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Intelligenza Artificiale in Sanità: tra impatto etico e innovazione

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AI in health care

...from big problems come great opportunities...

Transformative impact

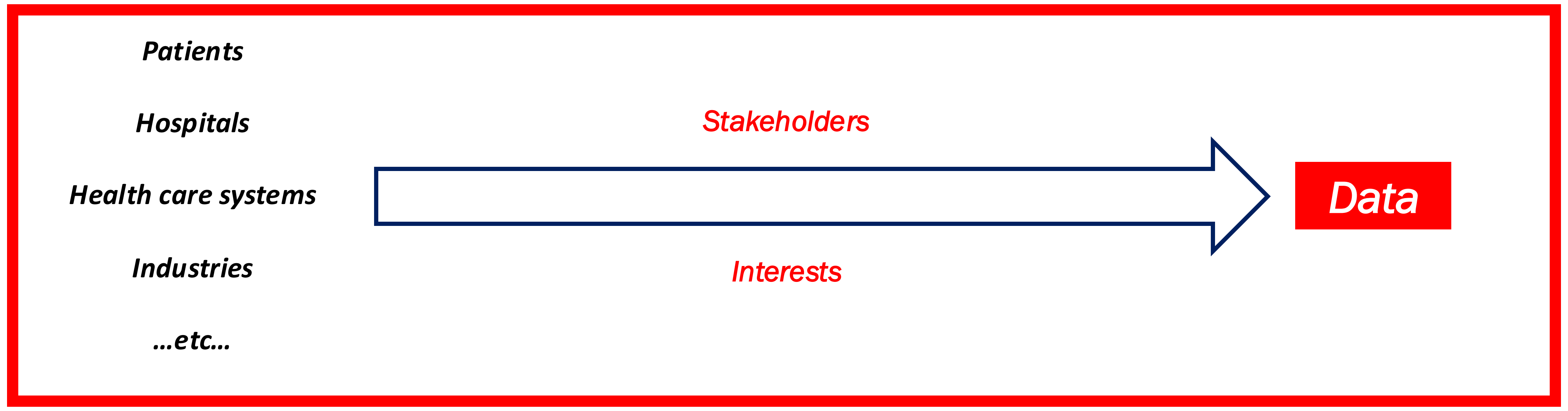
- Improvement of treatments
- Reduction of medical errors

AI in medicine: opportunities

- Analysis of clinical big data
- Tools for accurate and rapid diagnosis
- Clinical Decision Support Systems (CDSS)
- Development of new therapies

Generating data in health care, an irrepressible process

Modern medicine is highly complex, rapidly evolving, tightly connected with basic science, and characterized by an imperative need to personalize patients' management and treatments



Robust data infrastructures aimed at bridling, manipulating, aggregating, and linking patients' multiparametric data are widely-used pragmatic instruments that ultimately enable the observation and improve bedside practice and health care management

Liu et al. *Anesth Analg* 2015;121(6):1604–10.
Beitler et al. *Lancet Respir Med.* 2021 Jul

Data analysis in modern health care

- Culture of introspection and constant ***self-improvement*** as required characteristics.
- Evidence-based decision-making requires ***clinical research***;
- ***Technological evolution*** has forced physicians to consider (but rarely completely understand) at the same time multiple data, reflecting the adaptive or maladaptive attempts of patients' physiology to counteract the disease;
- Highly complex patients, for whom ***personalization*** of treatments is mandatory.
- ***Efficiency*** in using limited resources .

Beitler et al. *Lancet Respir Med.* 2021 Jul

Critical Care Medicine

- Critical illness is a final common representation of those pathophysiological mechanisms that produce organs dysfunction independently from the etiology.
- Patients in critical condition often lack the capacity to provide informed consent, making their inclusion in randomized controlled trials infrequent.
- Outcomes for these patients are significantly influenced by various confounding factors, both personal and environmental.

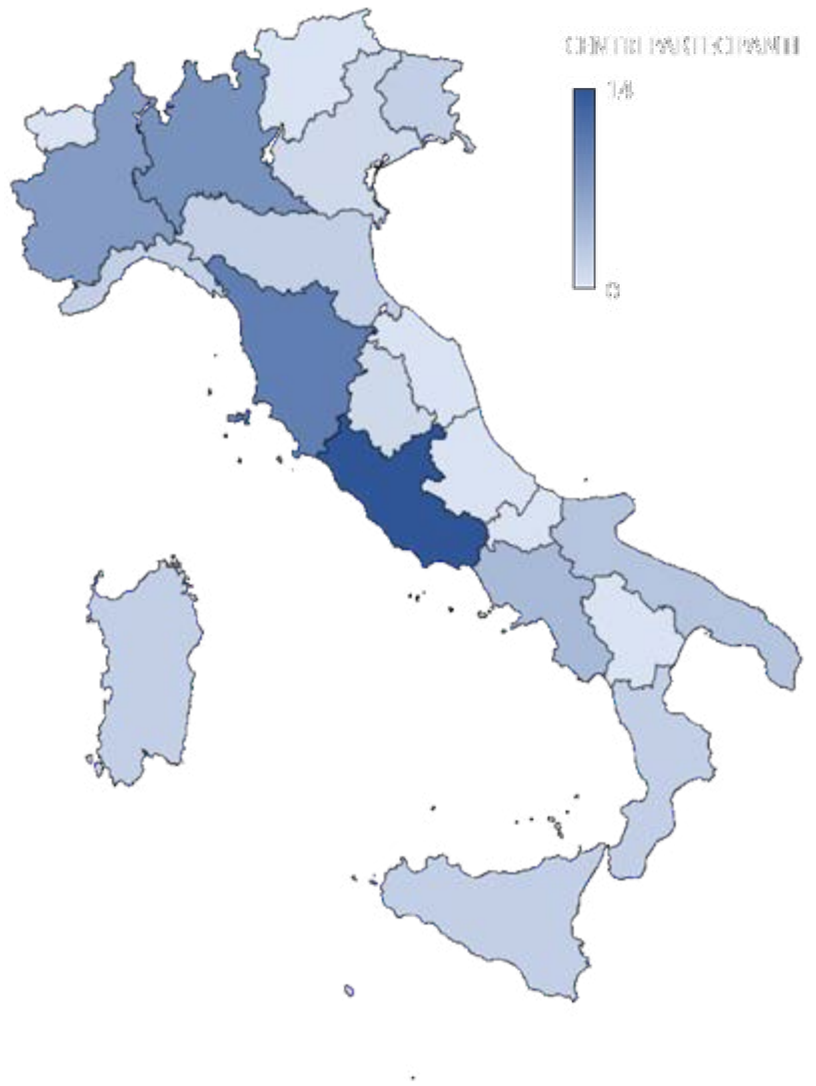
"Imprecise therapies" prescribed on generic phenotypes

"Not-EBM therapies" delivered as expert opinion

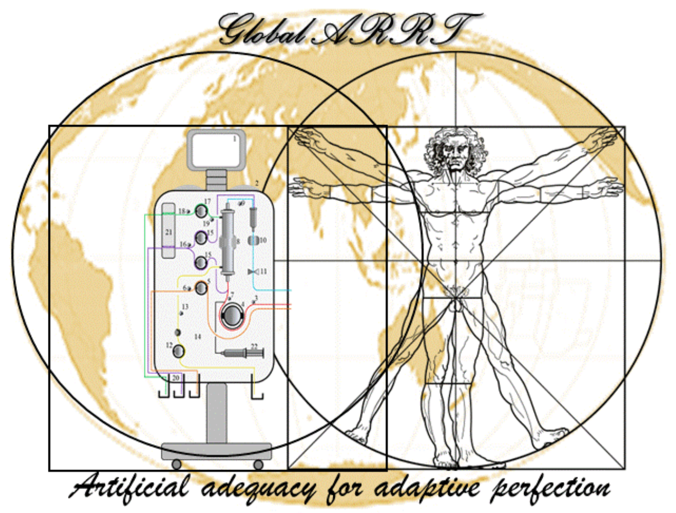
Is it ethical to ignore the potential of AI in routine clinical practice?

