



# Pancreatic Cancer Bake-Off Projects Updates

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# Updates

- ▶ Pancreatic cancer bake-off projects involve collaboration between
  - ❖ UPMC, MD Anderson (Mayo), Van Andel, UNMC, FHCRC
- ▶ **Bake-off 1:** analyses for individual labs completed with labs unblinded; candidate panels across labs developed by DMCC for validation
- ▶ **Bake-off 2:** data analysis ongoing
- ▶ **Bake-off 3:** pre-diagnostic samples sent to individual labs

# Bake-off 1 Cross-Lab Panels Development

- ▶ Objective: develop candidate cross-lab biomarker panels for validation in the follow-up team projects

# Samples for Panel Development

- ▶ Samples collected from
  - University of Pittsburgh
  - MD Anderson
- ▶ Distribution
  - PDAC Cases (n=71)
  - Controls (n=68)
    - Including both healthy and benign controls

# Candidate Markers Tested

Site	Marker
<b>VARI</b>	CA19-9, CA199:sTRA, and MUC5AC:sTRA
<b>MDACC</b>	TIMP1, LRG1, and CA19-9
<b>UNMC</b>	MUC5AC, MUC4
<b>UPMC</b>	CA19-9, angiotensin, and thrombospondin
<b>FHRC</b>	PMS2 (protein) and DCD, PODXL

A longer list of 36 markers were also explored

# Performance Criterion for Panel Assessment

- ▶ Area under the ROC curve
- ▶ Sensitivity at 95% (90%) specificity
  - towards the use of the biomarker to enrich the high-risk population for imaging surveillance
- ▶ Improvement over CA19.9
  - for panel development, we explored different lab CA19.9 assays. Panels presented were based on UPMC CA19.9, which is highly correlated with results from clinical CA19.9 assay

# Methods

- ▶ **LASSO (least absolute shrinkage and selection operator)**
  - tuning based on minimizing deviance
  - tuning based on 1SE rule (for more parsimonious model)
- ▶ **Classification tree**
  - Reasonable accuracy, suboptimal sensitivity at high specificity
- ▶ **Random Forest**
- ▶ **Support Vector Machine**
- ▶ **OR rule: test positive if either marker elevated**

**Random cross-validation** was conducted to compare performance of different algorithms, accounting for variability due to variable selection and model fitting

