



【专家简介】王炳顺,医学博士,上海交通大学医学院教授、博士生导师,现任临床医学研究院副院长、生物统计教研室主任。主要从事临床研究中的医学统计方法与妇幼保健流行病学研究,并积极推动医学科研文化建设与临床研究体系规范化发展。在 *Lancet*, *PNAS*, *Blood*, *eClinicalMedicine*, *J Stat Softw* 等期刊发表论文近百篇。主编《医学统计与临床研究》《SAS统计软件应用》《医学统计学及SAS应用》,副主编《临床试验设计与统计分析》等多部教材。作为项目负责人,主持国家自然科学基金、科技部“十三五”“十四五”国家重点研发计划课题及上海市软科学重点项目;担任全国医疗器械临床评价标准化技术归口单位专家组成员、国家药品监督管理局药品审评和医疗器械审评统计学专家,深度参与新药研发与创新医疗器械的临床评

价方法学体系建设。

从预测到因果:人工智能时代随机化试验的不可替代性

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【摘要】 人工智能(artificial intelligence, AI)正深度介入临床研究全流程,显著提升观察性研究在危险因素识别、风险分层与预后预测中的数据处理与分析效率。然而,预测性能的跃升并不等价于因果识别能力的提升。即便AI辅助的高维协变量处理与目标试验模拟等技术可使观察性研究在结构上逼近随机对照试验(randomized controlled trial, RCT),其因果解释仍然依赖“可忽略性假设”(假定所有关键混杂因素均已被准确测量并纳入分析模型),难以去除已知混杂因素未测量时的残余混杂,更无力应对未知混杂因素的干扰。相比之下, RCT在设计及实施层面通过随机化分配干预这一独特机制,在各对比组间同步平衡已知与未知混杂因素,为干预效应评价提供不可替代的因果识别基础。本文阐明“AI预测发现→因果推断逼近→随机试验确证”的三级递进证据路径,剖析AI融入RCT的方法学增效上限及其协同策略。在数据结构复杂、模型快速迭代、研究愈发高效的AI时代,必须高度警惕将“预测关联”误读并僭越为“因果结论”的方法学陷阱。坚守随机分配的不可预测性与随机化完整性,始终是筑牢RCT作为临床干预评价金标准地位不可替代的方法学基石。

【关键词】 人工智能(AI); 随机对照试验(RCT); 预测模型; 目标试验模拟; 因果推断

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From prediction to causality: why randomized trials still matter in the era of artificial intelligence

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【Abstract】 Artificial intelligence (AI) is becoming deeply embedded throughout clinical research and has substantially improved the efficiency of data processing and analysis in observational studies, including

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identification of risk factors, risk stratification, and outcome prediction. However, advances in predictive performance do not automatically translate into improved causal identification. Even when AI-assisted high-dimensional covariate processing and target trial emulation allow observational studies to approximate the structure of randomized controlled trials (RCTs), causal interpretation remains strongly dependent on the “ignorability assumption”, namely that all key confounders have been accurately measured and included in the model. Such approaches cannot eliminate residual confounding from unmeasured factors and are powerless against unrecognized confounders. By contrast, RCTs use randomized allocation at the design and implementation stages to balance measured and unmeasured confounders across comparison groups, thereby providing an irreplaceable basis for causal identification in intervention evaluation. This article delineates a tripartite, progressive evidence pathway: “AI-driven prediction discovery → approximation of causal inference → confirmation via randomized trials”, and analyzes the methodological boundaries and synergistic strategies associated with integrating AI into RCTs. In an era defined by complex data architectures, rapid model iteration, and the highly efficient, prolific generation of research literature, we must remain vigilant against the critical methodological trap of conflating “predictive association” with “causal effect”. Upholding the unpredictability of random allocation and the integrity of randomization remains the indispensable methodological cornerstone that secures the RCT’s status as the gold standard for evaluating medical interventions.

【Key words】 artificial intelligence (AI); randomized controlled trial (RCT); prediction model; target trial emulation; causal inference

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近年来,人工智能(artificial intelligence, AI)技术正深度介入临床研究的设计、实施与数据分析全链条^[1-6]。自然语言处理与机器学习算法可以助力解析电子病历、影像组学及真实世界数据(real-world data, RWD),实现疾病精准分层、受试者智能筛选、疗效动态预测及不良事件早期预警。这一系列方法学演进不仅重构了观察性研究的数据治理流程,更使其通过高维混杂因素控制、倾向评分(propensity score, PS)匹配与加权、目标试验模拟(target trial emulation, TTE)等策略,在研究框架上向随机对照试验(randomized controlled trial, RCT)的严谨标准持续靠拢^[7-13]。由此产生一个关键问题:当真实世界研究在形式上日益接近RCT时,AI增强的观察性研究能否取代RCT?

