Northern Cancer Alliance (NCA)

Guideline on Management of Bone Health in Men with Prostate Cancer

Document Information

Title:	**NCA Guideline on Management of Bone Health in Men with Prostate Cancer**
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Contents

1. Background

Men with locally advanced and metastatic prostate cancer (PC) are now living longer thanks to therapeutic advances, especially with systemic treatment options in addition to androgen deprivation therapy (ADT) and radiotherapy. Long term ADT is an established risk factor for secondary osteoporosis and fracture (1,2).

Evidence suggests that age related bone mineral density (BMD) decreases by 1% rising to 2-5 % per year in men with PC on GHRH agonist (3) and the risk of fractures increases by 40–50 % and linearly with prolonged duration of ADT up to 20% after 5 years (2,4). With more life-extending systemic options (including novel hormone pathway inhibitors, chemotherapy or radium-223) negatively impact bone marrow reserve and architect-risk of non-malignant fracture risks are further increased (5–8). This can lead to early death, poor quality of life and significant health and economic burden despite reduction of cancer related malignant skeletal events (2,8). A previous local audit has shown that a third of patients with PC show bone density changes at baseline (9). In keeping with previous studies, we also demonstrated that the commonly used fracture risk assessment score (FRAX) may underestimate the burden in this patient group (9,10).

Currently there is no established national guidance on prevention of secondary osteoporosis and protect bone health for men who are on ADT although European guidance (8,11) was followed by some centres including the Queen Elizabeth Hospital in Gateshead (referred as "the QEH model"). Recent recommendations have been produced by a UK Consensus Group for the assessment and management of prostate cancer treatment induced bone loss (8,12).

Lifestyle advice should also be offered to all patients commencing ADT. This involves a discussion about reducing alcohol intake and smoking, increasing dietary intake of calcium and vitamin D and encouragement of regular exercise as appropriate (8,12,13,14).

2. Proposed management

The Northern Cancer Alliance (NCA) has reviewed the available evidence and **recommend that:**

1. All men presenting to urology/oncology for treatment of prostate cancer should have bone health evaluation integrated into their management pathway.
2. This should be **at the earliest opportunity** either in clinic or via referral to a specialist via an agreed local pathway.
3. Oral bone protection agents (BPAs) treatments in most cases should be initiated as per agreed local arrangement and continued in primary care.
4. Patients intolerant of oral therapy should receive IV or subcutaneous BPAs as per local agreement.
5. Table 1 below details the NCA's recommendations on how to manage bone health for 3 main categories using the traffic light system:

Table 1. Proposed recommendations for bone health management in patients with prostate cancer

Risk Group	Patient Group	Investigations and Treatment	Comment	Notes/ Evidence
Population risk	Non-metastatic prostate cancer- Radical or Salvage Radiotherapy + 6-<24 months ADT	Consider FRAX scoring (or refer) and advise primary care on recommended treatment / follow up	As per general population risk management /primary care led	(8,15,18)
Risk-stratified	Non-metastatic prostate cancer- Radical or Salvage Radiotherapy + >=24 – 36 months ADT (usually **LHRHa)	Bone health assessment (as per Appendix A) - **FRAX score + baseline DEXA+/-follow up** **If BMD -2.5 (Osteoporotic)** *Offer: **1) Calcium and vitamin D supplement** (at least 1 g elemental calcium + 800 units colecalciferol per day - e.g., Calcichew D3 Forte 2 tabs OD, Adcal-D3 1 tab BD) + **2) PO Alendronic Acid 70mg weekly* or** Residronate 35 mg weekly.* *If intolerant of oral therapy to refer locally for* • *IV Zolendronic Acid **5 mg 12 monthly or*** • *SC Denosumab **60 mg 6 monthly***	Primary care led (e.g as part of the Wellman assessment) Or local arrangement • The QEH model • Urology CNS lead	(8,11,15,18)
Treat with BPA	***mHSPC on lifelong ADT + /- additional therapy e.g *upfront ****NHT and/or chemotherapy* ***mCRPC or nmCRPC on lifelong ADT + /- additional therapy e.g *Biclutamide or NHT or Dexamethasone, chemotherapy or Radium 223*	*Offer **all:*** ***1) Calcium and vitamin D supplement** (at least 1 g elemental calcium + 800 units colecalciferol per day - e.g., Calcichew D3 Forte 2 tabs OD, Adcal-D3 1 tab BD) +* ***2) PO Alendronic Acid 70mg weekly* or** Residronate 35 mg weekly.* *If intolerant of oral therapy to refer locally for* • *IV Zolendronic Acid **5 mg 12 monthly or*** • *SC Denosumab **60 mg 6 monthly***	Treatment recommended as FRAX/DEXA may underestimate fracture risk in this group Consider tolerability and compliance with PO therapy Vs higher rate of hypocalcaemia of IV/Sc treatment **Radium 223 patients have the highest risk of fragility fracture**	(5,8, 10 15,16, 17, 18)

