Dr John Petrie

Rheumatologist

QE Health

Groans and Bones - Concurrent Workshop Repeated

Friday, 21 June 2013	Start 11:00am	Duration: 55mins	Sigma
	Start 12:05pm	Duration: 55mins	Sigma

Groans and Bones

John Petrie

NZMA GP Conference 2013

ROTORUA

Disclaimer: Commercial support from...

- Lilly
- MSD
- Novartis
- Roche
- Pfizer
- Sanofi
- Wyeth
- Abbvie

Key Points

- Rheumatoid Arthritis
  - Importance of early referral of synovitis
  - Aggressive intervention with disease-modifying drugs
- Gout
  - Pain relief and Urate Lowering Therapy are the two distinct arms of Gout treatment
  - Treat to the target of 0.30
- Osteoporosis
  - The purpose of diagnosis is to prevent fragility fracture
  - Risk assessment tools perform better than screening with DEXA scanning

Pierre Auguste Renoir 1841-1919

A Paradigm Shift in the approach to Rheumatoid Arthritis

- Now:
  - Treat to Target
  - Remission induction
  - Damage prevention
  - Maintain function and productivity
- Then:
  - Symptom control
  - Moderation of disease progression
  - Accommodation of disability

What is RA?

RA: A Construct

- “A chronic, autoimmune inflammatory disease, characterised by joint swelling, joint tenderness and synovial joint destruction, leading to severe disability and premature mortality”

Features of the 1987 Criteria

- Developed to differentiate RA from other recognised arthritides
- Utilised characteristics of established disease
- Used in epidemiology and therapeutic research trials
- Relevant at a time when treatment goals were limited to diminishing disability

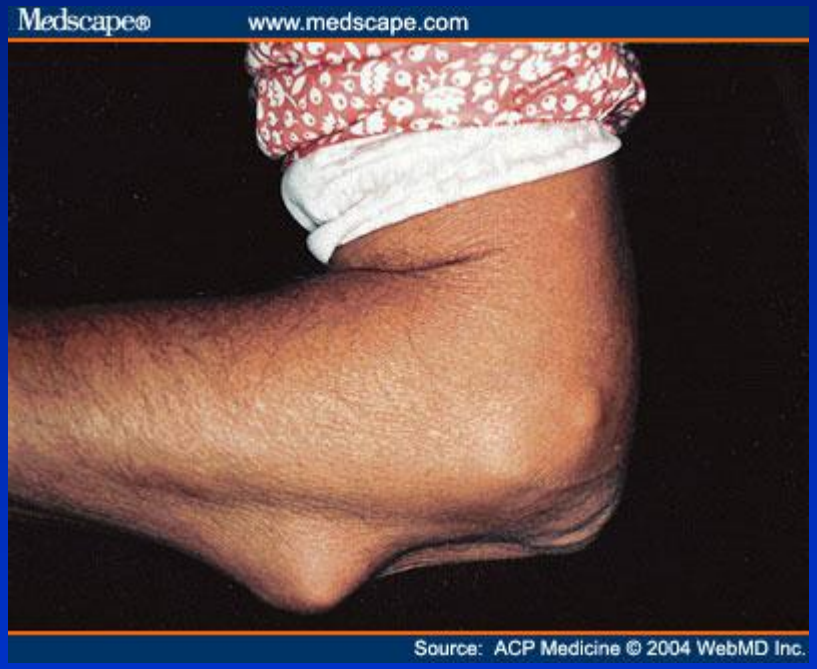
Table 3 – ACR criteria for the diagnosis of RA

At least 4 of the following 7 criteria must be met (criteria 1 through 4 must have been present for at least 6 weeks):

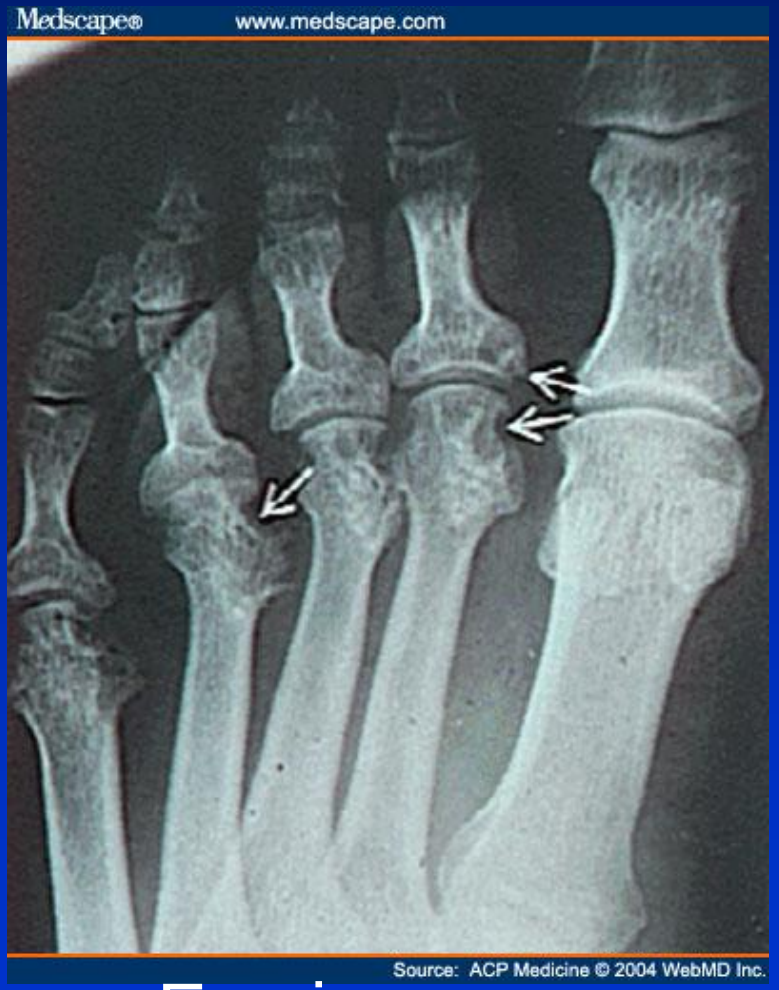
- Morning stiffness for at least 1 hour.
- At least 3 joint areas simultaneously had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician; the 14 possible areas are right or left PIP joint, MCP joint, wrist, elbow, knee, ankle, or MTP joint.
- At least 1 area swollen (as defined above) in a wrist, MCP joint, or PIP joint.
- Simultaneous involvement of the same joint areas on both sides of the body (bilateral involvement of PIP, MCP, or MTP joints is acceptable without absolute symmetry).
- Subcutaneous nodules over bony prominences or extensor surfaces or in juxta-articular regions, observed by a physician.
- Demonstration of abnormal amounts of serum RF by any method for which the result has been positive in < 5% of normal control subjects.
- Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (OA changes alone do not qualify).

ACR, American College of Rheumatology; RA, rheumatoid arthritis; PIP, proximal interphalangeal; MCP, metacarpophalangeal; MTP, metatarsophalangeal; RF, rheumatoid factor; OA, osteoarthritis.

Late Features of RA



Nodules



Erosions

Late Stages of RA

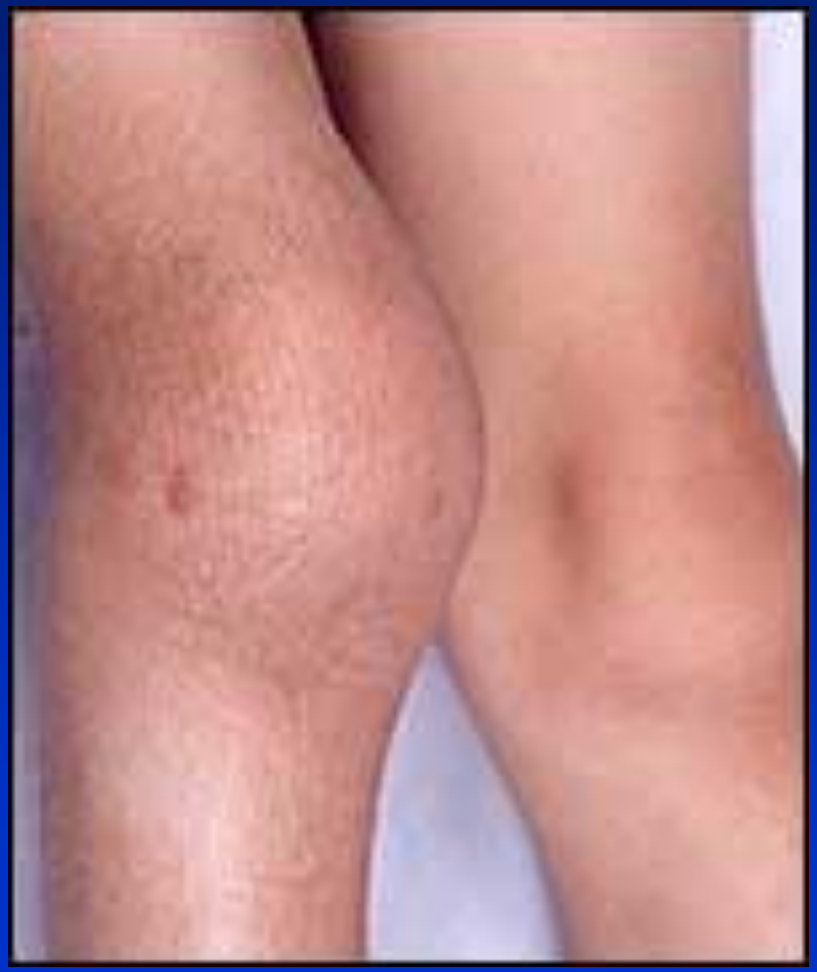
Impetus for Change

- Value of optimising DMARD use (MTX, GC)
- Benefits of early intervention; improving clinical outcomes and reducing disability
- Availability of new “biological” agents
- Development of a new prognostic indicator (Anti Citrullinated Peptide Antibodies, ACPA or Anti-CCP)

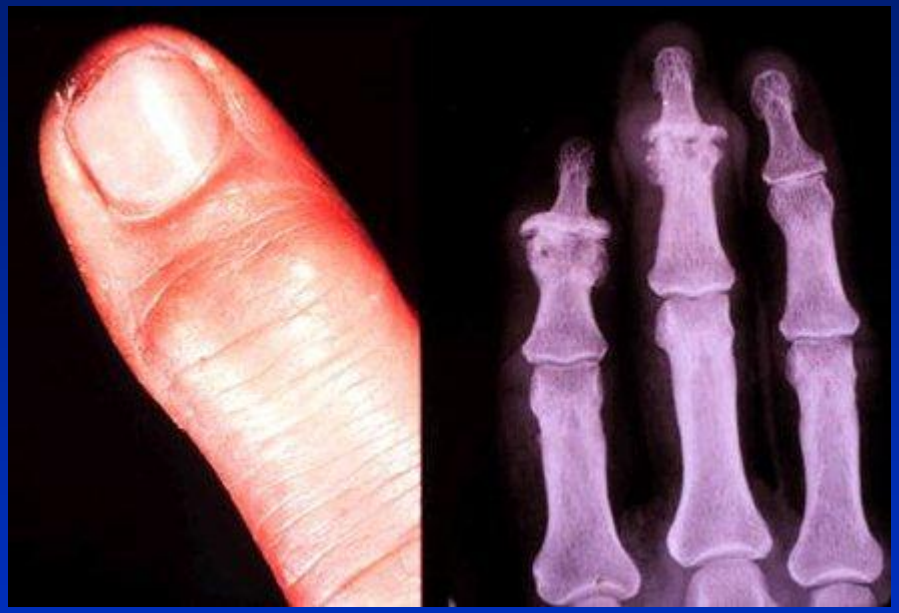
2010 ACR/EULAR RA Classification Criteria

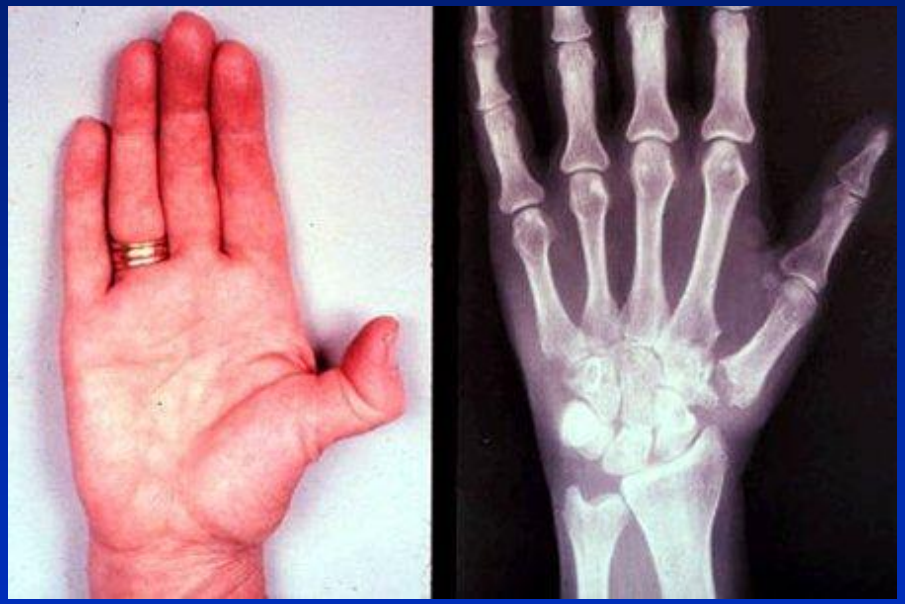
- Target population (who should be tested?): patients who
  - 1) have at least one joint with definite clinical synovitis (swelling)
  - 2) with the synovitis not better explained by another disease
- A score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA

Primary Entry Criterion: Swollen Joint



Not DIP, 1st CMC or 1st MTP





Characteristic distribution of Osteoarthritis

Categories A - D

- A: JOINT INVOLVEMENT

  Large, small, 1-10 or more — Score 0-5

- B: SEROLOGY

  RhF, Anti-citrullinated peptide Ab — Score 0-3

- C: ACUTE PHASE PROTEINS

  CRP/ESR normal/abnormal — Score 0-1

- D: DURATION OF SYMPTOMS

  < 6 weeks, ≥6 weeks — Score 0-1

A: Joint Involvement

- 1 large joint 0
- 2−10 large joints 1
- 1−3 small joints (with or without involvement of large joints) 2
- 4−10 small joints (with or without involvement of large joints) 3
- >10 joints (at least one small joint) 5

B: Serology

- Negative RF *and* negative ACPA 0
- Low-positive RF *or* low-positive ACPA 2
- High-positive RF *or* high-positive ACPA 3

C: Acute Phase Proteins

- Normal CRP *and* normal ESR 0
- Abnormal CRP *or* abnormal ESR 1

D: Duration of Symptoms

- <6 weeks 0
- ≥6 weeks 1

Significant Differences

- A requirement for the presence of a swollen joint, and the exclusion of alternative explanations
- Absence of requirement for symmetry
- Less emphasis on Rheumatoid Factor
- Absence of the features of longstanding disease
- No mention of morning stiffness

Recommended Initial Management of RA (or even *suspected* RA)

- Combination of Methotrexate and Low Dose Glucocorticoids (Prednisone) as soon as the diagnosis is made
- Target remission or low disease activity
- Use Leflunomide, sulfasalazine or gold injections if Methotrexate contraindicated
- Initiate a TNF inhibitor if DMARD/GC ineffective
- Change to another “Biological” if TNF inhibitor ineffective

EULAR recommendations for the treatment of RA
Ann.Rheum.Dis. 2010;69 (June):964-975

First-line Disease Modifying Anti-Rheumatic Drug

METHOTREXATE

Methotrexate Administration

- Rapid escalation of dose 10 →15 → 20mg at 2-4 weekly intervals
- Fortnightly monitoring of FBC & LFTs
- Folic Acid supplementation
- *Benefit expected in at least 80% of DMARD naïve patients*

Methotrexate Toxicity

- Gastrointestinal (nausea, vomiting, diarrhoea) 30%
- Hepatic (aminotransaminase elevation above ULN) 18·5%
- Skin/Hair (rash, alopecia, pruritis) 8·9%
- CNS (headache, depression, lethargy, malaise) 5·5%
- Cytopaenia 5·5%
- Lung (cough) 2·4% (pneumonitis 0·43%)
- DISCONTINUATION 2° TO AEs 10%

Not without controversy in the past…

GLUCOCORTICOIDS

Myths of Glucocorticoid Rx

- Useful only for anti-inflammatory action
- Use only as short term pain relief
- Side effects outweigh benefits
- “Wean” patients off ASAP
- A morning dose mimics the circadian rhythm and is physiologically appropriate

A Negative View of Glucocorticoids

- No dose-ranging studies
- Enthusiastic administration by treating physicians
- Indiscriminate use
- Absence of protocols or guidelines

