Preoperative Prognostication of Pancreatic Cancer

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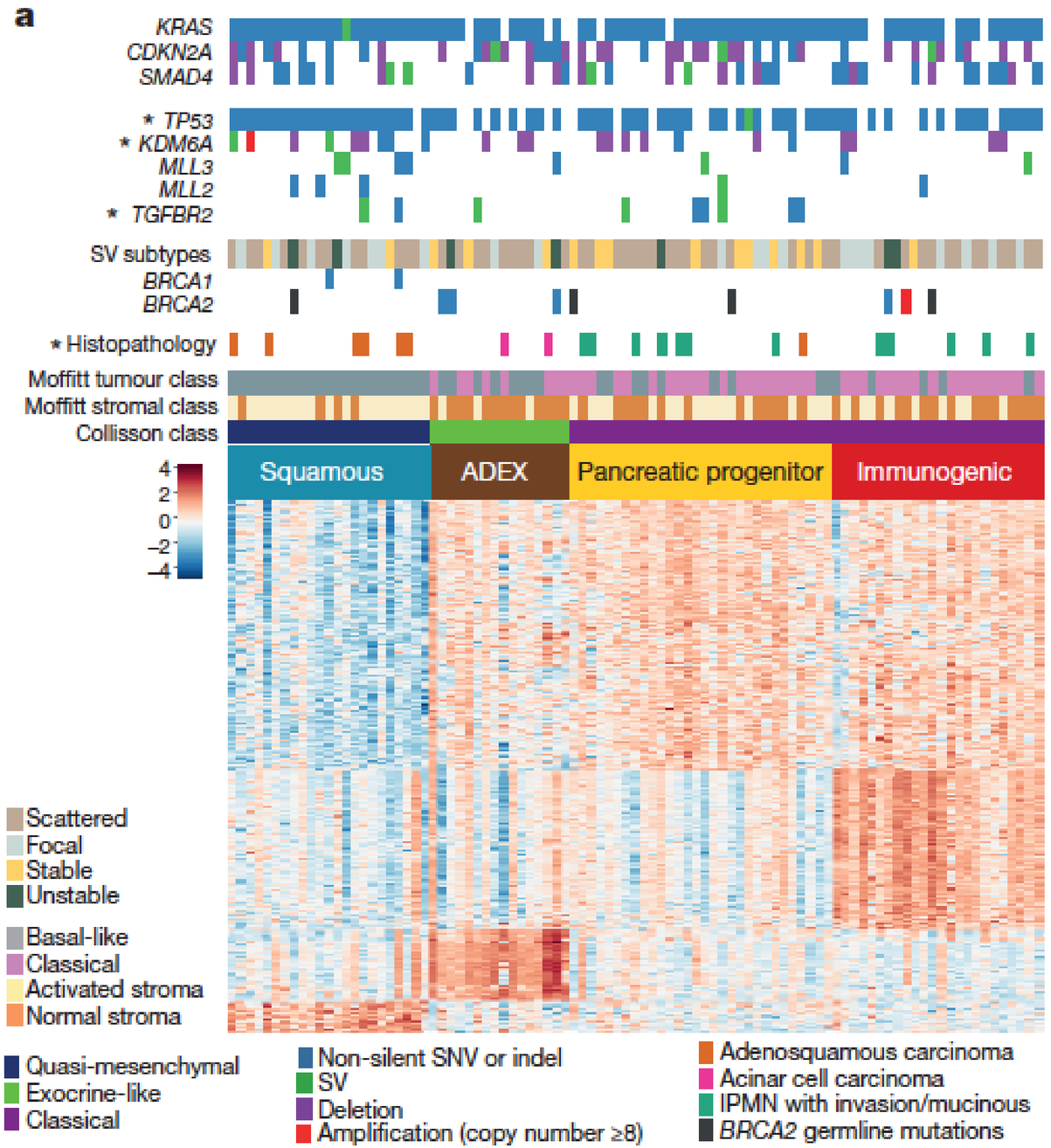
Conflict of Interest

U.S. Patent Application # 62/678,572, filed May 31, 2018	
Title:	Personalized Treatment of Pancreatic Cancer
Inventor(s):	Steven J. Hughes
Ref No.:	UF#-17233 (222110-8440)



Nature 2016: 531; 47-52.

CT-Based Borderline Resectable Disease ISGPS/NCCN

- CT findings of venous distortion of the SMV/portal venous axis even including short-segment venous occlusion with proximal and distal sufficient vessel length allowing safe reconstruction

- Encasement of the gastroduodenal artery up to the hepatic artery, with either short-segment encasement or direct abutment of the hepatic artery without extension to the celiac axis;

- Tumor abutment of the SMA but with no greater than 180° of the vessel wall circumference.

Surgery. 2014 Jun;155(6):977-88. doi: 10.1016/j.surg.2014.02.001. Epub 2014 Feb 7. PMID: 24856119
Pancreatology. 2018 Jan;18(1):2-11. doi: 10.1016/j.pan.2017.11.011. Epub 2017 Nov 22. PMID 29191513

Biologically-Based Borderline Resectable

- Ca19-9 > 500 IU/ml
- Regional LN metastasis by
  - EUS biopsy
  - PET-CT
- Others?

Pancreatology. 2018 Jan;18(1):2-11. doi: 10.1016/j.pan.2017.11.011. Epub 2017 Nov 22. PMID 29191513

Dig Liver Dis. 2018 Jan;50(1):84-90. doi: 10.1016/j.dld.2017.09.122. Epub 2017 Sep 22.

ORIGINAL ARTICLE

Precision Oncology in Surgery

Patient Selection for Operable Pancreatic Cancer

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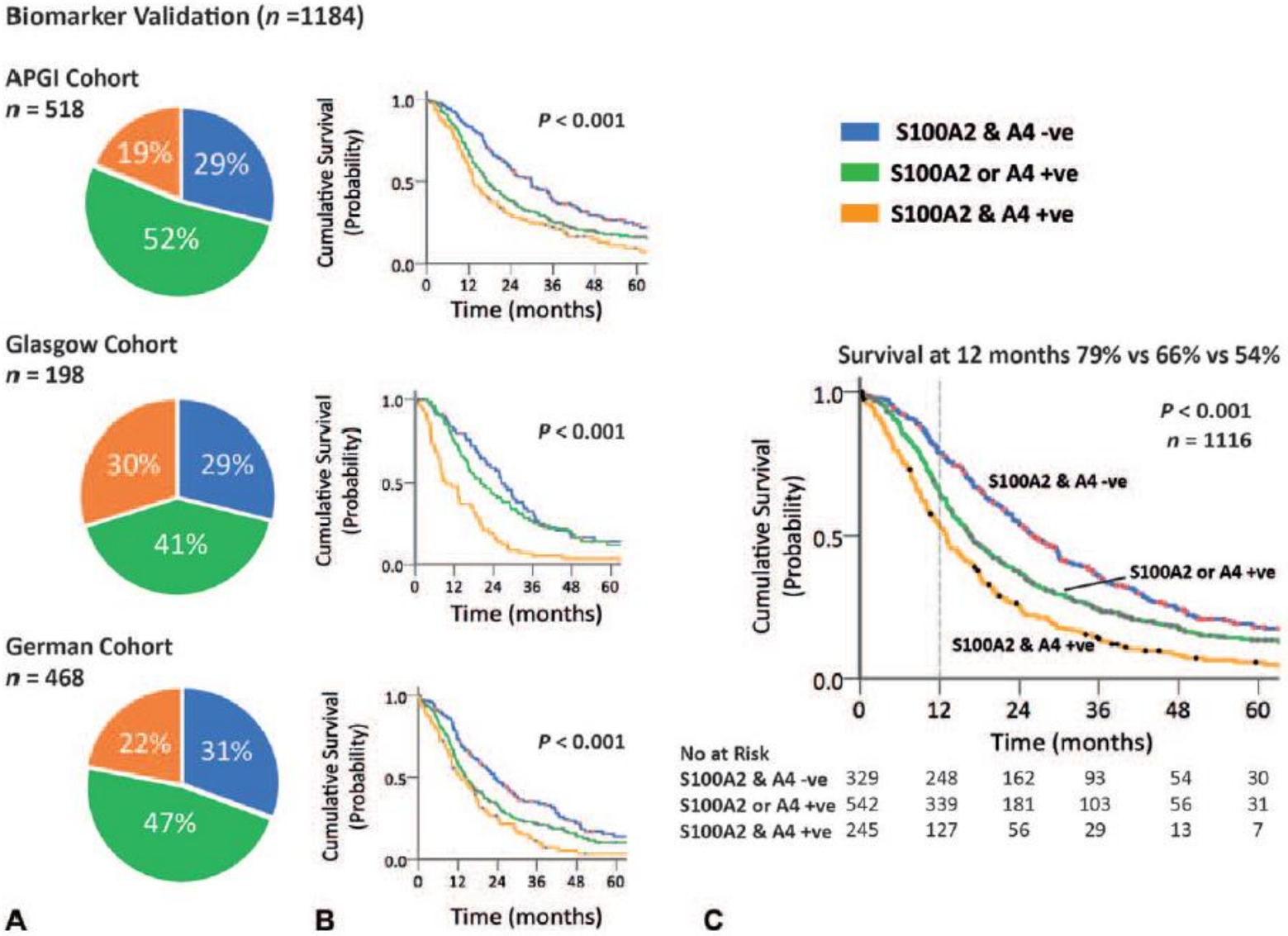
Ann Surg. 2018 Nov 30. doi: 10.1097/SLA.0000000000003143. [Epub ahead of print]