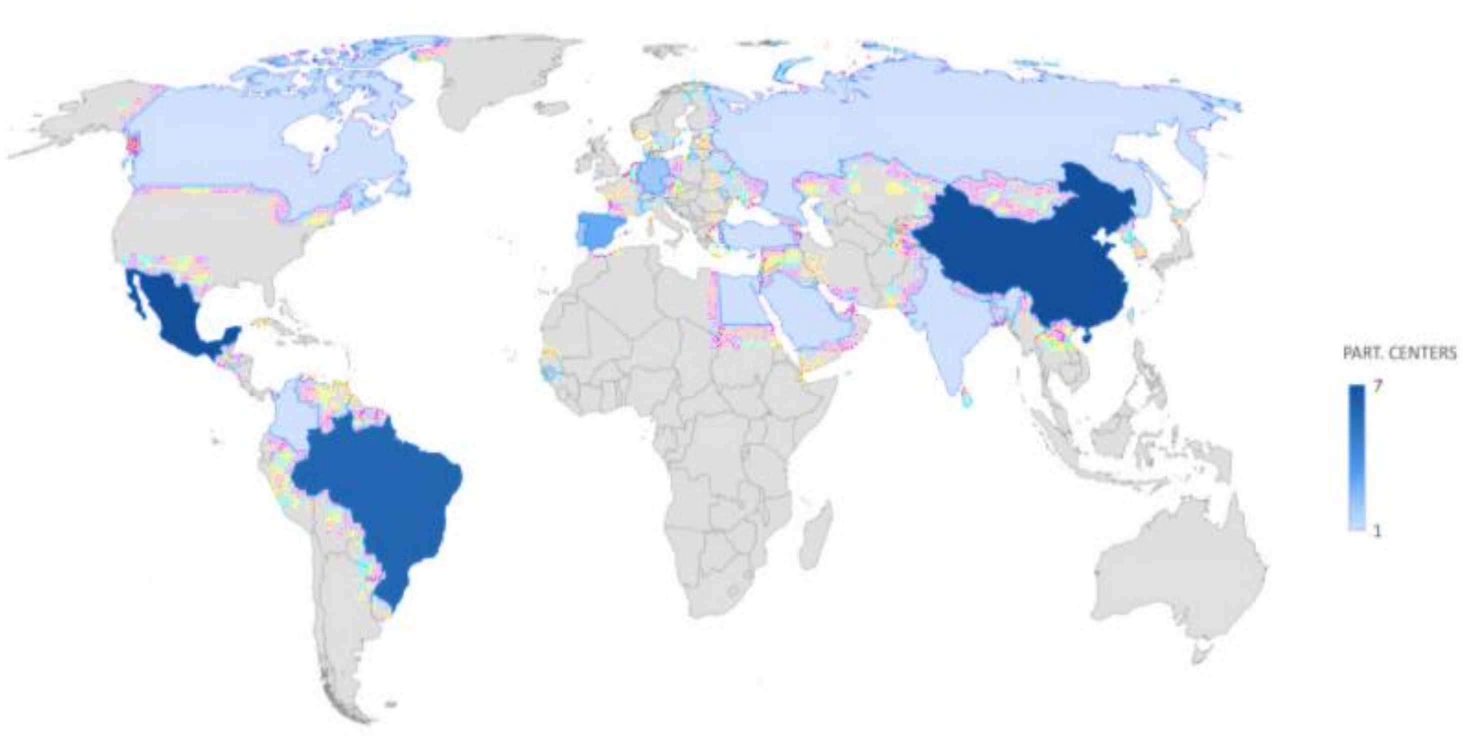
Beitler et al. *Lancet Respir Med.* 2021 Jul

