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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

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Abstract

Innovative evidence modalities—such as OMICS-guided clinical trials, causally interpretable meta-analyses (CMAs), and real-world evidence (RWE)—are increasingly recognized by leading professional organisations and regulatory authorities. A PubMed review revealed gaps in integrating these modalities into the current evidence hierarchies, underscoring the urgent need for a next-generation hierarchy that recognises modern science and regulatory standards.

To address this, a new A+ level of evidence is added to the traditional A, B, C hierarchy. Level A+ includes three or more OMICS-guided clinical trials, RCTs, and RWE, supported by multiple secondary evidence reports such as CMAs and/or Systematic Reviews (SRs). Level A includes fewer of these studies ± CMAs and SRs. Level B includes prospective or retrospective studies not meeting the above criteria. Level C includes case reports, laboratory data, expert opinion, and contested studies. Each level is further subdivided into four tiers based on the number and type of clinical reports and the number of secondary evidence available (see text for details).

Utilisation of this next-generation hierarchy in clinical practice is expected to streamline the integration of novel evidence into decision-making and facilitate a transparent transition from evidence to guideline recommendations.

Keywords: Evidence Hierarchy, Evidence-Based Medicine, OMICS, Real-World Evidence, GRADE Framework, Systematic Review, Causal Meta-Analysis, Precision Medicine, Guideline Development

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Background

Clinical decision-making and policy formulation, encompassing preventive strategies, diagnostic procedures, medical treatments, percutaneous interventions, and surgical procedures, rely primarily on evidence derived from scientific research.[1–3] Today, these scientific reports are subjected to ranking into A, B, and C levels of evidence. The concept first introduced by the Canadian Task Force on the Periodic Health Examination in 1979, further refined by David Sackett, the Oxford Centre for Evidence-Based Medicine (OCEBM), and others.[4–8] The current hierarchy ranks prospective randomized clinical trials (RCTs) and any type of systematic reviews (with or without meta-analysis) at the highest level, followed, sequentially, by non-randomized clinical trials, cohort studies, case series, case reports, experimental laboratory data, and expert opinions.[4–6]

Emerging evidence types, including large-scale studies using genomics, proteomics, metabolomics (OMICS)-guided clinical trials, causally interpretable meta-analyses, and real-world evidence (RWE), are increasingly recognized by leading regulatory agencies including the FDA and EMA.[9,10] These advances expose limitations in the traditional evidence hierarchy, highlighting the need for an updated framework in biomedical research and evidence-based medicine.[11–13]

Methods and results:

We conducted a comprehensive literature search in PubMed, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guide-

lines, to identify studies addressing evidence hierarchies that incorporate OMICS-guided trials, propensity-matched real-world evidence, and causal meta-analyses. From 529 titles identified within the last 10 years, 67 article abstracts were reviewed, 26 full texts read by the first two authors. None of the 26 articles included all the innovative evidence modalities mentioned above into a hierarchy of evidence. Four articles called for a revision of the current hierarchy: two focused primarily on artificial intelligence (AI)-guided analysis of evidence and its role in evidence-based medicine;[14,15] one article incorporated causal meta-analysis alone;[8] and the fourth removed the rigid divisions within the current evidence pyramid and proposed ranking various studies using wavy boundaries.[7] These findings call for a novel hierarchy that should address these limitations.