Low Dose Prednisone in RA

- Proven, valued effect in early symptomatic relief
- Substantive evidence of disease-modifying effect
- Favourable treatment continuation profile
- Only other intervention with such rapid disease suppression is with “Biologicals”
- Night-time dose physiologically beneficial

TNF Blockers

- Enbrel (etanercept)
- Remicade (infliximab)
- Humira (adalimumab)
- $25,000 per year
- Effective in approximately 50% of non-DMARD responsive sufferers

Not yet approved for use in for RA NZ

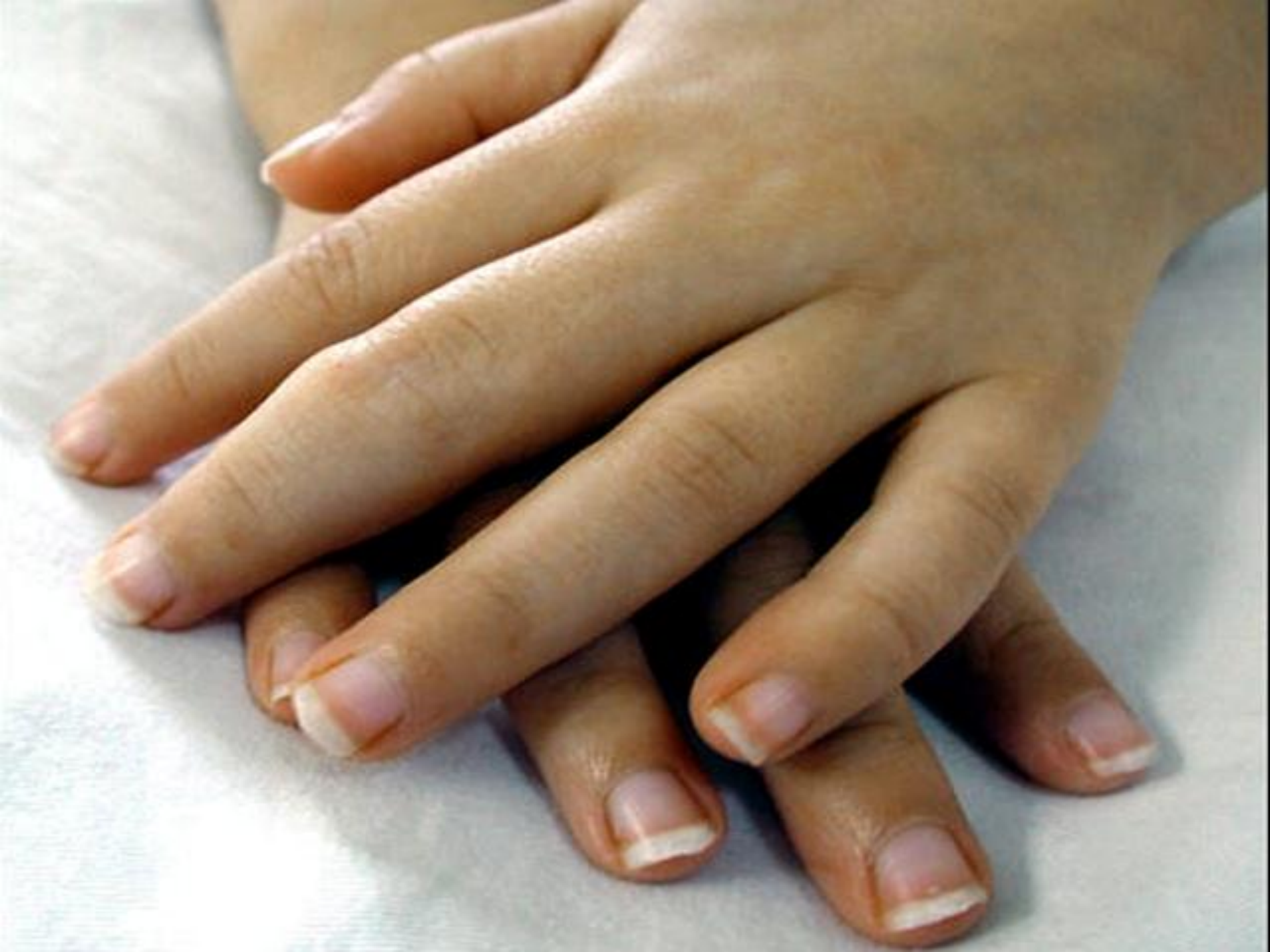
- Abatacept. An antibody to a surface marker “CD-80“ on T cells, a necessary costimulator for T cell activation
- Rituximab. An anti-B cell monoclonal antibody used in Lymphomas with good effect in RA patients
- Tocilizumab. An antibody to another cytokine, IL 6

New ARA/EULAR Diagnostic Criteria: Given at least 1 swollen, inexplicable joint:

- ***Joint involvement*** by size and number (0-5)
- ***Serology*** i.e. RhF & anti-CCP absent, low titre or high titre (0-3)
- ***Duration*** 0 <6 weeks> 1
- ***Acute Phase Reactants*** ESR/CRP absent 0, present 1
- ***Definite RA*** can be diagnosed with a total score of 6 or more

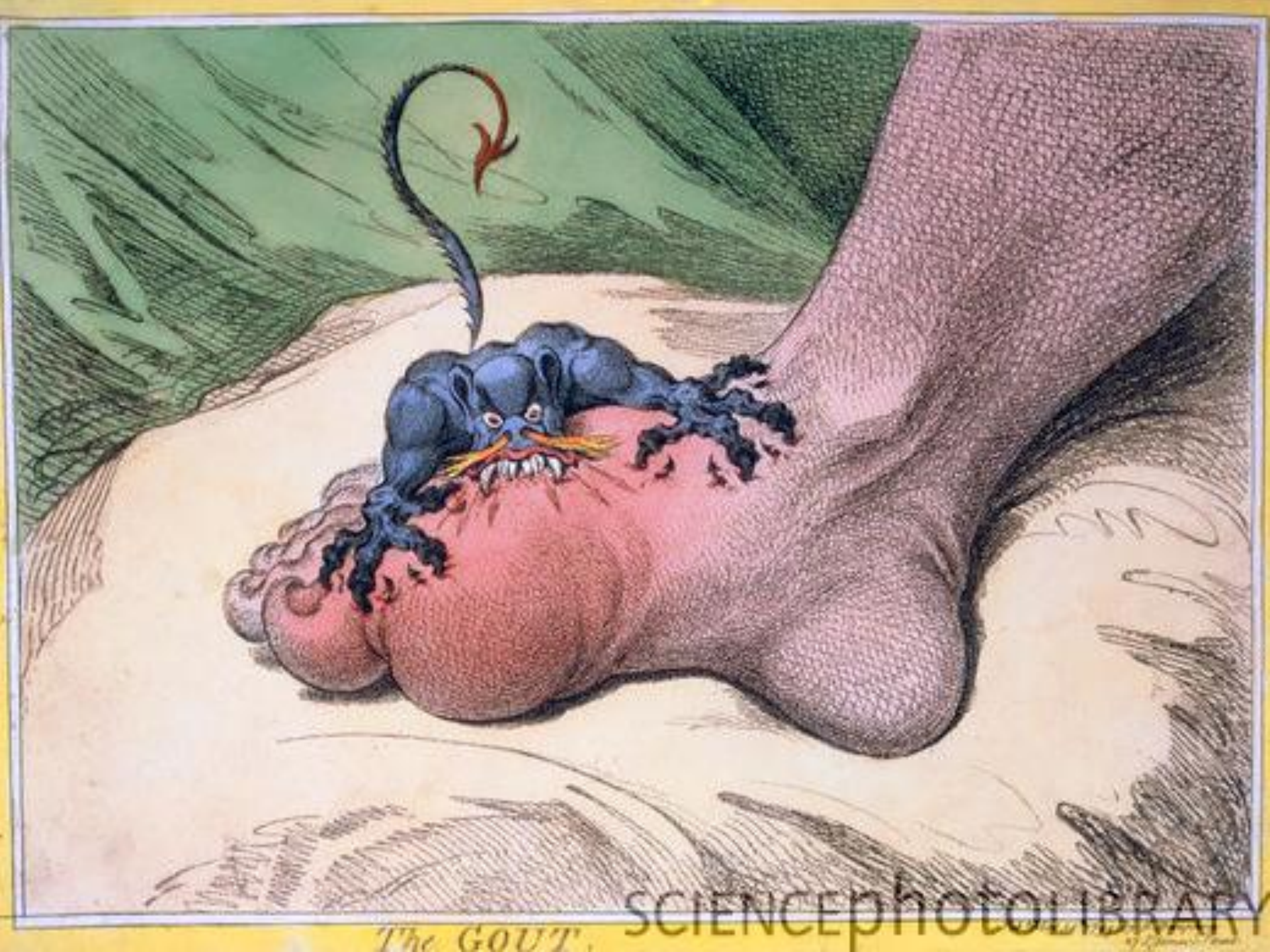
Treatment Options for RA

- Early introduction of Methotrexate and Oral Glucocorticoids
- Escalation to alternative Disease Modifying Anti-Rheumatoid Drugs (DMARDS)
- Consideration of “biologicals”; TNF inhibitors and alternatives
- EARLY REFERRAL TO RHEUMATOLOGISTS
- And we can stop this...

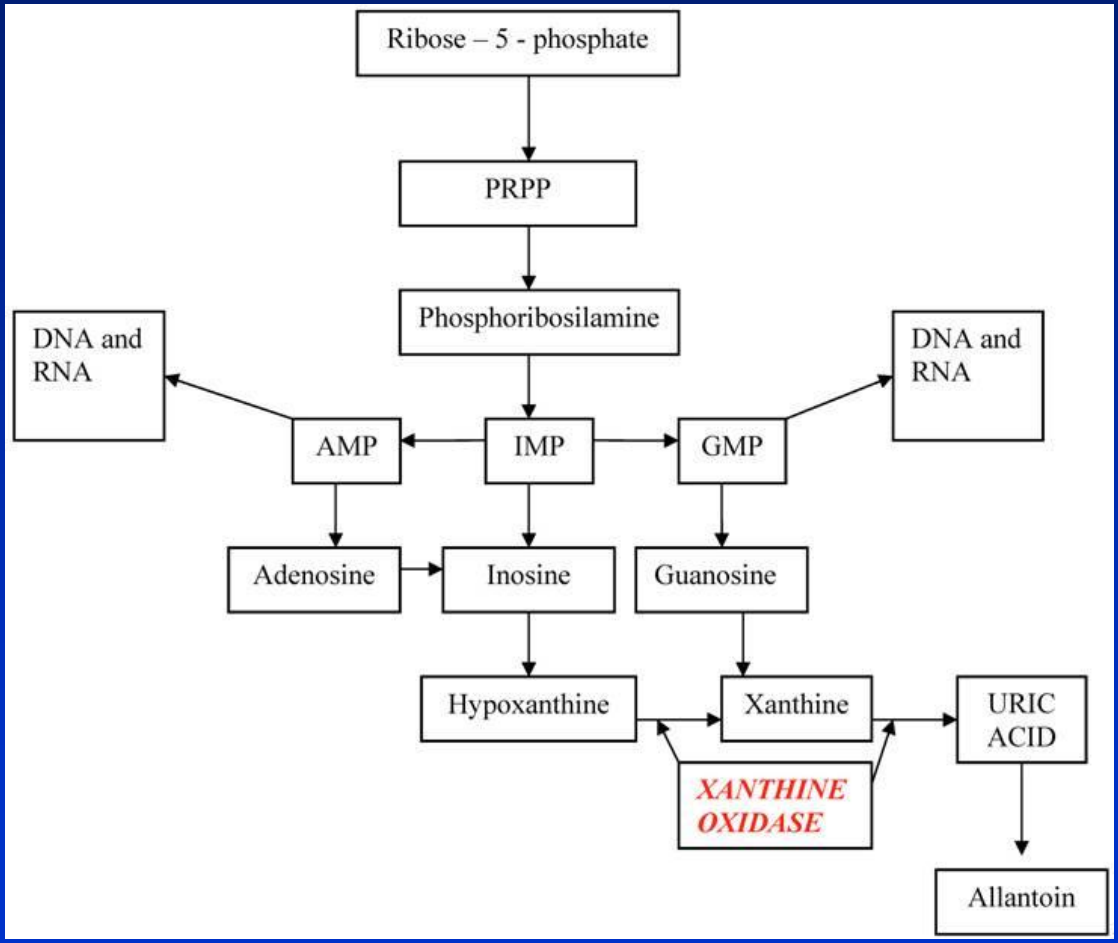


Let me make this Crystal, Clear

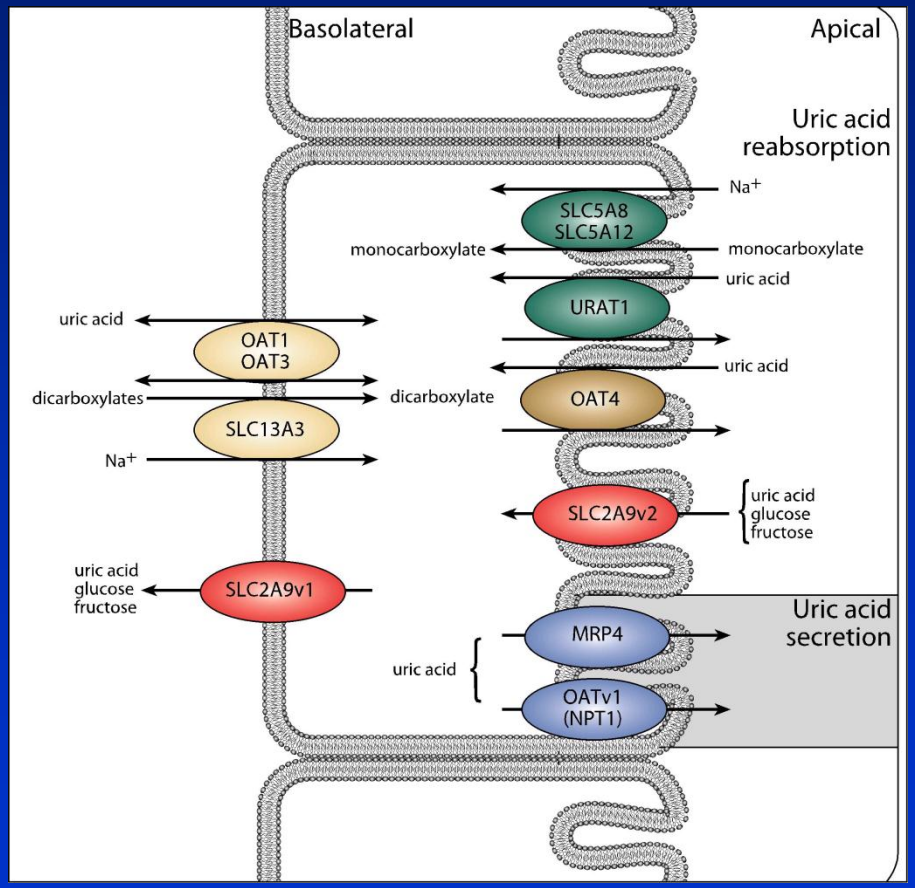
The Treatment of Gout



Uric Acid Pathway



Renal Urate Transporters



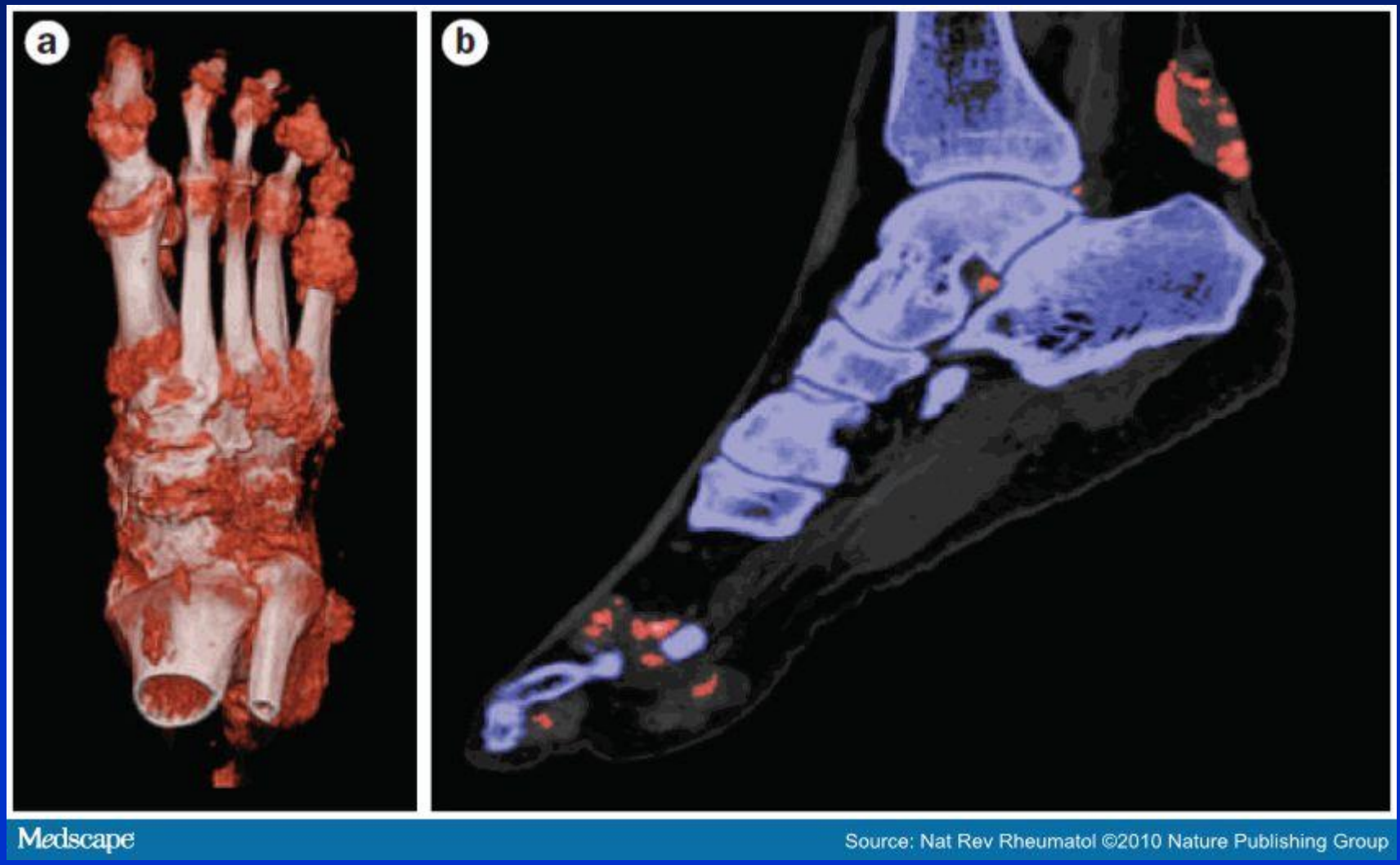
Augutin *J Biol Chem* 2004
Keembiyehetty *Mol Endocrinology* 2006

