Predictive Tools and Biomarkers for Severe Acute Pancreatitis a 20-year journey

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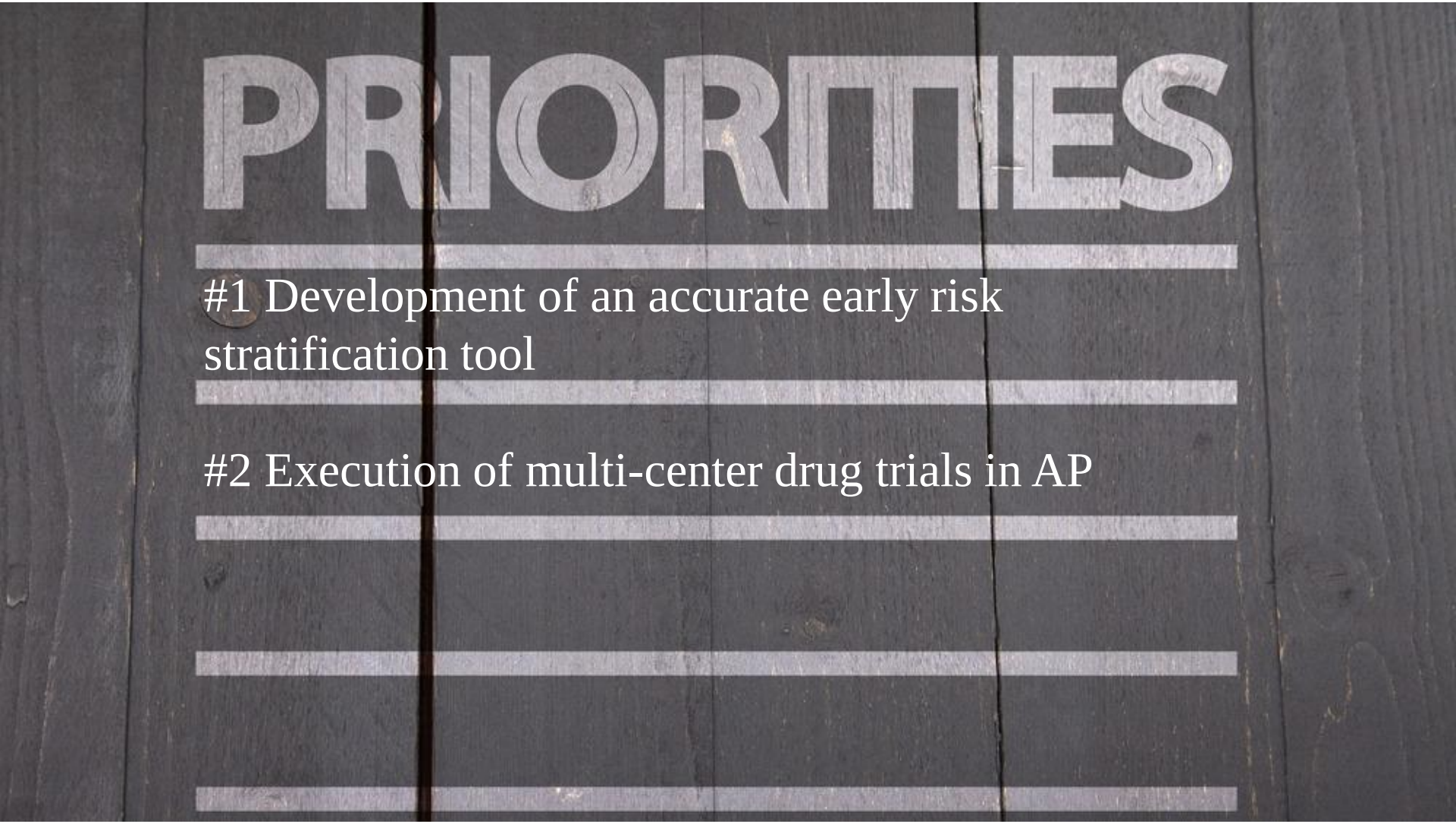
Acute Pancreatitis

>300k admissions/year; $3 billion



#1 Development of an accurate early risk stratification tool

#2 Execution of multi-center drug trials in AP

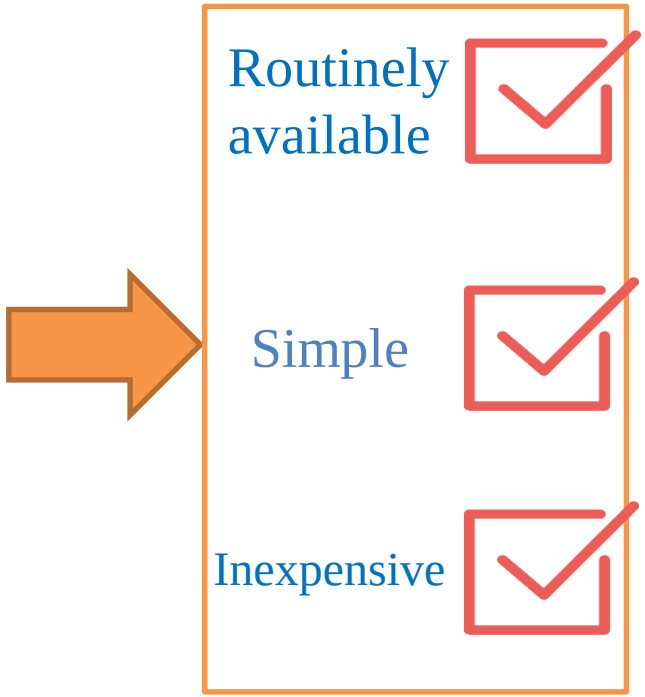
A prediction tool that is accurate, inexpensive and widely available in EARLY AP patients

Facilitate clinical trials

Predictive Tools Derived from Routine Clinical and Laboratory Parameters

BUN, Hematocrit, Creatinine

BISAP, Ranson's, APACHE-II, SIRS



Peak Cr predicts Pancreatic Necrosis

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Admission Hct	70.6% (53.8–83.2)	83.7 (74.8–89.9)	61.5 (45.9–75.1)	**88.5** (80.1–93.6)
48-h peak Cr	41.2 (26.4–57.8)	98.9 (94.2–99.8)	**93.3** (70.2–98.8)	82.1 (74.0–88.1)

CI, confidence interval; Cr, creatinine; Hct, hematocrit; NPV, negative predictive value; PPV, positive predictive value.

