

Biomarkers als substituut voor botbiopsie



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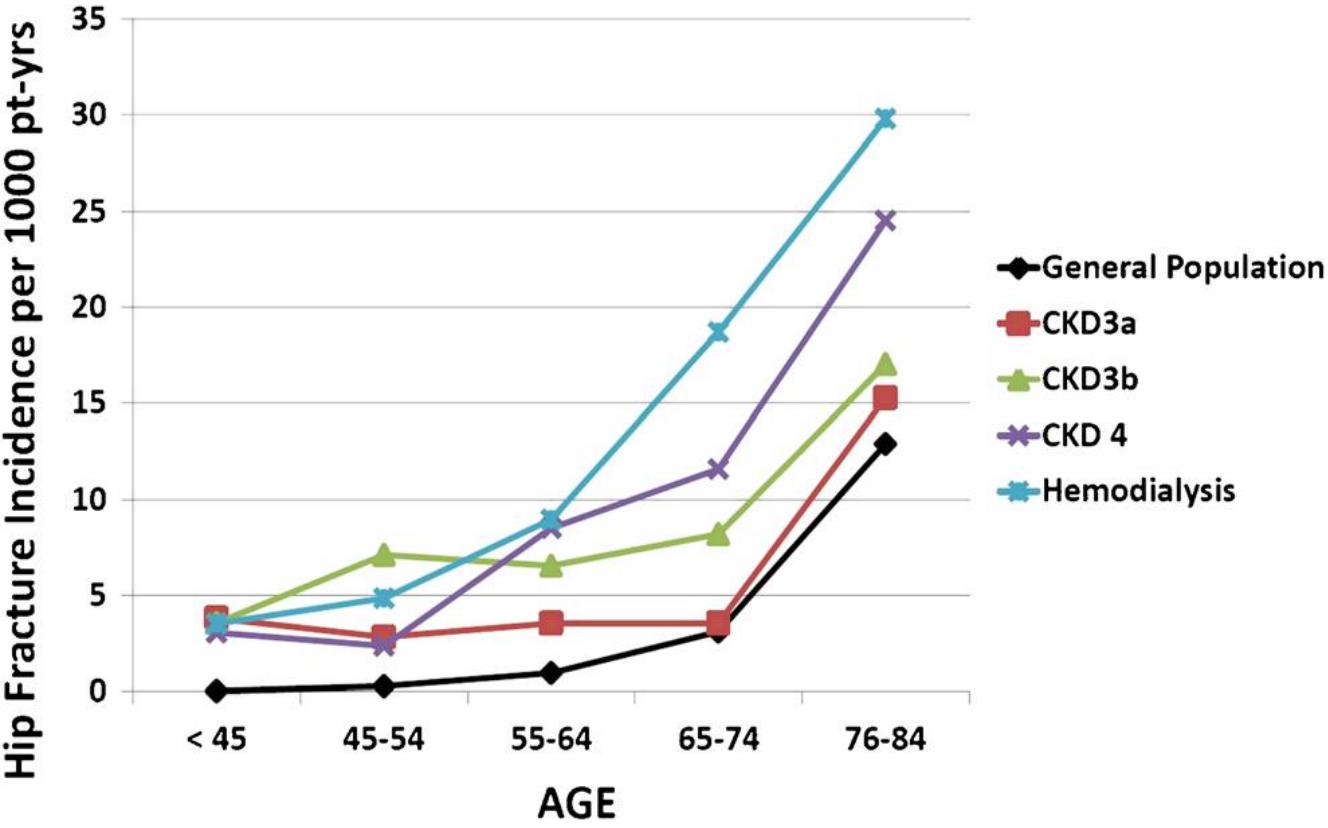
Papendal Dec 2021

Disclosures

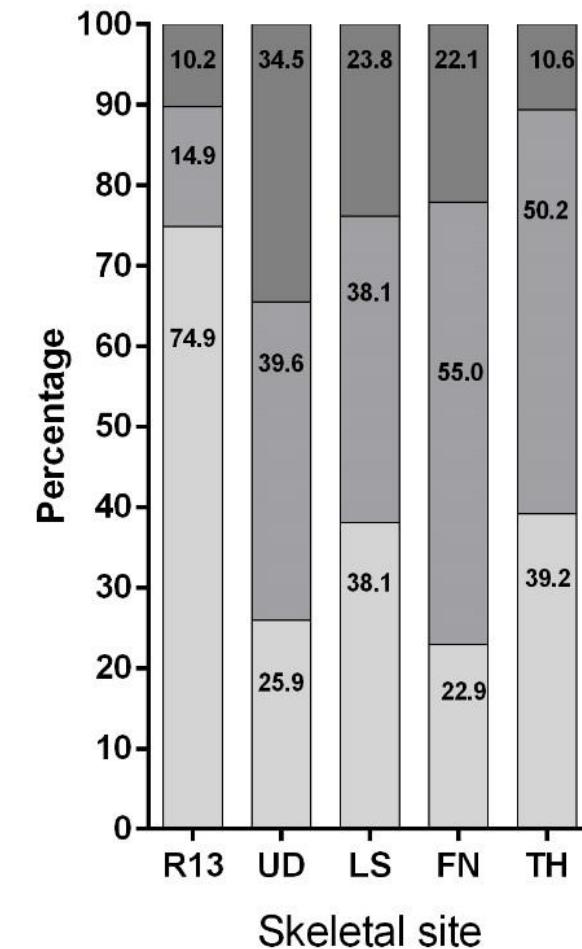
- I declare that I served as a consultant for or received honoraria and research support from:
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osteoporosis in CKD: epidemiology

Fractures



T-score < -2,5



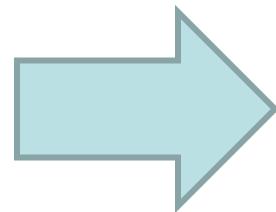
ESRD, n=518, 55 years,
renal transplant candidates



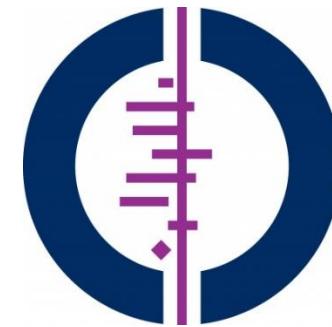
- osteoporosis
- osteopenia
- normal

Case study

- ♀, 55 years
- Familial: maternal hip frac (60 yrs).
- Medical history:
 - Age 53: Acute myocardial infarction; PTA + stenting
 - No history of fracture
- Therapy: clodiprogel
- W: 70 kg; L: 168 cm
- DXA: T hip -3,4



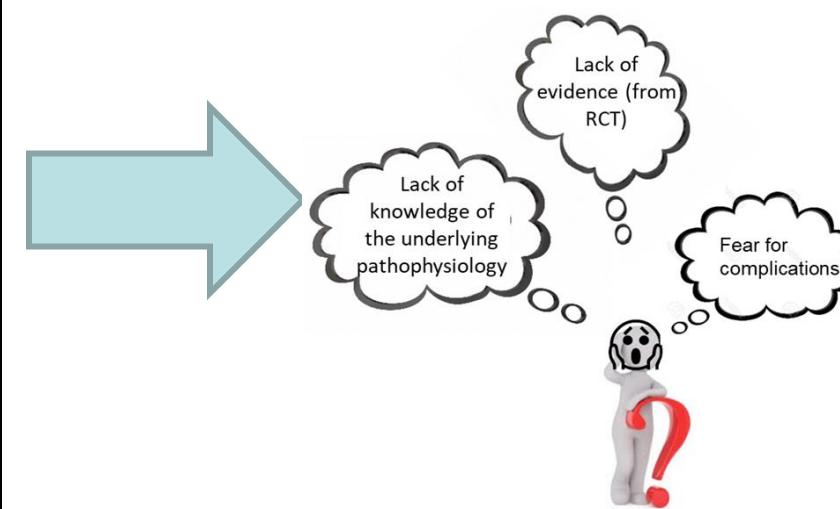
Evidence Based Medicine



“Act”

