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REVIEWER'S REPORT

Manuscript No.: JNHM- 143

Title: Laboratory Follow-up of Postmenopausal Osteoporosis by Recent Molecular Techniques: An Academic Commentary.

Recommendation:

Accept after minor revision

Rating	Excel.	Good	Fair	Poor
Originality			✔	
Techn. Quality			✔	
Clarity		✔		
Significance	✔			

Reviewer's ID: JPR-Bilqees Hamza

Detailed Reviewer's Report

The manuscript titled *"Laboratory Follow-up of Postmenopausal Osteoporosis by Recent Molecular Techniques: An Academic Commentary"* delivers an insightful, multi-dimensional overview of the rapidly evolving diagnostic landscape of postmenopausal osteoporosis (PMO). Postmenopausal osteoporosis stands as a critical global health burden characterized by rapid bone microarchitectural deterioration and micro-fracture risks driven by the postmenopausal decline in protective systemic estrogen. This academic piece contrasts established imaging methods against cutting-edge molecular diagnostics. While dual-energy X-ray absorptiometry (DXA) continues to serve as the undisputed diagnostic gold standard, its structural limitations—such as a long one-to-two-year latency period required to capture bone mineral density (BMD) adjustments—prevent the real-time monitoring of therapeutic efficacy.

The primary scholarly contribution of this work is its comprehensive mapping of advanced multi-omic frameworks to capture early skeletal metabolic shifts. The author successfully details how contemporary molecular layers—including genomics, transcriptomics, proteomics, metabolomics, epigenomics, and liquid biopsy assays—can transform passive clinical tracking into proactive, precision-guided monitoring. By identifying biological changes that occur weeks or months after starting a treatment, this commentary provides a strong theoretical basis for using integrated laboratory metrics to predict fracture risk, monitor patient adherence, and minimize treatment failure early.

Technical Strengths and Scholarly Merit

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The technical strength of this manuscript lies in its organized and logical evaluation of molecular diagnostics, progressing from validated clinical tools to emerging experimental techniques. The author begins by detailing standard bone turnover markers (BTMs), identifying procollagen type I N-terminal propeptide (PINP) as the primary indicator for osteoblastic bone formation and serum C-terminal telopeptide of type I collagen (CTX) as the premier marker for osteoclastic bone resorption. This foundation effectively bridges current clinical standards with upcoming multi-omic developments.

Methodologically, the review explores advanced omic spaces with excellent detail. The genomic section explains how polygenic risk scores (PRS) integrate variations across crucial pathways (such as Wnt signaling genes *LRP5, WNT16, SOST,* and the *RANK/RANKL/OPG* network) to stratify patient risk before bone loss occurs.

Similarly, the sections on epigenomics and transcriptomics highlight the role of circulating microRNAs (e.g., *miR-21, miR-29b, miR-133a*) and peripheral blood mononuclear cells as highly sensitive indicators of cellular aging and neuro-endocrine bone loss. The commentary also highlights proteomic innovations (tracking markers like sclerostin, periostin, and DKK1) and metabolomic signatures processed through machine-learning algorithms, demonstrating a sophisticated approach to data-driven clinical risk profiling.

Recommendations for Comprehensive Revision

Despite its undeniable scholarly value, the manuscript contains several critical citation misalignments and minor textual errors that must be resolved to meet the precise standards of leading peer-reviewed journals in molecular diagnostics and metabolic bone research.

The first recommendation addresses a series of specific citation mismatches where the in-text references do not match the evidence in the bibliography. In the transcriptomic monitoring section, the author references the role of key osteogenic transcription factors like *RUNX2* and *SP7* during anabolic treatments, citing reference five. However, looking at the bibliography reveals that reference five is a paper by Rivadeneira and Mäkitie focused on broad gene pathways and treatments, whereas the specific details on cellular senescence and bone aging are found in reference seven.

More noticeably, in the metabolomics section, the text lists specific metabolic signatures—such as alterations in amino acid, lipid, and energy metabolism—and attributes them to reference six. However, reference six is a paper by Hackl et al. entitled *"Circulating microRNAs as novel biomarkers for bone diseases,"* which covers non-coding RNA pathways rather than small-molecule mass spectrometry or metabolomics. The multi-omics and metabolomics data should instead be mapped to reference nine. The author must carefully cross-check and realign the entire bibliography to maintain the integrity of the citations.

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The second recommendation targets minor technical and grammatical typos within the text. In the section introducing proteomic innovations, a typographical error appears in the opening sentence, which reads: "Proteomics examines the entire mines spectrum of proteins...". The word "mines" is a clear text error and must be corrected to "entire spectrum" or "proteome" to preserve professional tone and readability.

Additionally, the author should ensure consistency in chemical and genetic terminology, keeping gene symbols italicized (e.g., *SOST, LRP5*) while keeping their corresponding serum proteins in standard text to align with international nomenclature guidelines.

The third recommendation suggests expanding the discussion on the barriers to clinical implementation. While the challenges section notes limitations such as assay standardization, biological variability, and cost constraints, it remains brief. The manuscript would be strengthened by providing specific details on how pre-analytical variables (such as circadian rhythms, fasting states, and recent exercise) impact the reliability of CTX and PINP assays. Explaining these practical laboratory challenges would make the commentary much more useful for clinicians looking to adopt these molecular techniques.

Final Review Conclusion

"Laboratory Follow-up of Postmenopausal Osteoporosis by Recent Molecular Techniques: An Academic Commentary" is a well-crafted, forward-looking article that captures the major shift occurring in endocrine and bone metabolism testing. It successfully shows how combining advanced omics data with traditional DXA imaging can overcome the limitations of current monitoring methods, paving the way for personalized medicine.

The technical citation mismatches and minor typographical errors noted do not detract from the overall quality of the author's work. Correcting these references, fixing the prose errors, and slightly expanding the clinical challenges section will elevate this manuscript to its full potential. Therefore, this article is recommended for publication subject to Minor Revision.