* as per primary osteoporosis treatment algorithm (18) – see Figure 1 in appendix.
**LHRHa-luteinising hormone-releasing hormone analogues
***mHSPC- metastatic hormone sensitive prostate cancer; mCRPC-Metastatic castrate resistant prostate cancer; nmCRPC—non-metastatic castrate resistant prostate cancer
****NHT novel hormone therapy e.g. Apalutamide or Enzalutamide or Abiraterone and Prednisolone, Darolutamide or other newer agents.

3. References:

1. Morote J, Morin JP, Orsola A, Abascal JM, Salvador C, Trilla E, et al. Prevalence of Osteoporosis During Long-Term Androgen Deprivation Therapy in Patients with Prostate Cancer. Urology. 2007 Mar;69(3):500–4.

2. Shahinian VB, Kuo Y-F, Freeman JL, Goodwin JS. Risk of Fracture after Androgen Deprivation for Prostate Cancer. N Engl J Med. 2005 Jan 13;352(2):154–64.

3. Greenspan SL, Wagner J, Nelson JB, Perera S, Britton C, Resnick NM. Vertebral fractures and trabecular microstructure in men with prostate cancer on androgen deprivation therapy. J Bone Miner Res. 2013 Feb;28(2):325–32.

4. Aksnes LH, Bruland ØS. Some musculo-skeletal sequelae in cancer survivors. Acta Oncol (Madr). 2007;46(4):490–6.

5. Smith M, Parker C, Saad F, Miller K, Tombal B, Ng QS, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019 Mar 1;20(3):408–19.

6. Myint ZW, Momo HD, Otto DE, Yan D, Wang P, Kolesar JM. Evaluation of Fall and Fracture Risk Among Men With Prostate Cancer Treated With Androgen Receptor Inhibitors: A Systematic Review and Meta-analysis. JAMA Netw open. 2020 Nov 2;3(11):e2025826.

7. Graff JN, Baciarello G, Armstrong AJ, Higano CS, Iversen P, Flaig TW, et al. Efficacy and safety of enzalutamide in patients 75 years or older with chemotherapy-naive metastatic castrationresistant prostate cancer: Results from PREVAIL. Ann Oncol. 2016 Feb 1;27(2):286–94.

8. Brown JE, Handforth C, Compston JE, Cross W, Parr N, Selby P, et al. Guidance for the assessment and management of prostate cancer treatment-induced bone loss. A consensus position statement from an expert group. J Bone Oncol. 2020 Dec 1;25:100311.

9. Hannaway N, Jiang X, Aspray T, Burns A, Ferguson J, Pedley ID, et al. 673P Assessing bone health and osteoporotic risk in patients requiring anti androgen therapy for prostate cancer. Ann Oncol. 2020 Sep 1;31:S539.

10. Volta AD, Mazziotti G, Maffezzoni F, Grisanti S, Palumbo C, Pedersini R, et al. Bone mineral density and frax score may not predict fracture risk in patients with cancer undergoing hormone deprivation therapies. J Clin Oncol. 2020;38(29):3363–6.

