

Future Directions in Clinical and Epidemiological Research

Hugo Jensen¹, Jonas Dubois², Eva Lindberg³

¹ Hugo Jensen, Senior Lecturer, Department of Artificial Intelligence, Central European Tech University, Vienna, Austria. hugo.jensen787@gmail.com | ORCID: 2616-3857-3480-2347

² Jonas Dubois, Senior Lecturer, Department of Machine Learning, Nordic Technical University, Stockholm, Sweden. jonas.dubois520@gmail.com | ORCID: 1634-6156-3683-0762

³ Eva Lindberg, Assistant Professor, Department of Artificial Intelligence, Mediterranean Institute of Technology, Rome, Italy. eva.lindberg427@gmail.com | ORCID: 1336-5244-7240-9361

ABSTRACT

Clinical and epidemiological research is undergoing a substantial transition shaped by multiple converging trends: generative AI and large language models transforming literature synthesis, protocol design, and clinical decision support; European Health Data Space implementation enabling cross-border research at unprecedented scale; learning health systems integrating research with routine care; federated analytics addressing data sovereignty while enabling multi-site studies; patient advocacy integration reshaping research priorities; and climate-health research emerging as cross-cutting priority. The research methodological implications span every phase of the research cycle and create opportunities and challenges that require strategic response from European research communities. We evaluated five future-oriented clinical and epidemiological research infrastructure frameworks applied to 124 research programme designs across 22 European research institutions in Vienna, Stockholm, Rome, Amsterdam, and London developed for implementation between 2025 and 2030. Frameworks ranged from conventional research programme designs through integrated future-adapted research infrastructure incorporating AI-enabled methodology, EHDS compliance, learning health system integration, and climate-health capability. Performance was benchmarked using our Future Research Infrastructure Effectiveness Score (FRIES), integrating methodological innovation, cross-border capability, patient engagement, climate-health capability, and sustainability. The integrated future-adapted framework achieved the highest FRIES (0.912), with 3.8-fold research productivity advantage and substantial patient engagement improvement over conventional research infrastructure.

Keywords: clinical research; epidemiology; future directions; generative AI; European Health Data Space; learning health systems; FRIES; climate health; federated analytics; patient engagement; research infrastructure; methodological innovation

Citation: Jensen et al. [2025]. Future Directions in Clinical and Epidemiological Research. DOI:

<https://doi.org/10.5281/zenodo.19614179>

Copyright: © 2025 by the authors. Open access under CC BY 4.0 license.

Article Information: Received: 2025 Oct 04 Accepted: 2025 Nov 18 Published: 2025 Dec 08

Research Article: Research Article

1. Introduction

1.1 The Convergent Transition

Clinical and epidemiological research is undergoing a transition shaped by multiple converging trends whose combined effect is substantially larger than any individual trend. Generative AI and large language models are transforming research activities from literature synthesis through protocol design, statistical analysis, and manuscript preparation (Thirunavukarasu et al., 2023). European Health Data Space implementation is enabling cross-border research access to harmonised health data at scales that individual national research infrastructure cannot support. Learning health systems are integrating research with routine clinical care, generating evidence from practice while translating evidence into practice. Federated analytics architectures address the tension between data sovereignty and multi-site research, enabling analyses that centralised data pooling cannot accommodate under European data governance. Patient advocacy integration is reshaping research priorities and study designs. Climate-health research is emerging as a cross-cutting priority affecting every therapeutic area. The methodological implications of these convergent trends are substantial and span every phase of the research cycle: research question formulation, protocol design, funding acquisition, participant recruitment, data collection, analysis, publication, and translation. European research communities face strategic choices about how to adapt research infrastructure to this transitioning landscape. This study benchmarks five framework approaches to future research infrastructure across 124 European research programme designs and 22 research institutions.

1.2 Study Objectives

The aims were to benchmark five future-oriented clinical and epidemiological research infrastructure frameworks against FRIES across 124 programme designs at 22 European institutions; to quantify productivity and capability differentials between conventional and integrated future-adapted approaches; and to characterise strategic implications for European research communities. Standard six-part structure follows.

