Leveraging AI in multi-omics oncology

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mCRC clinical trials with molecular data

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Clinical trial/Study name (phase) [country]	Treatment	Clinical Outcome	Oncoarray (GWAS)	Gene expression	Mutation panel
FIRE-3 (III) [Germany]	FOLFIRI/CET (N=260)	PFS, OS, TR	✓	✓ (HTG)	KRAS wildtype
	FOLFIRI/BEV (N=260)		✓		
TRIBE (III) [Italy]	FOLFOXIRI/BEV (N=230)	PFS, OS, TR	✓		KRAS, NRAS, BRAF
	FOLFIRI/BEV (N=230)		✓		
MAVERICC (II) [USA]	mFOLFOX6/BEV (N=161)	PFS, OS, TR	✓	✓ (Nano)	NGS
	FOLFIRI/BEV (N=163)		✓	✓ (Nano)	
MOMA (II) [Italy]	FOLFOXIRI/BEV (N=160)	PFS, OS, TR			RAS, BRAF
TRIBE-2 (III) [Italy]	FOLFOX/BEV → FOLFIRI/BEV (N=255)	PFS, OS, TR	✓		KRAS, NRAS, BRAF
	FOLFOXIRI/BEV (N=255)				
VALENTINO (II) [Italy]	FOLFOX/PANI vs 5FU/PANI maintenance (N=175)	PFS, OS, TR	✓		RAS, BRAF wildtype
MSI-H CRC (retrospective) [Italy]	CHEMO/IMMUNO (N=73)	PFS, OS, TR	✓		MSI, KRAS, NRAS, BRAF
JACCRO-CC05/06 (II) [Japan]	FOLFOX/CET (N=40)	PFS, OS, TR			RAS wildtype
	SOX/CET (N=37)				
JACCRO-CC11 (II) [Japan]	FOLFOXIRI/BEV (N=51)	PFS, OS, TR			RAS mutant
PANAMA (II) [Germany]	5FU/PANI vs 5FU maintenance (N=248)	PFS, OS, TR			RAS wildtype
CALGB/SWOG80405 Alliance (III) [USA]	CHEMO/BEV (N= 315)	PFS, OS, TR		✓ (RNAseq)	NGS
	CHEMO/CET (N=321)			✓ (RNAseq)	
	CHEMO/BEV+CET (N=207)			✓ (RNAseq)	
USC CRC CARIS Cohort * [USA]	Any (N=450)	OS, ToT		✓ (WTS)	WES

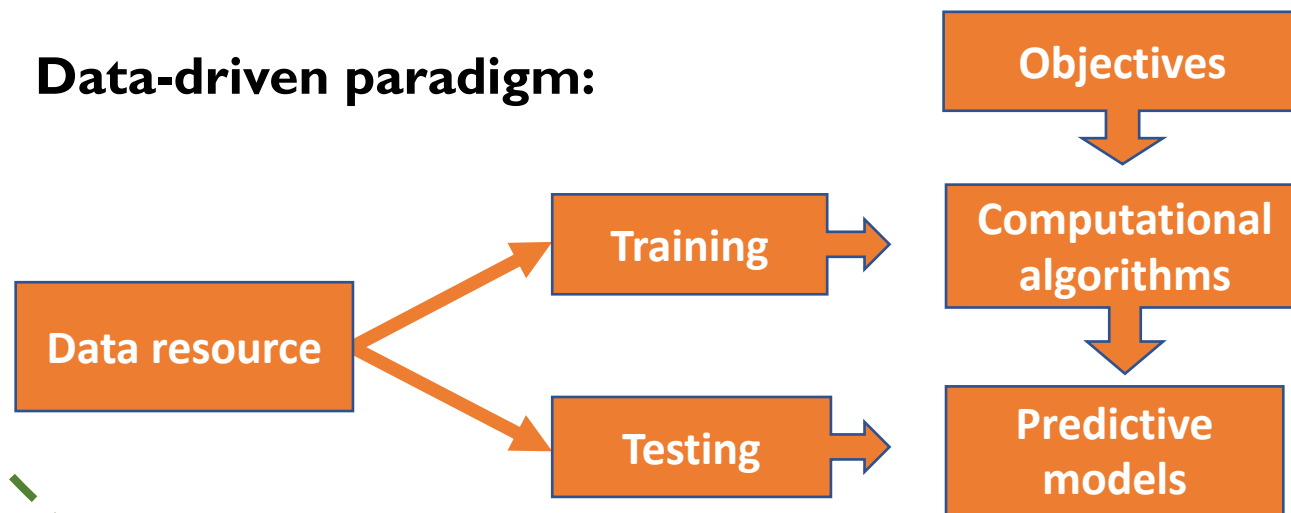# Objectives for the high-dimensional molecular data