11. Rizzoli R, Body JJ, Brandi ML, Cannata-Andia J, Chappard D, El Maghraoui A, et al. Cancer-associated bone disease. Osteoporos Int. 2013 Dec;24(12):2929–53.

12. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, et al. UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos. 2017;12(1).

13. Osteoporosis - prevention of fragility fractures | Health topics A to Z | CKS | NICE [Internet]. [cited 2021 May 12]. Available from: https://cks.nice.org.uk/topics/osteoporosis-prevention-of-fragility-fractures/

14. Owen PJ, Daly RM, Livingston PM, Fraser SF. Lifestyle guidelines for managing adverse effects on bone health and body composition in men treated with androgen deprivation therapy for prostate cancer: An update. Vol. 20, Prostate Cancer and Prostatic Diseases. Nature Publishing Group; 2017. p. 137–45.

15. Recommendations | Prostate cancer: diagnosis and management | Guidance | NICE.

16. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002;94(19):1458–68.

17. Jiang XY, Atkinson S, Pearson R, Leaning D, Cumming S, Burns A, et al. Optimising Radium 223 Therapy for Metastatic Castration-Resistant Prostate Cancer –5-year Real-World Outcome: Focusing on Treatment Sequence and Quality of Life. Clin Oncol. 2020;32(10):e177–87.

18. North of Tyne & Gateshead Guideline for the management of osteoporosis in primary care and review of patients taking bisphosphonates for 5 years Endorsed for use within North Tyneside, Northumberland, Newcastle and Gateshead by the North of Tyne and Gates. 2017.

19. CHOLECALCIFEROL WITH CALCIUM CARBONATE | Drug | BNF content published by NICE [Internet]. [cited 2021 May 17].
Available from: https://bnf.nice.org.uk/drug/colecalciferol-with-calcium-carbonate.html#

20. ALENDRONIC ACID | Drug | BNF content published by NICE [Internet]. [cited 2021 May 17].
Available from: https://bnf.nice.org.uk/drug/alendronic-acid.html#

21. ZOLEDRONIC ACID | Drug | BNF content published by NICE [Internet]. [cited 2021 May 12]. Available from: https://bnf.nice.org.uk/drug/zoledronic-acid.html#indicationsAndDoses

22. Himelstein AL, Foster JC, Khatcheressian JL, Roberts JD, Seisler DK, Novotny PJ, et al. Effect of longer-interval vs standard dosing of zoledronic acid on skeletal events in patients with bone metastases: A randomized clinical trial. JAMA - J Am Med Assoc. 2017 Jan 3;317(1):48–58.