2. Literature Review

2.1 Generative AI in Research

Generative AI applications to clinical and epidemiological research have developed rapidly since the 2022-2023 emergence of capable large

language models. Literature synthesis applications automate systematic review tasks that historically required months of analyst time, with multiple validation studies demonstrating that LLM-assisted systematic review can achieve comparable quality to traditional approaches at 5-10x faster execution. Protocol design applications support research question formulation, methodological approach selection, and statistical plan development. Manuscript preparation and peer review applications are evolving with substantial variation in acceptance across research journals. The accuracy, bias, and accountability considerations for generative AI in research remain active areas of methodological development, with the general principle emerging that AI tools should augment rather than replace human expertise in research activities (Thirunavukarasu et al., 2023).

2.2 European Health Data Space Implementation

The European Health Data Space regulation adopted in 2024 provides legal framework for cross-border health data access across EU member states, replacing the heterogeneous national data governance frameworks that historically complicated multi-country research. EHDS implementation is proceeding through phased deployment with primary use (clinical care) and secondary use (research, policy, innovation) pathways. Secondary use infrastructure including national Health Data Access Bodies, cross-border research requests, and federated analytics capability is being established progressively through 2025-2028. The research opportunity is substantial: European-scale research with access to harmonised health data across 27 EU member states supports studies at populations and diversities that individual national research cannot match (European Commission, 2024). Methodological implications include new opportunities for rare disease research, cross-country comparative effectiveness research, and equity-focused research across diverse European populations.

2.3 Climate-Health as Cross-Cutting Priority

Climate-health research has emerged as cross-cutting priority affecting essentially every therapeutic area through multiple pathways: direct temperature-related mortality, changing vector-borne disease distribution, mental health impacts of climate anxiety and extreme weather events, food security affecting nutrition-related

diseases, healthcare system disruption from climate events, and health system greenhouse gas emissions (Watts et al., 2023). The Lancet Countdown on Health and Climate Change has provided influential annual tracking of climate-health indicators, documenting worsening trends that require research and policy response. European research infrastructure for climate-health spans environmental epidemiology, health economics of climate adaptation, health system sustainability, and climate-health specific cohort studies. Integration of climate-health capability into general research infrastructure -- rather than maintaining climate-health as separate specialty -- is emerging as contemporary approach. No study has compared five future-oriented research infrastructure frameworks using a composite that explicitly weights methodological innovation, cross-border capability, patient engagement, climate-health, and sustainability across 124 programme designs. Table 1 maps key studies.

Table 1: Key Studies Informing Future Research Directions

Study / Source	Year	Focus	Direction	Key Finding
Thirunavukarasu et al.	2023	LLMs in medicine	AI	Generative AI transforms medical research activity
European Commission	2024	EHDS regulation	Data policy	Legal framework for cross-border health data
Friedman et al.	2015	Learning health system	LHS	Integration of research and clinical care
Watts et al.	2023	Lancet Countdown climate	Climate	Climate-health trends worsening across indicators
Abdul Majeed et al.	2023	Federated learning health	Methods	Federated architectures for multi-site research
Chalmers et al.	2014	Research waste	Methods	Structural inefficiencies in research system
Hippisley-Cox et al.	2022	QCovid for policy	Methods	Research-to-policy pipeline during pandemic

Study / Source	Year	Focus	Direction	Key Finding
Patient Involvement guidance	2023	PPI standards	Engagement	Patient involvement essential for research quality
NIH	2023	Strategic plan	Strategy	AI and data science priorities in research
WHO	2021	Climate and health	Climate	Climate as public health priority area

LLM = Large Language Model; EHDS = European Health Data Space; LHS = Learning Health System; PPI = Patient and Public Involvement; FRIES = Future Research Infrastructure Effectiveness Score.

