**Supplemental Figures S1-S12**

# De novo individualized disease modules reveal the synthetic penetrance of genes and inform personalized treatment regimens

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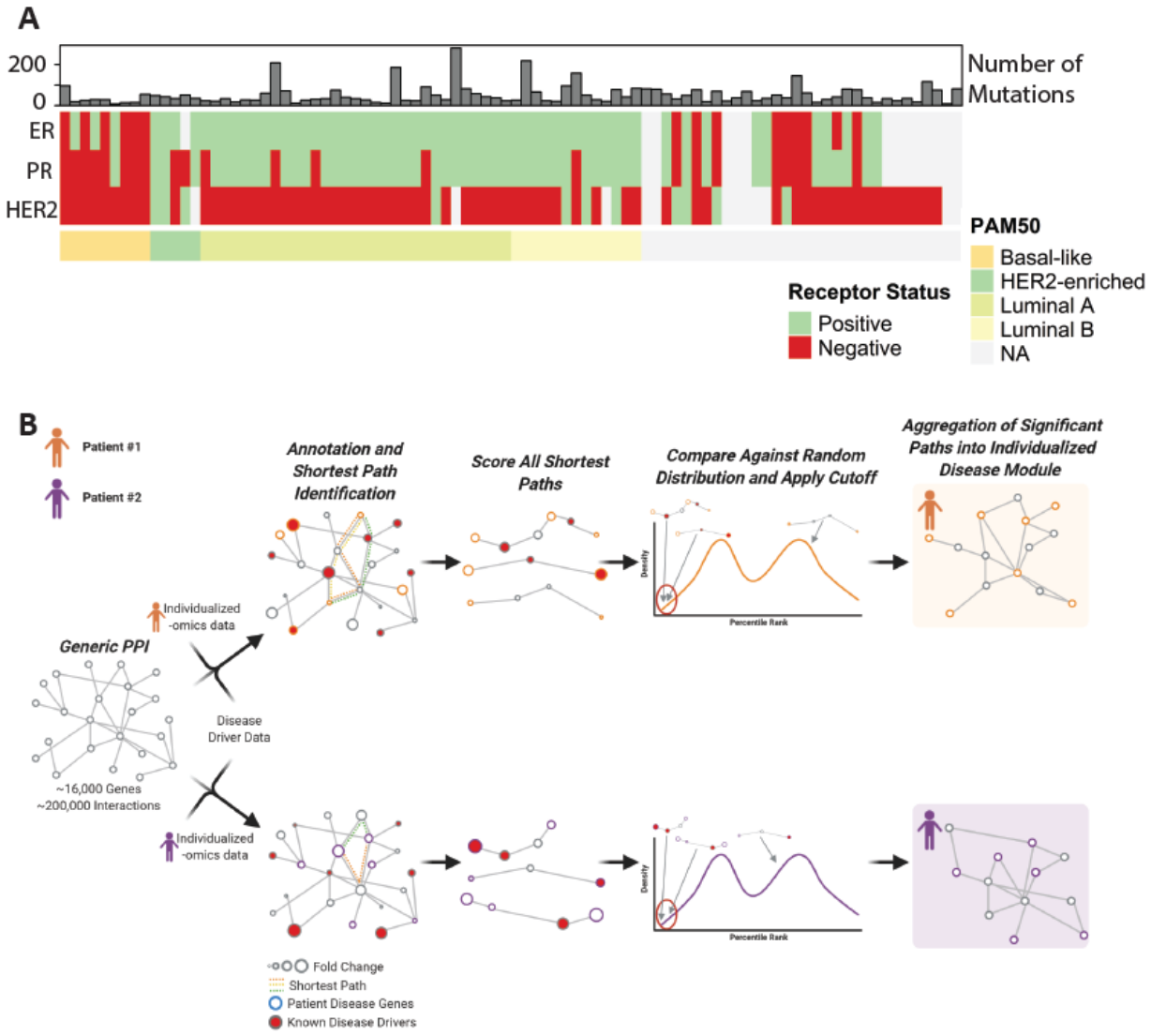
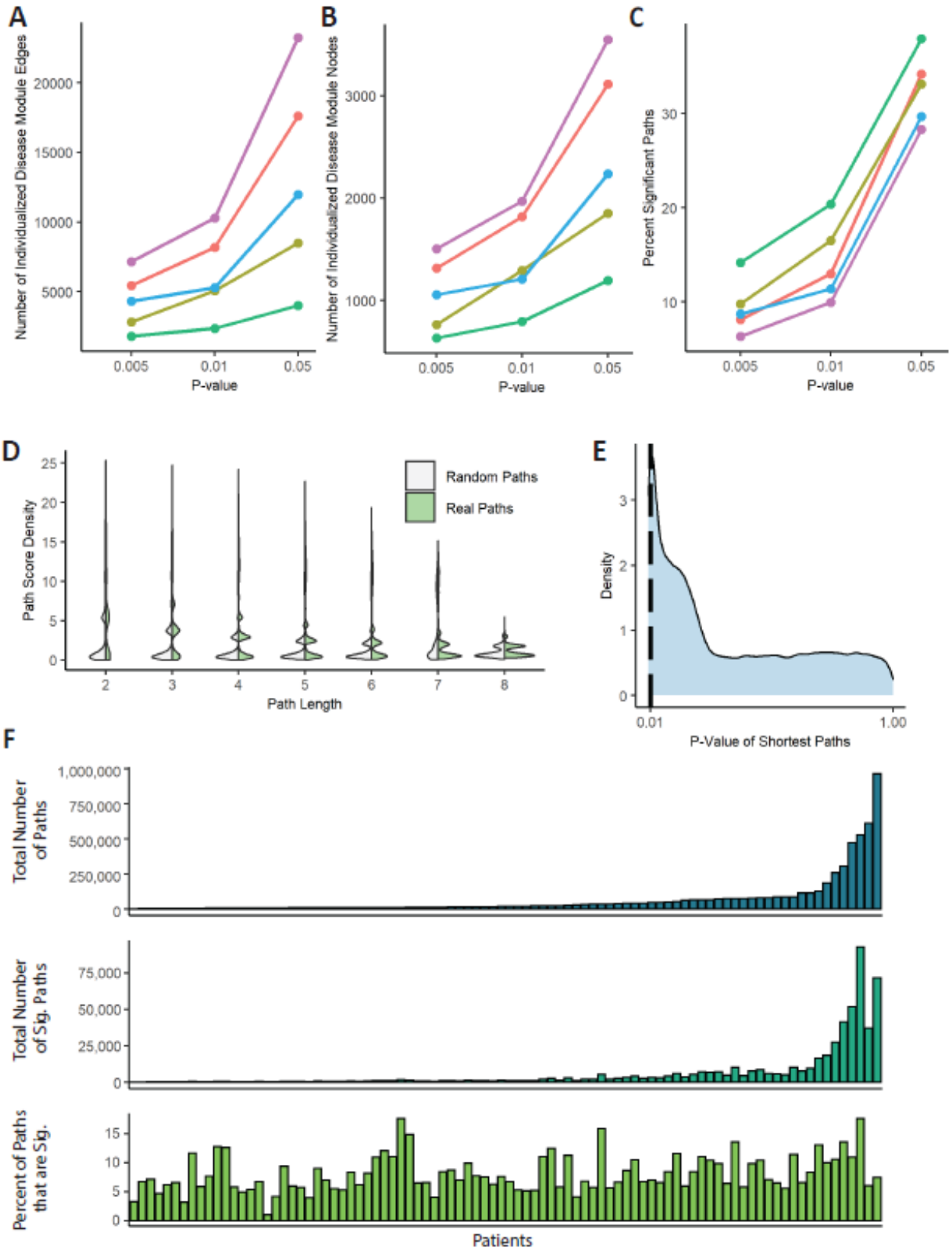



