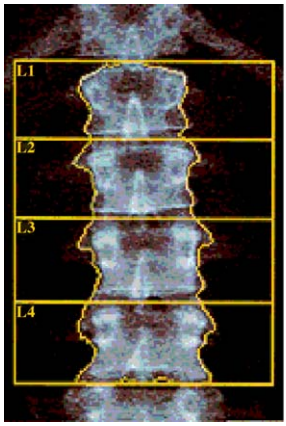
Additionally, BMC and BMD are influenced strongly by bone size; BMD corrects only for the area of bone studied but not the thickness of bone. For this reason, true (volumetric) bone density may be underestimated in patients with smaller bones and overestimated in larger children. Several methods have been proposed to adjust bone mass for the influence of bone size or lean body mass [66,68,77,78]. Estimates of volumetric bone density at the spine and femoral neck divide BMC by the estimated volume of bone in the region; total body BMC is corrected for relative height [78]. None of these correction models has been established as best by the gold standard of predicting childhood fracture. Furthermore, given two bones of equal density, the larger bone will be more resistant to fracture than the smaller one. Nonetheless, it is possible to estimate how much reduced BMD can be attributed to smaller bone size by calculating volumetric BMD. Limited pediatric norms for volumetric BMD have been published [63,65,66,78]. An example of a pediatric DXA interpretation is provided in Fig. 1.

Clinical implications of dual-energy x-ray findings

Osteoporosis is defined as "a disease characterized by low bone mass, microarchitectural deterioration of bone tissue, and a consequent increase in fracture risk" [34]. As this definition implies, reduced bone mass is but one risk factor for fracture, and it is the fracture risk that defines the disease. In elderly adults, however, low bone mass is a sufficiently powerful predictor of fracture that it has been used as a proxy for the diagnosis of osteoporosis. The World Health Organization (WHO) has set the criterion for osteoporosis as a BMD T score of less than -2.5; osteopenia is defined as a BMD T score between -1 and -2.5. BMD T scores are a key influence on therapeutic decision-making in the elderly [34].

The fracture risk associated with low BMD is far less certain in children and young adults. Patients with mild forms of osteogenesis imperfecta (OI), for example, have very low BMD but do not suffer spontaneous fractures. The International Society for Clinical Densitometry has determined that the diagnosis of osteoporosis in a young patient "should not be made on the basis of densitometric criteria alone" [51]. WHO criteria for osteopenia and osteoporosis are not appropriate for use in children, adolescents, and young adults. Terms such as low bone density for chronologic age may be used if the Z score is less than -2.0 [51]. By implication, the diagnosis of osteoporosis in a child requires additional clinical findings such as a history of low impact fracture.

Finding low bone mass on a pediatric DXA does not necessarily imply bone loss. Low bone mass in a child can result from inadequate gains of bone mineral, bone loss, or a combination of the two [10,79,80].



Pediatric interpretation of spine BMD

Z-score for age (14)*	-2.4
Z-score for bone age (12)	-1.2
Z-score for bone mineral apparent density**	-1.1

Fig. 1. Clinical case of a 14-year-old girl referred for bone density testing because of primary amenorrhea, weight loss, and suspected restrictive eating behavior. She had had a foot fracture in the past. Past medical history was noncontributory, and family history was negative for osteoporosis. On physical examination, she had a height and weight at the first percentile for age and Tanner 3 breast and Tanner 2 pubic hair development. No other abnormalities were seen. Lumbar spine (L_{2-4}) BMD was measured by DXA (Hologic Corp, Waltham, Massachusetts). The results were reported as a spine BMD of 0.668 g/cm^2 with a T-score of −3.4, in the osteoporotic range. T-score should not be included in the report of this 14-year-old. Analysis of Z-scores (standard deviations [SD] from pediatric reference means) indicates low BMD for chronologic age. Results within expected range when corrected for delayed bone age. When corrected for delayed bone age and small bone size (using estimated volumetric bone mineral apparent density or BMAD), the BMAD is 1.1 SD below expected. BMD within expected range if corrected for bone age and size. *Z-scores calculated from published normative data for Hologic [63]. **BMAD calculated using the equation of Carter and colleagues [77]. (Courtesy of Vibrant Life, Burbank, CA; with permission.).

Understanding this is critical, because most drugs used to treat osteoporosis in adults are anticatabolic agents that reduce bone loss. Children who fail to gain adequate bone mineral may require therapy that is anabolic or bone building. It is beyond the scope of this article to review the current therapies for pediatric osteoporosis and low bone mass [6,7]. At the very minimum, however, the finding of low bone mass should prompt a search for possible cause(s), including a review of overall nutrition, calcium intake, vitamin D stores (serum 25 hydroxyvitamin D), hormonal status, physical activity, and underlying disease status. All risk factors should be addressed.

The future of pediatric densitometry

The demand for bone density testing in children is likely to increase in coming years. Clinicians are aware of the importance of early bone health and the myriad threats to achieving optimal skeletal strength. Further research is needed to refine the indications for bone densitometry and to aid in

interpreting the results. DXA is a useful tool to evaluate the skeletal health of children with chronic disease or recurrent or low-impact fractures. These studies, however, must be interpreted with care by people who understand the influence of bone size, skeletal and sexual maturation, and body composition on BMC and BMD. Pediatric reference data collected using the latest densitometry software will help establish a more uniform definition of low bone mass [72,73]. Beyond this advance, there is a need to determine the best way to correct for bone size, maturity, body composition, and other variables. Assessments of bone geometry and quality using pQCT, biochemical turnover markers, and bone histomorphometry will also aid understanding of pediatric bone fragility. These data then must be tested to determine how well they predict current and future fractures, which is the ultimate concern for clinicians and patients. In the meantime, bone densitometry should be performed in centers familiar with the unique challenges in interpreting the results in children. Finally, treatment options need to be expanded to care for those children at greatest risk for bone fragility.

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