# Results

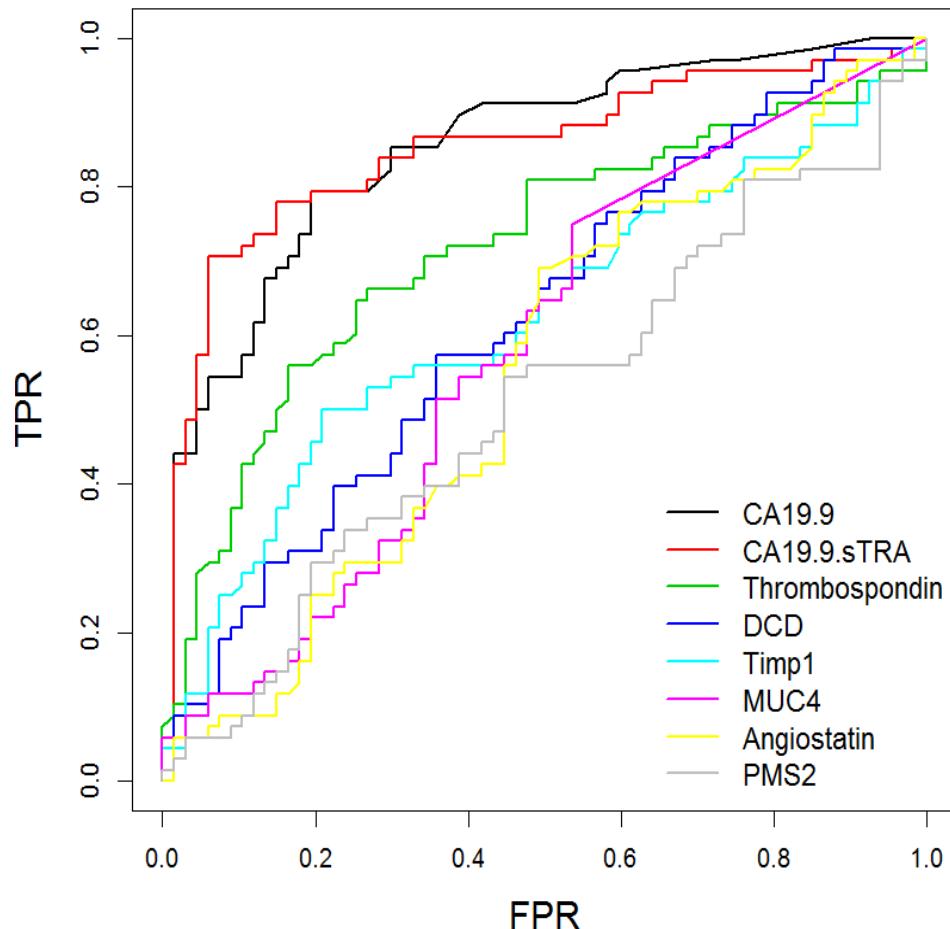
LASSO (deviance): 8-markers

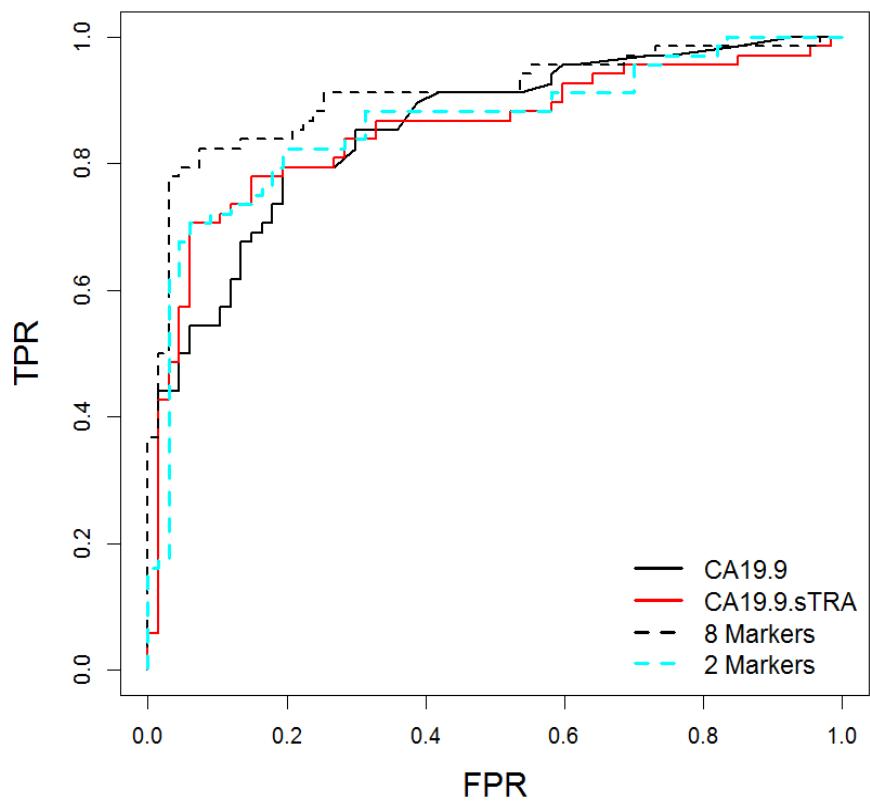
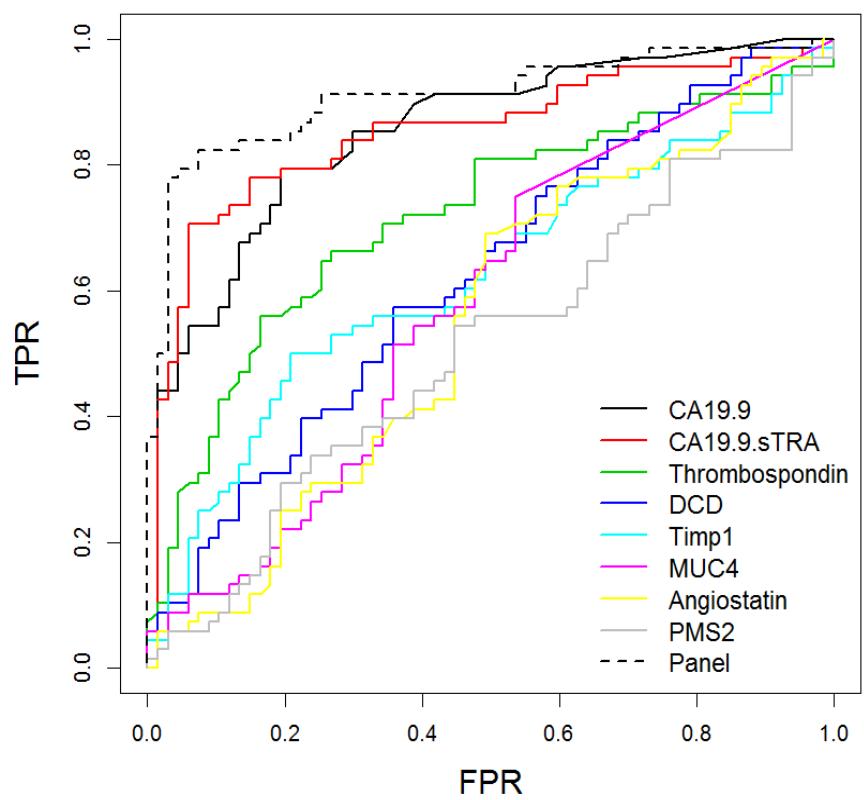
LASSO (1SE): 2 markers

(CA19.9+CA19.9TRA)

Site	Biomarker	AUC	Sensitivity at 95% specificity
-	CA199	0.85 (0.79, 0.91)	0.5 (0.23, 0.67)
VAI	sTRA	0.85 (0.77, 0.91)	0.57 (0.28, 0.77)
UPMC	Thrombospondin	0.72 (0.62, 0.81)	0.25 (0.09, 0.44)
FHCRC	DCD	0.62 (0.49, 0.71)	0.1 (0.02, 0.27)
MDACC	TIMP1	0.62 (0.49, 0.72)	0.15 (0.03, 0.32)
UNMC	MUC4	0.58 (0.48, 0.67)	0.09 (0.03, 0.18)
UPMC	Angiostatin	0.55 (0.47, 0.63)	0.06 (0.01, 0.13)
FHCRC	PMS2	0.51 (0.46, 0.62)	0.07 (0.01, 0.22)
All	Panel	0.91 (0.88, 0.98)	0.79 (0.55, 0.93)