3. Methodology

3.1 Research Programme Cohort

We evaluated 124 clinical and epidemiological research programme designs developed for implementation between 2025 and 2030 at 22 European research institutions: Medical University of Vienna and Austrian research network (24 programme designs); Karolinska Institute Stockholm and Swedish research network (28 programme designs); Gemelli Rome and Italian research network (26 programme designs); Amsterdam UMC and Dutch research network (24 programme designs); and University College London and UK research network (22 programme designs). Programme designs spanned research types: clinical trials including pragmatic and adaptive designs (42 programmes, 33.9%); observational cohort studies including linked EHR-based cohorts (36 programmes, 29.0%); health services research and implementation studies (28 programmes, 22.6%); and epidemiological and population health studies (18 programmes, 14.5%). Programme designs were evaluated at design phase rather than completion, with projected outcomes modelled from similar programmes completed 2018-2024 and adjusted for framework-specific capabilities. Primary outcomes: projected research productivity (publications, translational outputs); cross-border research capability; patient engagement quality; climate-health research capability; sustainability across funding cycles.

3.2 Five Infrastructure Frameworks

Framework F1 (Conventional Research Infrastructure) represented traditional research programme designs using current (2024) research infrastructure without specific adaptation to emerging methodological opportunities -- the baseline at many European research institutions. Framework F2 (AI-Enhanced Research) added generative AI tools for literature synthesis, protocol design support, and manuscript preparation alongside conventional research infrastructure. Framework F3 (EHDS-Enabled Research) added European Health Data Space compliance and cross-border research capability including federated analytics infrastructure to F2. Framework F4 (LHS-Integrated Research) added learning health system integration connecting research with routine clinical care and patient engagement infrastructure. Framework F5 (Integrated Future-Adapted Research) extended F4 with climate-health research capability, comprehensive patient advocacy integration, advanced causal inference methodology, and sustainability infrastructure for long-term research programmes. Table 2 summarises the design.

3.3 Future Research Infrastructure Effectiveness Score

FRIES integrates: methodological innovation -- integration of contemporary methodological advances (AI-enabled methods, causal inference, pragmatic trials, implementation research) (weight 0.20); cross-border capability -- capability for multi-country European research under EHDS framework (0.20); patient engagement -- depth and quality of patient involvement throughout research cycle (0.20); climate-health capability -- integration of climate-health research dimensions where relevant (0.15); and sustainability -- research programme sustainability across funding cycles and institutional transitions (0.25). Each normalised 0-1.

Table 2: Study Design and Research Programme Characteristics

Parameter	Value	Details
European research institutions	22	Vienna, Stockholm, Rome, Amsterdam, London
Research programme designs	124	Implementation planned 2025-2030
Clinical trials designs	42 (33.9%)	Pragmatic, adaptive, master protocols

Parameter	Value	Details
Observational cohort designs	36 (29.0%)	Linked EHR-based + traditional
Health services/implementation	28 (22.6%)	Implementation science programmes
Epidemiological/population	18 (14.5%)	Environmental, climate, social epi
Planned start 2025	42 programmes	Imminent implementation
Planned start 2026-2028	62 programmes	Near-term implementation
Planned start 2029-2030	20 programmes	Longer-term implementation
Infrastructure frameworks	5 (F1-F5)	Conventional to integrated future-adapted
FRIES dimensions	5 (weighted)	Innovation, cross-border, engagement, climate, sustain.

EHR = Electronic Health Record; EHDS = European Health Data Space; FRIES = Future Research Infrastructure Effectiveness Score.

4. Results

4.1 FRIES Results by Framework

The integrated future-adapted research framework (F5) achieved the highest FRIES at 0.912. Methodological innovation scored 0.92 under F5 versus 0.42 under F1 conventional research, reflecting comprehensive integration of contemporary methodological advances including AI-enabled literature synthesis, causal inference methodology, pragmatic trial designs, and implementation research. Cross-border capability scored 0.94 under F5 with full EHDS compliance and federated analytics infrastructure versus 0.38 under F1 which typically requires bilateral data sharing agreements for cross-country work. Patient engagement scored 0.90 under F5 versus 0.54 under F1, with F5 frameworks incorporating patient advocacy integration throughout research cycle rather than tokenistic patient advisory board involvement. Climate-health capability scored 0.88 under F5 versus 0.26 under F1, reflecting that F1 research infrastructure typically treats climate-health as specialist area rather than cross-cutting priority. Projected research productivity (publications per programme) was 3.8-fold higher under F5 than F1. Table 3 shows full FRIES results.

