PERMIT Workshop

Scoping review on machine learning methods for stratification

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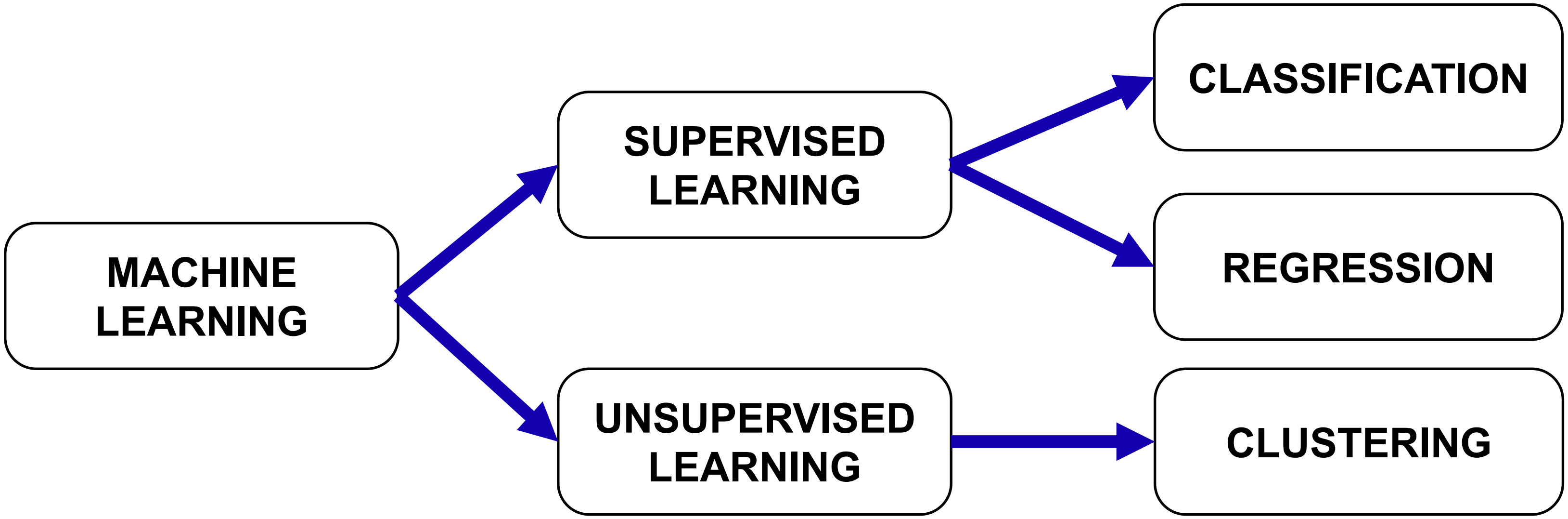
Scoping Review Objectives

GOALS:

- Inventory AI methods for omics-based patient stratification and their validation (supervised and unsupervised ML approaches)
- Identify limitations, challenges, gaps and existing recommendations



Research Questions

Machine learning methods for stratification:

- What are the main types of supervised and unsupervised ML methods for omics-based stratification? What are the recommended workflows?
- What are the specific strengths/weaknesses of different stratification approaches?