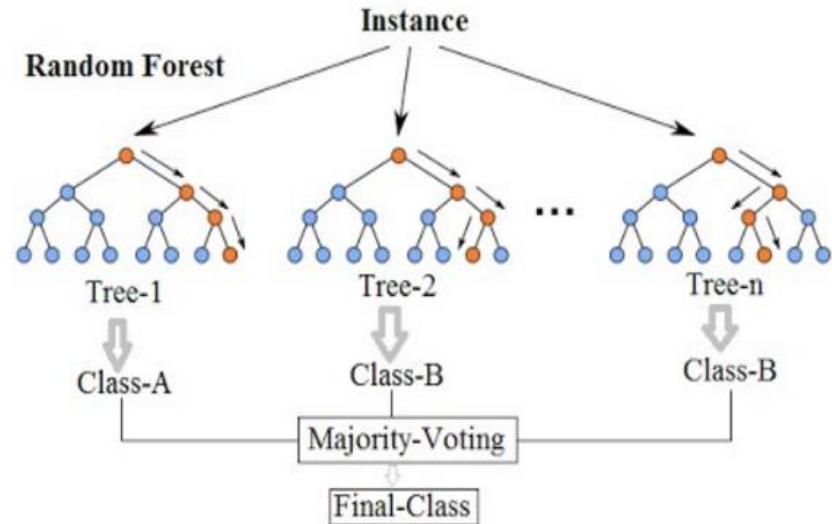
Markers selected (deviance)





	AUC		Sen at 95% spe		Sen at 90% spe	
	Naïve	CV	Naïve	CV	Naïve	CV
CA199	0.85	0.85	0.5	0.54	0.54	0.61
8 marker	0.91	0.84	0.79	0.61	0.82	0.69
2 marker	0.86	0.84	0.68	0.62	0.72	0.7

# Random Forest



- We included a variable selection component in RF
  - Select a parsimonious set with RF CV-performance close to the maximum
  - Refit RF based on the parsimonious set

# Random Forest

- ▶ Small performance improvement compared to LASSO
- ▶ Panels derived has similar CV-AUC as CA199, with 10–12% increase in sensitivity at 95% and 90% specificity

- (I): CA199+CA199.sTRA+Thrombospondin
- (II): (I)+MUC5AC+MUC4
- (III): (I)+CA125+MUC5AC\*
- (IV): (III)+IGFBP3\*

\*: start from the longer list of markers

Similar performance across panels

# OR Rule Development

- ▶ Start with CA199 and CA199.sTRA and add the 3<sup>rd</sup> marker
- ▶ Test positive if  
CA199 **OR** CA199.sTRA **OR** marker 3 is elevated

	Spe		Sen	
	Naïve	CV	Naïve	CV
CA199+CA199.sTRA	0.91	0.89	0.75	0.73
CA199+CA199.sTRA+Angiostatin	0.91	0.89	0.79	0.76

CV performance of  
CA199 alone  
Sen=0.61 at 90% Spe

# Summary

- ▶ CA199.sTRA combined with CA199 helps improve sensitivity at high specificity
- ▶ Potential to add additional markers to further improve performance
- ▶ Propose to fix a few candidate panels based on LASSO, Random Forest, OR rules to test in bake-off 2 project