临床研究的核心命题,并非单纯探寻数据中的统计关联,而是确证特定干预能否真实改变患者的临床结局。预测关联与因果效应评价属于不同层面,干预效果判断需要依赖明确的因果识别框架^[14-16]。为了厘清不同研究策略与研究类型在临床研究证据链中所处的不同环节及其合理位置,可以参考从“预测”到“因果”的证据递进路径(图1):观察性研究与AI位于前端,负责发现线索、提出假设;目标试验模拟与因果推断策略居于中端,负责增强

因果效应逼近;RCT居于终端,负责完成因果效应的检验^[14-22]。在数据愈加复杂、模型愈加庞大的AI时代,守住RCT这一因果识别法宝,是防止预测性证据被误读为因果性结论的关键所在。AI赋能RCT,而RCT确证AI系统的临床效用,AI与随机化之间应建立深度的双向协同关系。

AI模型无法替代RCT的核心逻辑 AI模型擅长在海量数据集中识别模式和关联,但不能明确区分因果关系与虚假相关。从因果推断的基本原理来看,预测能力并不直接等同于因果识别能力。根据Pearl的因果阶梯理论^[14],AI主要活跃于“关联”层,其预测性能回答的是“谁更可能发生结局”,却不能自动跨越至“干预”层,回答“如果实施某项干预,结局是否会改变”。观察性分析即使纳入大量协变量,仍然依赖Rubin潜在结果框架下的“可忽略性假设”:研究者必须假定影响治疗选择并与结局相关的重要混杂因素均已被准确测量,并已在模型中得到充分调整^[15-16]。但在真实临床场景中,隐匿的疾病进展、医师处方偏好、患者经济能力与价值取向、治疗与随访依从性等关键预后因素,往往难以被完整记录在结构化数据库中,这构成了AI难以仅通过事后建模完全解决已知但未测量的混杂问题,更无法应对目前尚未认识到的潜在未知混杂。

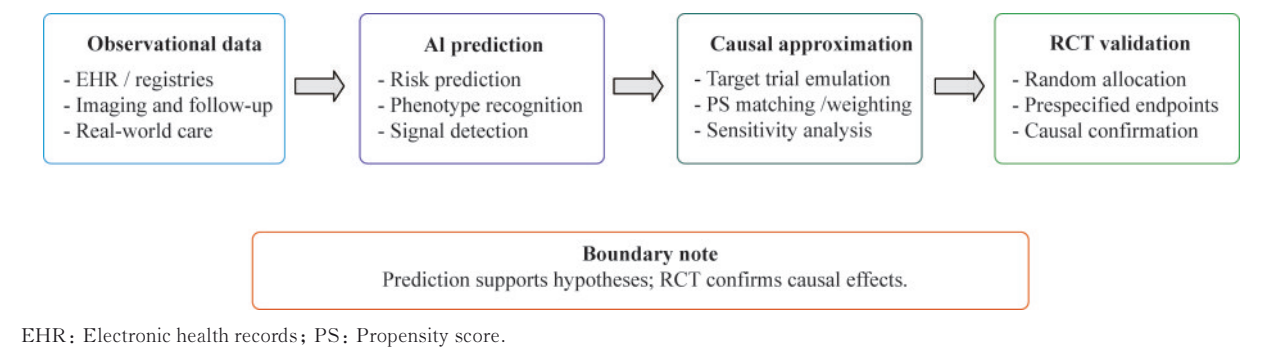


图1 从观察数据中建模预测到因果推断和试验验证的证据进展

Fig 1 Progression of evidence from modeling and prediction in observational data to causal inference and trial validation

AI预测的精确度不等同于因果效应评估的准确度。AI模型的优势在于从既有数据中发现复杂关联,并对个体未来风险、治疗反应倾向或不良事件概率进行预测^[1-6]。例如,一个模型可以预测患者未来发生心血管事件的风险,也可以提示某类患者在既往数据中使用某药后的结局较好;但这并不意味着该药本身导致了所观察到的效应值。选择该药可能受到基线病情、医师经验、患者经济能力、依从性和医疗资源可及性的共同影响。若这些因素同时影响治疗选择与结局观测,单纯大量增加模型参数以提高模型预测精度并不能完成因果识别及客观效应的准确刻画(表1)。