Real-world data on EBP: the ARRT Registry



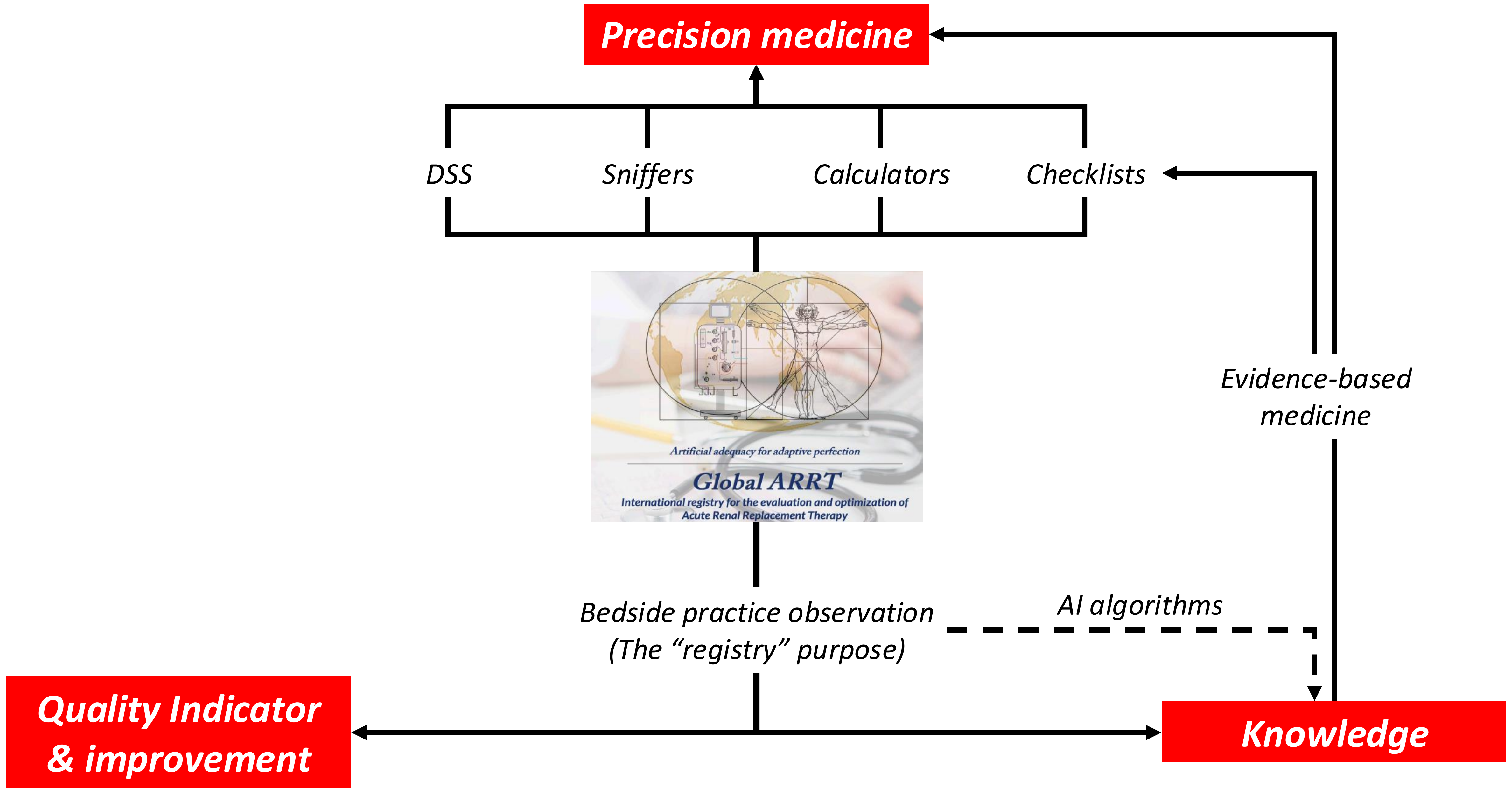
www.arrt.eu



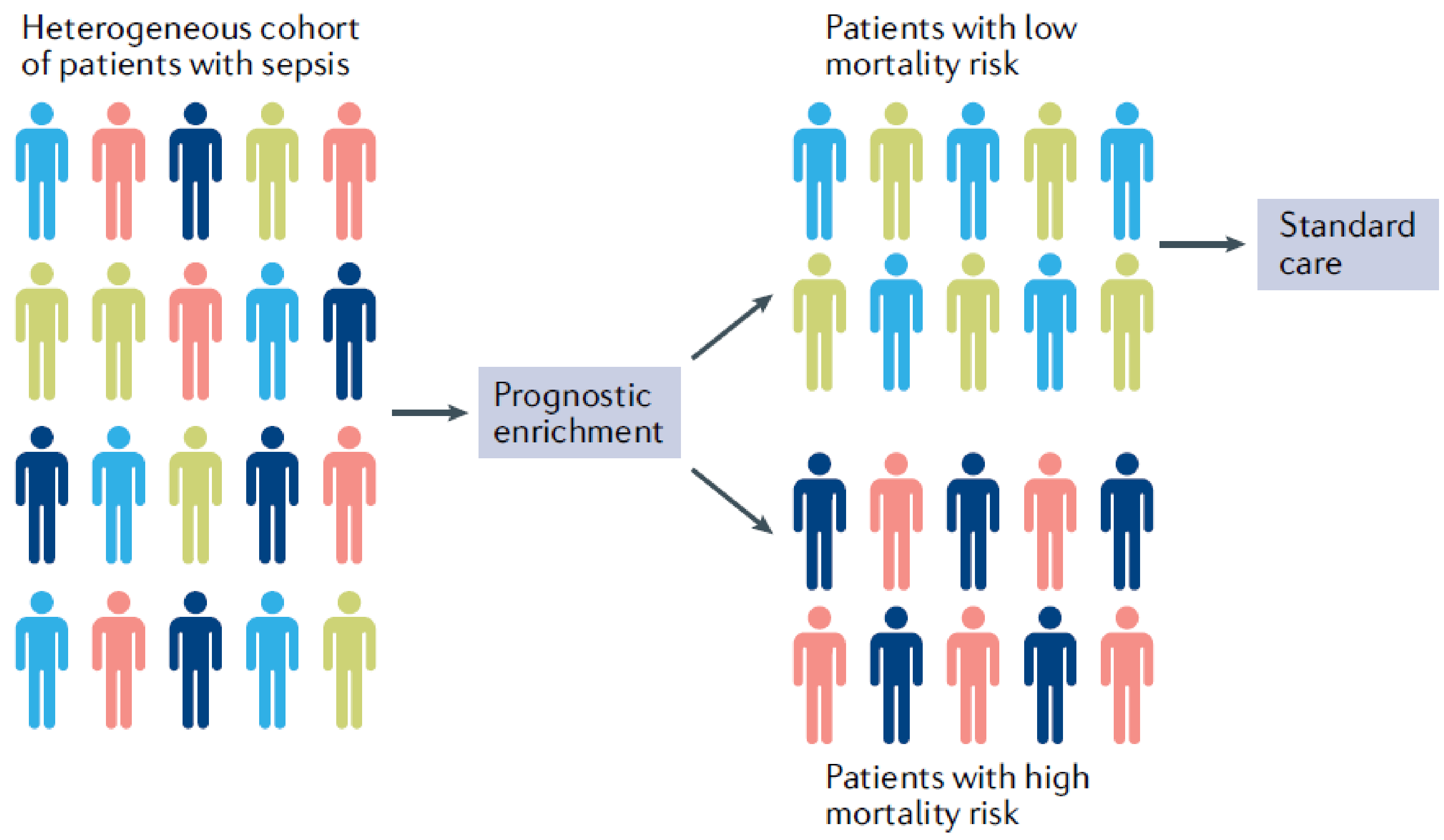


EBP: Extracorporeal Blood Purification

The Global ARRT registry



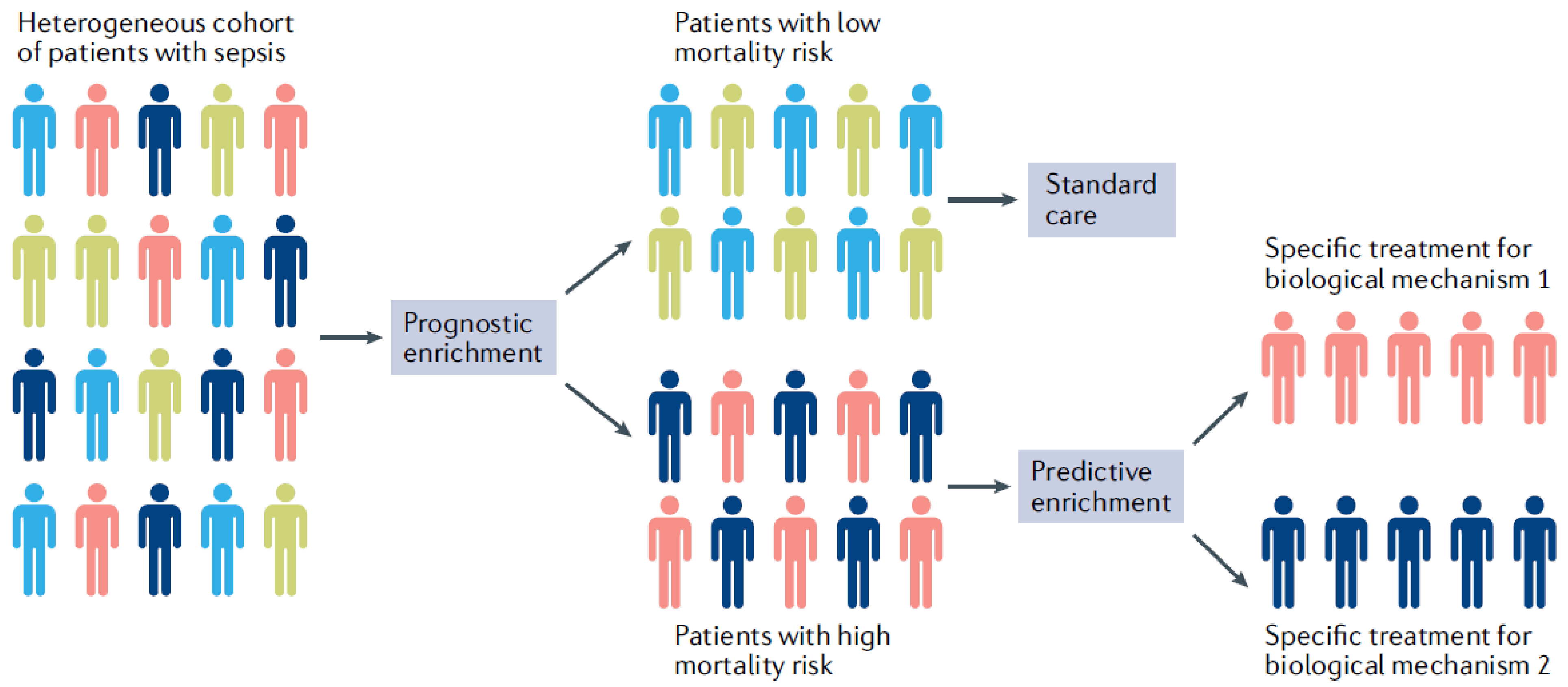
Enrichment strategies to guide therapies in the ICU



To date, perhaps the most well-developed predictive enrichment strategies for ICU patients are based on **gene expression signatures**.

Stanski NL, Wong HR. *Nat Rev Nephrol*. 2020. 20(16); doi: https://doi.org/10.1038/s41581-019-0199-3

Enrichment strategies to guide therapies in the ICU



Unlike prognostic enrichment, the separation of patients for the purposes of predictive enrichment does not necessarily take into account patient demographic characteristics, clinical course or outcomes.

Instead, **predictive enrichment strategies** seek to group patients with the overarching goal of **identifying patients likely to respond to a given therapeutic intervention**.

Stanski NL, Wong HR. *Nat Rev Nephrol*. 2020. 20(16); doi: https://doi.org/10.1038/s41581-019-0199-3

Enrichment strategies to guide EBP in the ICU

Post-hoc analyses of clinical trials

Utilize prognostic and predictive enrichment strategies to re-analyse existing data. These analyses will not provide definitive results but might provide a rationale for further testing of previously failed therapies and inform future clinical trial design.

EUPHAS	Abdominal sepsis
ABDOMIX	Peritonitis-induced septic shock
EUPHRATES	Peritonitis-induced septic shock with EAA>0.6

An **attempt** to apply **single biomarker-based enrichment strategies** to conduct interventional clinical trials in EBP.

Stanski NL, Wong HR. *Nat Rev Nephrol*. 2020. 20(16); doi: https://doi.org/10.1038/s41581-019-0199-3

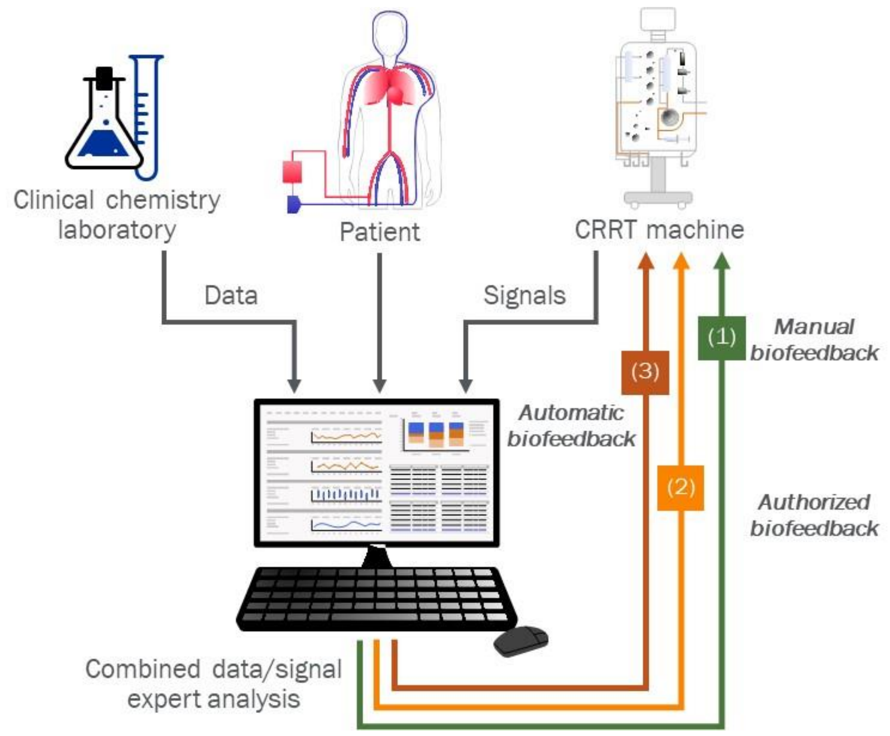
Enrichment strategies to guide EBP in sepsis

Limitations:
- Uncertainty about timing of testing
- Not applicable at bedside
- Delayed response
- Expensive

Cost-effective enrichment prognostic and predictive analyses require pragmatic inputs that should be available (or at least readily obtainable) at the bedside within a reasonable timeframe.