The Next Generation Hierarchy

The ideal next generation hierarchy of evidence should:

1. Employ clear, intuitive, and accessible classification systems tailored for diverse stakeholders including clinicians, researchers, policymakers, and patients.
2. Distinguish between multiple (three or more) consistent publications from limited (less than three) reports within each evidence category to reflect the weight of corroborated evidence.
3. Recognize OMICS-guided tools and clinical trials that have received validation and approval from regulatory authorities, emphasizing their growing importance.
4. Recognize propensity-matched real-world evidence (pm-RWE) that have received validation and approval from regulatory authorities, to enhance inferential reliability.
5. Recognize causal meta-analyses as a distinct category, acknowledging their superior capacity for causal inference compared to conventional meta-analyses.
6. Align consistently with GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework, thereby facilitating the transition from evidence to clinical practice guideline development.
7. Clearly differentiate randomized controlled trials (RCTs) from non-randomized controlled (non-RCTs) studies, and further categorize prospective and retrospective studies.
8. Recognize systematic reviews (SRs) adhering to established standards (e.g., PRISMA guidelines) as separate and more rigorous entities compared to non-standardized reviews, perspectives and view points.
9. Distinguish OMICS-guided case reports from traditional case reports, given the robust evidence these OMICS - guided reports provide.
10. Recognize OMICS-guided laboratory findings, AI-assisted laboratory data and computational modelling, as well as other expert opinions.
11. Maintain flexibility to accommodate evolving combinations of the above criteria as scientific methods and data sources continue to evolve.
12. Be amenable to automation and integration within electronic health record systems to streamline evidence application in clinical practice.
13. Support dynamic and continuous updating capabilities to incorporate emerging scientific evidence efficiently and in real time.
14. Respect the relative value ascribed to existing evidence types, to cause the least distortion to the understanding of clinical guidelines previously draft ed existing hierarchy of evidence.
15. Differentiate between primary evidence (clinical studies) and secondary evidence (CMAs and SRs).

Therefore, we propose a Next Generation Hierarchy of Evidence that incorporates a new "A+ level" and redefined A, B, and C levels of evidence, as presented in Figure 1.

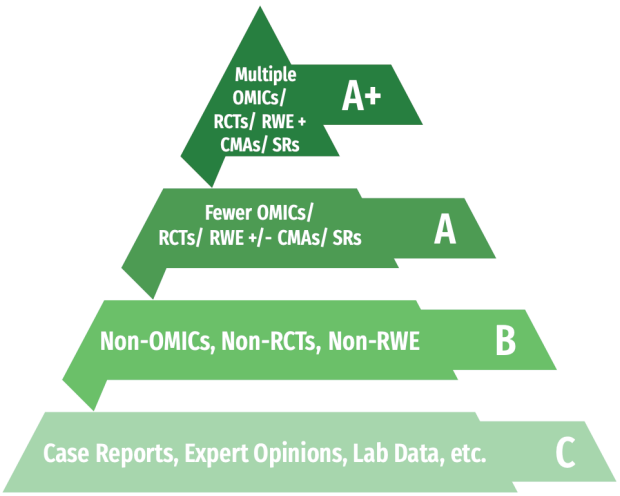

Figure 1: Next Generation Hierarchy of Evidence in Medicine, depicting the four primary levels of evidence:
Level A+ including multiple (3 or more) OMICS-guided clinical trials, multiple RCTs and multiple real-world evidence that are supported by more than one CMAs and three or more systematic reviews.
Level A including one or more OMICS-guided clinical trials, one or more RCTs and one or more real-world evidence that may or may not be supported by secondary evidence, including CMAs and systematic reviews.
Level B includes non-OMICS-guided clinical trials, non-RCT, non-RWE, prospective and retrospective studies.
Level C includes case reports, expert opinions, lab data etc.

(r-OMICS = recognized OMICS-guided clinical trials; RCTs = randomized controlled trials; RWE = real-world evidence; CMA = causal meta-analysis; SRs = systematic reviews; non-RCT = non-randomized controlled trials/studies).

The four primary levels of evidence are further subdivided into four sub-levels each, resulting in a total of 16 distinct sublevels of evidence. To clarify the rank of every piece of evidence, these 16 levels are displayed in Table 1.

