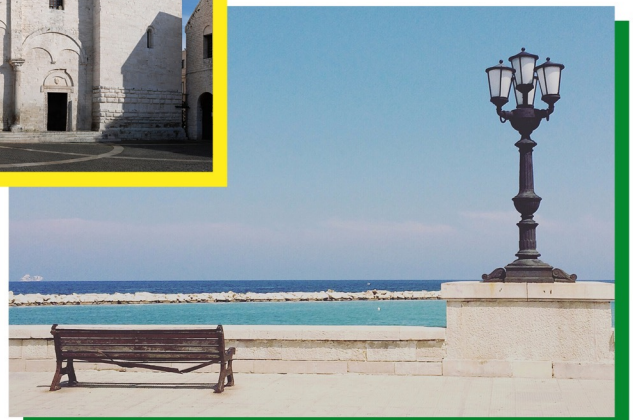
FONDAZIONE ITALIANA LINFOMI

LATE EFFECTS
GUARIRE DAL LINFOMA E VIVERE BENE



Prevenzione dell'Osteoporosi

Bari, 17-18 febbraio 2023

Aula Magna
Università degli Studi di Bari "Aldo Moro"

Ombretta Annibali,MD,PhD
Fondazione Policlinico Campus Bio medico, Roma

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen-Cilag					X		
Amgen					x		
Takeda							X

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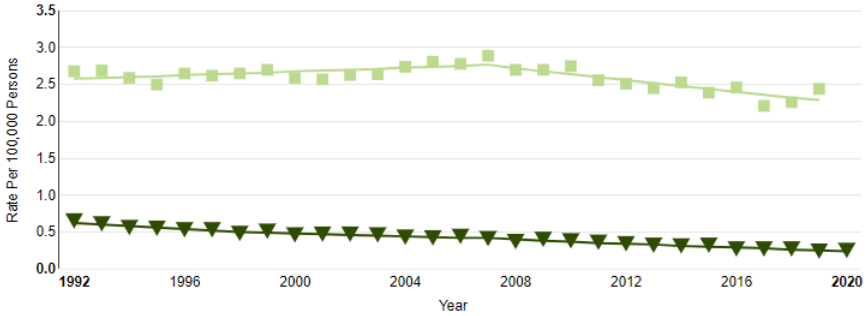
Hodgkin Lymphoma

Estimated New Cases in 2022	8,540
% of All New Cancer Cases	0.4%
Estimated Deaths in 2022	920
% of All Cancer Deaths	0.2%

5-Year Relative Survival

89.1%

2012–2018



Non Hodgkin Lymphoma

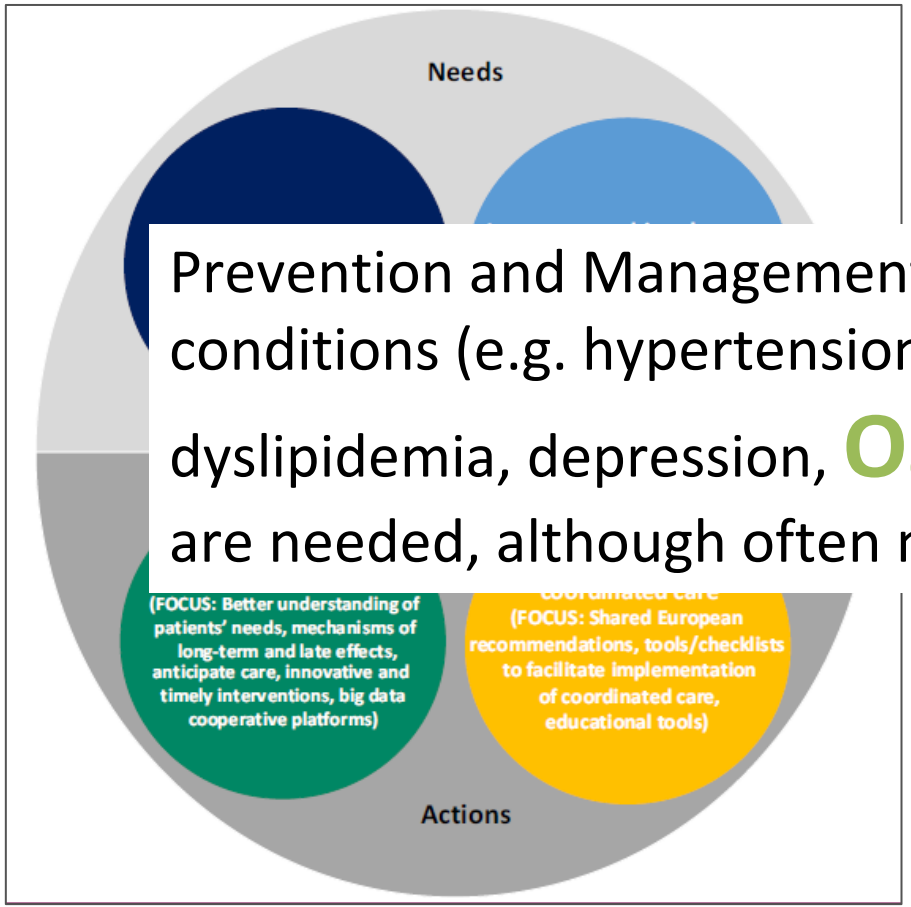
Estimated New Cases in 2022	80,470
% of All New Cancer Cases	4.2%
Estimated Deaths in 2022	20,250
% of All Cancer Deaths	3.3%

