Table E1

Fanconi Anemia	
Entrez ID	Symbol
6233	RPS27A
7311	UBA52
378708	CENPS
84126	ATRIP
84464	SLX4
199990	FAAP20
1325	CORT
64858	DCLRE1B
64789	EXO5
353497	POLN
2067	ERCC1
91442	FAAP24
2175	FANCA
2187	FANCB
2176	FANCC
2177	FANCD2
2178	FANCE
2188	FANCF
2189	FANCG
55215	FANCI
55120	FANCL
57697	FANCM
27033	ZBTB32
146956	EME1
22909	FAN1
80198	MUS81
64710	NUCKS1
10635	RAD51AP1
5892	RAD51D
165918	RNF168
9025	RNF8
6117	RPA1
6118	RPA2
6119	RPA3
5888	RAD51
9937	DCLRE1A
201254	CENPX
7314	UBB
7316	UBC
29089	UBE2T
7398	USP1
7507	XPA
2072	ERCC4
7517	XRCC3
80233	FAAP100
548593	SLX1A
675	BRCA2
83990	FANCJ
79728	PALB2
5889	RAD51C
672	BRCA1
5810	RAD1

Translesion Synthesis	
Entrez ID	Symbol
6233	RPS27A
7311	UBA52
199990	FAAP20
201973	PRIMPOL
5424	POLD1
5425	POLD2
10714	POLD3
57804	POLD4
5427	POLE2
5429	POLH
11201	POLI
51426	POLK
353497	POLN
5980	REV3L
51514	DTL
7706	TRIM25
9636	ISG15
10459	MAD2L2
55666	NPLOC4
5111	PCNA
25898	RCHY1
51455	REV1
5982	RFC2
5983	RFC3
5984	RFC4
5985	RFC5
5981	RFC1
6117	RPA1
6118	RPA2
6119	RPA3
7314	UBB
7316	UBC
9246	UBE2L6
7318	UBA7
7353	UFD1L
9100	USP10
124739	USP43
7415	VCP
22890	ZBTB1
9768	KIAA0101
7335	UBE2V1
7336	UBE2V2
27434	POLM
10721	POLQ
55339	WDR33
389898	UBE2NL

Homologous Recombination	
Entrez ID	Symbol
10213	PSMD14
472	ATM
641	BLM
84464	SLX4
672	BRCA1
675	BRCA2
119392	SFR1
126074	SWSAP1
55317	AP5S1
253714	MMS22L
375757	SWI5
8318	CDC45
8317	CDC7
135458	HUS1B
11144	DMC1
3980	LIG3
353497	POLN
10721	POLQ
51659	GINS2
7979	SHFM1
642636	RAD21L1
7334	UBE2N
55218	EXD2
2187	FANCB
84893	FBXO18
2237	FEN1
147872	CCDC155
348654	GEN1
548593	SLX1A
113510	HELQ
3364	HUS1
3014	H2AFX
54617	INO80
23514	SPIDR
9907	AP5Z1
84515	MCM8
254394	MCM9
286053	NSMCE2
4361	MRE11
10933	MORF4L1
4683	NBN
10111	RAD50
22909	FAN1
80198	MUS81
64859	OBCF2A
4796	TONSL
64710	NUCKS1
197370	NSMCE1
220064	ORAOV1
79728	PALB2
142	PARP1
10635	RAD51AP1
6421	SFPQ
5890	RAD51B
5889	RAD51C
5892	RAD51D
25788	RAD54B
8438	RAD54L
5932	RBBP8
5965	RECQL
51444	RNF138
6117	RPA1
6118	RPA2
6119	RPA3
5888	RAD51
5893	RAD52
9400	RECQL5
84296	GINS4
23137	SMC5
79677	SMC6
57599	WDR48
2072	ERCC4
7515	XRCC1
7516	XRCC2
7517	XRCC3
7528	YY1
23503	ZFYVE26
125150	ZSWIM7
146956	EME1
197342	EME2
2139	EYA2
5810	RAD1
5884	RAD17
23049	SMG1
63967	CLSPN
1017	CDK2
79035	NABP2
5536	PPP5C
8243	SMC1A
9126	SMC3
7156	TOP3A
151987	PPP4R2

Mismatch Repair	
Entrez ID	Symbol
3978	LIG1
5424	POLD1
5425	POLD2
10714	POLD3
57804	POLD4
2067	ERCC1
9156	EXO1
29072	SETD2
4292	MLH1
27030	MLH3
4436	MSH2
4437	MSH3
4438	MSH4
4439	MSH5
2956	MSH6
5395	PMS2
5378	PMS1
4595	MUTYH
5111	PCNA
5379	PMS2P1
5380	PMS2P2
5383	PMS2P5
10535	RNASEH2A
6117	RPA1
6118	RPA2
6119	RPA3
6996	TDG
11277	TREX1
25	ABL1
7161	TP73

Base Excision Repair	
Entrez ID	Symbol
328	APEX1
27301	APEX2
3978	LIG1
3980	LIG3
5423	POLB
5424	POLD1
5426	POLE
27343	POLL
10721	POLQ
1763	DNA2
2074	ERCC6
267004	PGBD3
2237	FEN1
3146	HMGB1
8091	HMGA2
3159	HMGA1
10075	HUWE1
8930	MBD4
4350	MPG
4595	MUTYH
79661	NEIL1
252969	NEIL2
55247	NEIL3
4913	NTHL1
4968	OGG1
142	PARP1
10038	PARP2
5111	PCNA
5428	POLG
55170	PRMT6
6117	RPA1
6118	RPA2
6119	RPA3
9401	RECQL4
8034	SLC25A16
23583	SMUG1
51548	SIRT6
6996	TDG
7374	UNG
10309	CCNO
55031	USP47
7486	WRN
7515	XRCC1
200558	APLF
4521	NUDT1
143	PARP4
25961	NUDT13