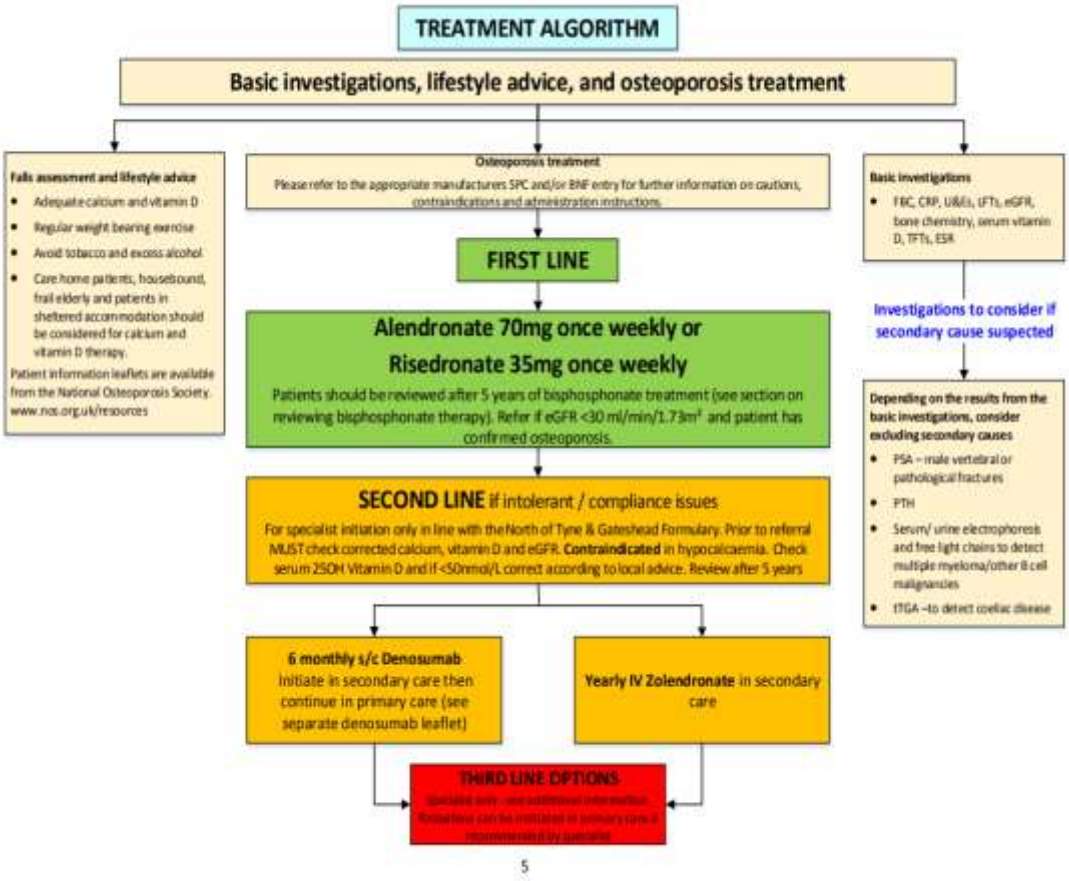
23. Hortobagyi GN, Van Poznak C, Harker WG, Gradishar WJ, Chew H, Dakhil SR, et al. Continued treatment effect of zoledronic acid dosing every 12 vs 4 weeks in women with breast cancer metastatic to bone: The OPTIMIZE-2 randomized clinical trial. JAMA Oncol. 2017 Jul 1;3(7):906–12.

24. DENOSUMAB | Drug | BNF content published by NICE [Internet]. [cited 2021 May 12]. Available from: https://bnf.nice.org.uk/drug/denosumab.html#indicationsAndDoses

25. Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A randomised, double-blind study. Lancet. 2011;377(9768):813–22.

4. Appendix

A) Figure 1. North of Tyne & Gateshead Guideline for the management of osteoporosis in primary care and review of patients taking bisphosphonates for 5 years (18).



http://www.northoftyneapc.nhs.uk/wp-content/uploads/sites/6/2018/01/Osteoporosis-guidelines-including-bisphosphonate-review-Dec-17.pdf

B) Table 2. ESMO Guidance for the assessment and management of prostate cancer treatment induced bone loss. A consensus position statement from an expert group (8)

All men starting or already receiving long-term ADT for Prostate Cancer should:

1. Be provided with individualised and patient-centred information, including appropriate lifestyle advice regarding optimisation of bone health.
2. Be referred to a supervised resistance and aerobic exercise programme of at least 12 weeks duration (in accordance with UK NICE guidelines) or as recommended in specific country guidelines.
3. Have daily calcium intake calculated to identify need for supplementation (using a tool such as the Edinburgh calculator http://www.cgem.ed.ac.uk/research/rheumatological/calcium-calculator).
4. Achieve or maintain adequate daily calcium (700- 1200mg) and vitamin D (800 IU) intake through dietary intake, sunlight exposure, and supplementation if needed.
5. Have their fracture risk assessed using FRAX® to determine 10-year probability of major osteoporotic and hip fracture https://www.sheffield.ac.uk/FRAX/tool.jsp ensuring that ADT is included as a secondary osteoporosis risk factor, and that glucocorticoid use required with any planned systemic cancer therapy is included in FRAX as a risk factor.
6. Wherever possible, undergo DXA to assess BMD, alongside FRAX, when ADT is commenced. BMD should *always* be measured when FRAX probabilities, calculated without BMD (but selecting the FRAX secondary osteoporosis box to recognise ADT), lie close to the intervention threshold (for example, the amber area on the chart available at https://www.sheffield.ac.uk/NOGG/result-nobmd.html?).
7. Those found to have a high probability of fracture should be offered appropriate pharmacological treatment. Choice of therapy should follow current NOGG guidance https://www.sheffield.ac.uk/NOGG/index.html: oral alendronate and risedronate, denosumab (subcutaneous) or zoledronic acid (intravenous) or as recommended in specific country guidelines.
8. Those close to but below the intervention threshold should have their FRAX/BMD reassessed after 12-18 months of ADT or at a change in systemic therapy. FRAX/BMD should be reassessed in patients who have been on ADT for 5 years.
9. Be investigated for other causes of secondary osteoporosis if BMD is within the osteoporosis range; this can best be achieved by referral to specialist centres for on-going management