5-Year Relative Survival

73.8%

2012–2018

[Surveillance, Epidemiology, and End Results Program (cancer.gov)]



Prevention and Management for chronic medical conditions (e.g. hypertension, diabetes, dyslipidemia, depression, **OSTEOPOROSIS**) are needed, although often not done systematically

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

…orship: promoting

…hip care
…ddress

in the care plan of cancer

(i) surveillance and management of physical effects of cancer and chronic medical conditions;
(ii) surveillance and management of psychological effects of cancer;
(iii) surveillance and management of social, work and financial effects of cancer;
(iv) surveillance for recurrences and new cancers;
(v) cancer prevention and overall health and well-being promotion.

https://doi.org/10.1016/j.annonc.2022.07.1941

OSTEOPOROSIS

is a chronic bone disease characterized by decreased bone mineral density (BMD), leading to increased fracture risk, a condition that affects more than 10 million individuals in the United States.

J Clin Oncol 30:3665-3674. 2012, Br J Haematol. 2022;198:431–442.

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The Epidemiology of Osteoporosis

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Abstract

Introduction—With a worldwide ageing population, the importance of the prevention and management of osteoporotic fragility fractures is increasing over time. In this review, we discuss in detail the epidemiology of fragility fractures, how this is shaped by pharmacological interventions and how novel screening programmes can reduce the clinical and economic burden of osteoporotic fractures.

Sources of data—PubMed and Google Scholar were searched using various combinations of the keywords 'osteoporosis', 'epidemiology', 'fracture', 'screening' 'FRAX, and 'SCOOP'.

Areas of agreement—The economic burden of osteoporosis-related fracture is significant, costing approximately $17.9 billion and £4 billion per annum in the USA and UK.

Osteoporosi: 9,4 miliardi di euro i costi per il Ssn delle fratture da fragilità nel 2017

560.000 nuovi casi di fratture ossee verificatisi in Italia nel 2017

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Risk Factors for low bone Mass and Osteoporosis

General

- Age: women 65 and older, men older than 70
- Caucasian or Asian ethnicity
- Family history of osteoporosis
- Has experienced a low-impact fracture
- Maternal or parental hip fracture
- Postmenopausal status

Lifestyle

- Cannot rise from a chair for extended time
- Cigarette smoking (active or passive)
- High alcohol intake (three or more drinks per day)
- Sedentary lifestyle; low physical activity

Nutrition

- High caffeine consumption
- Low calcium intake
- Vitamin D deficiency
- Thin: weight less than 127 lbs; BMI lower than 19

Medications (Long-Term Therapy)

- Aluminum (in antacids)
- Anticonvulsant therapy (phenobarbital, phenytoin)
- Aromatase inhibitor for breast cancer
- GnRH analog for prostate cancer
- Immunosuppressant agents
- Long-term corticosteroid use (5 mg prednisone per day for three months or longer)
- Long-term heparin use
- Parenteral progesterone
- Proton pump inhibitors
- Supraphysiologic doses of thyroxine
- Tamoxifen (premenopausal women)
- Total parenteral nutrition

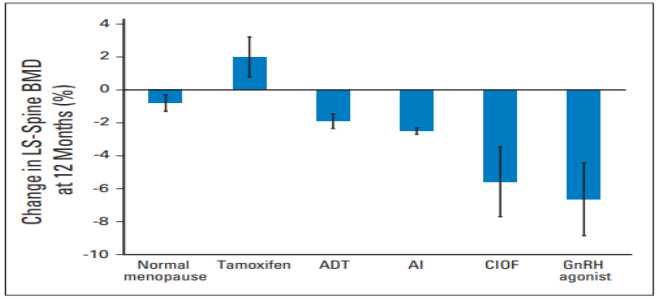
Clinical Journal of Oncology Nursing, 2011

Medical Conditions

Cancer-related
- Leukemia or lymphoma
- Multiple myeloma
- Solid organ or allogeneic stem cell transplantation