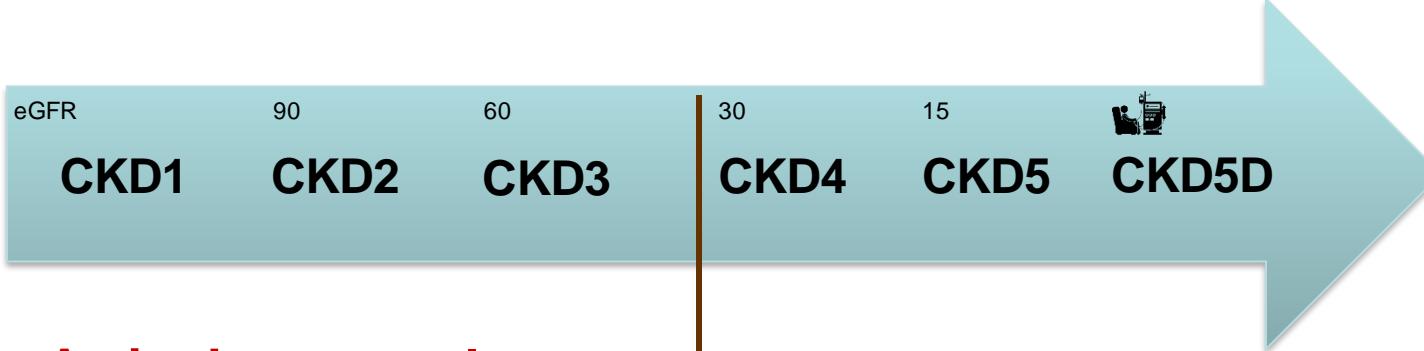
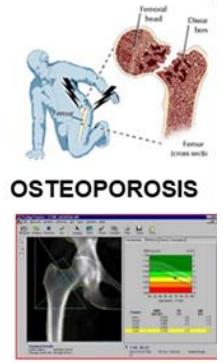
Case study

- ♀, 55 years
- Familial: maternal hip frac (60 yrs).
- Medical history:
 - Age 53: Acute myocardial infarction; PTA + stenting
 - **CKD G4 (ischemic nephropathy)**
 - No history of fracture
- Therapy: clodiprogel
- W: 70 kg; L: 168 cm
- DXA: T hip -3,4



“Wait and See”

Approach to patient with CKD AND Osteoporosis



As in the general population



Nihilism



European consensus statement



EUROPEAN CONSENSUS STATEMENT ON THE DIAGNOSIS AND MANAGEMENT OF OSTEOPOROSIS IN PATIENTS WITH CHRONIC KIDNEY DISEASE G4-G5D



Nephrologists



Pieter Evenepoel
Mathias Haarhaus
Jorge Cannata-Andia
MH Lafage-Proust
John Cunningham
Pablo Urena Torres

Diagnosis & Management of osteoporosis in CKD G4-5D



Expert consensus meeting



Consensus statement



Survey

Bone heads



Serge Ferrari
Dani Pietro-Alhambra
Kassim Javaid

Nephrol Dial Transplant (2020) 1–18
doi:10.1093/ndt/gta192



European Consensus Statement on the diagnosis and management of osteoporosis in chronic kidney disease stages G4–G5D

Pieter Evenepoel¹, John Cunningham², Serge Ferrari³, Mathias Haarhaus^{4,5}, Muhammad Kassim Javaid⁶, Marie-Hélène Lafage-Proust⁷, Daniel Prieto-Alhambra⁸, Pablo Ureña Torres^{9,10} and Jorge Cannata-Andia¹¹, on behalf of the European Renal Osteodystrophy (EUROD) workgroup, an initiative of the CKD-MBD working group of the ERA-EDTA, and the committee of Scientific Advisors and National Societies of the IOF¹

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Osteoporosis International
<https://doi.org/10.1007/s00198-021-05975-7>

REVIEW

SPECIAL REPORT



Diagnosis and management of osteoporosis in chronic kidney disease stages 4 to 5D: a call for a shift from nihilism to pragmatism

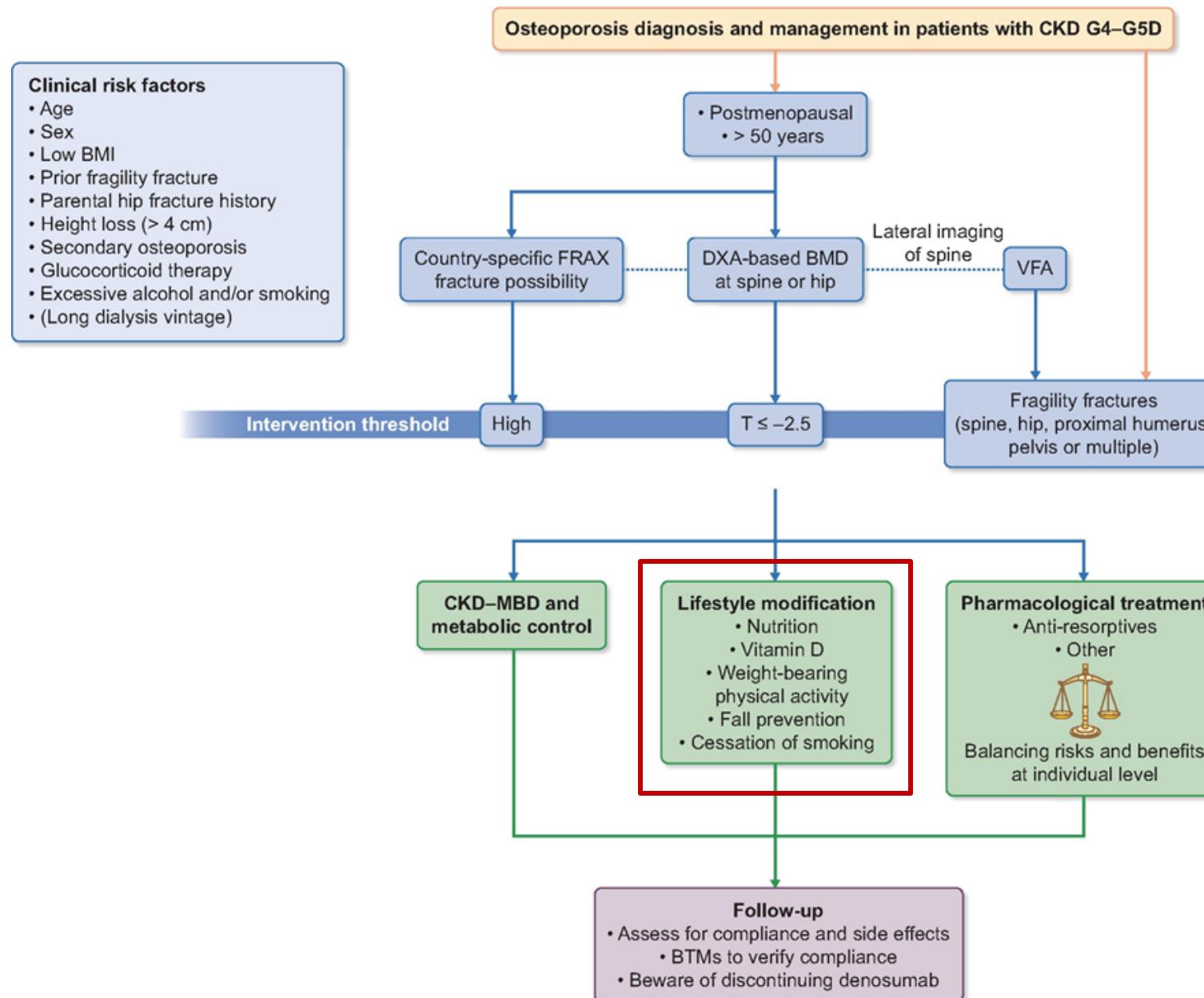
P. Evenepoel¹ · J. Cunningham² · S. Ferrari³ · M. Haarhaus⁴ · M.K. Javaid⁵ · M.-H. Lafage-Proust⁶ · D. Prieto-Alhambra⁷ · P.U. Torres^{8,9} · J. Cannata-Andia¹⁰ · on behalf of the European Renal Osteodystrophy (EUROD) workgroup - an initiative of the CKD-MBD working group of the ERA-EDTA - and the committee of Scientific Advisors and National Societies of the IOF

