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AI for patient stratification: Challenges and recommendations

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 874825

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Overview

- **Introduction**: AI for stratification – definitions, applications & workflows
- **Challenges**: Gaps and limitations in AI-based patient stratification
- **Recommendations 1**: Study design & planning
- **Recommendations 2**: Discovery & optimization
- **Recommendations 3:** Validation & interpretation
- **Example use cases / success stories**

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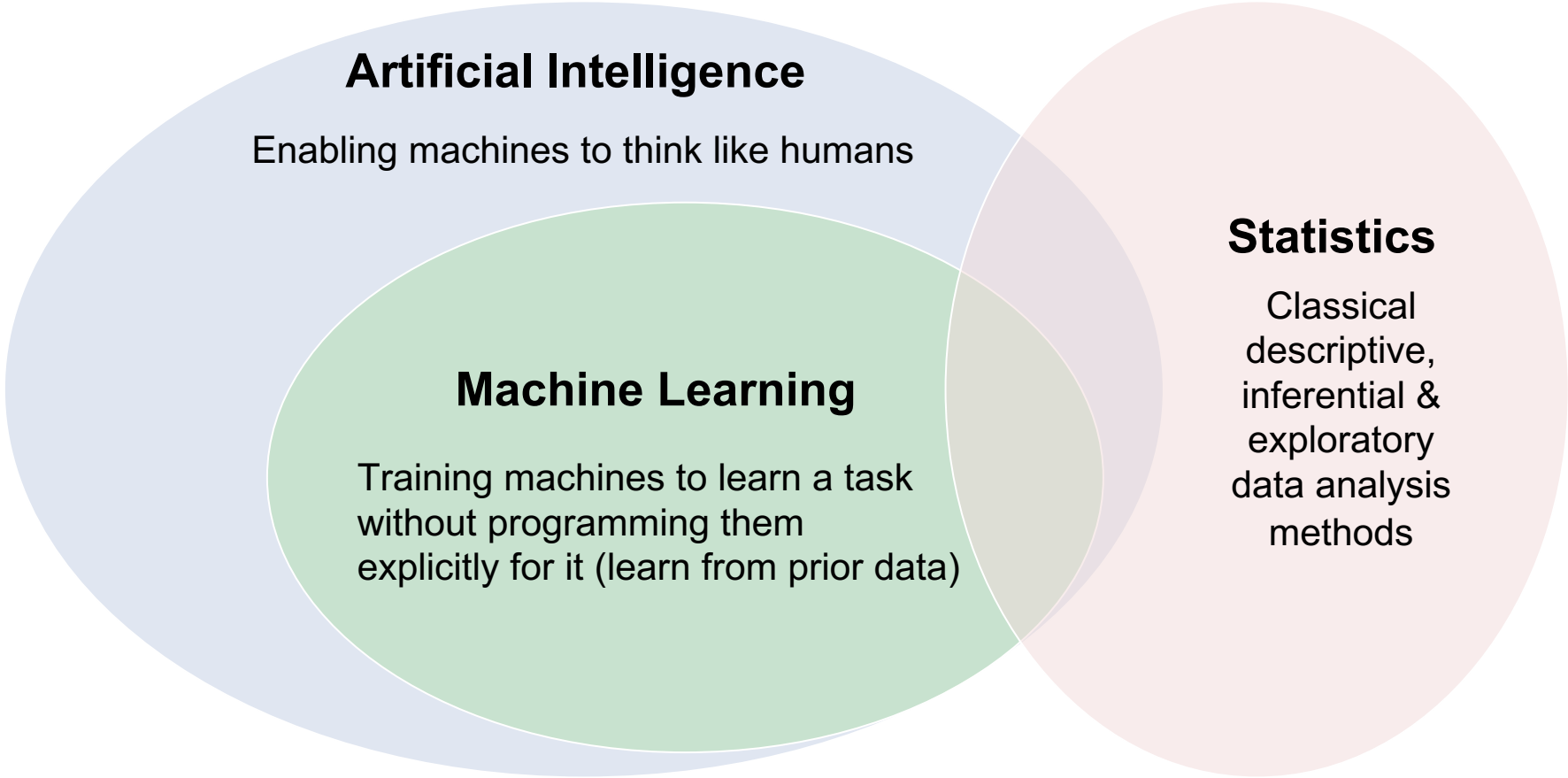
Definition: AI vs. classical statistics



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Applications: AI for patient stratification

AI algorithms have several applications in biomedical stratification:

- **Risk stratification** → differentiate between risk categories 
- **Diagnostic stratification** → differentiate between diseases & sub-types 
- **Prognostic stratification** → predict future diseases trajectories & outcomes 
- **Treatment / trial placement** → recommend the right treatment / clinical trial for each patient 

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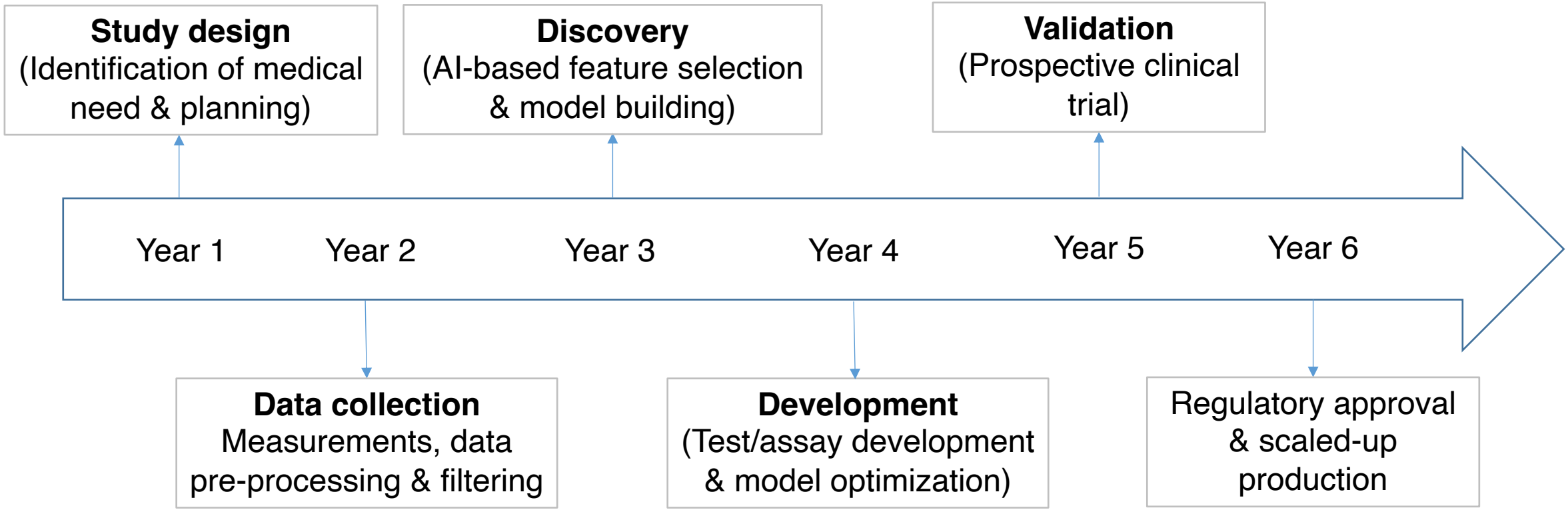
Typical workflow