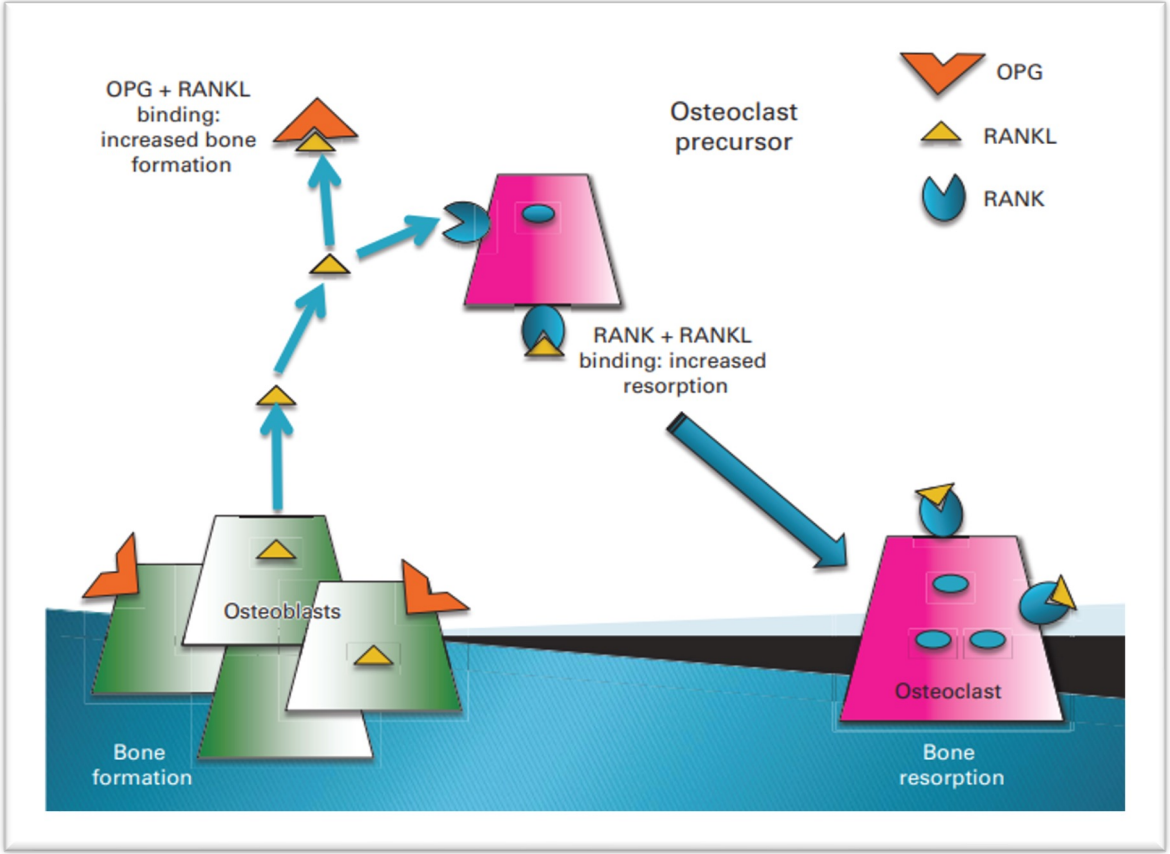
General
- Amyloidosis
- Ankylosing spondylitis
- Celiac disease
- Cerebral vascular accident
- Chronic obstructive pulmonary disease
- Congenital porphyria
- Cushing syndrome
- Dialysis
- Eating disorder (e.g., anorexia, bulimia)
- Gastric bypass
- Gastrointestinal surgery
- Gaucher disease
- Hemochromatosis
- Hemophilia
- HIV
- Hyperparathyroidism
- Hyperthyroidism
- Hypogonadism
- Hypophosphatasia
- Idiopathic scoliosis
- Inflammatory bowel disease
- Insulin-dependent diabetes
- Malabsorption syndrome, including gastrectomy or bariatric surgery
- Mastocytosis
- Multiple sclerosis
- Pernicious anemia
- Rheumatoid arthritis
- Severe liver disease
- Spinal cord transaction
- Thalassemia
- Weight loss

BMI—body mass index; GnRH—gonadotropin-releasing hormone



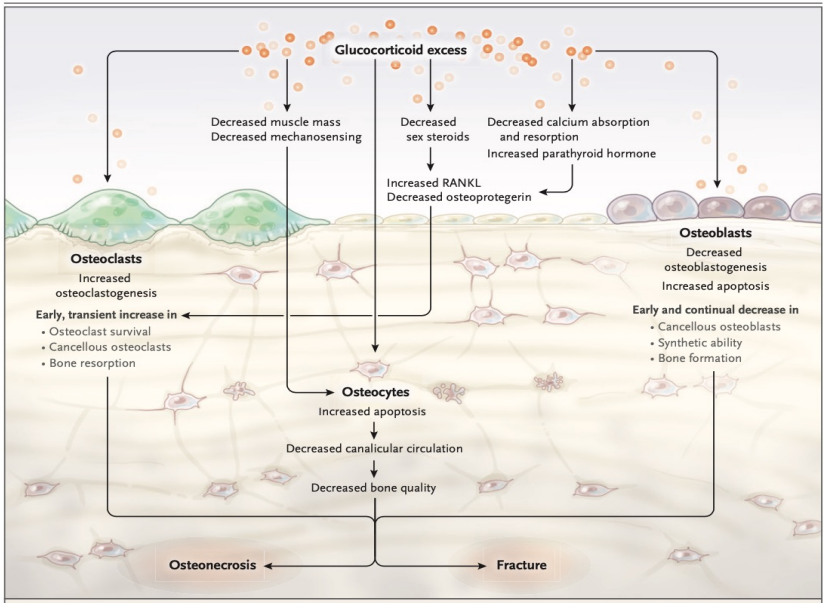
J Clin Oncol 30:3665-3674. 2012

NORMAL BONE REMODELING



J Clin Oncol 30:3665-3674. 2012, Br J Haematol. 2022;198:431–442.