Received: 1 March 2021 / Accepted: 21 April 2021
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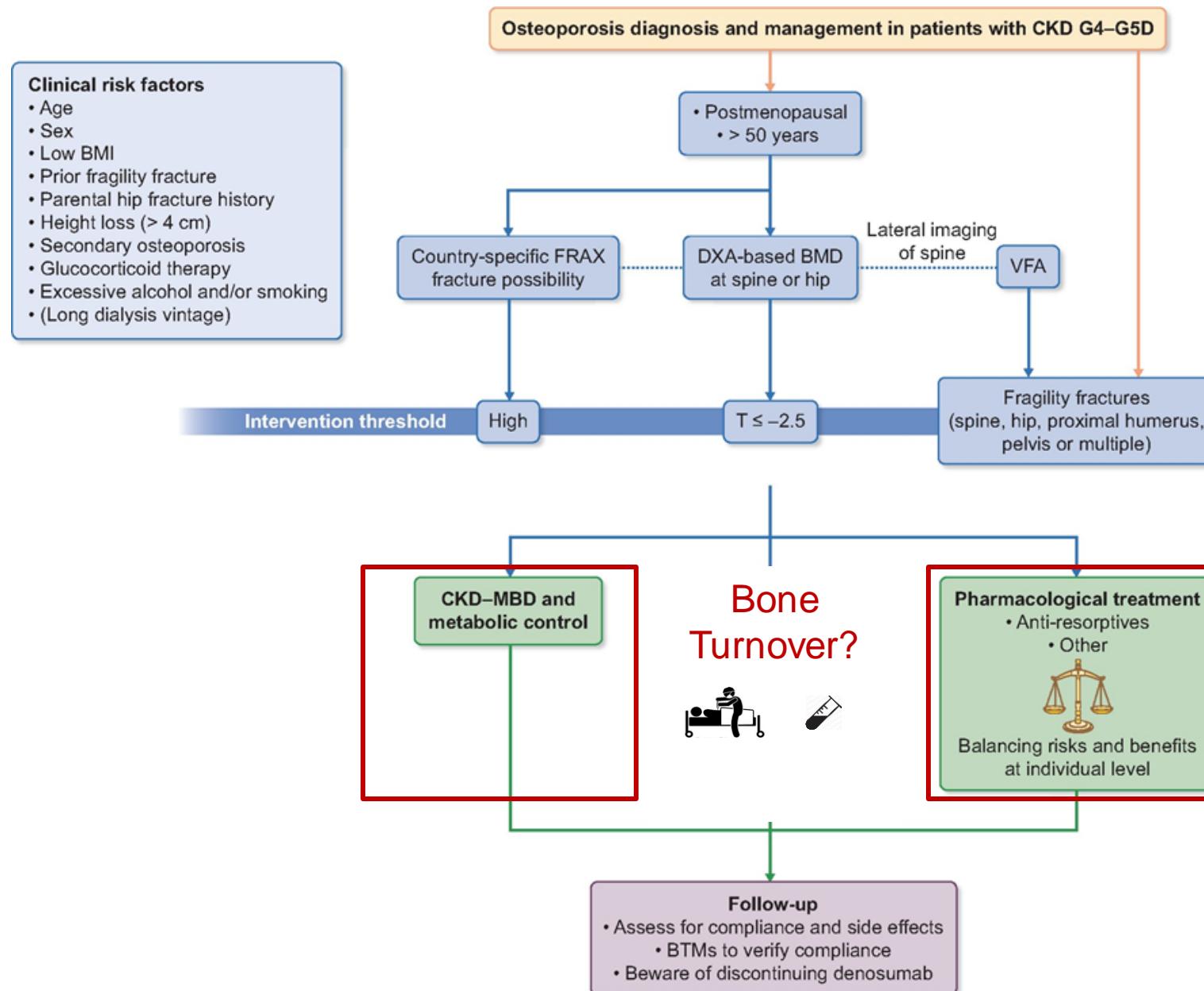
Abstract

The European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) CKD-MBD working group, in collaboration with the Committee of Scientific Advisors of the International Osteoporosis Foundation, published a position paper for the diagnosis and management of osteoporosis in patients with CKD stages 4–5D (eGFR < 30 mL/min 1.73 m²). The present article reports and summarizes the main recommendations included in this 2021 document. The following areas are reviewed: diagnosis of osteoporosis; risk factors for fragility fractures; fracture risk assessment; intervention thresholds for pharmacological intervention; general and pharmacological management of osteoporosis; monitoring of treatment, and systems of care, all in patients with CKD stages 4–5D. Guidance is provided for clinicians caring for CKD stages 4–5D patients with osteoporosis, allowing for a pragmatic individualized diagnostic and therapeutic approach as an alternative to current variations in care and treatment nihilism.

Diagnostic and therapeutic plan



Diagnostic and therapeutic algorithm

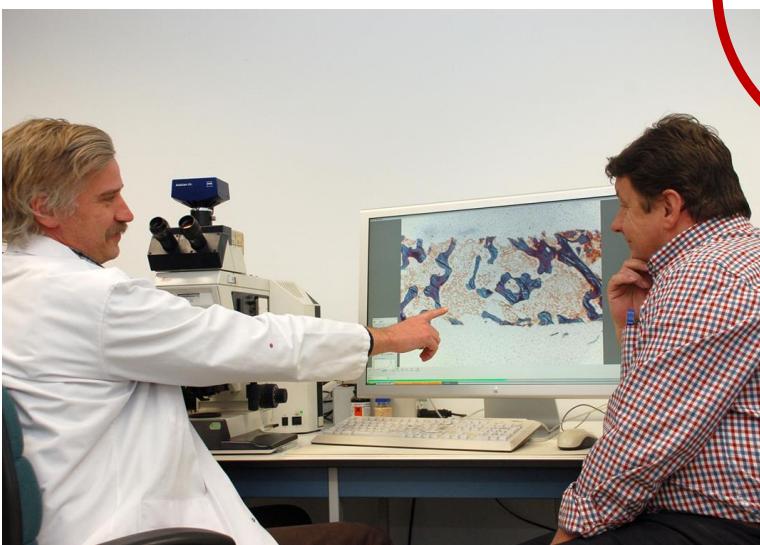
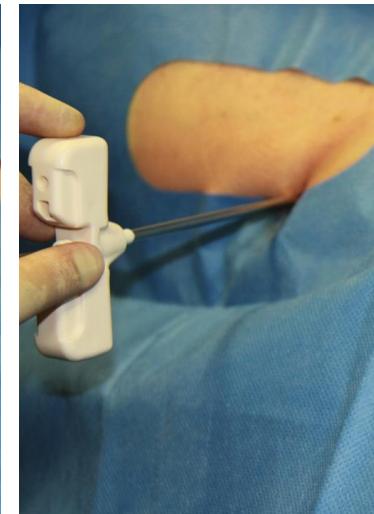