It is also recommended that further research is a key priority to:

10. Link FRAX-derived risk with actual fracture occurrence in this population.
11. Examine the effects of newer systemic therapies (including anti-androgens) for prostate cancer on the skeleton and fracture, particularly in the metastatic setting.
12. Monitor implementation of these guidelines in standard prostate cancer practice.

C) Treatment scheduling for bone protection agents

1. Calcium and vitamin D
    a. E.g Calcichew D3 Forte

BNF licensed indications (19):

Prevention and treatment of calcium and vitamin D deficiency

Calcichew-D3® Forte tablets contain calcium carbonate 1.25 g (calcium 500 mg or Ca^{2+} 12.5 mmol), colecalciferol 10 micrograms (400 units)

Tablets taken twice a day

Potential interactions – Calcium carbonate-containing antacids should preferably not be taken at the same time as other drugs since they may impair absorption.

b. Other choices (As per BNF):

Accrete D3® contains calcium carbonate 1.5 g (calcium 600 mg or Ca^{2+} 15 mmol), colecalciferol 10 micrograms (400 units);

Adcal-D3® tablets contain calcium carbonate 1.5 g (calcium 600 mg or Ca^{2+} 15 mmol), colecalciferol 10 micrograms (400 units);

Cacit® D3 contains calcium carbonate 1.25 g (calcium 500 mg or Ca^{2+} 12.5 mmol), colecalciferol 11 micrograms (440 units)/sachet;

Calceos® contains calcium carbonate 1.25 g (calcium 500 mg or Ca^{2+} 12.5 mmol), colecalciferol 10 micrograms (400 units);

Kalcipos-D® contains calcium carbonate (calcium 500 mg or Ca^{2+} 12.5 mmol), colecalciferol 20 micrograms (800 units);

Natecal D3® contains calcium carbonate 1.5 g (calcium 600 mg or Ca^{2+} 15 mmol), colecalciferol 10 micrograms (400 units);

2. Bisphosphonate (oral):
    a. Alendronic Acid

BNF licensed indications (20):

- Treatment of osteoporosis in men:
  10mg OD
- Alternative dose in female patients for postmenopausal oesteoporosis:

  70mg once weekly

Counselling (18):

Take on an empty stomach at least 30 minutes before breakfast or other medicines. Swallow whole with plenty of water (at least 200mL) while sitting or standing and remain upright for at least 30min after taking.

Advise patients on the rare risk of osteonecrosis of the jaw, osteonecrosis of the auditory canal, and atypical fractures.

Adherence with bone protection treatments:

- Ask if the patient adherent with bisphosphonate.

Contra-indications (18):

Abnormalities of oesophagus, factors which delay gastric emptying, hypocalcaemia, uveitis, scleritis.

Patients should be vitamin D replete, as bisphosphonates can aggravate osteomalacia.

Avoid if eGFR less than 35ml/minute/1.73m

    b. Alternative: Risedronate sodium

Indication (BNF):
Treatment of osteoporosis in men at high risk of fractures
By mouth

Adult (male)
35 mg once weekly.