Clinical registries & Artificial intelligence

Are we really capable today of controlling and analysing the multitude of variables that would enable us to target precise treatments in sepsis without the support of artificial intelligence?



Cerdá G, *et al. Blood Purif.* 2016; 46:248–265.

PC-1	
ICU admission for Kidney support	0.31001165036282474
Renal support for acid-base correction	0.23373635934098272
Renal support for metabolic burden control	0.2290216790846635
Cognitive impairment	0.22122205555540925
Mechanical ventilation	-0.2152300150023317
Postoperative admission	0.20858891035730237
Renal support for uremic control	0.19293326138773656
Abdominal infection	0.1848814602038733
ICU admission for Cardiovascular support	0.1829348922425553
PC-2	
Postoperative admission	-0.3017416362661792
Vasopressor requirements	-0.2858552383245631
Norepinephrine dose	-0.2806453582173453
ICU admission for Cardiovascular support	-0.2506387405258913
Renal support for fluid overload	-0.23181072753553797
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Cognitive impairment	0.21810542376346886
Mechanical ventilation	-0.18081938983928478
CKD	0.14744136659968823
Renal support for metabolic burden control	-0.12994565980086148
PC-3	
Renal support for uremic control	-0.39326156737416573
Postoperative admission	0.37499635996009945
Respiratory infection	-0.2917246630889216
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Abdominal infection	0.19277060392079665
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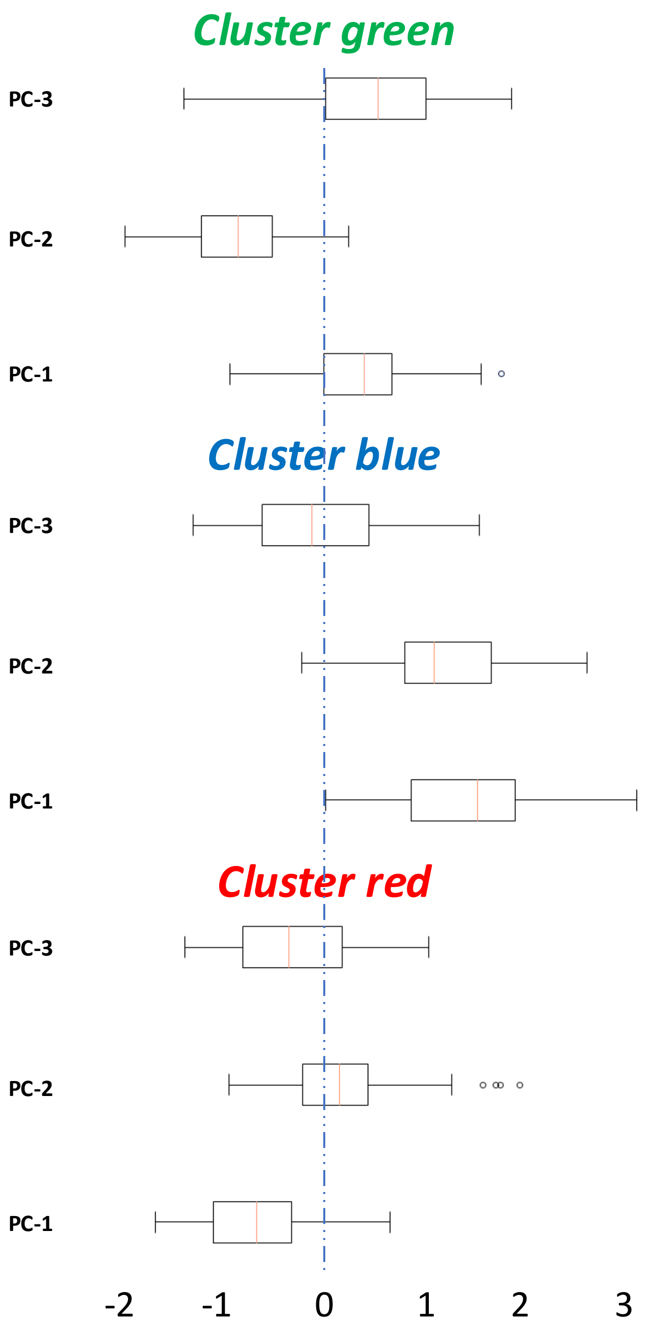
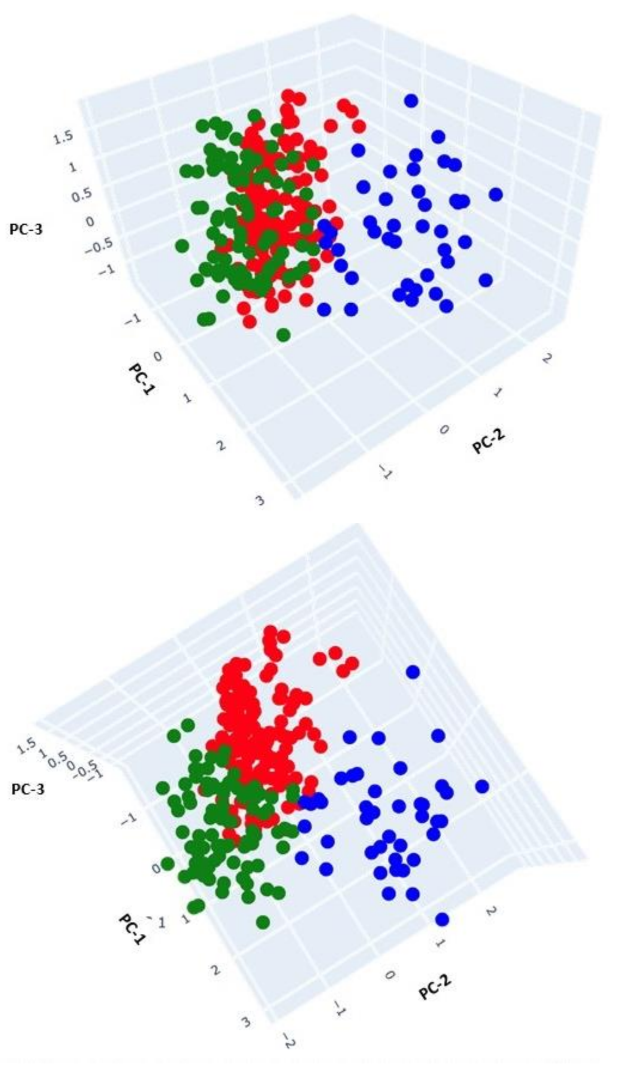
Urea (mg/dl)	-0.11732848592283396

