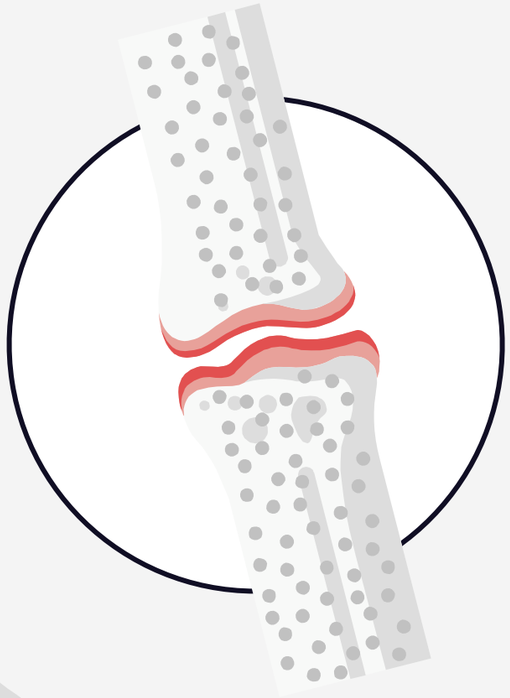
Critical Assessment of the Advantages and Limitations of Current Diagnostic techniques and an Evaluation of the Diagnostic Standard



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Clinical Risk Assessment Tools

Tool Name	Key Features	Usage
FRAX®	Integrates clinical risk factors ± BMD; 10-year fracture risk estimation	Worldwide; Clinical guidelines
QFracture	Includes additional comorbidities; UK based	Mainly UK
Garvan	Considers falls history; 5- and 10-year risk	Australia
Osteoporosis Self-Assessment Tool (OST)	Simple screening based on age and weight	Screening

Calculation Tool

Please answer the questions below to calculate the ten-year probability of fracture with or without BMD.

Continent Select a continent

Country Select a country

Local Reference Reference (optional)

About the risk factors

Questionnaire

1. Age (between 40 and 90 years) Age

2. Sex Female Male

3. Weight kg 0 kg / cm

4. Height cm 0

5. Previous Fracture X

6. Parent Fractured Hip X

7. Current smoking X

8. Glucocorticoids X

9. Rheumatoid arthritis X

10. Secondary osteoporosis X

11. Alcohol 3 or more units/day X

12. Femoral neck BMD Select BMD

Calculate | Clear

NEW

FRAXplus®

Fracture Risk Assessment Tool beta

Discover the advantages of FRAXplus®

FRAXplus® allows you to modify a probability result derived from conventional FRAX® estimates of probabilities of hip fracture and major osteoporotic fracture with knowledge of:

- Recency of osteoporotic fracture
- Higher than average exposure to oral glucocorticoids
- Information on trabecular bone score (TBS)
- Number of falls in the previous year
- Duration of Type 2 diabetes mellitus
- Concurrent information on lumbar spine BMD
- Hip axis length (HAL)
- Primary hyperparathyroidism
- Number of prior fractures

Caveat : There is no evidence base available to inform on the accuracy of multiple adjustments. Pragmatically, any adjustment should be made for the most dominant factor, i.e., that which is likely to have the greatest clinical relevance for the estimated probability.

Bone Turnover Markers in Osteoporosis

An updated consensus on the role of bone turnover markers in diagnosing and managing osteoporosis, with new guidance for chronic kidney disease patients.

Understanding Bone Turnover Markers

Formation Markers

PINP Serum procollagen type I N-propeptide and BALP measure bone-building activity by osteoblasts, indicating new bone formation.

Resorption Markers

β-CTX-I C-terminal telopeptide of type I collagen and TRACP5b **Tartrate-resistant acid phosphatase 5b** track bone breakdown by osteoclasts, showing bone loss activity.

Clinical Value

Fracture Risk Correlation:
Higher levels of bone turnover markers (BTMs), including β-CTX and PINP, are linked to increased fracture risk in postmenopausal women, regardless of bone mineral density (BMD). These markers reflect bone fragility caused by accelerated bone turnover, leading to weaker and less mineralized bone.

Monitoring Treatment and Adherence:
BTMs change more rapidly than BMD during osteoporosis therapy, making them useful for early monitoring of treatment response. A decline in β-CTX and PINP after starting antiresorptive drugs indicates reduced bone resorption and formation, helping clinicians assess drug efficacy, tailor therapies, and reinforce patient adherence.

Reference Markers Reaffirmed

Standard Osteoporosis

Serum PINP and **plasma β-CTX-I** remain the gold standard reference markers for patients with normal kidney function.

These markers show strong associations with fracture risk and treatment response, with standardized assays now available globally.

Chronic Kidney Disease

BALP and **TRACP5b** are recommended as reference markers for CKD patients, as they aren't affected by reduced kidney function.

Traditional markers accumulate in CKD, making them unreliable for assessing bone turnover in these patients.

Fracture Risk Prediction

21%

β-CTX-I Impact

Each standard deviation increase in β-CTX-I associates with 21% higher fracture risk in postmenopausal women.

30%

PINP Impact

PINP shows 30% increased fracture risk per standard deviation, demonstrating strong predictive value.

40%

BALP Impact

BALP indicates 40% higher fracture risk per standard deviation, particularly useful in CKD patients.

Meta-analyses confirm bone turnover markers independently predict fracture risk, though interaction with other risk factors requires further study.