***Supplemental Figure 1. Clinical characteristics of Breast Cancer cohort patients used in this study and extended network construction schematics.***

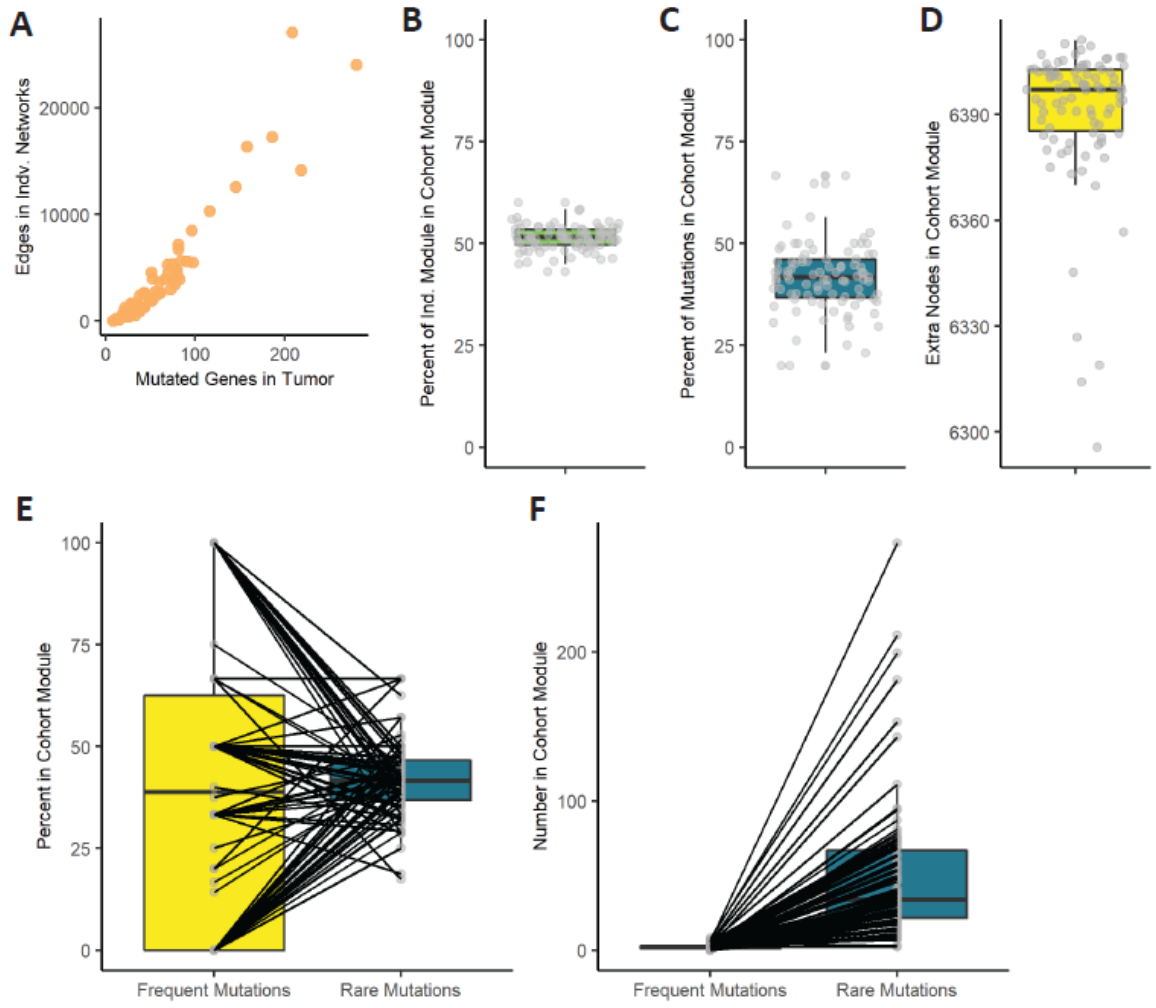
***A)*** *Heatmap describing the characteristics of the cohort's breast cancer tumors. The heatmap body shows hormone receptor (ER, PR and HER2) status as positive (green), negative (red), or not accessed (NA). PAM50 subtypes are documented by the bottom annotation, and the number of mutated genes in each patient is shown in the top histogram (available from TCGA BRCA project).*

***B)*** *Extended network construction schematics showing how network construction differs for two separate hypothetical patients #1 and #2.*


A
Number of Individualized Disease Module Edges
20000
15000
10000
5000
0.005
0.01
0.05
P-value
B
Number of Individualized Disease Module Nodes
3000
2000
1000
0.005
0.01
0.05
P-value
C
Percent Significant Paths
30
20
10
0.005
0.01
0.05
P-value
D
Path Score Density
25
20
15
10
5
0
Random Paths
Real Paths
2
3
4
5
6
7
8
Path Length
E
Density
3
2
1
0
0.01
1.00
P-Value of Shortest Paths
F
Total Number of Paths
1,000,000
750,000
500,000
250,000
0
Total Number of Sig. Paths
75,000
50,000
25,000
0
Percent of Paths that are Sig.
15
10
5
0
Patients

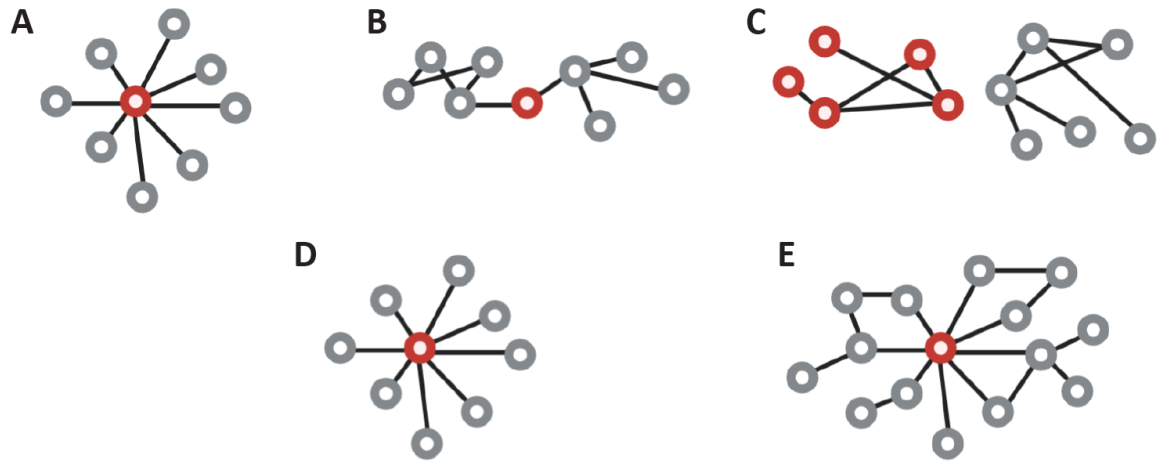
***Supplemental Figure 2. Characterization of path scoring and empirical p-value cutoffs.***

