Generalizable biomarker development for early prostate cancer detection

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ENAR

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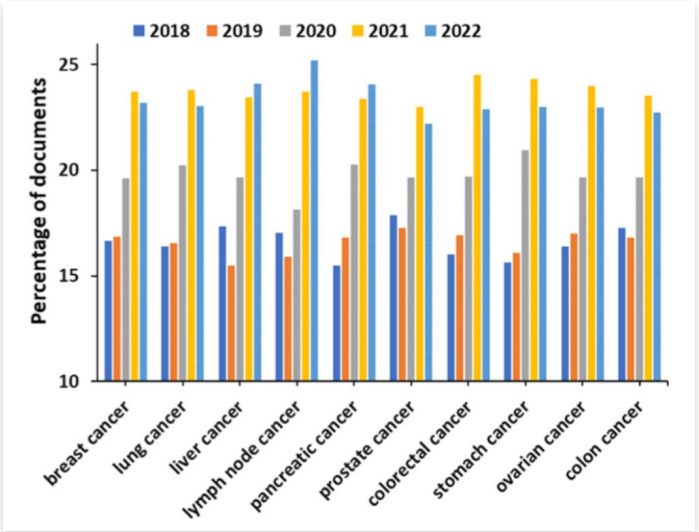
NIH NATIONAL CANCER INSTITUTE
Early Detection Research Network

Biomarker development for early cancer detection

- **Early detection of cancer** often leads to more effective treatment and a drastically higher chance of survival
  - However, **~50%** of cancers are detected at **late stages** [Crosby et al. (2022)]
- **Biomarkers** have long offered a valuable opportunity to improve early cancer detection
  - Pancreatic cancer: CA19-9
  - Breast cancer: HER2, BRCA1/2
- Ensuring the **reliability** of biomarkers is the goal, but very challenging ("the valley of death")
  - >500 biomarkers fail rigorous EDRN validation [Srivastava (2023)]



Growth of biomarker-related papers over time [Tenchov et al. (2024)]

Biomarker development for early prostate cancer detection

Prostate cancer: a leading cause of cancer death in the developed world

~ 1 in 8 men are diagnosed with prostate cancer in their lifetime

~ 1 in 44 men will die of prostate cancer

- **Unclear benefits of current screening** procedures via prostate-specific antigen (PSA)
  - High rate of invasive biopsies and false positives (i.e., overdiagnosis and overtreatment of indolent cancers)
- Can we create a reliable **non-invasive urine-based biomarker test** to detect prostate cancer with greater accuracy than PSA?

Source: American Cancer Society (2025)

Prior Work: MyProstateScore2.0 (MPS2)

Research

JAMA Oncology | Original Investigation

Development and Validation of an 18-Gene Urine Test for High-Grade Prostate Cancer

Jeffrey J. Tosoian, MD, MPH; Yuping Zhang, PhD; Lanbo Xiao, PhD; Cassie Xie, MS; Nathan L. Samora, MD; Yashar S. Niknafs, PhD; Zoey Chopra, MA; Javed Siddiqui, MS; Heng Zheng, MD; Grace Herron, BA; Neil Vaishampayan, BS; Hunter S. Robinson, MD; Kumaran Arivoli, BS; Bruce J. Trock, PhD; Ashley E. Ross, MD, PhD; Todd M. Morgan, MD; Ganesh S. Palapattu, MD; Simpa S. Salami, MD, MPH; Lakshmi P. Kunju, MD; Scott A. Tomlins, MD, PhD; Lori J. Sokoll, PhD; Daniel W. Chan, PhD; Sudhir Srivastava, PhD; Ziding Feng, PhD; Martin G. Sanda, MD; Yingye Zheng, PhD; John T. Wei, MD; Arul M. Chinnaiyan, MD, PhD; for the EDRN-PCA3 Study Group