PMID: 30570546



Ann Surg. 2018 Nov 30. doi: 10.1097/SLA.0000000000003143. [Epub ahead of print]

PMID: 30570546

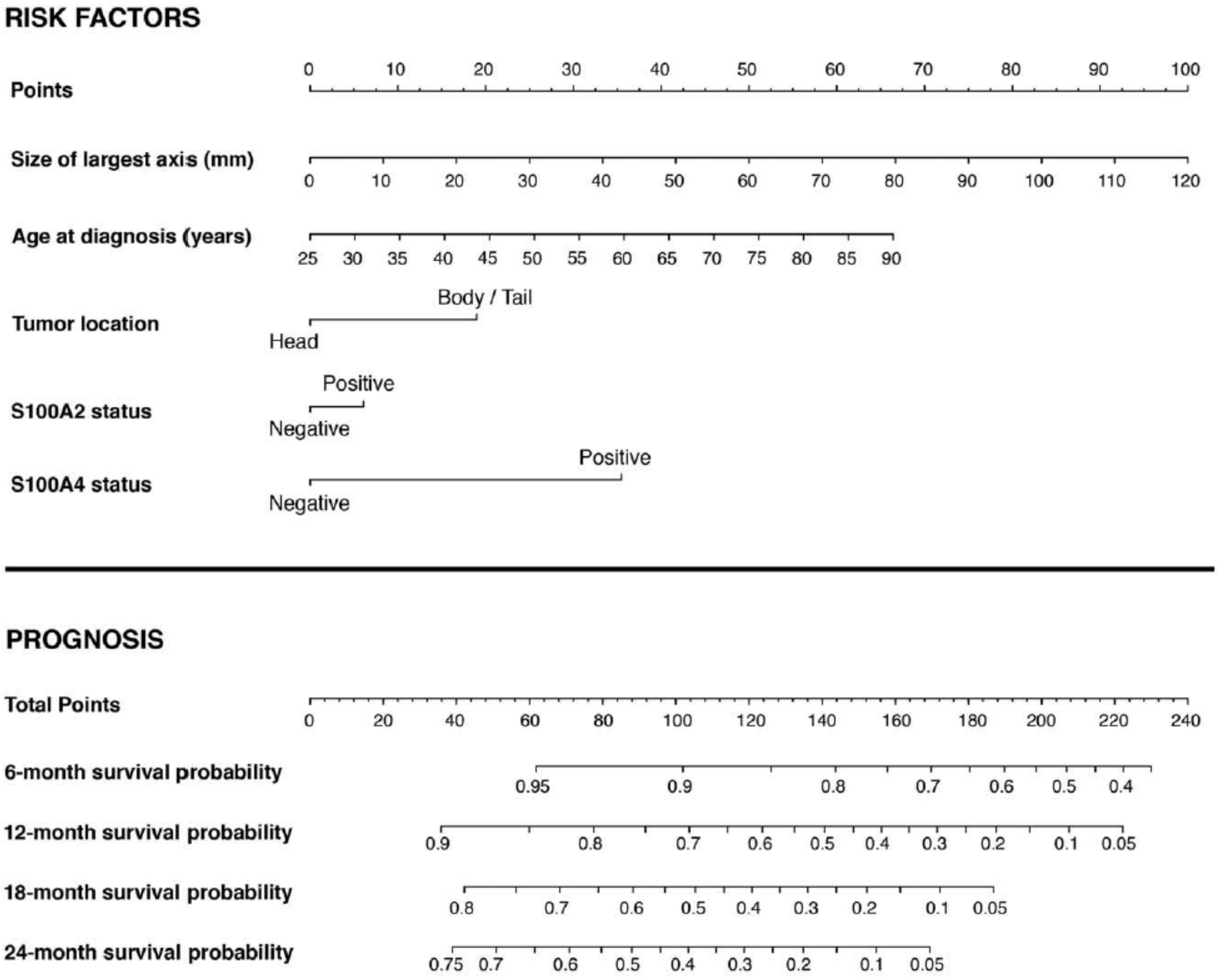


FIGURE 4. A preoperative molecular prognostic nomogram for resectable pancreatic cancer.

Ann Surg. 2018 Nov 30.

PMID: 30570546

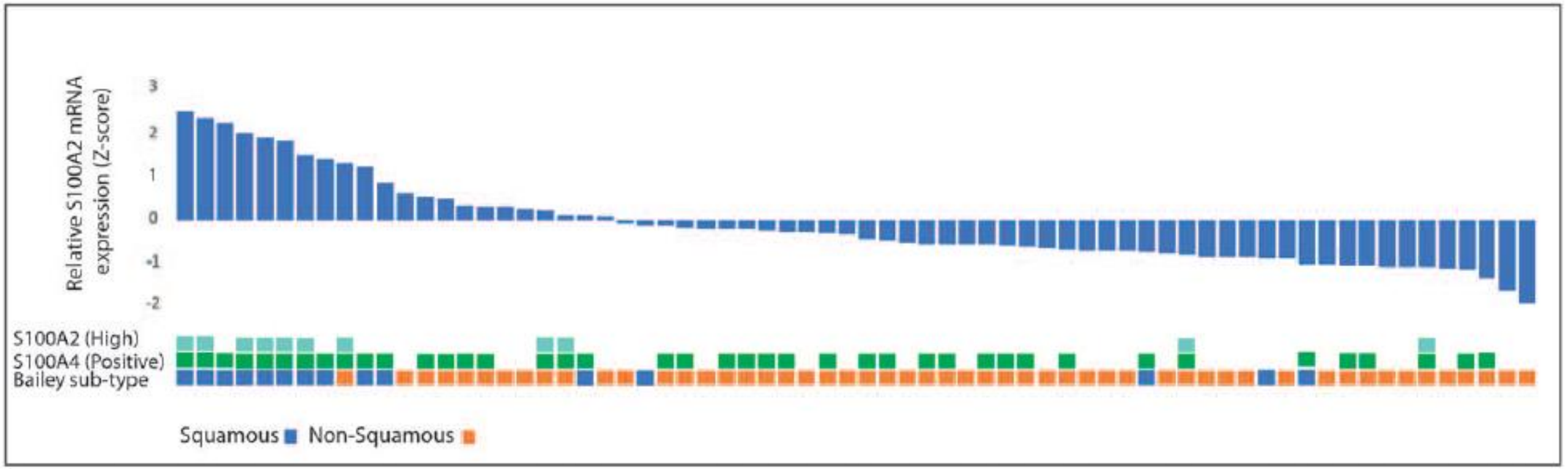
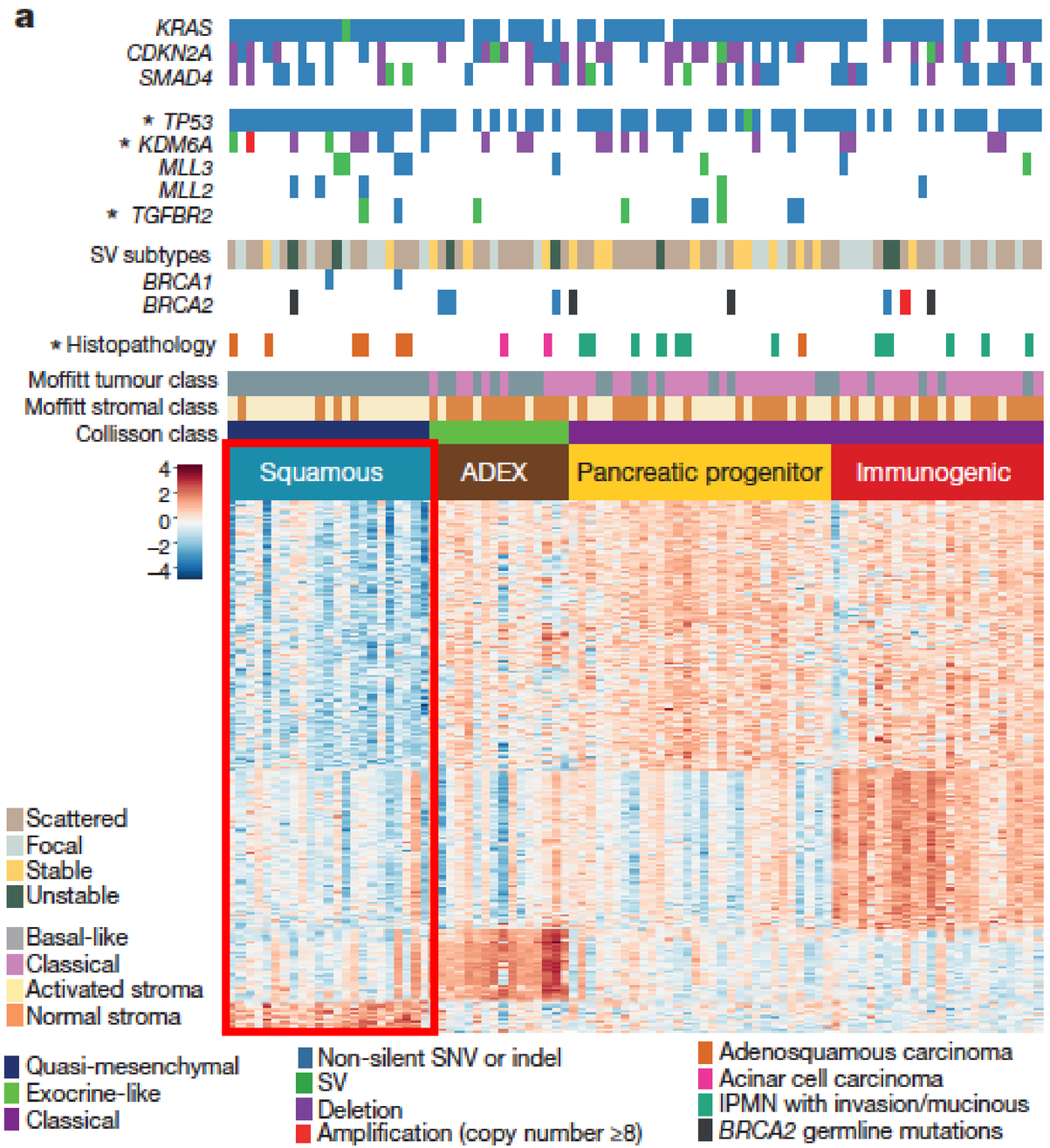