*Plots showing edge number* ***A)****, node number* ***B)****, and significant path percentages* ***C)*** *of the individualized disease modules of five patients subjected to three different p-value cut-offs (0.005, 0.01, and 0.05).* ***D)*** *Violin plots showing all patient path scores as density plots for random and real paths separated by path length.* ***E)*** *Density plot of all cohort empirical p-values combined.* ***F)*** *Bar charts displaying the total number of paths (top), the number of significant paths (middle), and the percent of paths that were considered significant (bottom) for each patient for a p-value <0.01. Each patient is represented by the vertically aligned columns across the three plots.*



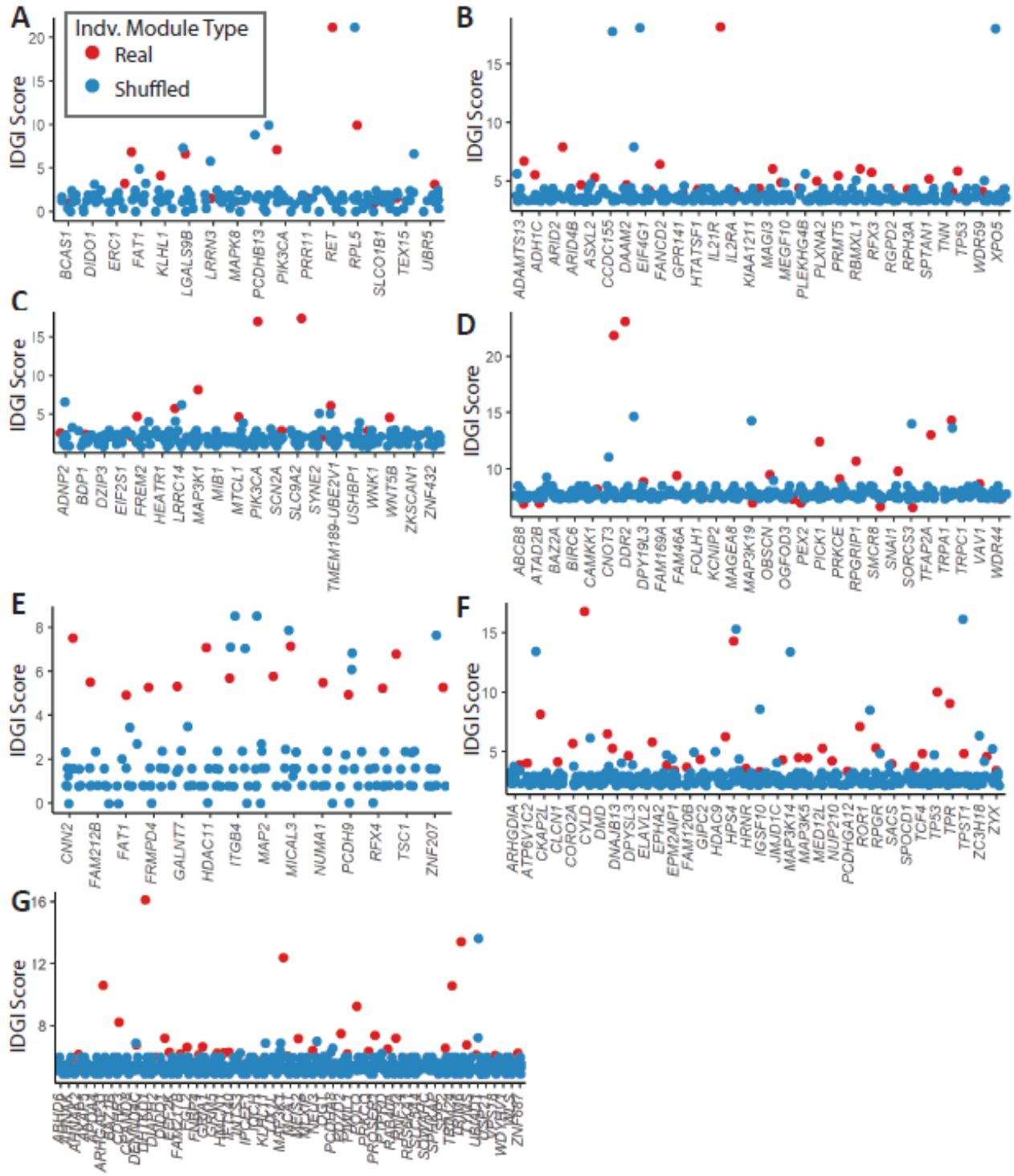

***Supplemental Figure 3. Individualized disease module characteristics and comparisons to cohort disease modules.***

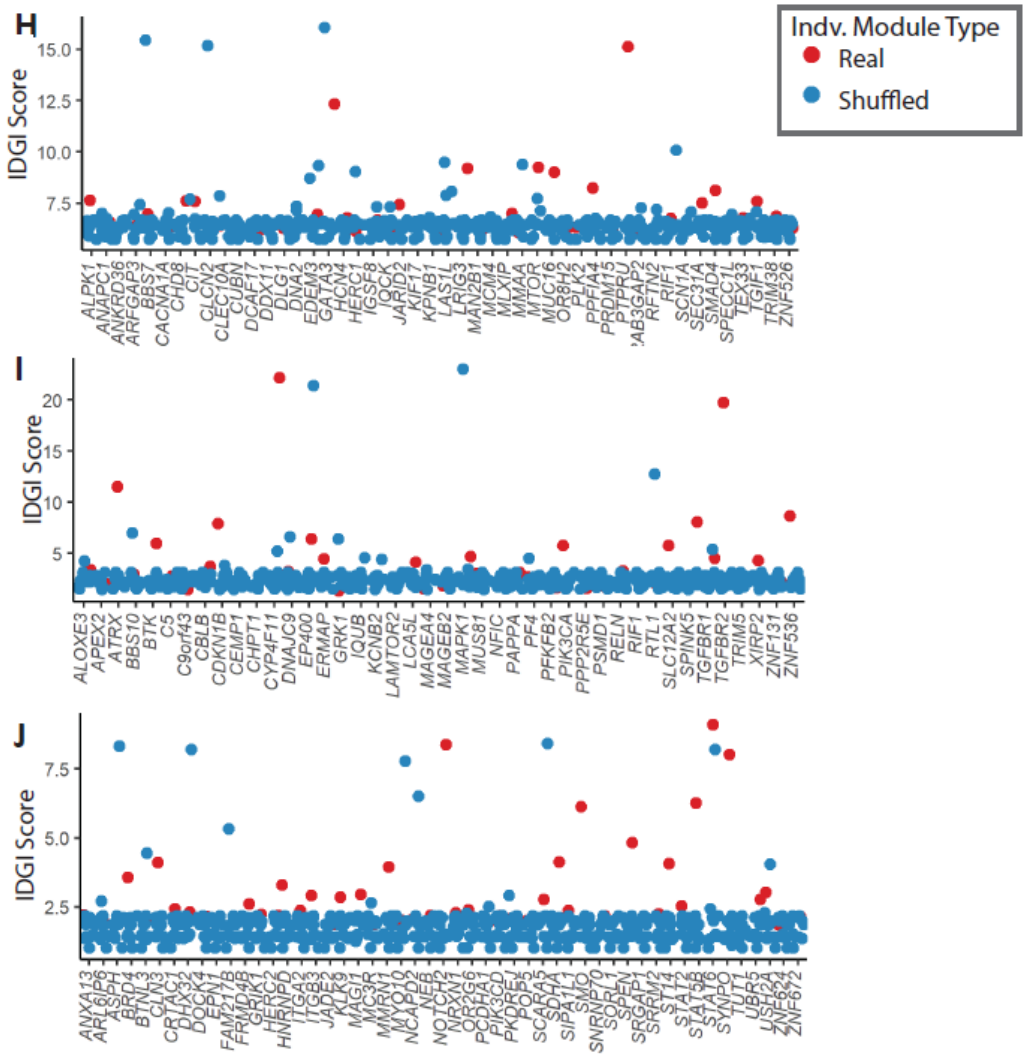
***A)*** *Scatter plot of the number of edges in the individualized disease networks versus the number of mutated genes in the tumor.* ***B-C)*** *The percent of individualized disease module nodes* ***B)*** *and mutations* ***C)*** *included in the cohort disease module.* ***D)*** *The number of nodes present in the cohort disease module that were not represented in individualized disease modules.* ***E-F)*** *The percentage* ***E)*** *and absolute number* ***F)*** *of frequent (≥5% of the TGCA BRCA cohort) and rare (<5% of TCGA BRCA cohort) mutations present in the cohort module.*




***Supplemental Figure 4. Schematic showing network components for IDGI score definition.***

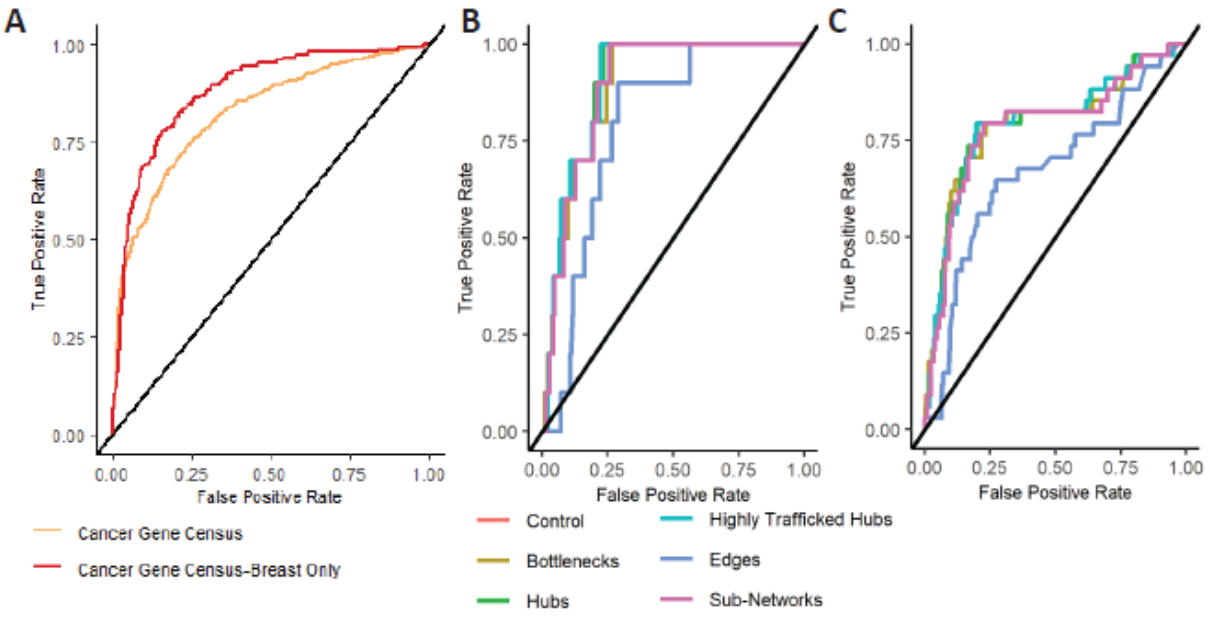
