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Supplementary appendix

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Online Appendix

Proteomic Biomarkers of Progressive Fibrosing Interstitial Lung Disease

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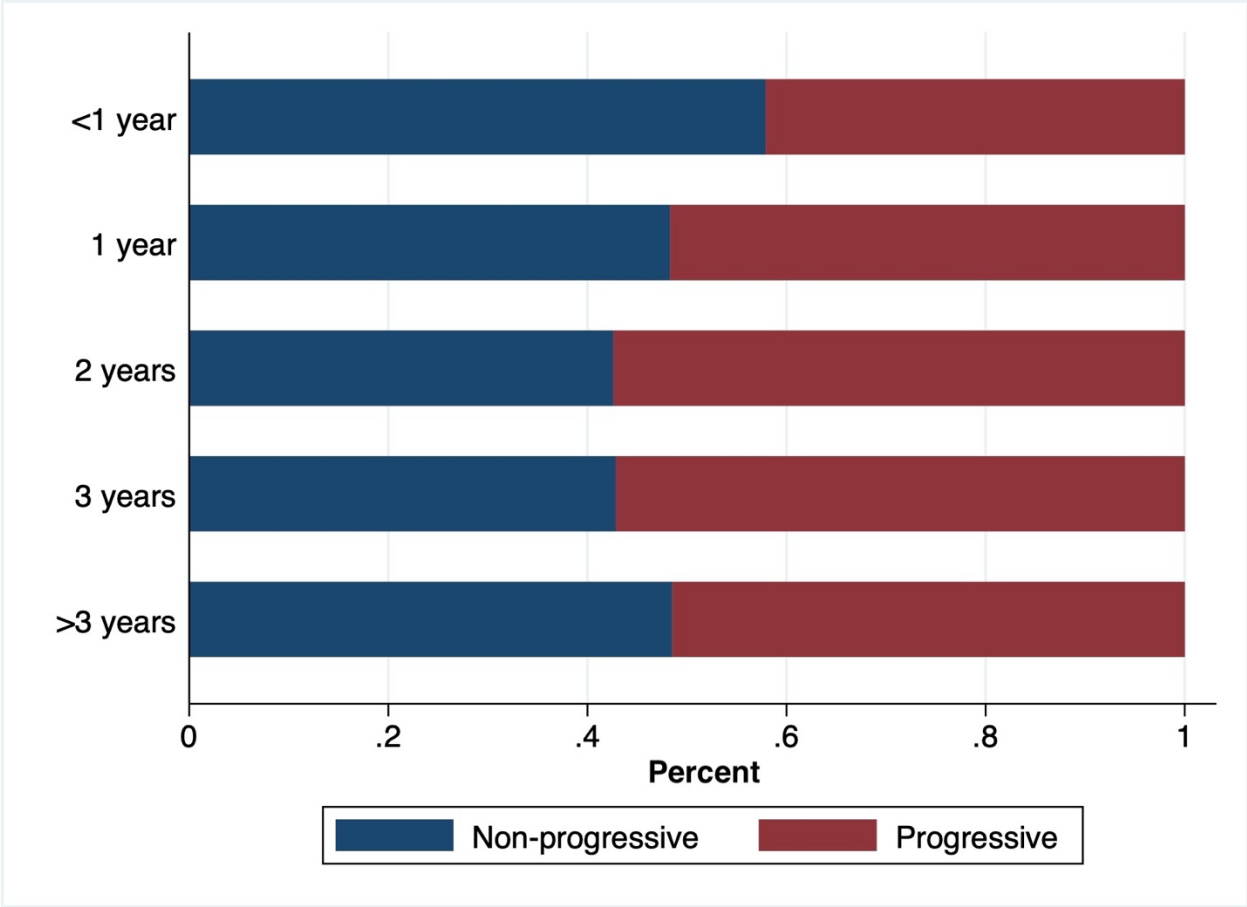


Figure S1. Proportion of patients experiencing ILD progression stratified by interval between ILD diagnosis and research blood draw.

Table S1. Discovery cohort association between all biomarkers and PF-ILD phenotype

Gene	Protein	Uniprot ID	OR	95% CI		FDR q-value
ACTN4*	Alpha-actinin-4	O43707	1.24	0.85	1.84	0.619
ADA	Adenosine deaminase	P00813	1.01	0.67	1.50	0.998
ADAM23	Disintegrin and metalloproteinase domain-containing protein 23	O75077	0.82	0.53	1.28	0.736
ADGRE2	Adhesion G protein-coupled receptor E2	Q9UHX3	1.14	0.75	1.74	0.852
AGER	Advanced glycosylation end product-specific receptor	Q15109	0.65	0.50	0.85	0.027
AGRN	Agrin	O00468	1.56	1.05	2.34	0.172
AGRP	Agouti-related protein	O00253	1.19	0.91	1.56	0.534
ALDH3A1	Aldehyde dehydrogenase, dimeric NADP-preferring	P30838	1.04	0.85	1.26	0.943
AMBN	Ameloblastin	Q9NP70	0.87	0.53	1.37	0.888
AMN	Protein amnionless [Cleaved into: Soluble protein amnionless]	Q9BXJ7	1.12	0.83	1.51	0.793
ANGPT1	Angiopoietin-1	Q15389	1.00	0.81	1.23	0.998
ANGPTL2	Angiopoietin-related protein 2	Q9UKU9	1.33	0.92	1.94	0.445
ANGPTL4	Angiopoietin-related protein 4	Q9BY76	1.73	1.25	2.45	0.025
ANXA11	Annexin A11	P50995	1.12	0.82	1.55	0.828
AOC1*	Amiloride-sensitive amine oxidase [copper-containing]	P19801	1.03	0.81	1.32	0.943
ARHGEF12	Rho guanine nucleotide exchange factor 12	Q9NZN5	1.02	0.85	1.24	0.949
ARNT*	Aryl hydrocarbon receptor nuclear translocator	P27540	0.80	0.60	1.06	0.424
ARTN*	Artemin	Q5T4W7	0.96	0.63	1.41	0.945
ATP5IF1	ATPase inhibitor, mitochondrial	Q9UII2	0.97	0.81	1.17	0.943
AXIN1	Axin-1	O15169	1.04	0.86	1.25	0.943
B4GALT1	Beta-1,4-galactosyltransferase 1	P15291	1.38	0.88	2.18	0.485
BACH1	Transcription regulator protein BACH1	O14867	1.03	0.82	1.29	0.945
BANK1	B-cell scaffold protein with ankyrin repeats	Q8NDB2	1.03	0.86	1.23	0.943
BCL2L11	Bcl-2-like protein 11, Isoform BimL	O43521-2	1.34	0.86	2.14	0.544
BCR	Breakpoint cluster region protein	P11274	1.09	0.90	1.33	0.712
BID	BH3-interacting domain death agonist	P55957	0.93	0.74	1.16	0.828
BSG	Basigin	P35613	3.00	1.50	6.20	0.033
BTN2A1	Butyrophilin subfamily 2 member A1	Q7KYR7	0.94	0.59	1.48	0.943
BTN3A2	Butyrophilin subfamily 3 member A2	P78410	0.97	0.66	1.42	0.970
C1QA	Complement C1q subcomponent subunit A	P02745	1.91	1.04	3.55	0.208
CASP2*	Caspase-2	P42575	1.07	0.84	1.36	0.895
CCL11	Eotaxin	P51671	1.47	0.97	2.25	0.308
CCL13	C-C motif chemokine 13	Q99616	1.05	0.85	1.31	0.914
CCL17	C-C motif chemokine 17	Q92583	1.23	1.05	1.45	0.096
CCL20	C-C motif chemokine 20	P78556	1.26	1.04	1.53	0.126
CCL21	C-C motif chemokine 21	O00585	1.04	0.78	1.40	0.943
CCL22	C-C motif chemokine 22	O00626	1.25	0.97	1.62	0.352
CCL23	C-C motif chemokine 23	P55773	1.62	1.15	2.31	0.073