Bold values are most clinically important values.

Prospective, single center study of 129 subjects

Muddana V, …, Papachristou GI. Am J Gastroenterol 2009

BUN predicts Mortality

Cohort	BUN	Creatinine	APACHE II
BWH	0.84 (0.70-0.94)	0.86 (0.78-0.94)	0.89 (0.81-0.98)
DPSG	0.82 (0.74-0.90)	0.74 (0.63-0.84)	0.72 (0.63-0.82)
UPMC	0.91 (0.83-0.99)	0.96 (0.94-0.99)	0.92 (0.85-0.98)
Overall	0.84 (0.79-0.90)	0.79 (0.72-0.86)	0.80 (0.74-0.87)

Prospective, multicenter study of 1,043 subjects

Wu B, Papachristou GI, et al. Arch Intern Med 2011

Admission Hct & BUN Rise at 24 h

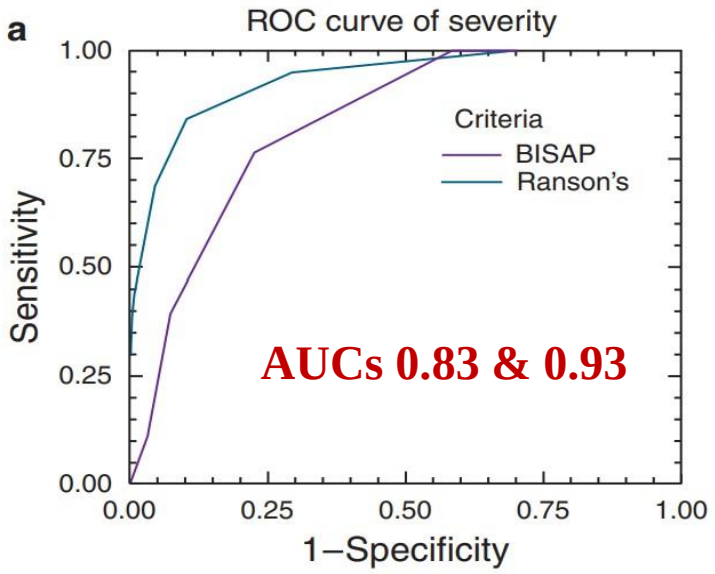
	Sensitivity	Specificity	PPV	NPV	AUC	Complete data[a]
Admission BUN ≥20 mg/dl	54.55 (47.53-61.43)	75.44 (72.41-78.29)	35.19 (29.99-40.66)	87.16 (84.54-89.49)	0.65 (0.61-0.69)	77%
Admission hematocrit ≥44%	59.16 (51.83-66.20)	74.24 (70.98-77.32)	36.57 (31.19-42.21)	87.87 (85.09-90.29)	0.67 (0.63-0.71)	69%
Admission creatinine ≥1.8 mg/dl	24.88 (19.23-31.25)	93.37 (91.51-94.93)	47.75 (38.18-57.44)	83.62 (81.15-85.89)	0.59 (0.56-0.62)	79%
Admission APACHE-II ≥8	68.42 (61.96-74.40)	64.50 (61.57-67.36)	28.94 (25.15-32.97)	90.63 (88.34-92.59)	0.66 (0.63-0.70)	95%
Rise in BUN at 24 h	62.68 (55.74-69.25)	78.71 (75.81-81.41)	41.85 (36.33-47.53)	89.61 (87.21-91.70)	0.71 (0.67-0.74)	77%
Rise in hematocrit at 24 h	29.84 (23.45-36.87)	84.49 (81.72-86.99)	32.57 (25.69-40.05)	82.75 (79.91-85.35)	0.57 (0.54-0.61)	69%
Rise in creatinine at 24 h	50.23 (43.32-57.14)	81.14 (78.39-83.68)	39.34 (33.49-45.42)	87.01 (84.51-89.24)	0.66 (0.62-0.69)	79%

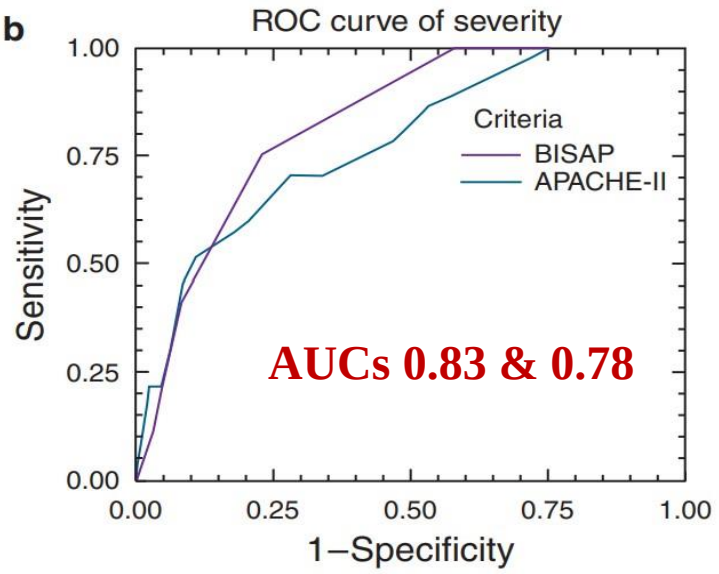
Prospective, multicenter study of 1,612 subjects

Koutroumpakis E, …, Papachristou GI. Am J Gastroenterol 2015

BISAP, Ranson's, APPACHE-II and CTSI

AUC (95% CI)	Severity	PNec	Mortality
BISAP	0.81 (0.74–0.87)	0.78 (0.69–0.85)	0.82 (0.67–0.91)
Ranson's	0.94 (0.89–0.97)	0.85 (0.79–0.90)	0.95 (0.90–0.98)
APACHE-II	0.78 (0.71–0.84)	0.72 (0.64–0.78)	0.94 (0.89–0.97)
CTSI	0.84 (0.76–0.89)	0.98 (0.94–1.00)	0.83 (0.75–0.89)