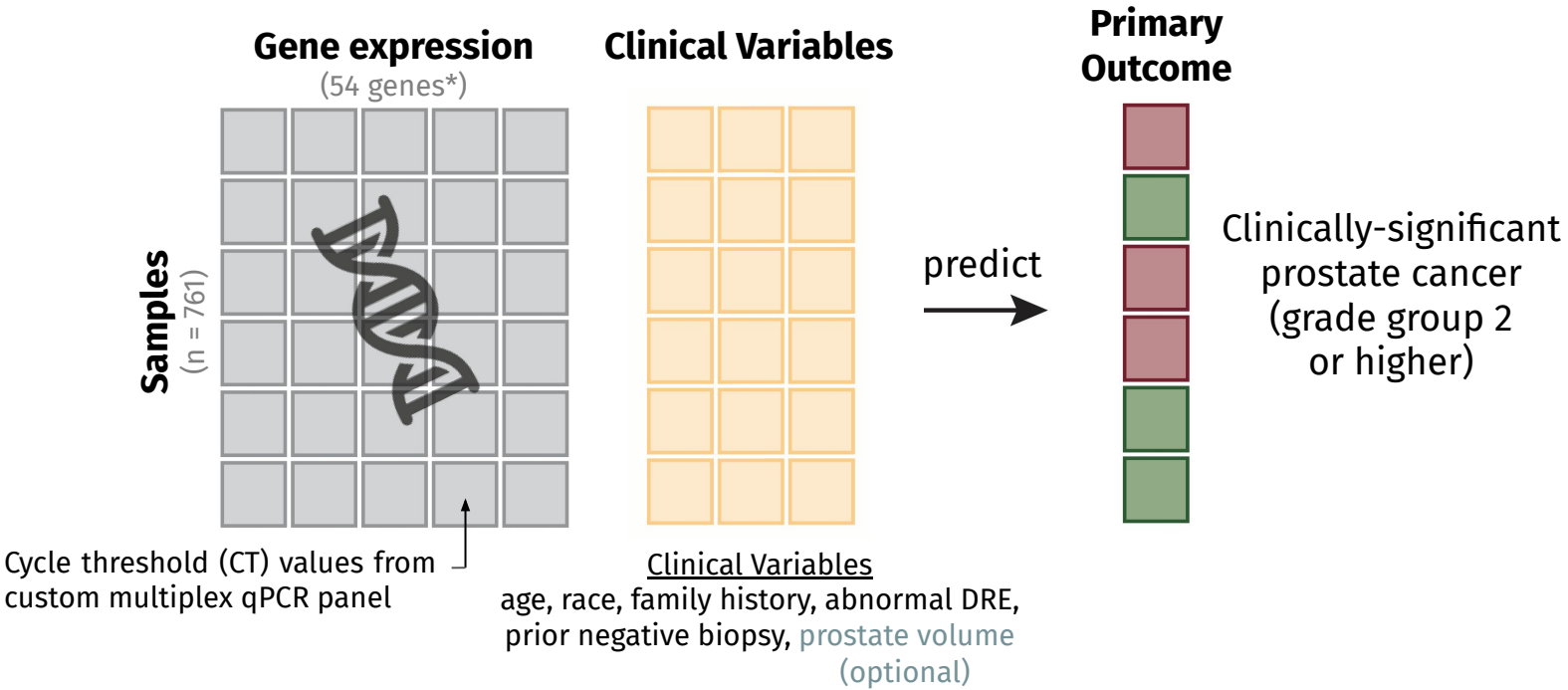
IMPORTANCE Benefits of prostate cancer (PCa) screening with prostate-specific antigen (PSA) alone are largely offset by excess negative biopsies and overdetection of indolent cancers resulting from the poor specificity of PSA for high-grade PCa (ie, grade group [GG] 2 or greater).

OBJECTIVE To develop a multiplex urinary panel for high-grade PCa and validate its external performance relative to current guideline-endorsed biomarkers.

Supplemental content

Prior Work: MyProstateScore2.0 (MPS2)

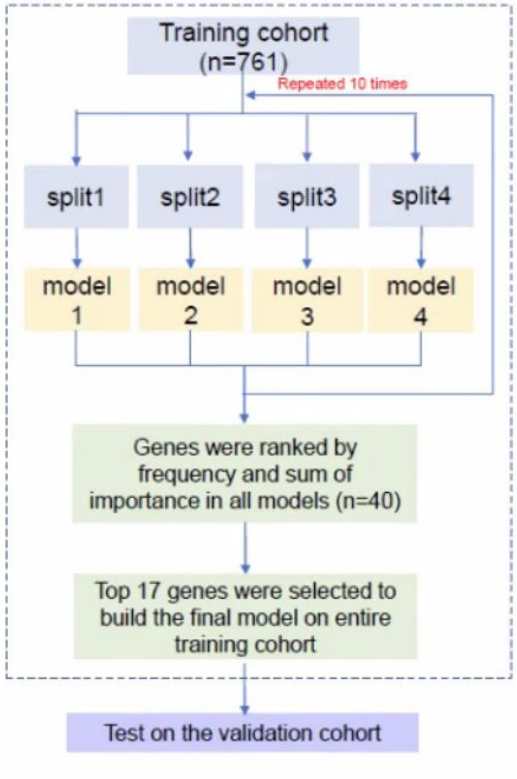
Training/Development Cohort Data



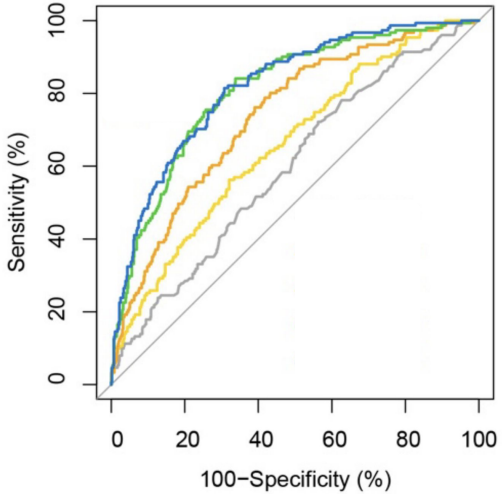
* Carefully selected out of 58,724 genes based on differential expression and predefined nomination criteria

Prior Work: MyProstateScore2.0 (MPS2)