CCL24	C-C motif chemokine 24	O00175	1.28	1.05	1.57	0.119
CCL25	C-C motif chemokine 25	O15444	1.20	0.88	1.66	0.593
CCL26	C-C motif chemokine 26	Q9Y258	0.96	0.79	1.15	0.933
CCL28	C-C motif chemokine 28	Q9NRJ3	1.02	0.79	1.31	0.982
CCL3	C-C motif chemokine 3	P10147	1.01	0.83	1.23	0.993
CCL4	C-C motif chemokine 4	P13236	1.00	0.83	1.20	0.998
CCL7	C-C motif chemokine 7	P80098	1.18	1.00	1.41	0.258
CCN2	CCN family member 2	P29279	1.13	0.82	1.56	0.815
CD160	CD160 antigen	O95971	0.88	0.69	1.11	0.615
CD200	OX-2 membrane glycoprotein	P41217	0.89	0.54	1.48	0.934
CD200R1	Cell surface glycoprotein CD200 receptor 1	Q8TD46	0.67	0.46	0.97	0.197
CD22	B-cell receptor CD22	P20273	0.96	0.75	1.25	0.943
CD244	Natural killer cell receptor 2B4	Q9BZW8	0.75	0.48	1.19	0.562
CD276	CD276 antigen	Q5ZPR3	1.67	1.19	2.39	0.048
CD4	T-cell surface glycoprotein CD4	P01730	1.56	0.94	2.63	0.353
CD40	Tumor necrosis factor receptor superfamily member 5	P25942	1.01	0.75	1.36	0.997
CD40LG	CD40 ligand	P29965	1.11	0.90	1.38	0.711
CD48	CD48 antigen	P09326	0.95	0.65	1.40	0.943
CD58	Lymphocyte function-associated antigen 3	P19256	0.69	0.33	1.40	0.684
CD6	T-cell differentiation antigen CD6	P30203	0.81	0.62	1.06	0.424
CD70	CD70 antigen	P32970	1.16	0.82	1.63	0.745
CD79B	B-cell antigen receptor complex-associated protein beta chain	P40259	1.24	0.95	1.63	0.423
CD83	CD83 antigen	Q01151	1.22	0.88	1.71	0.582
CD84	SLAM family member 5	Q9UIB8	0.78	0.50	1.21	0.608
CDON	Cell adhesion molecule-related/down-regulated by oncogenes	Q4KMG0	0.92	0.58	1.48	0.943
CDSN	Corneodesmosin	Q15517	1.02	0.72	1.43	0.993
CEACAM21	Carcinoembryonic antigen-related cell adhesion molecule 21	Q3KPI0	1.05	0.87	1.27	0.895
CEP164*	Centrosomal protein of 164 kDa	Q9UPV0	0.95	0.74	1.20	0.928
CHRD1	Chordin-like protein 1	Q9BU40	1.27	0.90	1.80	0.520
CKAP4	Cytoskeleton-associated protein 4	Q07065	1.74	1.15	2.68	0.095
CKMT1A_CK MT1B	Creatine kinase U-type, mitochondrial	P12532	1.11	0.89	1.37	0.711
CLEC4A	C-type lectin domain family 4 member A	Q9UMR7	1.36	0.92	2.03	0.424
CLEC4C	C-type lectin domain family 4 member C	Q8WTT0	0.84	0.67	1.05	0.424
CLEC4D	C-type lectin domain family 4 member D	Q8WXI8	1.40	1.09	1.83	0.096
CLEC4G	C-type lectin domain family 4 member G	Q6UXB4	1.31	0.83	2.09	0.596
CLEC7A	C-type lectin domain family 7 member A	Q9BXN2	1.08	0.84	1.39	0.882
CLIP2	CAP-Gly domain-containing linker protein 2	Q9UDT6	1.08	0.92	1.28	0.716
CLSTN2	Calsyntenin-2	Q9H4D0	1.17	0.81	1.69	0.748
CNTNAP2	Contactin-associated protein-like 2	Q9UHC6	0.81	0.56	1.15	0.575
COL9A1	Collagen alpha-1	P20849	0.78	0.57	1.07	0.424

COLEC12	Collectin-12	Q5KU26	1.66	1.10	2.53	0.126
CRELD2	Protein disulfide isomerase CRELD2	Q6UXH1	1.06	0.79	1.41	0.943
CRHBP	Corticotropin-releasing factor-binding protein	P24387	0.93	0.58	1.49	0.943
CRIM1	Cysteine-rich motor neuron 1 protein	Q9NZV1	1.96	1.15	3.42	0.122
CRKL	Crk-like protein	P46109	1.03	0.86	1.24	0.943
CRLF1	Cytokine receptor-like factor 1	O75462	1.35	0.85	2.20	0.553
CSF1	Macrophage colony-stimulating factor 1	P09603	1.58	1.01	2.52	0.254
CSF3	Granulocyte colony-stimulating factor	P09919	1.19	0.90	1.59	0.564
CST7	Cystatin-F	O76096	1.43	1.19	1.75	0.006
CTRC	Chymotrypsin-C	Q99895	0.93	0.76	1.14	0.828
CTSC	Dipeptidyl peptidase 1	P53634	1.20	0.87	1.64	0.608
CTSO	Cathepsin O	P43234	0.96	0.59	1.57	0.978
CXADR	Coxsackievirus and adenovirus receptor	P78310	1.31	0.95	1.81	0.402
CXCL1	Growth-regulated alpha protein	P09341	0.99	0.83	1.17	0.975
CXCL10	C-X-C motif chemokine 10	P02778	0.75	0.63	0.89	0.025
CXCL12	Stromal cell-derived factor 1	P48061	1.12	0.74	1.68	0.895
CXCL14	C-X-C motif chemokine 14	O95715	0.95	0.72	1.26	0.943
CXCL17	C-X-C motif chemokine 17	Q6UXB2	1.68	1.28	2.24	0.006
CXCL3	C-X-C motif chemokine 3	P19876	0.97	0.81	1.16	0.943
CXCL6	C-X-C motif chemokine 6	P80162	1.09	0.88	1.36	0.782
CXCL8	Interleukin-8	P10145	1.39	1.08	1.80	0.106
CXCL9	C-X-C motif chemokine 9	Q07325	0.86	0.72	1.01	0.308
DAG1	Dystroglycan	Q14118	1.01	0.72	1.40	0.998
DAPP1	Dual adapter for phosphotyrosine and 3-phosphotyrosine and 3-phosphoinositide	Q9UN19	0.95	0.81	1.12	0.850
DBNL	Drebrin-like protein	Q9UJU6	1.08	0.89	1.31	0.788
DECR1	2,4-dienoyl-CoA reductase, mitochondrial	Q16698	0.95	0.79	1.14	0.895
DFFA	DNA fragmentation factor subunit alpha	O00273	1.11	0.89	1.39	0.712
DGKZ*	Diacylglycerol kinase zeta	Q13574	1.04	0.75	1.45	0.943
DNAJA2	DnaJ homolog subfamily A member 2	O60884	1.11	0.89	1.39	0.711
DNER	Delta and Notch-like epidermal growth factor-related receptor	Q8NFT8	0.89	0.52	1.51	0.930
DNPH1	2'-deoxynucleoside 5'-phosphate N-hydrolase 1	O43598	0.92	0.67	1.27	0.905
DPP10	Inactive dipeptidyl peptidase 10	Q8N608	1.85	1.34	2.59	0.006
EDAR	Tumor necrosis factor receptor superfamily member EDAR	Q9UNE0	0.83	0.71	0.98	0.168
EGF	Pro-epidermal growth factor	P01133	1.02	0.85	1.23	0.943
EGLN1	Egl nine homolog 1	Q9GZT9	1.21	1.00	1.47	0.251
EIF4G1	Eukaryotic translation initiation factor 4 gamma 1	Q04637	1.14	0.93	1.43	0.561
EIF5A*	Eukaryotic translation initiation factor 5A-1	P63241	0.91	0.51	1.59	0.943
ENAH	Protein enabled homolog	Q8N8S7	1.34	0.98	1.85	0.296
ENPP5	Ectonucleotide pyrophosphatase/phosphodiesterase family member 5	Q9UJA9	1.30	0.88	1.98	0.534

ENPP7	Ectonucleotide pyrophosphatase/phosphodiesterase family member 7	Q6UWV6	1.00	0.85	1.18	0.998
EPCAM	Epithelial cell adhesion molecule	P16422	1.00	0.83	1.20	0.998
EPHA1	Ephrin type-A receptor 1	P21709	0.88	0.57	1.36	0.889
EPO	Erythropoietin	P01588	1.28	1.08	1.53	0.060
ERBB3	Receptor tyrosine-protein kinase erbB-3	P21860	0.68	0.34	1.32	0.608
ESM1	Endothelial cell-specific molecule 1	Q9NQ30	0.78	0.53	1.14	0.534
F2R	Proteinase-activated receptor 1	P25116	0.97	0.76	1.25	0.945
FABP1	Fatty acid-binding protein, liver	P07148	1.13	0.97	1.32	0.423
FABP9	Fatty acid-binding protein 9	Q0Z7S8	0.78	0.59	1.03	0.352
FASLG	Tumor necrosis factor ligand superfamily member 6	P48023	0.60	0.43	0.82	0.028
FCAR	Immunoglobulin alpha Fc receptor	P24071	1.71	1.27	2.33	0.012
FCRL2	Fc receptor-like protein 2	Q96LA5	1.02	0.79	1.32	0.978
FCRL3	Fc receptor-like protein 3	Q96P31	0.91	0.71	1.17	0.815
FCRL6	Fc receptor-like protein 6	Q6DN72	1.04	0.85	1.27	0.943
FGF19	Fibroblast growth factor 19	O95750	0.88	0.72	1.07	0.534
FGF2*	Fibroblast growth factor 2	P09038	1.25	1.00	1.56	0.258
FGF5	Fibroblast growth factor 5	P12034	1.11	0.76	1.62	0.895
FIS1	Mitochondrial fission 1 protein	Q9Y3D6	0.92	0.74	1.14	0.782
FKBP1B*	Peptidyl-prolyl cis-trans isomerase FKBP1B	P68106	1.04	0.90	1.20	0.914
FLT3LG	Fms-related tyrosine kinase 3 ligand	P49771	1.32	0.93	1.89	0.424
FOXO1	Forkhead box protein O1	Q12778	0.98	0.81	1.18	0.950
FST	Follistatin	P19883	1.06	0.74	1.53	0.943
FSTL3	Follistatin-related protein 3	O95633	1.79	1.25	2.59	0.027
FXYD5*	FXYD domain-containing ion transport regulator 5	Q96DB9	1.01	0.83	1.23	0.997
GAL	Galanin peptides [Cleaved into: Galanin; Galanin message-associated peptide]	P22466	0.88	0.70	1.11	0.662
GALNT3	Polypeptide N-acetylgalactosaminyltransferase 3	Q14435	1.18	0.83	1.69	0.711
GBP2*	Guanylate-binding protein 2	P32456	1.18	0.95	1.47	0.463
GLOD4	Glyoxalase domain-containing protein 4	Q9HC38	1.06	0.68	1.66	0.943
GMPR	GMP reductase 1	P36959	0.96	0.72	1.27	0.943
GOPC	Golgi-associated PDZ and coiled-coil motif-containing protein	Q9HD26	1.03	0.87	1.22	0.943
GZMA	Granzyme A	P12544	0.99	0.80	1.22	0.993
GZMB	Granzyme B	P10144	1.00	0.88	1.15	0.997
HCLS1	Hematopoietic lineage cell-specific protein	P14317	1.05	0.78	1.40	0.943
HEXIM1	Protein HEXIM1	O94992	1.12	0.90	1.39	0.686
HGF	Hepatocyte growth factor	P14210	2.29	1.53	3.49	0.003
HLA-DRA*	HLA class II histocompatibility antigen, DR alpha chain	P01903	0.86	0.56	1.30	0.815
HLA-E	HLA class I histocompatibility antigen, alpha chain E	P13747	1.13	0.72	1.77	0.895
HPCAL1	Hippocalcin-like protein 1	P37235	1.13	0.88	1.46	0.711
HSD11B1	Corticosteroid 11-beta-dehydrogenase isozyme 1	P28845	1.14	0.78	1.65	0.828