# Pancreatic Cancer Bake-off 2

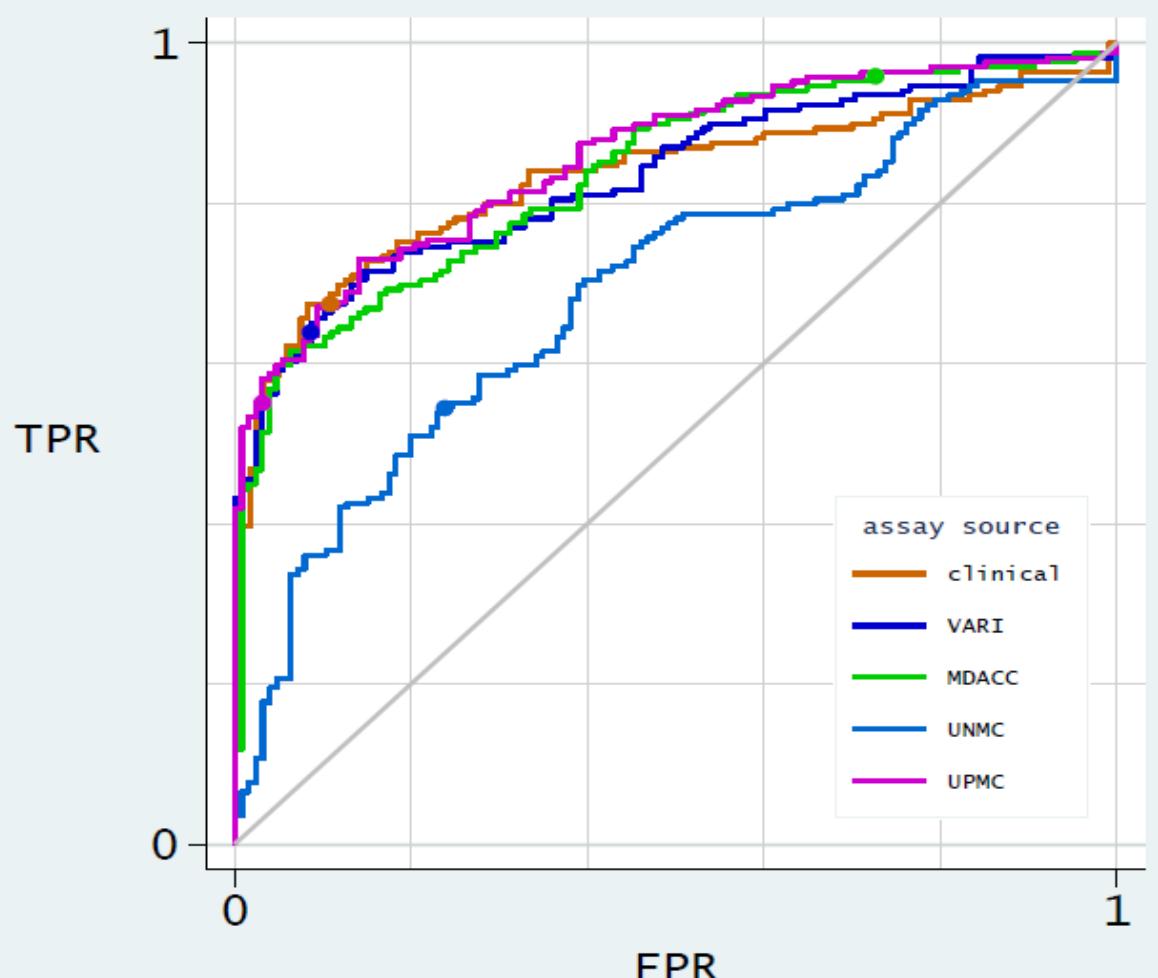
- ▶ 340 Case/Control samples from UPMC and MD Anderson
- ▶ Cases: PDAC, high grade IPMN/MCN, other pancreatic cancers (cholangiocarcinoma, neuroendocrine tumors, ampullary carcinoma)
- ▶ Controls: healthy control with or w/o family history, pancreatitis, benign biliary obstruction, low grade MCN/IPMN and benign cysts

# CA199 Assays Evaluation

- ▶ Individual labs use research CA199 assays for biomarker (panel) development.
- ▶ Important to understand quality in research CA199 assay and to have a common CA199 standard for gauging individual marker's performance and/or their incremental value over CA199

# CA199 Assays

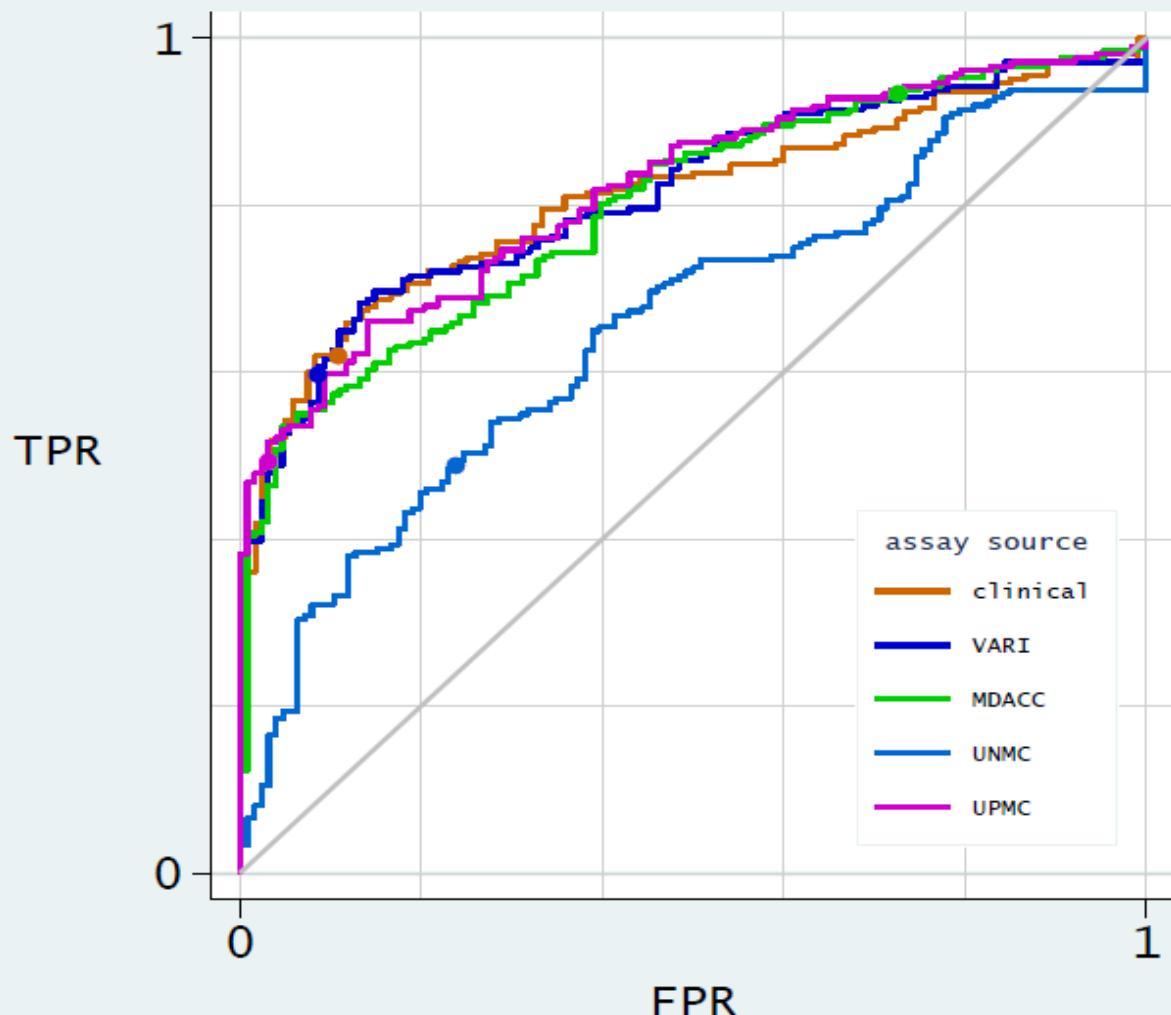
- ▶ Clinical CA199 measure provided by UPMC and MD Anderson
- ▶ Research CA199
  - ❖ UPMC (Lokshin)
  - ❖ Van Andel (Haab)
  - ❖ MD Anderson (Hanash)
  - ❖ UNMC (Batra)
- ▶ Evaluate classification performance of clinical and research assays and assess their correlations