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Gaps and challenges

(1) study design and sample size selection

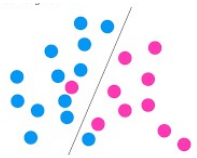
→ underpowered studies, imbalanced study groups, dropouts

(2) data pre-processing, filtering and normalization

→ inadequate choice of approaches, lack of standards

(3) model building (algorithm selection, parameter choice/optimization)

→ modeling approach not suitable for input data, overfitting or underfitting



(4) model optimization & calibration

→ biased parameter selection procedures, missing calibration step

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Gaps and challenges

(5) integration of prior biological knowledge

→ relevant prior data ignored, ineffective data integration methods

(6) model performance assessment

→ inadequate evaluation methods & performance metrics, lack of robustness

(7) validating model performance

→ cohort-specific biases, choice of suitable validation schemes

(8) ensuring model interpretability and biological plausibility

→ use of black-box instead of white-box modeling methods

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Recommendations (1)

1) Planning phase

Challenge/Risk/Gap	Recommendations
Insufficient sample size / study underpowered	• Pilot study for prior sample size estimation • Algorithmic biospecimen matching & selection methods • Integration of complementary biological data to increase power
Imbalanced study groups	• Detailed prior plan for further subject recruitment • Address class imbalance in the modeling (e.g., weighting, under-sampling)
Dropouts in longitudinal studies	• Detailed prior plan for further subject recruitment • Address dropouts in the modeling phase (e.g., bias checks) • Carefully consider possible causes of missing data with domain experts

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Recommendations (2)

2) Discovery & modeling phase

Challenge/Risk/Gap	Recommendations
Inadequate data pre-processing	• Apply quality control analyses before and after data pre-processing • Assess distribution assumptions using statistical tests • Apply pre-processing techniques tailored specifically to observed distributions
Modeling approach is not suitable	• Compare multiple modeling approaches using a cross-validation • Consider combining multiple learning approaches (ensemble learning)
Model is too complex or too simple (overfitting or underfitting)	• Adjust model complexity (regularization) and optimize using a cross-validation • Combine feature selection methods with subsequent learning algorithms

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Recommendations (3)

3) Validation phase

Challenge/Risk/Gap	Recommendations
Validation is not robust enough	• Consider both the discovery and validation study in the sample size estimation • Use robust cross-validation methods and multiple performance metrics
The predictive model does not generalize across different cohorts / populations	• Consider a meta-analysis of datasets from other cohorts for feature selection • Plan an external validation on a distinct cohort / population
Insufficient model interpretability	• If model interpretability is required, choose "white-box" learning algorithms • Use structured machine learning approaches guided by prior biological knowledge from cellular pathways and networks to build interpretable models

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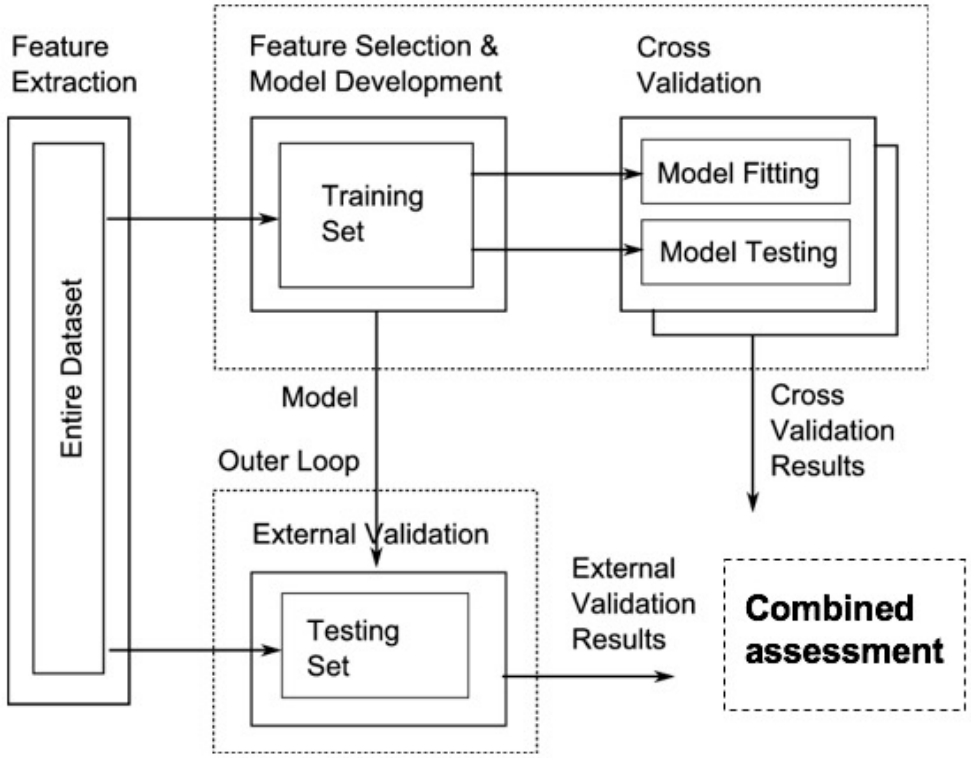
Recommendations (4)