HSPA1A	Heat shock 70 kDa protein 1A	P0DMV8	1.04	0.83	1.30	0.943
ICA1	Islet cell autoantigen 1	Q05084	1.08	0.88	1.33	0.821
ICAM4	Intercellular adhesion molecule 4	Q14773	1.09	0.78	1.55	0.899
IDS	Iduronate 2-sulfatase	P22304	0.32	0.05	1.86	0.545
IFNG*	Interferon gamma	P01579	0.90	0.78	1.03	0.424
IFNGR1	Interferon gamma receptor 1	P15260	1.42	0.79	2.59	0.582
IFNLR1	Interferon lambda receptor 1	Q8IU57	0.66	0.40	1.06	0.362
IKBKG	NF-kappa-B essential modulator	Q9Y6K9	1.01	0.82	1.24	0.997
IL10	Interleukin-10	P22301	1.04	0.89	1.22	0.914
IL10RA	Interleukin-10 receptor subunit alpha	Q13651	1.39	1.05	1.86	0.155
IL10RB	Interleukin-10 receptor subunit beta	Q08334	1.43	0.88	2.34	0.471
IL11*	Interleukin-11	P20809	0.98	0.78	1.24	0.979
IL12B	Interleukin-12 subunit beta	P29460	0.82	0.68	0.98	0.171
IL12RB1	Interleukin-12 receptor subunit beta-1	P42701	0.88	0.59	1.30	0.828
IL13*	Interleukin-13	P35225	0.87	0.65	1.13	0.704
IL15	Interleukin-15	P40933	1.33	0.94	1.90	0.417
IL15RA	Interleukin-15 receptor subunit alpha	Q13261	1.05	0.73	1.51	0.943
IL16	Pro-interleukin-16 [Cleaved into: Interleukin-16	Q14005	1.23	0.92	1.66	0.497
IL17A*	Interleukin-17A	Q16552	0.94	0.66	1.32	0.943
IL17C	Interleukin-17C	Q9P0M4	1.39	1.13	1.71	0.029
IL17D	Interleukin-17D	Q8TAD2	0.92	0.63	1.34	0.936
IL17F*	Interleukin-17F	Q96PD4	0.90	0.73	1.10	0.686
IL17RB	Interleukin-17 receptor B	Q9NRM6	1.34	1.00	1.81	0.258
IL18	Interleukin-18	Q14116	1.01	0.73	1.40	0.997
IL18R1	Interleukin-18 receptor 1	Q13478	1.06	0.68	1.66	0.943
IL1A*	Interleukin-1 alpha	P01583	0.99	0.76	1.28	0.997
IL1B	Interleukin-1 beta	P01584	1.19	0.92	1.56	0.534
IL1R2	Interleukin-1 receptor type 2	P27930	1.58	0.90	2.85	0.424
IL1RL2	Interleukin-1 receptor-like 2	Q9HB29	0.88	0.60	1.28	0.828
IL1RN	Interleukin-1 receptor antagonist protein	P18510	1.57	1.24	2.00	0.006
IL2	Interleukin-2	P60568	0.93	0.59	1.47	0.943
IL20*	Interleukin-20	Q9NYY1	0.95	0.69	1.30	0.943
IL20RA*	Interleukin-20 receptor subunit alpha	Q9UHF4	1.18	0.82	1.72	0.716
IL22RA1	Interleukin-22 receptor subunit alpha-1	Q8N6P7	0.84	0.57	1.22	0.716
IL24*	Interleukin-24	Q13007	0.99	0.73	1.32	0.993
IL2RB*	Interleukin-2 receptor subunit beta	P14784	0.95	0.64	1.39	0.943
IL32	Interleukin-32	P24001	1.02	0.77	1.35	0.979
IL33*	Interleukin-33	O95760	0.86	0.63	1.18	0.712
IL3RA	Interleukin-3 receptor subunit alpha	P26951	0.98	0.58	1.65	0.993
IL4*	Interleukin-4	P05112	1.15	0.92	1.45	0.569

IL4R	Interleukin-4 receptor subunit alpha	P24394	1.52	1.08	2.16	0.126
IL5*	Interleukin-5	P05113	0.93	0.83	1.03	0.520
IL5RA	Interleukin-5 receptor subunit alpha	Q01344	1.38	1.07	1.80	0.118
IL6	Interleukin-6	P05231	1.19	1.02	1.39	0.187
IL7	Interleukin-7	P13232	1.06	0.83	1.34	0.928
IRAK1	Interleukin-1 receptor-associated kinase 1	P51617	1.10	0.87	1.39	0.775
IRAK4	Interleukin-1 receptor-associated kinase 4	Q9NWZ3	1.03	0.86	1.23	0.943
ISM1	Isthmin-1	B1AKI9	1.03	0.70	1.53	0.975
ITGA11	Integrin alpha-11	Q9UKX5	0.58	0.39	0.87	0.088
ITGA6	Integrin alpha-6	P23229	0.76	0.57	1.01	0.278
ITGB6	Integrin beta-6	P18564	3.17	2.20	4.70	<0.001
ITM2A	Integral membrane protein 2A	O43736	1.19	0.90	1.58	0.575
JCHAIN	Immunoglobulin J chain	P01591	1.05	0.83	1.32	0.940
JUN	Transcription factor AP-1	P05412	1.40	1.07	1.87	0.126
KLRB1	Killer cell lectin-like receptor subfamily B member 1	Q12918	0.79	0.57	1.09	0.471
KLRD1	Natural killer cells antigen CD94	Q13241	1.13	0.85	1.52	0.748
KRT19	Keratin, type I cytoskeletal 19	P08727	2.10	1.69	2.66	<0.001
KYNU	Kynureninase	Q16719	1.12	0.76	1.64	0.889
LAIR1	Leukocyte-associated immunoglobulin-like receptor 1	Q6GTX8	1.14	0.85	1.52	0.740
LAMA4	Laminin subunit alpha-4	Q16363	0.70	0.47	1.04	0.349
LAMP3	Lysosome-associated membrane glycoprotein 3	Q9UQV4	1.19	0.81	1.75	0.716
LAP3	Cytosol aminopeptidase	P28838	0.82	0.59	1.13	0.569
LAT	Linker for activation of T-cells family member 1	O43561	1.05	0.82	1.34	0.943
LGALS4	Galectin-4	P56470	1.41	1.09	1.84	0.096
LGALS9	Galectin-9	O00182	1.26	0.90	1.78	0.520
LGMN	Legumain Phospholysine phosphohistidine inorganic pyrophosphate phosphatase	Q99538	0.92	0.61	1.39	0.943
LHPP	Leukemia inhibitory factor receptor	Q9H008	1.08	0.82	1.41	0.895
LIFR	Leukemia inhibitory factor receptor	P42702	2.54	1.39	4.73	0.036
LILRB4	Leukocyte immunoglobulin-like receptor subfamily B member 4	Q8NHJ6	1.01	0.73	1.40	0.997
LRRN1	Leucine-rich repeat neuronal protein 1	Q6UXX5	0.57	0.38	0.84	0.055
LSP1	Lymphocyte-specific protein 1	P33241	1.23	0.93	1.63	0.471
LTA	Lymphotoxin-alpha	P01374	0.77	0.57	1.03	0.346
LTBR	Tumor necrosis factor receptor superfamily member 3	P36941	1.68	1.09	2.62	0.144
LTO1*	Protein LTO1 homolog	Q8WV07	0.81	0.53	1.19	0.686
LY6D	Lymphocyte antigen 6D	Q14210	1.28	0.90	1.81	0.498
LY75	Lymphocyte antigen 75	O60449	1.05	0.71	1.56	0.943
LY9	T-lymphocyte surface antigen Ly-9	Q9HBG7	1.04	0.69	1.58	0.952
MANF	Mesencephalic astrocyte-derived neurotrophic factor	P55145	1.05	0.88	1.26	0.895
MAP2K6	Dual specificity mitogen-activated protein kinase kinase 6	P52564	1.02	0.83	1.24	0.978
MAPK9	Mitogen-activated protein kinase 9	P45984	1.08	0.77	1.52	0.925