*Schematics demonstrating IDGI scoring components including* ***A)*** *hubs,* ***B)*** *bottlenecks,* ***C)*** *separate network components,* ***D)*** *lowly trafficked hubs, and* ***E)*** *highly trafficked hubs.*


A
Indv. Module Type
Real
Shuffled
IDGI Score
BCAS1 DIDO1 ERC1 FAT1 KLHL1 LGALS9B LRRN3 MAPK8 PCDHB13 PIK3CA PRR11 RET RPL5 SLCO1B1 TEX15 UBR5
B
IDGI Score
ADAMTS13 ADH1C ARID2 ARID4B ASXL2 CCDC155 DAAM2 EIF4G1 FANCD2 GPR141 HTATSF1 IL21R IL2RA KIAA1211 MAGI3 MEGF10 PLEKHG4B PLXNA2 PRMT5 RBMXL1 RFX3 RGPD2 RPH3A SPTAN1 TNN TP53 WDR59 XPO5
C
IDGI Score
ADNP2 BDP1 DZIP3 EIF2S1 FREM2 HEATR1 LRRC14 MAP3K1 MIB1 MTCL1 PIK3CA SCN2A SLC8A2 SYNE2 TMEM189-UBE2V1 USHBP1 WNK1 WNT5B ZKSCAN1 ZNF432
D
IDGI Score
ABCB8 ATAD2B BAZ2A BIRC6 CAMKK1 CNOT3 DDR2 DPY19L3 FAM169A FAM46A FOLH1 KCNIP2 MAGEA8 MAP3K19 OBSCN OGFOD3 PEX2 PICK1 PRKCE RPGRIP1 SMCR8 SNAI1 SORCS3 TFAP2A TRPA1 TRPC1 VAV1 WDR44
E
IDGI Score
CNN2 FAM212B FAT1 FRMPD4 GALNT7 HDAC11 ITGB4 MAP2 MICAL3 NUMA1 PCDH9 RFX4 TSC1 ZNF207
F
IDGI Score
ARHGDIA ATP6V1C2 CKAP2L CLCN1 CORO2A CYLD DMD DNAJB13 DPYSL3 ELAVL2 EPHA2 EPM2AIP1 FAM120B GIPC2 HDAC9 HPS4 HRNR IGSF10 JMJD1C MAP3K14 MAP3K5 MED12L NUP210 PCDHGA12 ROR1 RPGR SACS SPOCD1 TCF4 TP53 TPR TPST1 ZC3H18 ZYX
G
IDGI Score