Bone biopsy

General anesthesia/local anesthesia ± light sedation

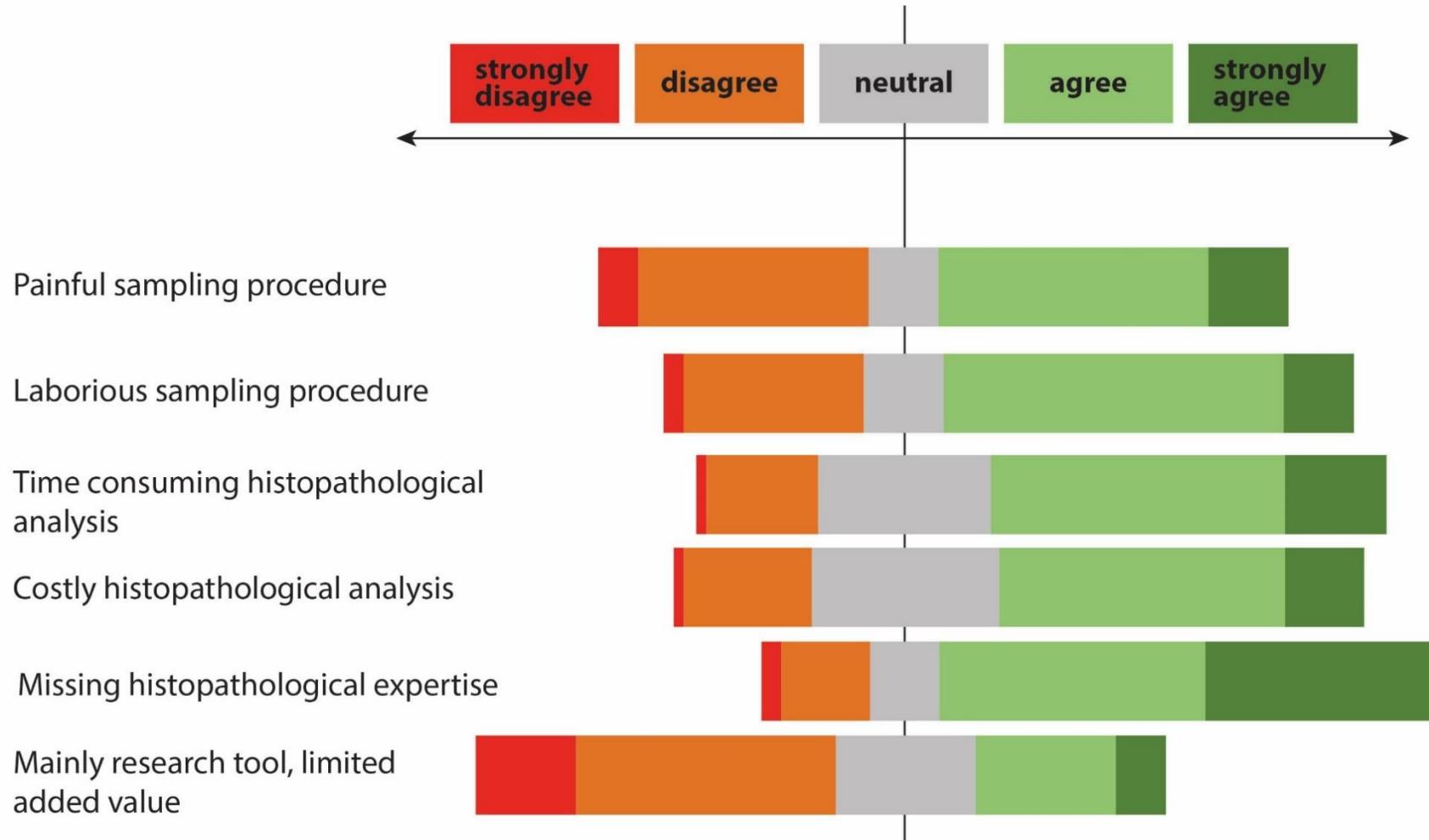


BiopsyBell needle, 3.8 mm inner diameter (7G)
Horizontal (trans)iliac approach



Bone biopsy

Question: Perceived constraints to bone biopsy?



Bone biopsy: SWOT analysis

Strengths

Gold standard to assess
bone health
(TMV- μ architecture)

Weaknesses

Invasive-laborious-costly
Lack of standard- &
harmonization
Link with bone outcomes
missing