Table 1: Next Generation Hierarchy of Evidence in Medicine

1º Levels	2º Levels and Type of Evidence			
A+	A I+	Recognized OMICS clinical trials* a. ≥ 3 publications and b. > 1 causal meta-analyses and/or c. ≥ 3 systematic reviews (with or without meta-analyses)	A II+	Other OMICs and/or RCTs a. ≥ 3 publications and b. > 1 causal meta-analyses and/or c. ≥ 3 systematic reviews (with or without meta-analyses)
	A III+	Recognized PM-RWE** a. ≥ 3 publications and b. > 1 causal meta-analyses and/or c. ≥ 3 systematic reviews (with or without meta-analyses)	A IV+	Other RWE a. ≥ 3 publications and b. > 1 causal meta-analyses and/or c. ≥ 3 systematic review (with or without meta-analyses)
A	A I	Recognized OMICS clinical trials* a. ≥ 1 publications and b. ≤ 1 causal meta-analyses and/or c. < 3 systematic reviews (with or without meta-analyses)	A II	Other OMICs and/or RCTs a. ≥ 1 publications and b. ≤ 1 causal meta-analyses and/or c. < 3 systematic reviews (with or without meta-analyses)
	A III	Recognized PM-RWE** a. ≥ 1 publications and b. ≤ 1 causal meta-analyses and/or c. < 3 systematic reviews (with or without meta-analyses)	A IV	Other RWE a. ≥ 1 publications and/or b. ≤ 1 causal meta-analyses and/or c. < 3 systematic reviews (with or without related meta-analyses)
B	B I	Non-OMICS, Non-RCTs, Non-RWE Prospective Studies a. ≥ 3 publications and b. > 1 causal meta-analyses and/or c. ≥ 3 systematic reviews (with or without meta-analyses)	B II	Non-OMICS, Non-RWE Retrospective Studies a. ≥ 3 publications and b. > 1 causal meta-analyses and/or c. ≥ 3 systematic reviews (with or without meta-analyses)
	B III	Non-OMICS, Non-RCTs, Non-RWE Prospective Studies a. ≥ 1 publications and b. ≤ 1 causal meta-analyses and/or c. < 3 systematic reviews (with or without meta-analyses)	B IV	Non-OMICS, Non-RWE Retrospective Studies a. ≥ 1 publications and b. ≤ 1 causal meta-analyses and/or c. < 3 systematic reviews (with or without meta-analyses)
C	C I	≥ 3 OMICS-guided case reports	C II	≥ 3 Non-OMICS-guided case reports
	C III	a. 1-2 OMICS-guided case reports b. OMICS laboratory reports c. AI- assisted computer modelling d. ≥ 3 survey-based studies. e. non-systematic reviews and Perspectives f. ≥ 3 controversial studies***	C IV	a. 1-2 non-OMICS guided case reports b. non-OMICS laboratory reports c. non-AI-assisted computer modelling d. 1-2 survey-based studies e. Viewpoints, and other expert opinions f. 1-2 controversial studies

(*) OMICS-guided clinical trials that are recognized by regulatory authorities.
(**) Propensity-matched real-world evidence that is recognized by regulatory authorities.
(***) Studies with multiple (three or more) opposing studies and/or statements voiced by professional organizations.

Discussion

The next-generation hierarchy of evidence places OMICS-guided clinical trials, recognized by established regulatory authorities, above traditional non-OMICS randomized controlled trials (RCTs). Despite the substantial difference between the number of patients typically enrolled in RCTs and those included in RWE studies, we propose retaining RCTs above propensity-matched RWE—even when the latter was recognized by regulatory bodies. This approach reflects the understanding that, regardless of large sample sizes and/or the use of propensity score matching in RWE reports, it may not provide the balance of both known and unknown prognostic factors offered by randomization, as highlighted by Agoritsas et al.[16]

The next-generation hierarchy assigns greater weight to types of evidence based on three or more studies versus those based on only one or two. It also designates causal meta-analyses as higher-level secondary evidence than conventional (association-based) meta-analyses, prioritizing demonstrated causality over simple correlation.[17,18] Confidence in the evidence can be adjusted according to the frequency with which results are replicated and by the presence or resurgence of contradictory findings.