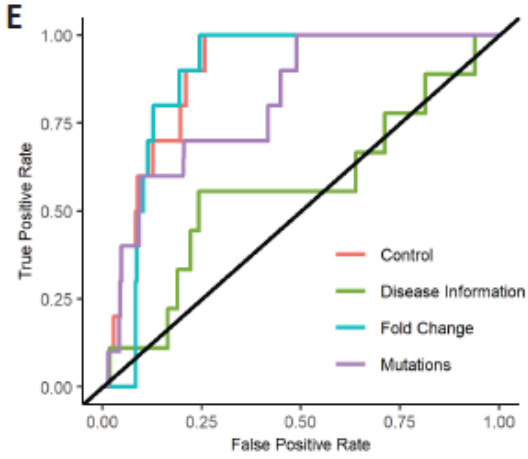

***Supplemental Figure 5. Randomized validation of IDGI scores showing relevance of real scores.***

***A-J)*** *Dot plots for patients (n=10) that underwent randomized shuffle validations. Shuffled scores are shown in blue, and real scores are shown in red.*




D

| Removed Component | AUC (Breast) | AUC (All) |
|---|---|---|
| Control | 0.89 | 0.785 |
| Bottlenecks | 0.888 | 0.79 |
| Edges | 0.789 | 0.669 |
| Hubs | 0.898 | 0.793 |
| Highly Trafficked Hubs | 0.899 | 0.792 |



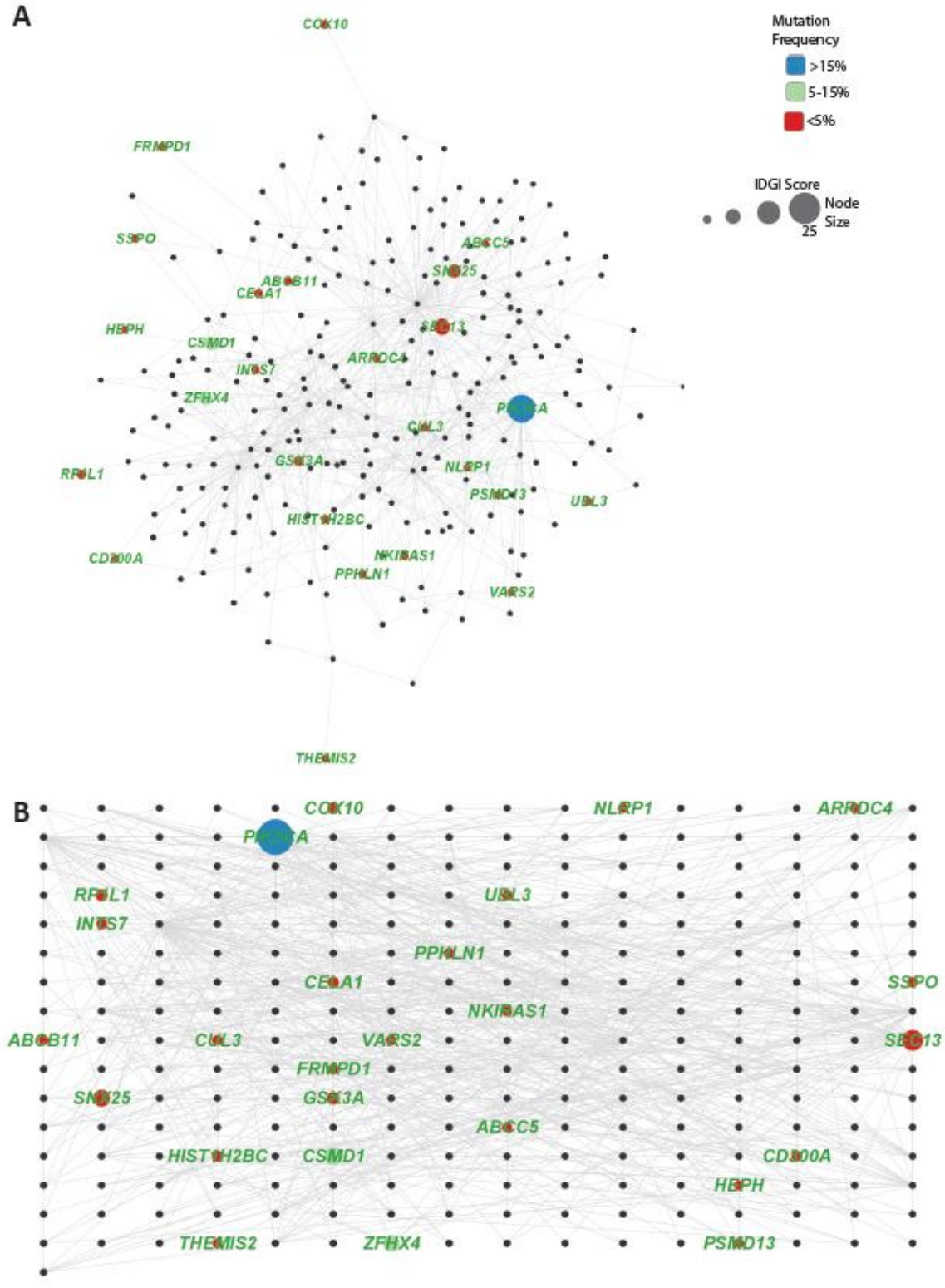

F

| Removed Component | AUC (Breast) |
|---|---|
| Control | 0.89 |
| Fold Change | 0.879 |
| Mutations | 0.811 |
| Disease Information | 0.562 |

***Supplemental Figure 6. IDGI score for detection of known cancer drivers and ablation studies showing importance of score components.***