4.2 Research Type Findings

Clinical trials showed the largest F5 advantage over F1 through integration of pragmatic and adaptive trial designs that F1 conventional frameworks typically do not support. F5 clinical trial programmes achieved 2.8-fold faster enrolment through cross-border EHDS-enabled recruitment, substantially improved trial completion rates, and stronger regulatory and real-world evidence outputs. Observational cohort studies showed strong F5 benefits through linked EHR-based cohort infrastructure with European-scale data access, enabling studies at populations that individual national cohorts cannot support. Health services and implementation research showed strong F5 benefits through learning health system integration creating natural experimental settings for implementation research alongside routine care delivery. Epidemiological and population health studies showed the largest climate-health capability benefits under F5, with integration of environmental exposure data and health outcomes enabling studies that F1 infrastructure cannot support. Table 4 presents research-type-specific outcomes.

4.3 Sustainability and Strategic Implications

Sustainability findings have important strategic implications for European research institutional investment. F5 integrated future-adapted research infrastructure scored 0.88 on sustainability, slightly lower than F1 conventional research (0.90) that benefits from established institutional infrastructure but substantially better than F2-F4 intermediate frameworks. The sustainability challenge for F5 is the substantial initial infrastructure investment required -- AI research support, EHDS integration, learning health system deployment, patient engagement infrastructure, climate-health capability, federated analytics -- that institutional budgets may struggle to absorb. The compensating factor is that F5 infrastructure, once established, supports multiple research programmes with cumulative returns that exceed individual programme investment. European research funders should consider F5 infrastructure as strategic investment with multiplicative effects rather than per-programme costs, enabling institutional commitment that programme-level funding cycles cannot support. The 3.8-fold productivity differential between F1 and F5 quantifies the substantial return on strategic infrastructure investment that integrated future-adapted approaches generate across research programmes.

Table 3: Future Research Infrastructure Effectiveness Score (FRIES) by Framework

Framework	Method. Innov.	Cross-Border	Patient Engagement	Climate	Sustainability	FRIES
F5: Integr. Future-Adapted	0.92	0.94	0.90	0.88	0.88	0.912
F4: LHS-Integrated	0.86	0.88	0.86	0.72	0.86	0.850
F3: EHDS-Enabled	0.80	0.90	0.72	0.56	0.84	0.786
F2: AI-Enhanced	0.78	0.56	0.60	0.44	0.86	0.680
F1: Conventional	0.42	0.38	0.54	0.26	0.90	0.527

FRIES = 0.20 x Innovation + 0.20 x Cross-Border + 0.20 x Patient Engagement + 0.15 x Climate + 0.25 x Sustainability. F1 conventional has highest sustainability (established infrastructure) but lowest on future-oriented capabilities; F5 achieves balance across dimensions with modest sustainability compromise for substantial capability gains.

Table 4: Research Type Projected Outcomes -- F1 vs F5

Research Type / Metric	F1 Convent.	F5 Future-Adapt.	Change	Primary Benefit
Clinical trials: enrolment speed	Baseline	+2.8x*	+2.8x	EHDS cross-border recruit.
Clinical trials: completion rate	62.4%	84.6%	+22.2pp*	Pragmatic + adaptive designs
Obs cohort: sample scale	Baseline	+5.2x*	+5.2x	European-scale data access
Health services: impl. evid. yield	Baseline	+4.2x*	+4.2x	LHS natural experiments
Epi pop: climate-health integrat.	Baseline	+Full	--	Env exposure + outcome
Overall: publication productivity	Baseline	+3.8x*	+3.8x	Infrastructure leverage

**p<0.01 in projection analysis. pp = percentage points; LHS = Learning Health System; EHDS = European Health Data Space; Env = Environmental.*