Prospective, single center study of 185 subjects

Papachristou GI, et al. Am J Gastroenterol 2010

Head-to-Head Score Comparison

Score	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC	Complete data[a]
APACHE-II	7	0.84 (±0.11)	0.71 (±0.06)	0.49 (±0.11)	0.93 (±0.08)	0.77 (±0.07)	96%
BISAP	2	0.61 (±0.20)	0.84 (±0.04)	0.54 (±0.10)	0.87 (±0.10)	0.72 (±0.10)	100%
Glasgow	2	0.85 (±0.08)	0.83 (±0.07)	0.61 (±0.06)	0.95 (±0.05)	**0.84** (±0.06)	98%
HAPS	1	0.70 (±0.11)	0.53 (±0.21)	0.32 (±0.11)	0.85 (±0.13)	0.62 (±0.06)	99%
JSS	2	0.59 (±0.13)	0.92 (±0.05)	0.70 (±0.16)	0.88 (±0.07)	0.76 (±0.07)	95%
Panc 3	1	0.76 (±0.15)	0.52 (±0.05)	0.34 (±0.11)	0.87 (±0.11)	0.64 (±0.06)	99%
POP	9	0.57 (±0.15)	0.76 (±0.06)	0.43 (±0.16)	0.85 (±0.08)	0.67 (±0.09)	99%
Ranson	2	0.66 (±0.09)	0.78 (±0.10)	0.49 (±0.17)	0.88 (±0.08)	0.72 (±0.06)	98%
SIRS	2	0.70 (±0.18)	0.71 (±0.04)	0.43 (±0.10)	0.88 (±0.11)	0.70 (±0.10)	98%
BUN	23	0.56 (±0.10)	0.86 (±0.05)	0.57 (±0.14)	0.86 (±0.05)	0.71 (±0.03)	98%
Creatinine	1	0.77 (±0.09)	0.59 (±0.04)	0.38 (±0.08)	0.89 (±0.04)	0.68 (±0.06)	98%
Validation cohort							
APACHE-II	7	0.97 (±0.08)	0.44 (±0.06)	0.14 (±0.04)	0.99 (±0.02)	0.71 (±0.05)	100%
BISAP	2	0.62 (±0.20)	0.76 (±0.04)	0.20 (±0.06)	0.96 (±0.04)	0.69 (±0.11)	100%
Glasgow	2	0.65 (±0.24)	0.82 (±0.05)	0.22 (±0.08)	0.97 (±0.02)	**0.74** (±0.10)	91%
HAPS	1	0.73 (±0.26)	0.58 (±0.09)	0.12 (±0.06)	0.97 (±0.02)	0.66 (±0.09)	92%
JSS	2	0.42 (±0.19)	0.89 (±0.05)	0.23 (±0.18)	0.95 (±0.01)	0.66 (±0.11)	91%
Panc 3	1	0.62 (±0.31)	0.52 (±0.05)	0.11 (±0.05)	0.94 (±0.04)	0.57 (±0.16)	100%
POP	9	0.46 (±0.31)	0.81 (±0.04)	0.16 (±0.12)	0.95 (±0.02)	0.64 (±0.16)	90%
Ranson	2	0.46 (±0.28)	0.80 (±0.03)	0.16 (±0.11)	0.95 (±0.02)	0.63 (±0.15)	91%
SIRS	2	0.69 (±0.16)	0.58 (±0.04)	0.11 (±0.03)	0.96 (±0.03)	0.64 (±0.01)	93%
BUN	23	0.65 (±0.26)	0.81 (±0.04)	0.21 (±0.09)	0.97 (±0.03)	0.73 (±0.13)	96%
Creatinine	1	0.77 (±0.20)	0.63 (±0.07)	0.14 (±0.12)	0.97 (±0.02)	0.70 (±0.11)	98%

Prospective, dual center study: Training of 256; Validation Cohort 397 subjects

Mounzer R, ..., Papachristou GI. Gastroenterology 2012

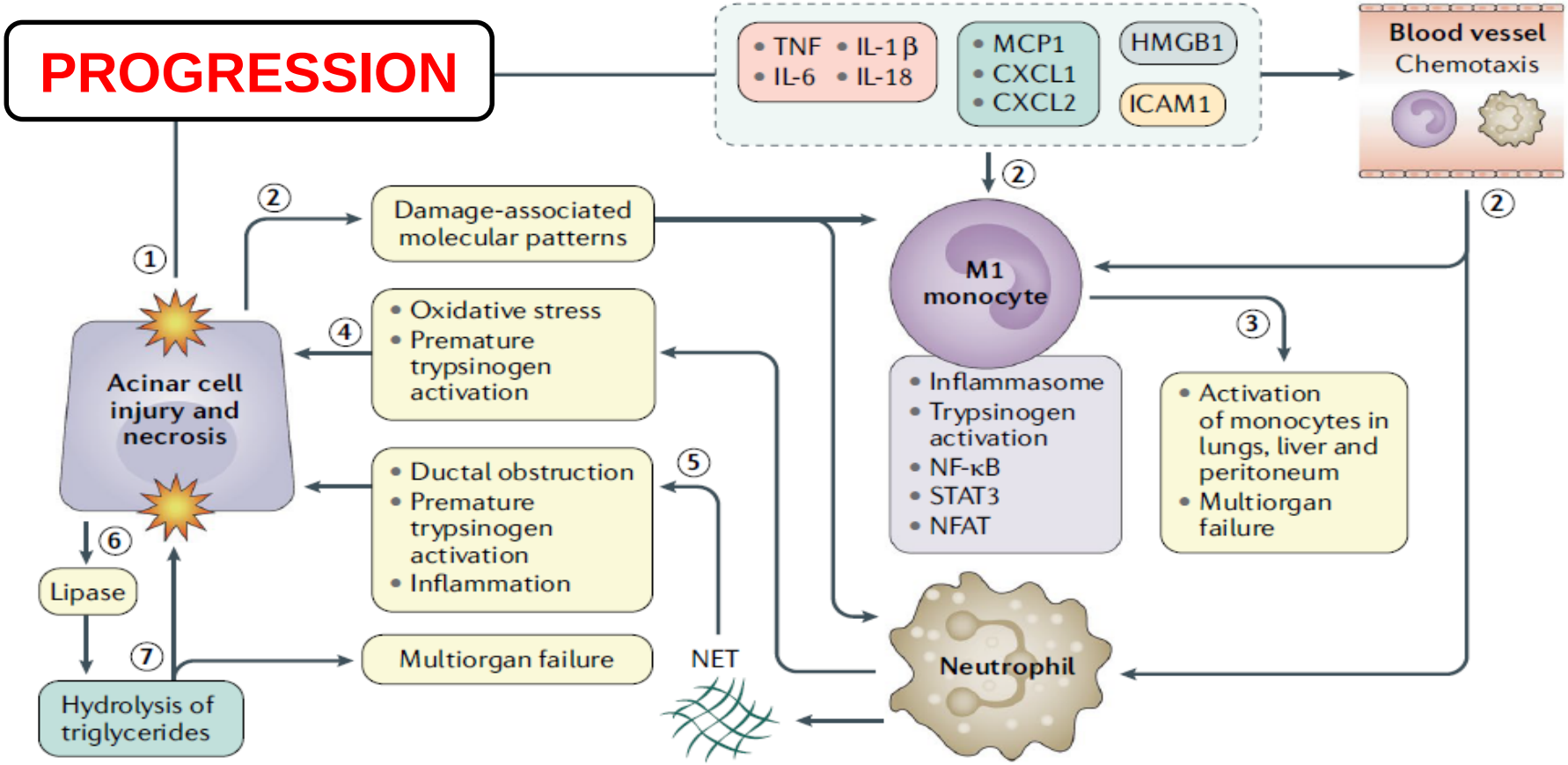
Laboratory Tests and **Clinical Scores**