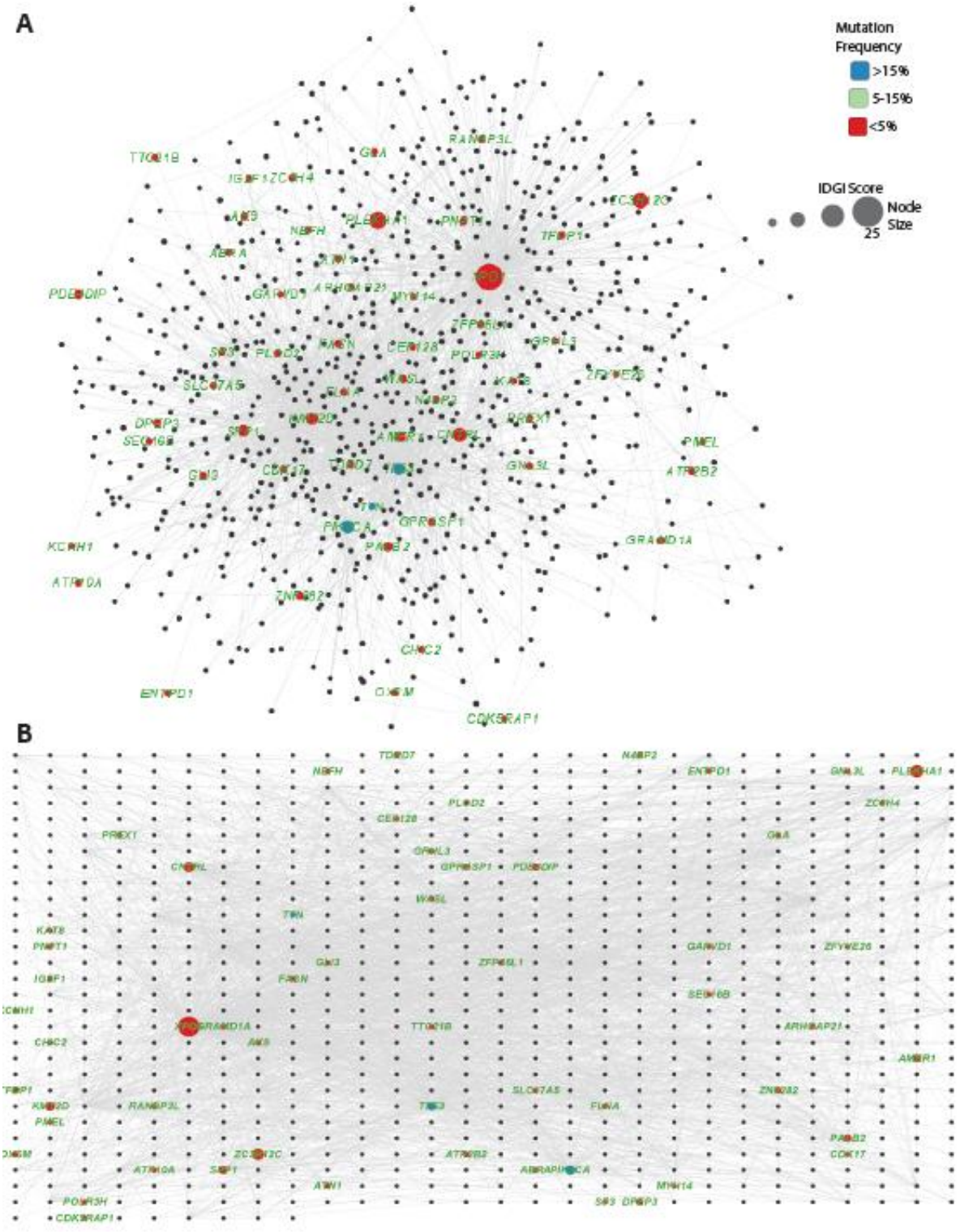
***A)*** *Receiver operating characteristic (ROC) curve for cooperativity score recovery of Cancer Gene Census (CGC genes) for all cancers (orange) or breast cancers (red).* ***B-C)*** *ROC curve for*

*recovery of CGC **B)** breast cancer genes and **C)** all cancer genes with individual gene score components deleted. **D)** AUC values for the ROC curves shown in panels **S6B** and **S6C**. **E)** Receiver operating characteristic (ROC) curves for the ablation of each path score component compared to the control (no ablation), and its ability to recover breast cancer genes in the CGC. **F)** AUC values for the ROC curve in **S6E**.*



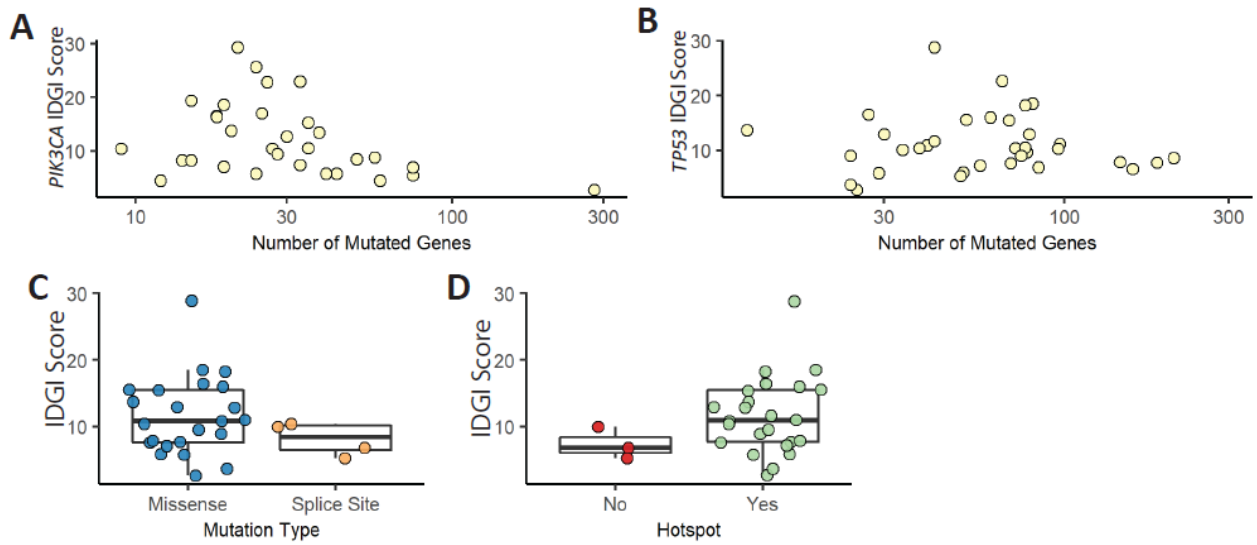

***Supplemental Figure 7. Full individualized disease modules.***

***A-B)*** *Full disease module for patient shown in* ***Figure 3A*** *shown in a* ***A)*** *network and* ***B)*** *grid view.*