This logic is supported by:

1. **FDA Approvals Without RCTs:** The FDA has more recently approved numerous anticancer drugs based on surrogate endpoints like progression-free survival and response rate—often in the absence of RCT data.[19] This approach has become especially prevalent with targeted and precision therapies, where a traditional RCT may be impractical.[19–21] The FDA has also approved drugs based on responses observed in retrospective real-world omics-guided studies. More recent approvals have followed positive response rates from non-RCTs leveraging real-world data (RWD) and OMICS-guided data.[21,22]
2. **Compelling Academic Support for RWE and OMICS-Guided Trials Validity:** Leading researchers showed that RWE and omics-guided trials can offer faster, more personalized, and sometimes more accurate evidence of efficacy.[1,23,24] "Home-run" trials for rare cancers demonstrate that using matched genomics and real-world clinical settings enables rapid evaluation of therapies, increases trial accessibility, and can yield robust evidence for select populations.[1,23,24]
3. **Causal Meta-Analysis and Inference:** There is a growing consensus that causal inference methods and causal meta-analysis provide a rigorous framework for synthesizing evidence across a variety of sources—by focusing on well-defined causal effects in real-world populations. This addresses many limitations of traditional meta-analyses and enables clearer policy and practice recommendations, especially in complex or heterogeneous clinical areas.[17,18] Modern clinical guidelines are increasingly adopting causal language and explicit causal inference frameworks to bridge the gap between study data and actionable, patient-centred recommendations.[18]

Furthermore, the four primary levels of the proposed hierarchy facilitate the progression from evidence to recommendations in alignment with the GRADE framework, that serves as the cornerstone of clinical practice guideline development.[25,26] However, the new hierarchy does not explicitly address certain domains such as risk of bias, directness of evidence, and publication bias, which are best evaluated within the structured GRADE system. While both approaches share similar foundational principles, GRADE involves a thorough assessment of evidence quality by expert panels, over extended time periods, and is specifically designed for guideline development.[25] Moreover, the next generation hierarchy complements GRADE by integrating novel data sources and advanced analytical techniques, making it more adaptable for practical, everyday clinical decision-making.

The subdivision of the four primary levels of evidence into a total of 16 distinct strata greatly enhances the precision and granularity of the clinical research hierarchy. This system recognizes established evidence types, such as RCTs and meta-analyses, while also accounting for critical factors—including the number of supporting studies using innovative evidence modalities, links to secondary evidence such as causal meta-analyses, as well as systematic reviews, reproducibility within three years, AI support, and expert opinion.

It also takes into account if the published data was contradicted by other more recent reports and/or statements issued by professional organizations. By capturing these nuanced distinctions, it moves beyond traditional broad categories to reflect subtle variations in evidence strength. As a result, guideline developers, clinicians, and policymakers can more clearly assimilate the specific studies and data underpinning each recommendation.

Conclusion

This redefined hierarchy keeps pace with the rapidly evolving landscape of biomedical research. By integrating OMICS-guided studies and laboratory reports, RWE, and causally interpretable meta-analyses it represents a transformative shift in how evidence is evaluated and translated into clinical practice guidelines. The next generation hierarchy may enable guideline developers, clinicians, and policymakers to clearly identify the rationale behind recommendations, specifying exactly which study types and datasets underpin each level of practice guideline recommendations.

Declarations of Interest

Reida M. El Oakley and Carlos A. Mestres are Co-Editors-in-Chief of the Journal of the Best Available Evidence in Medicine. Khairya K. Elmuttardi is Managing Editor. Adel Altawaty, Adel El Taguri, Riyad Bendardaf, Salvatore Lentini, Jérôme Cau, Murad Ghrew, Tarek Momenah, Abdelsalam Almatmed, and Mario Petrou serve on the editorial board.

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