have reached their maximal efficacy in

predicting clinical AP outcomes (Necrosis, POF, Death)

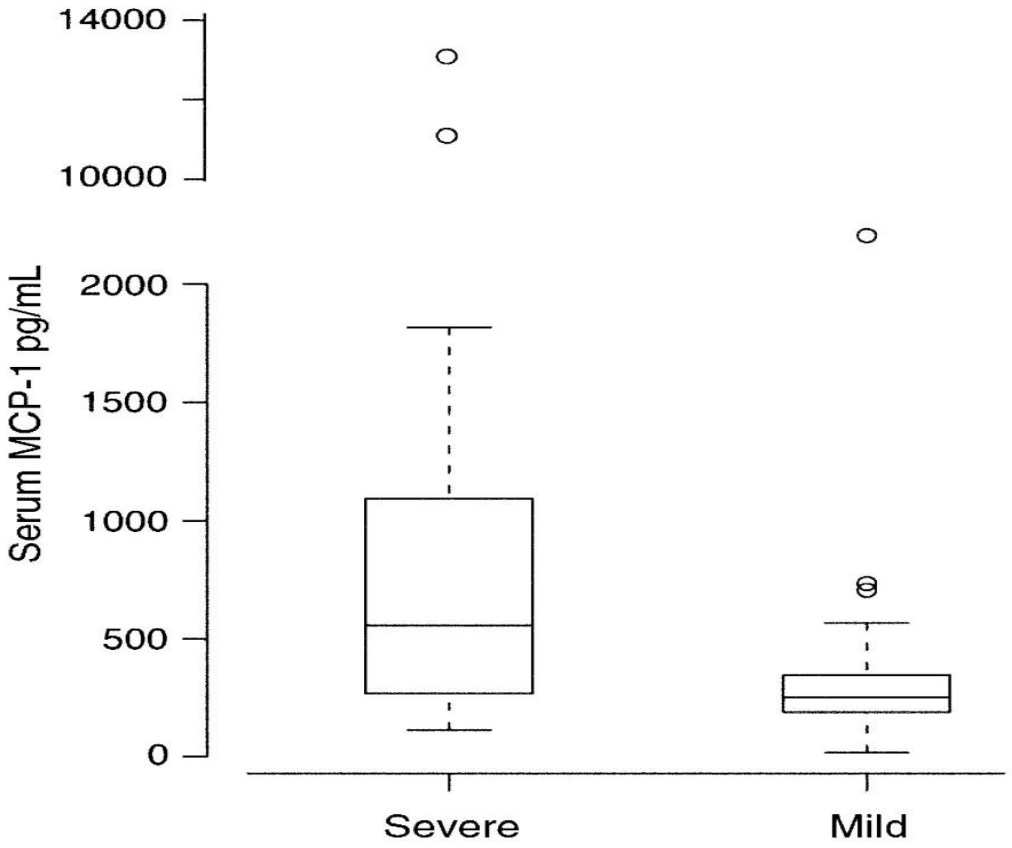
with only a **modest accuracy** of ≤80%

Cytokines



Lee PJ, Papachristou GI. Nat Rev Gastroenterol 2020

Monocyte Chemotactic Protein-1 (MCP-1)