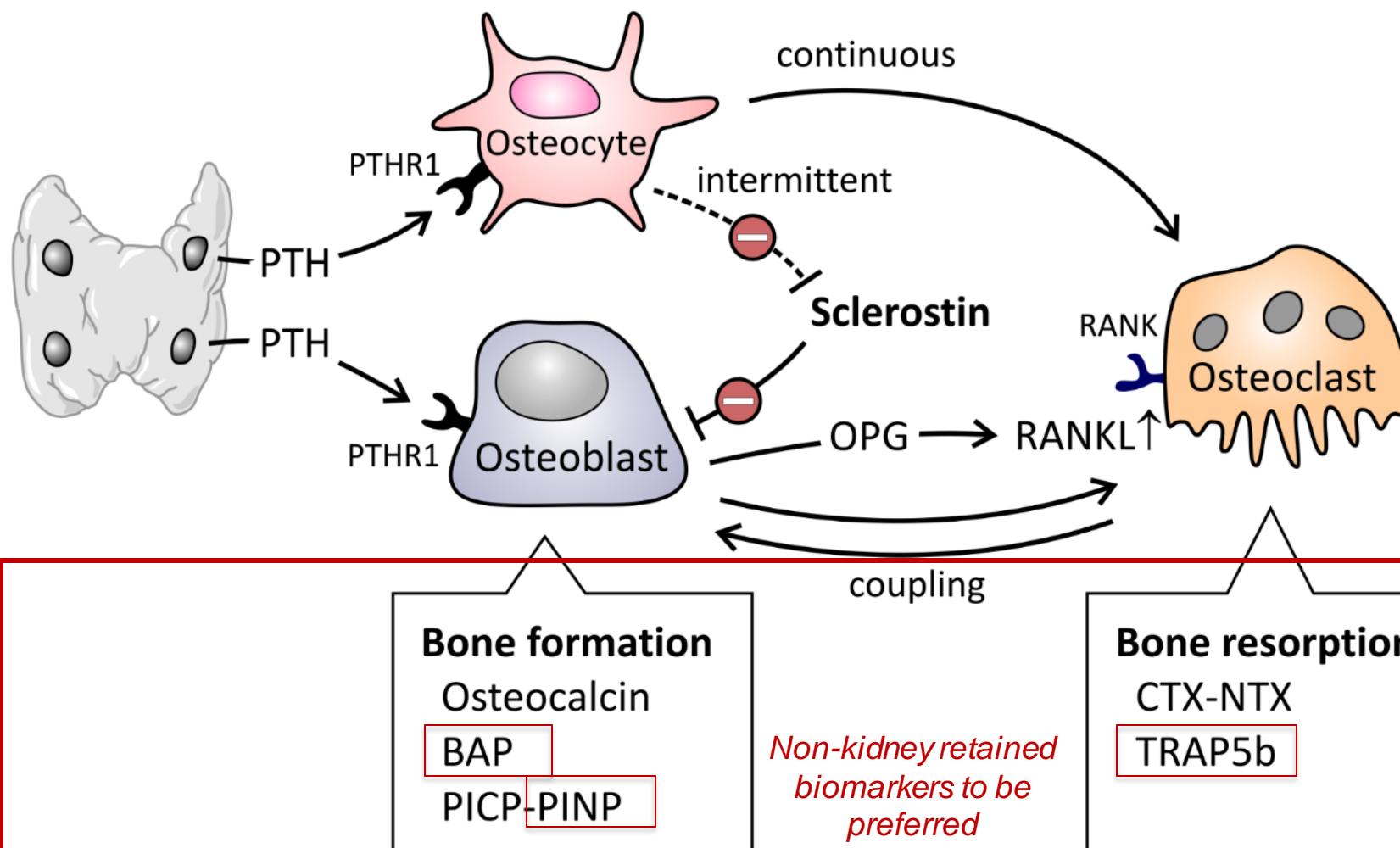
Opportunities

Small needles

Threats

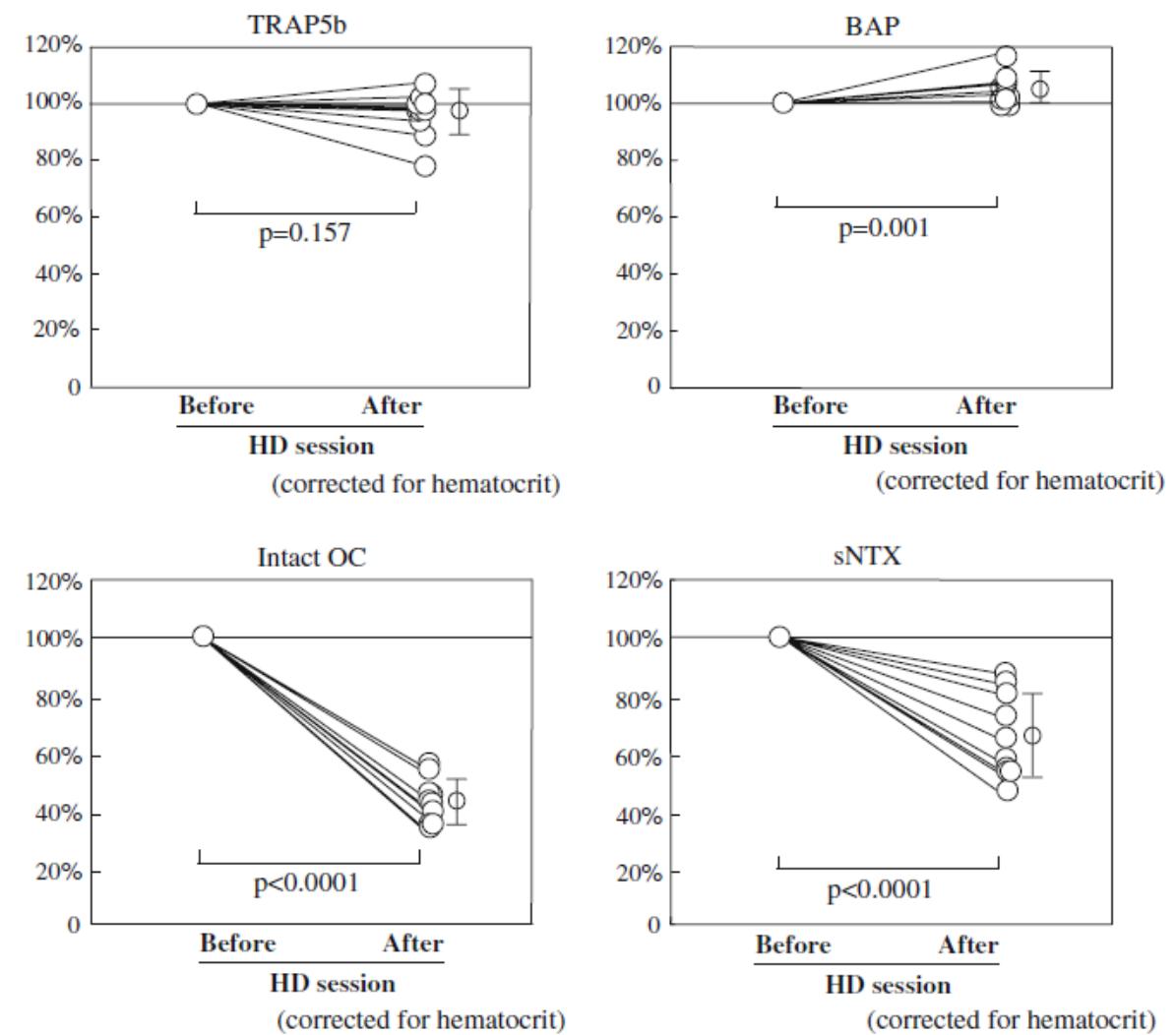
Waning expertise

Bone biomarkers



Bone biomarkers

- Variability is less for bone turnover markers than PTH (LSC 20-30%)
- Effect of dialysis fairly limited
- Recent fracture will increase bone turnover markers for 3 – 6 months
- BsAP – up to 20% cross-reactivity with liver isoforms; tAP adequate surrogate of BsAP (in the absence of liver disease)



Bone turnover markers: diagnostic performance

AJKD

Original Investigation



Diagnostic Accuracy of Bone Turnover Markers and Bone Histology in Patients With CKD Treated by Dialysis

Stuart M. Sprague, DO,¹ Ezequiel Bellorin-Font, MD,² Vanda Jorgetti, MD, PhD,³ Aluizio B. Carvalho, MD, PhD,⁴ Hartmut H. Malluche, MD,⁵ Aníbal Ferreira, MD, PhD,⁶ Patrick C. D'Haese, PhD,⁷ Tilman B. Drièke, MD,⁸ Hongyan Du, MB, MS,¹ Thomas Manley, RN, CRNA,⁹ Eudocia Rojas, MD,² and Sharon M. Moe, MD¹⁰

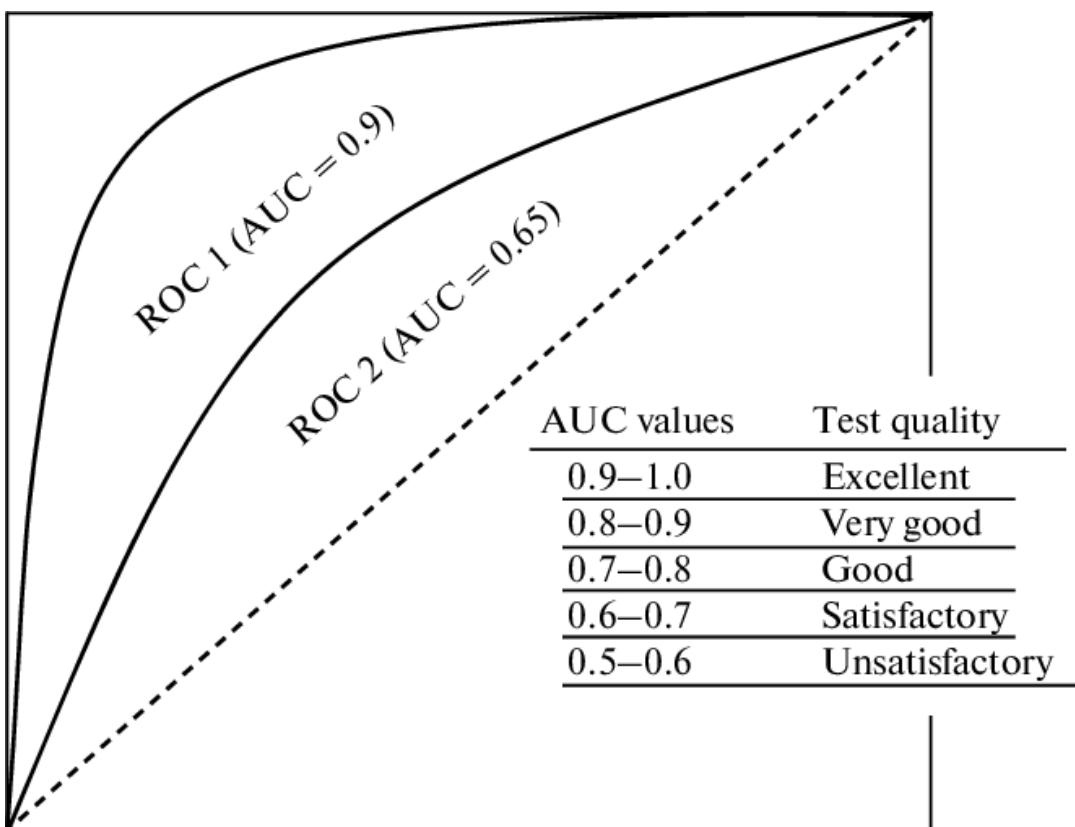


Table 3. AUROCs of Circulating Bone Biomarkers to Distinguish High and Low Bone Turnover From Nonhigh and Nonlow Bone Turnover as Assessed by BFR/BS

Blood Sample Marker	N	AUROC (95% CI)	Best Cutoff
Low vs Nonlow			
iPTH, pg/mL	280 vs 196	0.701 (0.653-0.750)	103.8
wPTH, pg/mL	260 vs 180	0.712 (0.662-0.761)	48.0
bALP, U/L	273 vs 190	0.757 (0.713-0.801)	33.1
P1NP, ng/mL	280 vs 1,197	0.650 (0.599-0.701)	498.9
Combined iPTH + bALP	272 vs 188	0.718 (0.670-0.767)	NA
Combined wPTH + bALP	257 vs 174	0.743 (0.695-0.790)	NA
High vs Nonhigh			
iPTH, pg/mL	81 vs 395	0.724 (0.663-0.786)	323.0
wPTH, pg/mL	75 vs 365	0.678 (0.611-0.746)	61.4
bALP, U/L	77 vs 386	0.711 (0.655-0.767)	42.1
P1NP, ng/mL	81 vs 396	0.743 (0.689-0.797)	621.1
Combined iPTH + bALP	76 vs 384	0.718 (0.658-0.779)	NA
Combined wPTH + bALP	72 vs 359	0.691 (0.628-0.725)	NA