marker	AUC	sens(spec=.90)	spec(sens=.90)
clinical	0.83 (0.78,0.88)	0.67 (0.57,0.76)	0.27 (0.13,0.59)
VARI	0.83 (0.79,0.88)	0.66 (0.55,0.75)	0.42 (0.22,0.57)
MDACC	0.84 (0.79,0.88)	0.62 (0.55,0.71)	0.51 (0.35,0.63)
UNMC	0.69 (0.63,0.75)	0.36 (0.20,0.48)	0.23 (0.14,0.32)
UPMC	0.86 (0.82,0.90)	0.67 (0.56,0.75)	0.52 (0.37,0.66)

binary calls	sensitivity	specificity
clinical	0.67 (0.60,0.74)	0.89 (0.82,0.94)
VARI	0.64 (0.56,0.71)	0.91 (0.85,0.95)
MDACC	0.96 (0.92,0.98)	0.27 (0.20,0.36)
UNMC	0.54 (0.47,0.62)	0.76 (0.68,0.83)
UPMC	0.55 (0.48,0.62)	0.97 (0.92,0.99)

Binary call based on threshold of 37 U/ml

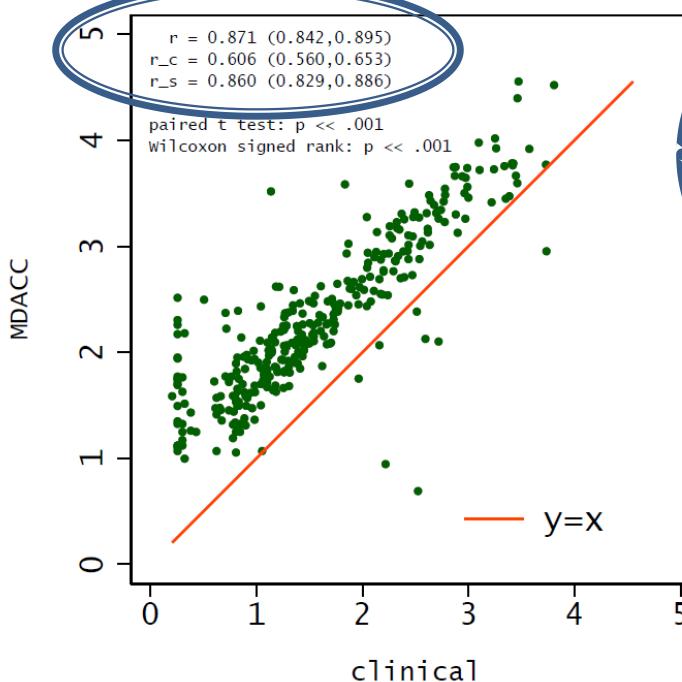
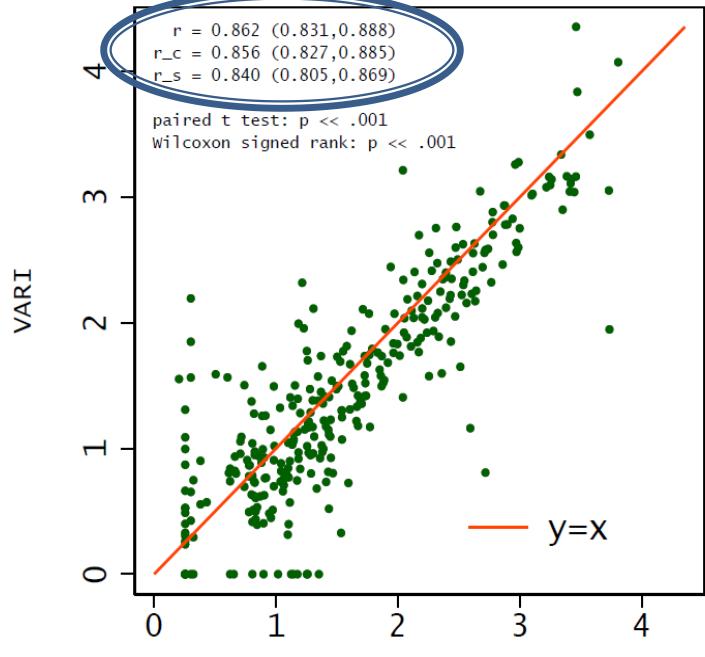