→ Use robust and reproducible model building & validation frameworks



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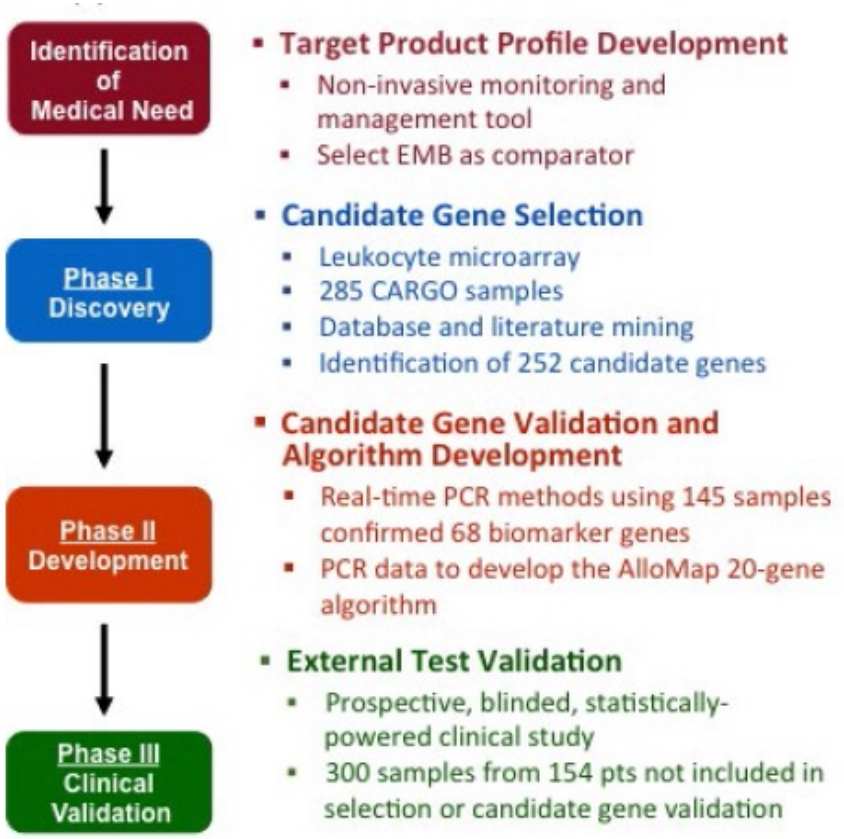
Example use cases (1)

AlloMap® signature: Predict risk of heart transplant rejection

- Knowledge-guided biomarker discovery: combine prior pathway knowledge with statistical analyses

- Rigorous multi-stage validation: sensitive rtPCR validation + statistically powered external testing



(source: Deng, J Clin Transl Res, 2016)

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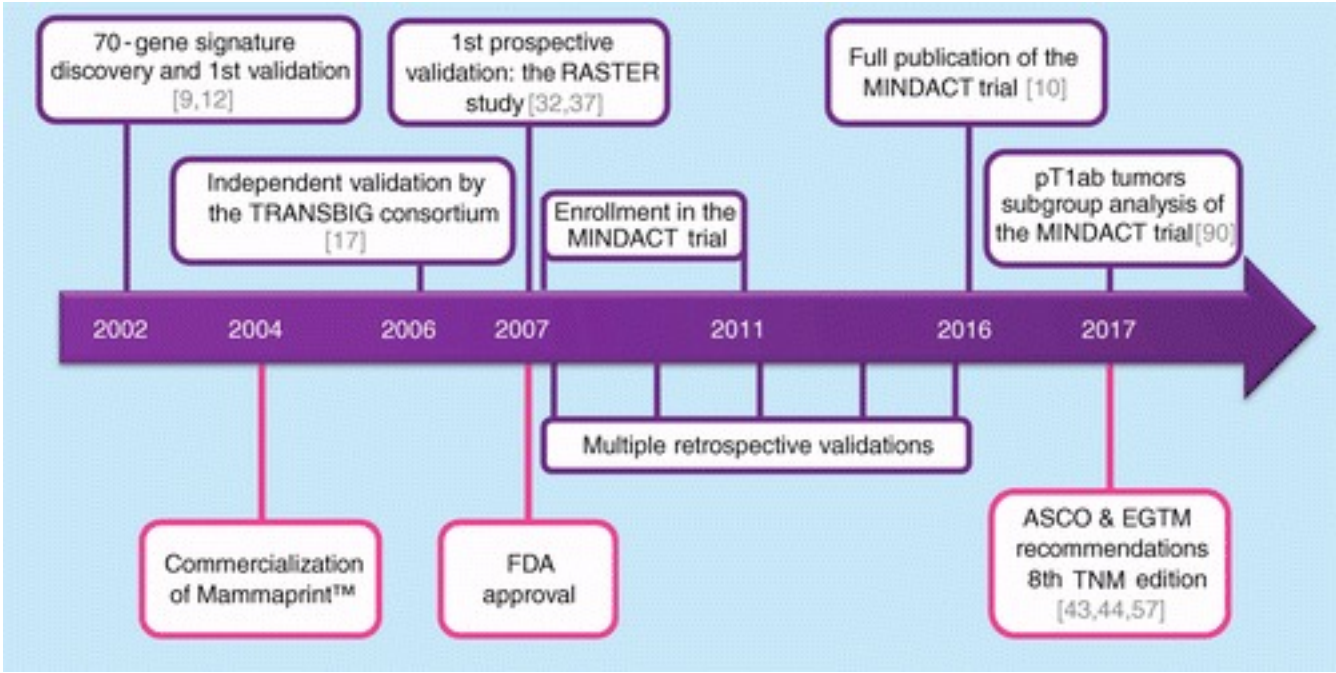
Example use cases (2)

MammaPrint® signature:
Estimate breast cancer risk of recurrence

- Early and stringent filtering procedure: Reducing candidate predictive features from 25k to a signature of 70 genes

- Robust external validation: Several independent validation studies on external cohorts with large sample sizes



(source: Brandão et al., Future Med., 2019)

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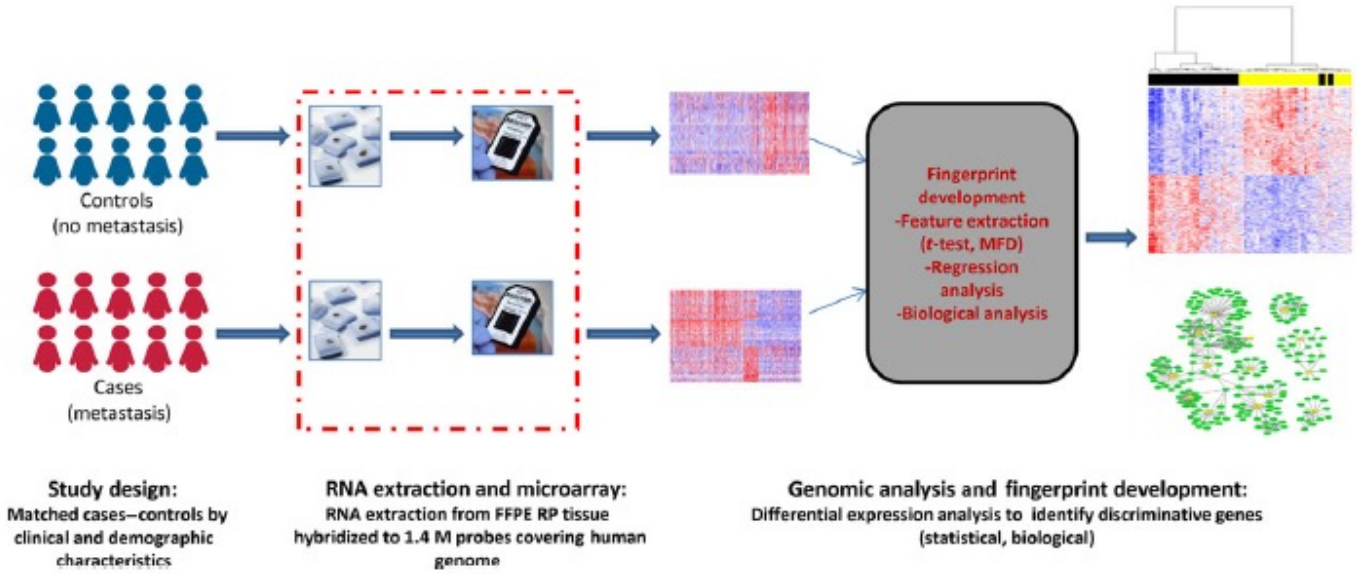
Example use cases (3)