Bone turnover markers: diagnostic performance

CLINICAL RESEARCH

www.jasn.org



Diagnostic Accuracy of Biomarkers and Imaging for Bone Turnover in Renal Osteodystrophy

Syazrah Salam ^{1,2,3}, Orla Gallagher, ³ Fatma Gossiel, ^{2,3} Margaret Paggiosi, ^{2,3} Arif Khwaja, ¹ and Richard Eastell ^{2,3}

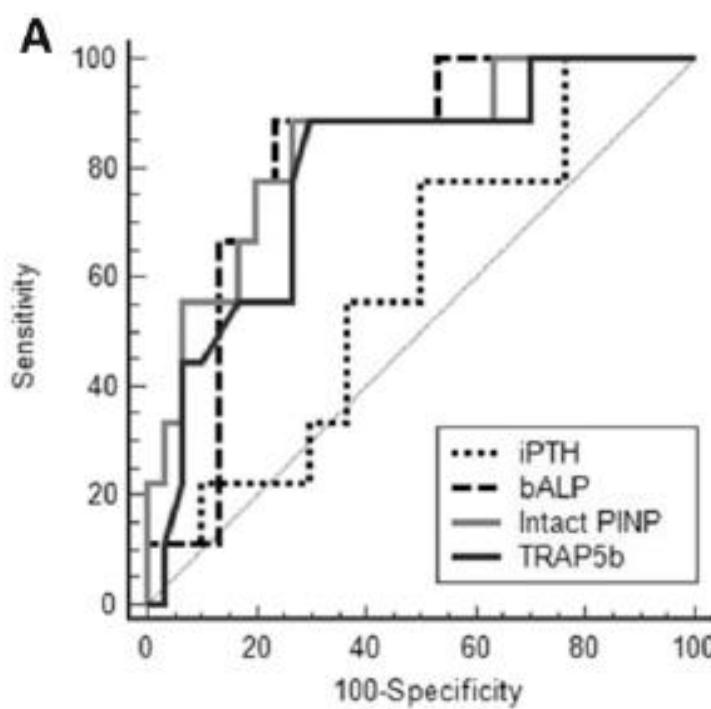


Table 4. Diagnostic accuracy of biomarkers for identifying patients with high bone turnover

Biomarkers	AUC (95% CI)	Criterion	Sensitivity, %	Specificity, %	PPV, %	NPV, %
iPTH	0.760 (0.60 to 0.88)	>327 pg/ml	53	96	90	75
Intact PINP	0.765 (0.61 to 0.88)	>107 ng/ml	53	92	82	74
Total PINP	0.725 (0.56 to 0.85)	>142 ng/ml	75	68	60	81
bALP	0.750 (0.59 to 0.87)	>31 µg/L	56	83	69	74
tALP	0.670 (0.51 to 0.81)	>102 IU/L	65	73	61	76
CTX	0.762 (0.61 to 0.88)	>2.39 ng/ml	53	96	90	75
TRAP5b	0.710 (0.55 to 0.84)	>4.6 U/L	81	58	57	82

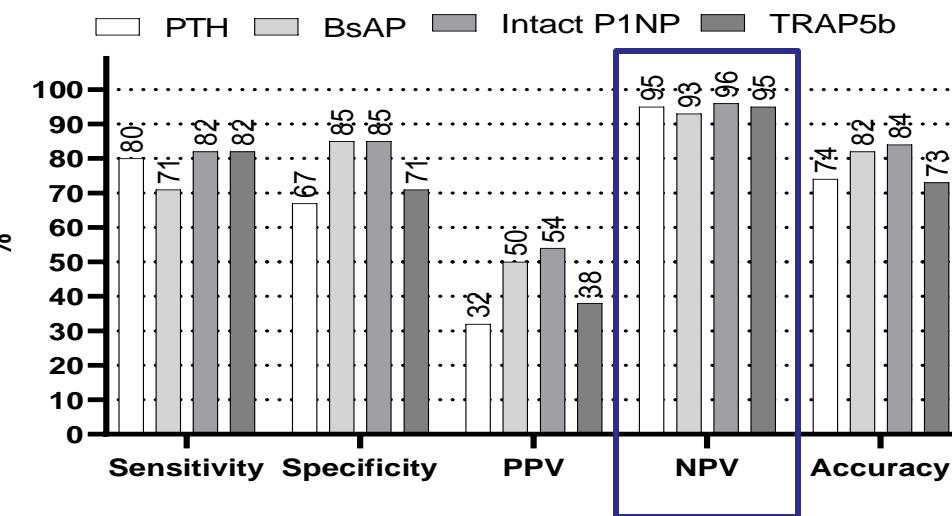
AUC, area under the receiver operating characteristic curve; 95% CI, 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value; iPTH, intact parathyroid hormone; PINP,

Bone turnover markers: diagnostic performance

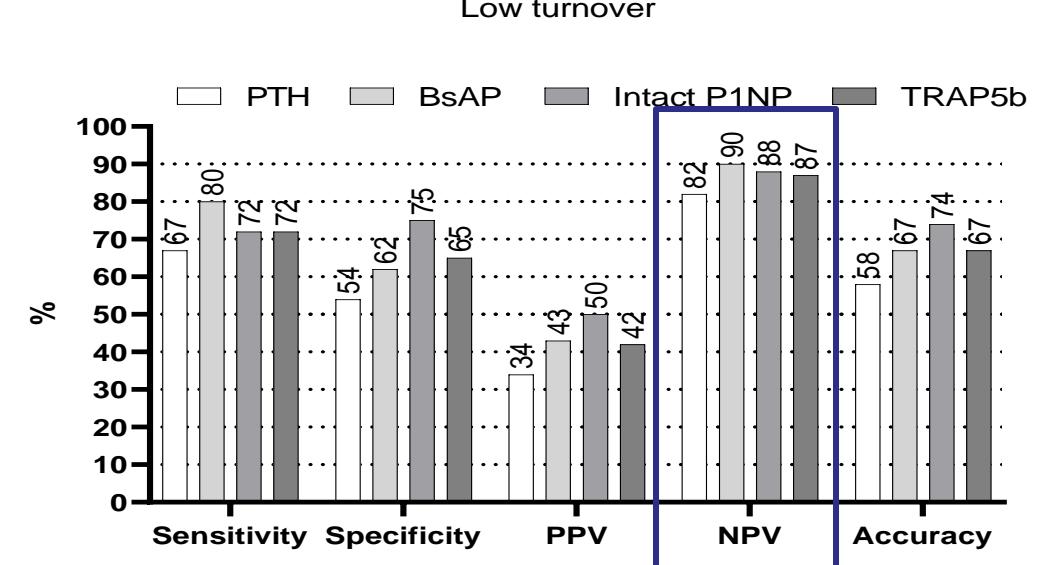


Leuven bone biopsy study (n=199)

High turnover



Low turnover



Bone turnover markers overall show a high negative predictive value, rendering them valuable in excluding either low or high turnover.

Bone turnover markers: diagnostic performance

Consistency:

	<i>High turnover</i>		<i>Low turnover</i>	
	Salam	Jørgensen	Salam	Jørgensen
IDS-iSYS				
BsAP, ug/L	>31	>33.7	<21	<24.2
Intact PINP, ng/mL	>107	>120.7	<57	<49.8
TRAP5b, U/L	>4.6	>5.05	<4.6	<3.44