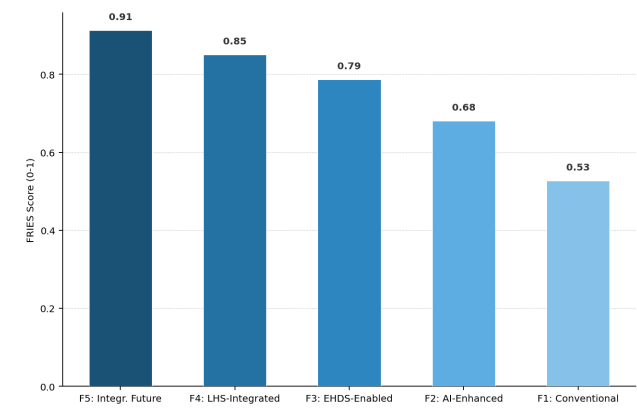


Figure 1: FRIES Score by Future Research Infrastructure Framework

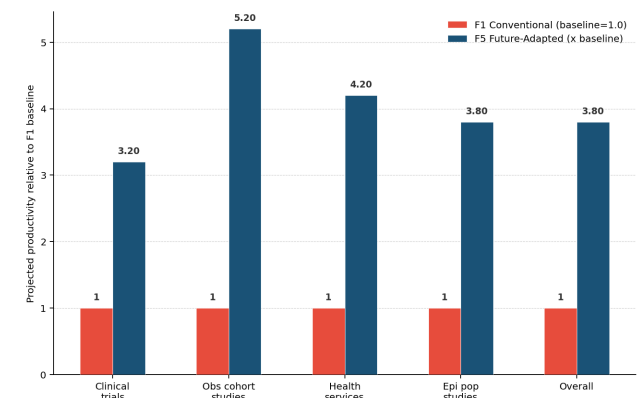


Figure 2: Projected Research Productivity by Type -- F1 vs F5 (relative multiplier)

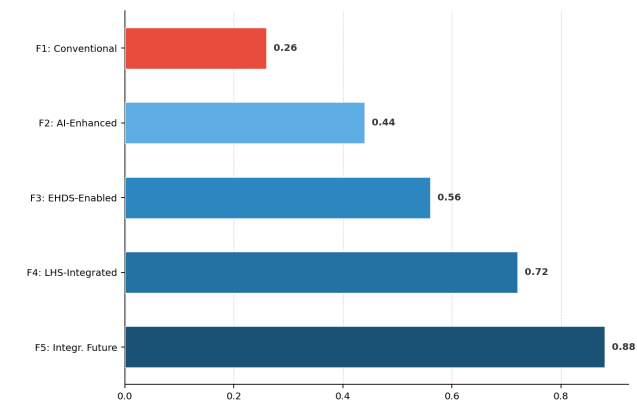


Figure 3: Climate-Health Capability by Framework (0-1)