Renal Urate Transporters Are Genetically Associated with Gout

- Same alleles in different groups
- Effect sizes stronger in Maori and PI
- Potential transportasome genetic test

	SLC2A9 (GLUT9)	ABCG2	SLC17A1 (NPT1)
Maori	✓✓✓✓	-	✓
Pacific Island	✓✓✓✓	✓✓	✓
Caucasian	✓	✓	✓

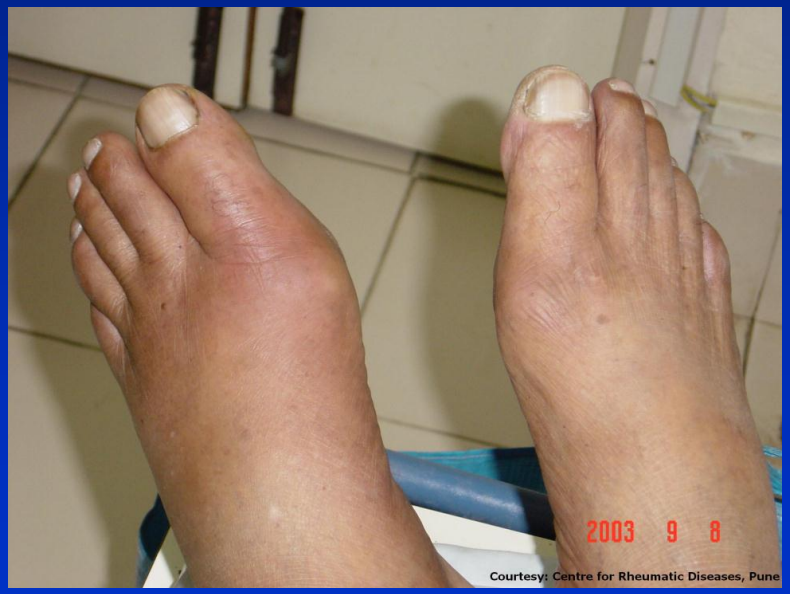
Urate load in asymptomatic patients

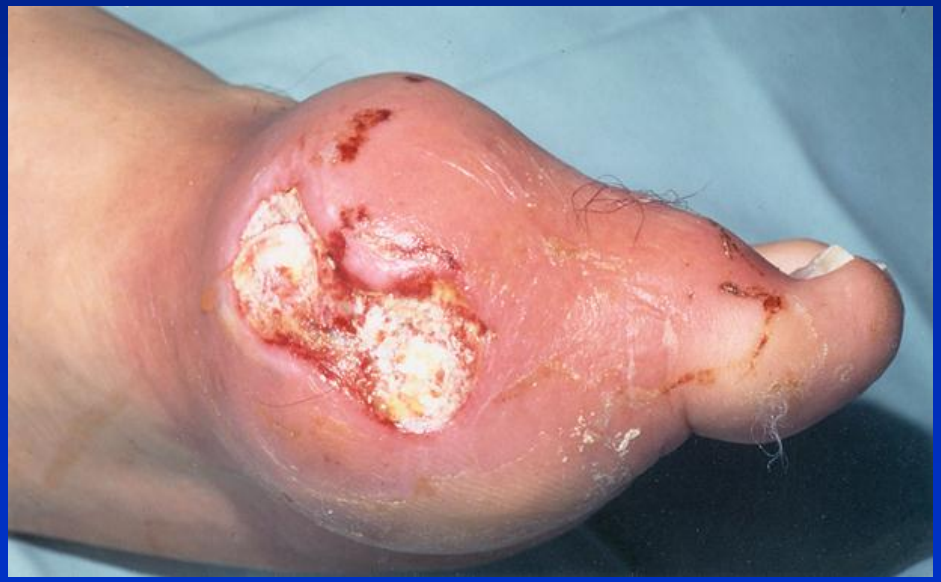


The Two Independent Arms of Gout Management

ACUTE PAIN, AND THE RELIEF OF SUFFERING

URATE LOWERING THERAPY, PROPHYLAXIS





Both Patients and Health Professionals confuse the two

Management of Gout

Acute treatment of Pain

- NSAID or Coxib (Diclofenac, Naproxen, Etoricoxib)
- Colchicine
- Prednisone
- Intra-articular steroid
- ACTH
- Anakinra, Canukinamab

Prevention by reducing Urate load

- Allopurinol
- Probenecid
- Febuxostat
- Benzbromarone
- Pegloticase
- “RDEA594”

Obstructions to long-term management of Gout

- Confusing the two goals; pain relief and prophylaxis
- Poor communication
- Argument amongst providers
- Misunderstanding the duration and objectives of treatment

Patient issues

- Lack of understanding
- Non-compliance, non-adherence, non-concordance
- Bad experiences with prior therapy
- “Know your number”

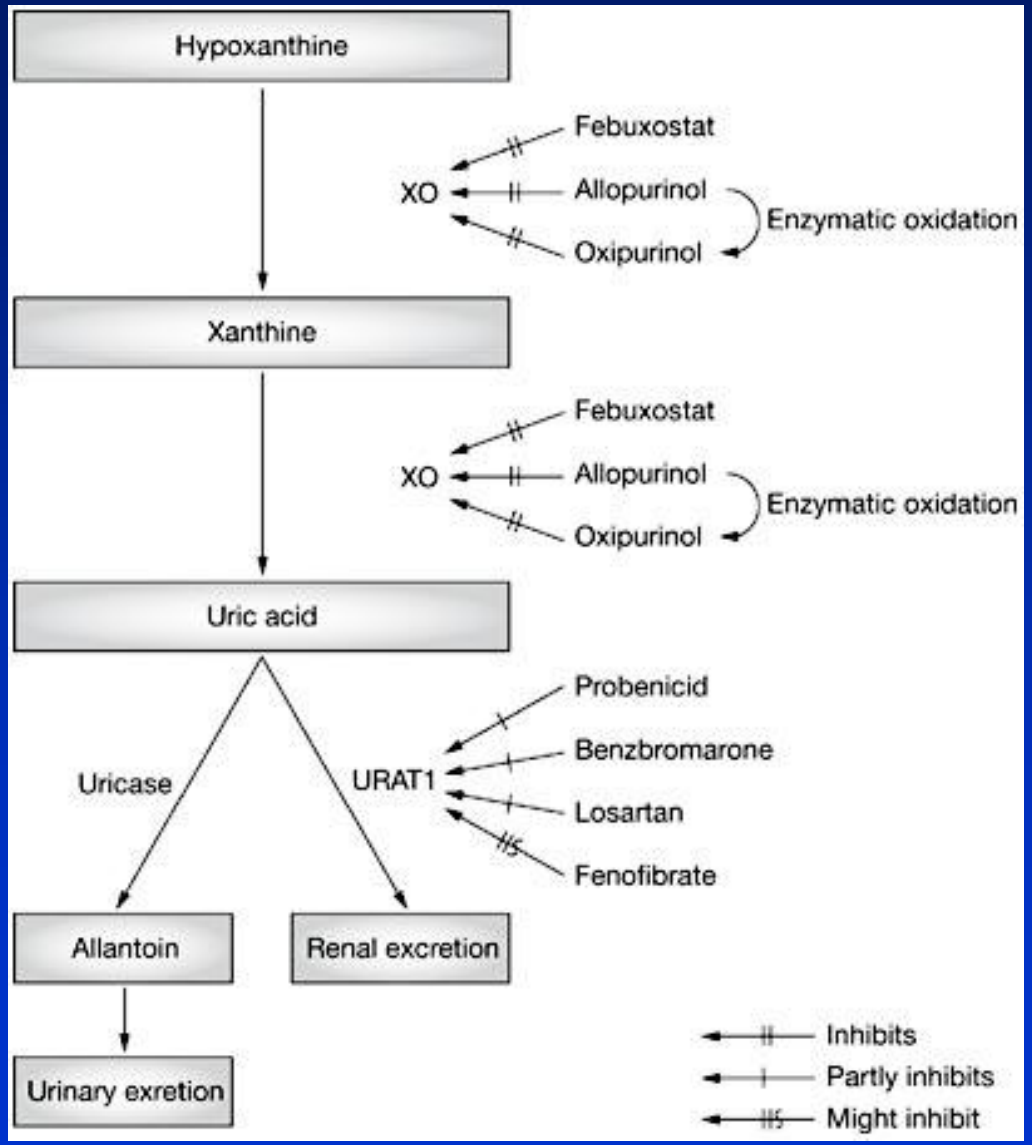
Provider issues

- Failure to understand or inform
- Undo bad habits
- Treat to Target
- Monitor SUA
- Get ***over*** the 300mg allopurinol hurdle

Urate Lowering Therapy

- Allopurinol
- Probenecid
- Febuxostat
- Benzbromarone
- Pegloticase

Urate lowering Targets



Establishing Allopurinol Therapy

- Lifelong therapy, chronic disease model
- Dose escalation on initiation - monthly
- Cover first 6 months with NSAID or colchicine or glucocorticoid
- Do not stop allopurinol for acute attacks

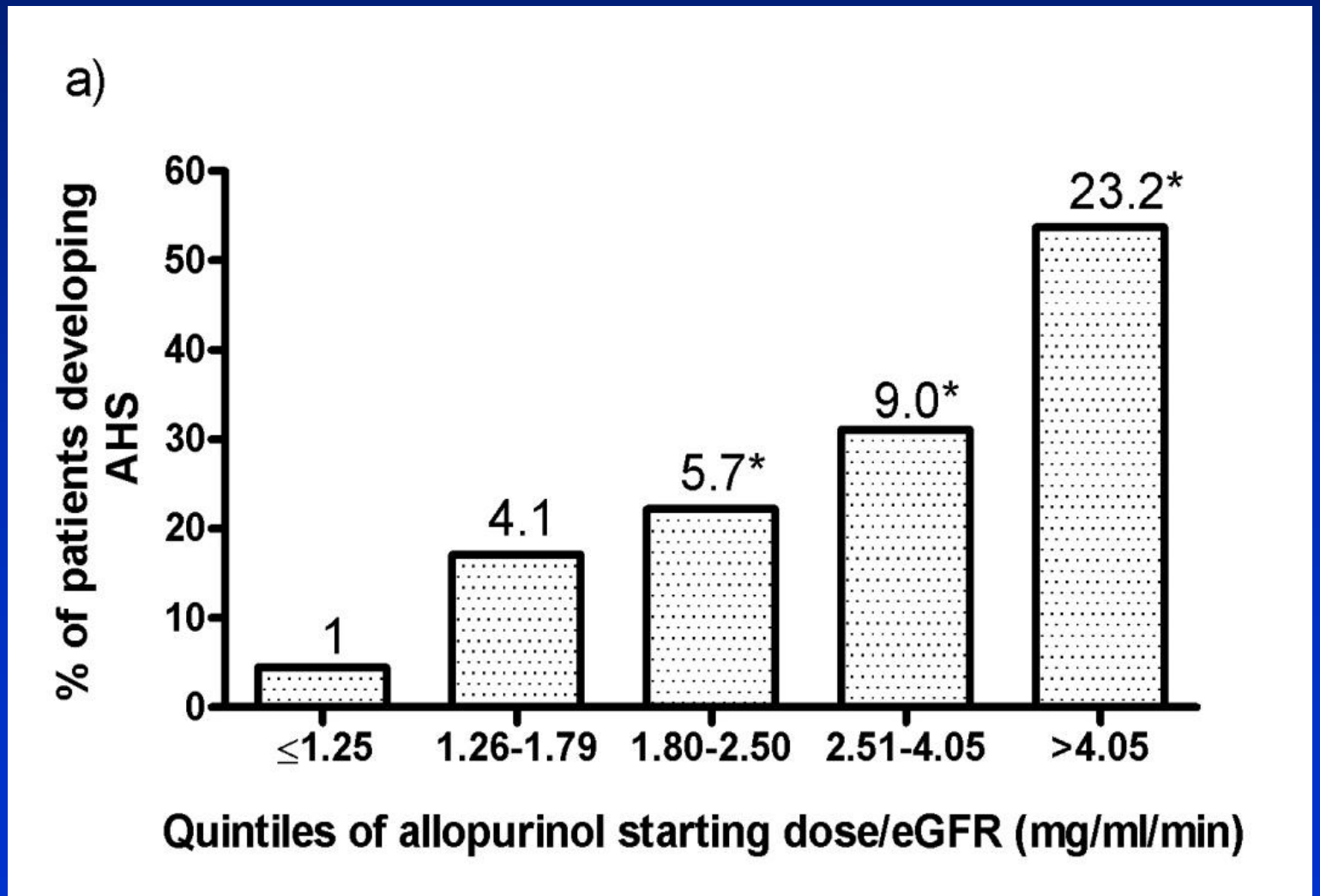
How Low Should You Go?

0.30 mmol/L

AHS

- The true incidence of AHS is unknown, estimated to be ~0.1%.
- Many cases of AHS have occurred in patients treated for asymptomatic hyperuricaemia
- Mortality associated with AHS as high as 27%
- No cure for AHS, early recognition and drug withdrawal are important
- Management - supportive care

Relationship between starting dose and AHS



Starting Dose for Allopurinol in patients with renal compromise

- 1.5mg/ml eGFR
- Increase at monthly intervals to target
- Assess compliance if target not achieved

Stamp LK, Chapman PT et al. Rheumatology 2013;52:34-44

Benzbromarone

- Inhibitor of URAT-1
- Effective even in renal failure
- Withdrawn because of hepatic toxicity
- Metabolised by CYP2C9, poor metaboliser alleles of which may help predict susceptible patients
- May soon be available in NZ

Take Home Messages

- Importance of differentiating treatment goals
- “Know your Number”
- Potential new therapies

If It Ain’t Broke, Then FRAX It

- A bare bones approach to Osteoporosis

Take-home message:

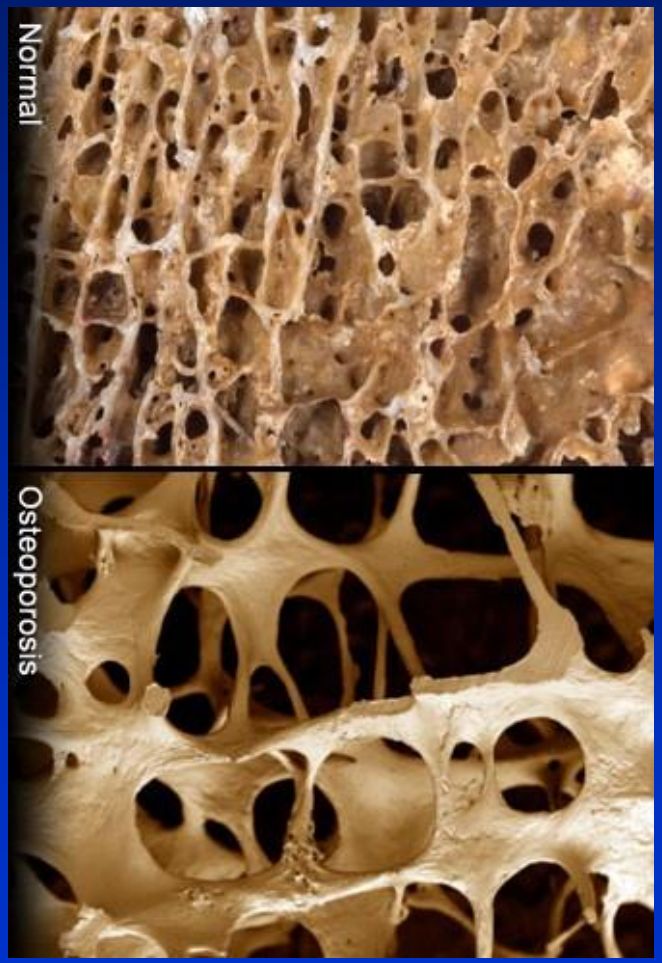
- Osteoporosis in post-menopausal women:
  - Those with a T score ≤ -2.5 are at most risk of fracture
  - A T score of ≤ -2.5 is NOT sufficient to initiate drug treatment
  - 82% of women who fracture will have a T score > -2.5
- Management should be directed by *absolute* fracture risk rather than T score alone

Siris ES et al Arch Int Med 2004;164:1108-1112

What is Osteoporosis?