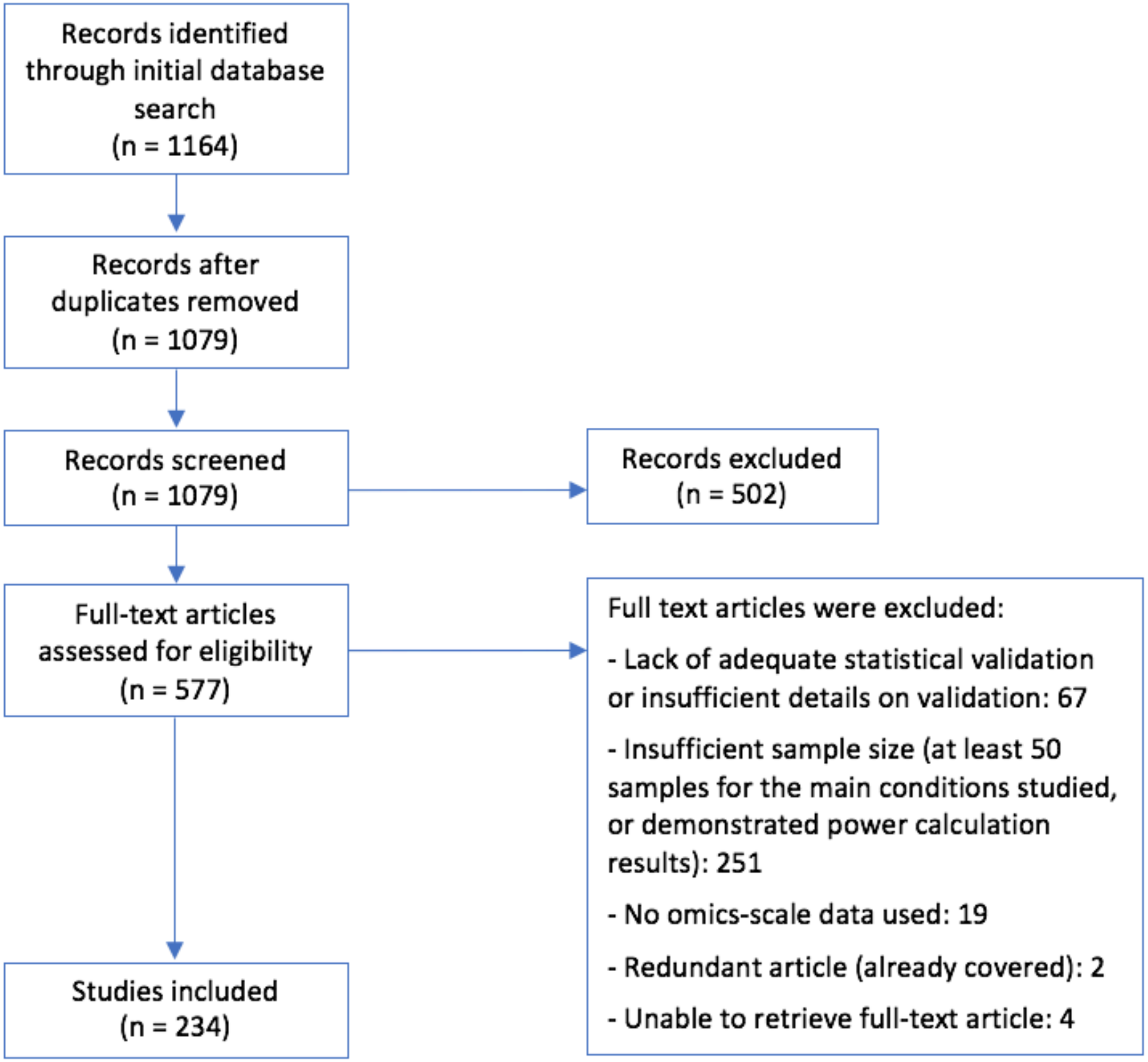
Validation methods:

- Which validation methods are available to assess accuracy, robustness and biomedical relevance? What are their strengths/weaknesses?

Applications:

- Which practical utility has been demonstrated in real-world settings (success/failure stories, lessons learned)?

Scoping Review Results: PRISMA flow diagram



Records identified through initial database search (n = 1164)

Records after duplicates removed (n = 1079)

Records screened (n = 1079)

Records excluded (n = 502)

Full-text articles assessed for eligibility (n = 577)