Non-Homologous End Joining	
Entrez ID	Symbol
10213	PSMD14
472	ATM
64421	DCLRE1C
79184	BRCC3
9577	BRE
580	BARD1
672	BRCA1
78996	C7orf49
286257	C9orf142
84142	FAM175A
79840	NHEJ1
64858	DCLRE1B
3978	LIG1
3980	LIG3
3981	LIG4
5422	POLA1
27343	POLL
27434	POLM
10721	POLQ
5591	PRKDC
7334	UBE2N
22992	KDM2A
8924	HERC2
8290	HIST3H3
29086	BABAM1
3014	H2AFX
8359	HIST1H4A
8366	HIST1H4B
8364	HIST1H4C
8360	HIST1H4D
8367	HIST1H4E
8361	HIST1H4F
8365	HIST1H4H
8294	HIST1H4I
8368	HIST1H4L
2547	XRCC6
7520	XRCC5
4292	MLH1
22976	PAXIP1
7336	UBE2V2
286053	NSMCE2
4361	MRE11
4683	NBN
10111	RAD50
9656	MDC1
27339	PRPF19
10524	KAT5
51588	PIAS4
51720	UIMC1
55183	RIF1
165918	RNF168
9025	RNF8
6419	SETMAR
23137	SMC5
9937	DCLRE1A
7341	SUMO1
7405	UVRAG
7468	WHSC1
7518	XRCC4
91419	ATP23
7158	TP53BP1
5965	RECQL
2072	ERCC4
7486	WRN
2139	EYA2
10432	RBM14
28990	ASTE1
4841	NONO
9232	PTTG1
5536	PPP5C
9126	SMC3

Chromatin Remodeling	
Entrez ID	Symbol
60	ACTB
86	ACTL6A
51412	ACTL6B
57180	ACTR3B
79913	ACTR5
64431	ACTR6
8289	ARID1A
196528	ARID2
29028	ATAD2
546	ATRX
22893	BAHD1
11176	BAZ2A
23476	BRD4
2186	BPTF
25855	BRMS1
10036	CHAF1A
8208	CHAF1B
1105	CHD1
9557	CHD1L
1106	CHD2
1107	CHD3
1108	CHD4
26038	CHD5
84181	CHD6
55636	CHD7
57680	CHD8
80205	CHD9
1487	CTBP1
10664	CTCF
140690	CTCFL
30827	CXXC1
7913	DEK
55929	DMAP1
8193	DPF1
5977	DPF2
8110	DPF3
57634	EP400
2074	ERCC6
1647	GADD45A
4616	GADD45B
10912	GADD45G
3054	HCFC1
3070	HELLS
6596	HLTF
10362	HMG20B
54556	ING3
54617	INO80
83444	INO80B
125476	INO80C
54891	INO80D
283899	INO80E
10524	KAT5
222229	LRWD1
114785	MBD6
9112	MTA1
57504	MTA3
10514	MYBBP1A
4641	MYO1C
4678	NASP
8467	SMARCA5
56916	SMARCAD1
50485	SMARCAL1
6599	SMARCC1
6601	SMARCC2
6602	SMARCD1
6603	SMARCD2
6604	SMARCD3
6605	SMARCE1
10847	SRCAP
29844	TFPT
7153	TOP2A
7155	TOP2B
7161	TP73
6944	VPS72
7528	YY1
11244	ZHX1
10467	ZNHIT1
84083	ZRANB3
8607	RUVBL1
10856	RUVBL2
26122	EPC2
23054	NCOA6
29128	UHRF1
25961	NUDT13
6594	SMARCA1