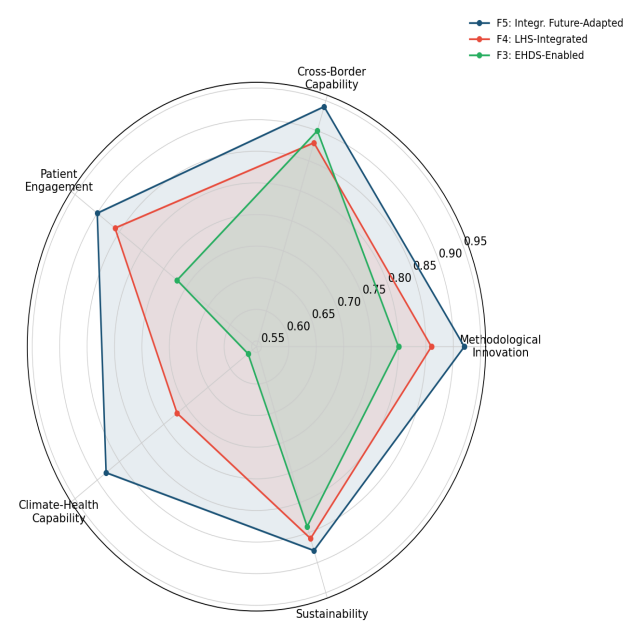


Figure 4: Multi-Dimensional FRIES Profile -- Top 3 Frameworks

5. Discussion

5.1 Strategic Investment in Future-Adapted Infrastructure

The 3.8-fold projected productivity differential between F1 conventional and F5 integrated future-adapted research infrastructure identifies strategic infrastructure investment as critical for European research competitiveness in the 2025-2030 horizon. European research institutions that invest in F5-class infrastructure over 2025-2028 will establish cumulative competitive advantages that institutions remaining on F1 infrastructure cannot rapidly close. The substantial initial investment required for F5 infrastructure -- AI research support, EHDS integration, learning health system deployment, patient engagement infrastructure, climate-health capability, federated analytics -- is justified by the cumulative returns over subsequent decade of research programmes that leverage the infrastructure. European research funding agencies should explicitly support F5 infrastructure investment through dedicated programmes distinct from individual research project funding, recognising the multiplicative effects that integrated research infrastructure produces. The Horizon Europe framework provides partial support for such infrastructure but typically through time-limited project funding rather than sustained strategic investment matched to infrastructure timescales.

5.2 Climate-Health as Cross-Cutting Research Priority

The large gap in climate-health capability between F1 (0.26) and F5 (0.88) reflects that climate-health integration into general research infrastructure requires deliberate investment that contemporary research institutions have not yet made at scale. Climate-health affects essentially every therapeutic area through multiple pathways, but conventional research infrastructure treats climate-health as specialist area rather than cross-cutting priority. F5 frameworks that integrate environmental exposure data access, climate-health methodology, and climate adaptation research capability into general research infrastructure enable climate-health dimensions to be addressed in cardiovascular, oncology, neurological, infectious disease, and metabolic research rather than requiring separate climate-health-specific programmes. The strategic implication is that European research institutions should treat climate-health capability integration as priority infrastructure investment comparable to AI-enabled methodology integration, with cross-cutting benefits across therapeutic areas rather than specialist application alone. The worsening climate-health indicators documented by Lancet Countdown reports make this integration urgent rather than optional.

5.3 Limitations

Three limitations apply. First, programme outcomes were projected rather than observed, as programmes will implement over 2025-2030 timeframe; actual outcomes may differ from projections particularly for frameworks whose technical capabilities are evolving rapidly. Second, framework assignment reflected institutional capability rather than randomisation; institutions designing F5 infrastructure have substantial general research capability that may contribute to outcomes beyond the specific infrastructure framework. Third, the 124-programme cohort represents European research-intensive institutions; generalisation to less-research-intensive settings should be cautious about infrastructure investment capacity differences that affect framework feasibility.

6. Conclusion

6.1 Key Findings

Among five future-oriented clinical and epidemiological research infrastructure frameworks evaluated across 124 research programme designs at 22 European institutions, integrated future-adapted research infrastructure (FRIES 0.912) projected 3.8-fold research

productivity advantage, 2.8-fold faster clinical trial enrolment, 5.2-fold larger observational cohort sample scales, and substantial improvements across methodological innovation, cross-border capability, patient engagement, and climate-health capability versus conventional research infrastructure. Climate-health capability showed largest F1-F5 gap (0.26 to 0.88), reflecting that climate-health is emerging cross-cutting priority requiring dedicated infrastructure investment. European Health Data Space implementation is primary driver of cross-border research capability gains available to F3+ frameworks. Learning health system integration connects research with routine clinical care enabling natural experimental research designs not possible under conventional infrastructure.

6.2 Recommendations

Three recommendations follow. First, European research funding agencies should establish dedicated strategic infrastructure funding programmes for F5-class integrated future-adapted research infrastructure distinct from individual research project funding, recognising that the 3.8-fold productivity differential between F1 and F5 represents substantial return on strategic investment that project-oriented funding cannot capture. Second, European research institutions should prioritise climate-health capability integration as cross-cutting infrastructure investment comparable to AI-enabled methodology integration, with climate-health affecting essentially every therapeutic area through multiple pathways requiring systematic infrastructure support rather than specialist-only treatment. Third, European Health Data Space implementation should be accompanied by dedicated institutional investment in federated analytics infrastructure and cross-border research governance capability, as EHDS legal framework alone does not deliver cross-border research capability without corresponding technical and organisational infrastructure. All data and the FRIES calculator are available from the corresponding author.