Decipher® signature: Predict prostate cancer metastatic risk

- Combined statistical and bioinformatics analyses: Statistical + AI-based selection of predictive genes & biological filtering (pathway enrichment + network analyses)

- Robust discovery & validation: High statistical power & multiple distinct cohorts involved



(source: Alshalalfa et al., Biol. Cell, 2015)

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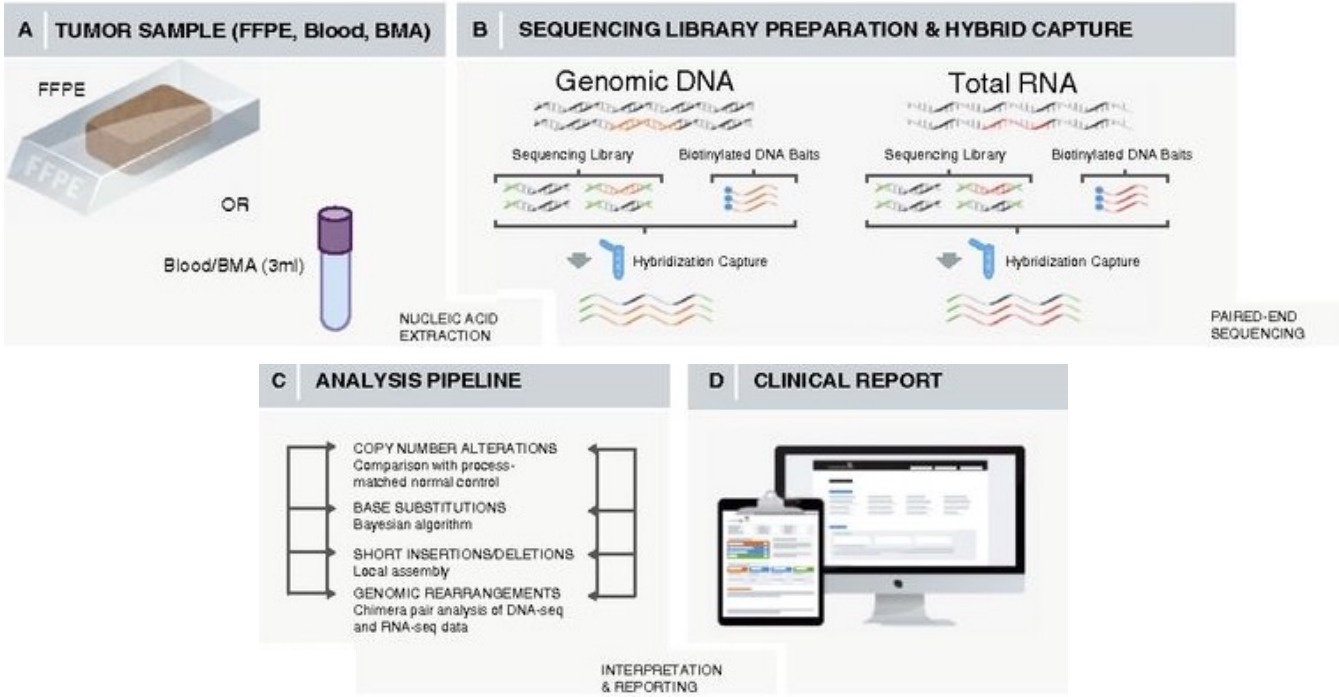
Example use cases (4)

FoundationOne™ Heme test:
Detect malignancies or solid tumours

- Integrating complementary information sources:
  Combines data from both RNA and DNA sequencing

- Result interpretability:
  Prior knowledge and data used to facilitate test result interpretation



(adapted from: He et al., Blood, 2016)

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Summary & Conclusion

Common gaps & limitations:

→ study design phase: many studies are underpowered, imbalanced, suffer from dropouts

→ model building phase: inadequate choice of methods, overfitting or underfitting

→ validation phase: external evaluation often missing or lacks robustness

Main recommendations:

→ involve interdisciplinary expertise (experimental, computational, clinical) in the study design

→ exploit prior biological knowledge & existing data integration frameworks

→ use early filtering & robust validation schemes

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Thank you for your attention!