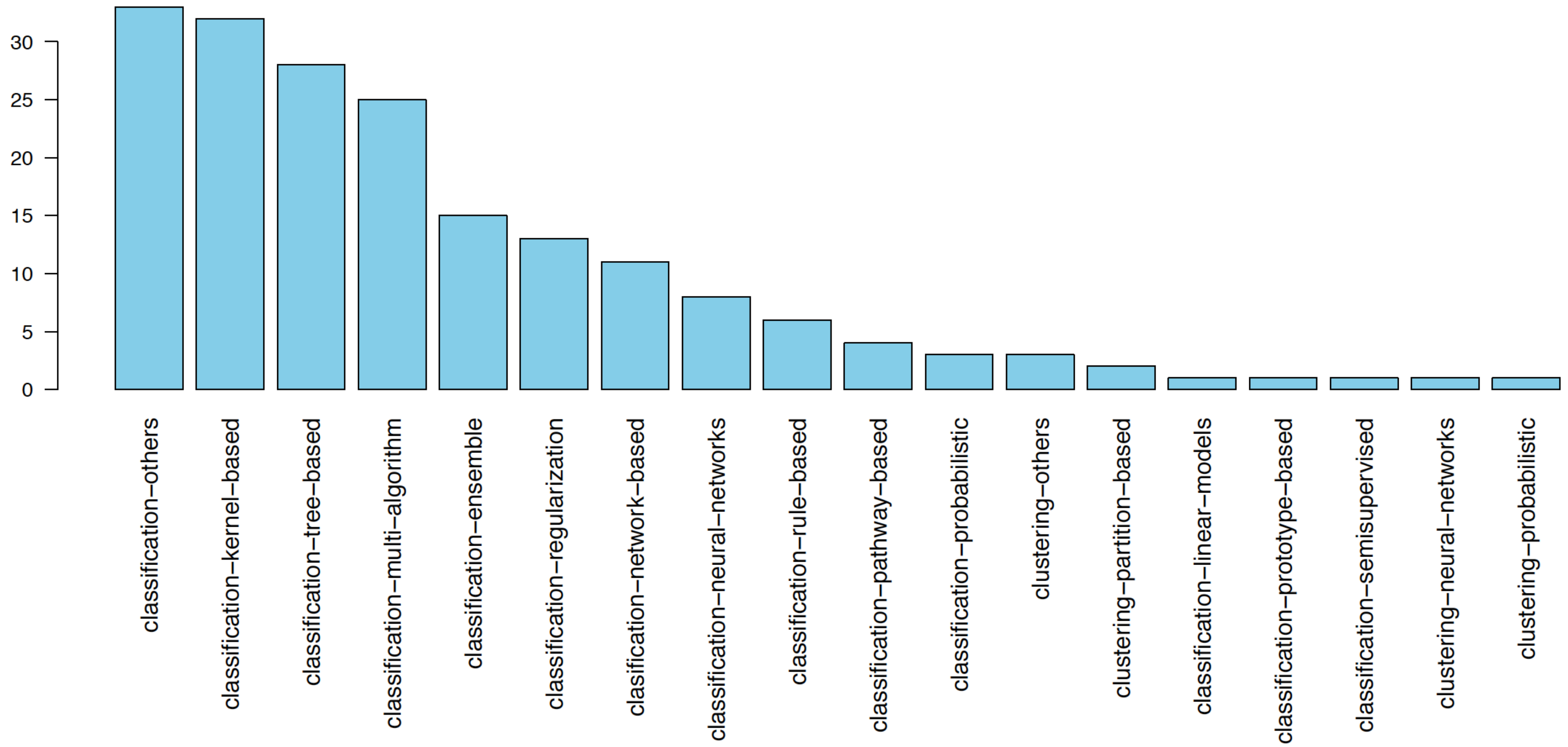
Full text articles were excluded:

- Lack of adequate statistical validation or insufficient details on validation: 67
- Insufficient sample size (at least 50 samples for the main conditions studied, or demonstrated power calculation results): 251
- No omics-scale data used: 19
- Redundant article (already covered): 2
- Unable to retrieve full-text article: 4

Studies included (n = 234)