Model Development



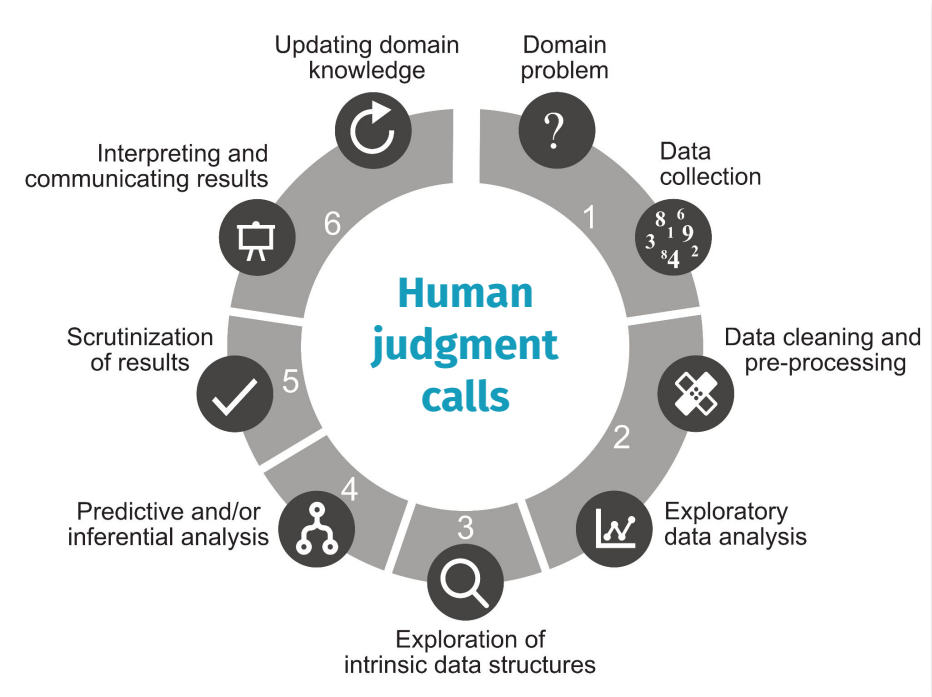
- **Final (locked) model:** logistic regression + elastic net using 18 genes and clinical variables as predictors
  - Why 18? Chosen to fit in OpenArray™ platform
- Evaluated on **external validation cohort from EDRN**



AUROC	Method	
81.8%	MPS2+	18 genes with prostate volume
80.7%	MPS2	18 genes without prostate volume
73.7%	MPS	3 genes + clinical
65.9%	PCPT	clinical only
59.7%	PSA	current standard

What's the problem? Unaccounted uncertainty

There are numerous **human judgment calls** (or choices) throughout MPS2 development



The Data Science Life Cycle [Yu and Barter (2024)]

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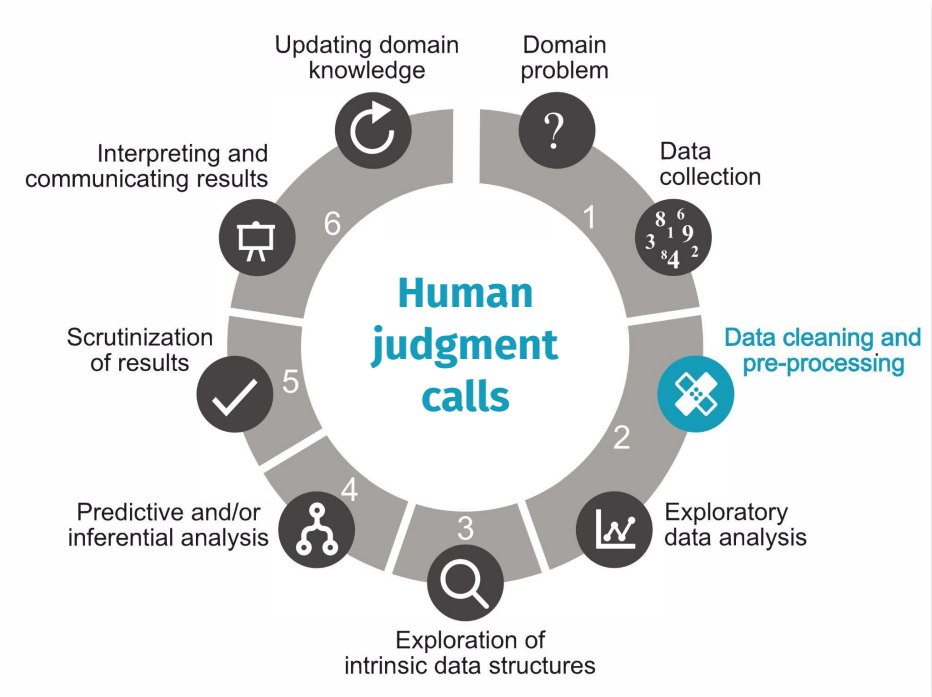

The Data Science Life Cycle [Yu and Barter (2024)]

Data Cleaning Choices

- How to threshold CT values if undetermined or no amplification
- Sample filtering/quality control choices
- ...