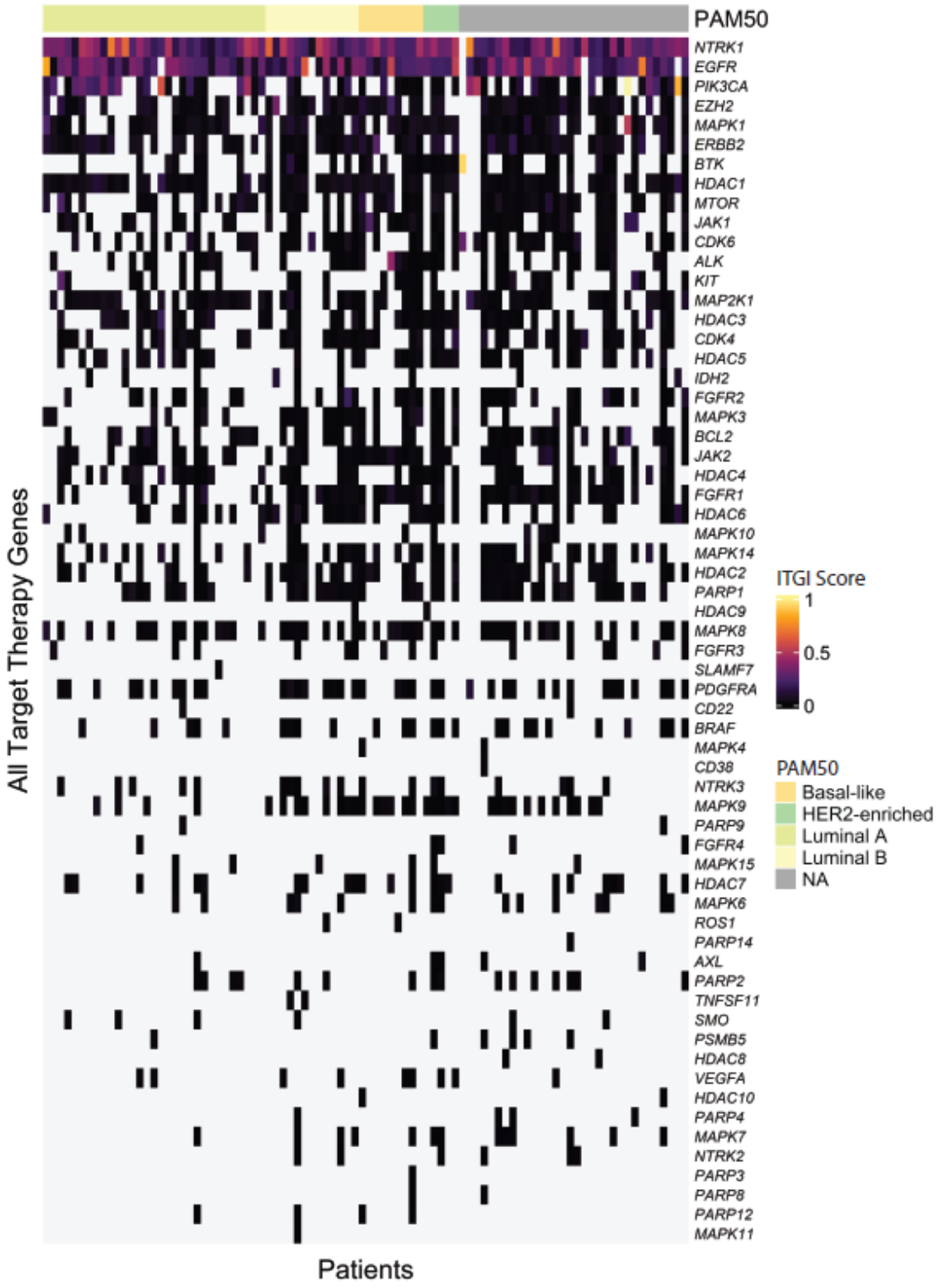

***Supplemental Figure 8. Full individualized disease modules.***

***A-B)*** *Full disease module for patient shown in* ***Figure 3B*** *shown in a* ***A)*** *network and* ***B)*** *grid view.*



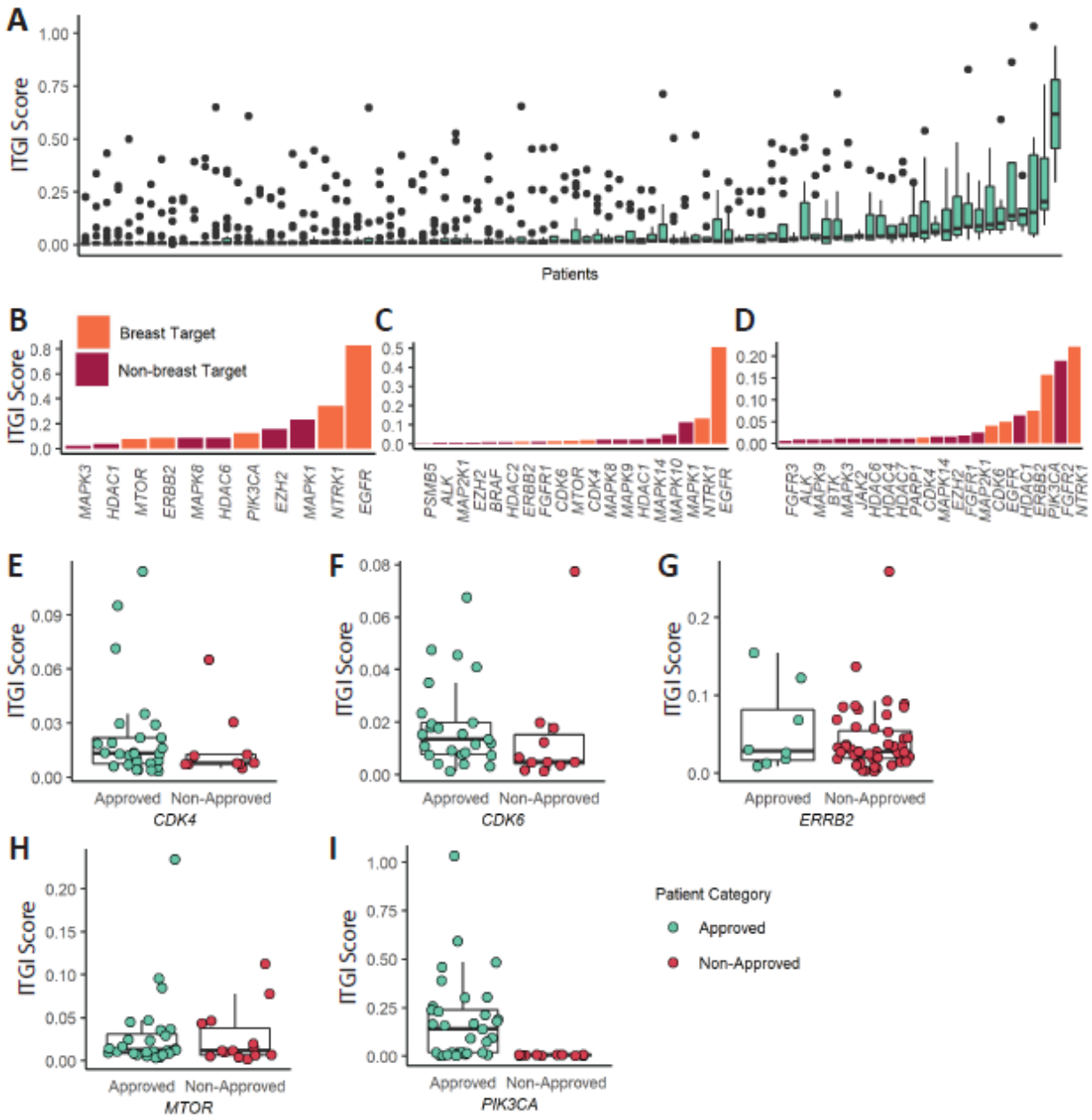

***Supplemental Figure 9. Gene importance relates to biological properties.***

***A)*** *and* ***B)*** *IDGI scores for TP53 and PIK3CA mutations versus the number of mutations within that tumor.* ***C)*** *IDGI score boxplots for missense and splice site TP53 mutations.* ***D)*** *IDGI score boxplots for TP53 missense mutations within and outside of mutational hotspots.*