FIGURE 3. High S100A2 and positive S100A4 expression correlates with the squamous subtype of PDAC. Patients are ranked according to S100A2 mRNA expression and the relative expression *z*-score is represented by a waterfall plot, IHC staining and Bailey subtype is shown below. High S100A2 and positive S100A4 expression associated strongly with the squamous subtype ($P < 0.001$).

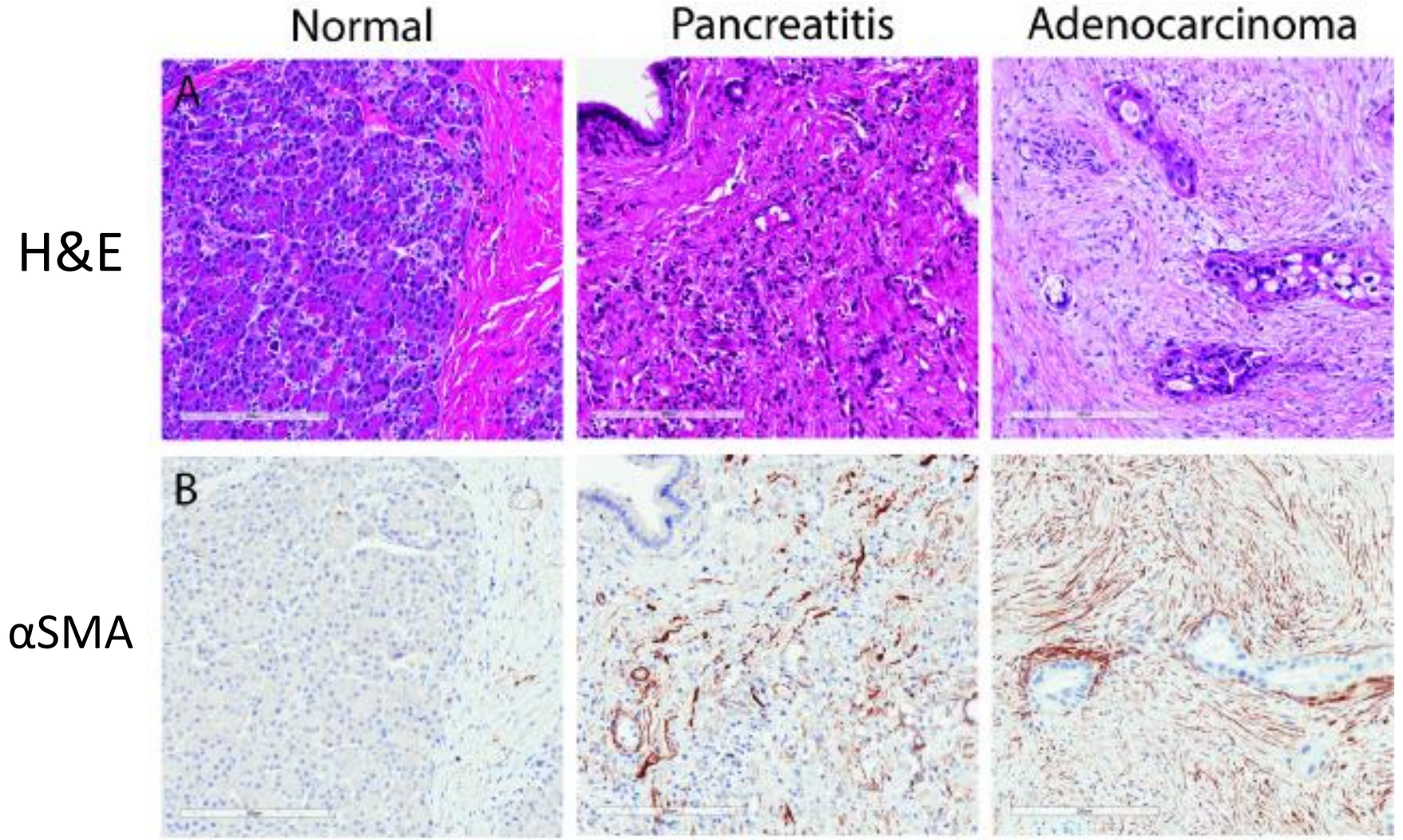
Ann Surg. 2018 Nov 30. doi: 10.1097/SLA.0000000000003143. [Epub ahead of print]

PMID: 30570546

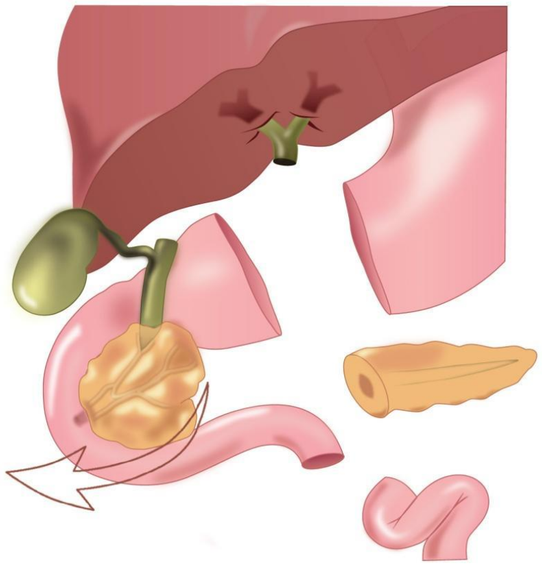


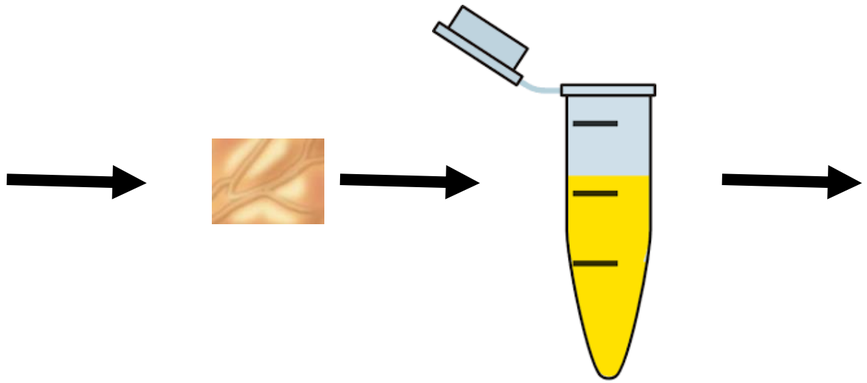
Nature 2016: 531; 47-52.