Monitoring Treatment Response

1. **Baseline Assessment**

   Measure markers before starting treatment to establish individual baseline levels.

2. **Early Response (3-6 months)**

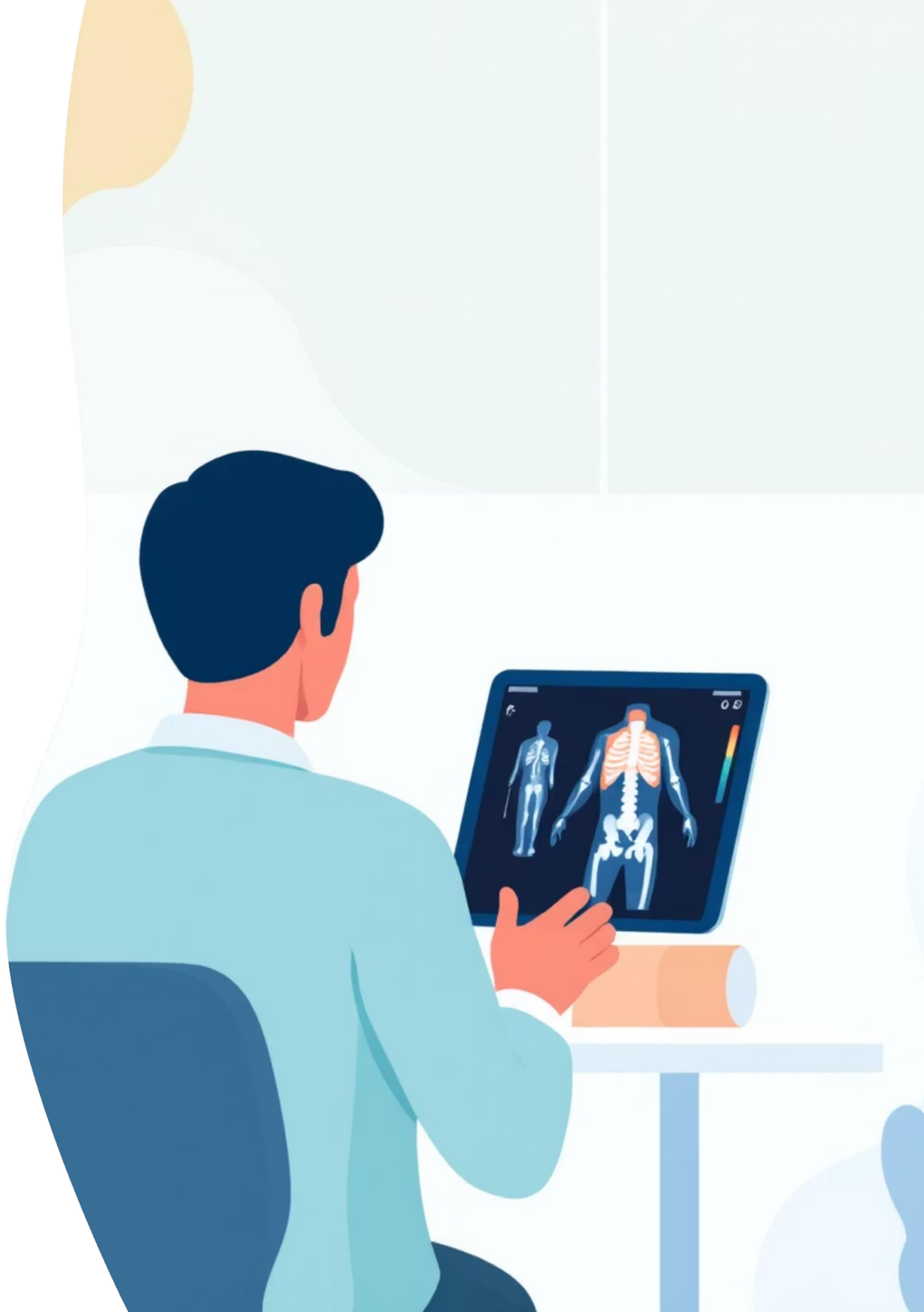
   Markers change rapidly with treatment—decreases of 30-80% indicate effective antiresorptive therapy.

3. **Treatment Monitoring**

   Regular measurements help identify non-adherence and guide treatment adjustments for optimal outcomes.

4. **Long-term Management**

   Continued monitoring supports medication adherence and helps manage treatment cessation safely.



Key Recommendations

01

Standardize Testing

Use harmonized assays with proper patient preparation: fasting for β-CTX-I, morning collection, consistent timing.

02

Expand Research

Conduct reference interval studies in diverse populations worldwide and examine marker interactions with FRAX risk factors.

03

CKD-Specific Approach

Implement BALP and TRACP5b as reference markers for chronic kidney disease patients to accurately assess bone health.