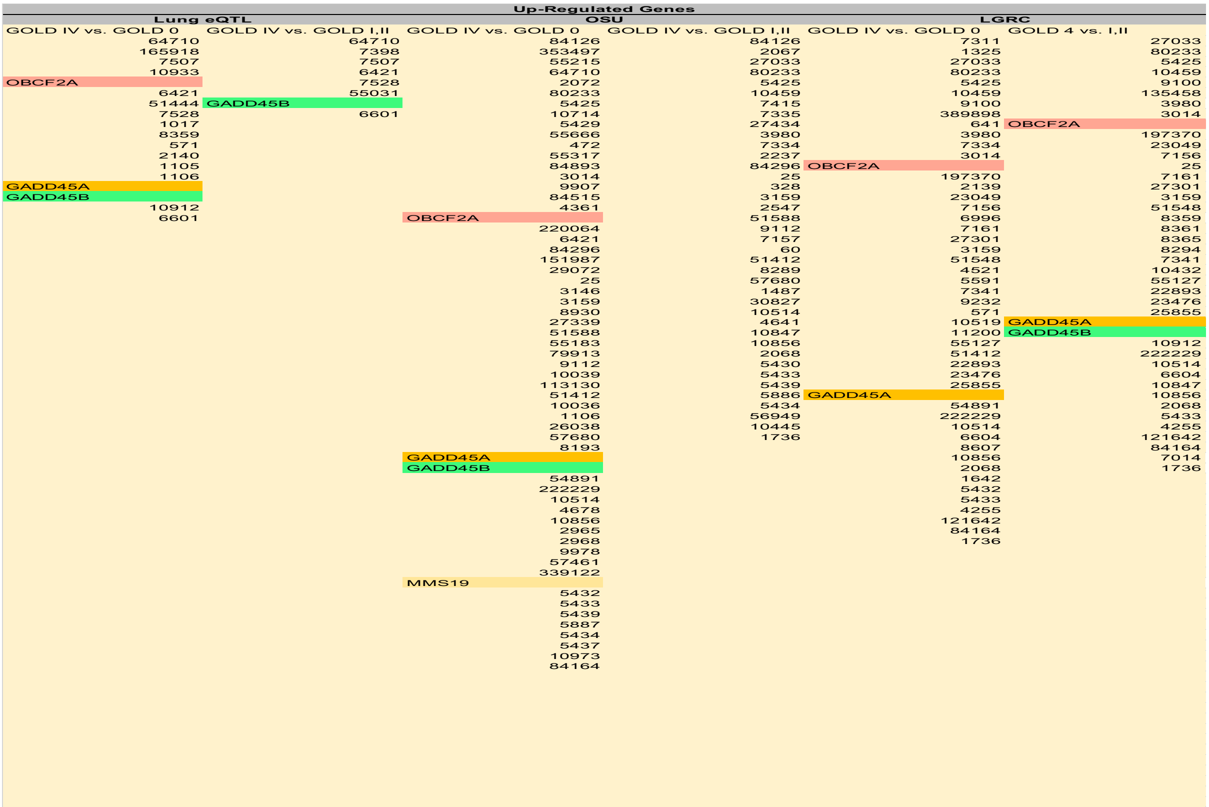
Nucleotide Excision Repair	
Entrez ID	Symbol
6233	RPS27A
7311	UBA52
9716	AQR
54778	RNF111
54841	BIVM
84464	SLX4
675	BRCA2
902	CCNH
1022	CDK7
4331	MNAT1
91603	ZNF830
9557	CHD1L
2873	GPS1
1069	CETN2
135458	HUS1B
2068	ERCC2
2071	ERCC3
2965	GTF2H1
2967	GTF2H3
2968	GTF2H4
404672	GTF2H5
9978	RBX1
8451	CUL4A
8450	CUL4B
1642	DDB1
10450	PPIE
64858	DCLRE1B
1643	DDB2
3978	LIG1
3980	LIG3
3981	LIG4
5423	POLB
5424	POLD1
5425	POLD2
10714	POLD3
57804	POLD4
5426	POLE
51426	POLK
27343	POLL
7329	UBE2I
7334	UBE2N
2067	ERCC1
2074	ERCC6
267004	PGBD3
1161	ERCC8
2176	FANCC
3150	HMGN1
10463	SLC30A9
3364	HUS1
57461	ISY1
339122	RAB43
57654	UVSSA
4287	ATXN3
64210	MMS19
7336	UBE2V2
22909	FAN1
79661	NEIL1
252969	NEIL2
55247	NEIL3
27339	PRPF19
4913	NTHL1
4968	OGG1
220064	ORAOV1
142	PARP1
5111	PCNA
5430	POLR2A
5431	POLR2B
5432	POLR2C
5433	POLR2D
5436	POLR2G
5438	POLR2I
5439	POLR2J
5886	RAD23A
5887	RAD23B
5892	RAD51D
5932	RBBP8
5982	RFC2
5983	RFC3
5984	RFC4
5985	RFC5
5981	RFC1
5434	POLR2E
5435	POLR2F
5437	POLR2H
5440	POLR2K
5441	POLR2L
6117	RPA1
6118	RPA2
6119	RPA3
29935	RPA4
9937	DCLRE1A
7341	SUMO1
6613	SUMO2
6612	SUMO3
23411	SIRT1
6917	TCEA1
7314	UBB
7316	UBC
85015	USP45
7874	USP7
56949	XAB2
7507	XPA
7508	XPC
2072	ERCC4
2073	ERCC5
7515	XRCC1
2033	EP300
7157	TP53
5037	HCNP
93973	ACTR8
8607	RUVBL1
25842	ASF1A
10445	MCRS1
4798	NFRKB

Direct Repair	
Entrez ID	Symbol
4255	MGMT
121642	ALKBH2
221120	ALKBH3
54784	ALKBH5
10973	ASCC3
51008	ASCC1
79068	FTO
84164	ASCC2

Telomere Repair	
Entrez ID	Symbol
80119	PIF1
23049	SMG1
23293	SMG6
79991	OBFC1
54386	TERF2IP
5976	UPF1
7013	TERF1
7014	TERF2
5884	RAD17
1017	CDK2
10728	PTGES3
1736	DKC1
5558	PRIM2
5557	PRIM1
23649	POLA2
80351	TNKS2

Table E1 List of DNA repair pathways genes. *Definition of abbreviations*: BER - Base excision repair, CR - Chromatin remodeling, DR - Direct repair, FA - Fanconi anemia, HR - Homologous recombination, MMR - Mismatch repair, NER - Nucleotide excision repair, NHEJ - Non-homologous end joining, TR - telomere repair, TLS - Translesion synthesis pathway.

Table E2 Upregulated Genes in Severe COPD



Up-Regulated Genes					
Lung eQTL		OSU		LGRC	
GOLD IV vs. GOLD 0	GOLD IV vs. GOLD I,II	GOLD IV vs. GOLD 0	GOLD IV vs. GOLD I,II	GOLD IV vs. GOLD 0	GOLD 4 vs. I,II
64710	64710	84126	84126	7311	27033
165918	7398	353497	2067	1325	80233
7507	7507	55215	27033	27033	5425
10933	6421	64710	80233	80233	10459
OBCF2A	7528	2072	5425	5425	9100
6421	55031	80233	10459	10459	135458
51444	GADD45B	5425	7415	9100	3980
7528	6601	10714	7335	389898	3014
1017		5429	27434	641	OBCF2A
8359		55666	3980	3980	197370
571		472	7334	7334	23049
2140		55317	2237	3014	7156
1105		84893	84296	OBCF2A	25
1106		3014	25	197370	7161
GADD45A		9907	328	2139	27301
GADD45B		84515	3159	23049	3159
10912		4361	2547	7156	51548
6601		OBCF2A	51588	6996	8359
		220064	9112	7161	8361
		6421	7157	27301	8365
		84296	60	3159	8294
		151987	51412	51548	7341
		29072	8289	4521	10432
		25	57680	5591	55127
		3146	1487	7341	22893
		3159	30827	9232	23476
		8930	10514	571	25855
		27339	4641	10519	GADD45A
		51588	10847	11200	GADD45B
		55183	10856	55127	10912
		79913	2068	51412	222229
		9112	5430	22893	10514
		10039	5433	23476	6604
		113130	5439	25855	10847
		51412	5886	GADD45A	10856
		10036	5434	54891	2068
		1106	56949	222229	5433
		26038	10445	10514	4255
		57680	1736	6604	121642
		8193		8607	84164
		GADD45A		10856	7014
		GADD45B		2068	1736
		54891		1642	
		222229		5432	
		10514		5433	
		4678		4255	
		10856		121642	
		2965		84164	
		2968		1736	
		9978			
		57461			
		339122			
		MMS19			
		5432			
		5433			
		5439			
		5887			
		5434			
		5437			
		10973			
		84164			

Table E2 Differentially expressed genes. Entrez IDs for differentially expressed genes in GOLD IV vs. GOLD 0 and GOLD IV vs. GOLD I, II in the Lung eQTL, LGRC, and OSU cohorts. For the 15 genes that were identified as differentially expressed across three cohorts, Entrez IDs have been replaced with gene symbols and color coded for easy identification.