MATN2	Matrilin-2	O00339	1.45	0.94	2.28	0.371
MEGF10	Multiple epidermal growth factor-like domains protein 10	Q96KG7	0.67	0.44	1.01	0.260
MEPE	Matrix extracellular phosphoglycoprotein	Q9NQ76	0.61	0.38	0.95	0.174
MERTK	Tyrosine-protein kinase Mer	Q12866	1.53	0.87	2.69	0.445
METAP1D	Methionine aminopeptidase 1D, mitochondrial	Q6UB28	1.01	0.83	1.22	0.997
MGLL	Monoglyceride lipase	Q99685	0.94	0.76	1.18	0.897
MGMT	Methylated-DNA--protein-cysteine methyltransferase	P16455	0.94	0.80	1.12	0.828
MICB_MICA	MHC class I polypeptide-related sequence B_A	Q29980_Q29983	1.05	0.95	1.17	0.711
MILR1	Allergin-1	Q7Z6M3	1.40	1.06	1.86	0.144
MLN	Promotilin [Cleaved into: Motilin; Motilin-associated peptide]	P12872	1.14	0.96	1.36	0.464
MMP1	Interstitial collagenase	P03956	1.39	1.13	1.74	0.036
MMP10	Stromelysin-2	P09238	1.62	1.30	2.06	0.002
MPIG6B	Megakaryocyte and platelet inhibitory receptor G6b	O95866	1.15	0.86	1.58	0.712
MVK	Mevalonate kinase	Q03426	1.15	0.93	1.41	0.534
MYO9B	Unconventional myosin-IXb	Q13459	1.06	0.88	1.28	0.835
MZB1	Marginal zone B- and B1-cell-specific protein	Q8WU39	1.36	1.04	1.78	0.168
NBN	Nibrin	O60934	1.06	0.89	1.25	0.828
NCF2	Neutrophil cytosol factor 2	P19878	1.15	0.98	1.36	0.352
NCK2	Cytoplasmic protein NCK2	O43639	1.00	0.85	1.18	0.998
NCLN*	Nicalin	Q969V3	0.88	0.63	1.14	0.712
NCR1	Natural cytotoxicity triggering receptor 1	O76036	0.97	0.73	1.29	0.952
NELL2	Protein kinase C-binding protein NELL2	Q99435	1.64	1.10	2.47	0.126
NFASC	Neurofascin	O94856	1.33	0.85	2.10	0.561
NFATC1	Nuclear factor of activated T-cells, cytoplasmic 1	O95644	0.97	0.80	1.18	0.943
NFATC3*	Nuclear factor of activated T-cells, cytoplasmic 3	Q12968	1.04	0.81	1.34	0.943
NME3	Nucleoside diphosphate kinase 3	Q13232	0.93	0.55	1.57	0.943
NPPC	C-type natriuretic peptide [Cleaved into: CNP-22; CNP-29; CNP-53]	P23582	1.16	0.89	1.51	0.608
NRTN*	Neurturin	Q99748	0.80	0.58	1.10	0.512
NT5C3A	Cytosolic 5'-nucleotidase 3A	Q9H0P0	1.02	0.83	1.25	0.975
NTF3	Neurotrophin-3	P20783	1.05	0.71	1.55	0.943
NUB1	NEDD8 ultimate buster 1	Q9Y5A7	1.00	0.83	1.20	0.998
NUDC	Nuclear migration protein nudC	Q9Y266	1.15	0.86	1.56	0.711
OMD	Osteomodulin	Q99983	0.90	0.66	1.24	0.850
OSCAR	Osteoclast-associated immunoglobulin-like receptor	Q8IYS5	1.06	0.72	1.57	0.943
OSM	Oncostatin-M	P13725	1.38	1.15	1.66	0.012
PADI2	Protein-arginine deiminase type-2	Q9Y2J8	1.17	0.96	1.44	0.424
PAPPA	Pappalysin-1	Q13219	1.16	0.85	1.58	0.711
PARP1	Poly [ADP-ribose] polymerase 1	P09874	0.95	0.80	1.12	0.889
PCDH1	Protocadherin-1	Q08174	0.57	0.27	1.16	0.424
PDGFB	Platelet-derived growth factor subunit B	P01127	1.03	0.84	1.27	0.943

PDLIM7	PDZ and LIM domain protein 7	Q9NR12	1.02	0.88	1.18	0.943
PGF	Placenta growth factor	P49763	1.22	0.75	2.00	0.758
PIK3AP1	Phosphoinositide 3-kinase adapter protein 1	Q6ZUJ8	1.00	0.80	1.25	0.998
PKLR	Pyruvate kinase PKLR	P30613	1.04	0.82	1.32	0.943
PLA2G4A	Cytosolic phospholipase A2	P47712	1.00	0.83	1.22	0.998
PLAUR	Urokinase plasminogen activator surface receptor	Q03405	3.78	2.34	6.29	<0.001
PLXNA4	Plexin-A4	Q9HCM2	0.92	0.74	1.13	0.775
PNLIPRP2	Pancreatic lipase-related protein 2	P54317	1.02	0.96	1.08	0.852
PNPT1*	Polyribonucleotide nucleotidyltransferase 1, mitochondrial	Q8TCS8	0.90	0.75	1.07	0.561
PON3	Serum paraoxonase/lactonase 3	Q15166	0.84	0.55	1.24	0.744
PPP1R9B	Neurabin-2	Q96SB3	1.03	0.87	1.23	0.943
PRDX3*	Thioredoxin-dependent peroxide reductase, mitochondrial	P30048	0.96	0.78	1.17	0.943
PRDX5	Peroxiredoxin-5, mitochondrial	P30044	1.09	0.84	1.43	0.828
PREB*	Prolactin regulatory element-binding protein	Q9HCU5	1.39	0.92	2.13	0.424
PRELP	Prolargin	P51888	1.06	0.66	1.73	0.943
PRKAB1	5'-AMP-activated protein kinase subunit beta-1	Q9Y478	1.17	0.90	1.54	0.582
PRKCQ*	Protein kinase C theta type	Q04759	0.77	0.52	1.11	0.520
PROK1	Prokineticin-1	P58294	1.26	1.04	1.53	0.144
PRSS8	Prostasin	Q16651	1.94	1.34	2.84	0.012
PSIP1	PC4 and SFRS1-interacting protein	O75475	1.07	0.91	1.25	0.783
PSMG3	Proteasome assembly chaperone 3	Q9BT73	0.99	0.71	1.40	0.998
PSPN	Persephin Parathyroid hormone/parathyroid hormone-related peptide receptor	O60542	1.01	0.89	1.14	0.970
PTH1R		Q03431	1.34	0.85	2.12	0.545
PTPN6	Tyrosine-protein phosphatase non-receptor type 6	P29350	0.99	0.79	1.24	0.993
PTPRM	Receptor-type tyrosine-protein phosphatase mu	P28827	1.41	0.75	2.68	0.644
PTX3	Pentraxin-related protein PTX3	P26022	1.28	0.94	1.74	0.424
RAB37*	Ras-related protein Rab-37	Q96AX2	0.81	0.66	1.00	0.251
RAB6A	Ras-related protein Rab-6A	P20340	0.73	0.52	0.99	0.258
RABGAP1L	Rab GTPase-activating protein 1-like	Q5R372	1.00	0.79	1.26	0.998
REG4	Regenerating islet-derived protein 4	Q9BYZ8	1.33	0.99	1.80	0.279
RGS8*	Regulator of G-protein signaling 8	P57771	0.91	0.75	1.11	0.712
ROBO1	Roundabout homolog 1	Q9Y6N7	1.71	1.05	2.86	0.196
SAMD9L	Sterile alpha motif domain-containing protein 9-like	Q8IVG5	1.09	0.88	1.34	0.780
SCG3	Secretogranin-3	Q8WXD2	0.69	0.46	1.04	0.340
SCGB1A1	Uteroglobin	P11684	1.51	1.17	1.96	0.029
SCGB3A2	Secretoglobin family 3A member 2	Q96PL1	1.55	1.31	1.85	<0.001
SCGN	Secretagoin	O76038	1.18	0.85	1.65	0.686
SCRN1	Secernin-1	Q12765	1.10	0.84	1.43	0.828
SELPLG	P-selectin glycoprotein ligand 1	Q14242	0.83	0.49	1.40	0.828
SERPINB8	Serpin B8	P50452	1.43	1.15	1.79	0.027