表1 预测性问题和因果性问题的区别

Tab 1 Differences between predictive and causal questions

Dimension	Prediction / association detection	Causal identification / intervention effect evaluation
Core question	Who is more likely to experience an outcome? Which variables are associated with it?	Does an intervention cause a change in the outcome?
Main data sources	Existing clinical data, real-world data, and multimodal medical data	Trial data collected under a prespecified protocol, with possible support from RWE
Main role of AI	Risk prediction, phenotype recognition, outcome alerts, and signal discovery	Assisting design, conduct, measurement, and analysis, while relying on causal design
Key assumptions	Future data are sufficiently similar to the training data/ ignorability assumption	Treatment and control groups are comparable, or explicit identification conditions are satisfied
Meaning of evidence	Generates hypotheses, signals risk, and supports decisions	Supports or refutes causal effect of intervention

RWE: Real world evidence.

AI模型并非天然中立的“算法黑箱”。受训练数据的来源偏倚、临床指标定义的异质性、数据缺失机制的复杂性、多中心间设备与技术壁垒、诊疗规范的时空演变等多重因素制约,算法输入端的不确定性极易转化为输出端的系统性偏差。这种数据与流程的制约不仅会导致误差的级联放大,更将严重削弱AI模型在真实世界复杂环境中的外部泛化能力。因而,AI时代不是偏倚消失的时代,而是偏倚形式更加复杂的时代。

对RCT研究框架的逼近并不意味着等价因果评估能力。为了克服观察性研究中普遍存在的混杂偏倚与选择偏倚等问题,一系列严谨的方法学框架和分析策略被建立。TTE是最具代表性的统一框架,而PS方法则是其核心的分析工具之一。TTE通过在设计阶段模仿RCT的严谨性,来提升

观察性数据的因果解读能力。研究者可以先设想一个理想RCT,明确研究对象、干预策略、对照策略、时间零点、随访规则、结局定义和分析方案,再用RWD尽量复刻RCT结构要素、尽最大可能去模拟执行设计方案^[7-9]。PS方法的核心思想是:在观察性研究中,个体接受某种治疗或暴露的概率往往受其基线特征(协变量)的影响,PS即是在给定一系列已测量协变量条件下,个体被分配到治疗组的条件概率。其核心作用是:将多个协变量降维成单个PS,借助PS匹配、分层、回归调整或者逆概率加权等备选技术,有效平衡治疗组和对照组基线特征,从而减少由已知混杂因素带来的偏倚,使观察性研究更接近RCT随机化分配所期望达到的基线均衡,因而往往被称为事后随机化。在这一过程中,AI可用于高维协变量提取、疾病表型识别、文本和影像

信息结构化,在TTE框架中借助PS等技术改善已测协变量的平衡^[10-11]。同时,通过预先确定研究方案,能有效规避“先看数据再分析”带来的偏倚,应按照相关研究报告规范和偏倚风险评价工具,对选择偏倚、混杂偏倚、暴露测量和结局测量偏倚进行透明呈现与评价^[12-13]。因此,AI增强的观察性研究框架可以不断接近RCT的结构。

但这种结构框架接近,并不意味着获得了与随机化分配相同的对已知和未知混杂因素的均衡能力。若仍有未测量因素同时影响治疗选择和结局,观察性研究即便在形式上模拟了RCT,也仍可能存在残余混杂。因此,AI增强的真实世界研究框架可以增强对RCT结构的逼近,却不能自动获得RCT检验因果效应的等价性。

随机化的因果检验价值与完整实施步骤

从历史起源到因果识别 Fisher的随机化思想和随后临床试验方法的发展,使预设方案、设立对照、随机分配和盲法实施逐渐构成现代RCT的基本框架^[17-22]。其中随机化之所以成为RCT的方法学核心,是因为它在设计阶段界定了治疗分配机制:治疗分配由随机机制决定,而不是由医师偏好、患者选择或疾病严重程度等因素决定。这样,治疗组与对照组在概率意义上能够平衡已知与未知的预后因素。从因果推断角度看,随机化最重要的作用是通过主动引入随机化分配机制本身来实现组间的

公平可比。因此,随机化与AI高维建模的差异,不是变量维度或参数多少的差异,而是识别机制设置上的差异。现代临床试验质量管理规范进一步强调研究问题、估计目标、方案预设、法规和伦理等要求,确保了随机化试验证据的可解释性与可审查性^[23-26]。