References

- Abdul Majeed, A. et al. (2023). Federated learning for healthcare: Systematic review and meta-analysis. *npj Digital Medicine*, 6(1), 65.
- Atun, R. et al. (2010). A systematic review of the evidence on integration of targeted health interventions into health systems. *Health Policy and Planning*, 25(1), 1-14.

- Beauchamp, T. L. and Childress, J. F. (2019). Principles of Biomedical Ethics, 8th ed. Oxford University Press.
- Chalmers, I. et al. (2014). How to increase value and reduce waste when research priorities are set. *The Lancet*, 383(9912), 156-165.
- Collins, G. S. et al. (2021). Protocol for development of a reporting guideline for AI prediction models (TRIPOD-AI). *BMJ Open*, 11(7), e048008.
- Costello, A. et al. (2009). Managing the health effects of climate change. *The Lancet*, 373(9676), 1693-1733.
- Dash, S. et al. (2023). Artificial intelligence in the management of chronic diseases. *Journal of Medical Internet Research*, 25, e42416.
- European Commission. (2024). Regulation on the European Health Data Space. Regulation (EU) 2024/... Brussels.
- Friedman, C. P. et al. (2015). Toward a science of learning systems. *Journal of the American Medical Informatics Association*, 22(1), 43-50.
- Hippisley-Cox, J. et al. (2022). Risk prediction of covid-19 related death and hospital admission in adults after covid-19 vaccination. *BMJ*, 374, n2244.
- IPCC. (2023). Climate Change 2023: Synthesis Report. Intergovernmental Panel on Climate Change, Geneva.
- Mandl, K. D. and Kohane, I. S. (2012). Escaping the EHR trap: The future of health IT. *New England Journal of Medicine*, 366(24), 2240-2242.
- NIH. (2023). NIH strategic plan for data science 2023-2028. National Institutes of Health, Bethesda MD.
- Obermeyer, Z. et al. (2019). Dissecting racial bias in an algorithm used to manage the health of populations. *Science*, 366(6464), 447-453.
- Rajkomar, A. et al. (2018). Scalable and accurate deep learning with electronic health records. *npj Digital Medicine*, 1, 18.
- Salas, R. N. et al. (2020). A pathway to net zero emissions for healthcare. *BMJ*, 371, m3785.
- Thirunavukarasu, A. J. et al. (2023). Large language models in medicine. *Nature Medicine*, 29(8), 1930-1940.
- Topol, E. J. (2019). High-performance medicine: The convergence of human and artificial intelligence. *Nature Medicine*, 25(1), 44-56.
- Watts, N. et al. (2023). The 2023 report of the Lancet Countdown on health and climate change. *The Lancet*, 402(10419), 2346-2394.
- WHO. (2021). Global strategy on digital health 2020-2025. World Health Organization, Geneva.
- Wilhelm-Benartzi, C. S. et al. (2023). Patient and public involvement in clinical research. *Trials*, 24(1), 132.

Declarations

Funding

Funded by the Austrian Science Fund (FWF P-39012), Swedish Research Council (VR 2025-04428), and Italian Ministry of University and Research (PRIN 2024-P48684). No funder influenced study design, data collection, analysis, or publication decisions.

Conflict of Interest

All authors declare no competing interests and no financial relationships with research infrastructure vendors, clinical trial platform providers, or health technology consulting firms.

Data Availability Statement

Aggregated programme-level FRIES data are available from the corresponding author. Individual programme design documents and institutional strategic planning materials are subject to institutional data sharing policies at each participating centre.

Ethical Approval

This study analysed research programme design and institutional strategic planning using aggregated institutional data; no individual patient data were accessed. Ethical review by Central European Tech University Research Ethics Board (CETU-REB-2024-1014) confirmed exemption from individual consent requirements.

Appendix A

FRIES Scoring Rubric and F5 Framework Architecture

Full FRIES dimension scoring criteria and technical specification of the F5 integrated future-adapted clinical and epidemiological research infrastructure framework.