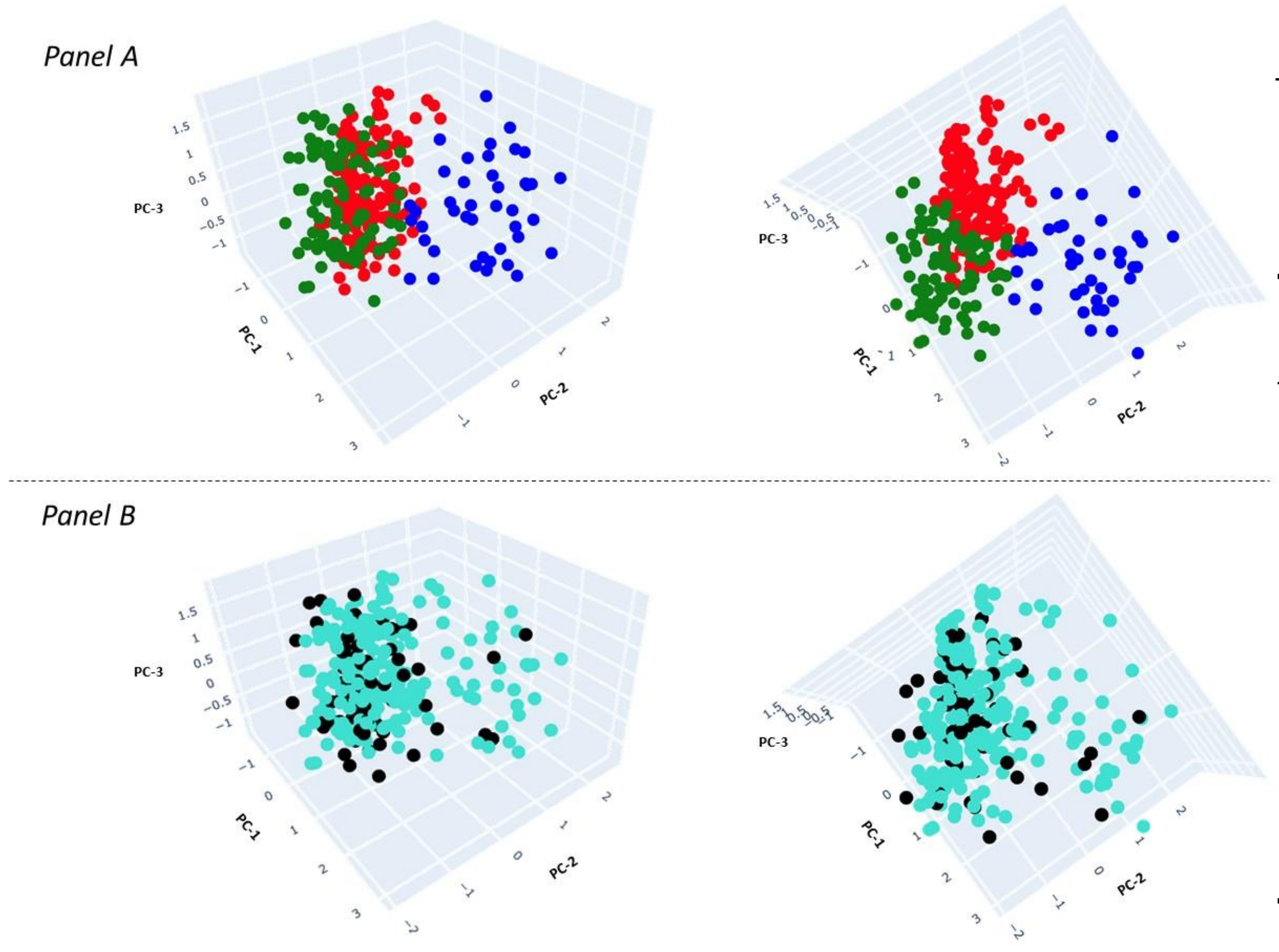
Under review - Critical Care Medicine





Red, Blue and Green cluster are represented using the principal components (PC) of the analysis

Clusters of patients treated with Oxiris & Mortality



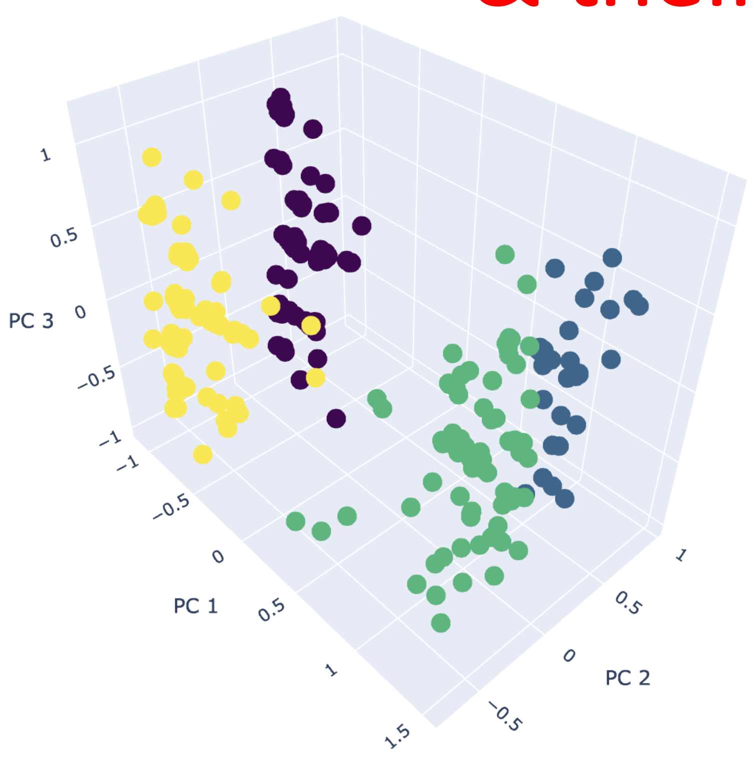
Under review - Critical Care Medicine

	Cl Blue (n=42, 15.2%)	Cl Red (n=146, 52.7%)	Cl Green (n=89, 32.1%)
SAPS II exp. mortality rate	41%	77%	83%
Mortality rate	16.7%	30.8%	21.3%

	Cl Blue (n=42, 15.2%)	Cl Red (n=146, 52.7%)	Cl Green (n=89, 32.1%)
CKD	+	+	--
ICU admission for cardiovascular support	-	-	++
ICU admission for kidney support	++	-	+
Postoperative admission	+	--	++++
Abdominal sepsis	+	--	+++
Respiratory sepsis	+	+	-
Cognitive impairment	+	-	-
Vasopressor requirements	--	-	+++
Norepinephrine dose	--	-	+++
Mechanical ventilation	--	+	+
Urea (mg/dl)	+	+	-
Renal support for acid-base correction	++	-	-
Renal support for metabolic burden control	+	-	+
Renal support for uremic control	++	-	-
Renal support for fluid overload	-	+	+

In Panel A, Red, Blue and Green cluster are represented using the principal components (PC) of the analysis. In panel B, patients who died are represented in black

Clusters of different prescriptions with Oxiris & their association with mortality



	Treatment A	Treatment B	Treatment C	Treatment D
Dead	20,8%	27,6%	30,2%	24,7%

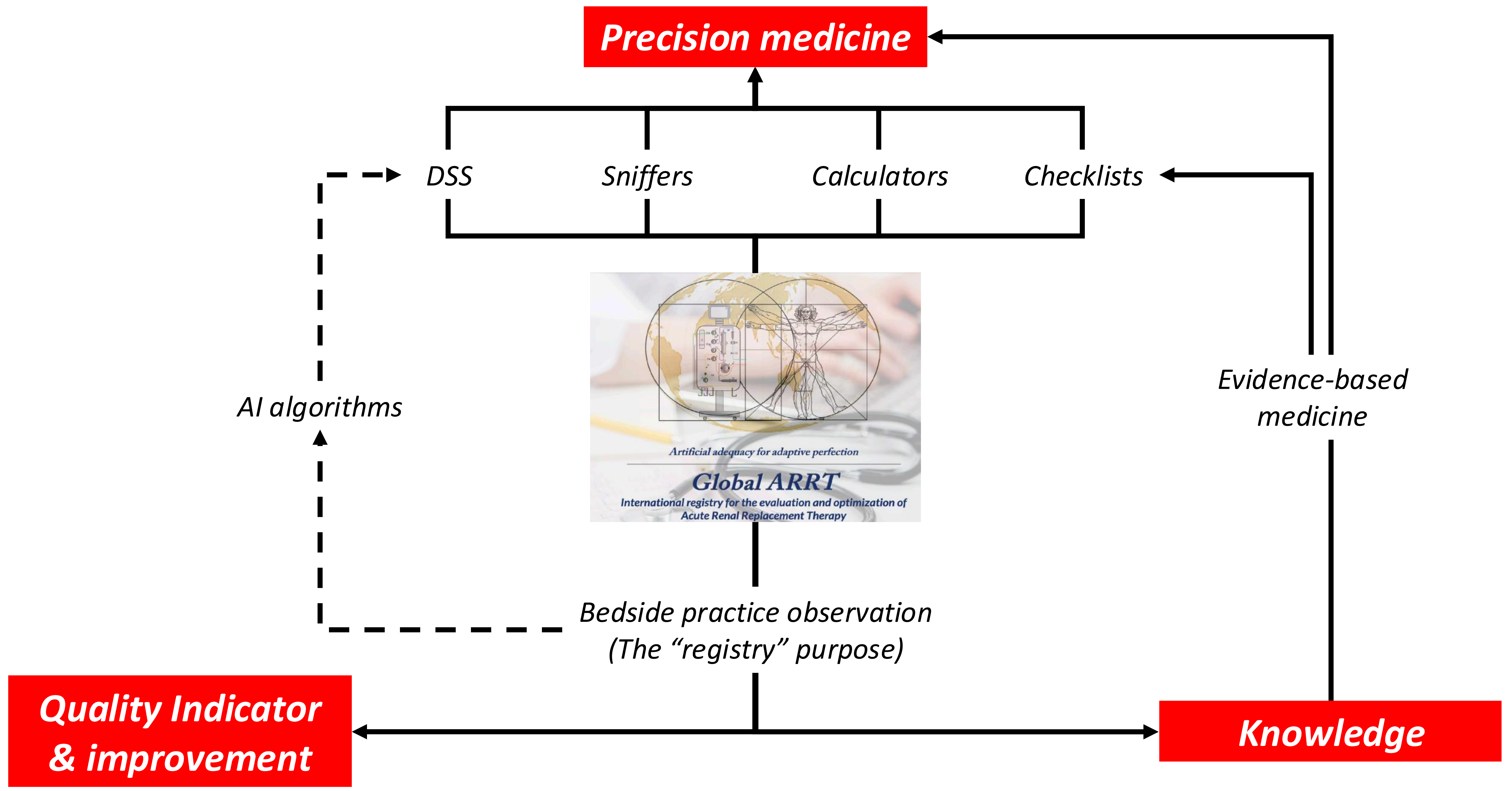
	Treatment A		Treatment B		Treatment C		Treatment D	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
Green	87,5%	12,5%	60%	40%	86,7%	13,3%	85,7%	14,3%
Red	82%	18%	85,7%	14,3%	59,3%	40,7%	66,6%	33,7%
Blue	68,4%	31,6%	70,6%	29,4%	88,2%	11,8%	78,9%	21,1%