随机化完整性所包含的3个步骤 在发表RCT论著时,在方法学章节假若仅仅简单声称该试验采用了“随机分组”,这并不意味着真正实施了高质量随机化。随机化完整性包括紧密关联的3个关键步骤:随机分配序列的生成、分配隐藏和分配实施(表2)。随机序列生成要求采用合适的随机化方法生成可重现又不可预测的序列;分配隐藏要求在临床试验参与者入组前,负责招募的研究人员不能事先获知其干预分配,以防选择偏倚;分配实施要求严格按照预设方案执行,并保留可稽查记录^[19-22,27-28]。需要强调的是,成功的分配隐藏并不只取决于严谨的管理流程,也取决于随机序列本身是否足够不可预测。传统区组随机化虽然确保了入组期间组间样本数量的均衡,但这种周期性平衡规律导致了序列的高度可预测,进而破坏了分配隐蔽性而导致选择偏倚。研究表明,相较于其他随机化策略,区组随机设计导致的选择偏倚风险可能激增3倍^[29]。由此可见,即便研究冠以RCT之名,若随机化方法选择不当,将实质性损害随机化的完整性,进而削弱其作为确证因果的方法学优势。

表2 RCT随机化完整性所包含的关键步骤
Tab 2 Critical components of randomization integrity in RCTs

Components	Methodological meaning	Notes
Random sequence generation	Ensures allocation unpredictability and prevents manipulation in participants enrollment	Use computer-generated random numbers or other explicit auditable mechanisms
Allocation concealment	Prevents investigators from selecting participants based on foreknowledge of upcoming assignments	Centralized randomization, IWRS, or sealed envelopes should be auditable
Allocation implementation	Ensures participants receive the intervention corresponding to their randomized assignment	Record protocol deviations and crossover

IWRS: Interactive web response system.

常用随机化方法及其拓展 临床试验中常用的随机化方法包括完全随机化、区组随机化和分层随机化等^[21-22](表3)。完全随机化方法最接近随机化基本原则,适用于样本量较大的研究;区组随机化(区组大小可以固定或变化)有助于保持治疗组和对照组样本量平衡;分层随机化将关键预后因素作为分层因素,在各层内实施完全随机化或区组随机化,提高组间可比性。需要注意的是,随机分配机制和分配不可预测性是因果解释的根基,区组随

机化的优势是确保试验过程中各治疗组例数的阶段性平衡,然而固定区组大小或分配模式可能形成可识别的周期规律,极大地增加了选择偏倚发生风险。针对区组随机化的弊端,新颖的三明治混合随机化(sandwich mixed randomization, SMR)巧妙整合完全随机化与区组随机化,在维持组间样本均衡性的同时增强分配不可预测性,极大降低选择偏倚发生风险^[29]。在区组随机化方法适用的任何RCT场景,SMR都可以作为区组随机化的优越替代。

表 3 临床试验中常用随机化方法的特点和局限性
Tab 3 Advantages and limitations of common randomization methods in clinical trials

Randomization method	Applicable scenarios	Advantages	Limitations
Complete randomization	Large trials with stable enrollment; interim treatment balance is not critical	Simple; highly unpredictable; lowest risk of selection bias	May cause treatment imbalance in small trials or during interim enrollment
Fixed block randomization	Trials requiring approximate treatment balance between group sizes throughout enrollment	Facilitates drug supply, site management, interim quality control, and interim analyses	If the block size is known, future assignments may become highly predictable
Variable block randomization	Trials requiring both interim balance and reduced deterministic assignments	Less deterministic allocation compared to fixed block sizes, while maintaining approximate treatment balance	Periodic treatment balancing remains, but predictability may still far exceed that of complete randomization
Sandwich mixed randomization	Any setting suitable for block randomization, especially non-blinded, single-center, or high selection-bias-risk trials	Improves allocation uncertainty while controlling treatment imbalance during recruitment	Relatively new; software implementation and application experience need wider dissemination

小规模或低成本 RCT 同样可以产出关键证据 RCT 位居循证医学证据金字塔的顶端,但是这并不意味着其实施必然受制于庞大的资源投入或极大样本量门槛。只要研究假设界定清晰、人群特征同质、干预方案标准化以及结局指标客观明确,即便是中小规模试验,或是依托常规医疗设施或卫生信息系统运行的低成本大规模试验,亦能产生改变临床实践的关