- “A chronic, progressive disease of multifactorial aetiology”
- “A systemic skeletal disease”
- “Brittle Bone Disease”
- An age-related decrease in mineralised osteoid, exacerbated by reduced gonadal function, predisposing to fragility fracture.

Osteoporotic bone loss



- Bone density is measured in grams of mineral per area or volume
- Bone quality is a function of
  - Architecture
  - Turnover rate
  - Mineralisation

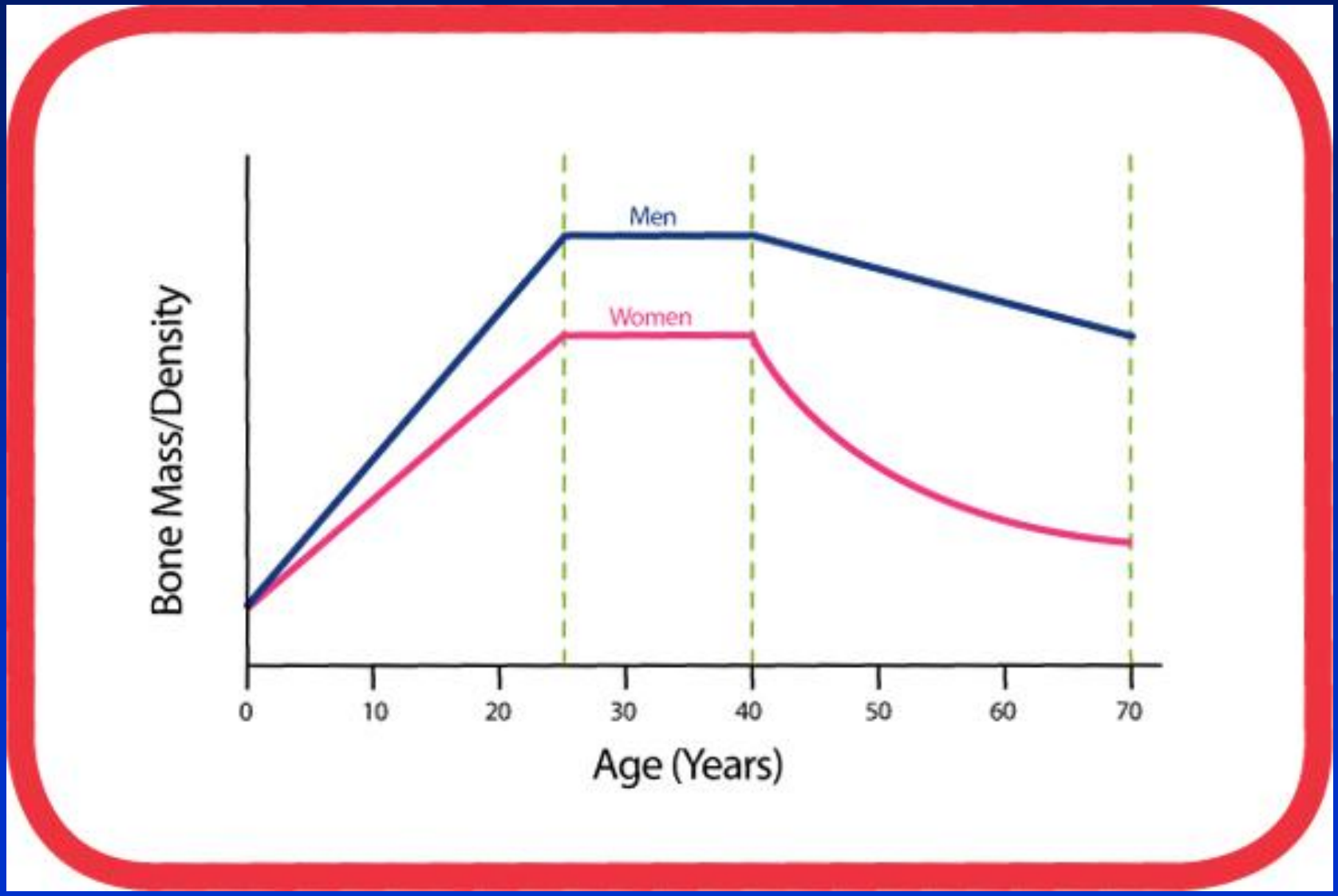
Extent of bone loss with age

- Age confers a 7 times greater risk of fracture for any given T score
- Women lose 30-40% of cortical, 50% of cancellous bone over their lifespan
- Men lose 15-20% cortical, 25-30% cancellous bone over theirs

Curr Opin Rheumatol 2012;24:554-60

Up To Date 2012

Involutional Osteoporosis

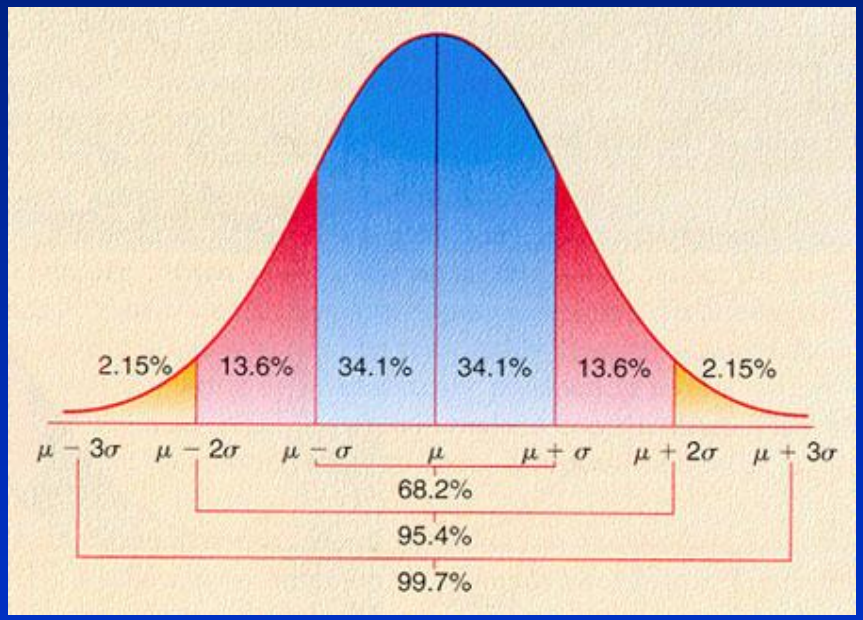


Dr Google

Operational definition of Osteoporosis

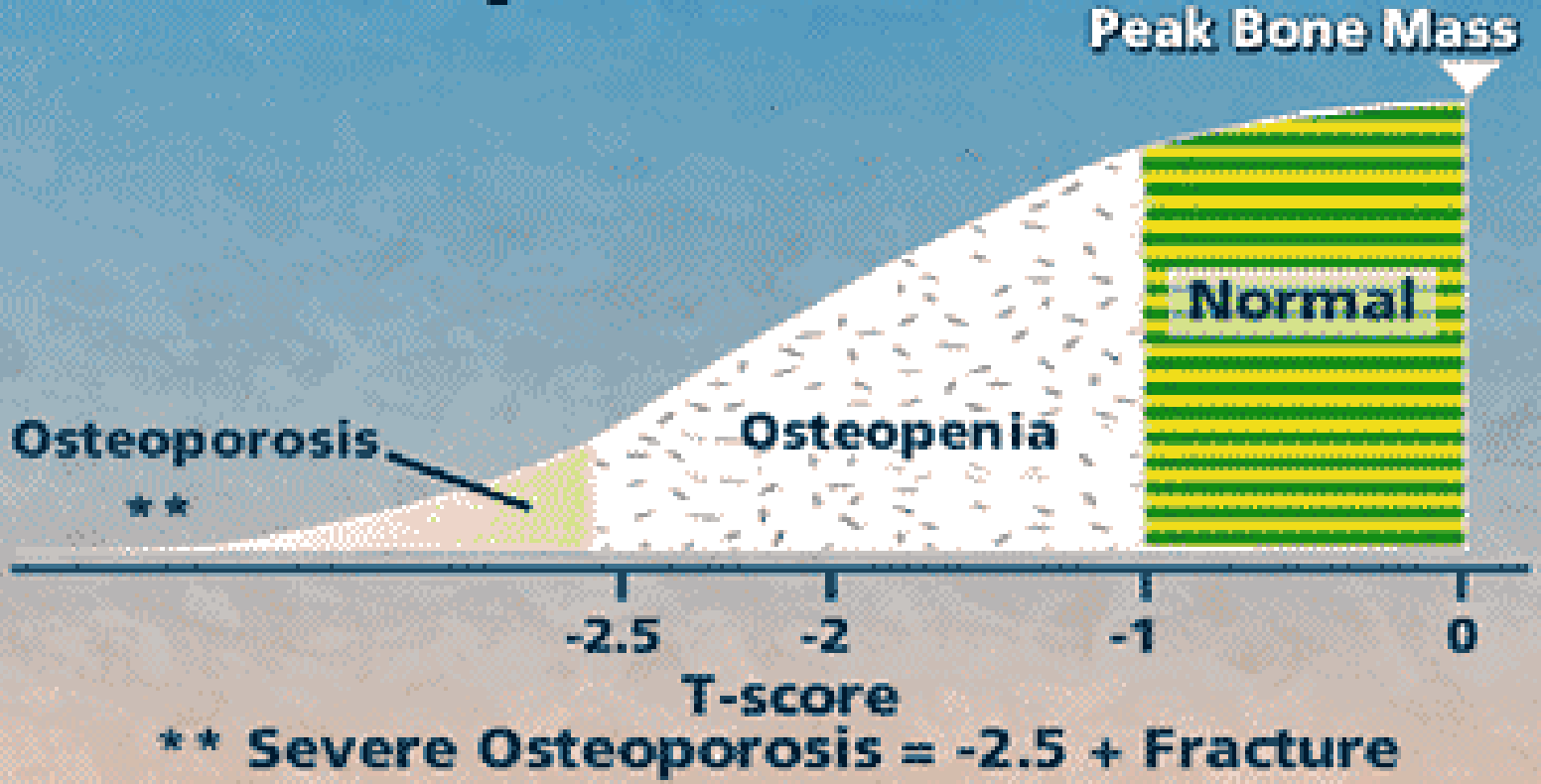
- A T score of ≤-2.5
- WHO 1994
- Initially defined for the purposes of epidemiology, this figure now masquerades as
  - A diagnostic test
  - A funding criterion
  - A treatment decision

What is a T score?



- A comparison to young normals, ie peak bone mass
- “Normal” T score is between -1 and +1, where 68% of the 30yr old population lie

World Health Organization (WHO) Osteoporosis Guidelines



** Severe Osteoporosis = -2.5 + Fracture

World Health Organization. *Guidelines for Preclinical Evaluation and Clinical Trials in Osteoporosis*, 1998.

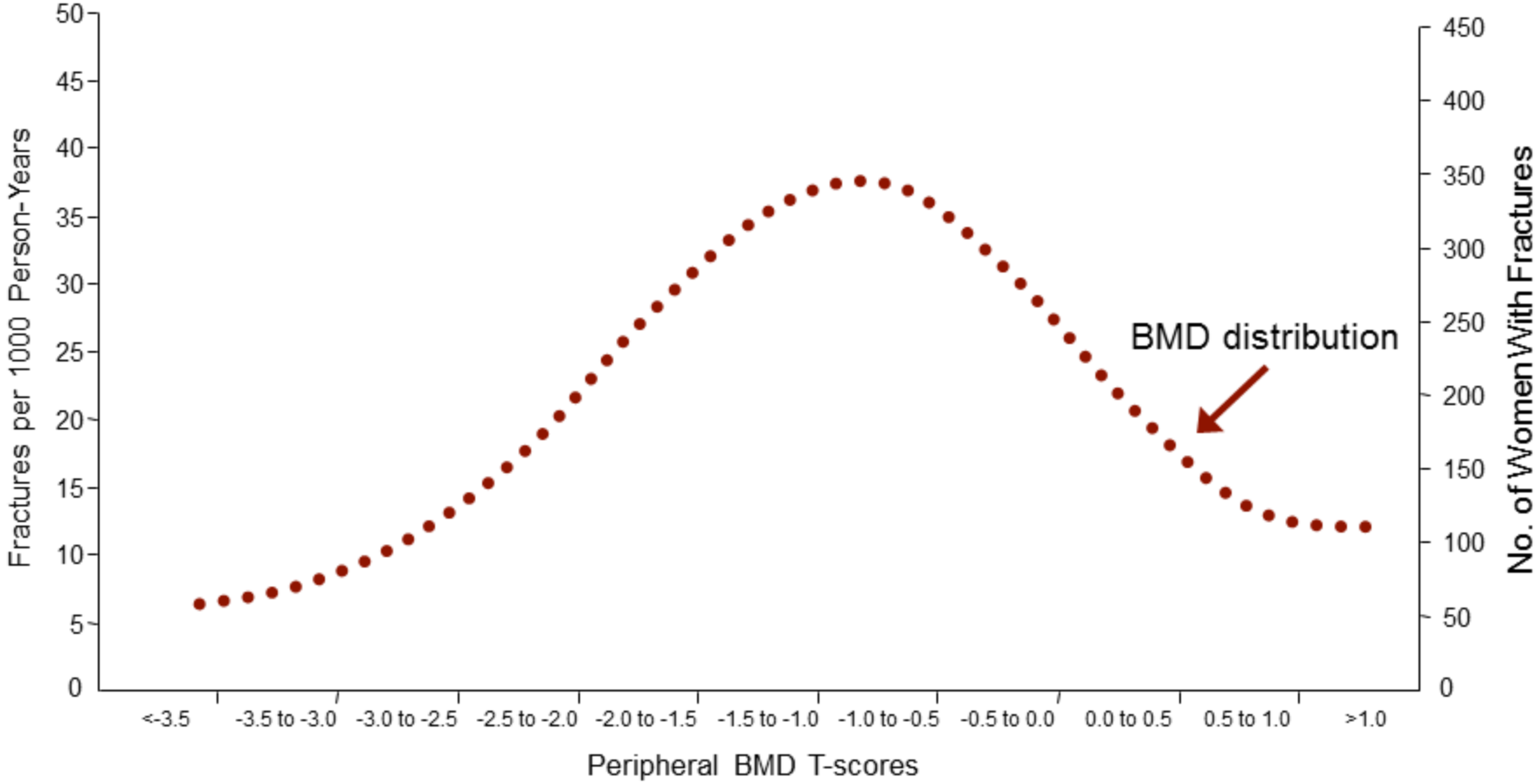
WHO Criteria for Postmenopausal Osteoporosis

The T-score compares an individual's BMD with the mean value for young normal individuals and expresses the difference as a standard deviation score.

Category	T-score
Normal	-1.0 and above
Low bone mass (osteopenia)	Between -1.0 and -2.5
Osteoporosis	Below -2.5

Kanis JA, et al. *J Bone Miner Res.* 1994;9:1137-1141.

Data From NORA
National Osteoporosis Risk Assessment



From Siris E, et al. *Arch Intern Med*. 2004;164:1108. Republished with permission.