Online quiz:
https://tinyurl.com/permedquestions

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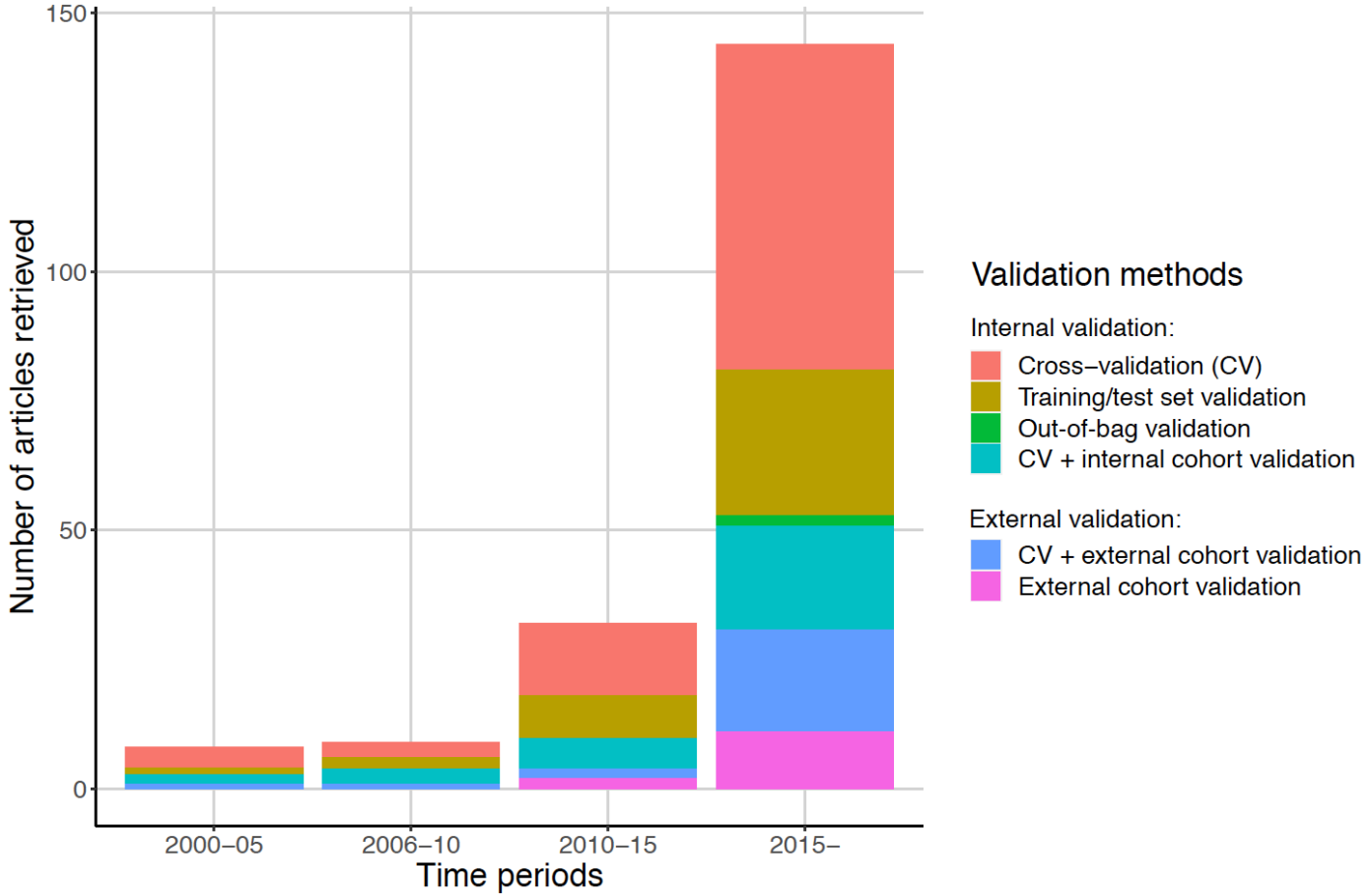
Gaps and challenges: Validation



→ Only a minority of published biomarker studies includes an external validation

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Example use cases

- Multiple omics-derived biomarker signatures already clinically validated
- Following best practices for computational modeling & analysis contributed to the study success

Name	Test approval (FDA-cleared and/or LDT)	Purpose	References
AlloMap® Heart	FDA-cleared, LDT	identifying heart transplant recipients with risk of cellular rejection	Yamani et al., J Heart Lung Transplant, 2007
MammaPrint®	FDA-cleared, LDT	breast cancer risk-of-recurrence assessment	Van't Veer et al., Nature, 2002
Prosigna® Assay / PAM50	FDA-cleared, LDT	breast cancer risk of distant recurrence prediction	Nielsen et al., BMC Cancer, 2014
Decipher®	LDT	prostate cancer metastatic risk prediction	Marrone et al., PLoS Curr., 2015
FoundationOne® Heme	LDT	test for haematologic malignancies, sarcomas or solid tumours	He et al., Blood, 2016

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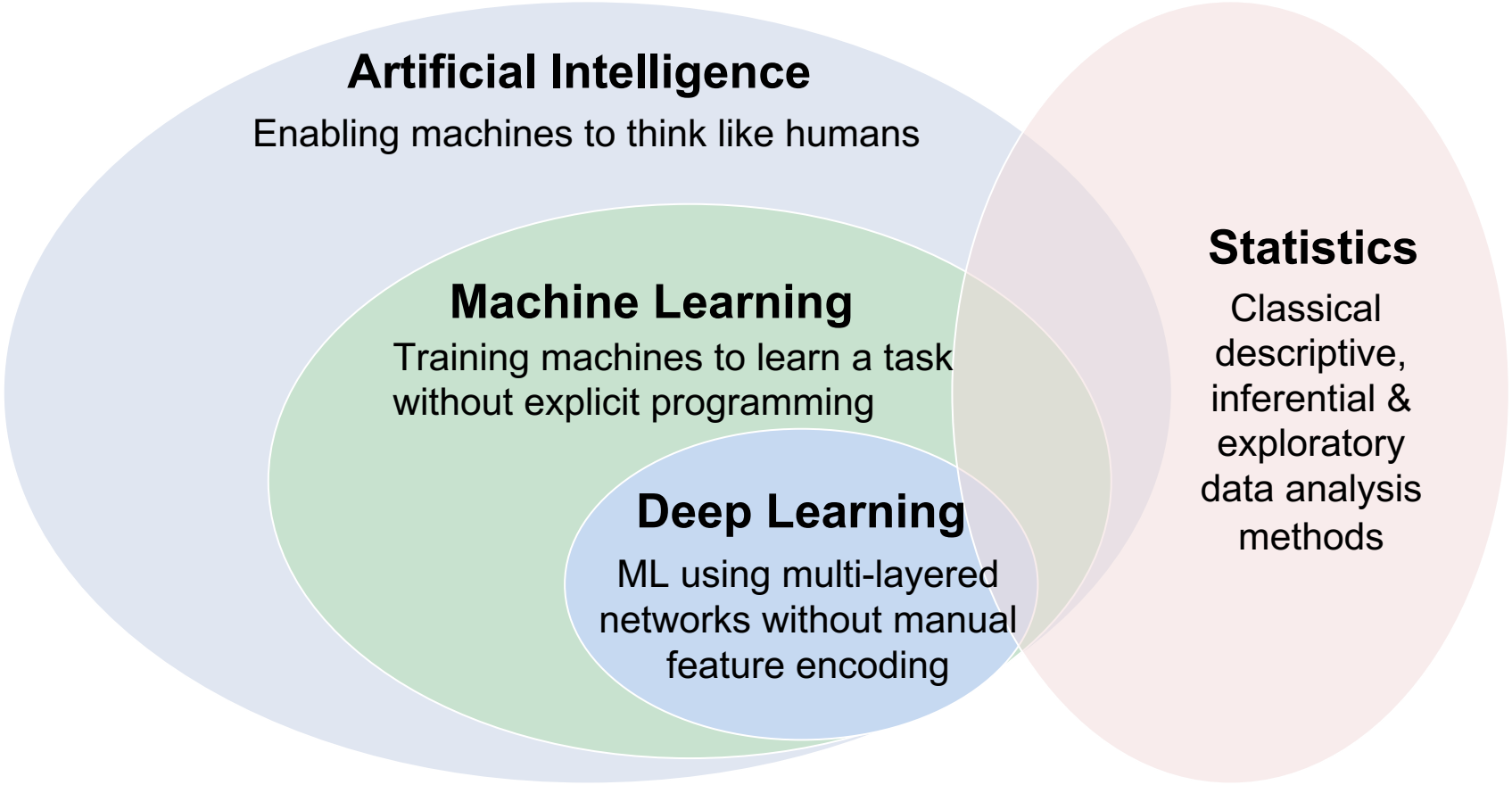
Definition: AI vs. classical statistics