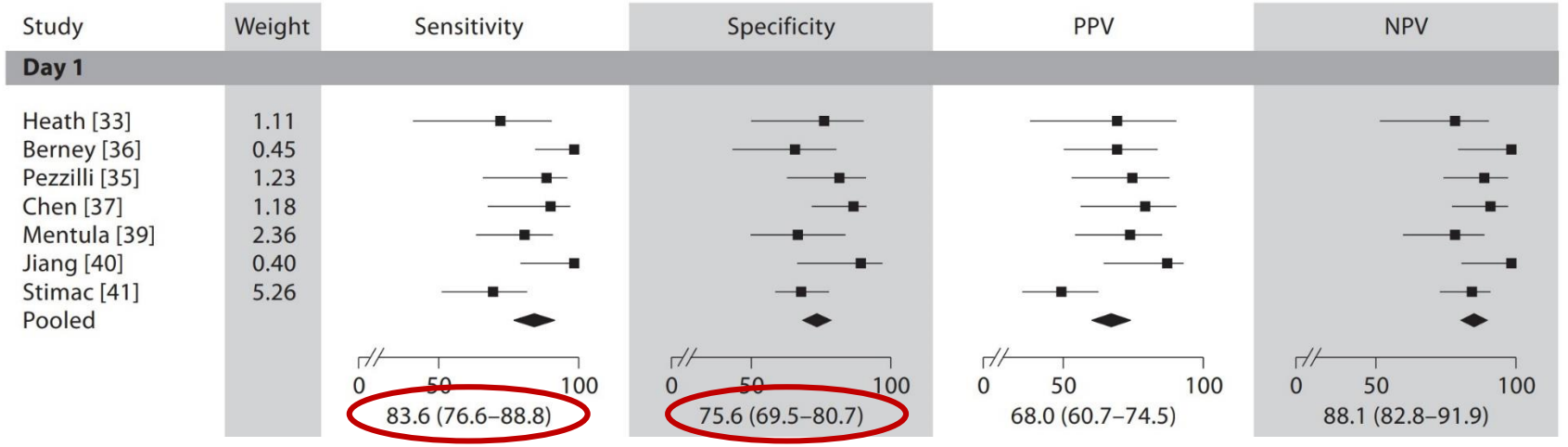


Prospective single center study of 77 subjects

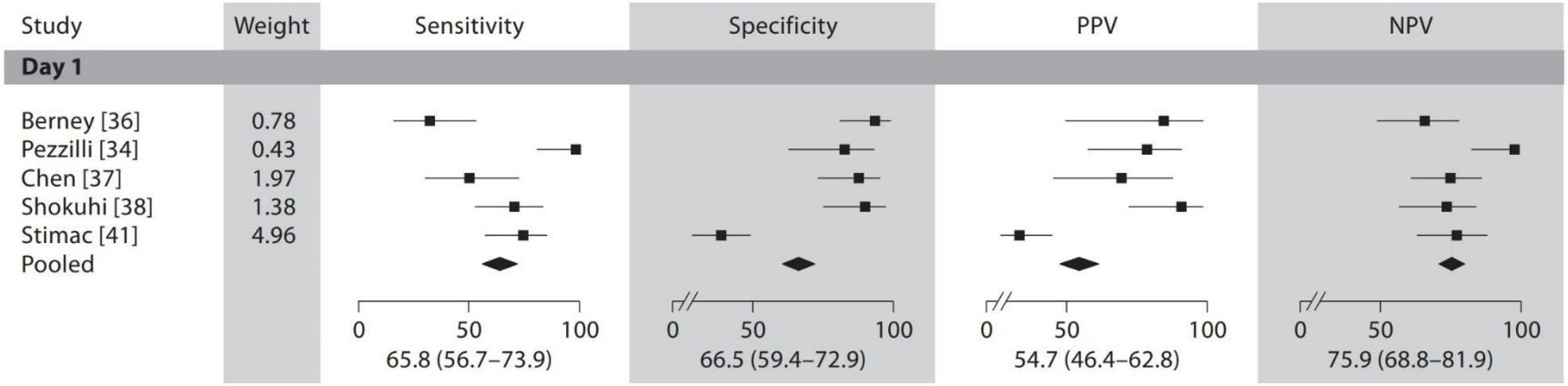
Papachristou GI, ..., Whitcomb DC. Clin Gastroenterol Hepatol 2005

IL-6 and IL-8

IL-6



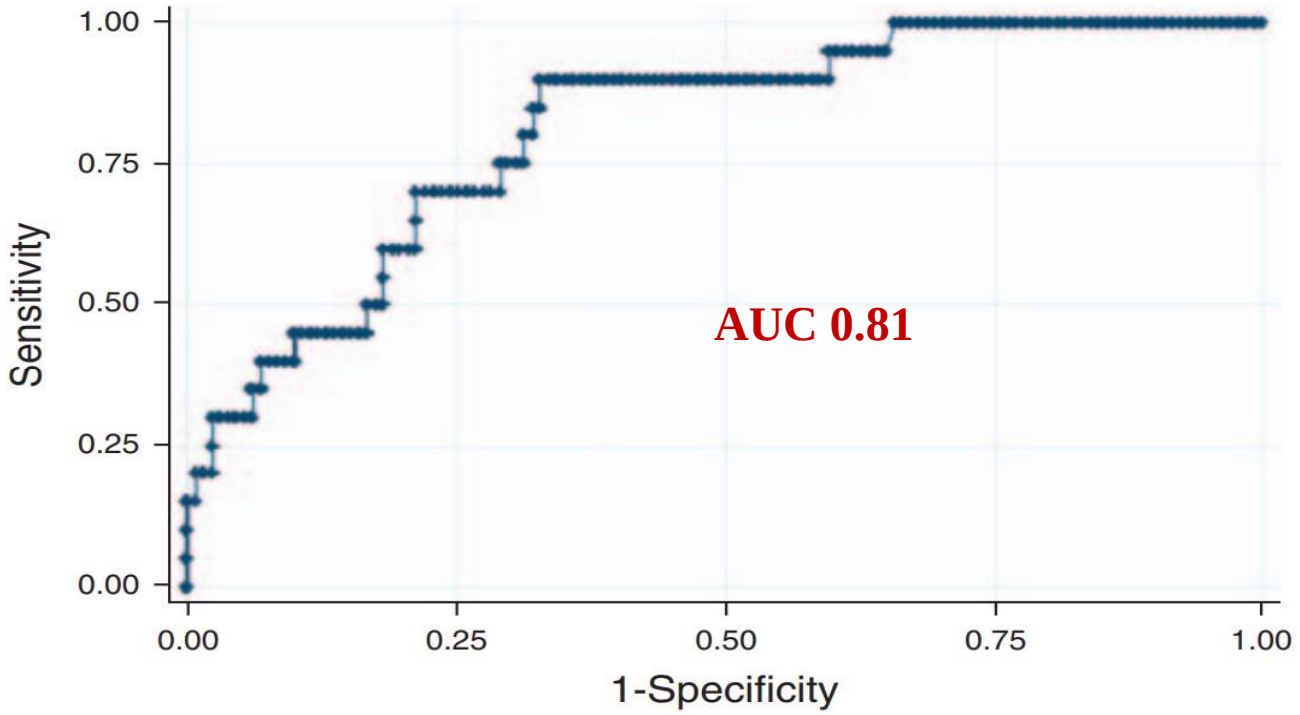
IL-8



Meta-analysis of 10 studies (150-385 subjects)