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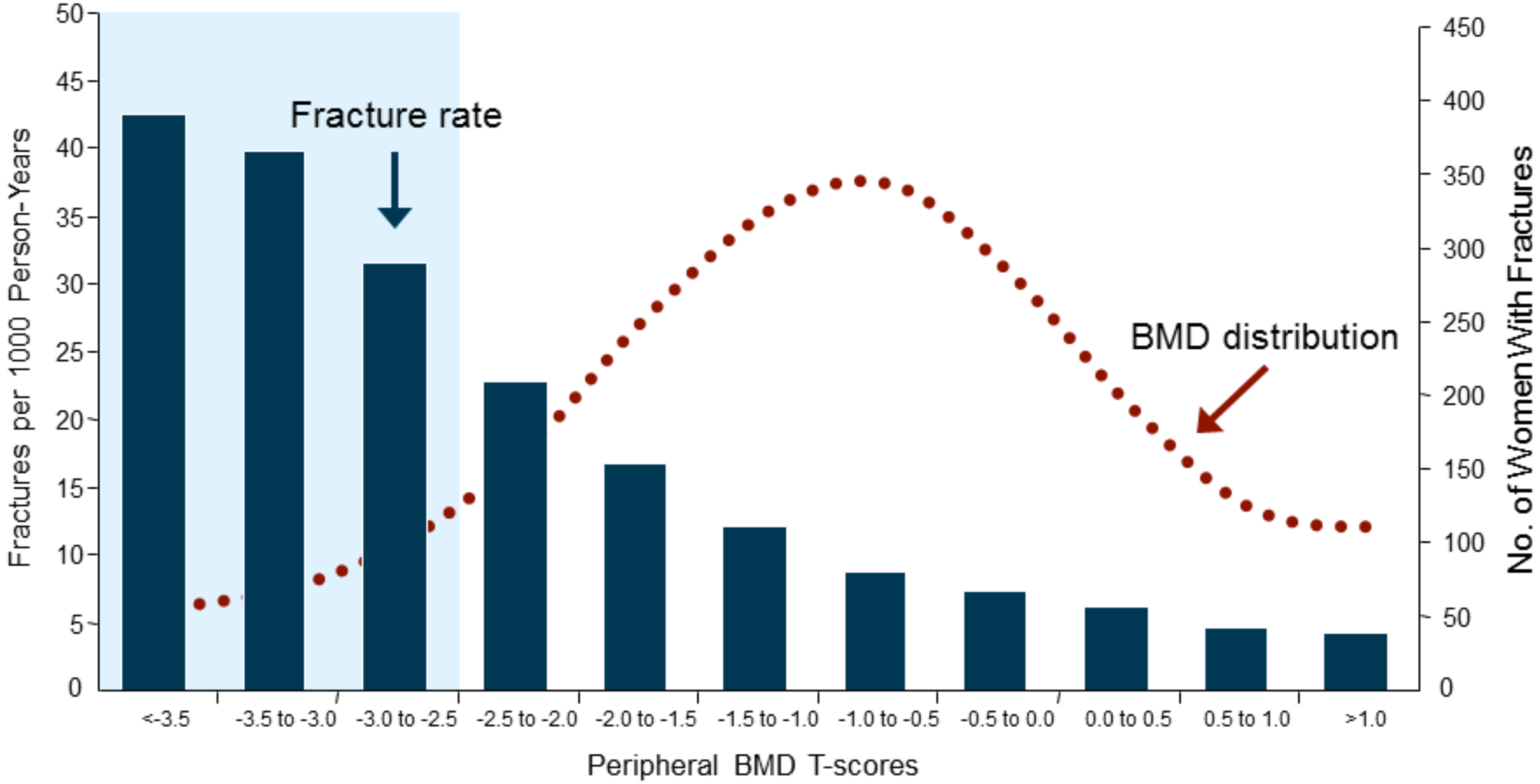

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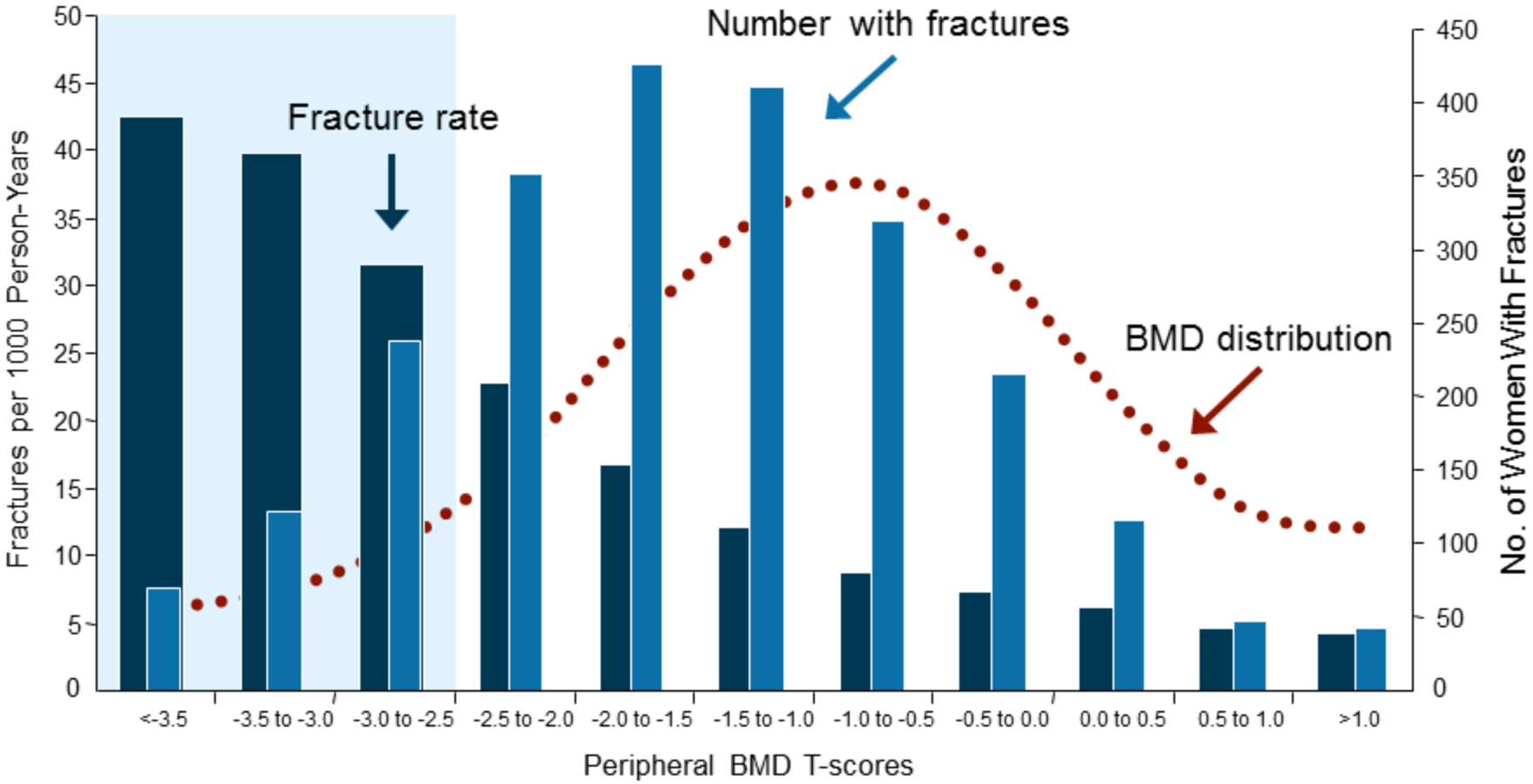


From Siris E, et al. *Arch Intern Med*. 2004;164:1108. Republished with permission.

Important Risk Factors for Fracture

- Age (major contributor to fracture risk)
- Sex (women > men)
- Low BMD
- Race
- Family history
- Previous fracture
- BMI (weight and height)
- Smoking

Kanis JA, on behalf of the World Health Organization Scientific Group. *2008 Technical Report*. University of Sheffield, UK: WHO Collaborating Center; 2008.

NICE Guidelines for fracture risk assessment

- All women > 65, all men > 75
- In younger women and men in the presence of clinical risk factors
- Do not assess in people < 50 in the absence of major risk factors
- *Do not routinely measure risk* without prior assessment with FRAX
- Consider DEXA when FRAX result is near an intervention threshold

NOF Treatment Criteria

- Using FRAX assessment tool:
  - A 10 year probability of any major fracture of 20%
  - A 10 year probability of hip fracture of 3%

FRAX® WHO Fracture Risk Assessment Tool

Home | Calculation Tool | Paper Charts | FAQ | References | English

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: New Zealand Name/ID: About the risk factors

Questionnaire:

1. Age (between 40-90 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 per day No Yes
12. Femoral neck BMD (g/cm²)
    Select DXA
    Clear Calculate

