Editorial

Journal of *the Best Available Evidence in* Medicine

https://doi.org/10.63720/v1i2006

Next Generation Hierarchy for Next Generation Medicine

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Invited: 21/10/2025

OPEN ACCESS

Published online: 11/11/2025

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In the evolving landscape of evidence-based medicine (EBM), traditional hierarchies of evidence—anchored by randomized controlled trials (RCTs) and systematic reviews—are increasingly being challenged by the emergence of new evidence modalities. The article "Redefining the Hierarchy of Evidence in Medicine in the Era of the Next Generation Clinical Trials and Real-World Evidence" by El Oakley et al. offers a compelling re-examination of how clinical evidence should be ranked in the era of precision medicine, OMICS-guided trials, and real-world data analytics.[1]

The authors highlight a critical limitation of conventional hierarchies such as the Oxford Centre for Evidence-Based Medicine (OCEBM) and GRADE systems: their failure to formally integrate innovative evidence sources including OMICS-guided trials, causally interpretable meta-analyses, and real-world evidence (RWE).[2,3] In doing so, they present a sophisticated framework—the "Next Generation Hierarchy of Evidence"—that proposes a novel top tier (A+) to accommodate rigorously validated OMICS-guided and propensity-matched real-world data recognized by regulatory authorities such as the FDA and EMA.[4,5]

This redefined framework arrives at a pivotal time. Regulatory agencies have increasingly acknowledged the legitimacy of RWE and OMICS-based approaches, particularly in oncology and rare diseases, where traditional RCTs are often infeasible or ethically challenging.[6,7] The FDA's approval of several therapies based on real-world evidence and surrogate endpoints exemplifies this paradigm shift, underscoring the urgency for a hierarchy that reflects these new evidence realities.[8]

The proposed four-tier hierarchy (A+, A, B, C) and its sixteen sublevels mark a significant advancement over the traditional pyramid model.[9] It introduces greater granularity by accounting for study multiplicity, causal inference capability, regulatory recognition, and reproducibility. Particularly notable is the explicit acknowledgment of causal meta-analysis (CMA) as a higher evidential standard than conventional meta-analysis—a recognition that aligns with modern advances in causal inference theory.[10,11]

By integrating emerging modalities, this framework bridges the gap between precision research and guideline development. It complements the GRADE framework rather than replacing it, offering a dynamic model that remains adaptable to evolving technologies and data ecosystems.[12] Importantly, it encourages harmonization between clinical research, regulatory policy, and patient-centered outcomes—a crucial triad for next-generation healthcare.[13]

However, this shift demands caution. While OMICS and RWE expand evidentiary inclusivity, they also raise new methodological concerns regarding bias, data harmonization, and reproducibility.[14,15] The transition to a next-generation hierarchy must therefore be guided by methodological rigor, transparent reporting, and multidisciplinary oversight to preserve the core tenets of EBM: validity, reliability, and applicability.[16]

The proposed Next Generation Hierarchy of Evidence represents an inflection point for modern clinical science. It not only acknowledges the evolving land-

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scape of biomedical data but also reimagines how evidence should be synthesized, graded, and applied in practice. As precision medicine and AI-driven analytics continue to transform research, frameworks like this will be instrumental in ensuring that evidence-based medicine remains both attainable and scientifically relevant.[17,18]

This editorial commends the authors' vision and the pragmatic inclusivity of their proposal. By incorporating OMICS-guided evidence, causal meta-analysis, and RWE within a structured hierarchy, their work provides an essential foundation for the future of evidence-based decision-making. It bridges the widening gap between classical evidence hierarchies and the complexities of modern biomedical research—paving the way toward a more responsive, data-integrated, and patient-centric model of evidence-based medicine.

References

1. El Oakley R, Elmuttardi K, Altawaty A, et al. Redefining the hierarchy of evidence in medicine in the era of the next generation clinical trials and real world evidence: a critical review and the next generation hierarchy. J Best Avail Evid Med. 2025;1(2):25-29
2. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). Journal of Clinical Epidemiology. 2011;64(4):407-415. doi: 10.1016/j.jclinepi.2010.07.017
3. Oxford Centre for Evidence-Based Medicine. Levels of evidence (March 2009). 2011.
4. U.S. Food and Drug Administration. Framework for FDA's real-world evidence program. 2019.
5. European Medicines Agency. Guideline on registry-based studies. 2020. doi: 10.12659/MSM.933554
6. Makady A, de Boer A, Hillege H, Klungel O, Goettsch W. What is real-world data? A review of definitions based on literature and stakeholder interviews. Value in Health. 2017;20(7):858-865. doi: 10.1016/j.jval.2017.03.008
7. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, Califf RM. Real-world evidence - what is it and what can it tell us? New England Journal of Medicine. 2016;375(23):2293-2297. doi: 10.1056/NEJMsb1609216
8. Corrigan-Curay J, Sacks L, Woodcock J. Real-world evidence and real-world data for evaluating drug safety and effectiveness. JAMA. 2018;320(9):867-868. doi: 10.1001/jama.2018.10136
9. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. BMJ Evidence-Based Medicine. 2016;21(4):125-127. doi: 10.1136/ebmed-2016-110401
10. Pearl J, Mackenzie D. The book of why: The new science of cause and effect. 2018. doi:10.56645/jmde.v14i31.507
11. Hernán MA, Robins JM. Causal inference: What if. 2020. doi: 10.1111/biom.13321
12. Schünemann HJ, Brożek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. 2019.
13. Concato J, Corrigan-Curay J, Wang SV. Real-world evidence: Pragmatic trials and regulatory considerations. Clinical Trials. 2021;18(4):473-481. doi: 10.1056/NEJMp2200089
14. Makady A, Goettsch W. Review of regulatory guidance for the use of real-world evidence for pharmaceutical approvals. Pharmacoeconomics. 2018;36(12):1393-1403.
15. Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and impact of real-world clinical data for the practicing clinician. Advances in Therapy. 2018;35(11):1763-1774. doi: 10.1007/s12325-018-0805-y
16. Ioannidis JPA. Why most clinical research is not useful. PLoS Medicine. 2016;13(6):e1002049. doi: 10.1371/journal.pmed.1002049
17. Topol E. Deep medicine: How artificial intelligence can make healthcare human again. 2019.
18. Collins FS, Varmus H. A new initiative on precision medicine. New England Journal of Medicine. 2015;372(9):793-795. doi: 10.1056/NEJMp1500523