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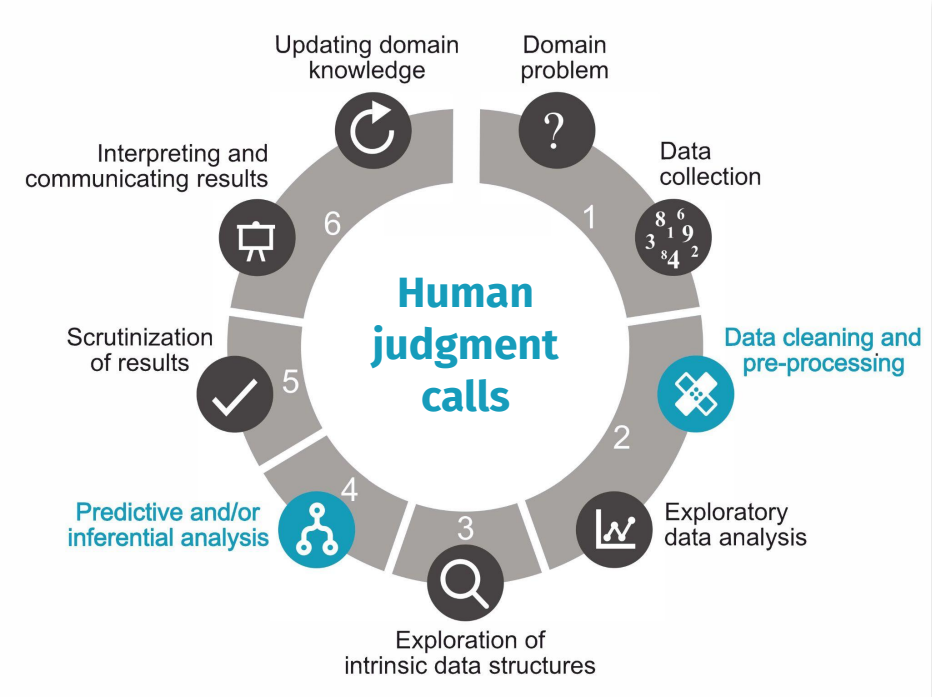
Modeling Choices

- Which model?
- Which clinical variables?
- Which genes?
- ...



The Data Science Life Cycle [Yu and Barter (2024)]

Data Cleaning Choices

- How to threshold CT values if undetermined or no amplification
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At a minimum, our scientific conclusions should be **stable** across **reasonable data and modeling perturbations**

[Ioannidis (2005); Kraft et al. (2009); Donoho (2010); Casadevall and Fang (2011); Nosek et al. (2012); Yu (2013), Gelman and Loken (2014), ...]

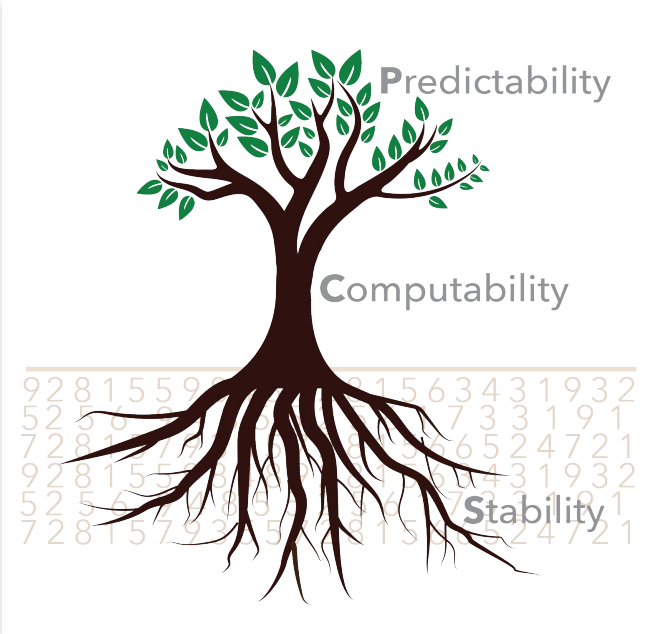
PCS Framework for Veridical Data Science [Yu and Kumbier (2020)]

Three principles for **veridical (trustworthy) data science**

Predictability: is my model a good representation of reality (as measured by prediction accuracy)?

Computability: is my pipeline computable?

Stability: are my model/findings stable across reasonable perturbations of the data science life cycle?