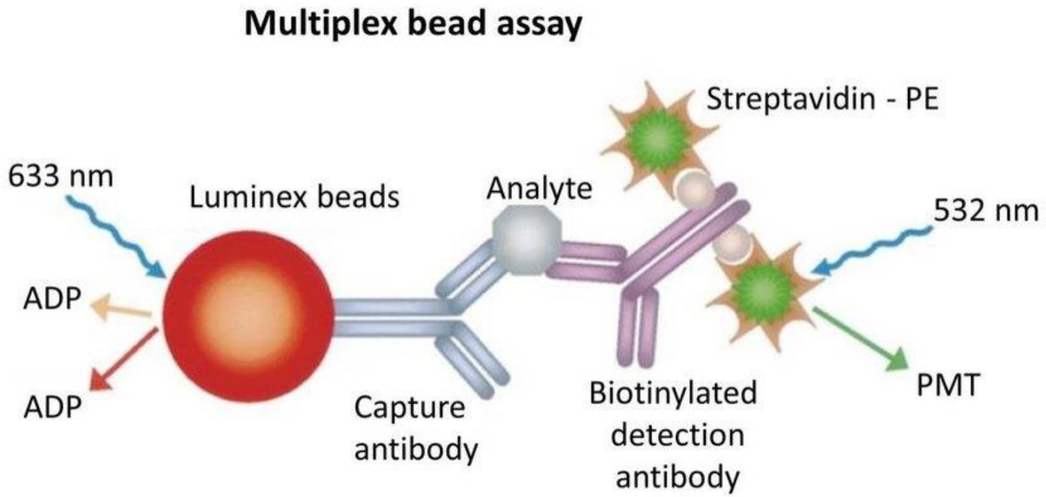
Desmoplastic Response/Stroma



Methods







Surgical Resection

82 PDAC and 77 benign or pancreatitis

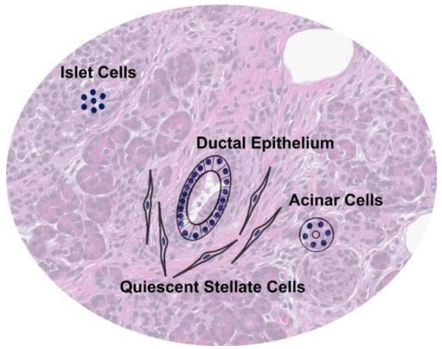
Pancreatic Tissue

Protein Lysate

41 protein multiplex assay

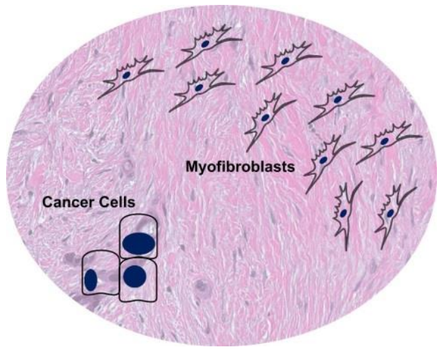
The inflammatory milieu is altered in pancreatic cancer compared to health and chronic inflammation

Benign



versus

Malignant



	Normal pancreas ($n = 6$)	Pancreatitis ($n = 9$)	Pancreatic cancer ($n = 36$)	*P* value nonmalignant vs. Pancreatic cancer	*P* value pancreatitis vs. Pancreatic cancer
Growth factors					
FGF-2	761 (221)	951 (187)	1674 (177)	.009	.063
PDGF-BB	117 (46)	102 (48)	244 (63)	.02	.022
VEGF	151 (46)	76 (20)	252 (59)	.119	.046
Chemokines					
Eotaxin	21.8 (12.8)	21.4 (12.9)	90.4 (16.3)	<.001	.002
Fractalkine	55.1 (12.8)	43.0 (9.4)	71.1 (3.6)	.010	.009
Gro	163 (6	96)	531 (87)	.007	.043
IP-10	69	70 (32)	(148)	<.001	<.001
MCP1		378 (104)		<.001	<.001
MCP3	9)	2.5 (0.8)	3)	<.001	<.001
MDC	1)	70 (36)	3)	<.001	.009
MIP-1α	4.9)	16.9 (7.6)	6)	.001	
MIP-1β	1)	14.3 (5.0	1)	.007	.008
RANTES	7	106	(235)	.032	.178
Cytokines					
GM-CSF	4.1 (2.0)	1.4 (0.3)	14.0 (3.9)	<.001	<.001
IFN	13.0 (2.7)	8.7 (2.3)	19.9	.033	.01
IL-1α	1.8 (0	3.2 (0.6)	12.2 (2.0)		
TNFα	1.6 (0.7)	1.4 (0.4)	3.3 (0.4)	.002	.010

Concentrations expressed as mean (SE) in units of pg/mg protein. All significant comparisons are shown for which $P < 0.05$ using the Mann Whitney U test

BMC Cancer, 2015 Oct 24;15(1):783.

Univariate analysis of overall survival

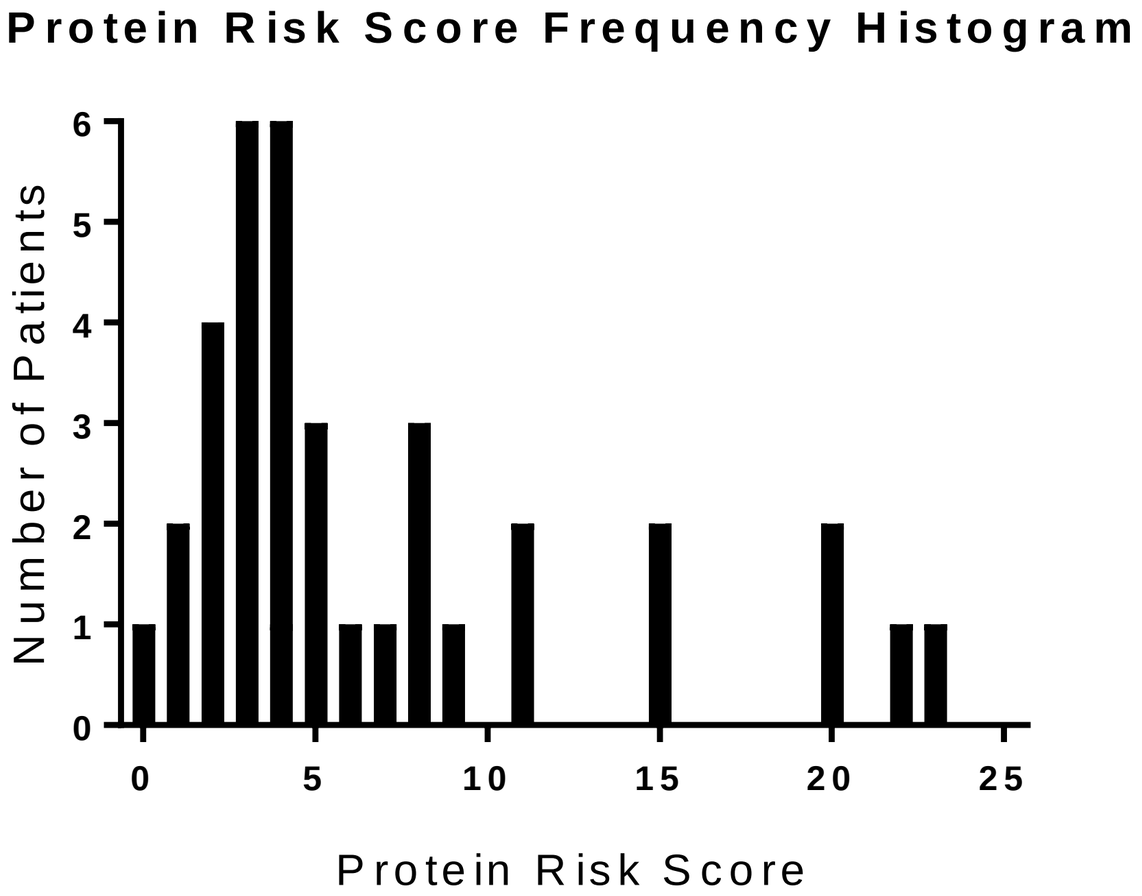
Parameter	Reference	HR	95% CI	p-value
Age (years)	61-75	1.13	0.75 – 1.70	0.5712
CA19-9*, U/ml	49-797	1.32	0.92 – 1.90	0.1372
Neoadjuvant Therapy	None	1.04	0.46 – 2.39	0.9180
Tumor Size	2.6-4.4	1.10	0.80 – 1.52	0.5428
Pathologic N Stage 1	N Stage 0	1.58	0.54 – 4.56	0.3955
# Positive Lymph Nodes	1-6	1.99	1.22 – 3.24	0.0059
Positive Lymph Node Ratio	0.04-0.24	2.38	1.48 – 3.82	0.0004
Grade	Moderate-Poor	1.84	0.90 – 3.74	0.0937
Procedure				0.0045
	Distal Pancreatectomy-PD	0.25	0.09 – 0.74	
	Total Pancreatectomy-PD	5.03	1.03 – 24.5	
Positive Margin	Negative Margin	2.40	1.10 – 5.21	0.0271
PV Resection	No PV Resection	2.90	1.03 – 8.12	0.0429