Contra-indications
Hypocalcaemia

Cautions, further information:

Atypical femoral fractures; oesophageal abnormalities; other factors which delay transit or emptying (e.g. stricture or achalasia); upper gastro-intestinal disorders

3. Zolendronic Acid (ZA)

BNF licensed indications (21):

- 4mg IV ZA every 3-4wks for prevention of skeletal events in presence of bone metastases
- 5mg IV ZA yearly in 'patients with osteoporosis'

2x RCTs - ZA given 12 weekly was not inferior to 4 weekly with regard to skeletal events (22,23)

- 795 cancer patients (including prostate, breast, myeloma) (22)
- 416 women with metastatic breast cancer (23)

So current recommendation would be 4mg IV 4 weekly ZA, but these RCTs suggest that 12 weekly is adequate.

4. Denosumab

BNF licensed indications (24):

'Prolia' - 60mg every 6 months for bone loss associated with hormone ablation in men with prostate cancer at risk of #

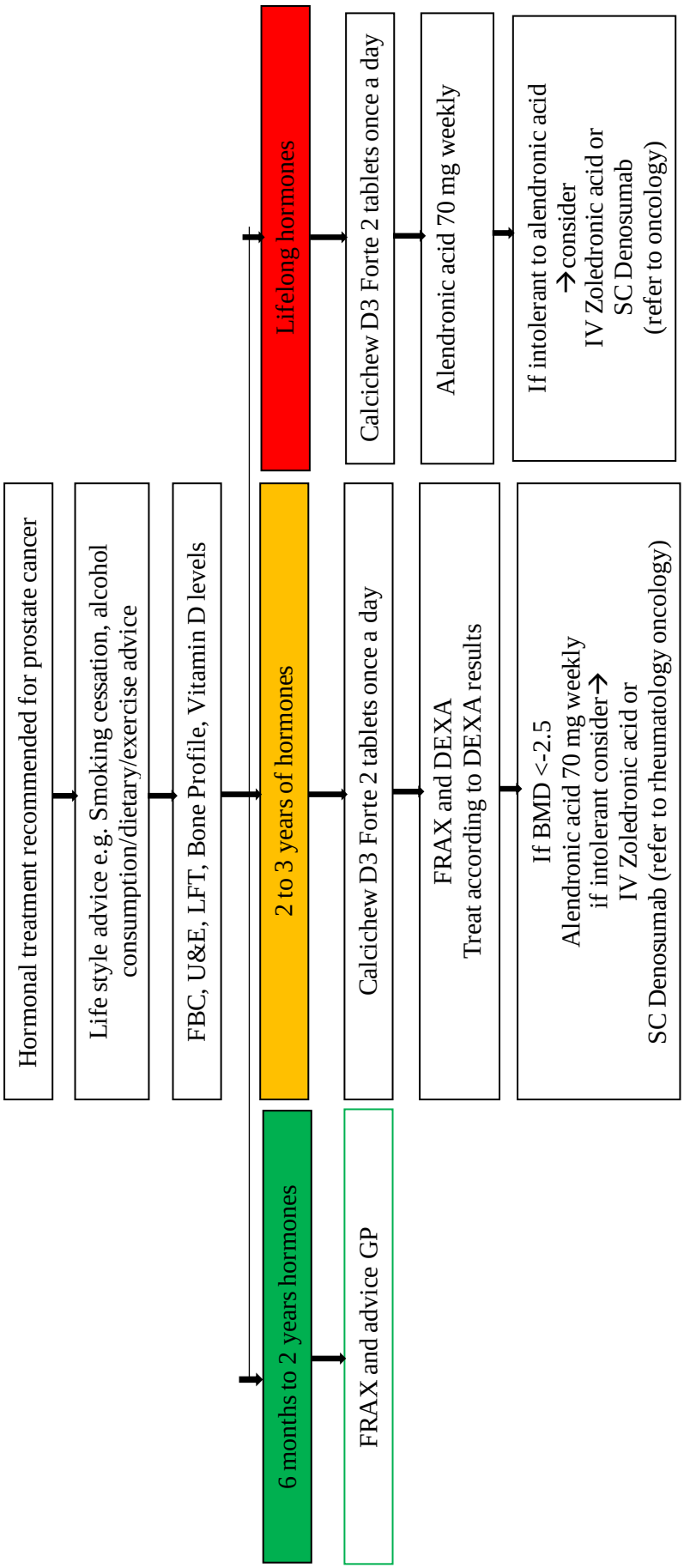
- 'Xgeva' - 120mg 4 weekly for patients with bone metastases for #prevention