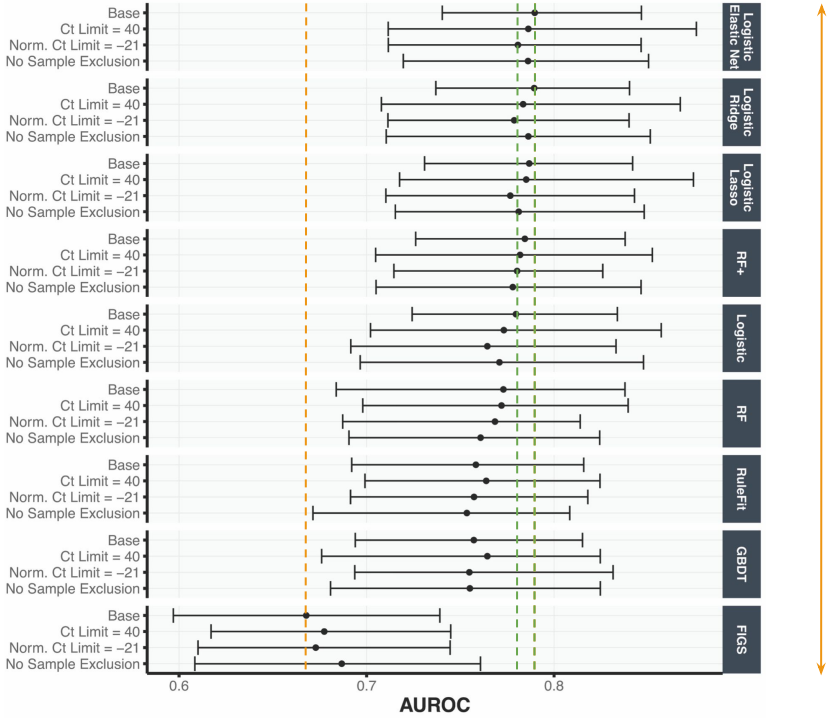
Credits: Rebecca Barter

Stress-testing MPS2 under the PCS framework

Data preprocessing pipelines

<2% difference in mean AUROC across data preprocessing pipelines

Inner 95% quantile range of AUROCs from repeated CV



Methods

Up to >10% difference in mean AUROC across prediction methods

Difference between mean AUROC across data preprocessing pipelines << across methods

Improving MPS2 using the PCS framework

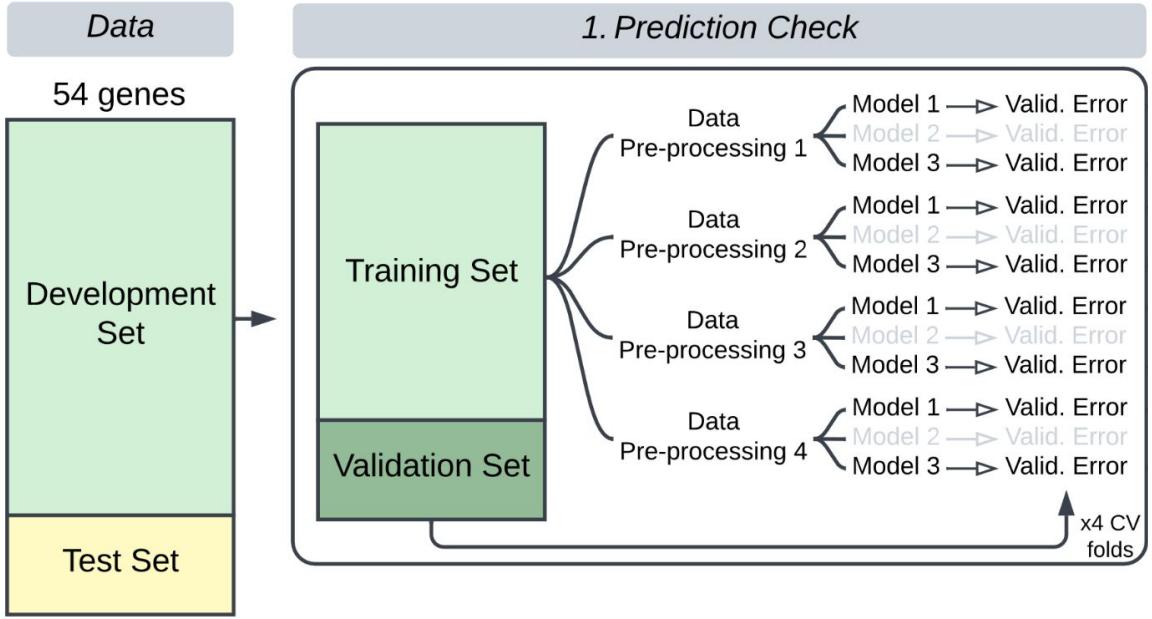
Beyond stress-testing, the PCS framework can also be used to improve the model development process.

Example: Do we need all 18 genes or can we develop a simpler, cheaper gene panel?