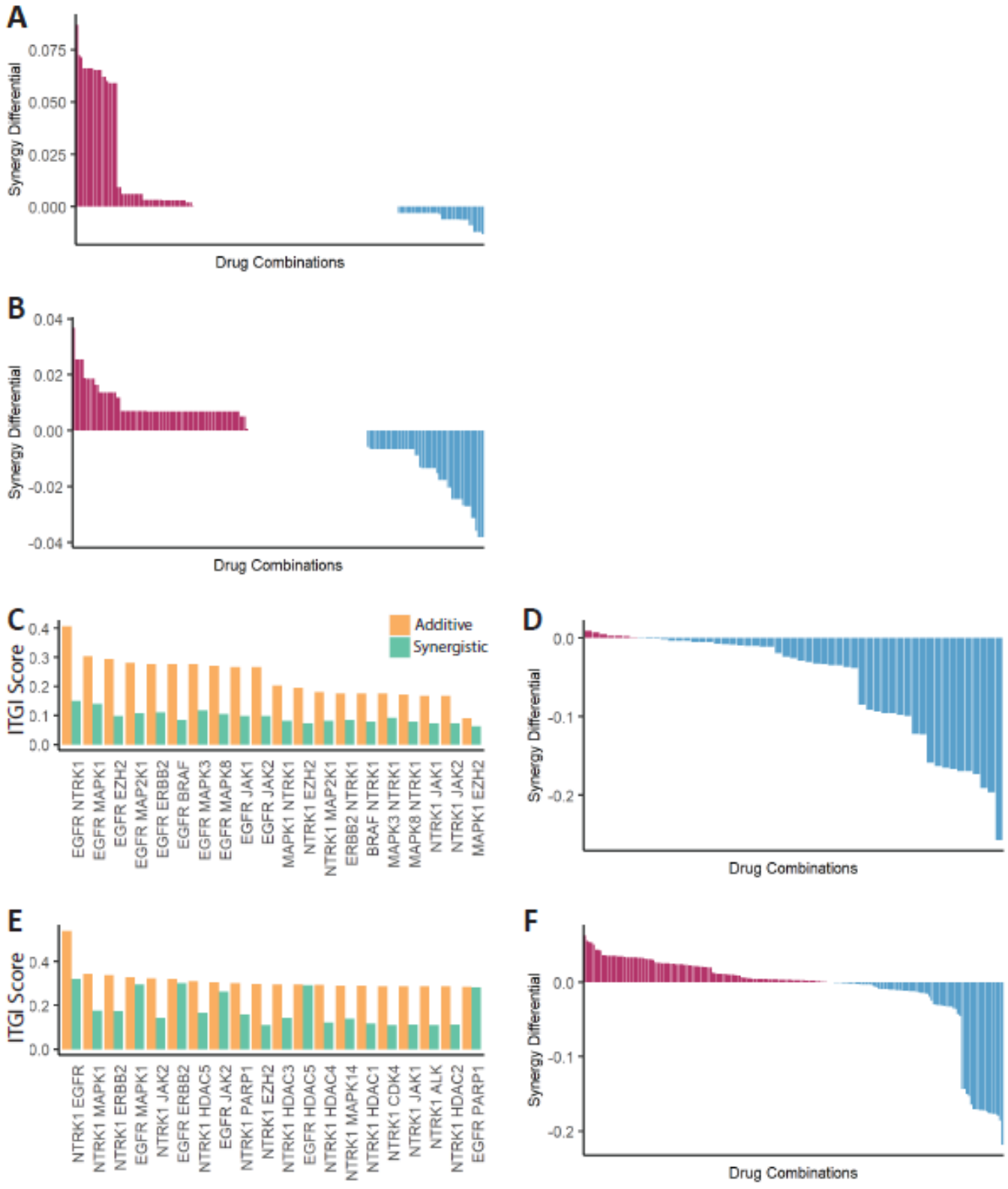

***Supplemental Figure 10. Diversity of targeted therapy responses.***

*Extended heatmap showing ITGI scoring for all target therapy genes in all BC patients.*




***Supplemental Figure 11. Individualized therapeutic target prioritization with individual network destabilization.***

***A)*** *Boxplots showing target score across each cohort patient.* ***B-D)*** *Target scoring for individual patients.* ***E-I)*** *Targeting score for targets approved for a subset of breast cancer patients show by approved patients (green) and non-approved patients (red). Approval indications are documented in* ***Data S1.***


A
Synergy Differential
0.075
0.050
0.025
0.000
Drug Combinations
B
Synergy Differential
0.04
0.02
0.00
-0.02
-0.04
Drug Combinations
C
ITGI Score
0.4
0.3
0.2
0.1
0.0
Additive
Synergistic
EGFR NTRK1
EGFR MAPK1
EGFR EZH2
EGFR MAP2K1
EGFR ERBB2
EGFR BRAF
EGFR MAPK3
EGFR MAPK8
EGFR JAK1
EGFR JAK2
MAPK1 NTRK1
NTRK1 EZH2
NTRK1 MAP2K1
ERBB2 NTRK1
BRAF NTRK1
MAPK3 NTRK1
MAPK8 NTRK1
NTRK1 JAK1
NTRK1 JAK2
MAPK1 EZH2
D
Synergy Differential
0.0
-0.1
-0.2
Drug Combinations
E
ITGI Score
0.4
0.2
0.0
NTRK1 EGFR
NTRK1 MAPK1
NTRK1 ERBB2
EGFR MAPK1
NTRK1 JAK2
EGFR ERBB2
NTRK1 HDAC5
EGFR JAK2
NTRK1 PARP1
NTRK1 EZH2
NTRK1 HDAC3
EGFR HDAC5
NTRK1 HDAC4
NTRK1 MAPK14
NTRK1 HDAC1
NTRK1 CDK4
NTRK1 JAK1
NTRK1 ALK
NTRK1 HDAC2
EGFR PARP1
F
Synergy Differential
0.0
-0.1
-0.2
Drug Combinations

***Supplemental Figure 12. Synergistic and redundant combinatorial targeting across several patients.***

***A-B)*** *Additional representative drug synergy differential (synergistic - additive).* ***C)*** *and* ***E)*** *Bar plots showing the top combinations of patients with redundant targeting.* ***D)*** *and* ***F)*** *Drug synergy differential for these patient's therapeutic combinations.*