PDAC  
 +High grade IPMN/MCN  
 +other pancreatic cancer  
 vs  
 all benign/healthy

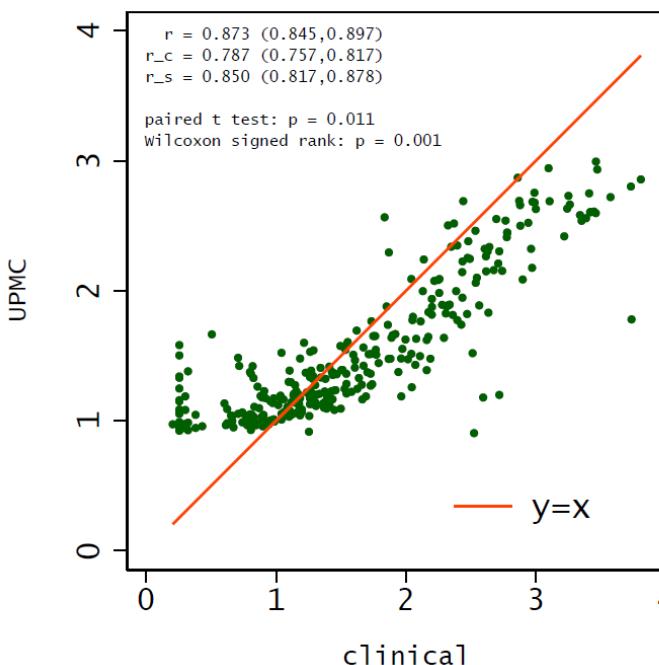
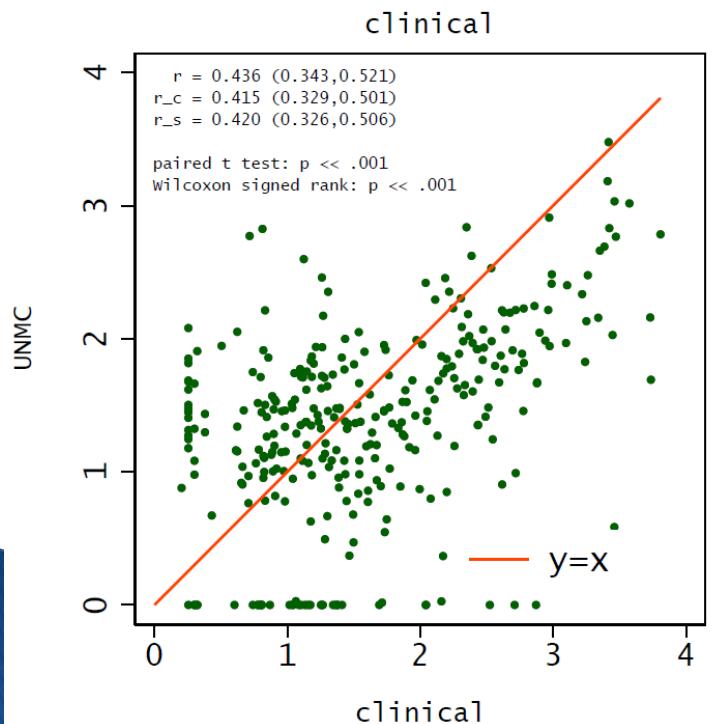
marker	AUC	sens(spec=.90)	spec(sens=.90)
clinical	0.81 (0.76,0.85)	0.62 (0.52,0.71)	0.27 (0.18,0.45)
VARI	0.81 (0.77,0.86)	0.62 (0.49,0.72)	0.40 (0.22,0.54)
MDACC	0.80 (0.75,0.84)	0.56 (0.49,0.65)	0.39 (0.24,0.55)
UNMC	0.66 (0.60,0.71)	0.32 (0.18,0.43)	0.22 (0.13,0.30)
UPMC	0.82 (0.77,0.86)	0.60 (0.49,0.69)	0.41 (0.25,0.57)

binary calls	sensitivity	specificity
clinical	0.62 (0.55,0.68)	0.89 (0.82,0.94)
VARI	0.60 (0.53,0.66)	0.91 (0.85,0.95)
MDACC	0.93 (0.89,0.96)	0.27 (0.20,0.36)
UNMC	0.49 (0.42,0.56)	0.76 (0.68,0.83)
UPMC	0.49 (0.43,0.56)	0.97 (0.92,0.99)