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Computational analysis & modeling stage

- What this stage comprises
  - This stage covers the computational pre-processing, quality control, statistical and machine learning analysis of the collected data for patient stratification
- How this stage fits in the pipeline
  - Preparations for this stage are already required during the early study design (e.g. to conduct a sample size calculation, define the analysis plan)
  - During a project, this stage follows after the biological data collection
  - This stage lays the ground for the experimental validation of a candidate biomarker model for stratification, derived from the computational analyses

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Methodology

Collection and structuring of material & discussion points for the working sessions

Discussion, extension and revision of collected material on machine learning & validation methods

Structuring and revision of challenges and suggested recommendations

Write-up of machine learning & validation method recommendations

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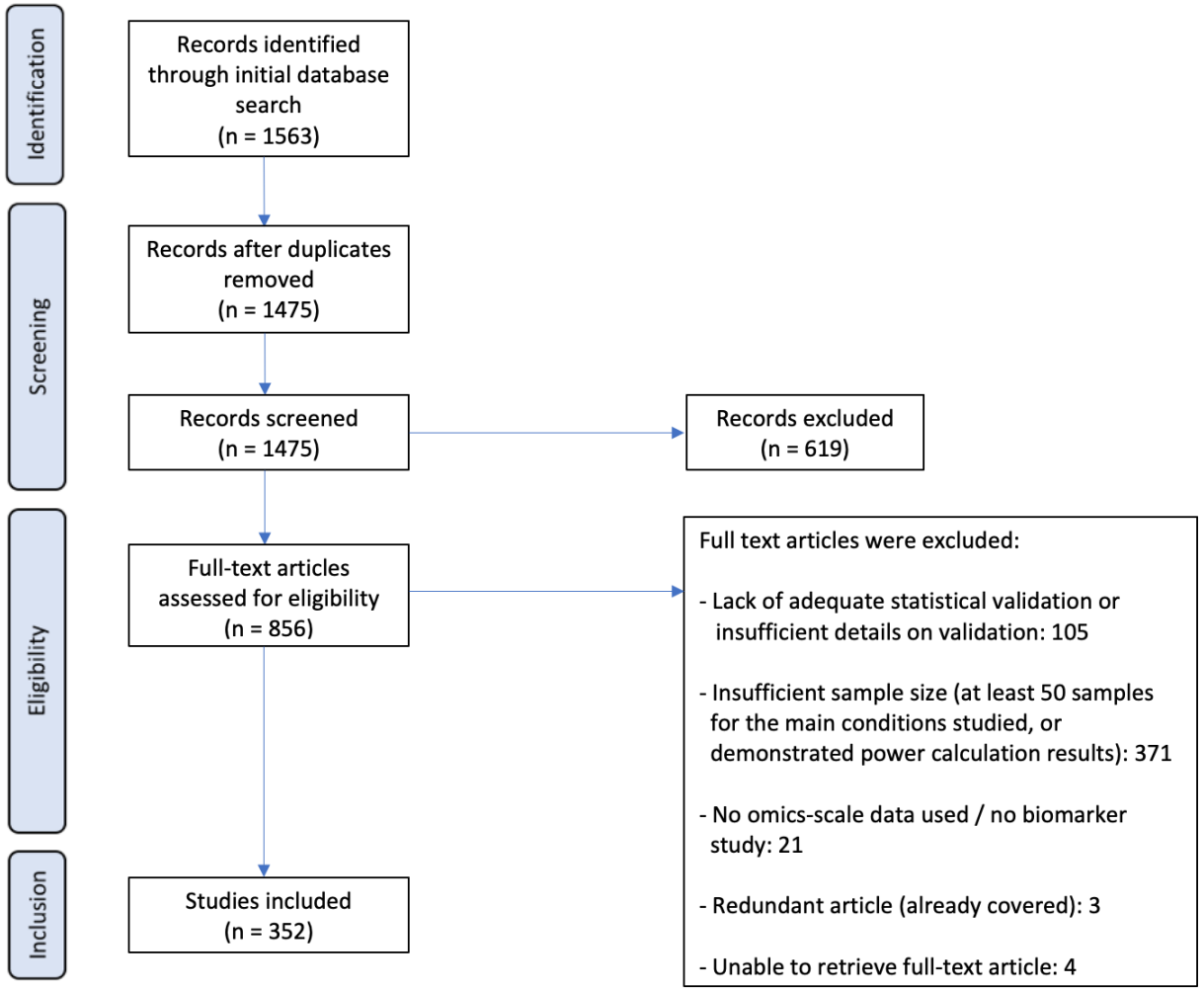
Methodology: Scoping Review



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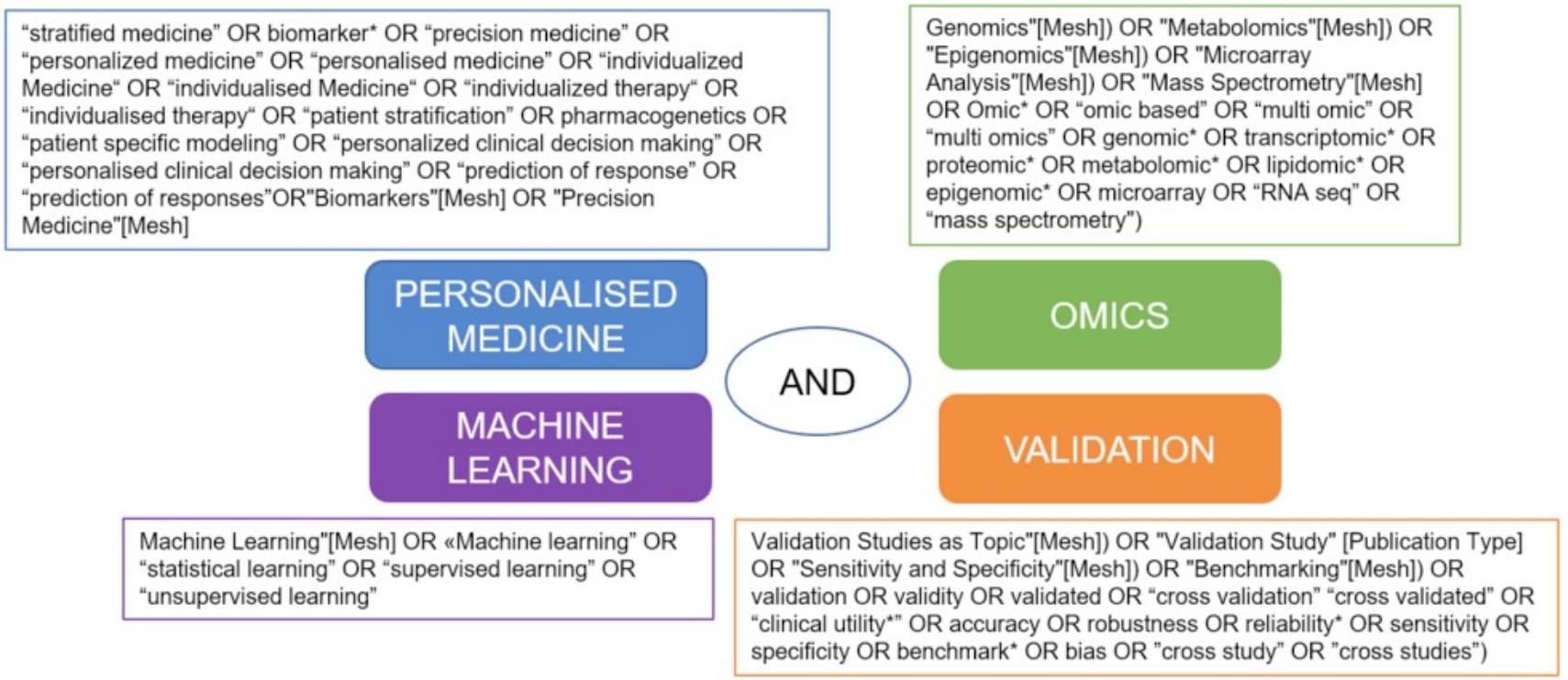
Methodology: Scoping Review