Individual analyte association with overall survival

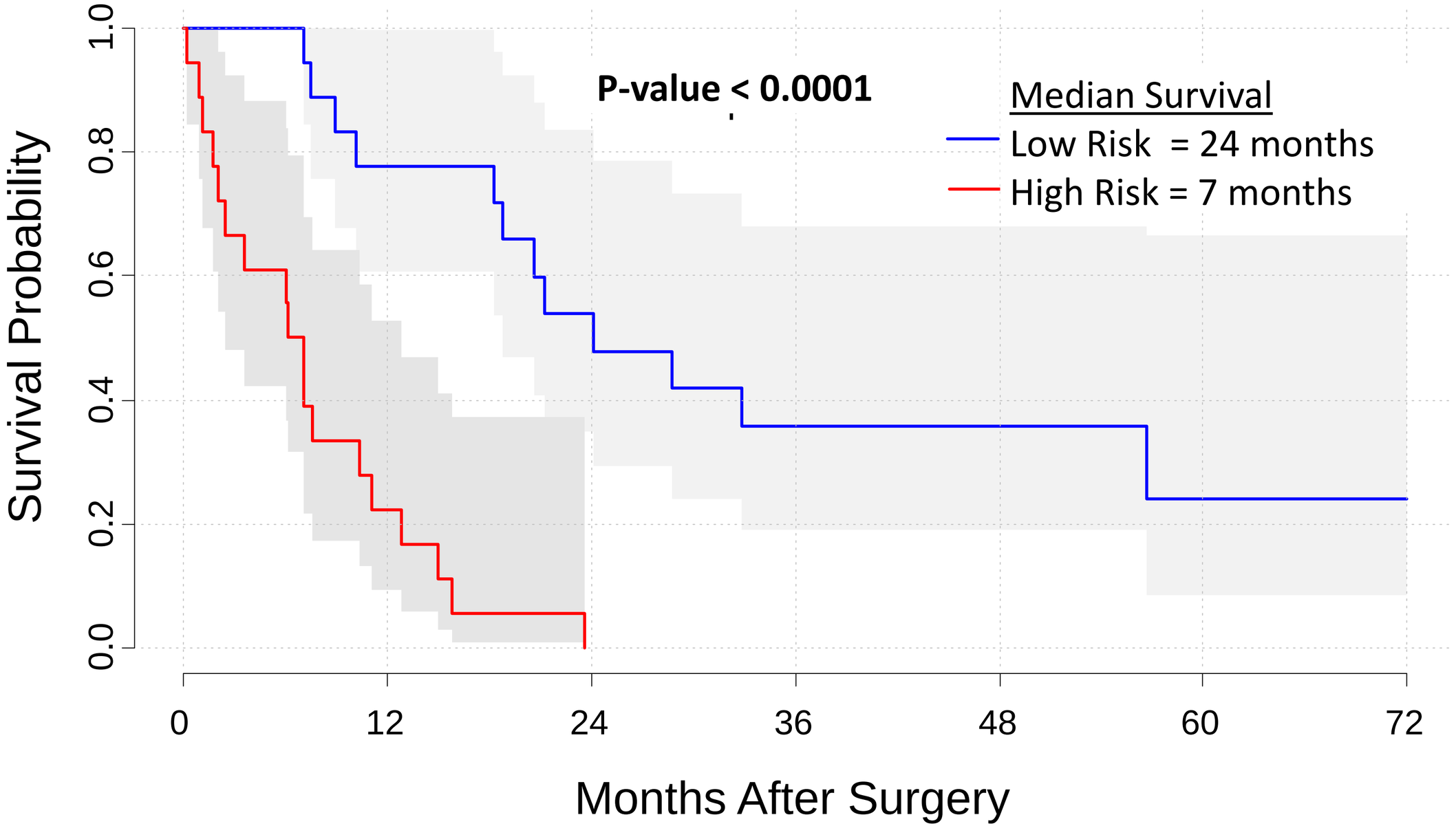
Analyte	HR	95% CI	p-value	Adjusted p-value
FGF-2	0.61	0.43-0.88	0.0072	0.2530
IL-4	0.54	0.34-0.85	0.0082	0.2530
G-CSF	1.47	1.05-2.05	0.0247	0.2881
Eotaxin	0.63	0.42-0.95	0.0290	0.2881
PDGF-AA	1.45	1.00-2.09	0.0486	0.3404
Flt-3L	0.66	0.43-1.02	0.0607	0.3540
TNF-alpha	0.60	0.34-1.06	0.0798	0.3992
RANTES	0.56	0.28-1.11	0.0988	0.4321
MDC	0.71	0.47-1.08	0.1100	0.4321
IL-13	0.71	0.46-1.10	0.1234	0.4321