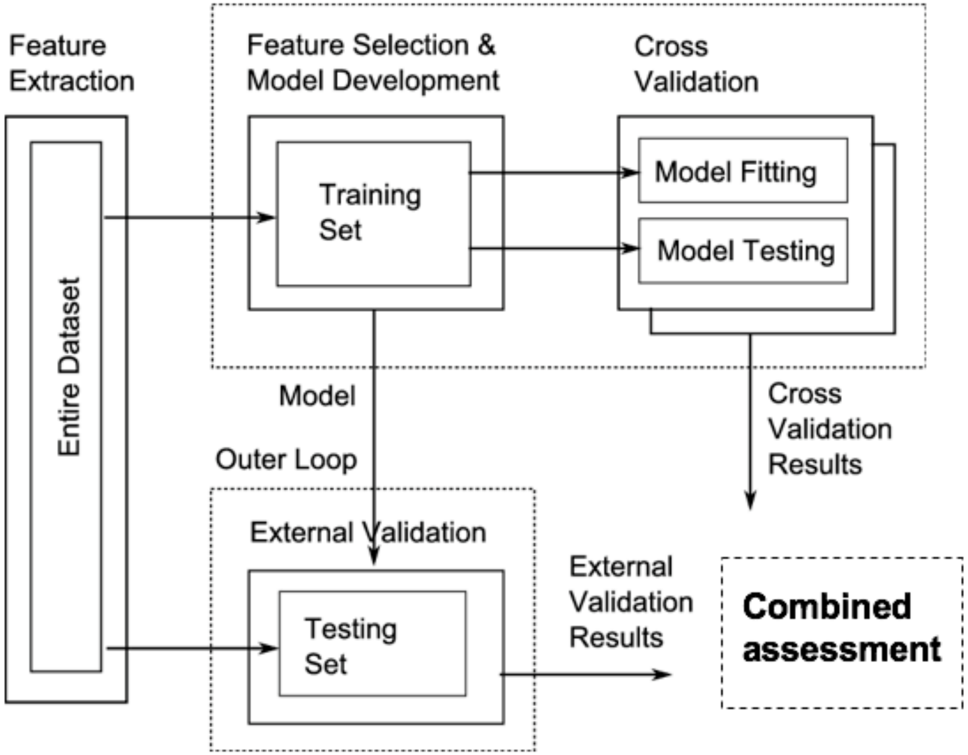
Results: Used ML methodologies

- Over-represented approaches: Tree- and kernel-based ML methods
- Under-represented approaches: Probabilistic, prototype-based and neural network based ML methods



Results: Used validation methodologies

- Common methods: Training/test set split + cross-validation on training data (LOOCV, 10-fold CV), metrics: accuracy, AUC
- Less frequent: External cohort validation, robust bootstrapping and & bolstered CV approaches, metrics: F1, MCC, PR-AUC



Main gaps & limitations identified (1)

Study design and documentation related issues:

(1) study group design and sample size selection

(underpowered, imbalanced)

(2) statistical evaluation

(robustness/completeness, multiple hypothesis testing)

(3) clarity of clinical applications

(primary/secondary outcomes)

(4) study documentation

(settings/parameters, reproducibility)

Main gaps & limitations identified (2)

Issues affecting model reliability, robustness and interpretability:

(5) Sampling & blocking design
(batch effects and biases)

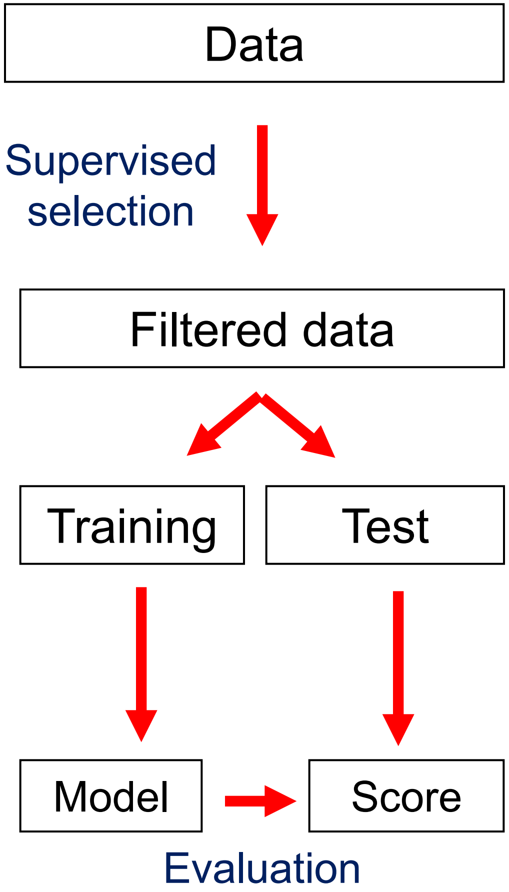
(6) data pre-processing, filtering and normalization
(lacking standards)

(7) integration of prior biological knowledge
(pathway/network knowledge, multi-omics analyses)