Cluster of different prescription with Oxiris are represented using the principal components (PC) of the analysis.

Some signals suggest potential effects of specific treatment clusters on specific patient clusters.

Under review - Critical Care Medicine

The Global ARRT registry



Computational science & In-silico Medicine

Biology and *Medicine*
or
Physics and *Engineering*

Computational methods allow *unprecedented levels of complexity* to be handled;

New sequencing and imaging technologies, and new biomedical technologies in general, allow detailed information about the physiology and pathology of individuals to be measured continuously and non-invasively.

Predict or estimate quantities of a specific patient that would be impossible or very difficult to measure directly.

In-Silico Medicine uses cutting-edge technologies to create computer models of individual subjects that can aid diagnosis, predict prognosis and simulate the effects of available therapies to personalise treatment.

In-silico medical technologies fall into two broad categories:

- Those used to support medical decision-making for an individual patient: **Digital patient technologies**, where computer models are used to support medical decision-making in diagnosis, prognosis or treatment planning;
- Those used to ensure the safety and efficacy of new medical products (drugs or devices): **In-silico Trials technologies**, where computer models are used to reduce the cost, duration and use of animal and human testing.

Viceconti M. *IEEE J Biomed Health Inform*. 2021 Oct;25(10):3977-3982

In-silico in-vivo human study

	Reduce	Refine	Replace
Preclinical In Vitro/Ex Vivo Experiments	Reduce the number or duration of in vitro/ex vivo experiments	Improve the predictive accuracy of safeness and/or effectiveness provided by the in vitro or ex vivo experiment	Replace entirely a portion or all the required in vitro or ex vivo experiments
Preclinical Animal Experiments	Reduce the number of animals involved in the experiment, or its duration	Alleviate the suffering of the animals involved, or improve the predictive accuracy of the safeness and/or effectiveness provided by the animal experiment	Replace animal experiments in the prediction of the expected safety and/or efficacy for a new treatment during the clinical experimentation
Clinical Human Experiments	Reduce the number of humans involved in the experiment, or its duration	Reduce the risks for the humans involved, or improve the predictive accuracy of the safeness and/or effectiveness provided by the human trials	Replace human experiments in the prediction of the expected safety and/or efficacy for a new treatment during real-world, post-marketing use

Viceconti M. *IEEE J Biomed Health Inform*. 2021 Oct;25(10):3977-3982

Before in silico medicine can have its full positive impact, it is essential to complete the digital revolution in clinical information.

This requires ongoing steps:

- The completion of the digitisation of information, including the creation of an appropriate infrastructure (i.e. **Digital Transformation**)
- **Interoperability** among information systems through the mandatory implementation of technical standards;
- The possibility of **clinical data secondary use** (i.e. different from the primary use for which the data were collected) for research and innovation purposes, in compliance with the applicable laws on privacy and ownership of health data.

PC-1	
ICU admission for Kidney support	0.31001165036282474
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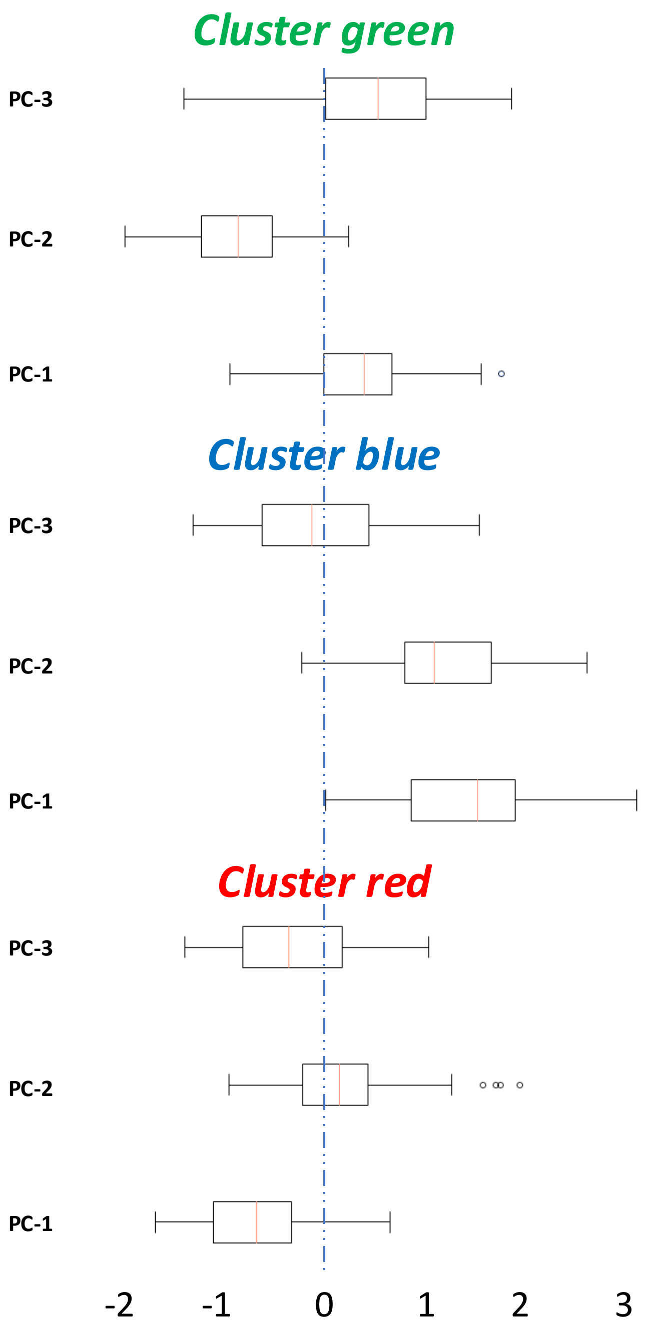
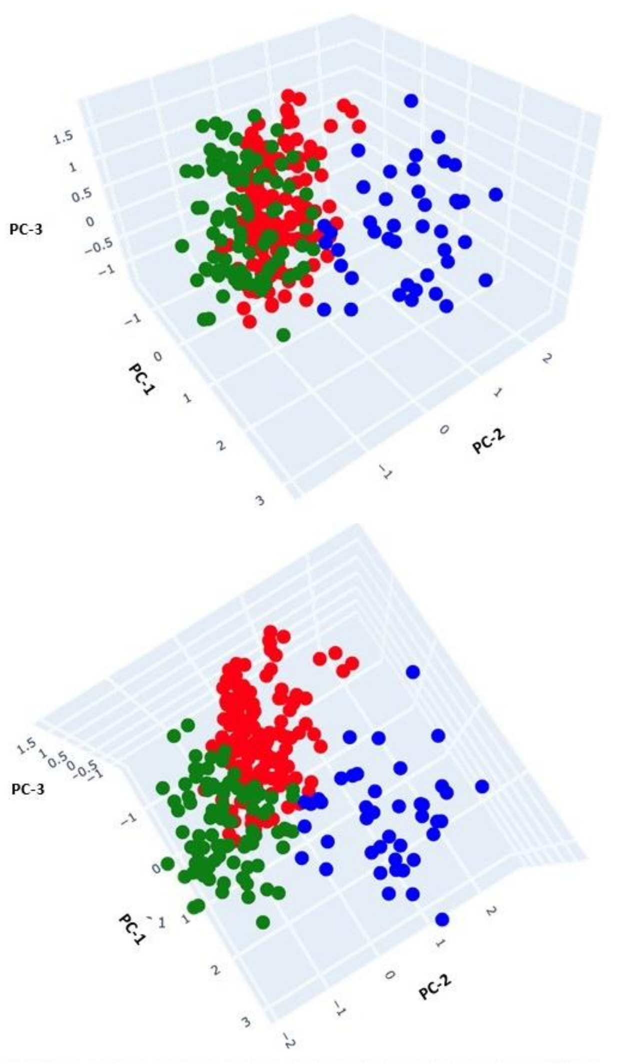
Under submission - ICM