04

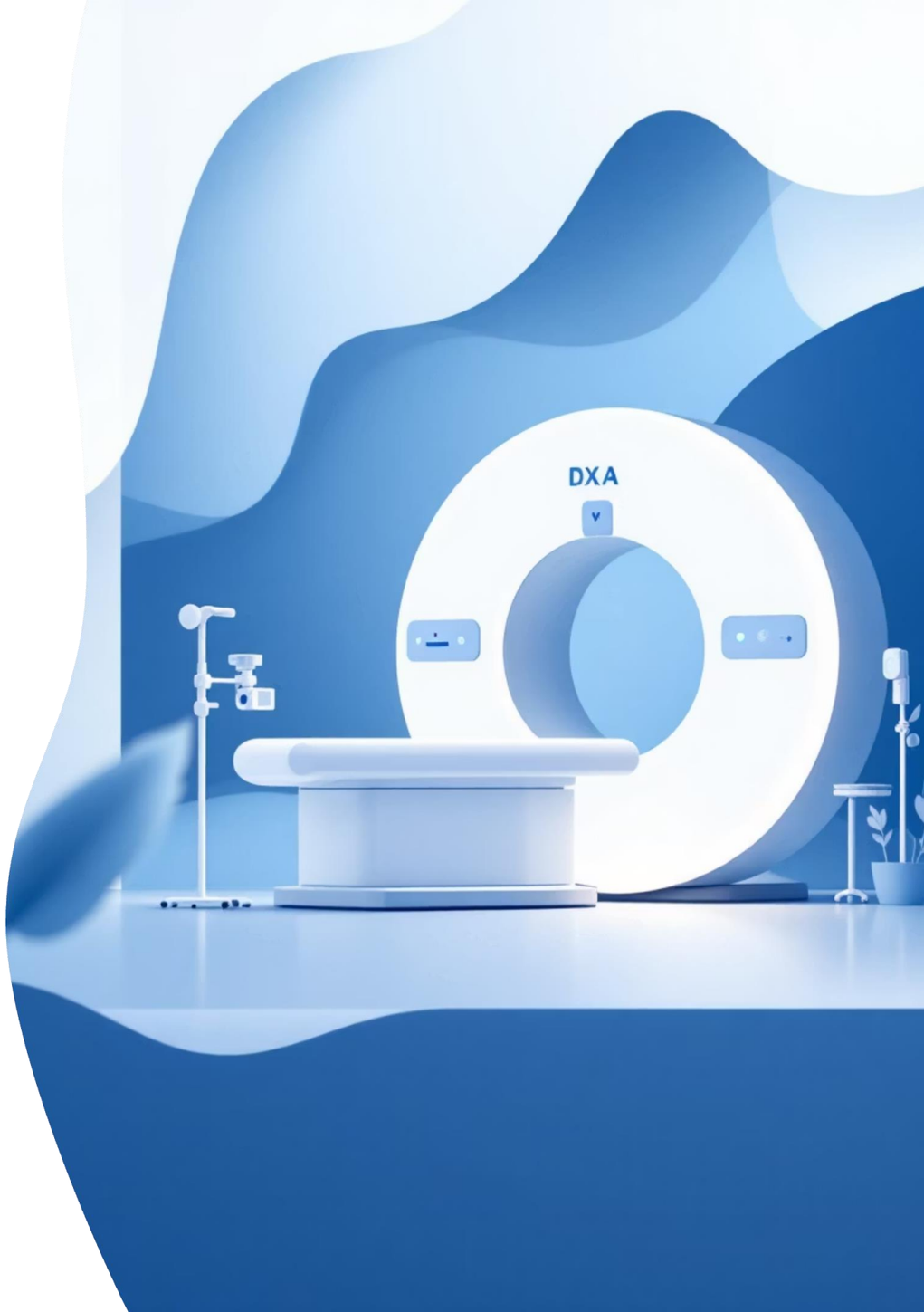
Clinical Integration

Incorporate bone turnover markers into routine practice for fracture prediction, treatment monitoring, and improving patient adherence.

DXA Best Practices

Dual-energy X-ray absorptiometry (DXA) revolutionized osteoporosis diagnosis and management since the 1980s. This updated guideline provides comprehensive recommendations for technical procedures, clinical interpretation, and best practices.

Endorsed by 14 international societies including AACE, ASBMR, EANM, ECTS, IOF, and ISCD.



Quality Control: Foundation of Accuracy

01

Daily Calibration

Scan calibration block and spine phantom at least 3 times weekly before patient use.

02

Precision Assessment

Each facility must determine precision error and calculate least significant change (LSC).

03

Cross-Calibration

Required when replacing scanners—scan phantom 10 times on each system, measures within 1%.

04

Service Thresholds

If results fall outside acceptable limits, contact field service engineer immediately.

Clinical Indications for DXA

Screening Populations

- All women ≥65 years
- Men ≥70 years
- Postmenopausal women <65 with risk factors
- Men 50-69 with risk factors

High-Risk Conditions

- Prior fragility fracture
- Chronic glucocorticoid use
- Hyperparathyroidism
- Cancer with endocrine therapy

Secondary Osteoporosis

- Rheumatoid arthritis
- Malabsorption disorders
- Hypogonadism
- Type 2 diabetes

DXA Printouts: Common Features

- Patient demographics
- Image of skeletal site
- Graph (age vs BMD)
- Numerical results