Table E2 (cont) Downregulated Genes in Severe COPD

Down-Regulated Genes					
Lung eQTL		OSU		LGRC	
GOLD IV vs. GOLD 0	GOLD IV vs. GOLD I,II	GOLD IV vs. GOLD 0	GOLD IV vs. GOLD I,II	GOLD IV vs. GOLD 0	GOLD IV vs. GOLD I,II
64858	64858	6233	2175	64858	FANCC
64789	64789	7311	FANCL	FANCC	FANCL
FANCC	5888	1325	64710	FANCL	57697
2188	79728	64789	9025	57697	22909
FANCL	51514	2175	9937	22909	10635
10635	7706	FANCC	POLI	9937	9937
9025	22890	2188	51426	7314	7398
5888	8318	FANCL	51455	7507	7507
79728	3364	57697	5984	5889	5889
5810	220064	22909	RFC1	672	672
POLI	4439	64710	253714	201973	201973
51514	55247	5892	113510	5427	5427
7706	8034	9025	84515	POLI	POLI
51455	NUDT1	6117	4361	51514	51426
RFC1	64421	9937	10111	5985	5980
22890	22992	201254	25788	RFC1	51514
55339	WHSC1	7316	79677	7318	9636
10213	2140	7398	23503	124739	5111
55218	51567	7507	4436	11144	51455
348654	9557	548593	5423	55218	5984
254394	114785	79728	267004	348654	5985
220064	29844	5889	3146	23514	RFC1
125150	7153	672	NUDT1	254394	7318
197342	10450	5424	64421	10111	22890
5884	DDB2	10714	84142	220064	119392
5378	7329	57804	XRCC4	25788	11144
NEIL1	MMS19	POLI	91419	5893	7979
8034	93973	5980	28990	79677	348654
143		7706	9665	23503	113510
NUDT1		51455	23064	9126	23514
64421		5983	8467	29072	84515
BRCC3		5984	29028	4436	254394
3981		5985	546	5378	286053
22992		RFC1	1106	7508	10111
WHSC1		124739	84181	NEIL1	25788
XRCC4		7415	55636	55247	5965
2140		7336	80205	4913	23137
9112		55339	6596	4968	79677
51567		253714	114785	10038	23503
1106		11144	7155	55031	5884
114785		55218	23054	NUDT1	9126
7153		254394	54841	BRCC3	9156
6944		4361	404672	5422	29072
54778		10933	DDB2	8364	4436
91603		10111	10463	WHSC1	5378
10450		220064	4287	28990	7508
DDB2		25788	MMS19	83666	8930
57654		5893	29935	9665	NEIL1
MMS19		79677	6612	5883	4968
85015		57599	OBFC1	11176	10038
93973		7515	5558	84181	55031
OBFC1		7528		10664	143
		23503		6596	NUDT1
		2139		4641	BRCC3
		1017		6601	84142
		8243		6605	3981
		9126		26122	5422
		9156		23054	WHSC1
		4436		54841	XRCC4
		2956		2071	91419
		5378		MMS19	83666
		4595		2073	1653
		5383		5037	157570
		10535		25842	9665
		11277		OBFC1	5885
		1763		5557	23064
		3146			8467
		10075			56916
		NEIL1			64431
		4913			196528
		4968			11176
		10038			84181
		55170			7913
		8034			6596
		23583			54556
		7374			6605
		55031			7155
		7486			11244
		NUDT1			26122
		64421			6594
		BRCC3			54841
		580			1022
		286257			404672
		84142			DDB2
		5422			3150
		5591			10463
		8924			MMS19
		8366			2073
		8364			25842
		8360			7013
		8368			5557
		2547			
		22976			
		9656			
		6419			
		7405			
		WHSC1			
		XRCC4			
		91419			
		7158			
		28990			
		4841			
		83666			
		1653			
		9665			
		9112			
		5885			
		23064			
		56916			
		6647			
		5883			
		60			
		86			
		64431			
		196528			
		29028			
		546			
		22893			
		2186			
		8208			
		9557			
		1108			
		84181			
		80205			
		1487			
		10664			
		55929			
		8110			
		57634			
		6596			
		10362			
		54556			
		114785			
		4641			
		6601			
		6604			
		6605			
		7155			
		11244			
		84083			
		23054			
		6594			
		9716			
		54778			
		54841			
		1022			
		2068			
		404672			
		8451			
		DDB2			
		1161			
		3150			
		10463			
		MMS19			
		5430			
		5436			
		5887			
		5435			
		5440			
		29935			
		6613			
		6917			
		2073			
		25842			
		221120			
		10973			
		79068			
		80119			
		OBFC1			
		54386			
		10728			
		5558			
		5557			
		23649			

Table E3

	GOLD 0	GOLD I, II	GOLD IV
n	20	14	23
Age (years)	62.7±9.8	70.0±10.3	54.2±6.9
Male Gender	11 (55)	10 (71.4)	16 (69.2)
Pack-years	30±23 [4]	50±23	54±7
Smoking Status (n)	[2]	[2]	
Current	1	2	0
Former	15	10	22
Never	2	0	1
Coexisting Malignancy	19 (95)	13 (93)	0 (0)

Table E3 Demographic characteristics of lung tissue samples used for RNAseq. Data are expressed as n (%) or mean ± standard deviation unless otherwise stated [] represents missing samples.