- We developed a **simplified MPS2 (sMPS2)** model, which uses only **7 genes** and achieves similar accuracy as the 18-gene MPS2 model.
- Key Steps:
  - Use **prediction performance as a reality check** and exclude models that don't fit the data well
  - Select **features** that were **stably important** across **data and model perturbations**
  - Very careful **data splitting**

sMPS2: Model Development

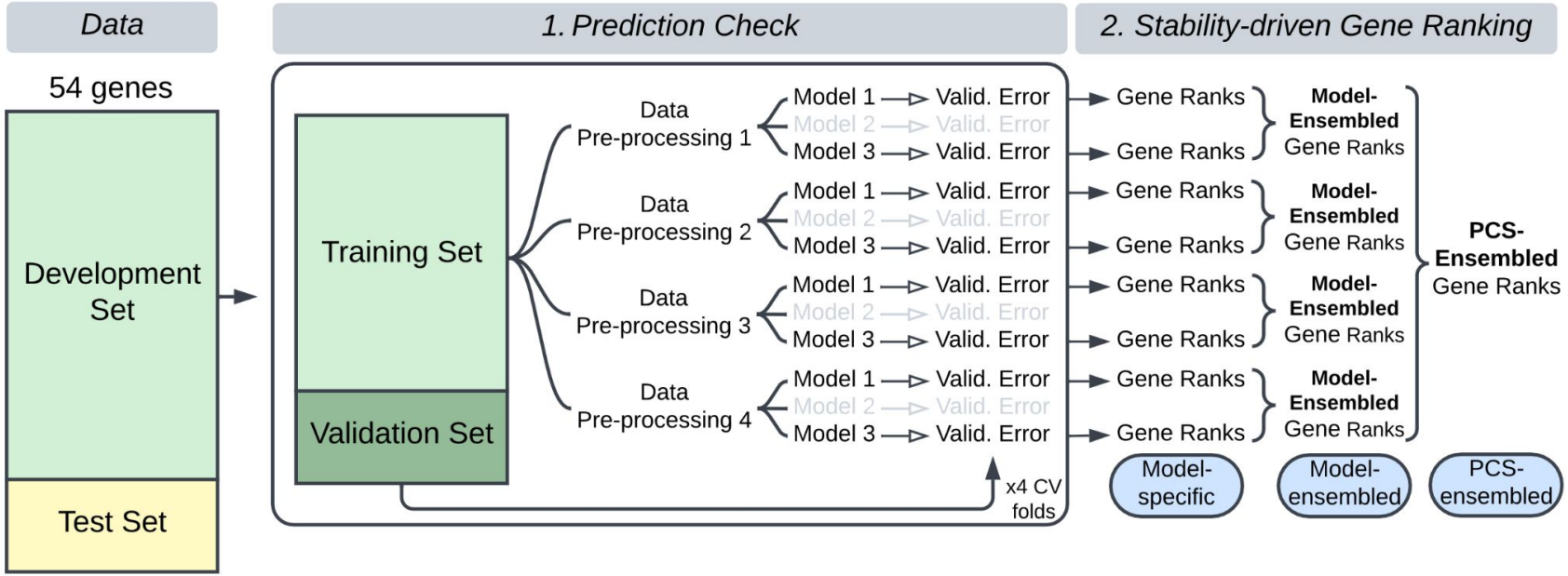
sMPS2: Model Development



Use prediction performance as a reality check

(Exclude pipelines (e.g., FIGS) with poor fits)