Patient Positioning: Critical for Accuracy

Lumbar Spine

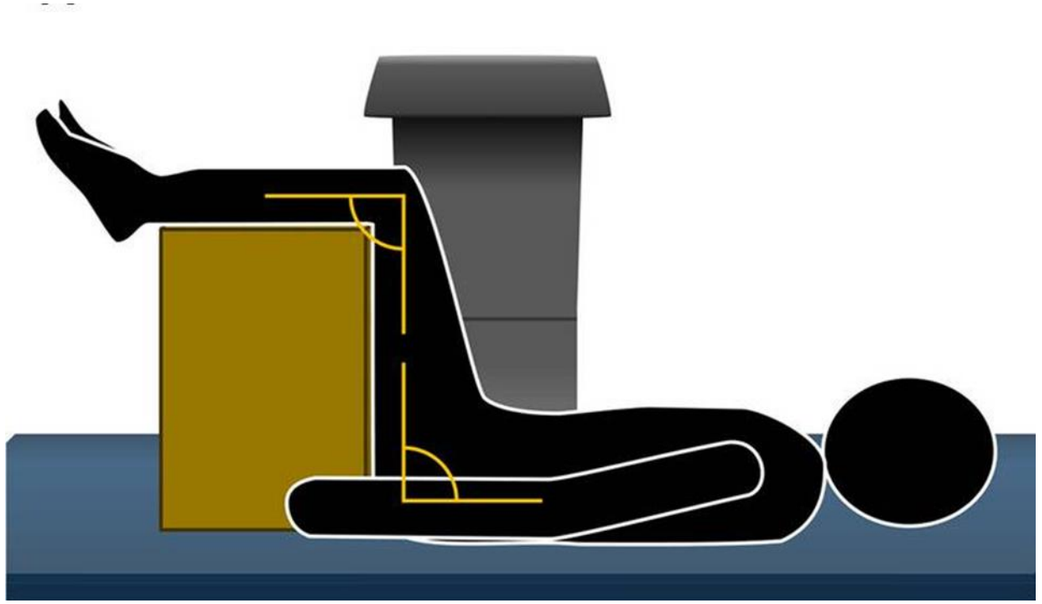
Patient supine, legs straight. Hips and knees flexed to 90° using positioning device to reduce lordosis and maximize vertebral area.

Hip

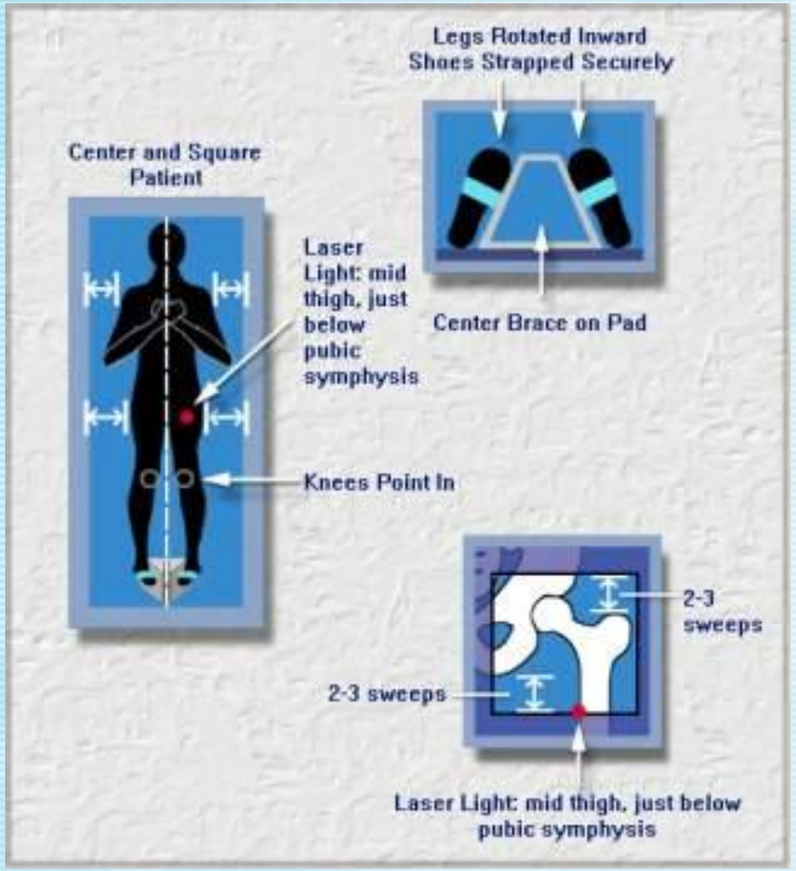
Scan non-dominant hip. Internal rotation 15-20° using foot positioning device. Lesser trochanter barely visible confirms proper rotation.