Table E4

	Cluster 1	Cluster 2	Cluster 3	p-value
n	65	32	72	
Age (years)	66.2 ±10.1	65.2± 8.3	64.9±9.8	0.72
Male Gender	38 (58.4)	18 (56.3)	39 (54.2)	0.88
Pack-years	60±35	50±31	54±38	0.28
Smoking Status (n)				0.98
Current	5	2	4	
Former	58	29	65	
Never	2	1	3	
Coexisting Malignancy	48 (73.8)	14 (43.8)	35 (48.6)	0.003

Table E4 Demographic characteristics of patient clusters. Data are expressed as n (%) or mean ± standard deviation unless otherwise stated.

Table E5

	PATHWAYS	**FDR**
Cluster 3 vs. Control	Immune response_IL-5 signaling via JAK/STAT	2.58416E-14
	Development_PEDF signaling	1.74796E-08
	Renal tubulointerstitial injury in Lupus Nephritis	1.74796E-08
	Immune response_IL-17 signaling pathways	1.74796E-08
	Immune response_IL-3 signaling via JAK/STAT, p38, JNK and NF-kB	1.74796E-08
	Signal transduction_NF-kB activation pathways	1.74796E-08
	Immune response_IL-10 signaling pathway	2.43031E-08
	Immune response_HSP60 and HSP70/ TLR signaling pathway	4.70008E-08
	Th17 cells in CF	2.98976E-07
	Apoptosis and survival_Anti-apoptotic TNFs/NF-kB/Bcl-2 pathway	8.5043E-07
	Neurogenesis_NGF/ TrkA MAPK-mediated signaling	9.74958E-07
	Cell adhesion_ECM remodeling	1.04107E-06
	Immune response_TLR2 and TLR4 signaling pathways	4.58091E-06
	Development_Regulation of epithelial-to-mesenchymal transition (EMT)	4.91049E-06
	Myeloid-derived suppressor cells and M2 macrophages in cancer	4.91049E-06
	Immune response_HMGB1/RAGE signaling pathway	4.91049E-06
	T follicular helper cell dysfunction in SLE	6.89479E-06
	Apoptosis and survival_APRIL and BAFF signaling	7.88042E-06
	Transcription_Role of VDR in regulation of genes involved in osteoporosis	8.35924E-06
	Rheumatoid arthritis (general schema)	8.35924E-06
	PDE4 regulation of cyto/chemokine expression in inflammatory skin diseases	8.35924E-06
	Immune response_Oncostatin M signaling via JAK-Stat	1.19474E-05
	Role of B cells in SLE	1.60612E-05
	Immune response_Oncostatin M signaling via MAPK	1.93912E-05
	Immune response_IL-6 signaling pathway via JAK/STAT	2.52669E-05
	Glomerular injury in Lupus Nephritis	2.86506E-05
	Development_ERBB-family signaling	3.64516E-05
	Immune response_OX40L/ OX40 signaling pathway	4.92197E-05
	Immune response_B cell antigen receptor (BCR) pathway	5.87773E-05
	Immune response_Role of HMGB1 in dendritic cell maturation and migration	7.06489E-05
	Dysregulation of germinal center response in SLE	7.61744E-05
	Apoptosis and survival_Lymphotoxin-beta receptor signaling	8.41162E-05
	Expression targets of Tissue factor signaling in cancer	8.41162E-05
	Stimulation of TGF-beta signaling in lung cancer	9.00069E-05
	Immune response_IL-18 signaling	9.01493E-05
	Signal transduction_PTMs in BAFF-induced non-canonical NF-kB signaling	9.40188E-05
	Th17 cells in CF (mouse model)	0.000102011
	PDE4 regulation of cyto/chemokine expression in arthritis	0.000102011
	Immune response_Bacterial infections in normal airways	0.000102011
	Role and regulation of Prostaglandin E2 in gastric cancer	0.000102011
	Immune response_MIF-mediated glucocorticoid regulation	0.000111028
	Immune response_TNF-R2 signaling pathways	0.000159031
	Immune response_PGE2 signaling in immune response	0.000159031
	Colorectal cancer (general schema)	0.000250931
	Cell adhesion_Chemokines and adhesion	0.000267804
	Immune response_IL-6-induced acute-phase response in hepatocytes	0.000300058
	Immune response_ICOS signaling pathway in T-helper cell	0.000301549
	PGE2 pathways in cancer	0.000402922
	Apoptosis and survival_Anti-apoptotic TNFs/NF-kB/IAP pathway	0.00050595
	Immune response_Role of PKR in stress-induced antiviral cell response	0.000614013

Table E5 cont.

