Reevaluating Former Standard Therapy

On **Interpretable Subgroups** of Primary Biliary Cirrhosis Patients

Guillaume Bonheure
Max Petruzzi

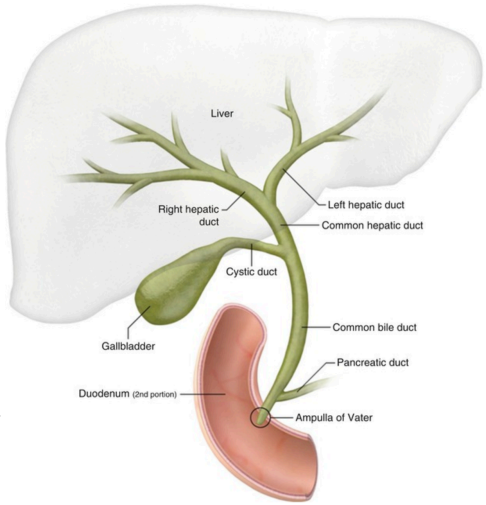
15.095 – Machine Learning Under a Modern Optimization Lens

Background

- **Primary Biliary Cirrhosis (PBC) :** autoimmune disease that causes destruction of ducts that transport bile

- **D-penicillamine** was the standard therapy for PBC for several years before it was replaced by **Ursodiol** due to its lower propensity for side effects

  Standard Therapy: treatment for certain disease that is accepted by medical experts and widely used



QUESTION:

- Is there a subgroup for which D-penicillamine might still be a more viable treatment option?

Methodology

- **Data set:** Results of randomized controlled trial for **D-penicillamine,** conducted by the Mayo Clinic between 1974 and 1984 (n=158 experimental, n=154 placebo)
- **Treatment effect:** Time elapsed before one of three outcomes: death, liver transplant, or completion of observation (alive) → Truncate top/bottom 10%, min-max scale, stack

- **Features:** 19 variables, including demographics (e.g. age and sex) and metrics of patient's condition before treatment (e.g. indicator variables for symptom presence and numerical lab results)
- **Formulation:** Based on *Lecture 16: Identifying Exceptional Responders in Randomized Trials*
- **Parameters:**
  - K = 15, consider 15 cuts for each feature
  - $S_0 = 4$, define a subgroup by, at most, 4 features

Results

	Control	Treatment	Difference	P-Value
Overall mean ATE	1.283	1.351	5.3%	0.513
Opt. Subgroup 1 mean ATE	1.038	1.897	82.8 %	0.0009
Opt. Subgroup 2 mean ATE	1.004	1.802	79.5%	0.001

Total patient overlap between two optimal subgroups constrained to be less than 20%

Optimal Subgroup 1

Feature	Lower Bound	Upper Bound
`Age`	37.5	56.1
`Hepato`	1	1
`Copper`	4.0	296.0
`Protime`	9.0	11.3

Hepato is a binary indicator variable for presence of hepatomegaly, **Copper** is urine copper (µg/day), and **Protime** is prothrombin time in seconds

Optimal Subgroup 2

Feature	Lower Bound	Upper Bound
`Alk.phos`	1258.5	11923.3
`Ast`	57.1	149.5
`Platelet`	133.6	491.4
`Protime`	9.6	12.5

Alk.phos and **Ast** are measures of enzyme activity in units of U/liter, and Platelet is number of platelets per cubic mL / 1000

Results (cont.)

Inverse subgroup represents the most negative treatment effect difference between experimental and control

	Control	Treatment	Difference	P-Value
Opt. Subgroup 2 mean ATE	1.510	0.584	-61.3%	0.0001

Inverse Subgroup

Feature	Lower Bound	Upper Bound
`Edema`	0.0	0.33
`Chol`	238.2	356.4
`Trig`	73.4	154.1
`Platelet`	62.0	348.3

Edema is a categorical variable with three levels, **Chol** is serum cholesterol in units of mg/dL, and **Trig** are triglycerides in units of mg/dL.

GLOBE Scores

Indication of pre-treatment risk of death, averaged per group

	All Patients	Opt. Subgroup 1	Opt. Subgroup 2	Inv. Subgroup
GLOBE score	8.8336	8.2451	9.1168	9.8958
% survival at:				
3 months	94	97	92	84
6 months	89	93	85	70
9 months	87	93	83	67
12 months	85	91	80	62
15 months	81	89	75	54
18 months	74	84	67	41
24 months	71	83	64	38

Extension

- Utilized dataset from **Ursodiol** clinical trial, current standard therapy (n=86 experimental, n=84 placebo)
- Contained dates for each of the same three outcomes we used previously → repeated same treatment effect calculation

	D-penicillamine			UDCA
	Overall	Opt. Subgroup 1	Opt. Subgroup 2	Overall
P-Value	0.513	0.0009	0.001	0.0490

Conclusions

- Not perfectly comparable populations
- However, **D-penicillamine** may be a viable treatment candidate for optimal subgroup members over **Ursodiol**
- Requires further cost-benefit analysis based on side effect risk