GLUCOCORTICOID INDUCED OSTEOPOROSIS-GIO



N EJM 379;26 nejm.org December 27, 2018

Arthritis & Rheumatology
AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY
American College of Rheumatology

Special Article | Free Access

2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

Correction(s) for this article

PTS receiving doses
≥2.5 mg/day for ≥3 months

R-CHOP/R-miniCHOP
4 cycles q21 days

	R-CHOP	R-miniCHOP		
Rituximab[c]:	375mg/m²	375mg/m²	iv	d1
CTX:	750mg/m²	400mg/m²	iv	d1
DOXO[d]:	50mg/m²	25mg/m²	iv	d1
VCR[e]:	2mg	1mg	iv	d1
PDN:	60mg/m²	40mg/m²	po	d1-d5

Receiving doses
≥24 mg/day for ≥18 weeks

Table 1. Risk Factors for Fractures in Patients Receiving Glucocorticoids.*

Category of Risk	Risk Factors
Related to glucocorticoid use	High daily dose of glucocorticoid (e.g., >7.5 mg of prednisone daily), cumulative dose of glucocorticoid >5 g, current or recent (<3 mo) use of glucocorticoid, glucocorticoid-associated myopathy that increases the risk of falls, glucocorticoid-induced hypogonadism
Related to underlying condition	Rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, biliary cirrhosis
Related to risk of osteoporosis	Age >55 yr; white race; female sex; menopause; smoking; excess alcohol use (>2 units per day)†; bone mineral density T score below –1.5; increased fall risk; endocrine disorders: hypogonadism, hyperparathyroidism, or hypoparathyroidism; malabsorption; BMI <18.5; previous fracture

* The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
† According to the U.K. National Health Service, a standard glass of wine (175 ml) is 2.1 units (www.nhs.uk/live-well/alcohol-support/calculating-alcohol-units/).

N EJM 379;26 nejm.org December 27, 2018

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.....on Lymphoma

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Reference	Study design	Pts	Treatment	BMD	Fractures
Cannabillas 2007	Cohort study NHL	13570 pts > 65 yrs 8152 CHT 5418 no CHT Follow-up 11 ys	High dose steroid	10% Osteoporosis in CHT vs 8,3% in no CHT	31% fractures in CHT versus 18,5%
Beach 2020	Cohort study based on Danish lymphoma registry	2589 NHL Age 64 years Matched to 12945 general population FU 5,4 ys	R-CVP or R-CHOP (-like)	10 ys cumulative risk of osteoporotic event 16,3% versus 13,5%	No reported
Svendsen 2016	Single –centre cohort study	111 DLBCL Median age 65 ys FU 5,2 ys	R-CHOP or R-CHOP like	BMD measured at L3 level decreased significately (76% BMD loss after 2 ys)	14% had new or progression vertebral fractures
Booth 2020	Cohort study from 10 UK centres	729 DLBCL patients > 70 ys . FU 6 months and up 18 months	R-CHOP full or attenuated(26%). CS doses 40 mg/m2 in 469 pts 100 mg fixed dose in 260 pts	Osteoporosis risk not reported	6.2% at 6 months and 11,4% at 18 months