	PATHWAYS	**FDR**
Cluster 2 vs. Control	Cytoskeleton remodeling_TGF, WNT and cytoskeletal remodeling	1.85677E-06
	Cytoskeleton remodeling_Cytoskeleton remodeling	2.62659E-05
	Cell adhesion_Integrin inside-out signaling in T cells	6.659E-05
	Immune response_CCL2 signaling	6.659E-05
	Cell adhesion_Histamine H1 receptor signaling in the interruption of cell barrier integrity	6.91542E-05
	Immune response_Classical complement pathway	0.000141904
	Immune response_Alternative complement pathway	0.000141904
	Cell adhesion_Plasmin signaling	0.000206069
	FGF signaling in pancreatic cancer	0.000303336
	Development_MAG-dependent inhibition of neurite outgrowth	0.000360669
	Immune response_C3a signaling	0.000466874
	Cell adhesion_Chemokines and adhesion	0.000466874
	Renal tubulointerstitial injury in Lupus Nephritis	0.000476109
	Signal transduction_IP3 signaling	0.000476109
	Immune response _CCR3 signaling in eosinophils	0.000476109
	Colorectal cancer (general schema)	0.000549706
	Immune response_Lectin induced complement pathway	0.000549706
	Alternative complement cascade disruption in age-related macular degeneration	0.000747639
	Development_Regulation of cytoskeleton proteins in oligodendrocyte differentiation and myelination	0.000968822
	Cytoskeleton remodeling_Regulation of actin cytoskeleton by Rho GTPases	0.001015361
	Cell adhesion_ECM remodeling	0.001015361
	Dysregulation of germinal center response in SLE	0.001085358
	Muscle contraction_GPCRs in the regulation of smooth muscle tone	0.001085358
	Complement pathway disruption in thrombotic microangiopathy	0.001605382
	Cytoskeleton remodeling_Substance P mediated membrane blebbing	0.001637494
	Airway smooth muscle contraction in asthma	0.001652474
	Impaired inhibitory action of lipoxins on neutrophil migration in CF	0.001652474
	B cell signaling in hematological malignancies	0.001652474
	Immune response_T cell subsets: secreted signals	0.001726088
	Development_Regulation of epithelial-to-mesenchymal transition (EMT)	0.002397985
	Cell adhesion_Endothelial cell contacts by junctional mechanisms	0.002397985
	Apoptosis and survival_NGF/ TrkA PI3K-mediated signaling	0.002637393
	Chemotaxis_Inhibitory action of lipoxins on IL-8- and Leukotriene B4-induced neutrophil migration	0.002637393
	Muscle contraction_Regulation of eNOS activity in endothelial cells	0.002642032
	Immune response_B cell antigen receptor (BCR) pathway	0.002642032
	Cell adhesion_Tight junctions	0.002649148
	G-protein signaling_H-RAS regulation pathway	0.002649148
	Muscle contraction_Relaxin signaling pathway	0.002649148
	Neurophysiological process_ACM regulation of nerve impulse	0.002649148
	Cell cycle_Role of Nek in cell cycle regulation	0.00271413
	Cell adhesion_Gap junctions	0.007040667
	Resolution of inflammation in healing myocardial infarction	0.007040667
	Development_Regulation of lung epithelial progenitor cell differentiation	0.007040667
	Oxidative stress_Activation of NADPH oxidase	0.007231906
	ENaC regulation in normal and CF airways	0.007231906
	Glomerular injury in Lupus Nephritis	0.007746357
	Cytoskeleton remodeling_Reverse signaling by Ephrin-B	0.008199773
	Chemotaxis_CCR1 signaling	0.008199773
	Stimulation of TGF-beta signaling in lung cancer	0.008199773
	Development_Role of G-CSF in hematopoietic stem cell mobilization	0.008331283

Table E5 cont.

	PATHWAYS	**FDR**
Cluster 1 vs. Control	Immune response_IL-5 signaling via JAK/STAT	2.46432E-08
	Neurogenesis_NGF/ TrkA MAPK-mediated signaling	1.80016E-05
	Immune response_IL-6 signaling pathway via JAK/STAT	2.26837E-05
	Immune response_IL-3 signaling via JAK/STAT, p38, JNK and NF-kB	2.26837E-05
	Immune response_IL-18 signaling	3.16719E-05
	Development_Transcription regulation of granulocyte development	3.93554E-05
	Immune response_IL-1 signaling pathway	8.65083E-05
	Reproduction_Gonadotropin-releasing hormone (GnRH) signaling	9.73401E-05
	Immune response_IL-17 signaling pathways	0.000206079
	K-RAS signaling in pancreatic cancer	0.000230174
	Immune response_CD40 signaling	0.000311612
	Immune response_TLR2 and TLR4 signaling pathways	0.000427075
	Development_GM-CSF signaling	0.000427075
	Immune response_HSP60 and HSP70/ TLR signaling pathway	0.00066774
	Immune response_Oncostatin M signaling via MAPK	0.000681542
	Immune response_MIF-mediated glucocorticoid regulation	0.000733887
	Immune response_TLR5, TLR7, TLR8 and TLR9 signaling pathways	0.000777029
	Development_ERBB-family signaling	0.000777029
	Immune response_IL-33 signaling pathway	0.000793299
	Immune response_IL-10 signaling pathway	0.00117069
	Immune response_Substance P-stimulated expression of proinflammatory cytokines via MAPKs	0.00118276
	Renal tubulointerstitial injury in Lupus Nephritis	0.001449424
	Glomerular injury in Lupus Nephritis	0.001933506
	Stimulation of TGF-beta signaling in lung cancer	0.001954887
	Development_PEDF signaling	0.00211156
	Development_EGFR signaling pathway	0.002168513
	Immune response_CCL2 signaling	0.003388931
	Immune response_Platelet activating factor/ PTAFR pathway signaling	0.003496915
	PGE2 pathways in cancer	0.003496915
	Immune response_IL-9 signaling pathway	0.003617684
	Development_YAP/TAZ-mediated co-regulation of transcription	0.003617684
	Transcription_Role of AP-1 in regulation of cellular metabolism	0.00454154
	IGF family signaling in colorectal cancer	0.004981025
	Immune response_Oncostatin M signaling via JAK-Stat	0.005028124
	Myeloid-derived suppressor cells and M2 macrophages in cancer	0.006685753
	Immune response_IL-27 signaling pathway	0.006698825
	T follicular helper cell dysfunction in SLE	0.006698825
	Muscle contraction_Regulation of eNOS activity in endothelial cells	0.006698825
	Development_Leptin signaling via JAK/STAT and MAPK cascades	0.007129372
	Transcription_Transcription regulation of aminoacid metabolism	0.007129372
	Development_Cross-talk between VEGF and Angiopoietin 1 signaling pathways	0.008122061
	Immune response_MIF-induced cell adhesion, migration and angiogenesis	0.008557024
	Development_TGF-beta-dependent induction of EMT via MAPK	0.009237917
	Immune response_Histamine H1 receptor signaling in immune response	0.009953739
	Immune response_CD137 signaling in immune cell	0.011248497
	Development_TGF-beta receptor signaling	0.011248497
	Immune response_C5a signaling	0.011248497
	Development_G-CSF-induced myeloid differentiation	0.011964976
	Immune response_IL-5 signaling via PI3K, MAPK and NF-kB	0.011964976
	Signal transduction_Additional pathways of NF-kB activation (in the cytoplasm)	0.012653182

Table E5 Global gene expression pathways. Analysis of global gene expression pathways associated with Clusters 1, 2, and 3 compared to control patients. The top 50 enriched pathways are listed for each comparison.