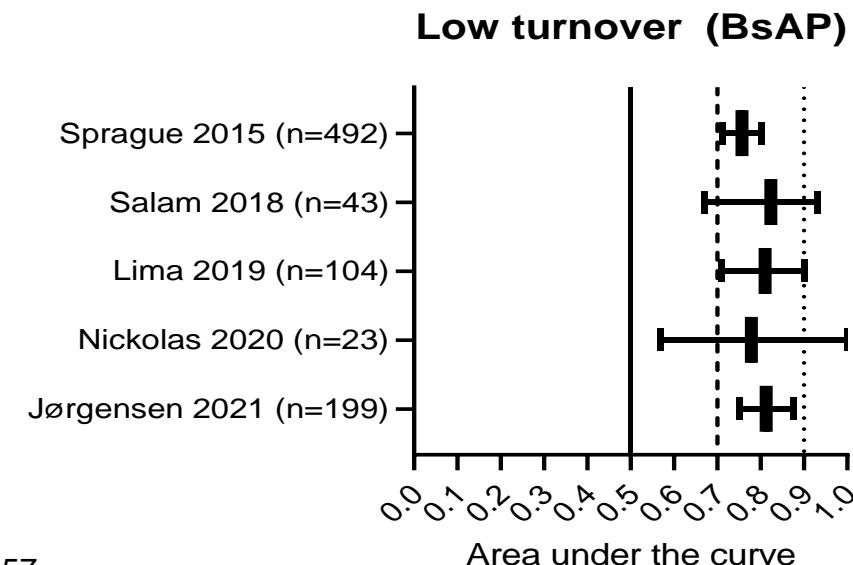
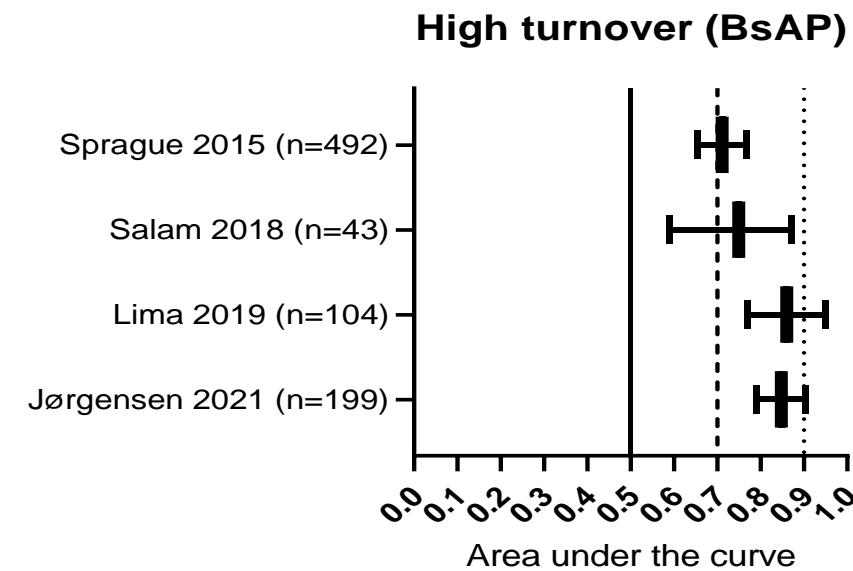
Lima et al ClinNephrol 2019-4-222

Sprague et al. AJKD 2016 67(4):559-566

Nickolas et al. JBMR Plus. 2020 ;4(5):e10353

Jørgensen et al. AJKD 2021 (ePub)