Literature search using Medical Subject Headings (MeSH) term keywords:



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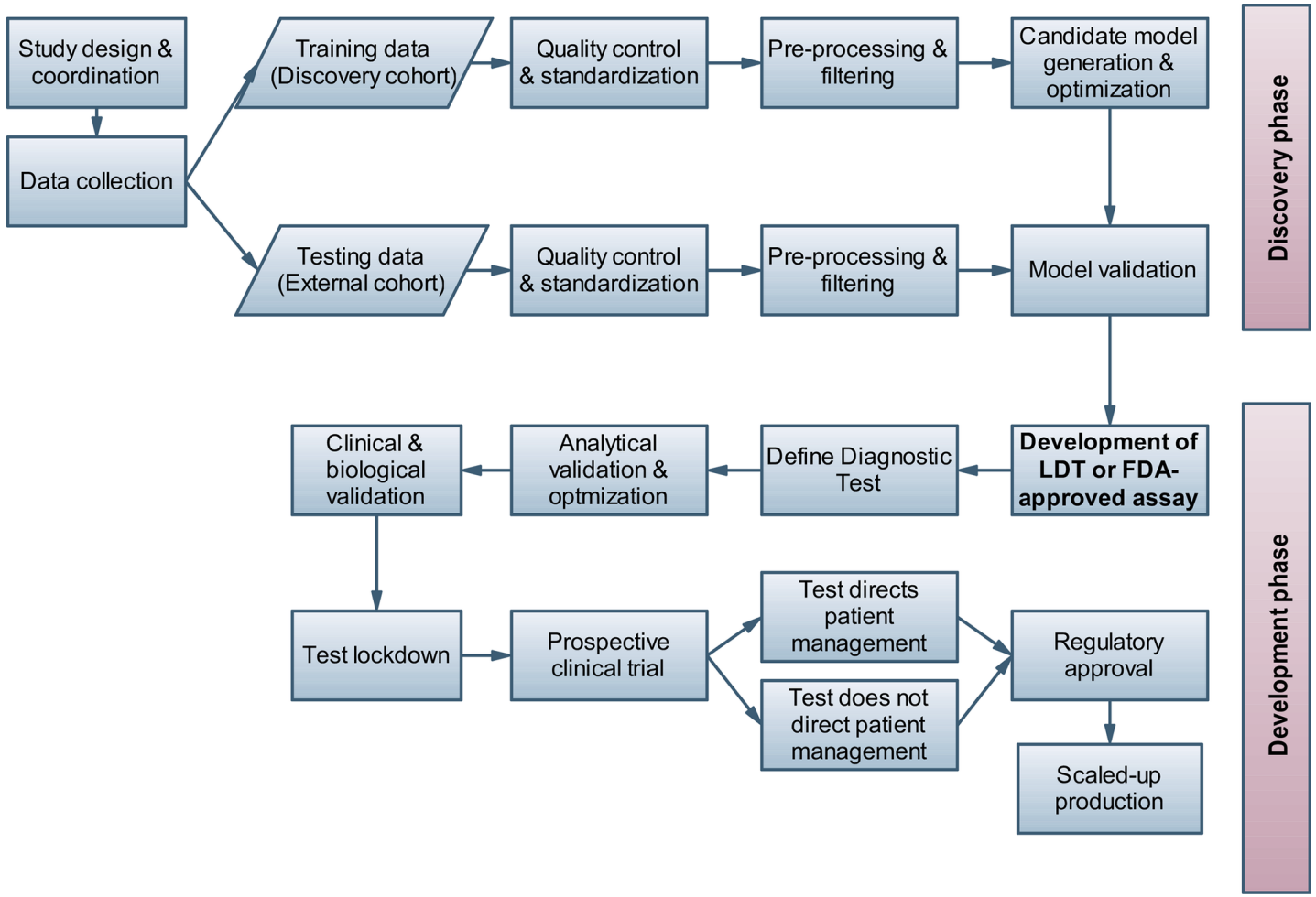
AI for stratification: Typical workflow



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Methodology: Recommendation structure

- Challenges/risks & associated recommendations are grouped by study phase:
  (1) Planning, (2) Discovery & Modeling, (3) Validation
- Tabular information collection format:

Challenge/Risk	**Likelihood** (low, medium or high)	**Impact** (low, medium or high)	**Recommendations / Mitigation strategies**
insufficient sample size	high	medium or high, depending on the study type	• Prior power estimation • Algorithmic biospecimen selection • Integration of complementary data (e.g. multi-omics data)

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Gaps and challenges: Overview