Aoun E, ..., Papachristou GI. Pancreatology 2009

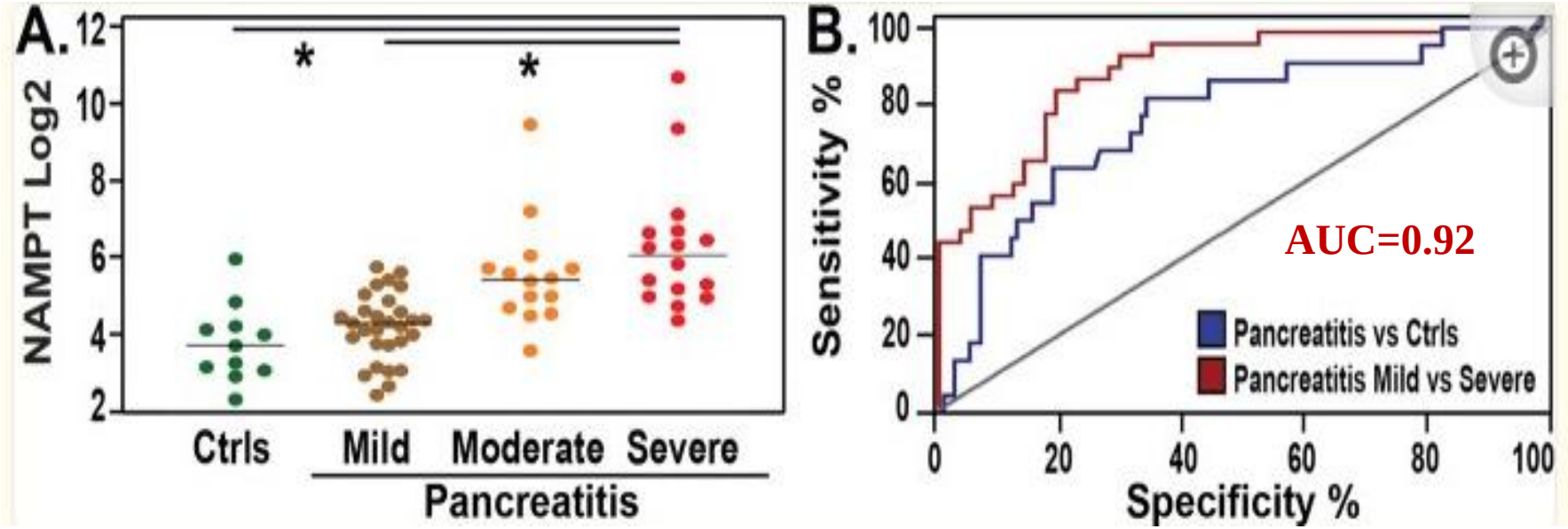
Angiopoietin-2



Prospective, dual center study of 151 subjects

Whitcomb DC, …, Papachristou GI. Am J Gastroenterol 2010

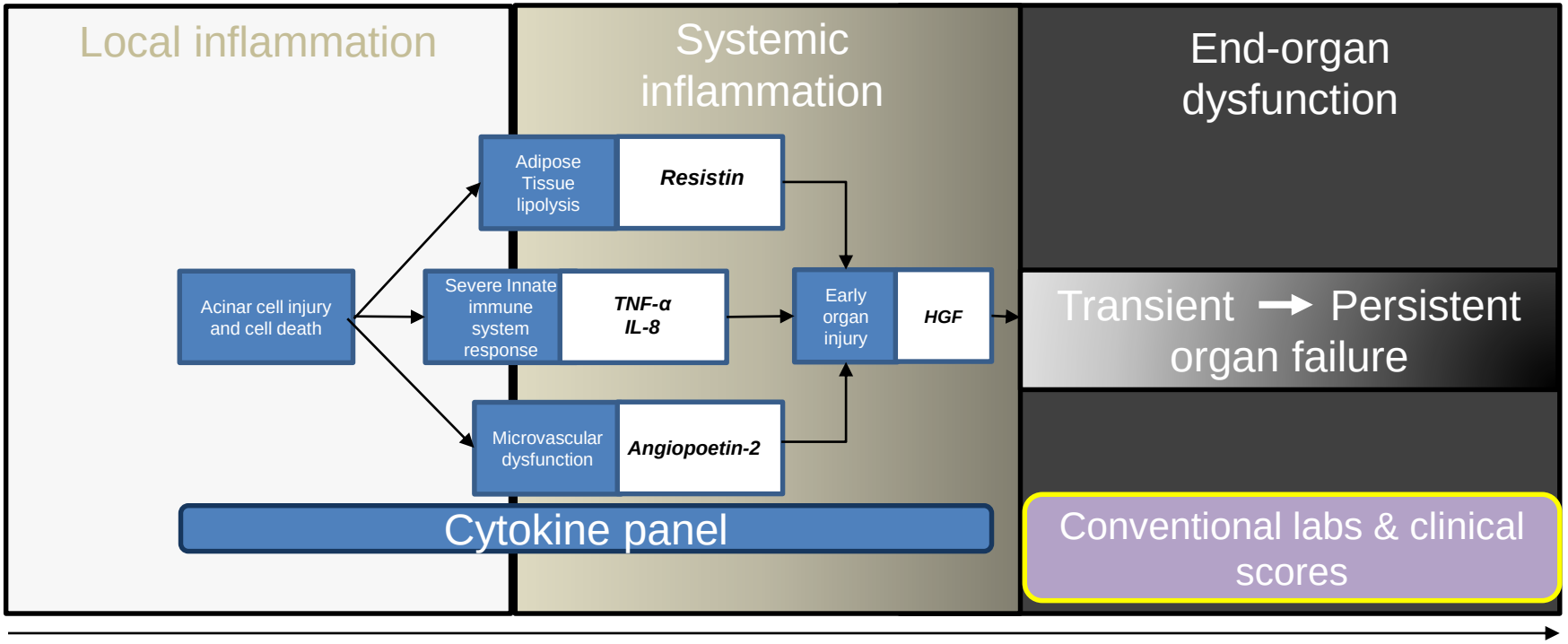
Nicotinamide Phosphoribosyl-Transferase (eNAMPT)



