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Next Generation Hierarchy for Next Generation Medicine

Mahmoud M. Buazzi

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Faculty of Medicine, Elmergib University, Khoms, Libya

Corresponding Author:

buazzi@gmail.com

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-

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.

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