Binary call based on  
 threshold of 37 U/ml



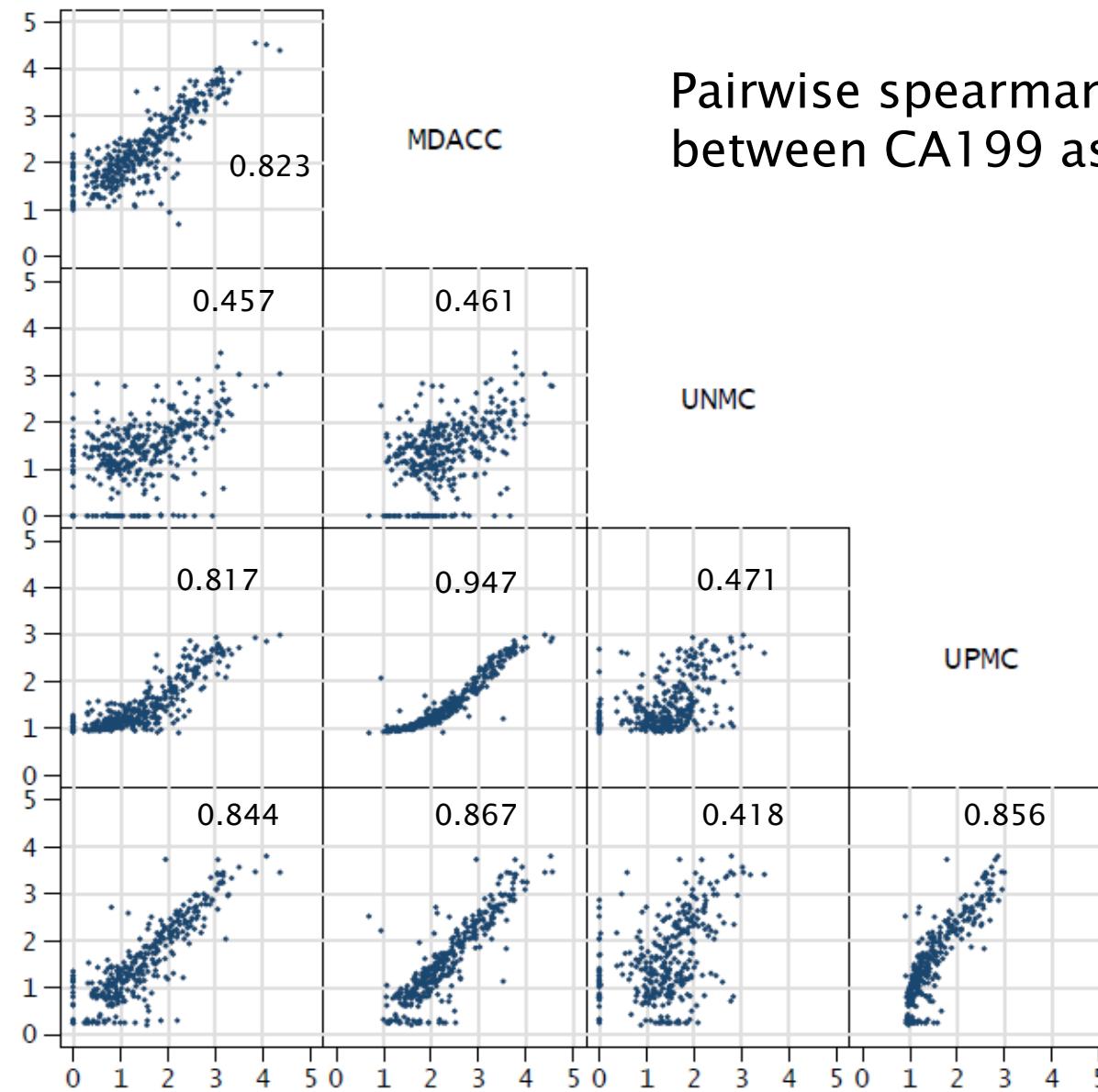
**r** :Pearson corr  
**r\_c** :concordance  
**r\_s** :Spearman corr



Values on the X and Y axis are  $\log_{10}(\text{CA199}+1)$

VARI

Pairwise spearman (rank) correlation  
between CA199 assays



# Summary

- ▶ High correlations observed between clinical CA199 assay and several research assays, with comparable performance with respect to AUC and sensitivity at high specificity
- ▶ Calibration can differ, suggesting the use of different thresholds for binary tests