Prospective multicenter study of 671 subjects: Trauma, Sepsis, ARDS, and AP

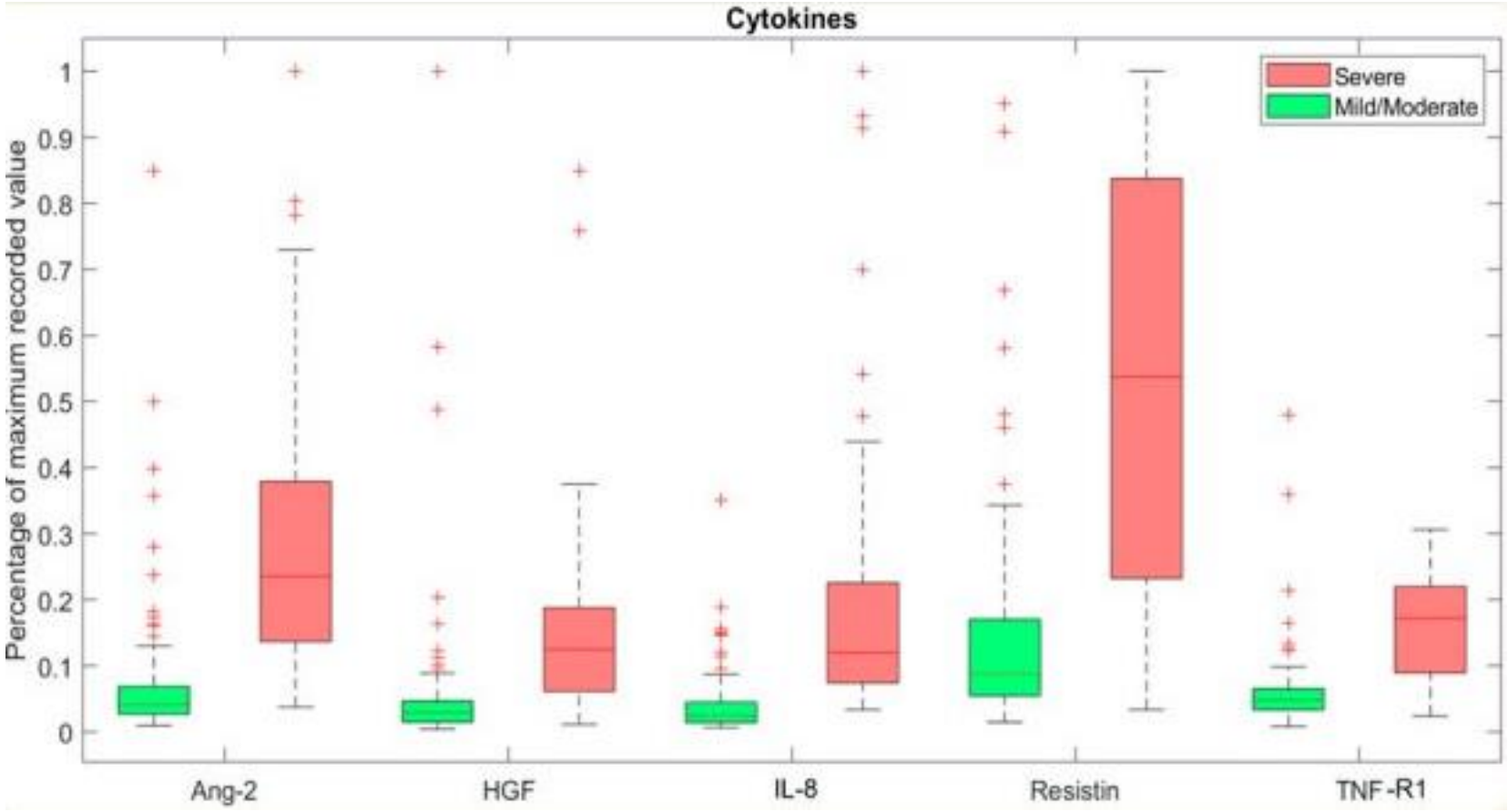
Bime C, Papachristou GI, et al. BMC Anesthesiol 2022