NG131 evidence review (15):

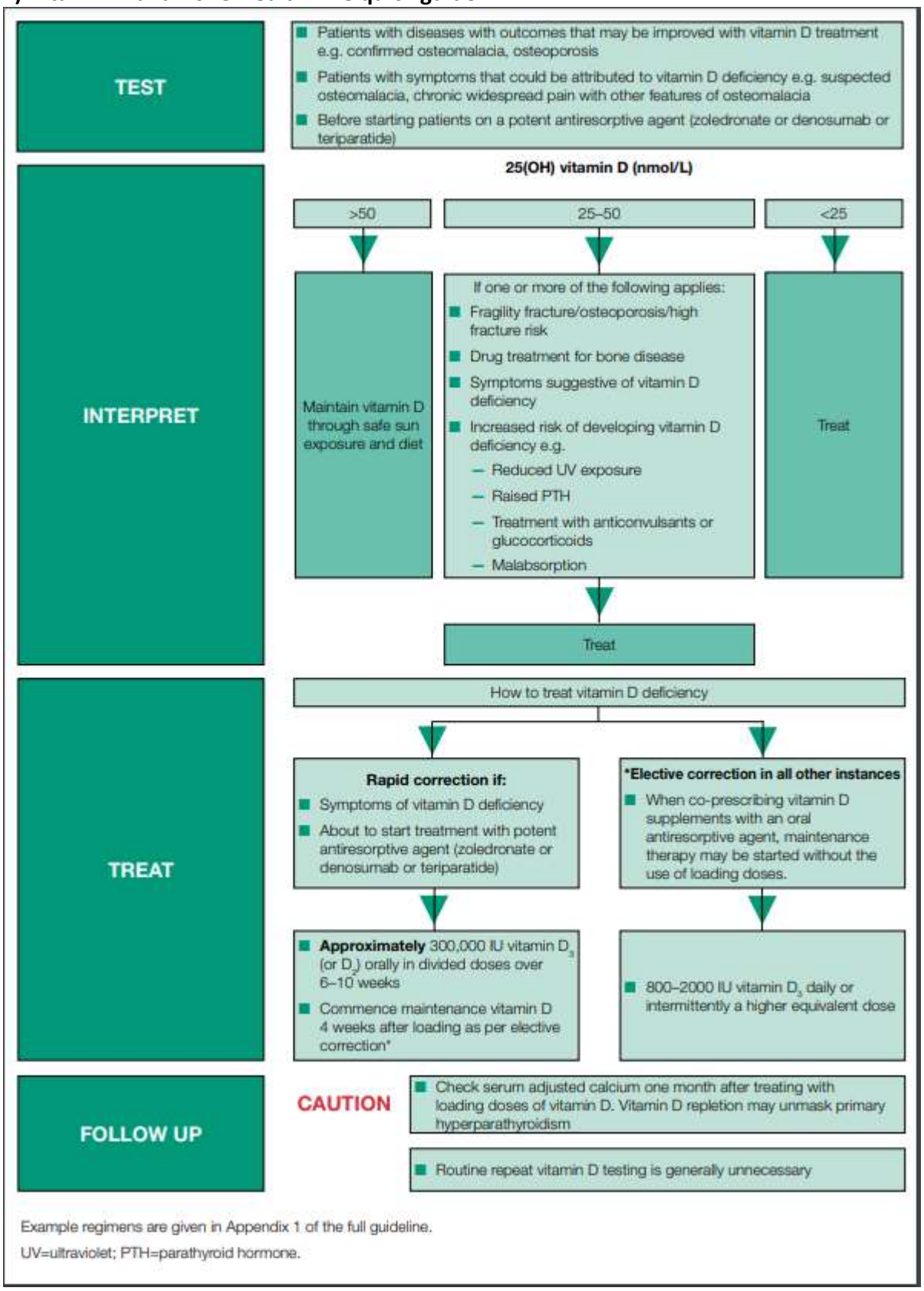
- 1.4.15 Consider Denosumab for people who are having androgen deprivation therapy and have osteoporosis if bisphosphonates are contraindicated or not tolerated.