Weight Conversion

Pounds → kg

Convert

Height Conversion

Inches → cm

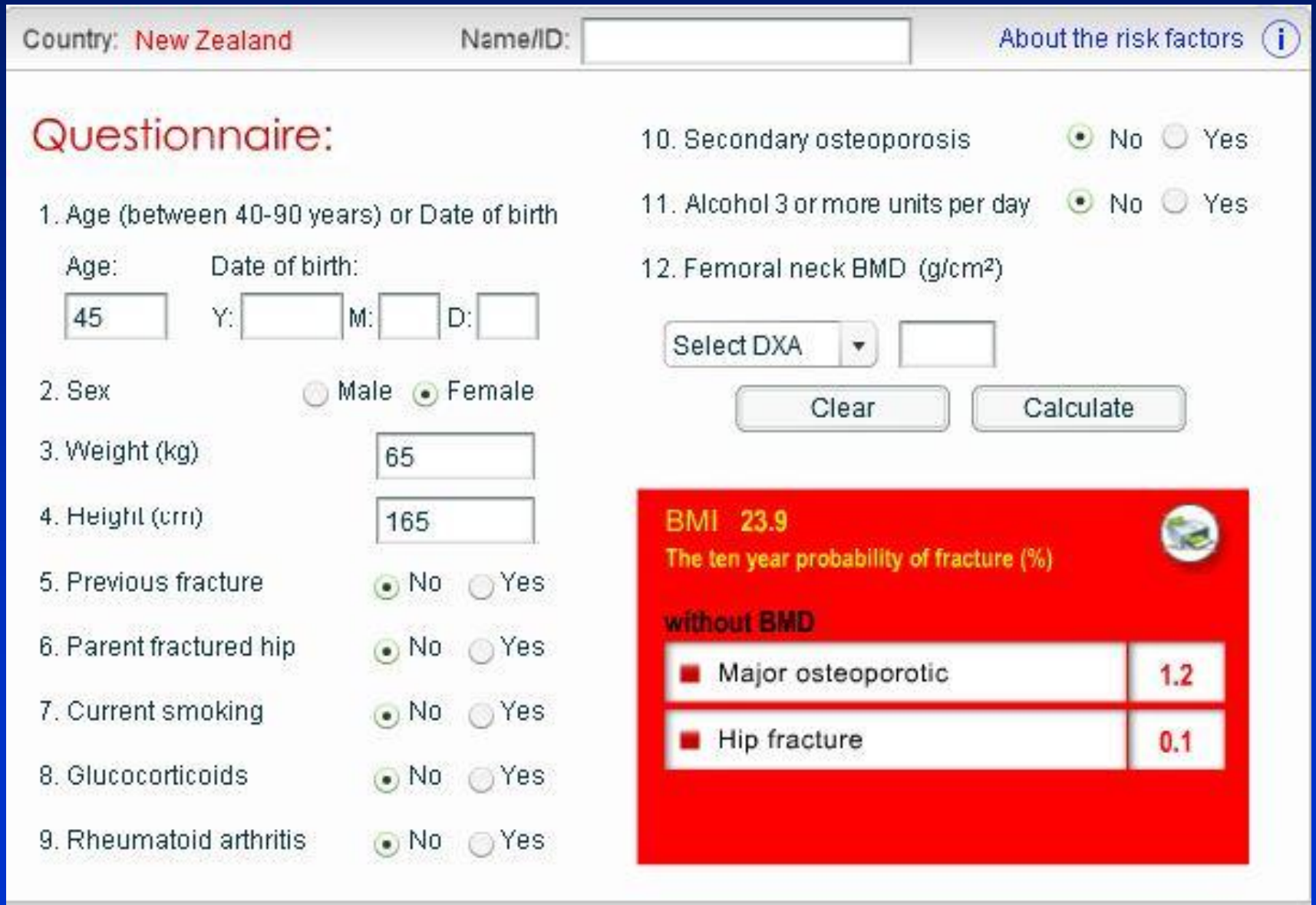
Convert

00011537

Individuals with fracture risk assessed since 1st June 2011

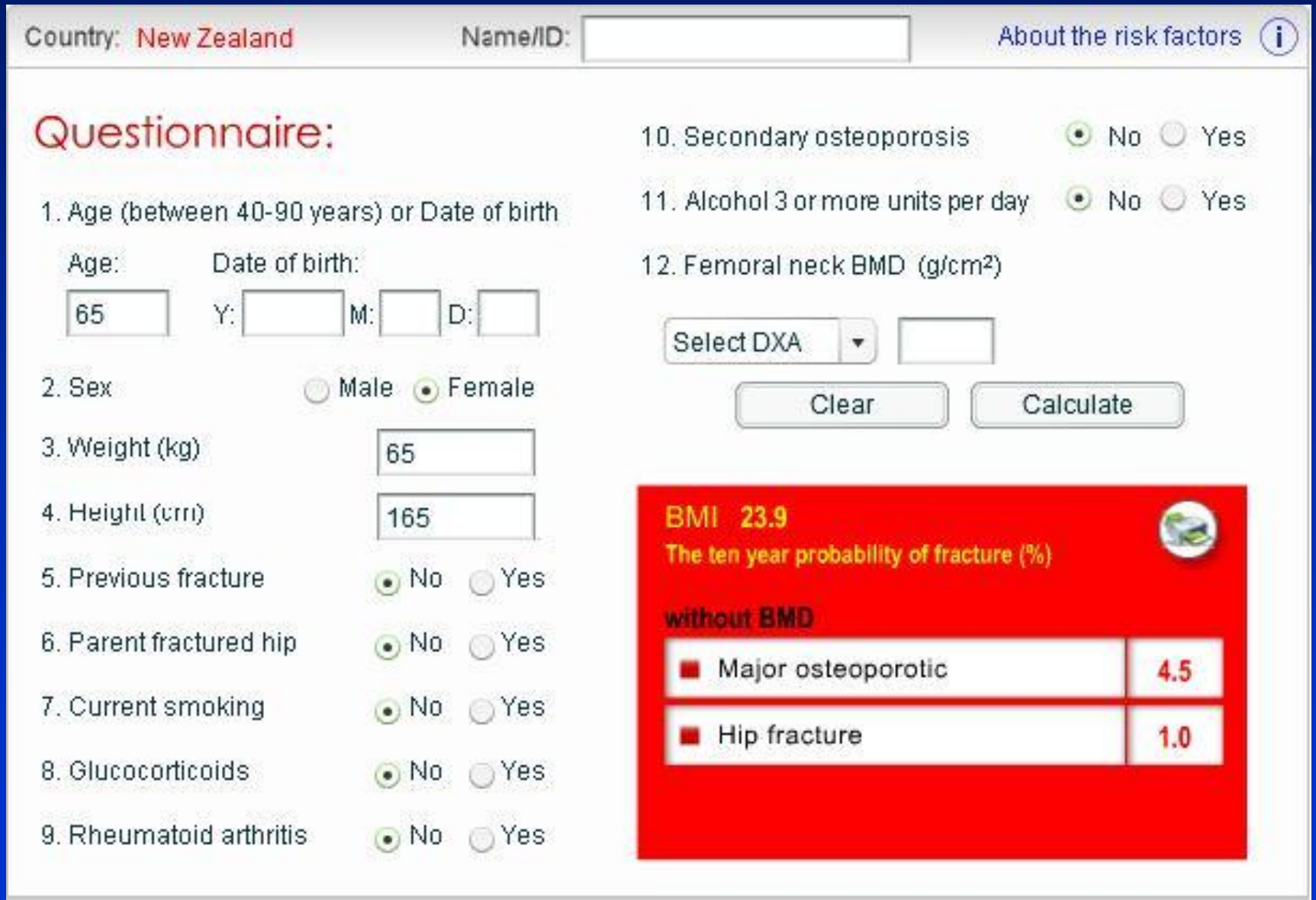
Case Presentation: Ms E McP

♀ Aet 45, normal BMI, no CRFs



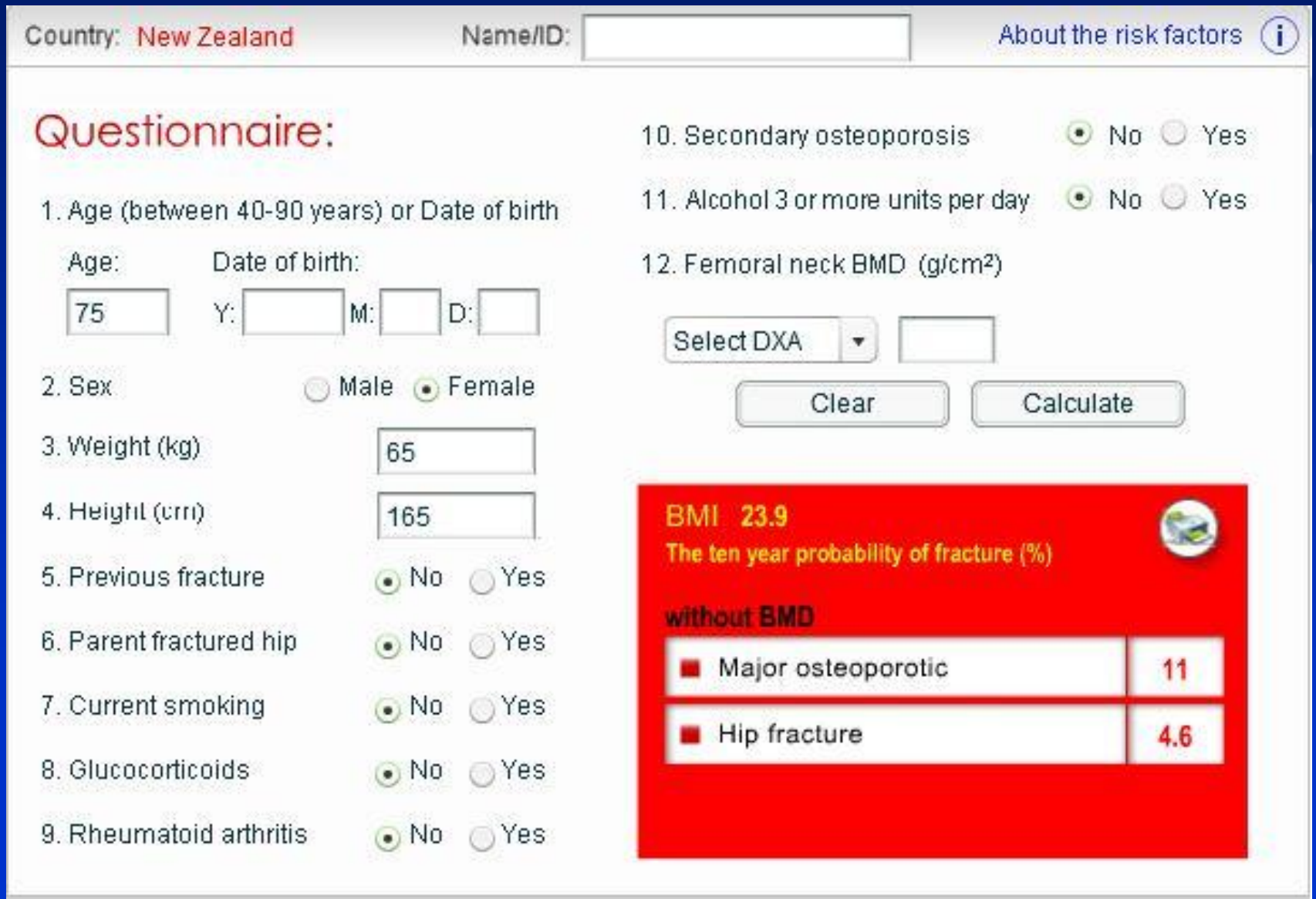
Case Presentation: Ms S S

♀ Aet 65, normal BMI, No CRFs

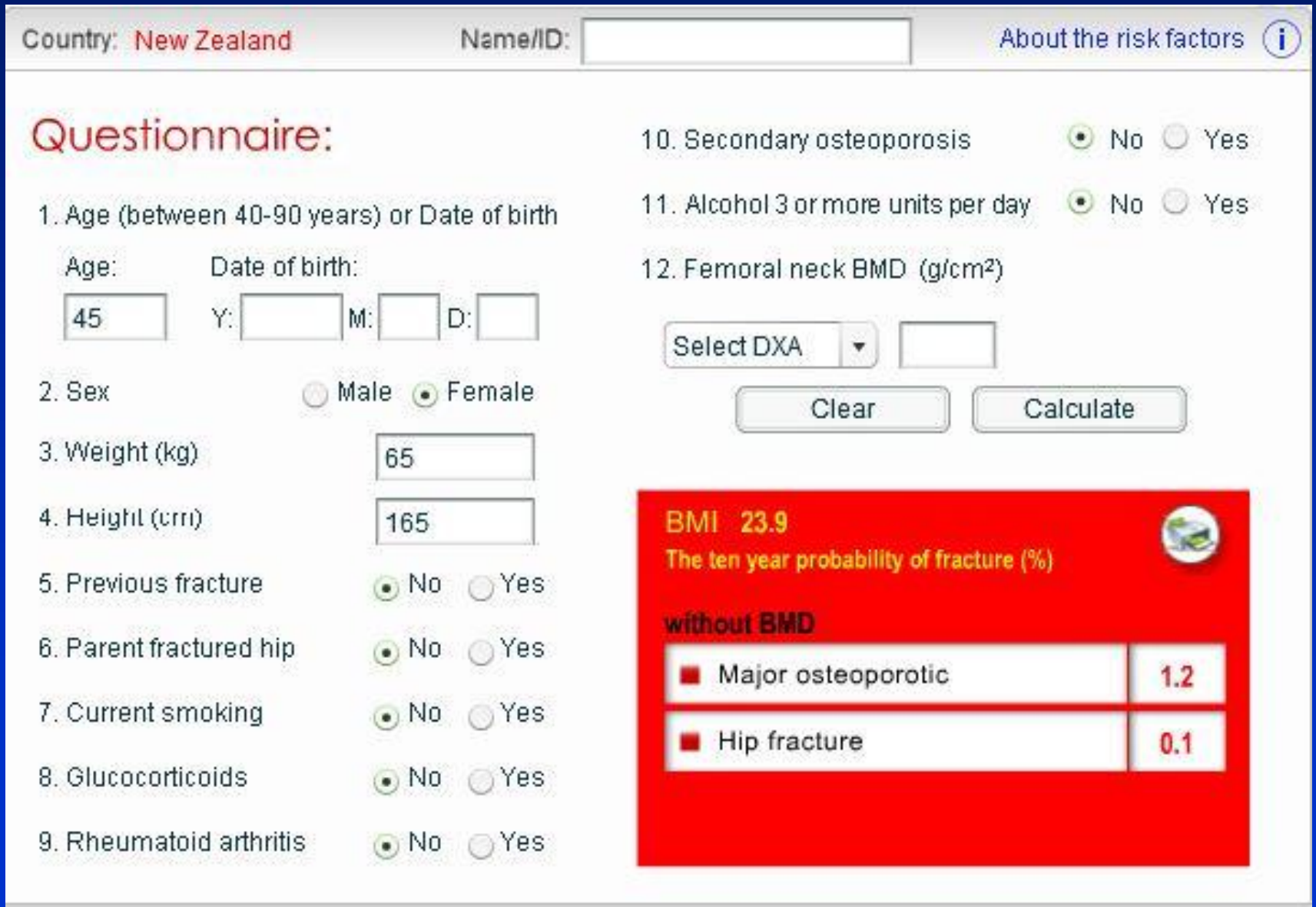


Case Presentation: Dame J D

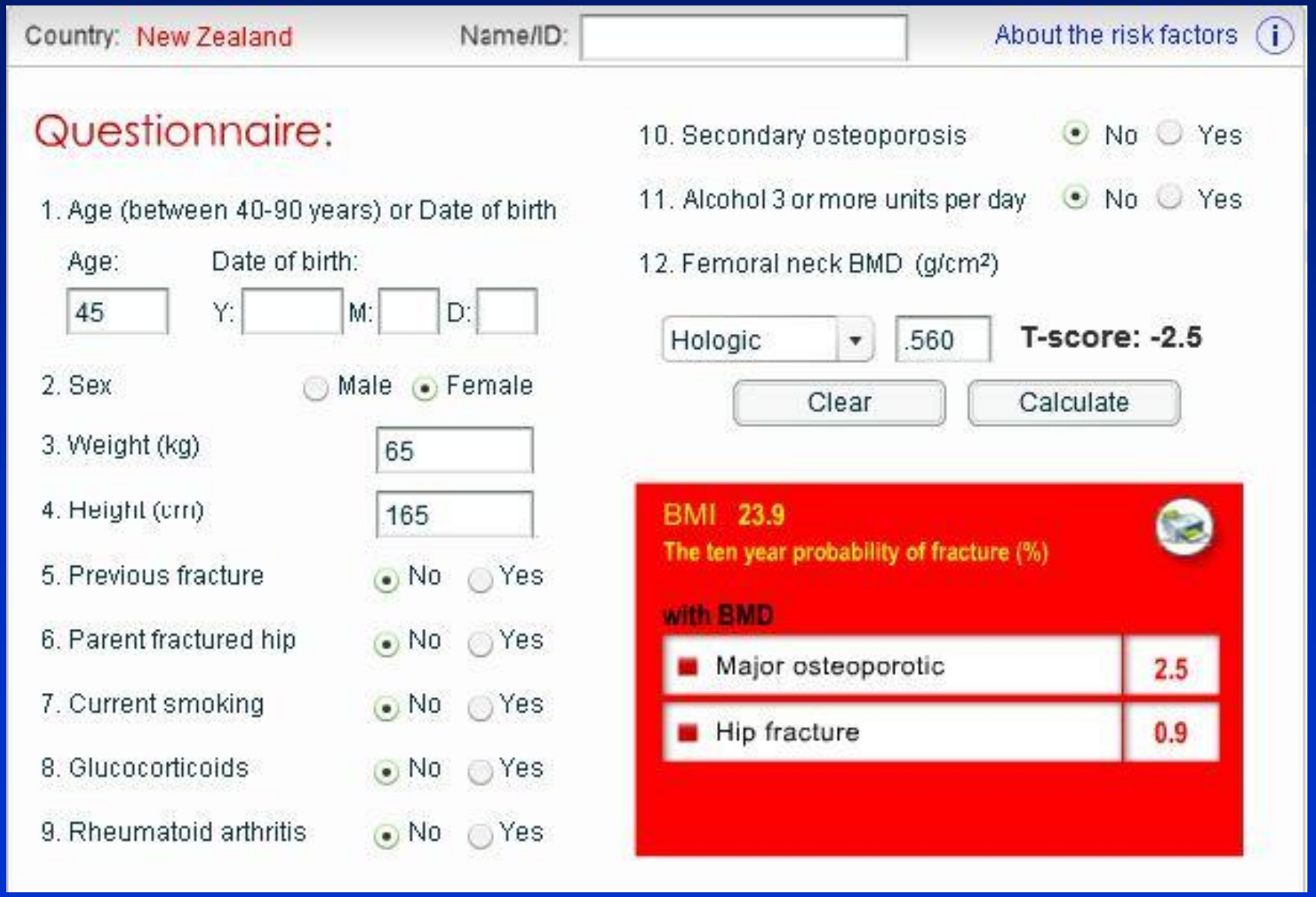
♀ Aet 75, normal BMI, No CRFs



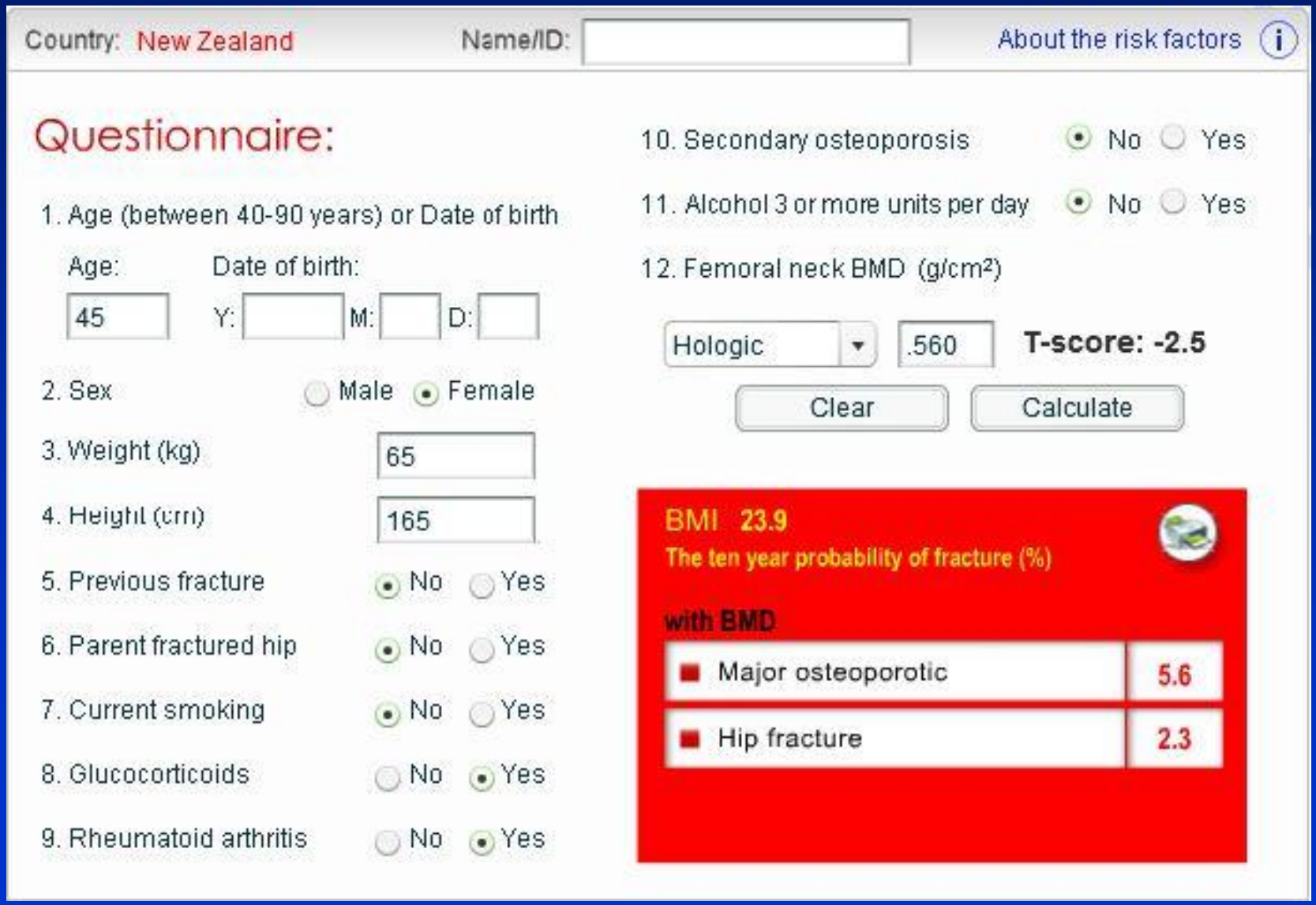
♀ Aet 45, normal BMI, no CRFs



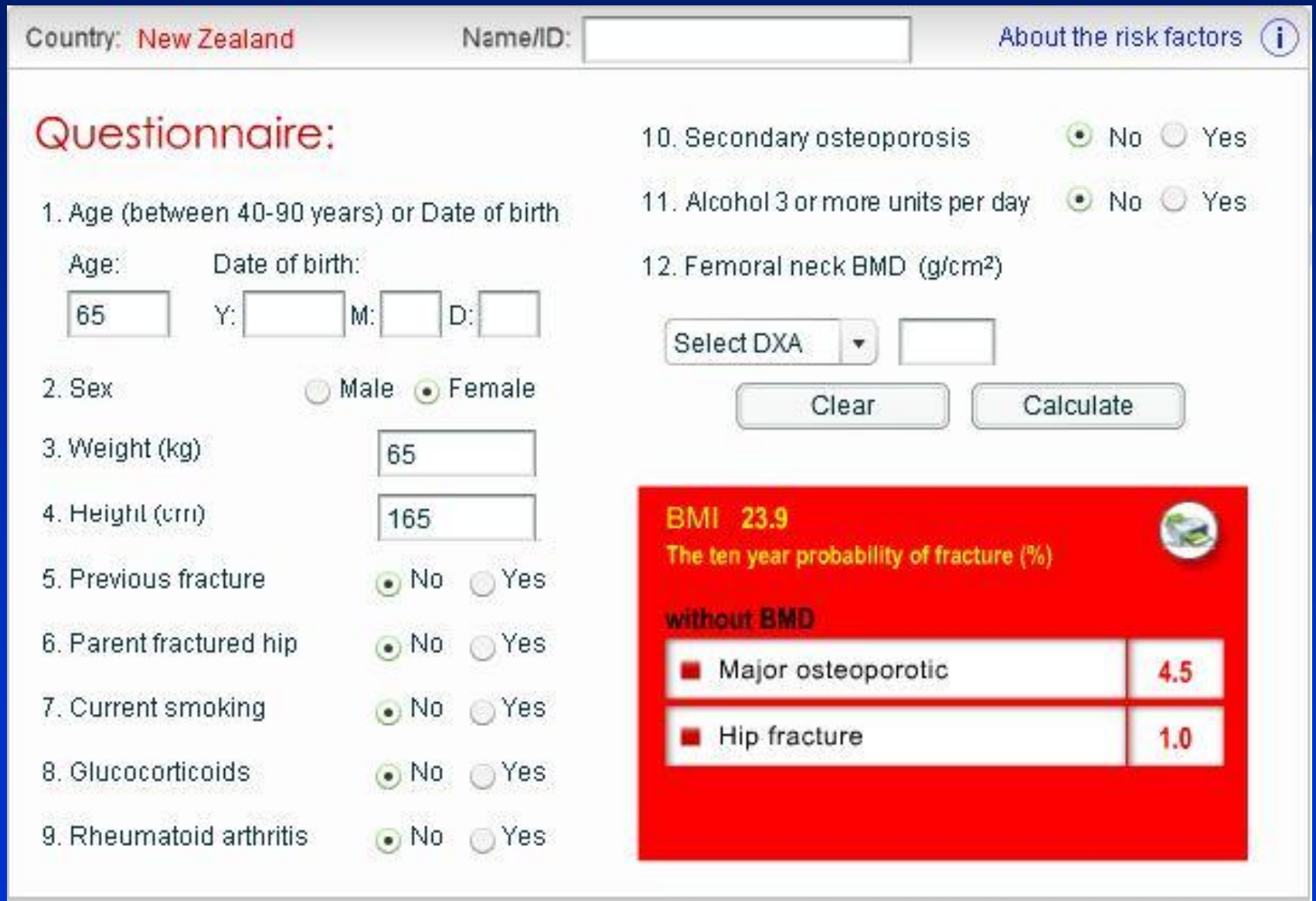
♀ Aet 45, normal BMI, T -2.5,



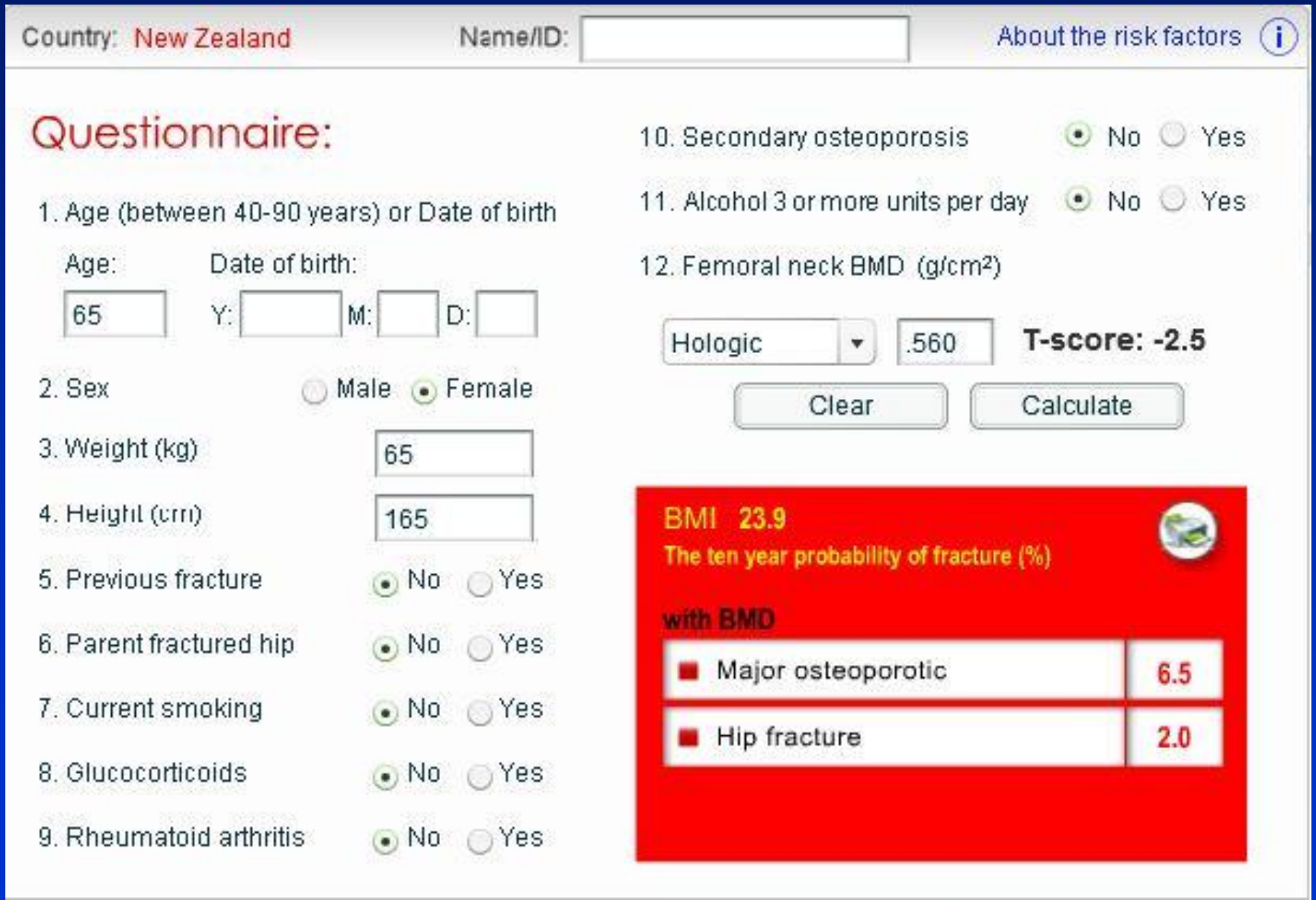
♀ Aet 45, normal BMI, T -2.5, RA + GC



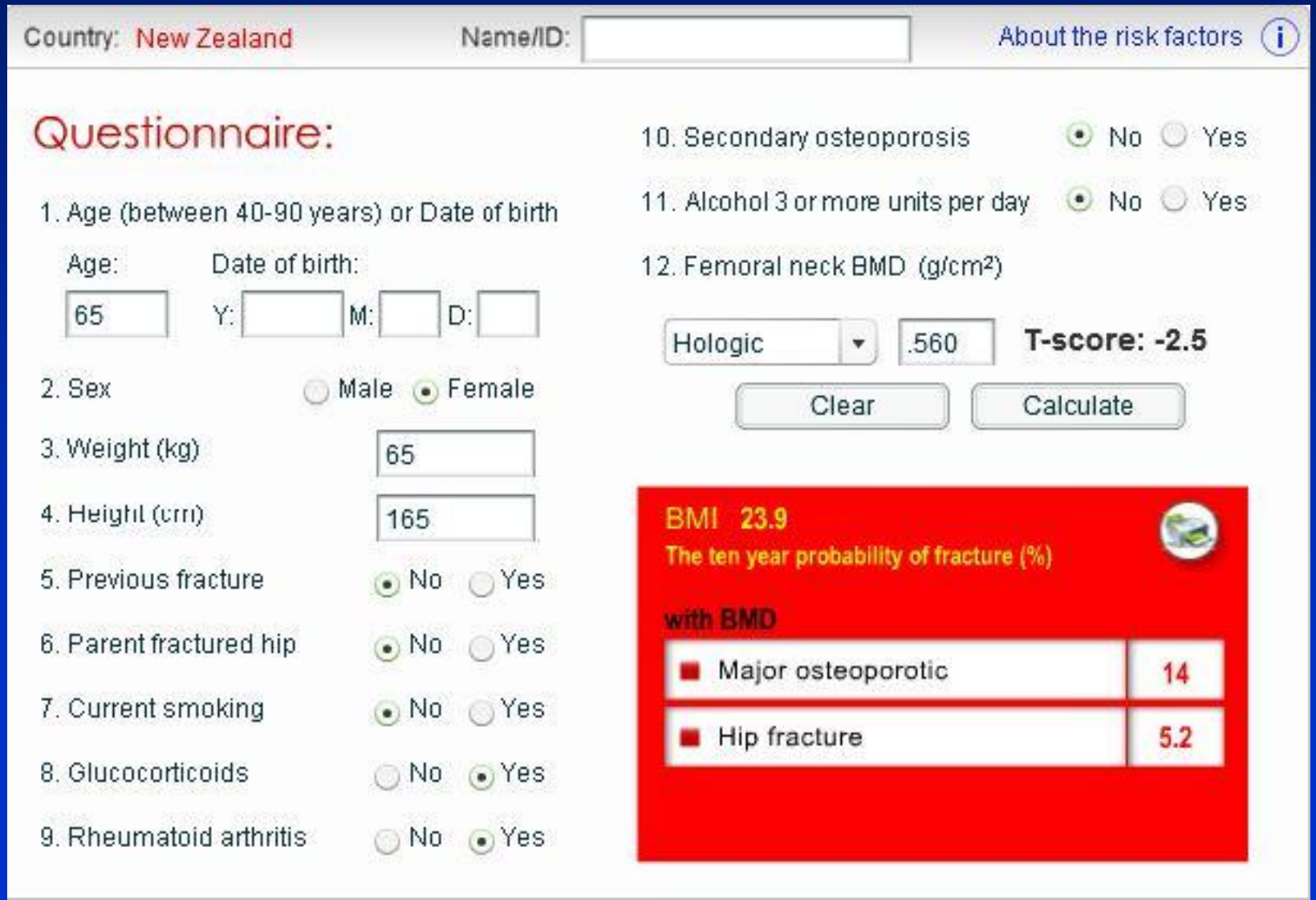
♀ Aet 65, normal BMI, No CRFs



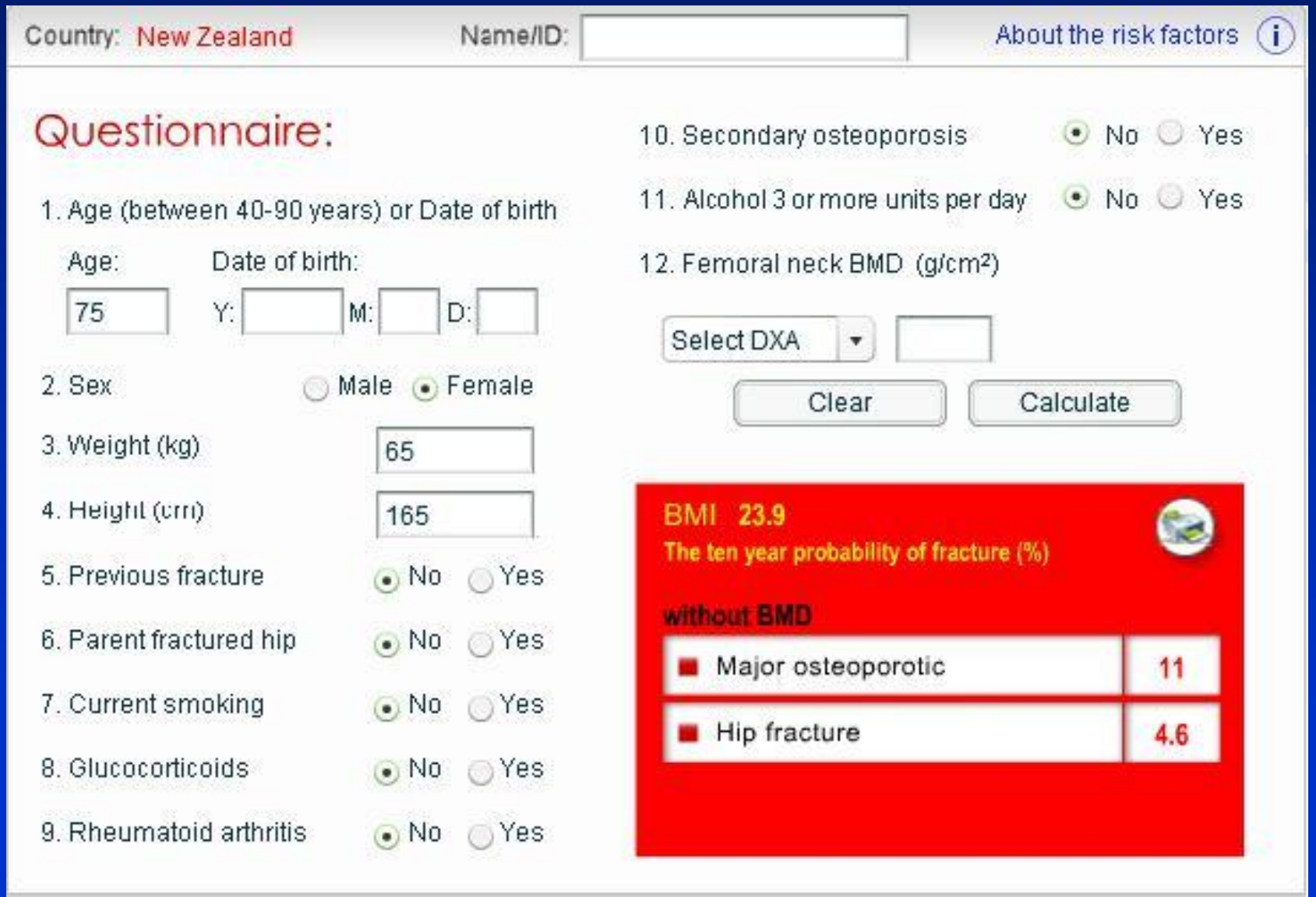
♀ Aet 65, normal BMI, T -2.5



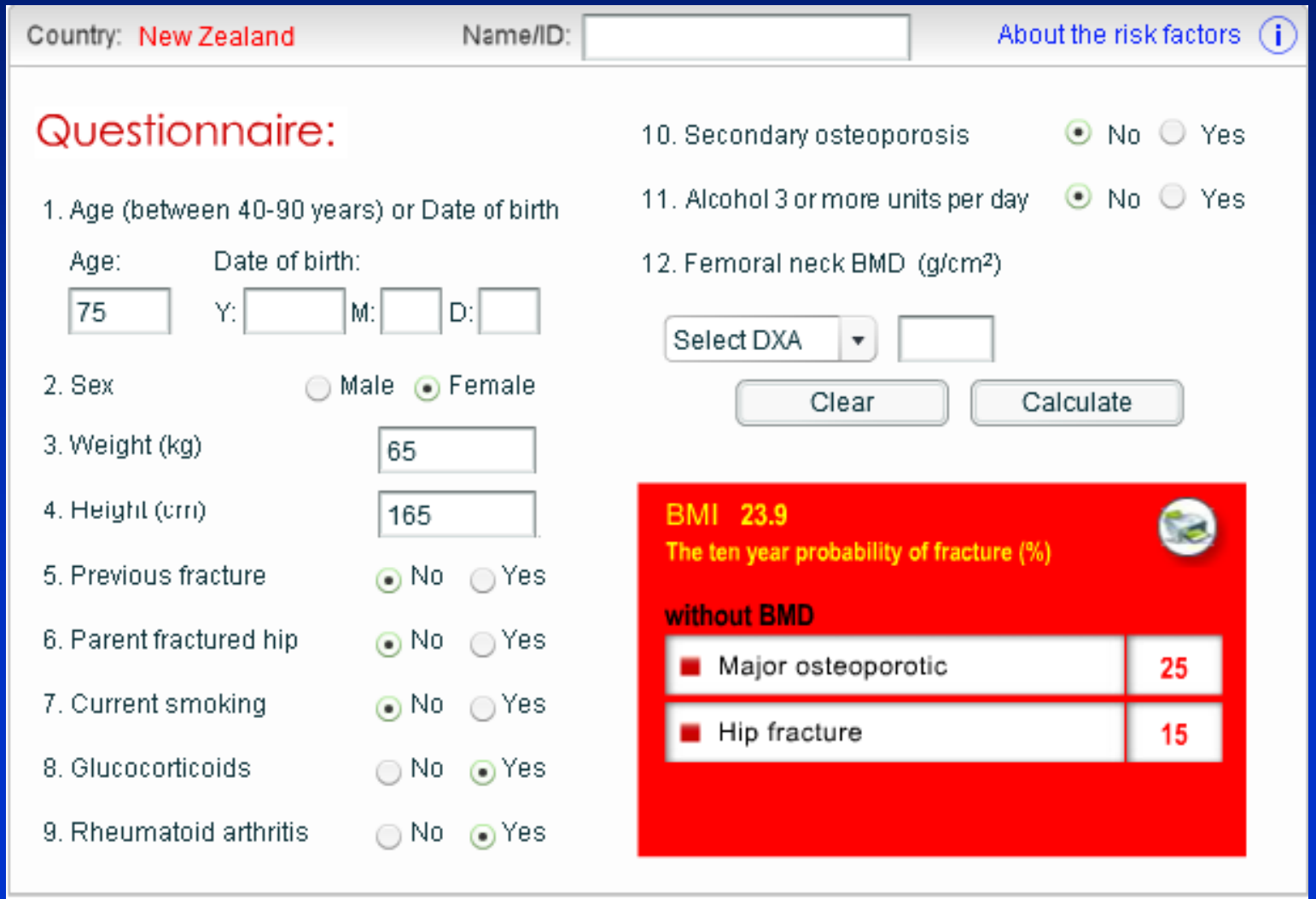
♀ Aet 65, normal BMI, T -2.5, RA + GC



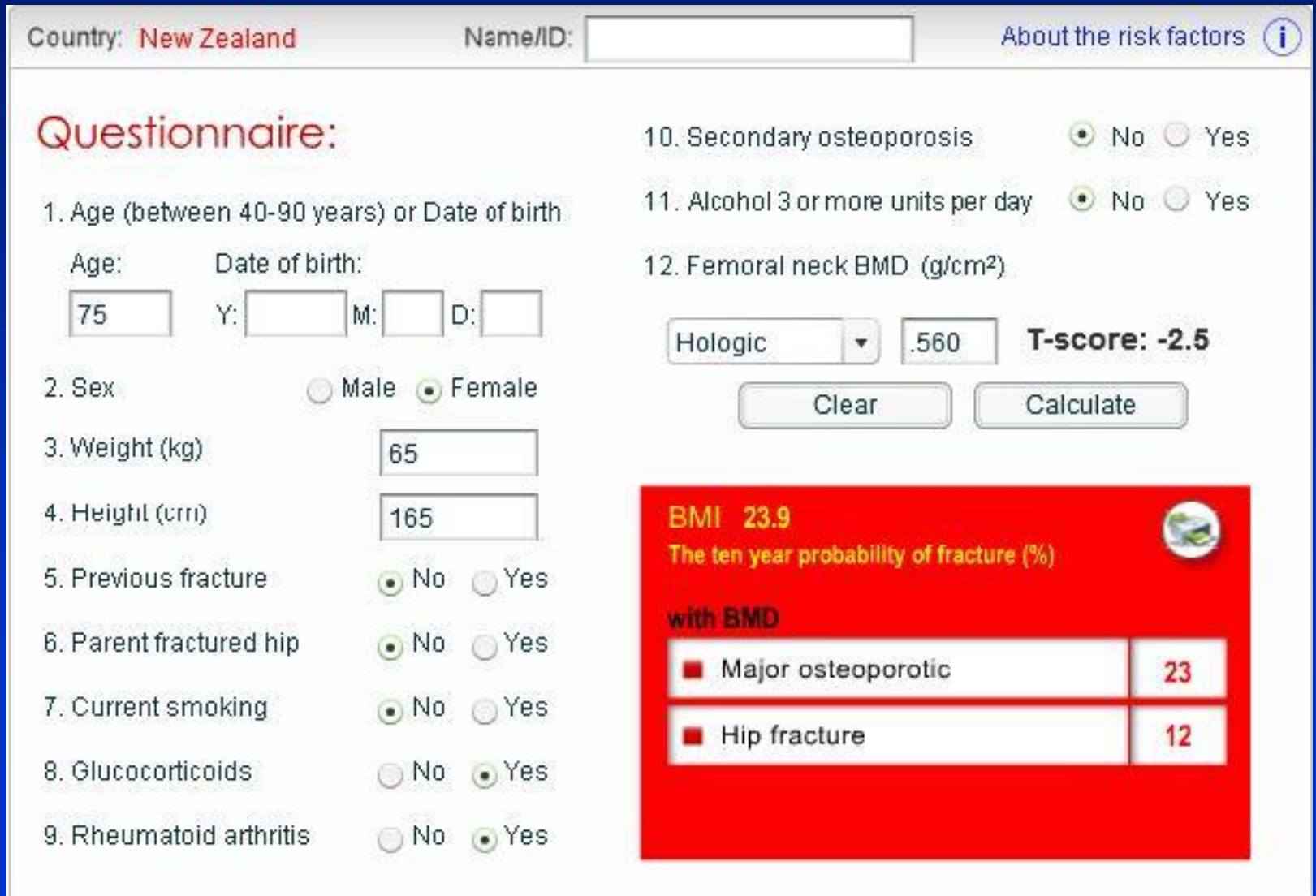