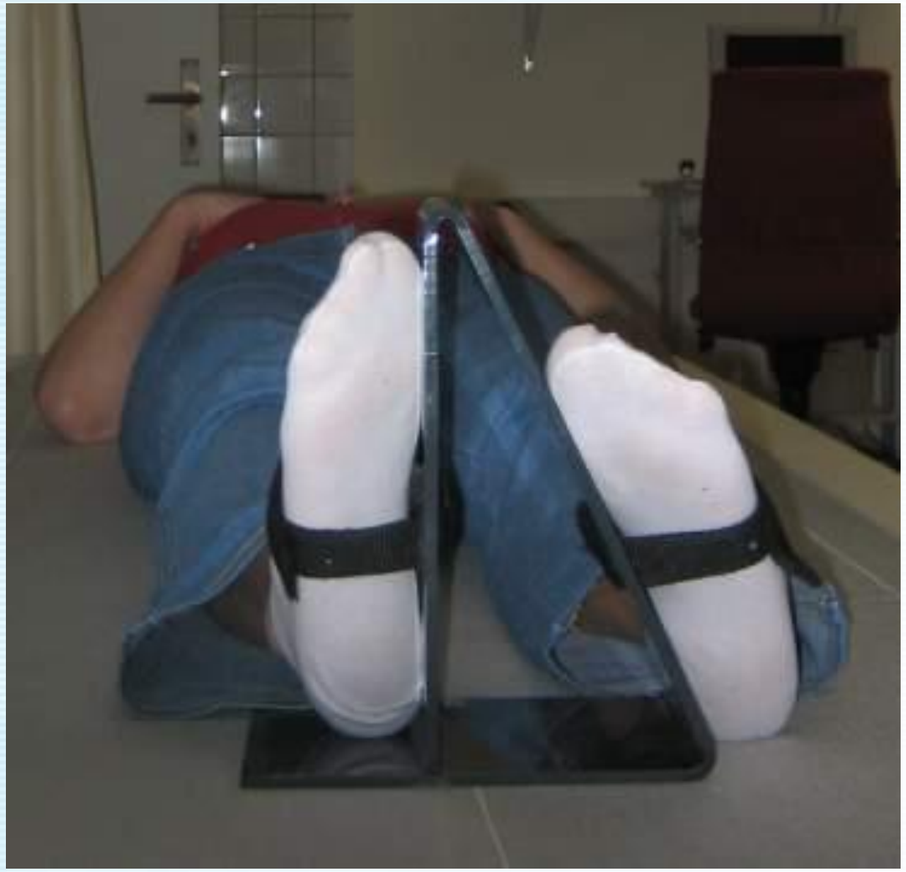
Forearm

Non-dominant arm when spine/hip unavailable or hyperparathyroidism present. Radius and ulna parallel to table.