Table E6

(A)

	BER		CR		DR		FA		HR		MMR		NER		NHEJ		TR		TLS	
	FDR	NES	FDR	NES	FDR	NES	FDR	NES	FDR	NES	FDR	NES	FDR	NES	FDR	NES	FDR	NES	FDR	NES
FEV1 Percent Predicted	0.14	1.28	0.31	1.09	0.18	-1.2	0.076	1.51	0.13	1.37	0.15	1.26	0.003	1.95	0.12	1.33	0.14	1.33	0.005	1.84
DLCO Percent Predicted	0.57	0.25	0.15	1.31	0.02	-1.61	0.042	1.62	0.18	1.26	0.2	1.22	0.048	1.57	0.55	0.23	0.15	-1.4	0.02	1.73
BODE	0.28	-1.11	0.23	-1.17	0.11	1.27	0.08	-1.43	0.06	-1.5	0.08	-1.4	0.006	-1.86	0.08	-1.38	0.045	-1.56	0.011	-1.88
SF-12 Score	0.37	1.13	0.64	0.65	0.38	-1.04	0.021	1.66	0.1	1.41	0.23	1.25	0.021	1.66	0.48	1.01	0.35	1.11	0.0045	1.92
SGRQ Score	0.67	-0.88	0.21	-1.23	0.22	1.16	0.058	-1.61	0.23	-1.24	0.5	-1	0.058	-1.61	0.39	-1.08	0.15	-1.34	0.092	-1.64
6MWD (meters)	0.16	1.26	0.25	1.13	0.17	-1.21	0.08	1.58	0.04	1.36	0.25	1.15	0.06	1.56	0.14	1.33	0.14	1.29	0.03	1.78
Percent Emphysema	0.13	-1.33	0.38	-1.04	0.04	1.44	0.017	-1.77	0.12	-1.34	0.36	-1.08	0.03	-1.67	0.13	-1.36	0.12	-1.39	0.019	-1.85

Correlation with Features of Decreased COPD severity (FDR)

<0.01

≥0.01 &<0.05

≥0.05 &<0.1

Not Significant

≥0.05 &<0.1

≥0.01 &<0.05

Correlation with Features of Increased COPD severity (FDR)

(B)

	BER		CR		DR		FA		HR		MMR		NER		NHEJ		TR		TLS	
	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ
FEV1 Percent Predicted	0.402	0.14	0.888	0.02	0.151	-0.13	0.020	0.20	0.056	0.17	0.044	0.18	<0.001	0.37	0.015	0.21	0.578	0.06	<0.001	0.33
DLCO Percent Predicted	0.523	0.08	0.543	0.12	0.017	-0.23	0.020	0.22	0.079	0.15	0.036	0.20	<0.001	0.38	0.135	0.13	0.204	0.13	<0.001	0.42
BODE	0.484	-0.11	0.888	-0.04	0.152	0.12	0.020	-0.20	0.052	-0.21	0.036	-0.20	<0.001	-0.38	0.015	-0.23	0.117	-0.16	<0.001	-0.37
SF-12 Score	0.580	0.06	0.888	-0.04	0.221	-0.10	0.013	0.23	0.052	0.18	0.053	0.17	<0.001	0.32	0.104	0.13	0.094	0.18	<0.001	0.32
SGRQ Score	0.826	0.02	0.888	0.01	0.006	0.26	0.020	-0.19	0.056	-0.16	0.122	-0.12	<0.001	-0.32	0.046	-0.17	0.094	-0.19	<0.001	-0.31
6MWD(meters)	0.523	0.08	0.888	-0.02	0.120	-0.16	0.020	0.20	0.056	0.17	0.111	0.14	0.002	0.25	0.015	0.22	0.117	0.16	0.001	0.28
Percent Emphysema	0.343	-0.16	0.543	-0.09	0.017	0.21	0.002	-0.28	0.052	-0.18	0.036	-0.20	<0.001	-0.37	0.015	-0.21	0.312	-0.10	<0.001	-0.37

Correlation with Features of Decreased COPD severity (*ρ*)

≥0.30

≥0.20 & <0.30

<0.20

Not Significant

<0.20

≥0.20 & <0.30

Correlation with Features of Increased COPD severity (*ρ*)

Table E6 Enrichment analysis. DNA repair pathways associated with markers of COPD severity based on **A)** GSEA (Normalized Enrichment Score (NES) and FDR) and **B)** Z-score (Correlation Coefficient (***ρ***) and p-value). *Definition of abbreviations*: FEV_1 – Forced expiratory volume in one second, DLCO - diffusing capacity of the lungs for carbon monoxide, SGRQ - St. George's Respiratory Questionnaire, BODE - body mass index, airflow obstruction, dyspnea, and exercise capacity , and SF-12 - Short Form Healthy Survey-12, BER - Base excision repair, CR - Chromatin remodeling, DR - Direct repair, FA - Fanconi anemia, HR - Homologous recombination, MMR - Mismatch repair, NER - Nucleotide excision repair, NHEJ - Non-homologous end joining, TR - telomere repair, TLS - Translesion synthesis pathway. 6-minute walk distance – (6MWD)