SH2D1A	SH2 domain-containing protein 1A	O60880	0.93	0.78	1.10	0.768
SHMT1	Serine hydroxymethyltransferase, cytosolic	P34896	0.94	0.78	1.13	0.828
SIGLEC1	Sialoadhesin	Q9BZZ2	1.00	0.74	1.34	0.998
SIGLEC10	Sialic acid-binding Ig-like lectin 10	Q96LC7	1.72	1.17	2.58	0.072
SIRPB1	Signal-regulatory protein beta-1	O00241	1.06	0.78	1.46	0.943
SIT1	Signaling threshold-regulating transmembrane adapter 1	Q9Y3P8	0.82	0.59	1.12	0.545
SKAP2	Src kinase-associated phosphoprotein 2	O75563	1.01	0.85	1.21	0.979
SLAMF1*	Signaling lymphocytic activation molecule	Q13291	1.04	0.82	1.33	0.943
SLAMF7	SLAM family member 7	Q9NQ25	0.99	0.77	1.29	0.998
SLC39A5	Zinc transporter ZIP5	Q6ZMH5	1.14	0.87	1.52	0.711
SMOC2	SPARC-related modular calcium-binding protein 2	Q9H3U7	0.93	0.68	1.26	0.925
SMPDL3A	Acid sphingomyelinase-like phosphodiesterase 3a	Q92484	0.99	0.76	1.30	0.998
SPINK4	Serine protease inhibitor Kazal-type 4	O60575	1.28	1.02	1.60	0.175
SPINT2	Kunitz-type protease inhibitor 2	O43291	1.59	1.06	2.41	0.169
SPON1	Spondin-1	Q9HCB6	2.64	1.78	4.01	<0.001
SPRY2	Protein sprouty homolog 2	O43597	1.01	0.87	1.18	0.968
SRPK2	SRSF protein kinase 2	P78362	1.03	0.87	1.22	0.943
STX8	Syntaxin-8	Q9UNK0	1.20	0.91	1.58	0.534
SULT2A1	Bile salt sulfotransferase	Q06520	0.96	0.73	1.26	0.943
TANK	TRAF family member-associated NF-kappa-B activator	Q92844	0.92	0.72	1.15	0.798
TBC1D5	TBC1 domain family member 5	Q92609	1.05	0.86	1.28	0.914
TFF2	Trefoil factor 2	Q03403	1.73	1.33	2.27	0.002
TGFA	Protransforming growth factor alpha [Cleaved into: Transforming growth factor alpha]	P01135	2.45	1.62	3.77	0.002
TGFB1	Transforming growth factor beta-1 proprotein [Cleaved into: Latency-associated peptide]	P01137	1.38	0.93	2.06	0.417
TIMP3	Metalloproteinase inhibitor 3	P35625	1.07	0.93	1.24	0.711
TLR3	Toll-like receptor 3	O15455	0.94	0.72	1.24	0.939
TNF	Tumor necrosis factor	P01375	1.01	0.83	1.21	0.993
TNFAIP8*	Tumor necrosis factor alpha-induced protein 8	O95379	0.90	0.63	1.26	0.850
TNFRSF11A	Tumor necrosis factor receptor superfamily member 11A	Q9Y6Q6	1.41	1.03	1.96	0.196
TNFRSF11B	Tumor necrosis factor receptor superfamily member 11B	O00300	1.85	1.24	2.82	0.039
TNFRSF13B	Tumor necrosis factor receptor superfamily member 13B	O14836	1.43	1.04	1.99	0.170
TNFRSF13C	Tumor necrosis factor receptor superfamily member 13C	Q96RJ3	1.01	0.74	1.38	0.997
TNFRSF14	Tumor necrosis factor receptor superfamily member 14	Q92956	1.23	0.82	1.85	0.686
TNFRSF4	Tumor necrosis factor receptor superfamily member 4	P43489	0.88	0.66	1.15	0.711
TNFSF10	Tumor necrosis factor ligand superfamily member 10	P50591	0.41	0.23	0.73	0.036
TNFSF11	Tumor necrosis factor ligand superfamily member 11	O14788	0.64	0.51	0.80	0.005
TNFSF12	Tumor necrosis factor ligand superfamily member 12	O43508	0.51	0.29	0.87	0.119
TNFSF13	Tumor necrosis factor ligand superfamily member 13	O75888	1.43	0.91	2.27	0.424
TPP1	Tripeptidyl-peptidase 1	O14773	1.31	0.91	1.92	0.464

TPSAB1	Tryptase alpha/beta-1	Q15661	0.80	0.59	1.09	0.497
TPT1*	Translationally-controlled tumor protein	P13693	0.93	0.73	1.18	0.884
TRAF2	TNF receptor-associated factor 2	Q12933	0.92	0.73	1.16	0.828
TREM2	Triggering receptor expressed on myeloid cells 2	Q9NZC2	1.29	1.00	1.67	0.258
TRIM21	E3 ubiquitin-protein ligase TRIM21	P19474	1.19	1.06	1.35	0.058
TRIM5	Tripartite motif-containing protein 5	Q9C035	1.12	0.90	1.40	0.672
VASH1*	Tubuliny-Tyr carboxypeptidase 1	Q7L8A9	0.98	0.81	1.18	0.945
VEGFA	Vascular endothelial growth factor A	P15692	1.39	1.05	1.86	0.152
VEGFD	Vascular endothelial growth factor D	O43915	1.38	0.92	2.11	0.424
WAS*	Wiskott-Aldrich syndrome protein	P42768	0.96	0.82	1.13	0.914
WFIKKN2	WAP, Kazal, immunoglobulin, Kunitz and NTR domain-containing protein 2	Q8TEU8	0.66	0.43	1.00	0.258
WNT9A	Protein Wnt-9a	O14904	1.48	0.98	2.25	0.278
YTHDF3	YTH domain-containing family protein 3	Q7Z739	1.03	0.84	1.26	0.943

* Excluded due to >10% missing data

Table S2. PF-ILD association for validated biomarkers in combined cohort (n=589)

Protein	Unadjusted			Adjusted*		
	OR**	95% CI	p-value	OR**	95% CI	p-value
AGER	0.60	0.48-0.74	<0.001	0.63	0.51-0.79	<0.001
ANGPTL4	1.79	1.37-2.34	<0.001	1.54	1.17-2.04	0.002
CXCL17	1.65	1.34-2.04	<0.001	1.43	1.14-1.79	0.002
DPP10	1.79	1.37-2.34	<0.001	1.63	1.25-2.14	<0.001
FASLG	0.61	0.48-0.79	<0.001	0.67	0.51-0.87	0.003
FCAR	1.68	1.33-2.13	<0.001	1.55	1.22-1.98	<0.001
HGF	2.19	1.60-2.99	<0.001	1.85	1.33-2.58	<0.001
IL17c	1.43	1.23-1.67	<0.001	1.36	1.15-1.61	<0.001
ITGB6	3.13	2.31-4.23	<0.001	2.68	1.95-3.67	<0.001
KRT19	2.00	1.67-2.38	<0.001	1.86	1.55-2.23	<0.001
MMP10	1.63	1.35-1.97	<0.001	1.45	1.18-1.76	<0.001
PLAUR	3.28	2.24-4.80	<0.001	2.64	1.77-3.93	<0.001
PRSS8	2.12	1.56-2.88	<0.001	1.81	1.31-2.48	<0.001
SCGB3A2	1.56	1.36-1.80	<0.001	1.45	1.25-1.67	<0.001
SPON1	2.46	1.78-3.40	<0.001	2.00	1.42-2.80	<0.001
TGFA	1.80	1.40-2.33	<0.001	1.72	1.29-2.29	<0.001
TNFRSF11B	1.99	1.44-2.74	<0.001	1.67	1.20-2.34	0.003

* Adjusted for center, ILD diagnosis and baseline GAP stage

** Per unit-change in log2 transformed biomarker concentration

Table S3. Association between validated biomarkers of PF-ILD and individual outcomes

Biomarker	Outcome	
	Death/Transplant (n=589)	≥10% FVC decline* (n=480)
	OR** (95% CI)	
AGER	0.68 (0.53-0.89)	0.60 (0.46-0.77)
ANGPTL4	2.08 (1.47-2.95)	1.49 (1.08-2.04)
CXCL17	2.54 (1.88-3.43)	1.23 (0.97-1.56)
DPP10	1.79 (1.31-2.46)	1.57 (1.16-2.12)
FASLG	0.51 (0.38-0.70)	0.76 (0.56-1.03)
FCAR	2.08 (1.55-2.79)	1.33 (1.01-1.75)
HGF	3.53 (2.39-5.24)	1.42 (0.98-2.06)
IL17C	1.68 (1.39-2.03)	1.21 (1.01-1.44)
ITGB6	4.51 (3.10-6.57)	2.05 (1.45-2.92)
KRT19	2.32 (1.86-2.90)	1.57 (1.29-1.91)
MMP10	2.00 (1.59-2.51)	1.29 (1.04-1.60)
PLAUR	7.44 (4.48-12.37)	1.65 (1.07-2.53)
PRSS8	2.23 (1.51-3.30)	1.75 (1.23-2.48)
SCGB3A2	1.86 (1.54-2.23)	1.29 (1.10-1.50)
SPON1	7.34 (4.53-11.87)	1.23 (0.84-1.78)
TGFA	2.24 (1.68-2.99)	1.31 (0.98-1.74)
TNFRSF11B	2.22 (1.48-3.32)	1.59 (1.10-2.29)