Positioning: Hip

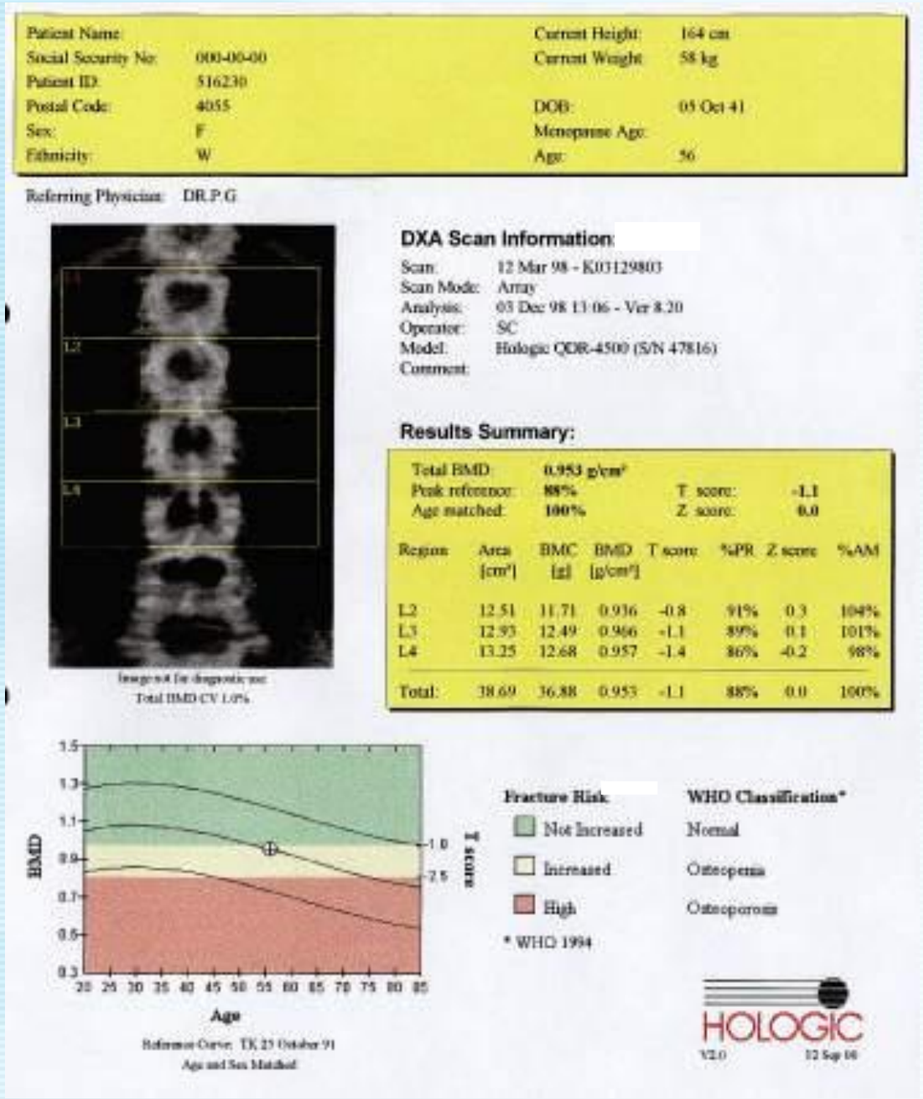




DXA Printouts: Hologic

Image

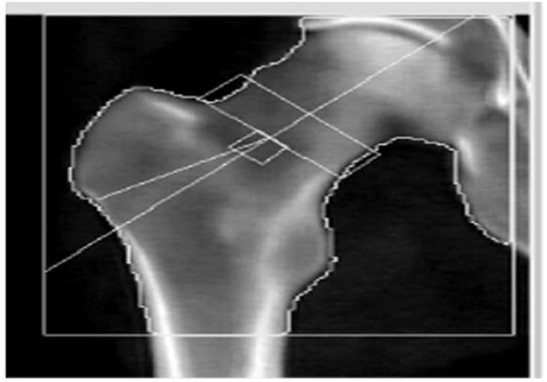
Graph

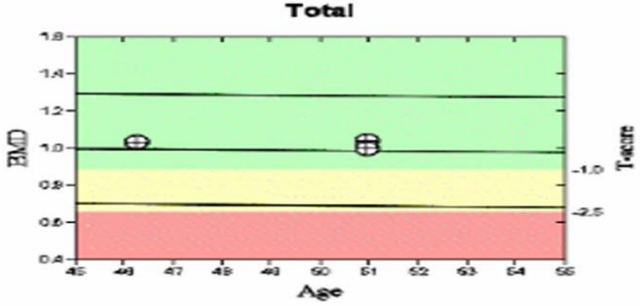


Demographics

Raw data
T- and Z-scores

A





Region	Area[cm²]	BMC[(g)]	BMD[g/cm²]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
Neck	5.99	4.90	0.818	-0.8	88	-0.1	99
Troch	13.43	11.02	0.820	0.3	106	0.6	111
Inter	33.20	38.84	1.170	-0.1	98	0.1	101
Total	**52.62**	**54.76**	**1.041**	**0.1**	**101**	**0.4**	**106**
Ward's	1.08	0.58	0.537	-1.8	68	-0.5	89

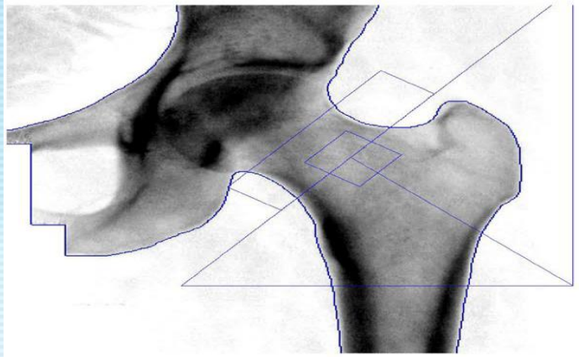
Scan Date	Age	BMD	T-score	BMD Change vs Baseline	BMD Change vs Previous
01.08.2023	50	1.041	0.1	0.8%	4.6%*
01.08.2023	50	0.995	-0.2	-3.6%*	-3.6%*
20.11.2018	46	1.032	0.0		

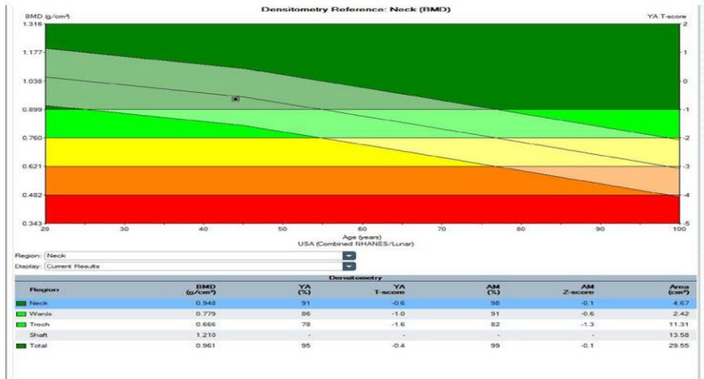
FRAX® Fracture Risk Assessment Tool

10-year Fracture Risk[1]	
Major Osteoporotic Fracture	**3.7%**
Hip Fracture	**0.3%**

Reported Risk Factors:
Netherlands, T-score(WHO)=-0.3, BMI=29.9, previous fracture, rheumatoid arthritis

B





DXA Image Interpretation

Review image quality and accuracy of scan acquisition and analysis

- Check patient positioning
- Check scan analysis
- Identify artifacts
- Disclaimer “Image not for diagnosis” is not a mandate to ignore the image

BMD Interpretation Standards

Diagnosis

- T-score: SD difference of patient's BMD compared to young healthy reference population; preferred for postmenopausal women, men >50, and perimenopausal women

- Z-score: SD difference from age- and sex-matched population; recommended for children, adolescents, premenopausal women, men <50 years
- IOF supports T-score use even in younger adults with skeletal fragility

Common Pitfalls: PARED Approach

Positioning

Verify correct patient alignment, rotation, and use of positioning devices.

Artifacts

Check for osteoarthritis, fractures, surgical hardware, implants, contrast material, or calcifications.

Regions of Interest

Ensure ROI placement is correct and analogous on follow-up scans.

Edge Detection

Verify software correctly identifies bone edges and boundaries.