♀ Aet 75, normal BMI, No CRFs



♀ Aet 75, normal BMI, RA + GC



♀ Aet 75, normal BMI, T-2.5, RA + GC



NOF Treatment Criteria

- Using FRAX assessment tool:
  - A 10 year probability of any major fracture of 20%
  - A 10 year probability of hip fracture of 3%

What can we expect from Bisphosphonates?

- Prospective, randomised and double-blind studies over 3-5 year periods suggest a total fracture *relative risk reduction* of 35-40%
- "Real world" analyses support a benefit of 22% *RRR* in compliant patients

Osteoporos Int 2010;21(4):679-88

Take-home message:

- Osteoporosis in post-menopausal women:
  - Those with a T score ≤ -2.5 are at most risk of fracture
  - A T score of ≤ -2.5 is NOT sufficient to initiate drug treatment
  - 82% of women who fracture will have a T score > -2.5
- Management should be directed by *absolute* fracture risk rather than T score alone

Key Points

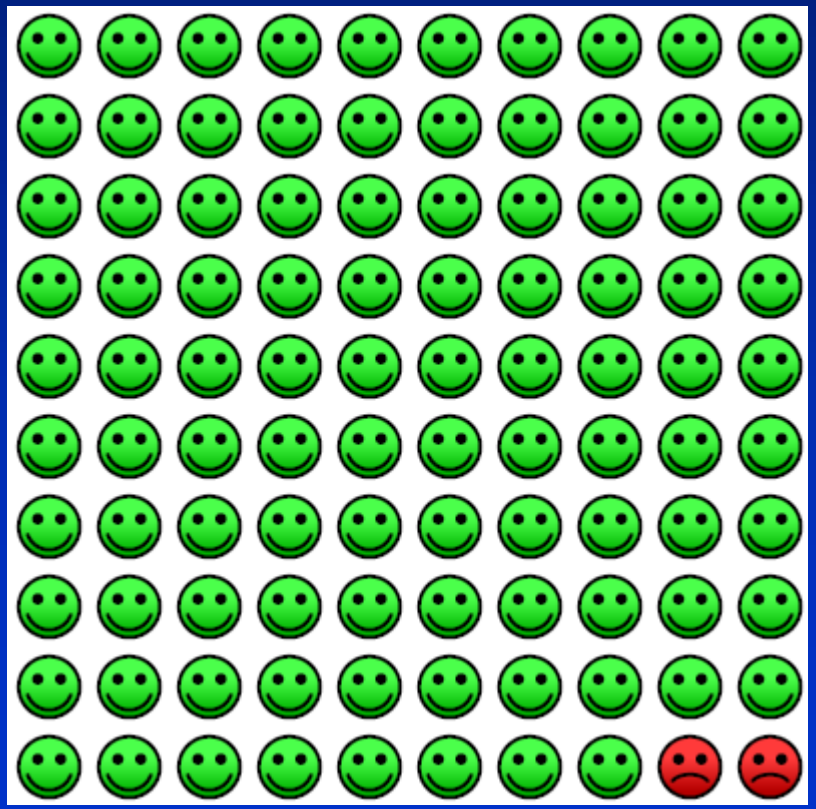
- Rheumatoid Arthritis
  - Importance of early referral of synovitis
  - Aggressive intervention with disease-modifying drugs