Randomised control trial (25):
1904 CRPC patients randomised - median time to first skeletal-related event was 20.7 months with 120mg SC Denosumab compared with 17.1 months with 4mg 4 weekly IV ZA. However, twice as much hypocalcaemia with Denosumab.

D) Figure 2. Bone Health Management in Men with Prostate Cancer – Simplified



E) Vitamin D and Bone Health: The quick guide



https://d3pw27xtndcm0o.cloudfront.net/Uploads/r/e/i/algorithmforthemanagementofvitamindandbonehealthinadults_75237.pdf

F) Template bone health management letters to GP

Letter 1 - Sample template letter to GP – non metastatic patients (Amber group)
(Note- in this example, FRAX assessment and DEXA request were initiated at the urology clinic. They may also be initiated directly by GP at the urologist/oncologist's request.)

Dear Dr [GP's name],

Recommendation of Bone Health management in men with localised Prostate Cancer on ADT

[Patient name; NHS number] has a diagnosis of localised prostate cancer and requires X years of androgen deprivation therapy (ADT) alongside radiotherapy. A bone health assessment has been performed to manage cumulative high risk of secondary osteoporosis and fragility fracture, along with provision of lifestyle advice.

Baseline bloods and a DEXA scan has been requested to provide a baseline measurement of bone density. Mr [Patient name] will hear from the radiology department directly about this appointment in the near future. Please manage as per DEXA report e.g. starting treatment if confirmed osteoporosis or repeat scan in the recommended intervals. Please refer to local Rheumatology team if there are any concerns regarding tolerability the oral bisphosphonate as alternative treatment with IV zolendronic acid or denosumab could be considered.

A dental check has been advised if there is a history of poor dentition prior to starting bisphosphate therapy. Please consult the Pharmacy or Rheumatology Team for any drug-related queries. In the event of intolerance to ALL types of oral treatment, please contact us to consider alternative route of administration.

Many thanks,

Letter 2 – Sample template letter to GP – metastatic patients (Red group)

Dear Dr [GP's name],

Recommendation of Bone Protection Agents in Metastatic Prostate Cancer

[Patient name; NHS number] has a diagnosis of metastatic prostate cancer and requires lifelong androgen deprivation therapy (ADT). He will receive [additional system anticancer therapy] alongside ADT. A bone health assessment has been performed to manage cumulative high risk of secondary osteoporosis and fragility fracture, along with provision of lifestyle advice. We recommend the following as per the National Osteoporosis Society's guideline:

1. Baseline vitamin D level check.

2. If vitamin D level is less than 50 nmol/L BUT patient is asymptomatic, please prescribe bone protection agents including:
   a) **Weekly bisphosphonate** (e.g. alendronic acid 70mg weekly); AND
   b) **Calcium and vitamin D3** supplement (e.g. Calcichew D3 Forte 2 tabs OD or Adcal-D3 chewable tablet 1 BD).

   We would be grateful if you could add these to his repeat prescriptions.

3. If vitamin D level is **less than 50 nmol/L AND** patient is **symptomatic**, please prescribe a loading course of colecalciferol (e.g. colecalciferol 25,000 units twice a week for 6 weeks) before commencing bone protection agents as above.

A dental check has been advised if there is a history of poor dentition prior to starting bisphosphate therapy. He has also been counselled with side effects of bisphosphonate therapy, especially with oesophagitis and osteonecrosis of the jaw.

Please consult the Pharmacy or Rheumatology Team for any drug-related queries. In the event of intolerance to ALL types of oral treatment, please contact us to consider alternative route of administration.

Many thanks,

[NMP's name]
[NMP's job position]