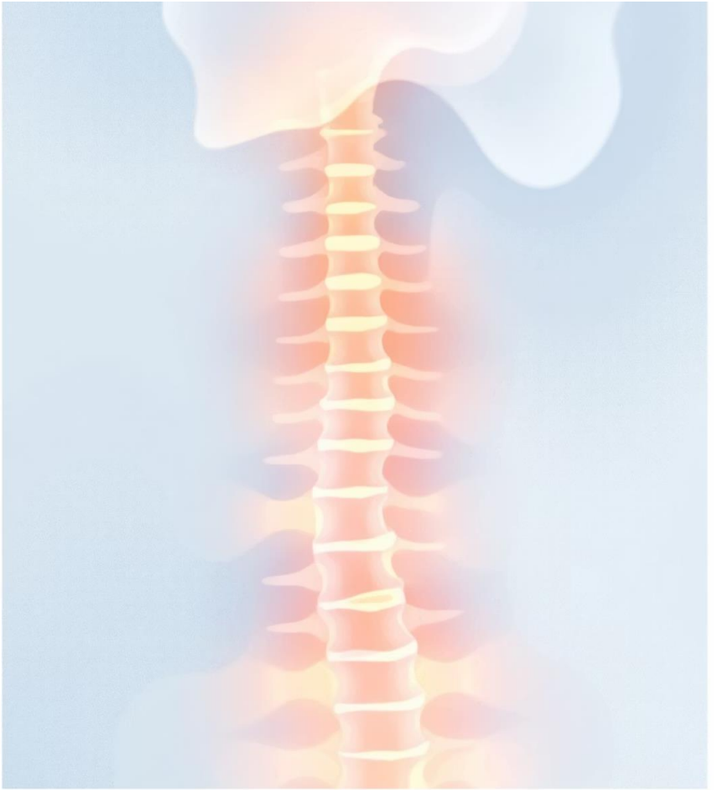
Demographics & Database

Confirm patient information, risk factors, and appropriate reference database selection.

Vertebral Fracture Assessment (VFA)

VFA uses low-dose lateral spine imaging to diagnose vertebral fractures from T4-L4. Perform VFA when:

- T-score <-1.0 with age ≥70 (women) or ≥80 (men)
- Historical height loss >4 cm
- Self-reported prior vertebral fracture
- Glucocorticoid therapy ≥5 mg/day for ≥3 months



Monitoring Treatment Response

Baseline

Initial DXA establishes starting BMD values for future comparison.

1

1-2 Years

Anabolic therapy may show significant lumbar spine changes after 1 year.

2

2-3 Years

Anti-resorptive therapy typically requires 2-3 years to exceed LSC threshold.

3

Individualized

Adjust intervals based on therapy type, baseline BMD, and clinical factors.

4

Maximum acceptable LSC: 5.0% for total hip, 5.3% for lumbar spine. Use absolute BMD values (g/cm^2), not T-scores, for comparison.

Repeat BMD technical considerations

- Repeat BMD scans should ideally be done at the same facility using the same DXA system, software, scan mode, patient positioning, and same hip/forearm sides.
- BMD comparison uses absolute BMD values (g/cm^2), not T- or Z-scores.
- Each facility should calculate its own precision error and Least Significant Change (LSC) for each skeletal site using repeated scans on representative patients.
- Changes in lumbar spine and total hip BMD must exceed LSC to be clinically significant.
- ISCD recommends max acceptable LSC of 5.0% for total hip and 5.3% for lumbar spine per technologist.
- Absolute BMD change (g/cm^2) preferred over % change in clinical practice.

Advanced DXA Applications

Trabecular Bone Score (TBS)

Assesses bone microarchitecture quality.

Abdominal Aortic Calcification

VFA images can identify AAC using 24-point or simplified 8-point scoring systems, predicting cardiovascular events.

Atypical Femur Fractures

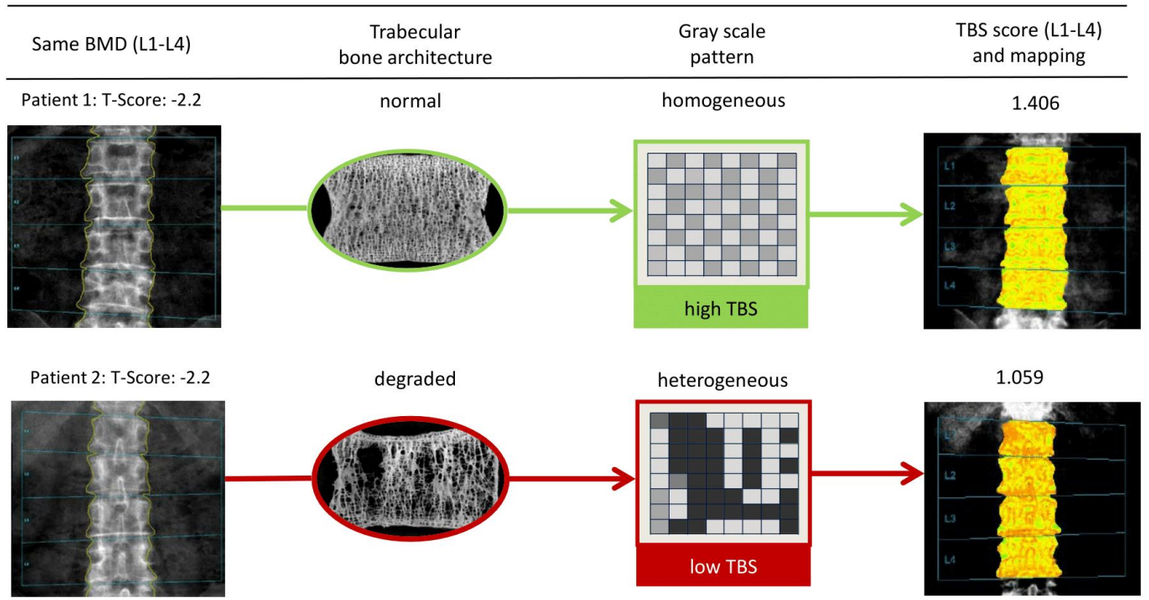
Full-femur imaging detects incomplete atypical fractures—focal cortical thickening with/without lucent line on lateral cortex.