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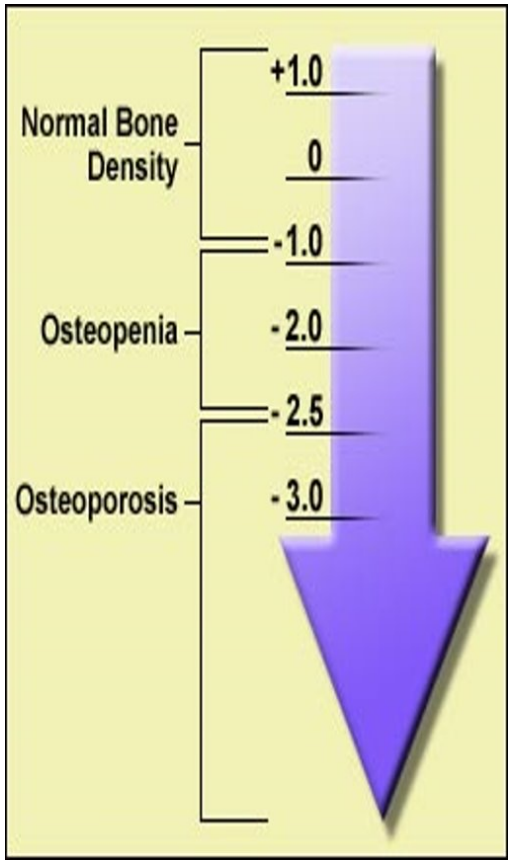
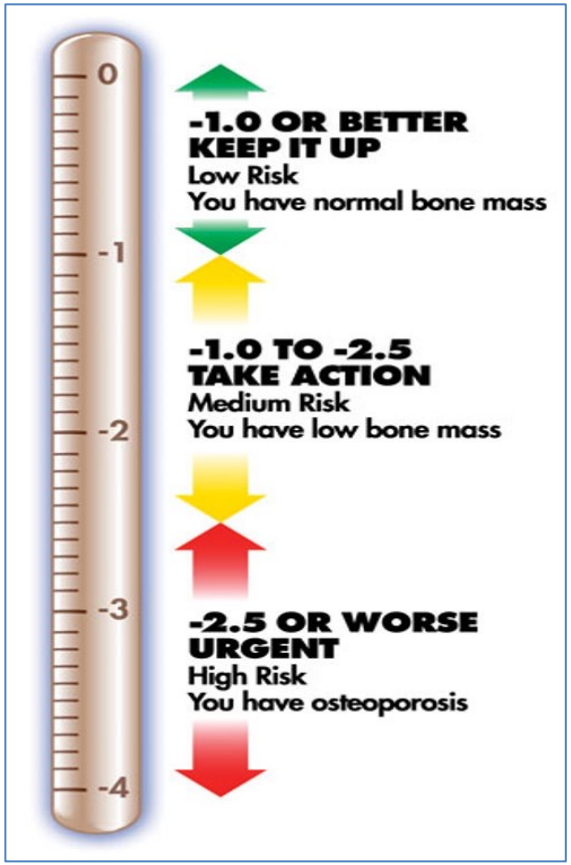
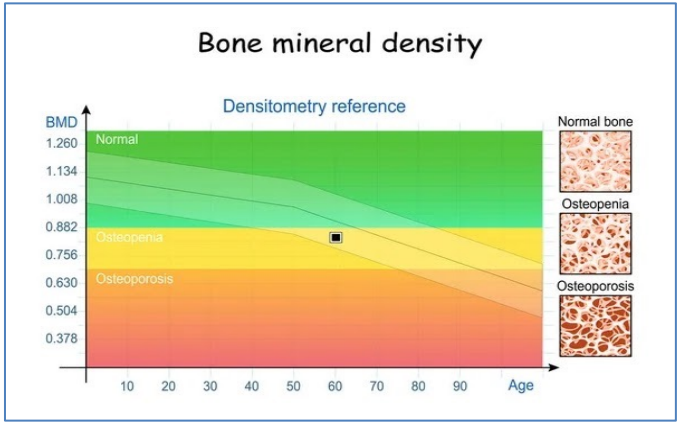
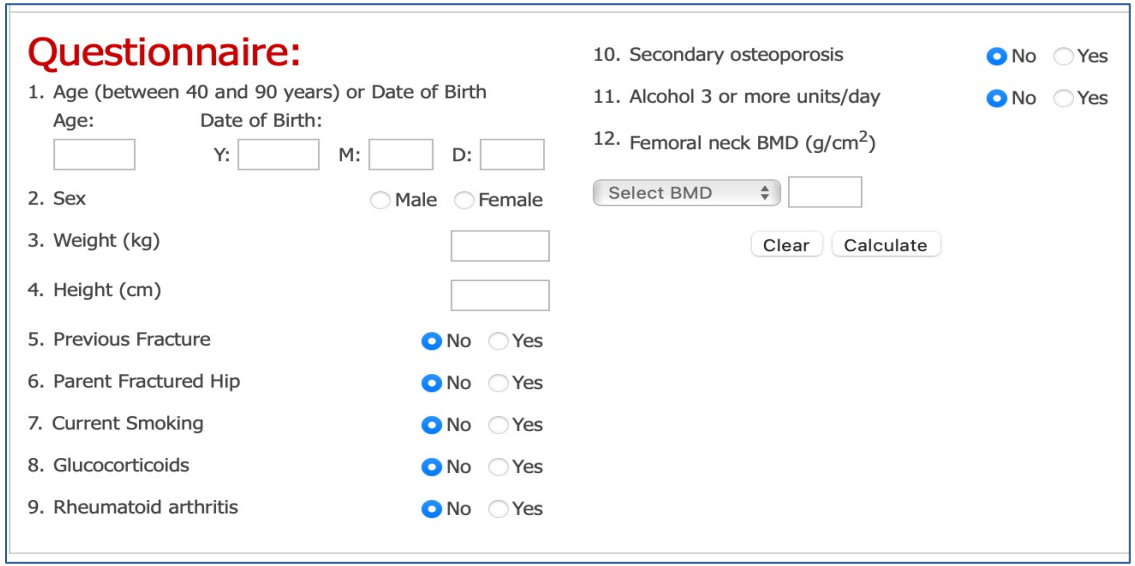
DUAL-ENERGY X-RAY ABSORPTIOMETRY (DEXA)









Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: Date of Birth: Y: M: D:
2. Sex ○ Male ○ Female
3. Weight (kg)
4. Height (cm)
5. Previous Fracture ● No ○ Yes
6. Parent Fractured Hip ● No ○ Yes
7. Current Smoking ● No ○ Yes
8. Glucocorticoids ● No ○ Yes
9. Rheumatoid arthritis ● No ○ Yes
10. Secondary osteoporosis ● No ○ Yes
11. Alcohol 3 or more units/day ● No ○ Yes
12. Femoral neck BMD (g/cm^2)