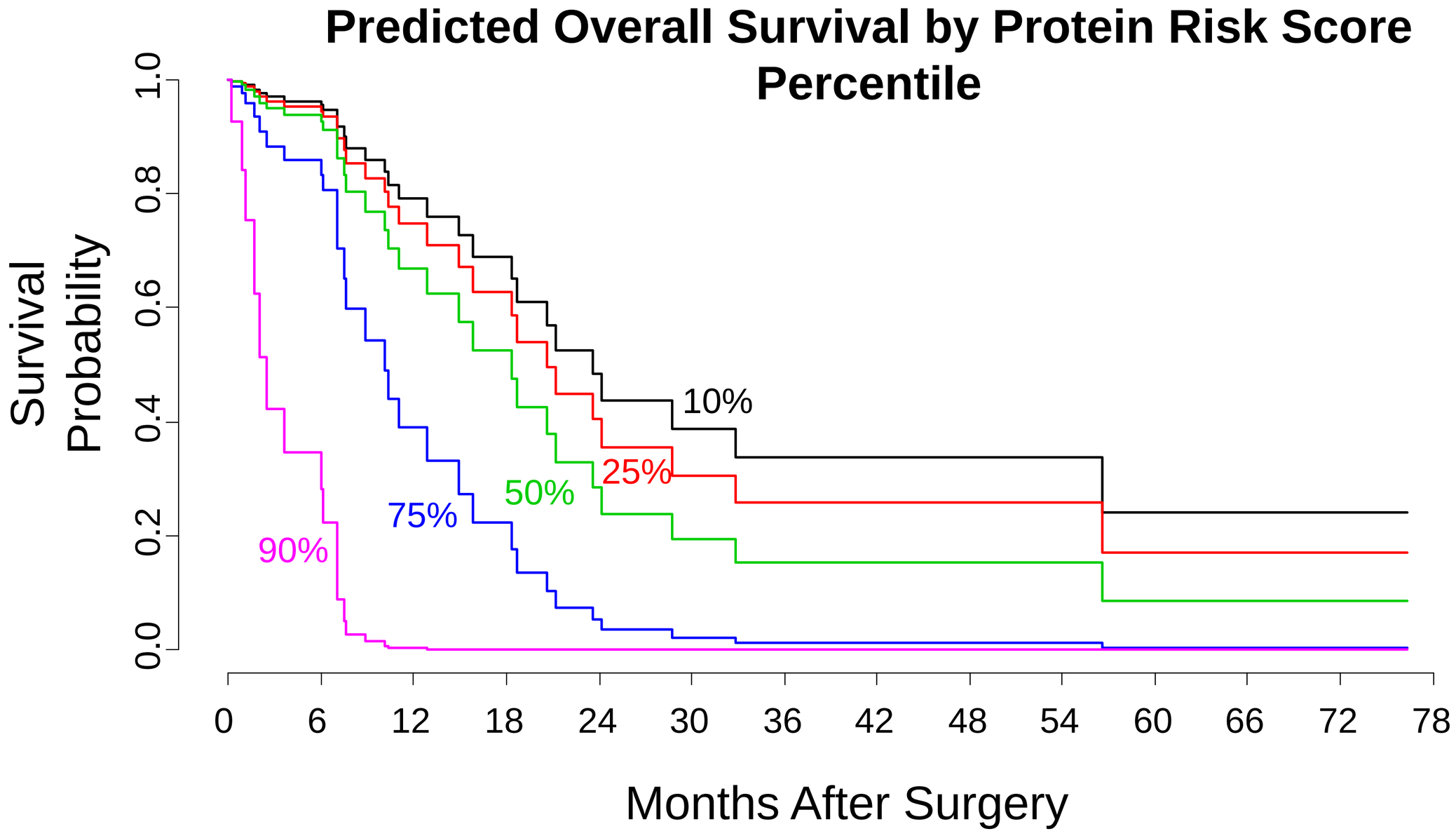
Analyte coefficients

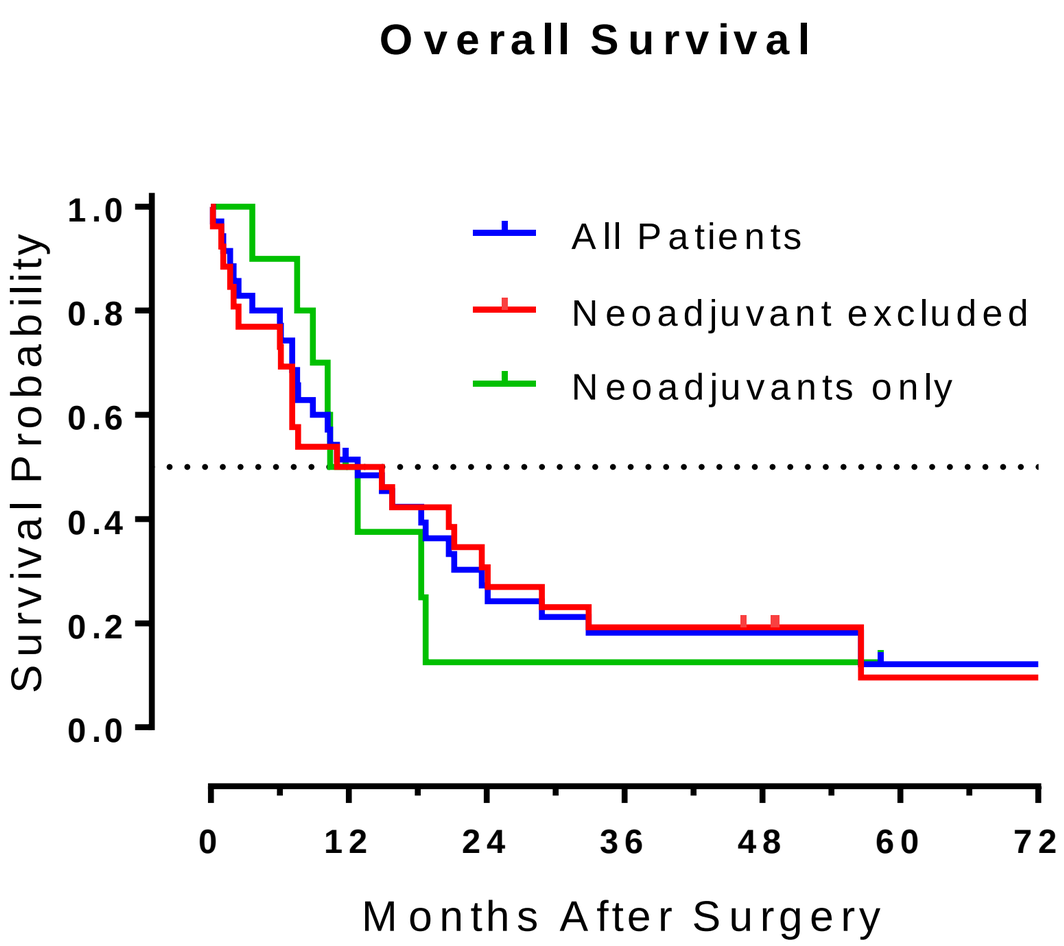
Covariate	Penalized Coefficient	Unpenalized Coefficient
FGF-2	-.287	-.463
Eotaxin	-.164	-.466
G-CSF	.280	.491
GM-CSF	.070	.256
IL-13	-.125	-.462
IL-4	-.725	-.648
IP-10	-.036	-.161
RANTES	-.263	-.360

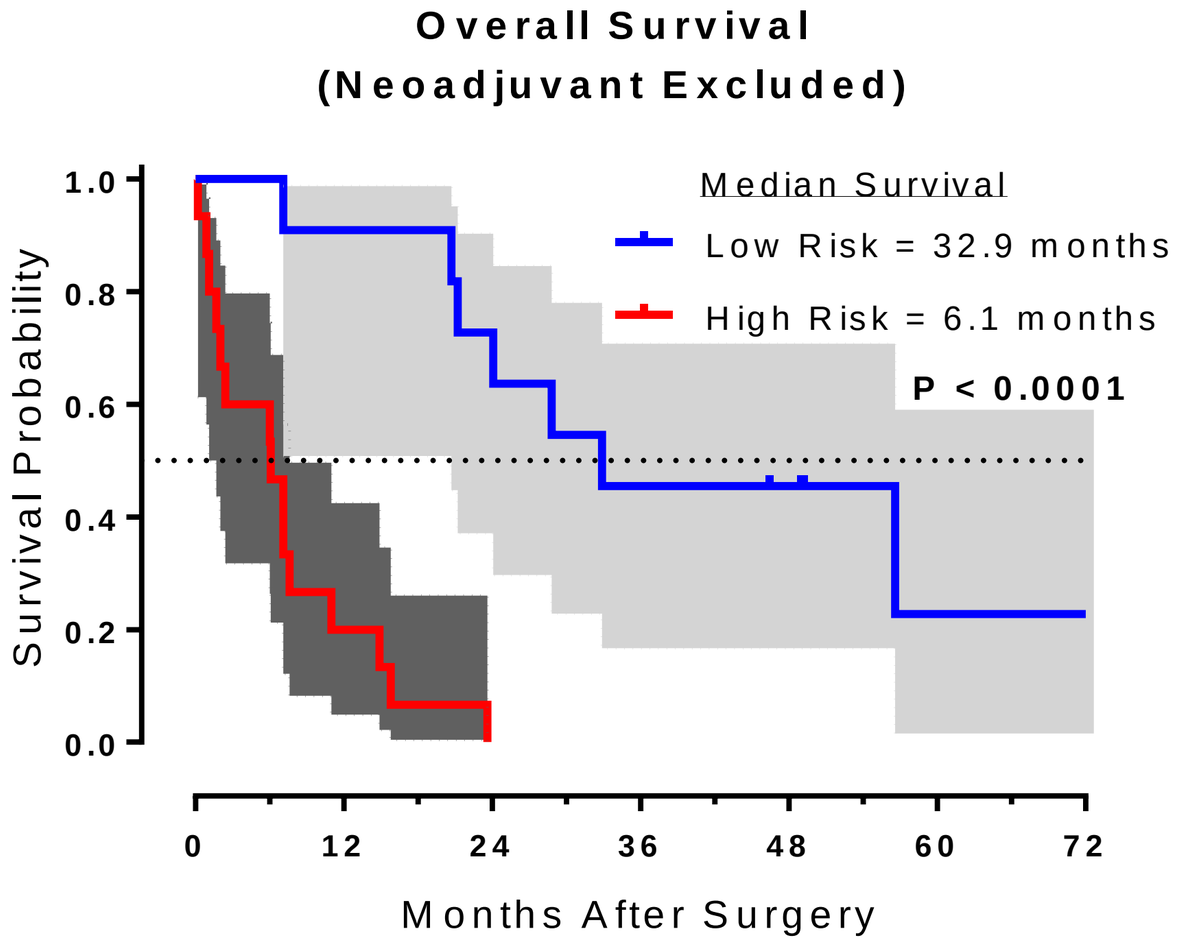

Protein Risk Score Frequency Histogram
Number of Patients
0
1
2
3
4
5
6
0
5
10
15
20
25
Protein Risk Score