Whole Body Composition

Measures total/regional BMC, lean mass, fat mass. Useful for sarcopenia assessment and cardiometabolic risk stratification.

Trabecular Bone Score (TBS)

- TBS is a DXA-based software applied to lumbar spine BMD images, usable retrospectively without repeat scans.
- It assesses pixel-level texture variations in DXA images to provide an indirect measure of bone microarchitecture.
- High TBS indicates strong, fracture-resistant trabecular bone; low TBS reflects frail, fracture-prone microarchitecture.
- TBS predicts fragility fracture risk independently of BMD and clinical risk factors in adults over 50.
- Useful in monitoring response to anabolic or long-term denosumab therapy; less so for bisphosphonates or short-term denosumab.



Quantitative Computed Tomography (QCT)

Quantitative Computed Tomography (QCT) is an advanced imaging technique that utilizes CT scans to provide accurate, volumetric measurement of bone mineral density (BMD) at the spine and hip, enabling separate assessment of trabecular and cortical bone compartments. Unlike Dual-energy X-ray Absorptiometry (DXA), which provides two-dimensional areal BMD, QCT calculates true volumetric density in mg/cm^3 for a more precise evaluation of bone quality.

Pros and Cons of QCT

Pros	Cons
Volumetric (3D) BMD measurement, allows differentiation of trabecular vs. cortical bone	Higher radiation dose than DXA (although modern protocols and devices minimize exposure)
Not affected by osteophytes, vascular calcifications, or patient positioning errors that bias DXA results	Cost and availability: requires CT scanner and specialized software
Useful in patients with significant vertebral deformities, high/low BMI, or post-surgery (where DXA is limited)	Less longitudinal outcome data for fracture prediction compared to DXA; less experience monitoring therapy
More sensitive to changes in trabecular bone, which is more metabolically active and responds sooner to disease and therapy	May be confounded by bone marrow adiposity or metallic hardware/artifacts
Can be performed opportunistically on routine CT scans (phantomless QCT methods)	Contrast media, hardware, or inability to position may limit scan quality or interpretability

Indications for QCT Use

- Screening for osteoporosis in high-risk populations (women ≥65 years, men ≥70 years; younger adults with risk factors or prior low-impact fractures)
- Assessment of BMD in patients with abnormal bone metabolism, including those with:
  - Endocrine disorders affecting bone (hyperparathyroidism, Cushing syndrome, hyperthyroidism)
  - Chronic disorders (chronic kidney disease, malabsorption syndromes, chronic steroid use, multiple myeloma, organ transplant, prolonged immobilization)
  - Prior fracture or imaging findings suggestive of demineralization
- Monitoring effectiveness of osteoporosis therapy, especially with agents impacting trabecular bone
- Evaluation of BMD where DXA is unreliable due to obesity, degenerative disease, post-surgical changes, or presence of spinal hardware
- Pediatric bone densitometry in select conditions (e.g., bone dysplasia, endocrine disturbances, chronic disease with risk of fracture) where DXA is problematic

MRI in BMD Measurement

Magnetic Resonance Imaging (MRI) provides noninvasive, radiation-free imaging of bone microarchitecture and marrow composition, offering detailed insights into trabecular and cortical bone structure beyond simple BMD quantification. Unlike DXA or QCT, which measure total bone mineral density directly, MRI can quantify microarchitecture (e.g., trabecular thickness, connectivity, cortical porosity), estimate fat and water content, and assess marrow signal properties—sometimes using novel scoring systems such as M-score or VBQ score to estimate osteoporosis risk

Pros and Cons of MRI

Pros	Cons
No ionizing radiation exposure; safe for all ages, repetitive imaging possible	Costly; less widely available than DXA/QCT for BMD measurement
Provides information on bone quality: detects microstructural deterioration, marrow fat content, fracture risk	Cannot directly measure bone mineral density in mg/cm^3 or g/cm^2
Can be performed opportunistically using clinically indicated spine MRI scans; useful in patients with frequent MRI for other indications	Technical complexity; diverse pulse sequences, scanner models, and protocols reduce standardization
High sensitivity for marrow pathology, bone tumors, metastatic disease	Scan duration is longer; motion, claustrophobia, or presence of implants may limit imaging quality
Emerging MRI-derived scores (e.g., M-score, VBQ score) offer good sensitivity, specificity for opportunistic osteoporosis screening as adjunct methods	Validation is limited; not yet standardized for routine osteoporosis diagnosis or monitoring therapy

Conclusion & Key Takeaways

- **Integrated Approach is Essential:** Fracture risk assessment requires a combination of clinical risk factors (FRAX®), BMD measurement, and, where appropriate, Bone Turnover Markers and advanced tools like TBS.
- **DXA Remains the Cornerstone**: DXA is the primary tool for BMD measurement and diagnosis, with strict adherence to quality control and standardized interpretation (T-scores, Z-scores) being paramount for accuracy.
- **Beyond Areal BMD**: Advanced DXA applications (TBS, VFA) and other modalities (QCT, MRI) provide crucial insights into bone quality, microarchitecture, and secondary conditions, enriching the diagnostic process, especially in complex cases.
- **Tailored Patient Management:** The choice of diagnostic technique and monitoring interval should be individualized based on the patient's clinical profile, risk factors, comorbidities, and the specific therapy employed.