Select BMD

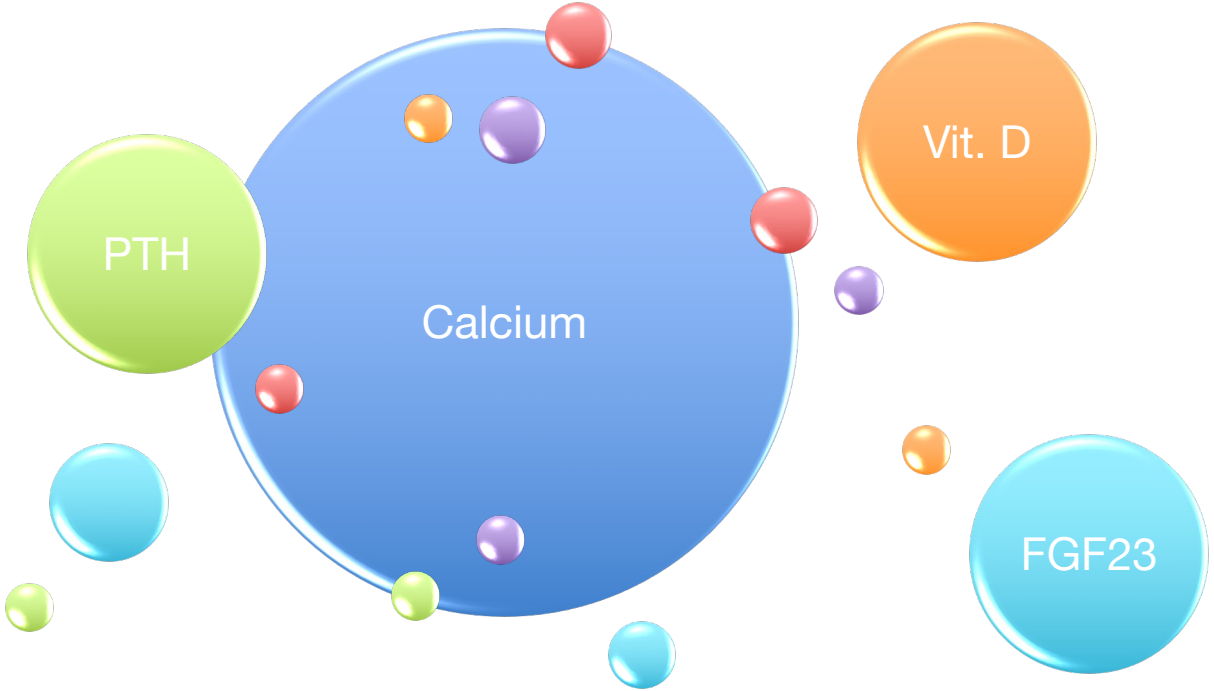
Clear Calculate

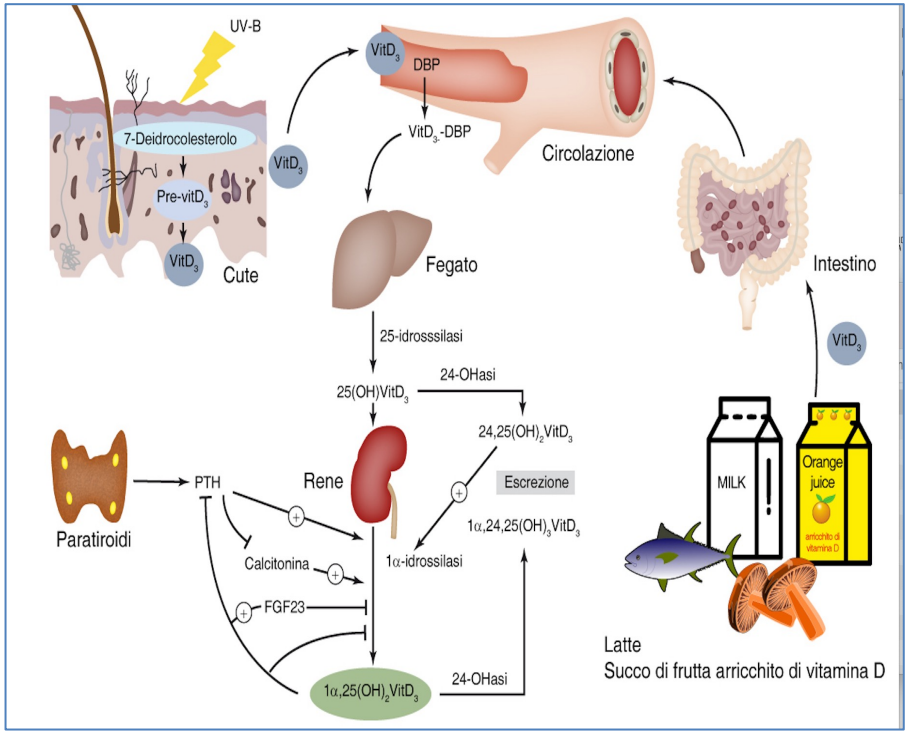
http://www.shef.ac.uk/FRAX/

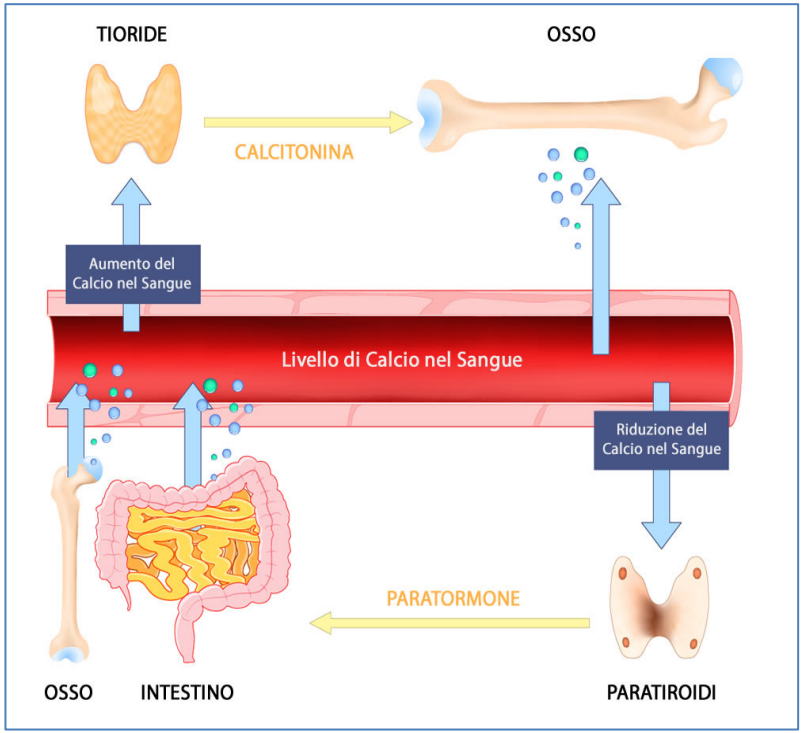
The National Bone Health Alliance recommends that a clinical diagnosis of osteoporosis may be made, when the Fracture Risk Assessment Tool (FRAX):

10-year probability of major osteoporotic fracture is ≥20 percent or the 10-year probability of hip fracture is ≥3 percent

Vitamin D-Ca+-PTH




UV-B
7-Deidrocolesterolo
Pre-vitD3
VitD3
Cute
VitD3
DBP
VitD3-DBP
Circolazione
Fegato
Intestino
25-idrosssilasi
25(OH)VitD3
24-OHasi
24,25(OH)2VitD3
Escrezione
1α,24,25(OH)3VitD3
1α-idrossilasi
Paratiroidi
PTH
Rene
Calcitonina
FGF23
1α,25(OH)2VitD3
24-OHasi
MILK
Orange juice
arricchito di vitamina D
Latte
Succo di frutta arricchito di vitamina D


TIORIDE
OSSO
CALCITONINA
Aumento del Calcio nel Sangue
Livello di Calcio nel Sangue
Riduzione del Calcio nel Sangue
PARATORMONE
OSSO
INTESTINO
PARATIROIDI

EVALUTATION

Table 1 Procedures proposed in the investigation of osteoporosis

Routine

- History and physical examination
- Blood cell count, sedimentation rate or C-reactive protein. Serum calcium, albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases
- Thyroid function tests
- Bone densitometry (DXA)

Other procedures, if indicated

- Lateral radiographs of lumbar and thoracic spine or DXA-based lateral vertebral imaging
- Serum protein immunoelectrophoresis and urinary Bence Jones proteins
- Serum 25-hydroxyvitamin D
- Plasma parathyroid hormone
- Serum testosterone, sex hormone binding globulin, follicle stimulating hormone, luteinizing hormone (in men)
- Serum prolactin
- 24 h urinary free cortisol/overnight dexamethasone suppression test
- Endomysial and/or tissue transglutaminase antibodies
- Isotope bone scan
- Markers of bone turnover
- Urinary calcium excretion

Other investigations, for example, bone biopsy and genetic testing for osteogenesis imperfecta, are largely restricted to specialist centres

the Fracture Risk Assessment Tool (FRAX)

Arch Osteoporos (2017) 12: 43

1° step

Lyfestyle measures

Regular exercise

Adults aged 19 to 64 should do at least 2 hours and 30 minutes of moderate-intensity aerobic activity, such as cycling or fast walking, every week.