Combining Cytokines



Lee PJ, …, Papachristou GI. Clin Transl Gastroenterol 2022

5-cytokine panel

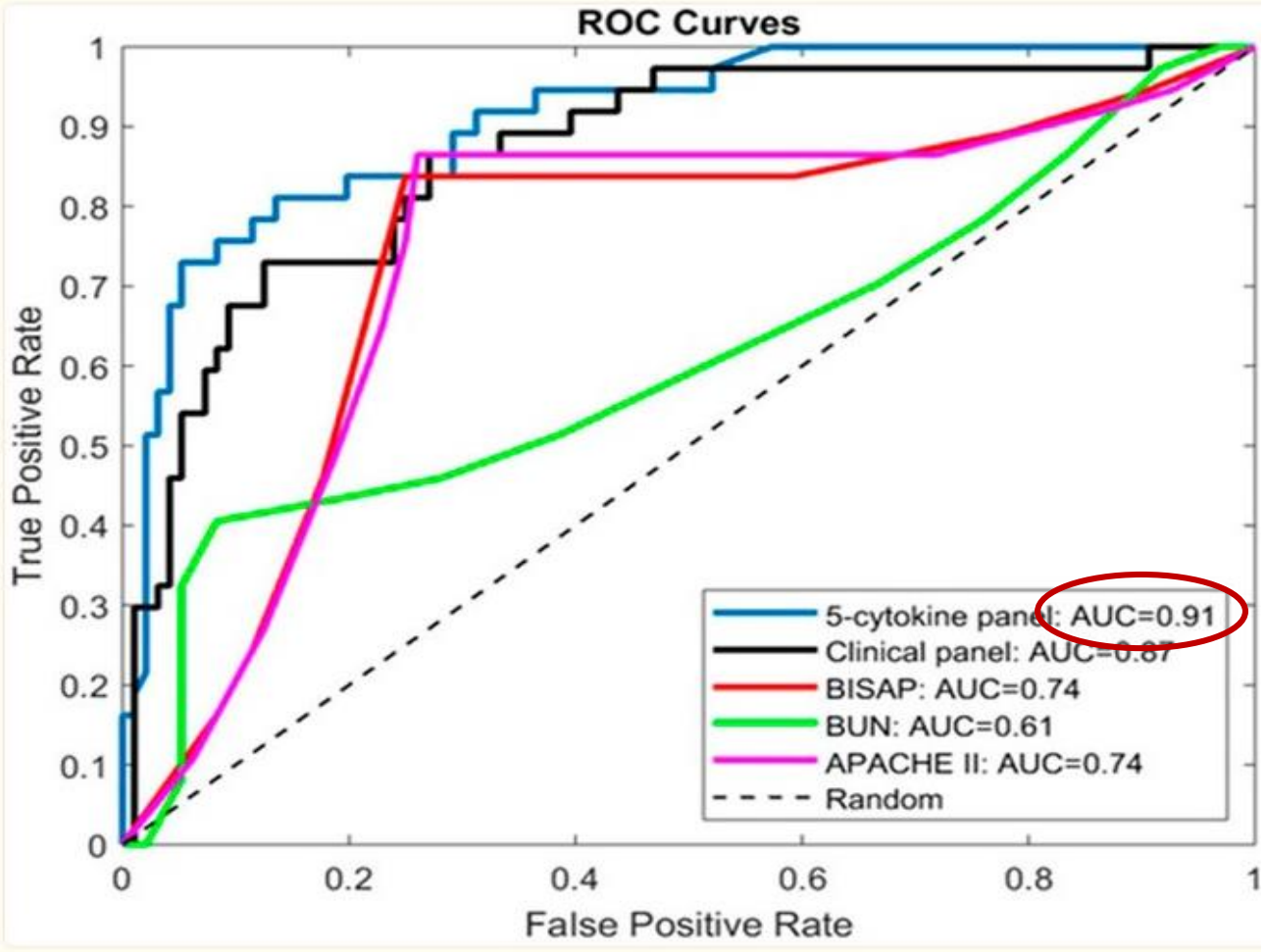


Prospective, single center study: Derivation of 60; Validation Cohort 133 subjects

Supported by a VA Merit Review Award

Lee PJ, …, Papachristou GI. Clin Transl Gastroenterol 2020

5-cytokine panel



Lee PJ, …, Papachristou GI. Clin Transl Gastroenterol 2020

MOSAIC Proposal

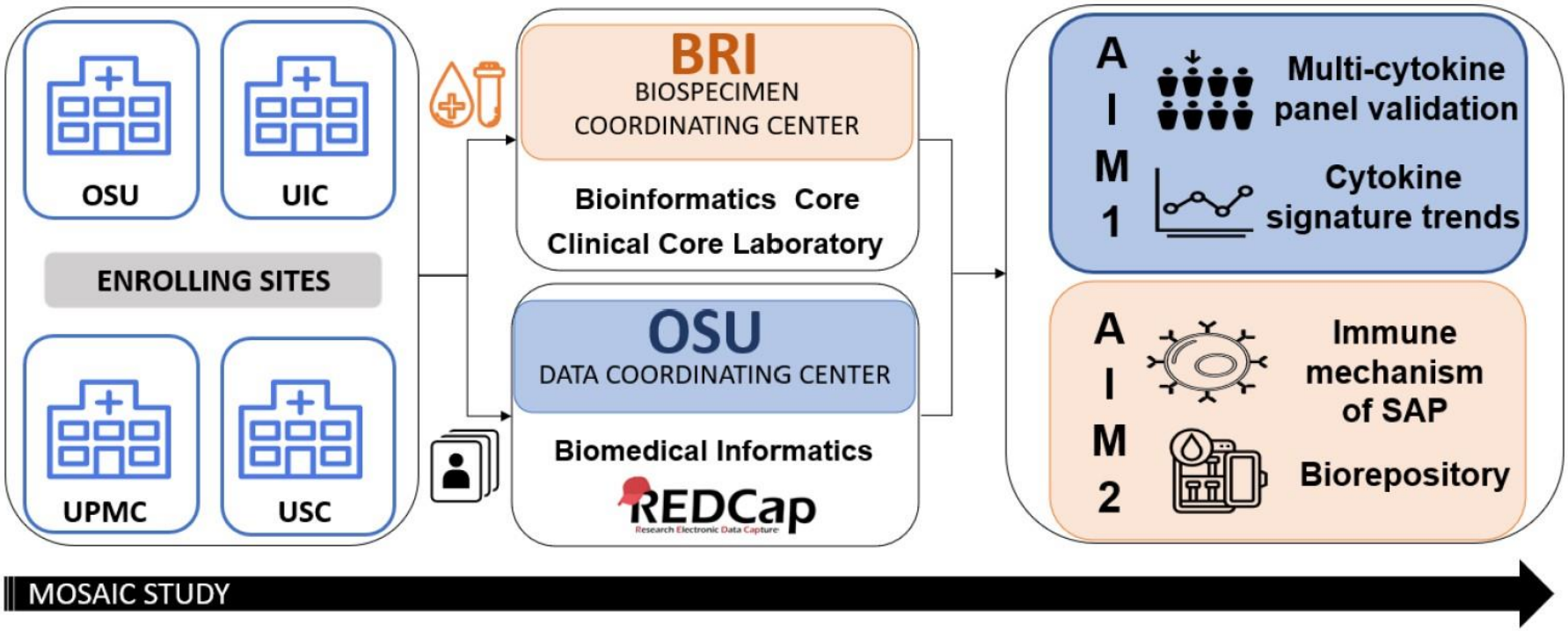
- **Aim 1: Validate the novel multi-cytokine panel for early prediction of SAP**

- Methods: Enrollment within 36 hrs of AP presentation

  Cytokines measurement using Olink, a well-established multiplex platform
- **Aim 1.1**: Validate multi-cytokine panel accuracy and compare it to existing prediction tools (BUN, SIRS)
- **Aim 1.2**: Correlate cytokine trends over time with clinically relevant AP outcomes (OF, LOS) in samples collected over course of AP hospitalization
- Expected Outcome: For the first time, the scientific community will have a highly accurate SAP predictive tool available for research purposes

- Future Directions: Development of a **point-of-care test** based on the multi-cytokine panel for real-time use at bedside

MOSAIC Study Network



MOSAIC

- Sample Size n=198
- Duration 5 years
- Part of the NIDDK T1DAP Consortium
- Collaborators
  - Cate Speake, Adam Lacy-Hulbert (BRI)
  - Peter Lee, Darwin Conwell (OSU)
  - Anna Evans (UPMC)
  - Cemal Yazici (UIC)
  - James Buxbaum (USC)

- Submitted in February 2022; **scored in 10th percentile**

Thank you