- **Biomarker development**
  - **Predictive (predicts response to treatment)**
  - **Prognostic (predicts outcome)**

- **New target identification**

Leveraging computational algorithms to identify patterns in molecular data

Conventional approach:

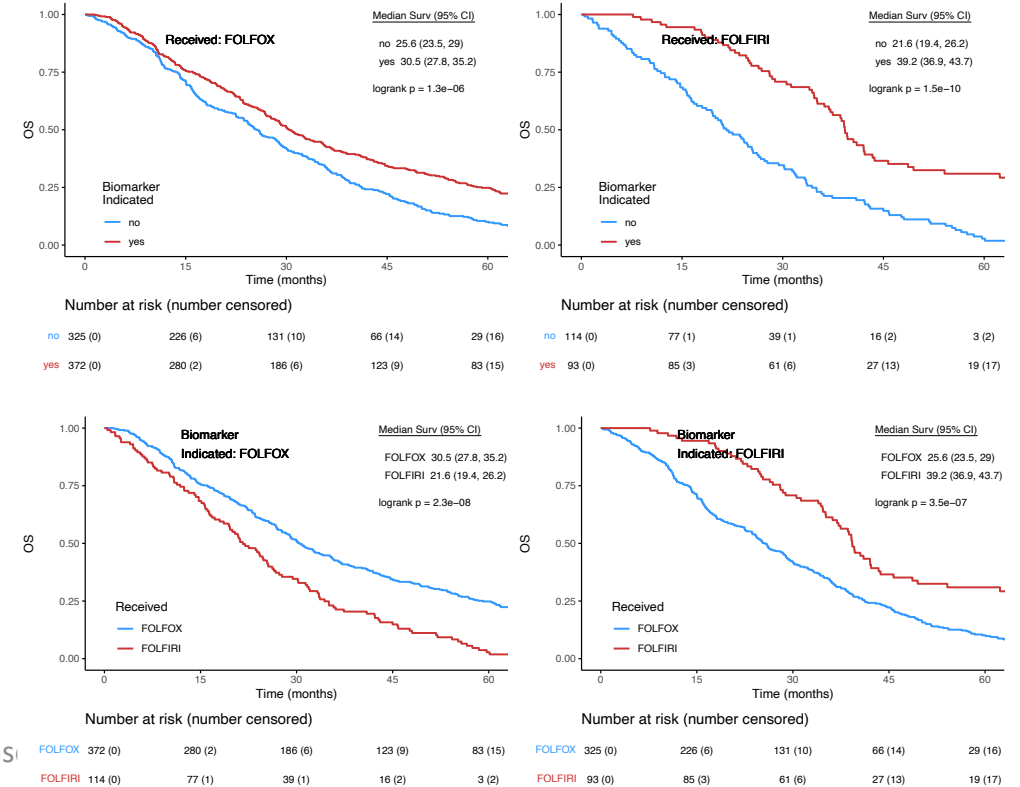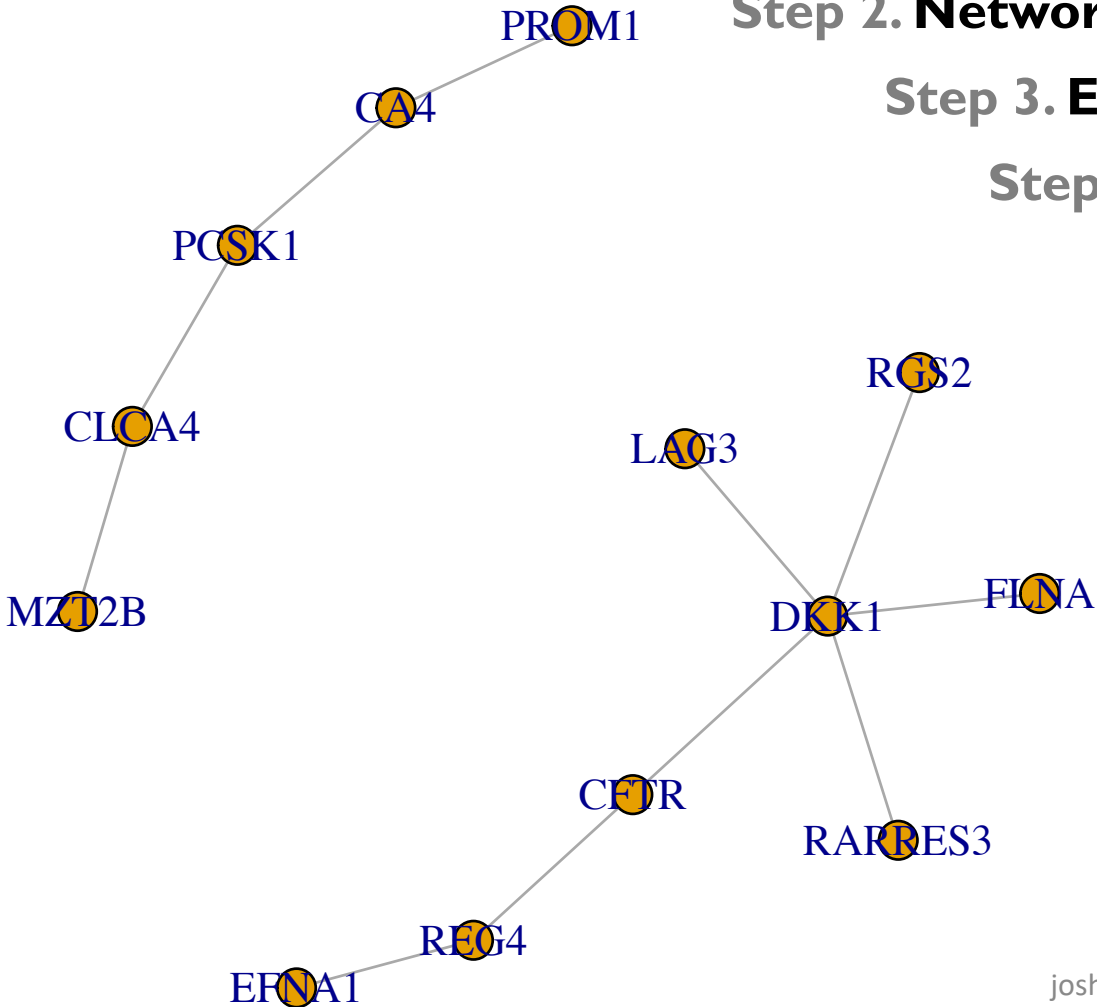Hypothesis → Model → Experimental design → Data collection → Hypothesis testing