- Gout
  - Pain relief and Urate Lowering Therapy are the two distinct arms of Gout treatment
  - Treat to the target of 0.30
- Osteoporosis
  - The purpose of diagnosis is to prevent fragility fracture
  - Risk assessment tools perform better than screening with DEXA scanning

QE HEALTH

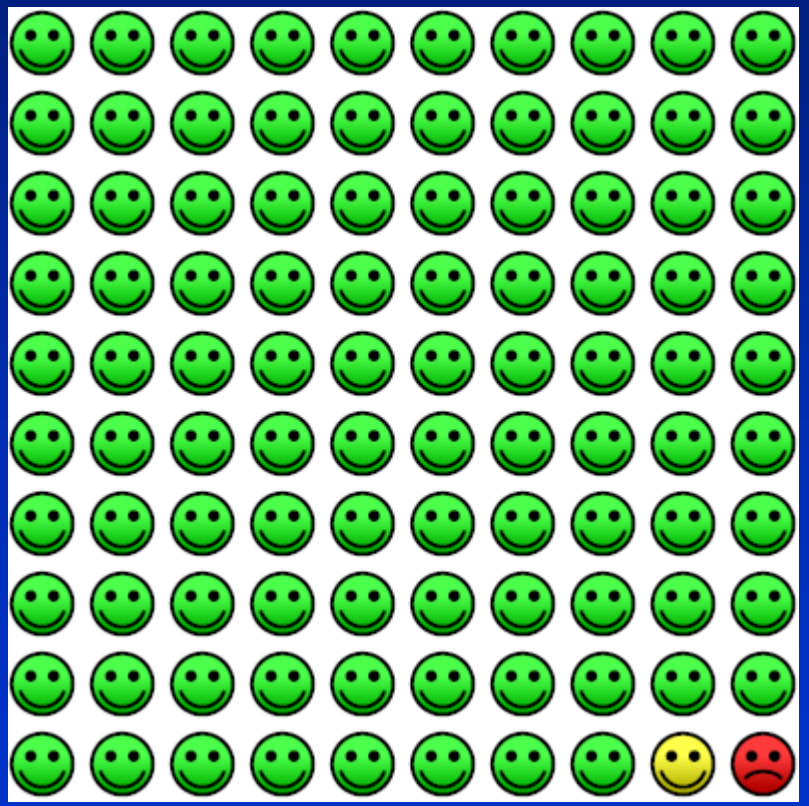
enhancing mind body & spirit

45 yr ♀, T score -2.5, 10 year # risk 2.3%

No treatment

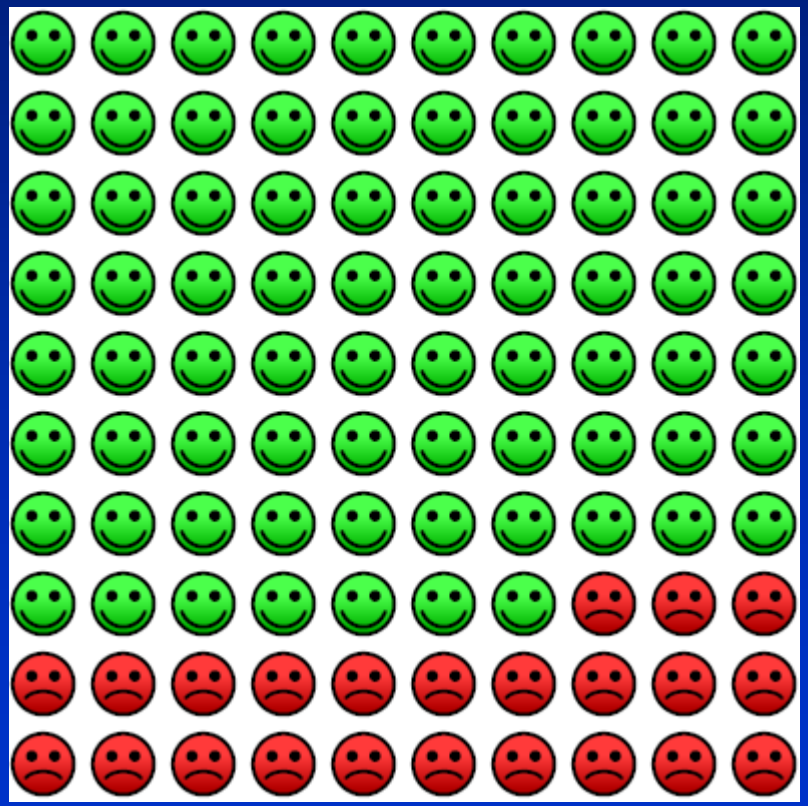


Bisphosphonate

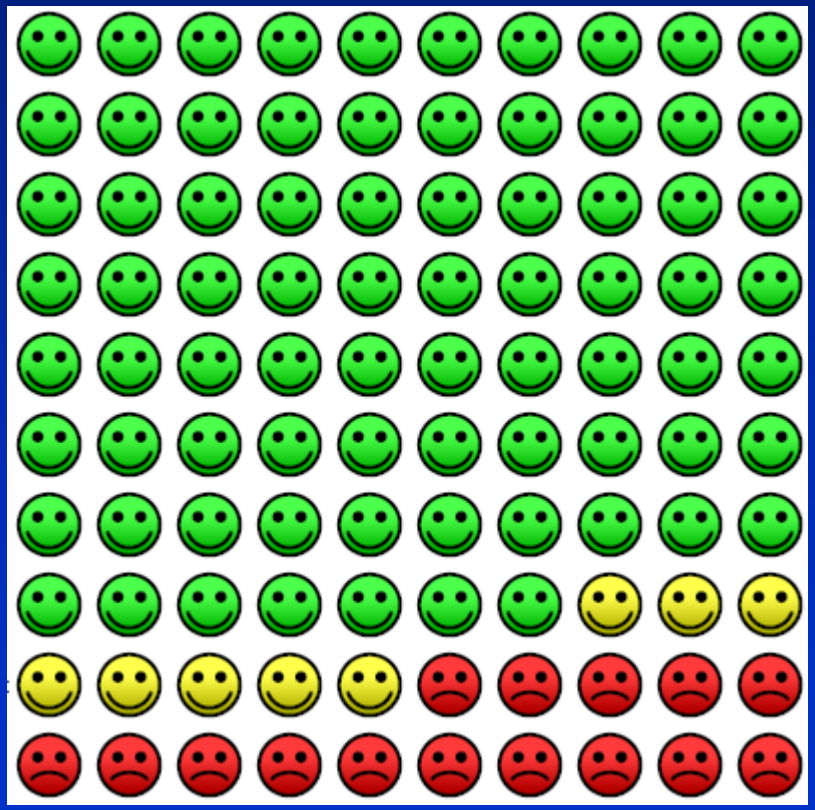


75 yr ♀, T score -2.5, 10 year # risk 23%

No treatment



Bisphosphonate



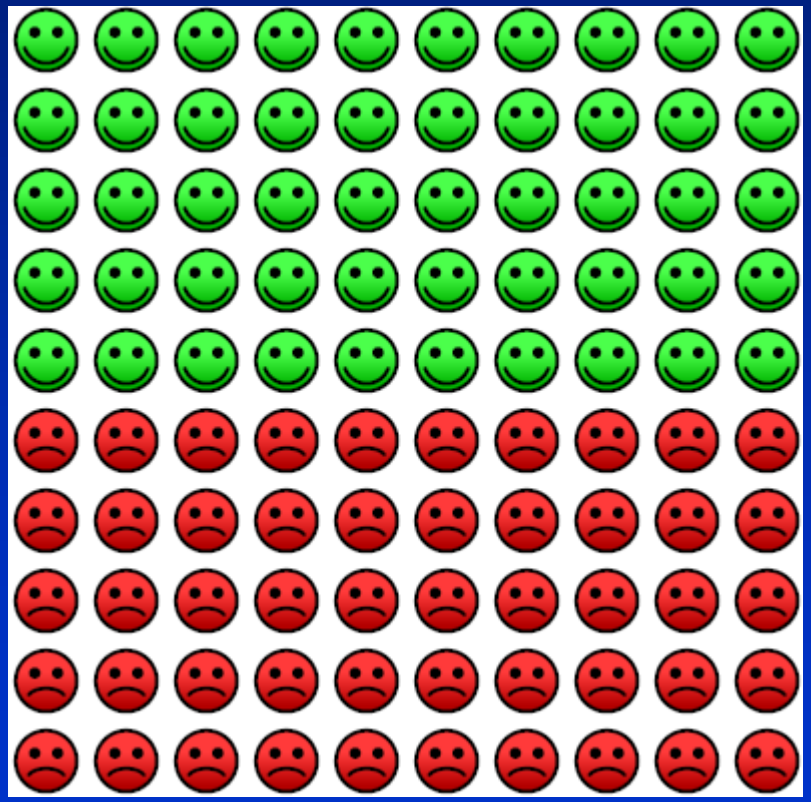
What do patients think?

- Justifiable risk for drug treatment:
  - Hip fracture
    - Patients 50% (25-60)
    - Doctors 10% (5-20); $p<0.0001$
  - Major osteoporotic fracture
    - Patients 50% (25-60)
    - Doctors 10% (10-20); $p<0.0001$
- Required reduction in Relative Risk
  - 50%

Douglas F, Petrie KJ, Cundy et al. Osteoporos Int 2012;23:2135-40

Patient expectation

50% risk of Fracture



50% risk reduction