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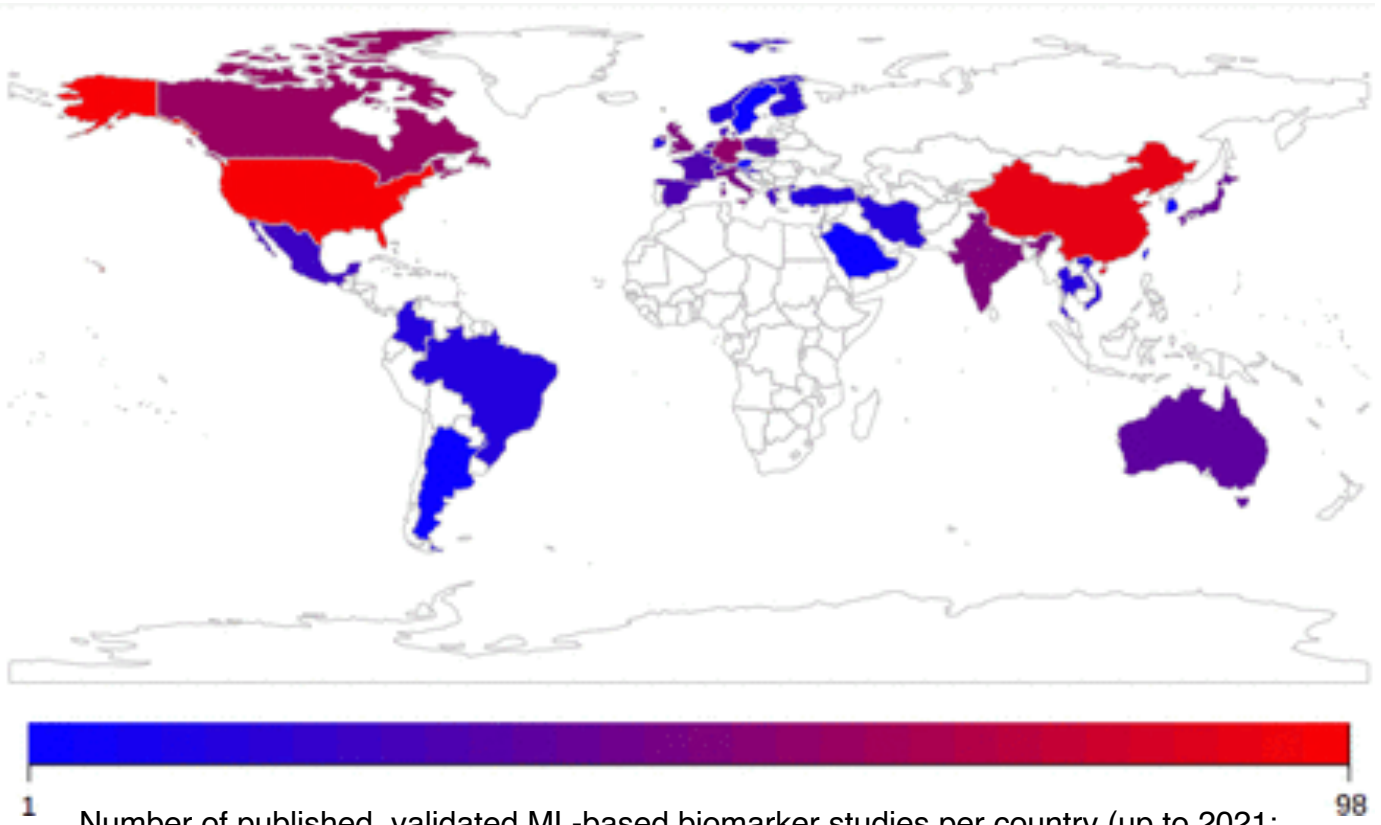
Gaps and challenges: Country representation



Number of published, validated ML-based biomarker studies per country (up to 2021; Glaab et al., BMJ Open, 2021)

→ Great imbalances in country representation among published studies on validated, machine learning derived biomarker signatures

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Gaps and challenges: Workflows

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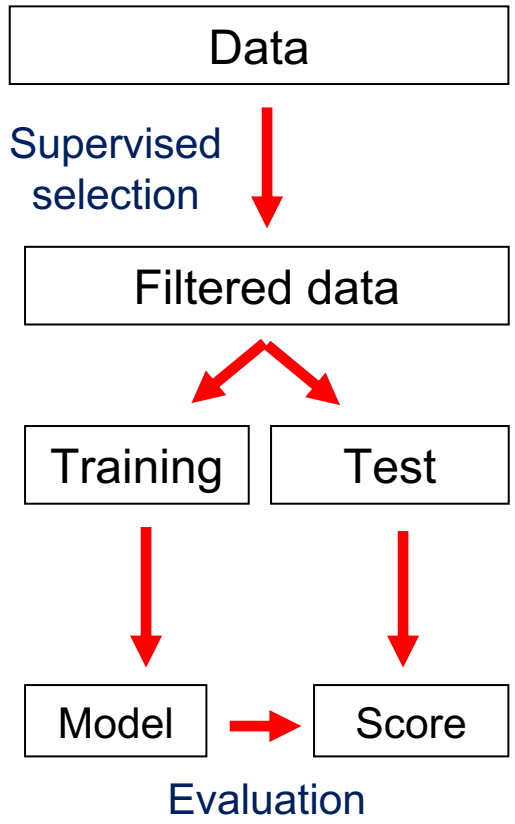
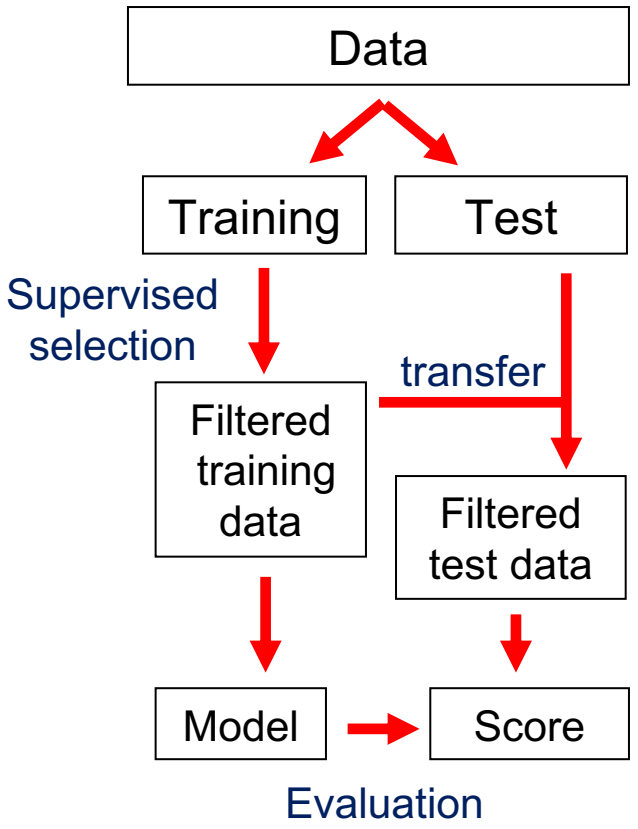
Error: Global feature selection



Suggested approach



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Example use cases – Main conclusions

Shared characteristics of prior successful uses cases:

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

- Integration of diverse data types & measurement technologies:
  exploiting pathway & network data & technological advances (e.g., progressing from microarray technology to deep sequencing, RT-PCR and digital PCR)

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

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