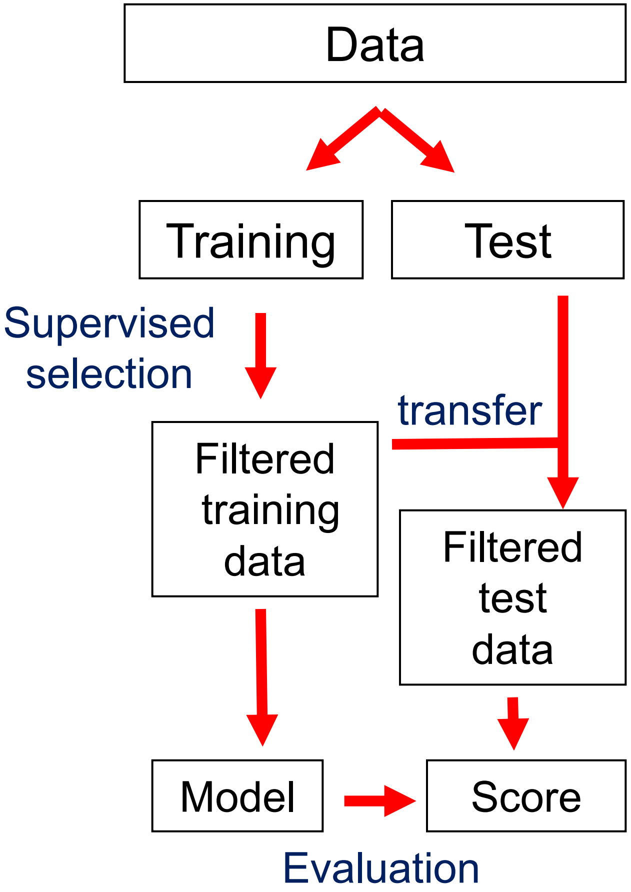
(8) Ensuring model interpretability and biological plausibility
(black-box vs. white-box models)

Gaps & limitations: Example

Common error: Global feature selection



Correct approach



Recommendations from the scoping review / literature

Data pre-processing, filtering & normalization:

→ use cross-validation to check if pre-processing leads to information loss

→ compare or combine multiple pre-processing approaches

Integration of prior knowledge & multi-omics analyses:

→ check prior literature on the cost/benefit of multi-omics analyses for the studied conditions / cell types, or conduct pilot analyses

→ use existing software & frameworks for integrative biological data analysis

Ensuring model interpretability & biological plausibility:

→ use dedicated methods to build interpretable models (e.g. rule learning)

→ use cellular pathway/network analysis & literature mining to guide modeling

Previous success stories

- Multiple omics-derived biomarker signatures already clinically validated
- Most tests are for cancer diseases, but first non-cancer applications exist

Name	Test approval (FDA-cleared and/or LDT)	Purpose	References
MammaPrint	FDA-cleared, LDT	breast cancer risk-of-recurrence assessment	Van't Veer et al., Nature, 2002
AlloMap Heart	FDA-cleared, LDT	identifying heart transplant recipients with risk of cellular rejection	Yamani et al., J Heart Lung Transplant, 2007
Prosigna Assay / PAM50	FDA-cleared, LDT	breast cancer risk of distant recurrence prediction	Nielsen et al., BMC Cancer, 2014
Oncotype DX	LDT	breast cancer risk-of-recurrence assessment	Kelley et al., Cancer, 2010
Decipher	LDT	prostate cancer metastatic risk prediction	Marrone et al., PLoS Curr., 2015

Previous success stories – Main conclusions

Shared characteristics of prior success stories as a guideline:

- Early filtering:
  rigorous statistical, clinical and biological filtering criteria applied (strict inclusion/exclusion criteria; multiple layers of statistical and ML-based feature selection; integration of prior knowledge)

- Continuous technological improvements:
  transition from cheap, low-sensitivity to high-sensitivity measurements (e.g. from microarray technology to deep sequencing, RT-PCR and digital PCR)

- Robust validation schemes:
  multi-level cross-validation, bootstrapping and external validation involving multiple performance metrics, large sample sizes, and multiple cohorts

Summary

Main gaps & limitations:

→ study design: many studies are underpowered, imbalanced

→ statistical validation: often incomplete, lacking robustness or even incorrect

→ study documentation: lack of details, irreproducible

Main proposed recommendations:

→ follow existing study design & documentation guidelines (e.g. NCI check list)

→ use robust validation schemes & early filtering

→ exploit prior biological knowledge & existing data integration frameworks

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