Data-driven paradigm:

Objectives → Computational algorithms → Predictive models

Data resource → Training

Data resource → Testing

Gene expression networks to predict response to FOLFIRI vs FOLFOX

Step 1. **Overall survival ~ coexpression*treatment**

Step 2. **Network components**

Step 3. **Elastic net (or other ML algorithm)**

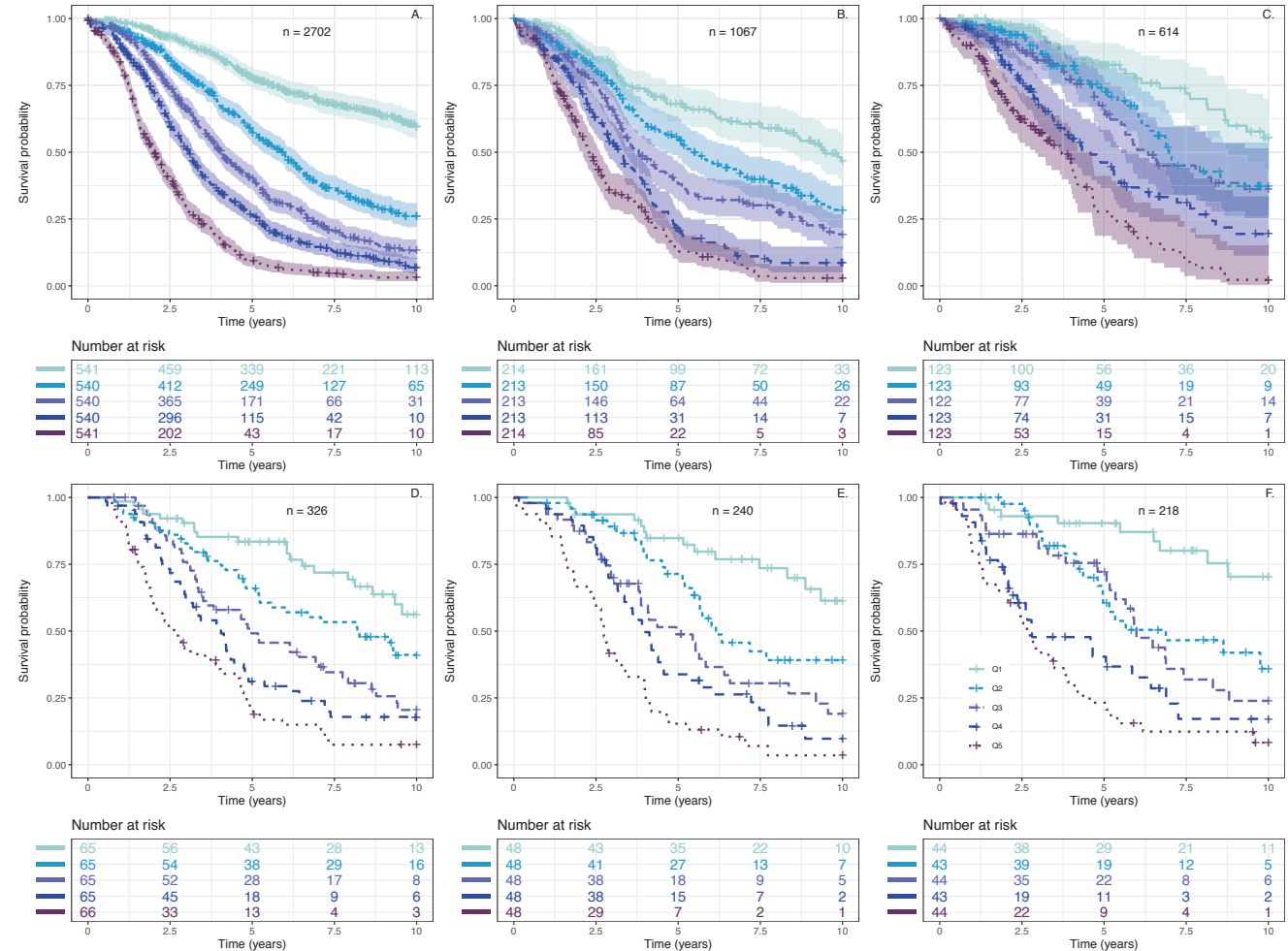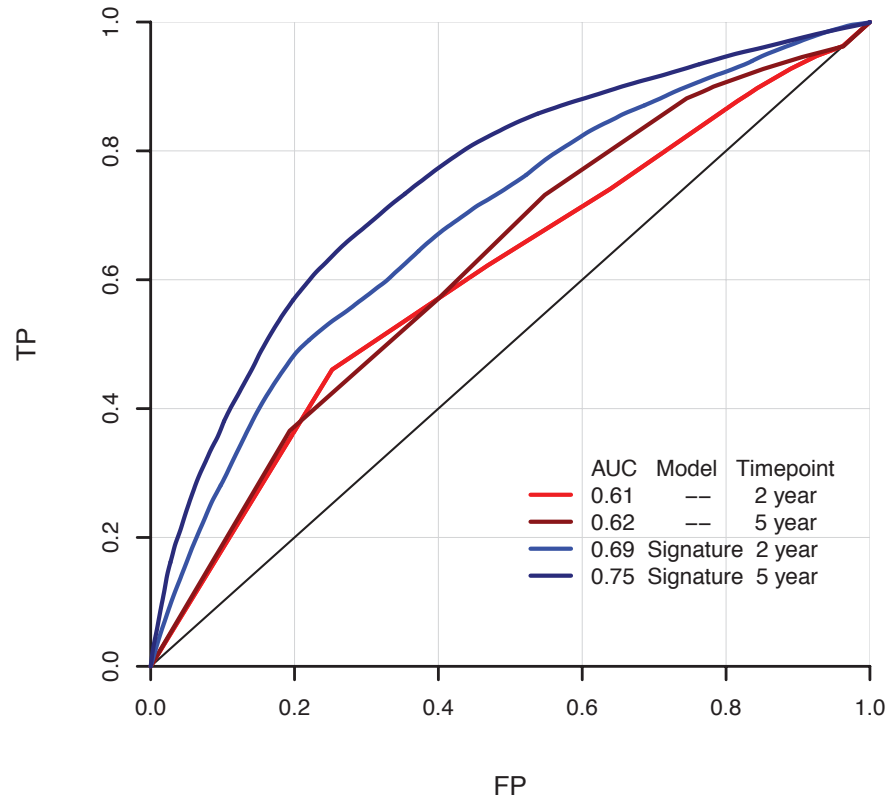**Step 4.** **Biomarker score for FOLFOX – FOLFIRI**

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Prognostic gene expression signature for overall survival

- **Biomarker development**
  - Predictive (predicts response to treatment)
  - Prognostic (predicts outcome)

- **Machine learning approaches to predict 2 yr and 5 yr OS**
  - Backward stepwise regression after filtering
  - Elastic net
  - Survival random forests
  - Gradient boosting

Millstein, J., Budden, T., Goode, E.L., Anglesio, M.S., Talhouk, A., Intermaggio, M.P., Leong, H.S., Chen, S., Elatre, W., Gilks, B. and Nazeran, T.,…, Ramus S.J. 2020. Prognostic gene expression signature for high-grade serous ovarian cancer. Annals of Oncology, 31(9), pp.1240-1250.

Prognostic gene expression signature for overall survival

- 276 of 513 genes replicated with FDR < 0.05 for OS

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