* Death/transplant events excluded

** Per unit-change in log2 transformed biomarker concentration

Table S4. HRCT morphology-stratified association between validated biomarkers and PF-ILD phenotype in combined cohort (n=589)

Protein	Definite/Probable UIP (n=135)	NSIP (n=212)	Other (n=242)	heterogeneity p value*
	OR** (95% CI)			
AGER	0.41 (0.27-0.64)	0.70 (0.49-1.00)	0.67 (0.45-0.97)	0.15
ANGPTL4	1.23 (0.80-1.91)	2.21 (1.32-3.68)	2.07 (1.30-3.30)	0.15
CXCL17	1.66 (1.14-2.41)	1.97 (1.31-2.97)	1.21 (0.84-1.74)	0.19
DPP10	2.76 (1.58-4.80)	1.32 (0.88-1.98)	1.71 (1.07-2.72)	0.11
FASLG	0.39 (0.24-0.64)	0.82 (0.55-1.23)	0.72 (0.44-1.18)	0.06
FCAR	1.41 (0.92-2.16)	1.38 (0.92-2.09)	2.30 (1.49-3.56)	0.18
HGF	2.75 (1.52-4.98)	1.31 (0.76-2.24)	2.64 (1.54-4.54)	0.11
IL17c	1.50 (1.13-2.00)	1.54 (1.15-2.06)	1.21 (0.94-1.56)	0.39
ITGB6	9.73 (4.47-21.16)	2.16 (1.24-3.75)	2.03 (1.32-3.11)	0.002
KRT19	2.39 (1.67-3.43)	1.68 (1.24-2.27)	1.95 (1.47-2.59)	0.34
MMP10	1.49 (1.06-2.08)	1.53 (1.08-2.17)	1.66 (1.22-2.27)	0.88
PLAUR	2.72 (1.36-5.42)	3.03 (1.59-5.77)	3.65 (1.87-7.14)	0.83
PRSS8	2.49 (1.42-4.40)	2.64 (1.42-4.89)	1.23 (0.74-2.02)	0.08
SCGB3A2	1.45 (1.12-1.87)	1.50 (1.16-1.92)	1.69 (1.32-2.15)	0.67
SPON1	1.96 (1.10-3.49)	1.71 (0.98-2.96)	4.05 (2.25-7.30)	0.08
TGFA	1.81 (1.16-2.82)	1.54 (1.02-2.32)	2.60 (1.51-4.46)	0.32
TNFRS11B	1.50 (0.86-2.60)	1.77 (1.00-3.13)	2.43 (1.36-4.34)	0.49

* Test of whether PF-ILD biomarker association varies by HRCT morphology

** Per unit-change in log2 transformed biomarker concentration

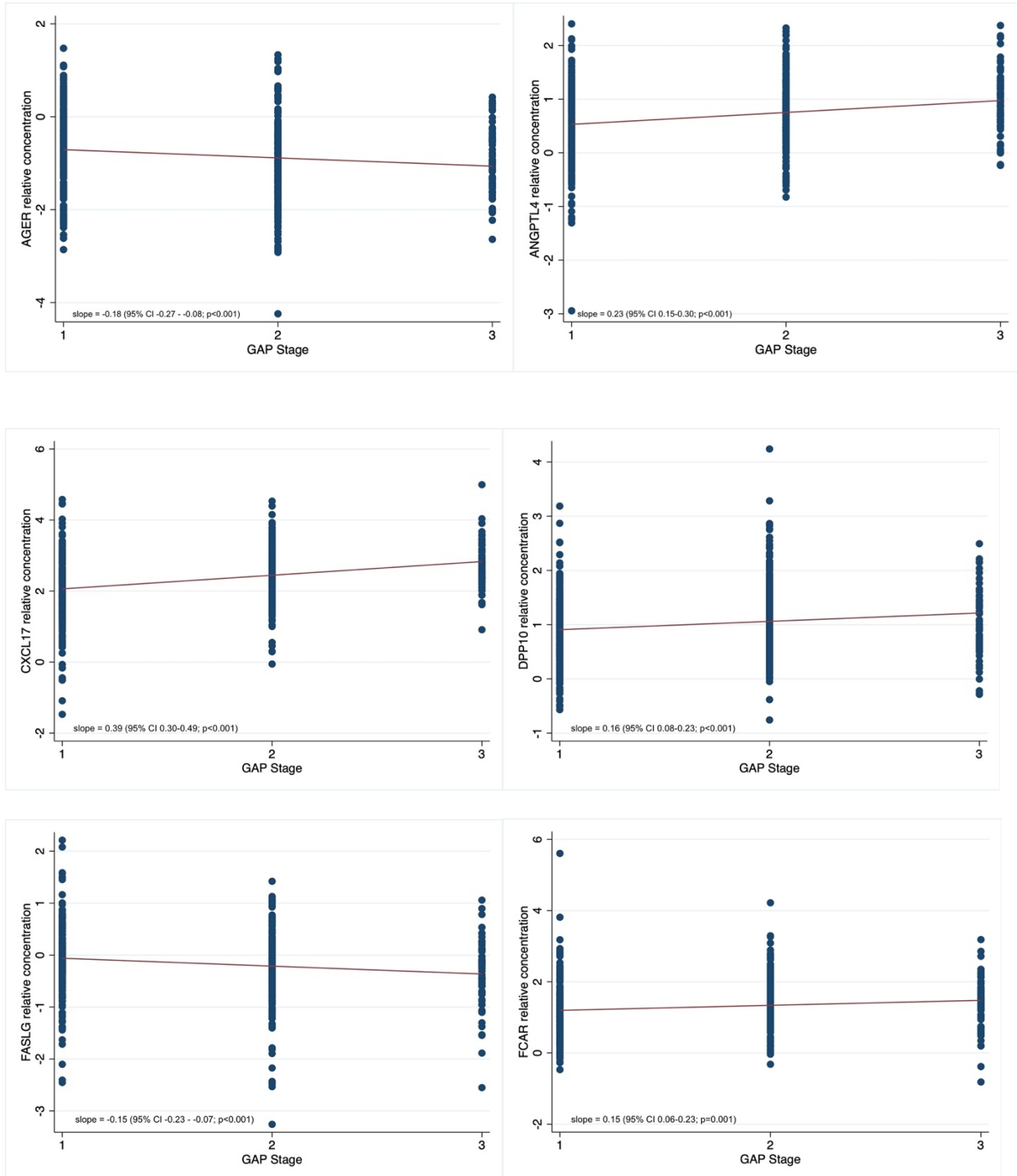
Table S5. GAP index-stratified PF-ILD association for validated biomarkers in combined cohort (n=589)