Salam et al. J Am Soc Nephrol 2018-29(5)-1557

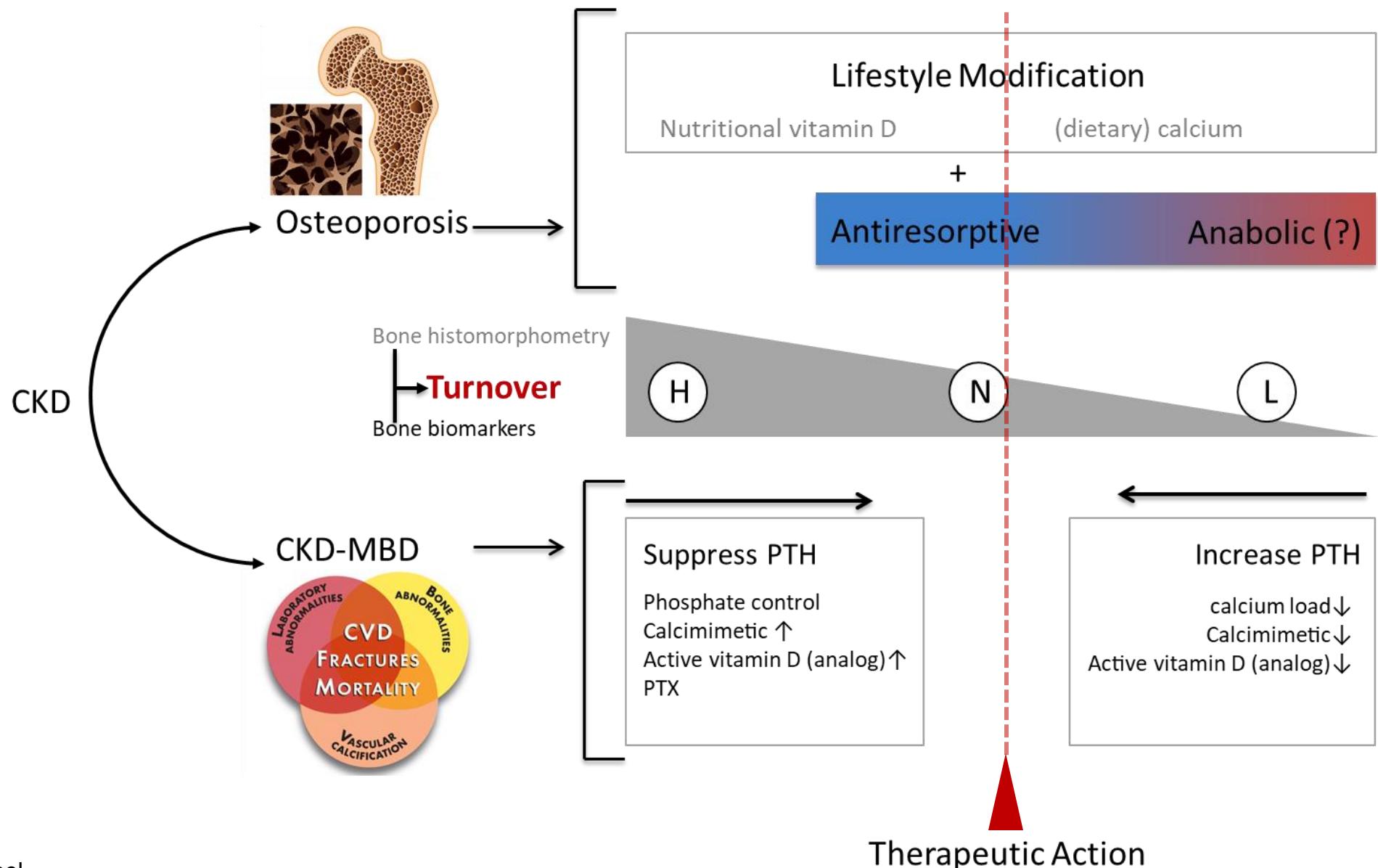


Bone turnover markers: diagnostic performance

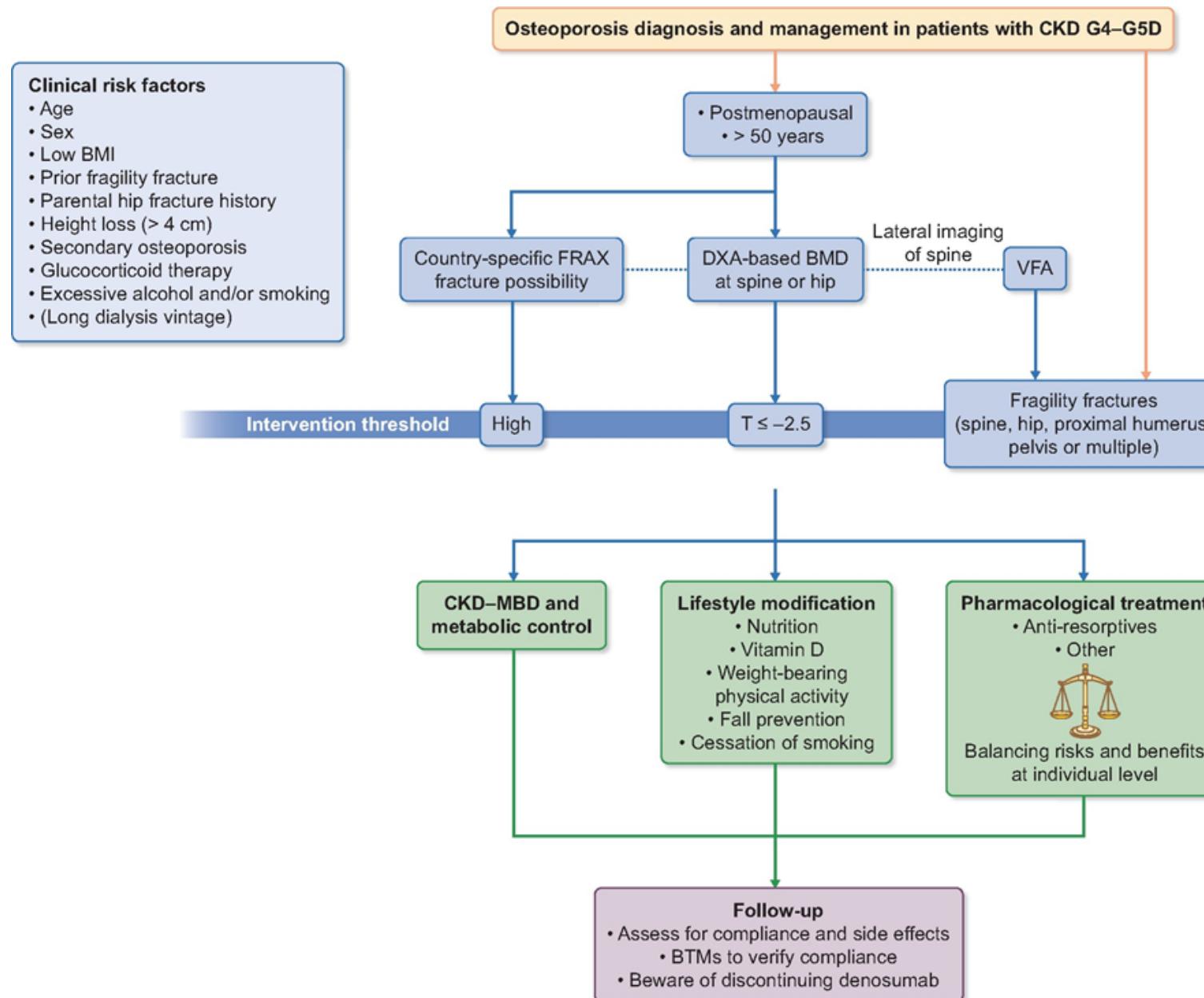
Bone turnover category discrimination:

	<i>High turnover</i>		<i>Low turnover</i>	
	Salam	Jørgensen	Salam	Jørgensen
IDS-iSYS				
BsAP, ug/L	>31	>33.7	<21	<24.2
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TRAP5b, U/L	>4.6	>5.05	<4.6	<3.44

Case study

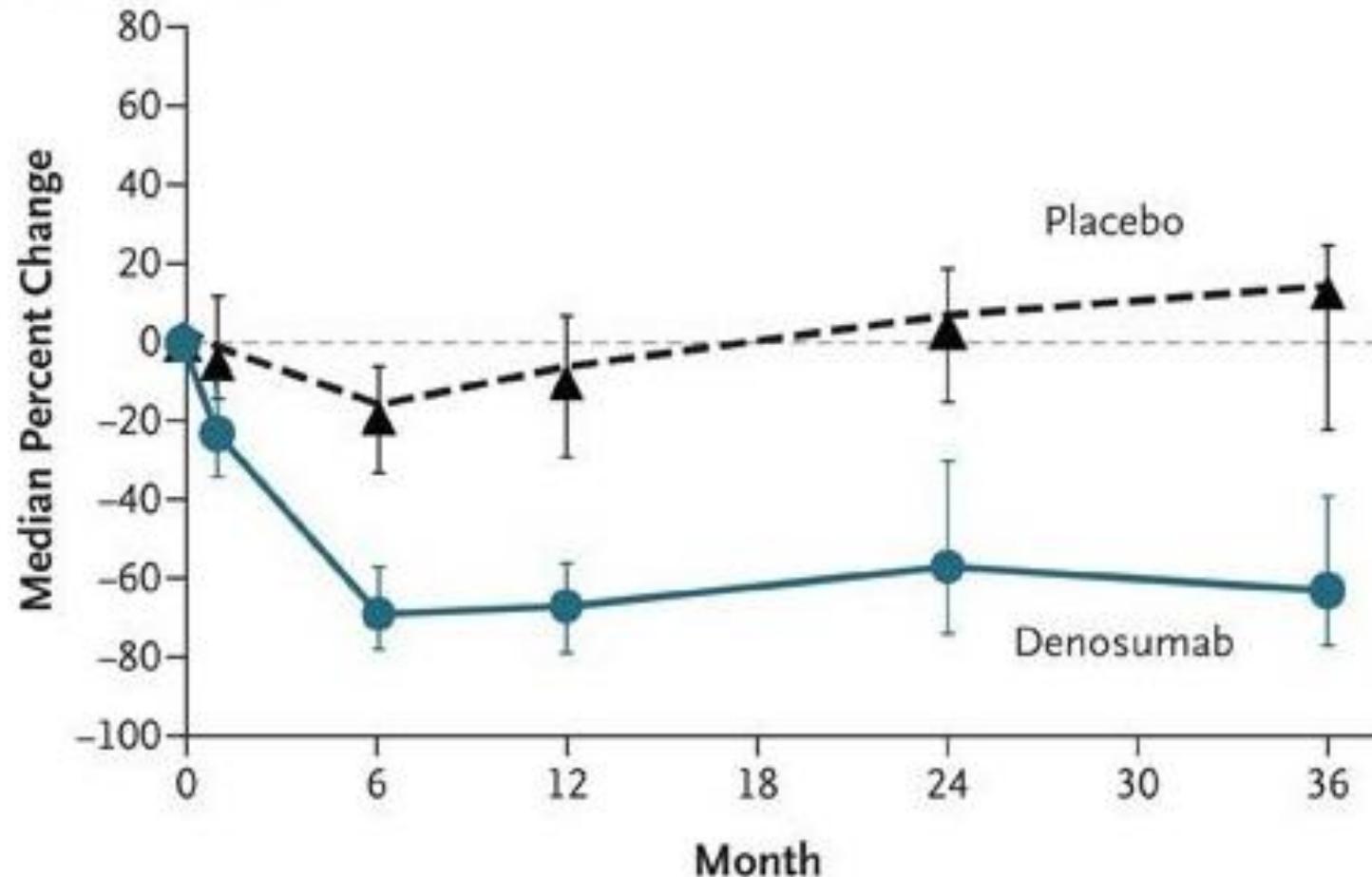


Diagnostic and therapeutic algorithm



BTM to evaluate therapeutic response

D Serum PINP



PINP, Procollagen I N - Terminal Propeptide.
Cummings SR et al. N Engl J Med 2009;361:756–765.

Conclusions

- BTMs may be helpful in stratifying therapy in patients with advanced CKD presenting with osteoporosis
 - Non-kidney cleared BTM to be preferred
 - Trends >> single point values to be preferred
 - inform on whole skeletal remodeling, short time lag
 - NPV >> PPV (excluding rather than confirming abnormal bone turnover)
 - Do not predict mineralization defects
- Diagnostic approach: integrating risk factors – imaging – biomarkers – histomorphometry
- BTMs may be helpful in monitoring therapeutic response.

A glimpse in the future

- Mathematical Modelling/Artificial Intelligence: integrating demographics, biochemistry (including BTMs) to calculate probability of low, normal and high bone turnover
- Increase diagnostic accuracy: expand the panel of bone turnover markers, e.g. to include miRNAs

Fracture probability

Country : UK 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 more units per day No Yes

12. Femoral neck BMD

BMI
The ten year probability of fracture (%)

without BMD

Major osteoporotic	<input type="text"/>
Hip fracture	<input type="text"/>

Bone turnover probability





SAVE THE DATE

JANUARY 20-22, 2022

5th European Renal Osteodystrophy Meeting
– for Clinicians and Researchers

CME – Controversies in renal osteodystrophy:
focus on adynamic bone (disease)

Research Forum – *submit your abstract!*

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European Renal Osteodystrophy (EUROD) Winter meeting - Leuven (Belgium) January 20-22, 2022