键证据。表 4 所列案例,从经典的中小规模 RCT(如 MRC 链霉素治疗肺结核和产前倍他米松预防早产儿呼吸窘迫等试验),再到依托常规医疗信息系统实施的大规模低成本 RCT(如 RECOVERY 和 TASTE 试验),充分印证了 RCT 的核心效能并非源于研究规模本身,而取决于严密的研究框架与不可撼动的随机分配完整性所共同构建的内部效度^[30-36]。

表 4 产生关键证据的小规模或低成本随机对照试验实例
Tab 4 Examples of small or low-cost RCTs producing key evidence

Example	Sample size	Intervention feature	Evidence contribution
MRC streptomycin trial for pulmonary tuberculosis ^[30]	107 patients	Random allocation under resource-limited conditions, with emphasis on allocation concealment	A methodological milestone for modern randomized controlled trials
Antenatal betamethasone for prevention of respiratory distress syndrome ^[31]	282 pregnant women	Low-cost existing drug evaluated with clear neonatal outcomes	Helped establish evidence for antenatal corticosteroid therapy in perinatal medicine
H. pylori eradication to reduce duodenal ulcer relapse ^[32]	100 patients	Antimicrobial/bismuth-based therapy with endoscopic follow-up	Supported the shift from acid suppression alone to causal treatment of peptic ulcer disease
Adjunctive dexamethasone for adult bacterial meningitis ^[33]	301 patients	Low-cost corticosteroid used as adjunctive therapy to antibiotics	Showed that inexpensive interventions can improve important clinical outcomes in rigorous RCT
Propranolol for infantile hemangiomas ^[34]	40 patients	Drug repurposing with placebo control and blinded volume/photo assessment	Moved observational signals into randomized validation and strengthened the treatment evidence chain
RECOVERY platform trial of dexamethasone for COVID-19 ^[35]	6 425 patients in the dexamethasone comparison	Platform RCT embedded in routine NHS care, with web-based randomization and routine health-data follow-up	Rapidly produced practice-changing evidence for a low-cost treatment in hospitalized COVID-19 patients
TASTE trial of thrombus aspiration in STEMI ^[36]	7 244 patients	Registry-based randomization and outcome data collection using national clinical registries	Demonstrated the feasibility of large-scale, low unit-cost RCTs and showed no mortality benefit of routine thrombus aspiration

NHS: National Health Service.

AI对随机化试验的赋能及其作用边界

AI 增强随机化试验效能及合规性 强调随机化的不可替代性,并不意味着排斥 AI。合理嵌入 AI 技术反而能够为 RCT 全过程提供显著的增效支持。在 RCT 设计与准备阶段:利用文献挖掘优化纳入排

除标准,通过 RWD 辅助样本量估算及分层因素的识别;在招募与执行阶段:基于电子病历(electronic medical record,EMR)数据挖掘实现受试者的精准预筛,实时监测依从性并预警不良事件,提升中心质量控制效率;终点评估与管理时:支持多模态结局数据

的智能化判读(如影像与病理特征),强化缺失数据识别、逻辑核查及稽查追踪的自动化能力^[1-6,37-39]。然而,上述应用必须严格受限于“预设工具”的方法学边界。AI模型版本、输入变量及人工复核机制均需在试验方案中明确定义;AI不可介入或改变随机分配序列的生成、分配隐藏保护及盲态执行等核心环节。对于涉及样本量重估、适应性调整等创新设计的统计学考量,AI技术的介入同样应严格参照适应性设计指南与方法学规范进行论证^[40-41]。

AI与随机化机制的双向协同 跨越算法技术潜力至临床真实获益,需要构建AI与随机化试验的双向协同关系。一方面,AI赋能RCT,提升了科学问题转化、人群异质性识别及数据管理效能;另一方面,RCT是确证AI系统临床效用的金标准。基于现有数据集在预测性能指标上的优秀表现,仅能证明AI模型具备特定的模式识别能力,不足以确立其临床实用价值。唯有通过严谨的前瞻性临床试验设计,在真实临床情境下对“AI应用系统”与“常规诊疗模式”进行随机化试验比较,评估其对诊疗效率或患者结局影响,方能真正确立AI的临床转化价值。CONSORT-AI、SPIRIT-AI及TRIPOD+AI等国际规范也明确指出,针对临床使用的AI模型必须强调干预流程与人机交互的透明度,最终的临床有效性仍需通过RCT予以确证^[37-39]。