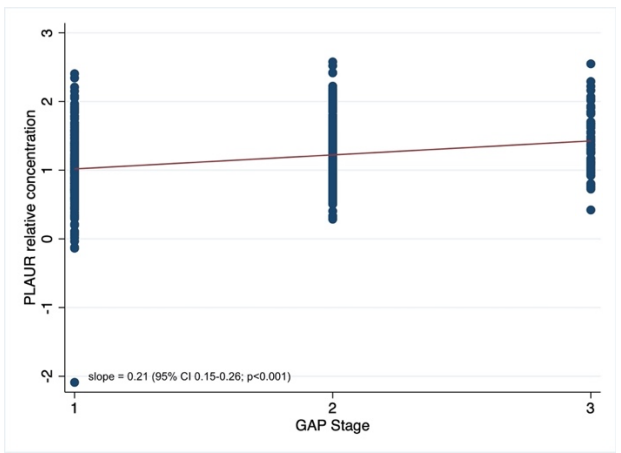
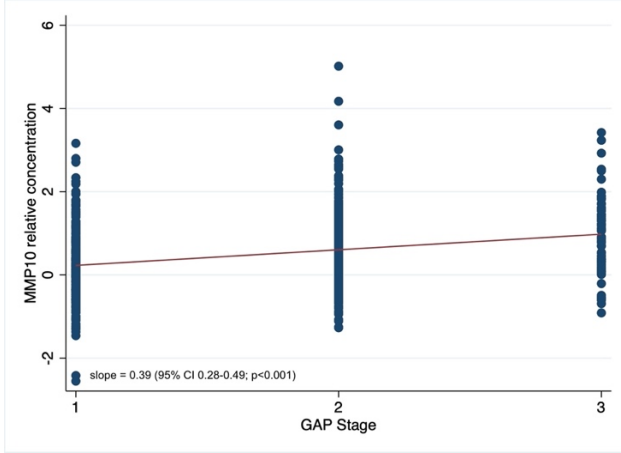
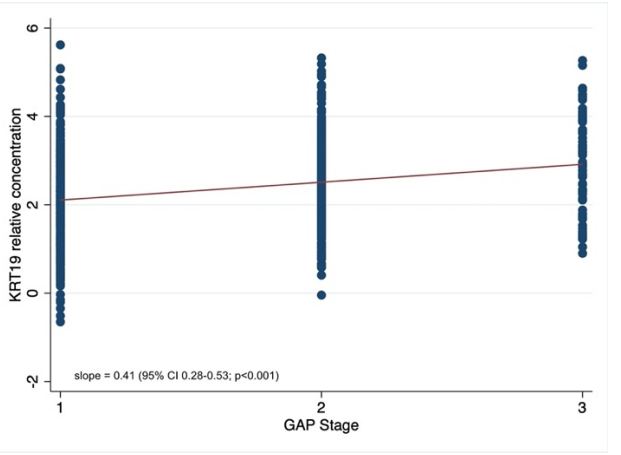
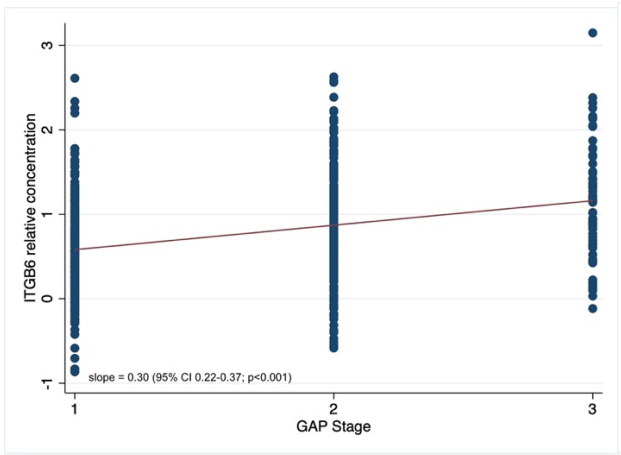
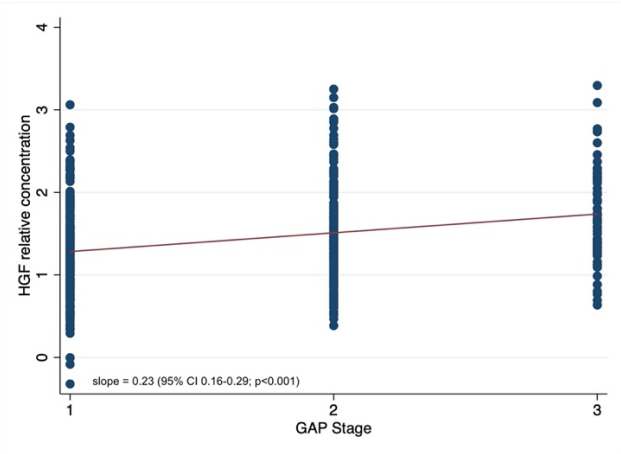
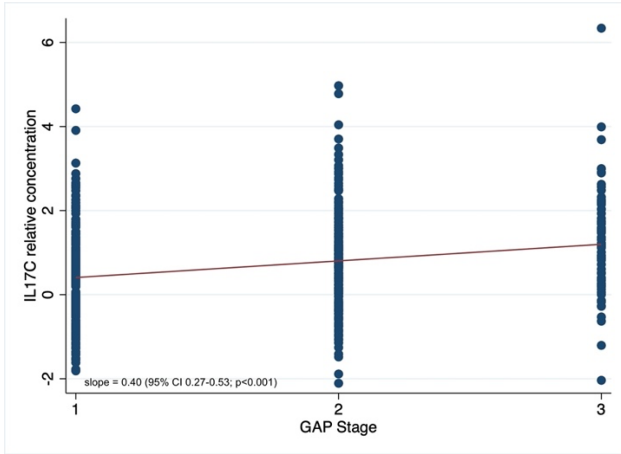
Protein	Stage I (n=267)	Stage II (n=252)	Stage III (n=70)	heterogeneity p value*
	OR** (95% CI)			
AGER	0.48 (0.33-0.69)	0.73 (0.54-0.98)	1.05 (0.53-2.12)	0.022
ANGPTL4	1.58 (1.05-2.37)	1.61 (1.05-2.48)	1.21 (0.50-2.90)	0.63
CXCL17	1.23 (0.91-1.67)	1.69 (1.19-2.39)	1.46 (0.67-3.18)	0.35
DPP10	1.41 (0.92-2.16)	2.01 (1.35-3.01)	1.08 (0.48-2.44)	0.88
FASLG	0.51 (0.33-0.78)	0.92 (0.64-1.32)	0.42 (0.17-1.01)	0.41
FCAR	1.50 (1.05-2.09)	1.63 (1.12-2.35)	1.73 (0.81-3.67)	0.65
HGF	1.86 (1.15-3.00)	1.93 (1.17-3.19)	1.40 (0.56-3.53)	0.61
IL17c	1.41 (1.09-1.83)	1.22 (0.97-1.53)	1.51 (0.96-2.35)	0.77
ITGB6	1.76 (1.09-2.83)	3.30 (2.05-5.32)	5.12 (1.89-13.86)	0.035
KRT19	1.65 (1.27-2.14)	1.87 (1.42-2.46)	3.32 (1.70-6.48)	0.096
MMP10	1.27 (0.93-1.74)	1.80 (1.33-2.43)	1.05 (0.63-1.77)	0.99
PLAUR	2.20 (1.23-3.91)	2.91 (1.59-5.33)	4.18 (1.19-14.63)	0.37
PRSS8	1.44 (0.92-2.26)	2.11 (1.30-3.43)	2.74 (0.95-7.96)	0.21
SCGB3A2	1.22 (1.0-1.50)	1.60 (1.28-2.00)	2.47 (1.36-4.49)	0.013
SPON1	1.49 (0.92-2.42)	2.25 (1.35-3.72)	5.72 (1.72-19.02)	0.067
TGFA	1.54 (1.04-2.27)	1.45 (0.99-2.12)	2.88 (1.13-7.34)	0.51
TNFRS11B	1.48 (0.92-2.38)	1.62 (0.97-2.72)	4.36 (1.38-13.73)	0.18

* Test of whether PF-ILD biomarker association varies by GAP stage

** Per unit-change in log2 transformed biomarker concentration

Figure S2. Scatter plots and linear regression estimates assessing the association between validated biomarkers and baseline GAP stage.