sMPS2: Model Development

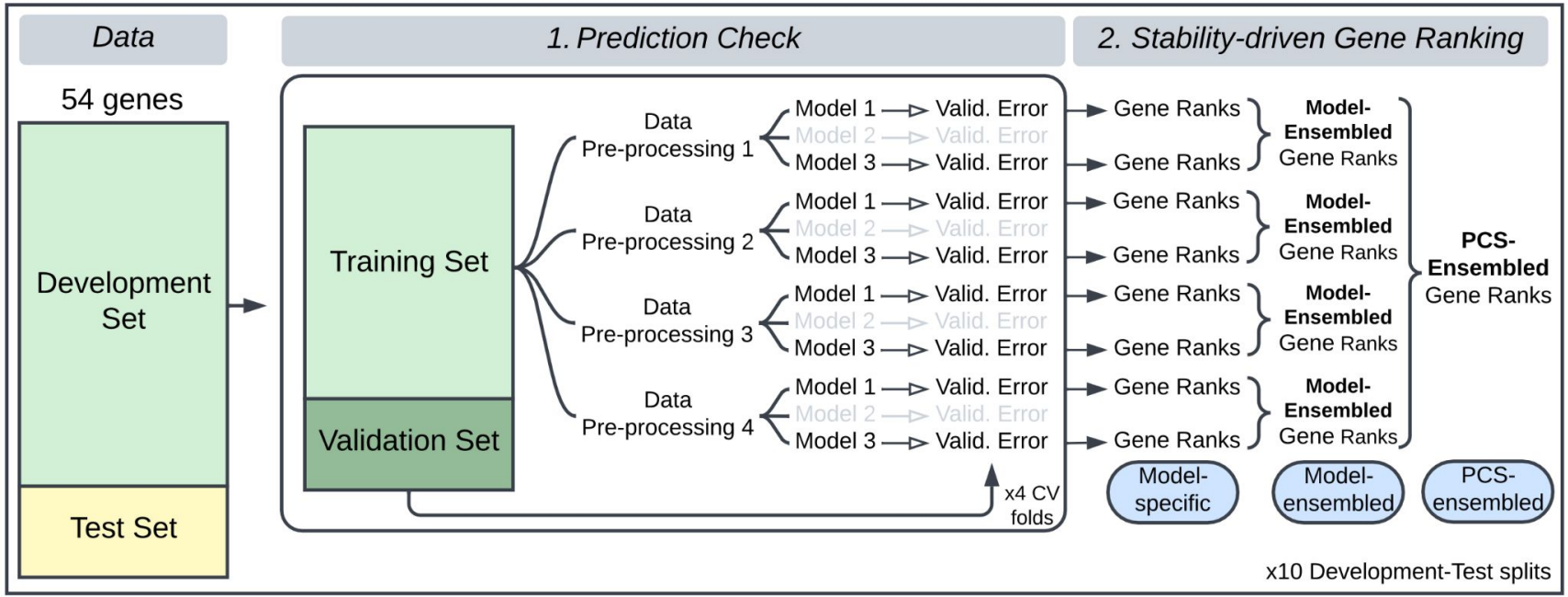


Use prediction performance as a reality check

(Exclude pipelines (e.g., FIGS) with poor fits)

Ensemble feature importances across data & model perturbations

sMPS2: Model Development



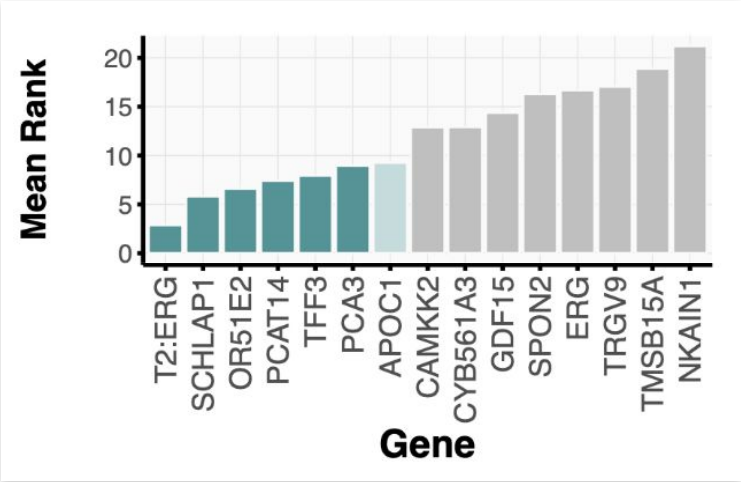
Use prediction performance as a reality check

(Exclude pipelines (e.g., FIGS) with poor fits)

Ensemble feature importances across data & model perturbations

sMPS2: Model Development

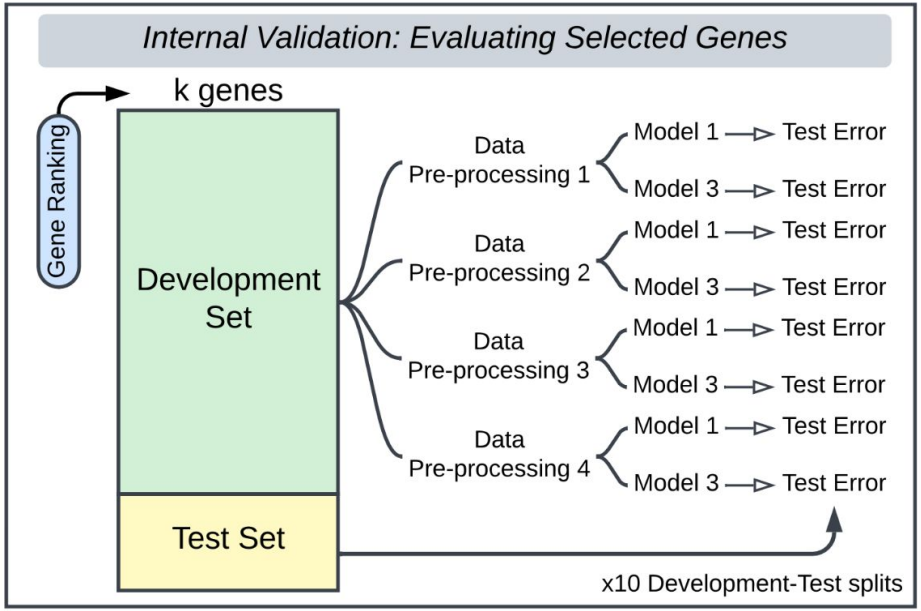
Examining these PCS-ensembled gene rankings reveals 6-7 very **staby important genes**

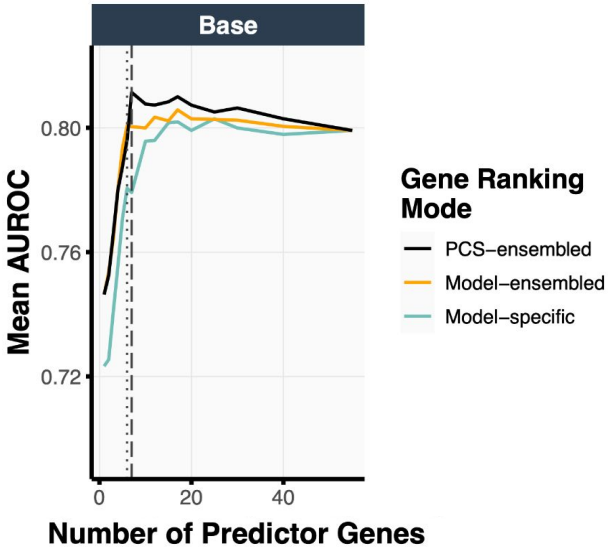


* Mean ranking is only one stability metric
  + There are many others ways to evaluate stability (e.g., % in top *k*)
  + Other stability metrics showed APOC1 is not as stable

sMPS2: Internal Validation

- 6-7 top stably important genes yielded the best (or competitively high) test AUROC compared to using different number of gene predictors
- PCS-ensembled gene rankings > model-ensembled or model-specific