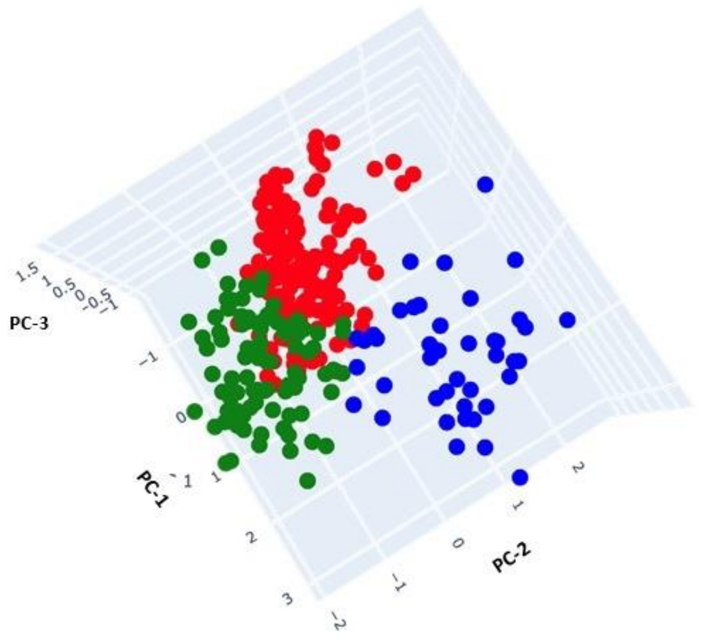




Red, Blue and Green cluster are represented regarding the principal components (PC) of the analysis

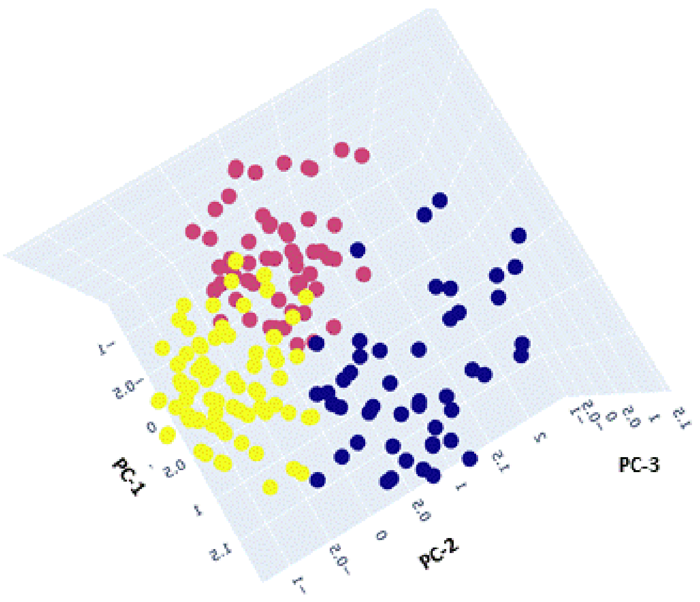
Generating Synthetic Twins

Observed patients



Real (n=277)	Cluster	Synthetic (n=277)
n=89, 32.1%	Cl Green	n=84, 30.3%
n=146, 52.7%	Cl Red	n=145, 52.3%
n=42, 15.2%	Cl Blue	n=48, 17.3%

Synthetic patients



Reproducing the multiple complex **interactions** among variables that persist across patient groups.

Hierarchical construction in which the underlying pathophysiological relationship is paramount and requires robust clinical guidance.

Under submission – ICM exp

Clusters of different prescriptions with Oxiris and their association with patient's outcome

Observed + Synthetic Patients N=554

	Treatment A	Treatment B	Treatment C	Treatment D	
Cl Green	0.30 [0.05-1.94], p=0.21	1.70 [1.25-3.24], **p=0.03**	0.49 [0.04-5.53], p=0.56	-	3.96 [0.78-20.09], p=0.10
Cl Red	0.29 [0.05-0.70], **p=0.02**	0.52 [0.06-4.71], p=0.56	1.07 [0.10-11.17], p=0.95	-	3.36 [0.74-15.27], p=0.12
Cl Blue	-	-	-	-	ref
	3.00 [0.59-15.26], p=0.19	2.25 [0.27-18.92], p=0.46	2.00 [0.24-16.61], p=0.52	ref	

Signals that should be considered in designing future comparative trials to refine the inclusion criteria, reduce the sample size to a realistically achievable population and define the "prescription" to be evaluated.

Is it ethical to ignore the potential of AI in clinical research?

Under submission – ICM exp

AI in health care

...from big problems come great opportunities...

Transformative impact

- Improvement of treatments
- Reduction of medical errors

AI in medicine: opportunities

- Analysis of clinical big data
- Tools for accurate and rapid diagnosis
- Clinical Decision Support Systems (CDSS)
- Development of new drugs

...with great power comes great responsibility...

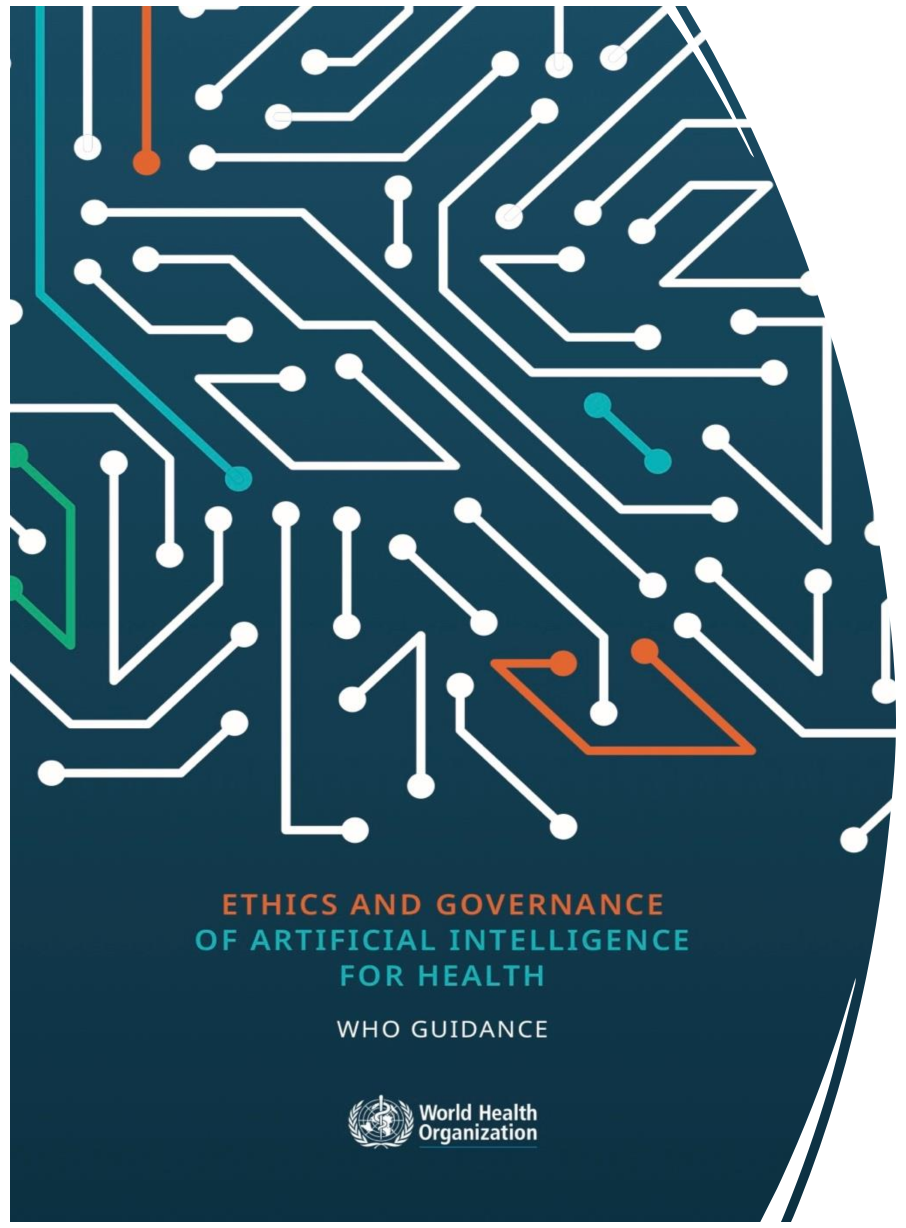
Risks

- Amplified health inequalities.
- Loss of patient dignity.