Table E7

Yellow	**FDR**
DNA damage_BER-NER repair	7.42E-03
Transcription_Chromatin modification	1.64E-02
DNA damage_DBS repair	1.88E-02
Salmon	
Development_Regulation of angiogenesis	1.68E-03
Transcription_Chromatin modification	8.39E-02
Light Yellow	
Cell adhesion_Amyloid proteins	5.31E-04
Cell adhesion_Cadherins	9.48E-03
Development_Neurogenesis_Synaptogenesis	3.72E-02
Cell adhesion_Cell junctions	3.87E-02
Signal transduction_WNT signaling	
Green	
Translation_Translation initiation	1.92E-02
Sky Blue	
Cell adhesion_Integrin-mediated cell-matrix adhesion	5.79E-02
Turqoise	
Inflammation_IL-6 signaling	8.32E-05
Cytoskeleton_Intermediate filaments	1.73E-04
Inflammation_Amphoterin signaling	2.35E-04
Apoptosis_Apoptotic nucleus	2.35E-04
Inflammation_Protein C signaling	4.86E-04
Cell cycle_G1-S Interleukin regulation	6.16E-04
Inflammation_Histamine signaling	6.16E-04
Development_Ossification and bone remodeling	6.16E-04
Apoptosis_Death Domain receptors & caspases in apoptosis	6.68E-04
Immune response_TCR signaling	1.13E-03
Immune response_Th17-derived cytokines	1.93E-03
Cell adhesion_Platelet-endothelium-leucocyte interactions	2.37E-03
Inflammation_IgE signaling	2.37E-03
Inflammation_Neutrophil activation	2.37E-03
Inflammation_MIF signaling	2.87E-03
Inflammation_IL-2 signaling	2.87E-03
Inflammation_IL-10 anti-inflammatory response	2.87E-03
Cardiac development_Role of NADPH oxidase and ROS	3.43E-03
Inflammation_TREM1 signaling	3.79E-03
Inflammation_Inflammasome	4.10E-03
Immune response_Innate immune response to RNA viral infection	4.93E-03
Reproduction_Feeding and Neurohormone signaling	5.13E-03
Inflammation_Innate inflammatory response	5.14E-03
Cell cycle_G1-S Growth factor regulation	7.22E-03
Immune response_BCR pathway	8.43E-03
Chemotaxis	9.71E-03
Apoptosis_Apoptotic mitochondria	1.46E-02
Apoptosis_Anti-Apoptosis mediated by external signals via PI3K/AKT	1.95E-02
Cell cycle_G1-S	2.63E-02
Inflammation_NK cell cytotoxicity	2.73E-02
Inflammation_IL-4 signaling	3.22E-02
Inflammation_IL-12,15,18 signaling	3.66E-02

Table E7 Pathway enrichment for weighted gene co-expression network modules (WGCNA). The enriched processes associated with the WGCNA modules most closely associated with clinical indices of COPD severity (FDR <0.05).

Table E8

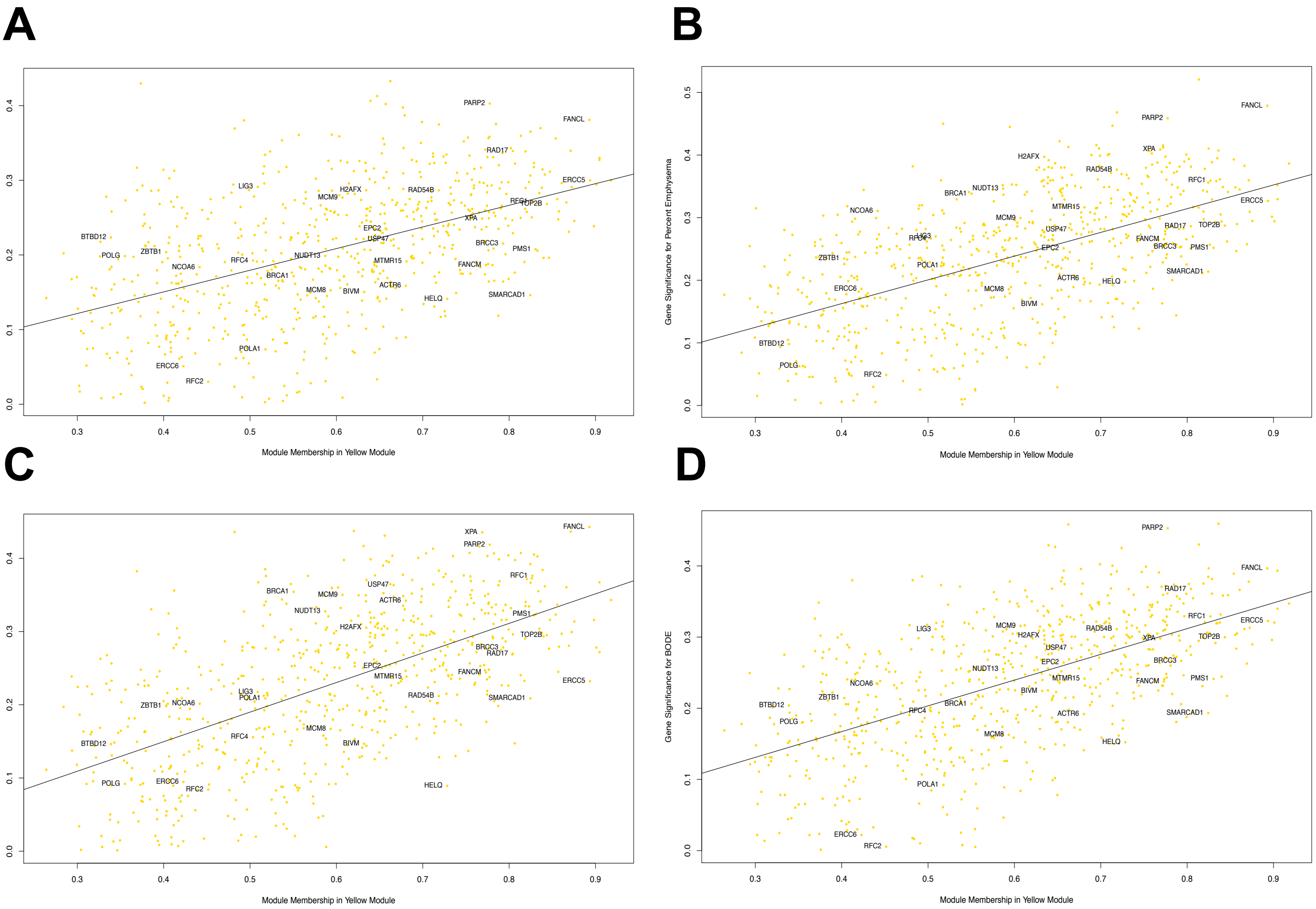


Figure E8 Gene significance (GS) versus module membership (MM) for the Yellow module. Weighted gene co-expression network analysis (WGCNA) derived MM were plotted against GS for the following traits: **A)** FEV$_1$ percent predicted **B)** percent emphysema **C)** DLCO percent predicted, and **D)** BODE index. All DDRT genes **(Supplemental Table 1)** within the module are identified.