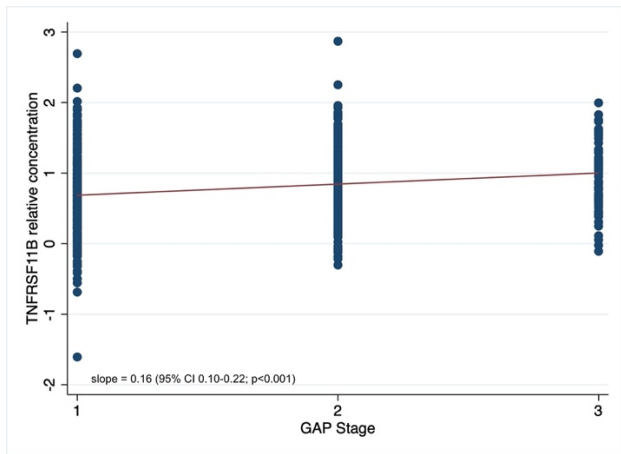
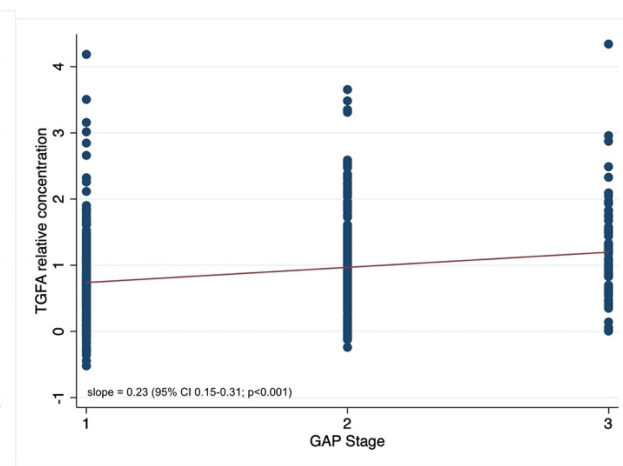
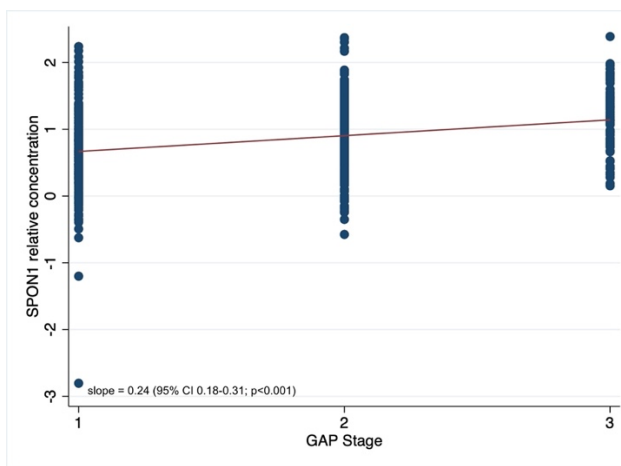
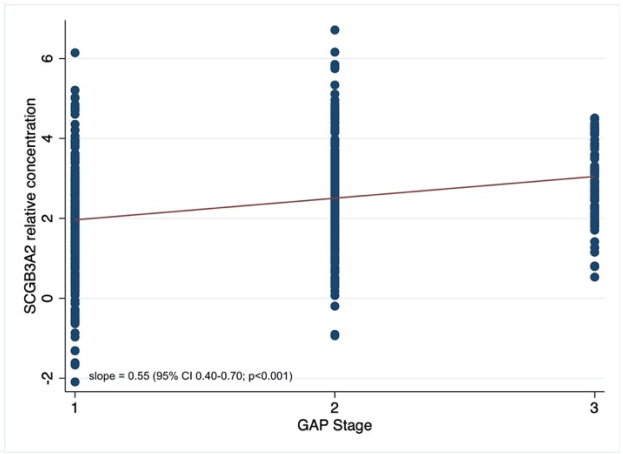
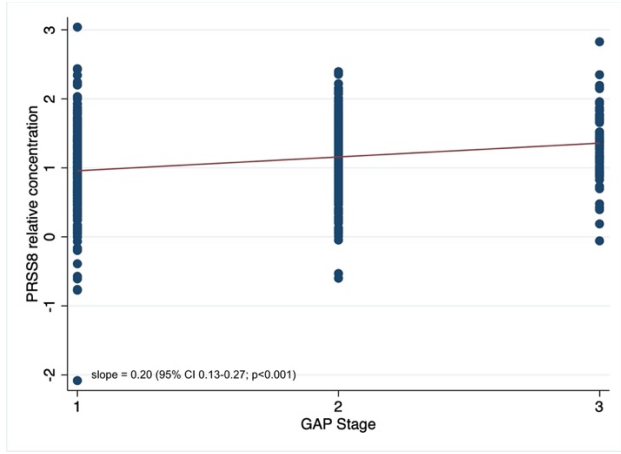
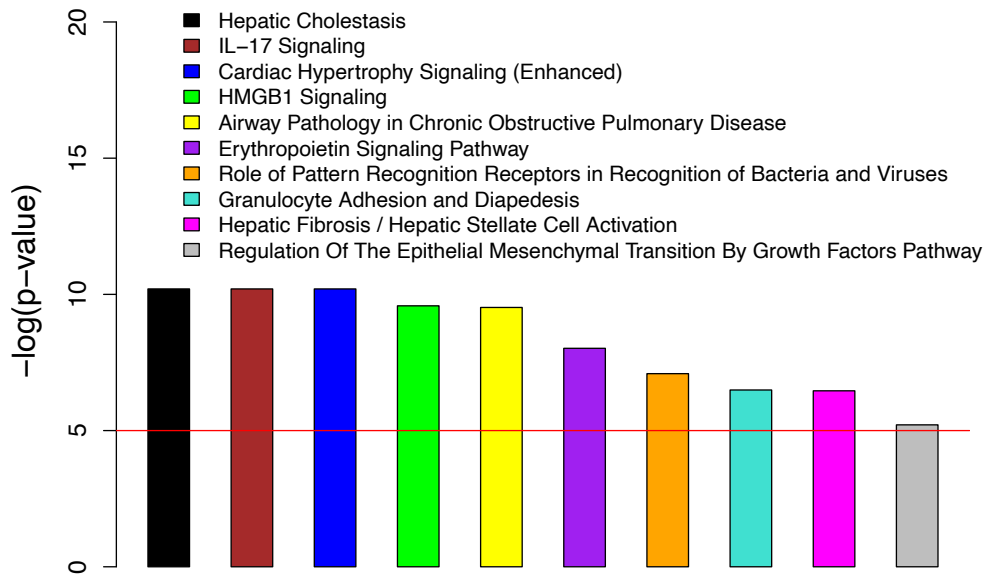


Figure S3. Pathway (a) and network (b) analysis of proteins associated with PF-ILD in the combined cohort at false discovery rate of <0.05.

a.



b.

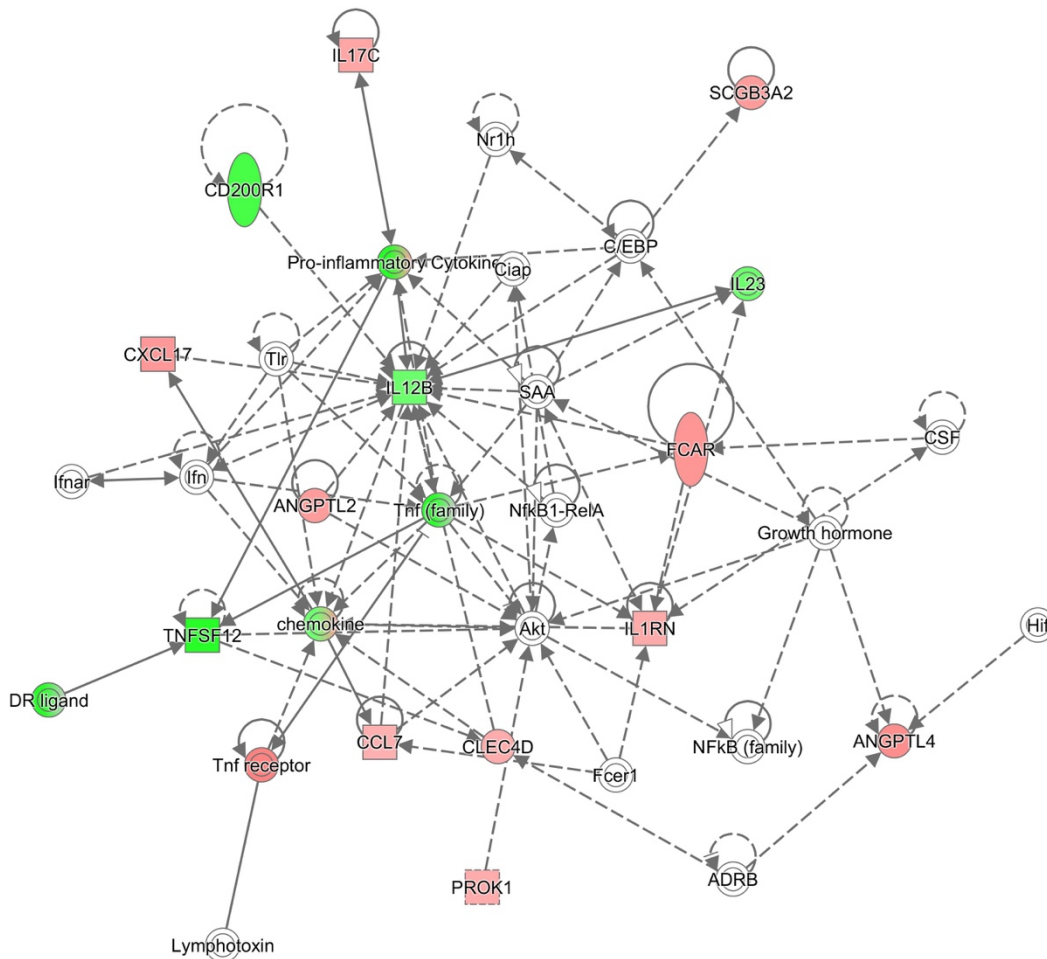


Table S6. Derivation cohort proteomic signature test performance characteristics by proteomic score threshold

Score Threshold	High-risk n (%)	Low-risk n (%)	Sensitivity	Specificity	PPV	NPV
0.20	198 (73.3)	72 (27.7)	0.91	0.37	0.46	0.88
0.30*	157 (58.2)	113 (41.9)	0.85	0.58	0.54	0.87
0.35	137 (50.7)	133 (49.3)	0.80	0.66	0.58	0.85
0.40	103 (38.2)	167 (61.9)	0.64	0.77	0.62	0.78
0.50	66 (24.4)	204 (75.6)	0.48	0.89	0.73	0.75

* Threshold chosen for proteomic signature classification

Abbreviations: PPV = positive predictive value; NPV = negative predictive value

Table S7. PF-ILD Proteomic Signature Test performance

PF-ILD PS	Derivation Cohort		Validation Cohort	
	PF-ILD Phenotype			
	(+)	(-)	(+)	(-)
High-Risk	85	72	37	37
Low-Risk	15	98	4	41
Sensitivity	0.85		0.90	
Specificity	0.58		0.53	
PPV	0.54		0.50	
NPV	0.87		0.91	

Abbreviations: PS = proteomic signature; PF-ILD = progressive fibrosing ILD; PPV = positive predictive value; NPV = negative predictive value

Figure S4. Theoretical ILD clinical trial sample size based on estimated one-year change in FVC for overall cohort (a) and when restricted to those with a high-risk proteomic signature (b)