PREVENT-PE随机化试验是一个典型的范式案例^[42]:这项研究的干预措施是在妊娠35~36周常规产检期间,采用母体因素、血流动力学和生物标志物建立的子痫前期发生风险预测模型,根据预测风险状况来决定是否安排提前分娩。结果显示,相比对照组即常规孕期保健模式,试验组在未增加不良结局的前提下有效降低了子痫前期发生率。这个案例凸显了算法模型推广应用前的原则要求:临床预测模型只有经过严格RCT验证其临床效用,才能切实转化为临床决策支持工具。

监管审查、外部验证与动态更新 AI系统的迭代特性给研究诚信和监管合规带来了独特的挑战。美国食品药品监督管理局(FDA)关于AI医疗软件“预变更控制计划”的指南强调,在保障器械全生命周期的安全有效性前提下允许器械搭载的AI技术“一次审评、多次迭代”;同样,欧洲药品管理局(EMA)的框架文件也强调,在AI的整个生命周期中必须严格执行数据质量控制、风险管理和透明度要求^[43-44]。使用AI工具的临床研究必须详尽记录模型版本、训练数据来源、目标人群、更新算法、漂移监测方案、人工审核标准以及责任边界(表5)。AI的作用在于提升研究效率,但绝不能替代方法学的透明度或可稽查性;它绝不应将科学过程掩盖在一个无法问责的“黑箱”之中。

表5 人工智能在随机对照试验中的整合:主要阶段和风险控制
Tab 5 AI integration in RCTs: main stages and risk controls

Stage	AI role	Potential benefit	Risk control
Design	Literature review, sample-size simulation, site selection, stratification-factor identification	Improves protocol efficiency and feasibility	Prespecify algorithm use and avoid post hoc selection
Recruitment and screening	EHR-based prescreening and phenotype recognition	Improves enrollment efficiency	Require human confirmation to prevent misclassification and selection bias
Random allocation	Centralized systems and stratification-factor suggestions	Improves procedural standardization	Conceal allocation sequences and prevent prediction of assignments
Endpoint assessment	Assisted reading of imaging, pathology, and text-based outcomes	Improves consistency and efficiency	Maintain blinding and lock model versions
Data governance	Missing-data detection, logic checks, and audit trails	Improves data quality	Keep logs to ensure traceability and reproducibility

EHR: Electronic health records.

从预测到因果:AI模型与随机试验的递进式证据架构 在AI时代,人工智能技术大幅优化了观察性研究的实施效率与数据洞察能力,同时,合理的证据生成架构可以重塑观察性研究的价值。观察性研究与真实世界证据因与临床实践高度契合,在识别新型病理特征、对高危人群进行分层,以及确立长期安全性和外部有效性方面表现卓越。AI进

一步强化了从医疗大数据中识别关联与进行风险预测的能力,使研究者能够更精准、更及时地提出临床假设。此外,TTE等因果推断新策略通过在人群选择、零点时间、干预措施定义及分析方案上贯彻科学严谨性,有效弥合了观察性研究框架与理想化RCT之间的方法学差距。

然而,方法学上的对齐并不等同于替代。观察

性研究能够提取“疗效信号”,AI能够优化“谁获益”的预测,而因果推断策略仅在特定假设下增强真实世界证据的可解释性。需要验证这些信号或研究假设时,RCT是不可或缺的研究框架;在评估新药或新技术能否真正改善临床结局时,RCT更是最灵敏和最可靠的首选确证标准。在因果证据的层级体系中,AI预测发现→因果推断逼近→随机试验确证三者间并非竞争替代关系,而是前后衔接、相互印证并校准的证据体系。

结语 AI高效赋能临床研究从海量数据中识别模式、预测风险及指导设计后续研究的能力,通过高维协变量处理、目标试验模拟和倾向评分等策略,使观察性研究在架构上逼近理想的RCT框架。然而,算法驱动下的预测性能跃升并不等同于因果识别能力的突破;单纯引入更多协变量亦难以消除未测量或未知混杂因素所致系统偏倚。RCT凭借特有的随机分配机制尽可能控制相关偏倚,为干预效应评价奠定了不可替代的因果检验基础。在数据异构与模型迭代加速的AI时代背景下,严格区分相关关系、预测预警与因果确证显得尤为关键。亟需警惕将预测性证据误读为因果性结论。坚守随机分配序列的不可预测性从而确保随机化的完整性,始终是确立并捍卫RCT金标准地位不可或缺的方法学核心。

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