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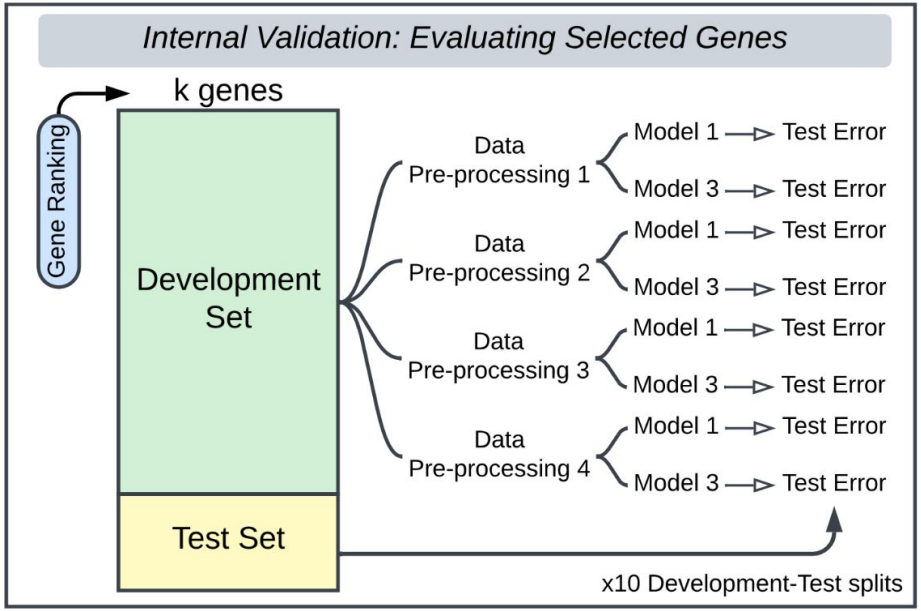

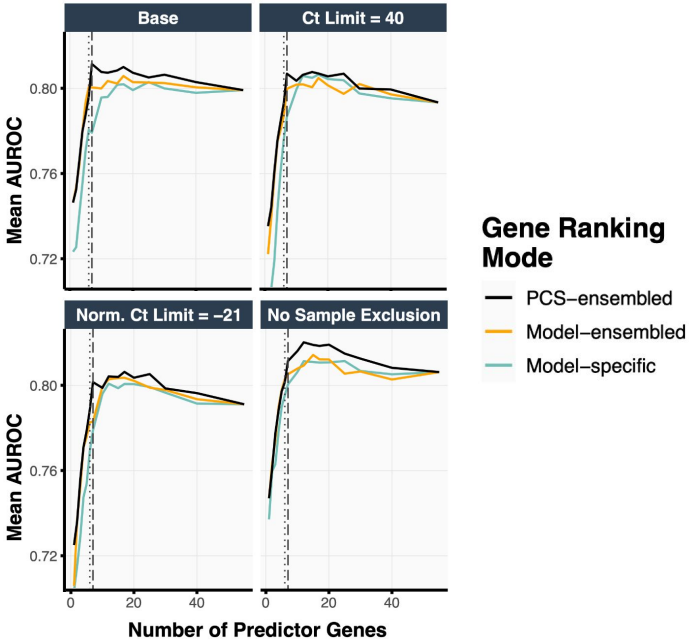

sMPS2: External Validation (EDRN)

+ **Final (locked) model:** logistic regression + ridge using 7 genes (6 stably important genes + 1 reference gene *KLK3*) and clinical variables

Without prostate volume

AUROC	Method	
80.7%	MPS2	18 genes
78.5%	**s^{8}MPS2**	8 genes
78.4%	**s^{7}MPS2**	7 genes
73.7%	MPS	3 genes
59.7%	PSA	current standard

With prostate volume

AUROC	Method	
81.8%	MPS2+	18 genes
80.9%	**s^{8}MPS2+**	8 genes
80.6%	**s^{7}MPS2+**	7 genes
73.7%	MPS	3 genes
59.7%	PSA	current standard

+ Difference between MPS2 and sMPS2 is smaller than uncertainty due to data preprocessing choices (~2%)

Summary and Discussion

Using the PCS framework, we:

- + Rigorously stress-tested MPS2 for early prostate cancer detection
- + Simplified the 18-gene MPS2 model to a 7-gene sMPS2 model with similar accuracy

Still, there are human judgment calls throughout this analysis

→ needs documentation and justification

Thank you!

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