Healthy eating

Stop smoking and drink less

Get some sun

Table 1. Dietary, Supplemental, and Pharmaceutical Sources of Vitamins D_2 and D_3.*

Source	Vitamin D Content
Natural sources	
Salmon	
Fresh, wild (3.5 oz)	About 600–1000 IU of vitamin D_3
Fresh, farmed (3.5 oz)	About 100–250 IU of vitamin D_3 or D_2
Canned (3.5 oz)	About 300–600 IU of vitamin D_3
Sardines, canned (3.5 oz)	About 300 IU of vitamin D_3
Mackerel, canned (3.5 oz)	About 250 IU of vitamin D_3
Tuna, canned (3.6 oz)	About 230 IU of vitamin D_3
Cod liver oil (1 tsp)	About 400–1000 IU of vitamin D_3
Shiitake mushrooms	
Fresh (3.5 oz)	About 100 IU of vitamin D_2
Sun-dried (3.5 oz)	About 1600 IU of vitamin D_2
Egg yolk	About 20 IU of vitamin D_3 or D_2

Arch Osteoporos (2017) 12: 43

2° step Calcium and vitamin D Supplementation

800-1000 mg Ca/day
600-800 UI Vit-D/day

Target :40 ng/ml

Nota 96

È appropriata la prescrizione di una determinazione della 25(OH) D.
Nell'interpretazione dei risultati considerare che il laboratorio potrebbe NON condividere i medesimi intervalli di normalità.

La determinazione della 25(OH) D, NON è appropriata.

Livelli di 25 (OH D		
0 – 12 ng/mL (0-30 nmol/L)	13-20 ng/mL (30-50 nmol/L)	>20 ng/mL (50 nmol/L)
Prescrizione di: colecalciferolo in dose cumulativa di 300.000 UI somministrabile in un periodo massimo di 12 settimane, suddivisibili in dosi giornaliere, settimanali o mensili (non oltre le 100.000 UI/dose per motivi di sicurezza)	Prescrizione di: colecalciferolo in dose giornaliera di 750-1.000 UI o in alternativa dosi corrispondenti settimanali o mensili.	Considerare altre possibili cause dei sintomi. Con l'eccezione di patologie ossee riconosciute, la supplementazione con vitamina D non è raccomandata e pertanto non rimborsata dal SSN.
Prescrizione di: calcifediolo 1cps 2 volte al mese	Prescrizione di: calcifediolo 1cps/mese	

Verifica dei livelli della 25OH D a tre mesi nel caso non vi sia risoluzione del quadro clinico di partenza

Arch Osteoporos (2017) 12: 43

Pharmacologic Agents for Treatment of Osteoporosis

ANABOLIC ANTIRESORPTIVE

Medication	Method/Dosage	Fracture Risk Reduction	Side Effects/Risks
Bisphosphonates*			*Oral alendronate, ibandronate, and risendronate.* Common: upper gastrointestinal irritation, musculoskeletal complaints; uncommon: esophageal ulcer, bone pain; rare: ONJ, atypical femur fractures *Intravenous ibandronate and zoledronic acid.* Common: bone pain with first dose zoledronic acid), musculoskeletal symptoms; uncommon: hypocalcemia; rare: ONJ, atypical femur fractures
Alendronate	Oral, 70 mg weekly	Vertebral, nonvertebral, hip	
Ibandronate	Oral, 150 mg monthly; Intravenous, 3 mg every 3 mo	Vertebral	
Risedronate	Oral, 35 mg weekly or 150 mg monthly	Vertebral, nonvertebral, hip	
Zoledronic Acid	Intravenous, 5 mg annually	Vertebral, nonvertebral, hip	
RANKL inhibitor			
Denosumab†	Subcutaneous, 60 mg every 6 mo	Vertebral, nonvertebral, hip	Common: eczema, nausea, injection site reactions; rare: ONJ, atypical femur fractures
SERMs			
Raloxifene‡	Oral, 60 mg daily	Vertebral	Common: leg cramps, hot flashes; uncommon: uterine polyps, deep venous thrombosis
Parathyroid hormone and related peptide analogues			
Teriparatide§	Subcutaneous, 20 mcg daily Approved for ≤2 y of use	Vertebral, nonvertebral	Common: nausea, arthralgia, leg cramps, hypercalcemia, hypercalcuria; uncommon: hyperuricemia, hypotension
Abaloparatide§	Subcutaneous, 80 mcg daily Approved for ≤2 y of use	Vertebral, nonvertebral	Common: dizziness, headache, nausea, palpitations, hypercalcemia, hypercalcuria

Ensrud KE, Crandall CJ. Osteoporosis. Ann Intern Med. 2017;167:ITC17–ITC32

Criteri nota 79 in prevenzione primaria

T-SCORE < -3 **T-SCORE < -4**

donne in menopausa o uomini di età ≥50 anni a rischio elevato di frattura

Indipendentemente dalla BMD

Blocco ormonale adiuvante

- Donne in menopausa con CR mammario
- Uomini (>50y) con CR prostatico

Trattamento > 3 mesi, anche solo in previsione, con prednisone ≥ 5 mg/die*

Familiarità per fratture vertebrale e femorale

Altre comorbidità

(BPCO,AR)

Tutti

Alendronato,; risedronato, zoledronato

II scelta : denosumab

I scelta: Alendronato, risedronato,

II scelta: Denosumab, zoledronato, ibadronato, SERM

FONDAZIONE ITALIANA LINFOMI

Take Home Message

- ✓ Lyfestyle Habits
- ✓ Vitamin D and Calcium Supplement
- ✓ Perform DXA and Frax
- ✓ Use of BP in GC patients
- ✓ Seek collaboration with Endocrinologist