# Acknowledgment

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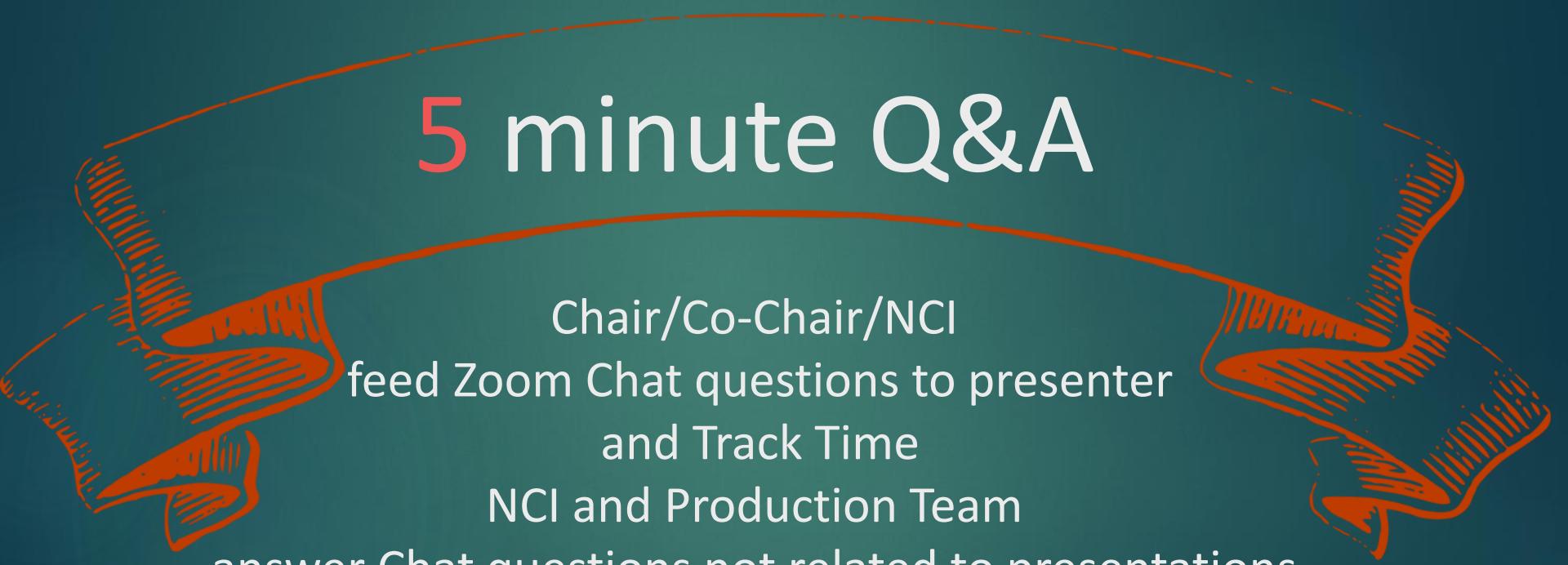
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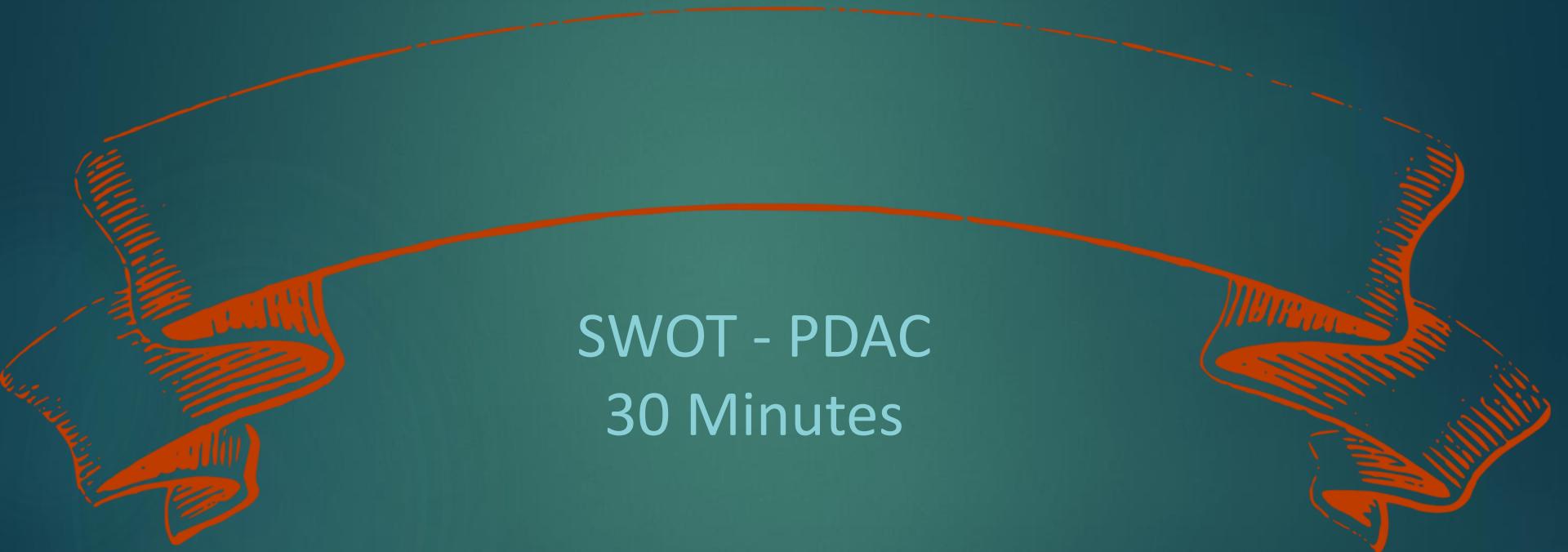


# 5 minute Q&A

Chair/Co-Chair/NCI  
feed Zoom Chat questions to presenter  
and Track Time  
NCI and Production Team  
answer Chat questions not related to presentations  
and use Slack



Team Project Group Discussion  
15 Minutes



# SWOT - PDAC

## 30 Minutes