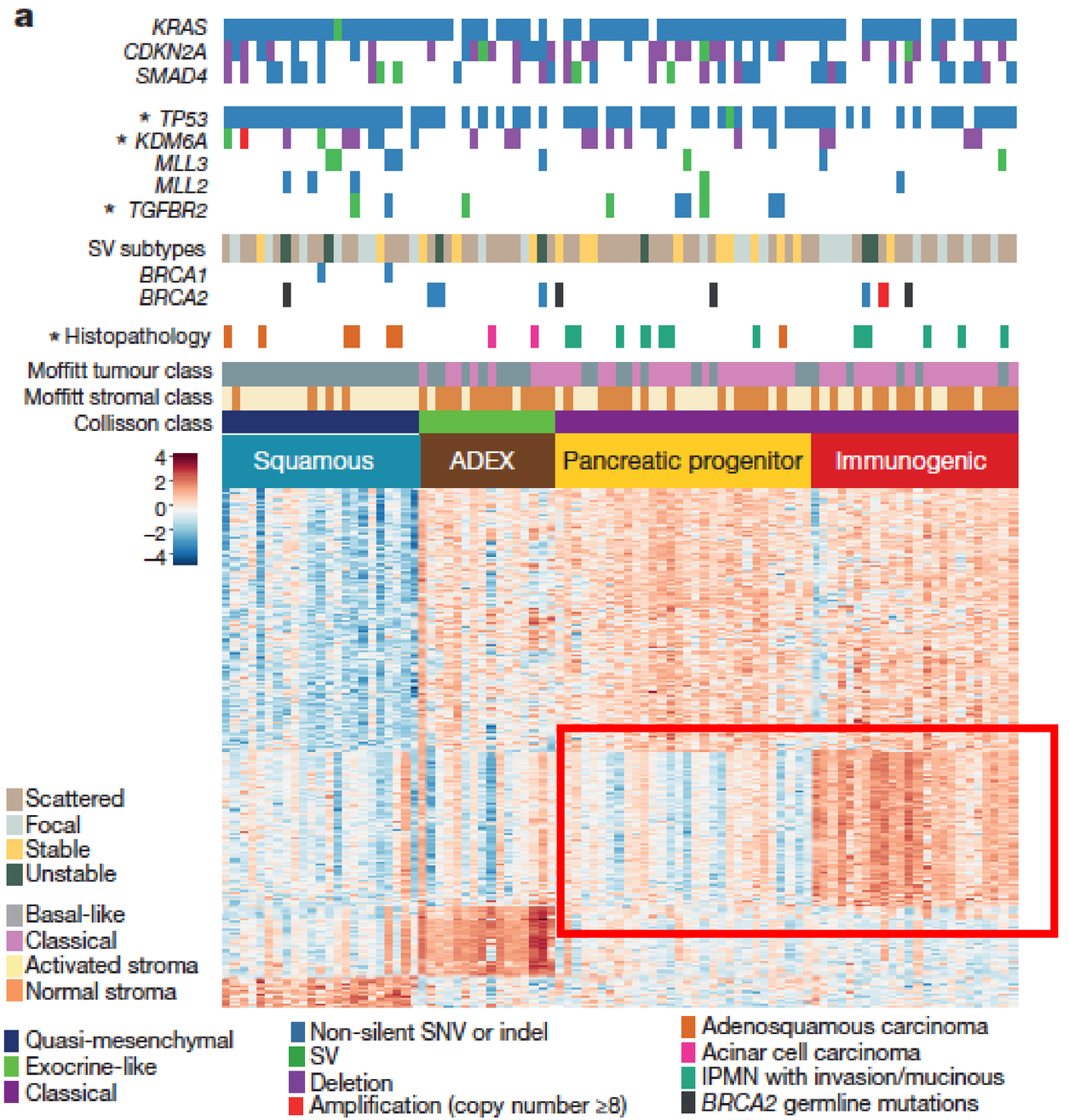
Overall Survival by Protein Risk Score



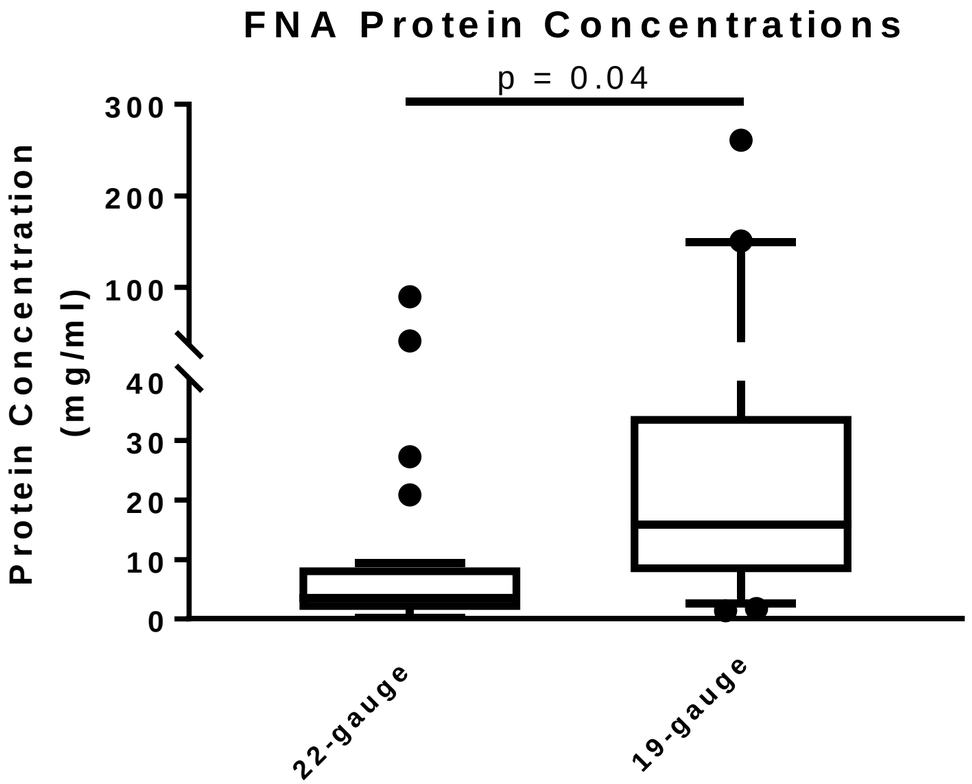

Predicted Overall Survival by Protein Risk Score Percentile
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
10%
25%
50%
75%
90%
0
6
12
18
24
30
36
42
48
54
60
66
72
78
Months After Surgery