Ethical responsibilities

- How to protect patient data?
- Can AI negatively influence medical choices (and autonomy)?
- Non-transparent systems can undermine the trust in the doctor-patient relationship.

Balance between Innovation and Human Values



A WHO warning:

- AI should prioritize the patient, ensuring that **dignity**, **health**, and **privacy** are the core drivers of innovation

Proposed solutions:

1. Regulations to avoid human rights violations.
2. Ensuring equity in treatment.
3. Ethical design of AI systems

1. Regulations to avoid human rights violations

The Privacy Challenge

Opportunities:

- Health data is essential for developing predictive models that can save lives.
- EHRs (electronic health records) feed advanced algorithms.
- A valuable resource, that presents complex ethical dilemmas.

Ethical issue:

- Protecting human dignity and well-being.
- Risk of abuse without adequate safeguards.

WHO recommendations:

- Oversee the collection and utilization of data.
- Balancing privacy and innovation.

Data protection & patient protection

Balancing privacy and innovation

- **Data protection:** Essential for ensuring privacy and security, yet may restrict access to data vital for developing life-saving algorithms.
- **Protecting patients:** Ethical priority is to improve clinical outcomes and ensure equity.
- **Balance needed:** While data protection is important, it should not be viewed as an absolute value; rather, it should serve broader ethical principles, such as safeguarding human dignity and well-being.

2. Ensuring equity in treatment

Stigma and inequalities

Problem of stigma:

- Predictive algorithms for genetic or mental illnesses.
- Risk of discrimination in access to care.
- Patients deemed 'at risk' may be excluded from insurance coverage.

Ethical objective:

- Prevent AI from amplifying inequalities.
- Fair treatment and respect for human rights.

When data perpetuates inequalities

- Algorithms for anesthetic dosage may not adequately account for patients of diverse ethnicities or physical characteristics, increasing the risk of complications.
- Similarly, radiological diagnosis algorithms have shown errors in results for non-Caucasian patients due to training data being predominantly based on white patients

Algorithms must be validated and tested on large, representative samples to minimize bias and reduce the risk of incorrect diagnoses or treatments

3. Ethical design of AI systems

Tools for a Safe and Ethical AI

Emerging technologies:

- Blockchain to track and protect data.
- Decentralised structure guaranteeing integrity and security.

Monitoring and regulation:

- Regular ethical and technical audits.
- Continuous monitoring to prevent abuse.

A balanced approach:

- Involve experts to balance innovation and protection of rights.
- Ethical planning at an early stage.

3. Ethical design of AI systems

Algorithmic fairness

Algorithms and their outcomes are unbiased and that they don't discriminate against individuals or groups based on sensitive attributes

Inclusive validation:

- Test on large and representative samples.

Control instruments:

- Algorithmic fairness audits.
- Domain adaptation techniques.

Ethical priority:

- Design inclusive systems at an early stage to avoid inequalities.

3. Ethical design of AI systems

Improve AI explainability

Explainable AI (XAI):

- Techniques that increase the transparency of AI models.
- It makes decision-making processes interpretable, improving the confidence of doctors and patients.
- Objective: to balance comprehensibility and precision without creating excessive complexity.

3. Ethical design of AI systems

Transparency

Detailing the source code, database, data inputs and analytical approaches

Transparency as an Ethical Principle:

- Complete documentation of the development and use of the algorithms.
- Critical human supervision to mitigate 'black box' risks

Benefits of Transparency:

- Trust in AI systems.
- *Accountability* in diagnosis and treatment.
- Safeguarding patients' rights.

Crucial Role in Medicine:

- Access and understanding for patients and doctors.
- Promoting equity and security.
- Overcoming the problem of trust with an ethical and explainable AI.

Algorithmic fairness

Discover Artificial Intelligence

Discover

Comment

The urgency of an algorethics

Paolo Benanti[1]

Received: 2 February 2023 / Accepted: 21 March 2023
Published online: 27 March 2023

Algorethics is a new branch of ethics that focuses on the moral aspects of algorithms and artificial intelligence systems. The word algorethic is a combination of algorithm and ethics coined by Paolo Benanti, professor of moral theology and bioethics at the Pontifical Gregorian University in Rome.

The concept establishes the **'rules of the game'** to ensure that AI systems are aligned with human values and social norms, promoting accountability, fairness and transparency.

Integration of ethical principles into algorithm development

Fundamental **principles** of Algorethics:

- ***Human-in-the-Loop (HITL):*** Ensure that human control remains central at every stage of the decision-making process.
- ***Algorithmic Stewardship:*** Establishing clear guidelines for the responsible use of AI, promoting transparency and fairness.
- ***Adaptability:*** Algorithms must be flexible and adapt to different contexts to meet local needs.

Principles of Algorethic

The main **requirements** of algorethics :

- **Human-Centered:** AI should enhance, not replace, human decision-making. It must maintain a degree of uncertainty by providing information on the accuracy and precision of its estimates, ensuring that human intervention remains integral to the decision-making process and preventing complete reliance on AI.

- **Adequacy:** The primary goal of AI in healthcare should be to align with and prioritize the best interests of the patient. The algorithm's focus must reflect patient needs, ensuring that AI addresses specific, meaningful problems while optimizing the use of limited resources.

- **Traceability:** Transparency is crucial; every step of the algorithm's development, from creation to validation, must be documented. The applicability of the AI, its results, and the development process should be clearly outlined in a standardized datasheet.

- **Customization:** AI algorithms should move away from a 'one-size-fits-all' approach, adapting to the diverse needs of both healthcare professionals and patients.

Operational proposals

Establishment of third-party bodies to verify IAs' compliance with ethical guidelines.

Proposal for a Regulation of the European Parliament and of the Council

LAYING DOWN HARMONISED RULES ON ARTIFICIAL INTELLIGENCE (ARTIFICIAL INTELLIGENCE ACT) AND AMENDING CERTAIN UNION LEGISLATIVE ACTS

EU Artificial Intelligence Act

An historic step for the European Union

- **Origin:**
  - Proposed by the European Commission (April 2021).
  - Final approval: European Parliament (March 2024), EU Council (May 2024).
- **Objective:**
  - Regulate the development and use of AI with legally binding regulations.
  - Ranking AI systems according to risk to security and citizens' rights.

Planned entities:

- IA Office: Monitoring and Compliance.
- European Artificial Intelligence Council: technical support.

National authorities:

- Designated in each Member State.
- Third-party conformity assessment for high-risk systems.

Local integration:

- Creation of **CAIDs** (Clinical AI Departments) for accountable governance in healthcare.

Conclusion: The Centrality of Ethics in Medical AI

Artificial intelligence has great potential to improve diagnosis, treatment, and healthcare processes. However, its development must be guided by strong ethical principles that protect patient dignity, safety, and rights.

Balancing Innovation and Human Rights
We must balance technological progress with fundamental human values, ensuring data privacy and preventing discrimination so that AI reduces inequalities.

Transparency and Human Control
Trust in AI relies on transparent and interpretable algorithms. Methods like Explainable AI and the Human-in-the-Loop approach are essential for maintaining human oversight.

Inclusiveness and Clinical Validity
Algorithms should be designed with representative data from diverse populations to ensure fairness. Continuous monitoring and ethical audits are necessary to address potential biases.

Importance of Regulation
Regulatory frameworks, such as the European AI Act, are crucial for the responsible use of AI. These regulations must be adaptable to promote equitable healthcare for all.

In summary, ethical integration of AI in healthcare is essential for ensuring that technology enhances human well-being.