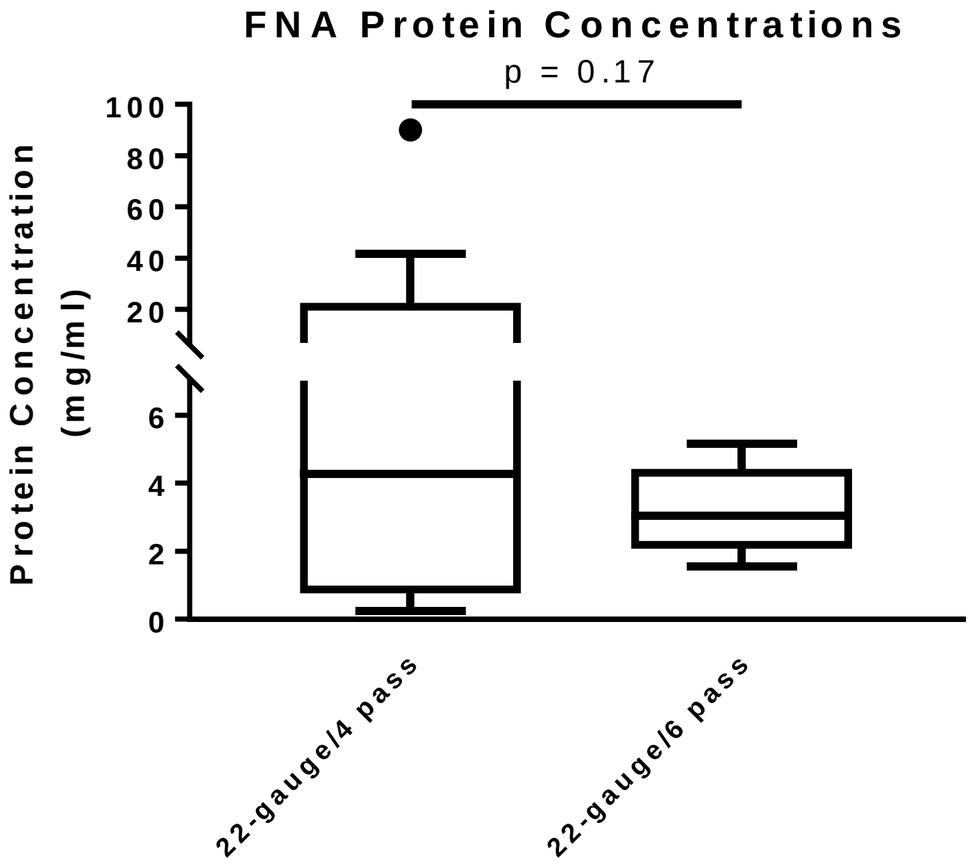

Overall Survival
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
All Patients
Neoadjuvant excluded
Neoadjuvants only
0
12
24
36
48
60
72
Months After Surgery

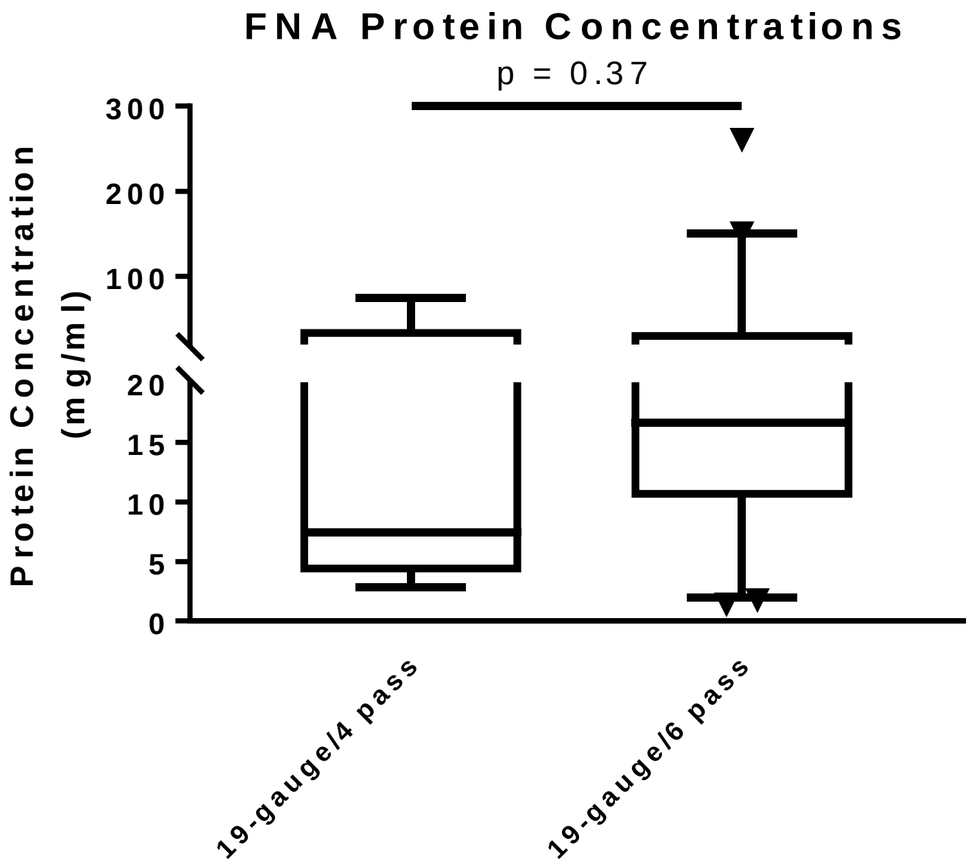

Overall Survival
(Neoadjuvant Excluded)
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Median Survival
Low Risk = 32.9 months
High Risk = 6.1 months
P < 0.0001
0
12
24
36
48
60
72
Months After Surgery

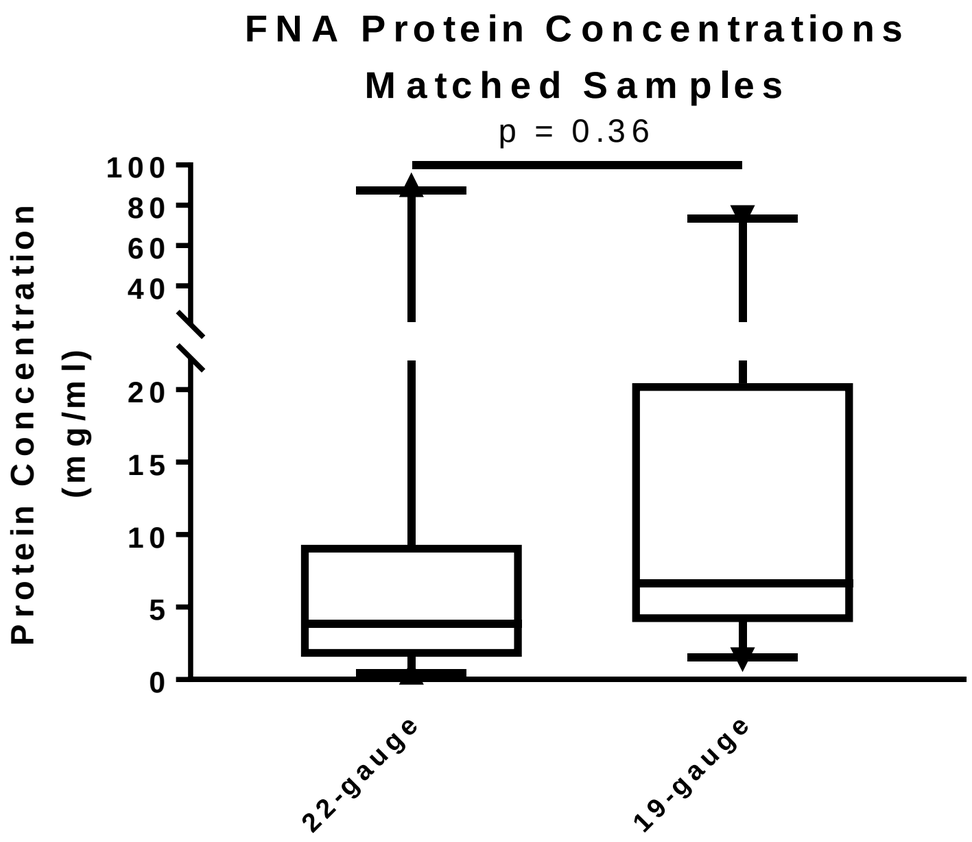


Nature 2016: 531; 47-52.


FNA Protein Concentrations
p = 0.04
Protein Concentration (mg/ml)
300
200
100
40
30
20
10
0
22-gauge
19-gauge


FNA Protein Concentrations
p = 0.17
Protein Concentration (mg/ml)
100
80
60
40
20
6
4
2
0
22-gauge/4 pass
22-gauge/6 pass


FNA Protein Concentrations
p = 0.37
Protein Concentration (mg/ml)
300
200
100
20
15
10
5
0
19-gauge/4 pass
19-gauge/6 pass


FNA Protein Concentrations
Matched Samples
p = 0.36
Protein Concentration (mg/ml)
100
80
60
40
20
15
10
5
0
22-gauge
19-gauge

Summary

- PDAC is a heterogenous disease
- Predictors of prognosis beyond TNM staging are in their infancy
  - Multiple systemic therapy options
  - Precision approaches
- Ca19-9 is the only biomarker presently in routine clinical use
- S100 family has been prospectively validated as a prognostic marker
- A chemokine/cytokine/growth factor signature may offer value
- EUS/FNA is a viable option to obtain these materials

54TH ANNUAL

Pancreas Club Meeting

May 1 - 2, 2020 IN **Chicago, IL**

The Drake

Acknowlegement

Translational Research Award (Hughes) 7/1/17-6/30-19

PanCAN $150,000/year

Protein Signatures Improve the Diagnostic Yield of Fine Needle Aspiration

This grant aims to use secreted protein concentrations to diagnose acellular samples from pancreatic lesion fine needle aspirations

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