# **Cell Systems**

# Systematic Evaluation of Molecular Networks for Discovery of Disease Genes

## **Graphical Abstract**



## **Highlights**

- Benchmarking of 21 molecular networks in recovering disease gene sets
- A composite network (PCNet) has improved performance over any single network
- Network performance is driven by increased edge density within disease gene sets

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## In Brief

We evaluate 21 human genome-wide interaction networks for their ability to recover 446 disease gene sets. While all networks can recover disease genes, we observe STRING, ConsensusPathDB, and GIANT networks to have the best performance overall. Performance scales with network size, suggesting that comprehensive interaction inclusion outweighs the detrimental effects of false positives. We create a parsimonious composite network with both high efficiency and performance. This work provides a benchmark for selection of molecular networks in human disease research.





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# Systematic Evaluation of Molecular Networks for Discovery of Disease Genes

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#### SUMMARY

Gene networks are rapidly growing in size and number, raising the question of which networks are most appropriate for particular applications. Here, we evaluate 21 human genome-wide interaction networks for their ability to recover 446 disease gene sets identified through literature curation, gene expression profiling, or genome-wide association studies. While all networks have some ability to recover disease genes, we observe a wide range of performance with STRING, ConsensusPathDB, and GIANT networks having the best performance overall. A general tendency is that performance scales with network size, suggesting that new interaction discovery currently outweighs the detrimental effects of false positives. Correcting for size, we find that the DIP network provides the highest efficiency (value per interaction). Based on these results, we create a parsimonious composite network with both high efficiency and performance. This work provides a benchmark for selection of molecular networks in human disease research.

#### INTRODUCTION

Molecular networks capture knowledge of diverse biochemical, statistical, and functional interactions that occur between genes and gene products. In a human disease setting, molecular networks augment both gene association and gene expression analysis, enabling the identification of novel genes and pathways associated with a particular disease phenotype (Carter et al., 2013). A common approach has been to leverage molecular network topology to discover new genes of interest that are functionally similar to a starting core of known disease genes (Kim et al., 2014; Lee et al., 2011; Leiserson et al., 2015; Paull et al., 2013; Qian et al., 2014; Vanunu et al., 2010). In this respect, networks enable a systematic "candidate gene approach" (Tabor et al., 2002) to the study of complex traits, whereby the candidates are identified by their proximity within molecular network neighborhoods to known genes associated with a particular disease. Many of these candidates might otherwise fall beneath significance thresholds for testing individual SNPs or genes in a genome-wide association analysis.

Using these principles, networks have identified genes functioning in a spectrum of diseases, including neurodevelopmental disorders such as autism (Willsey et al., 2013) and hereditary spastic paraplegia (Novarino et al., 2014), coronary artery disease (CARDIoGRAMplusC4D Consortium et al., 2013), and hypertension (Greene et al., 2015). For example, in hereditary spastic paraplegia three disease candidates identified by network analysis, *MAG*, *BICDL1*, and *REEP2*, were validated as having causal variants (Novarino et al., 2014). See Carter et al. (2013) for a review of the use of networks in the analysis of genotype-phenotype relationships.

In these types of studies, a network must first be constructed from an existing repository of molecular interactions. However, the number of these networks, as well as the number and types of molecular interactions within them, is rapidly growing. The PathGuide website at present tracks at over 700 pathway and molecular interaction databases available to the general public (Bader et al., 2006). More recently, Yu et al. (2013) reviewed nine major human-relevant network resources, and the Network Data Exchange (NDEx) (Pratt et al., 2015) has begun an attempt to provide a common public repository for biological network models of all types. Network databases can contain a variety of interaction types, such as protein-protein interactions, transcriptional regulatory interactions, genetic interactions, co-expression correlations, and kinase/phosphatase signaling relations. They can be populated by strategies such as systematic experimental screens, literature curation, and computational inference. Even accounting for the fact that most databases are tissue- and disease-context independent (Yeger-Lotem and Sharan, 2015), the diversity in molecular interaction curation and network construction methods can lead to significant differences in database content and utility for different types of analysis. As a consequence, from their very outset network biology studies must face a difficult question of determining which molecular networks are the most informative for the particular biological study at hand.

Here, we develop benchmarks to aid in selecting the most appropriate networks for a specific human disease or molecular

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#### Figure 1. Comparative Analysis of Gene Network Resources

The construction methods for each network are marked, along with the types of interactions they contain (yellow) for each molecular interaction network database evaluated. Interactions from the databases that are not used in our evaluation framework due to missing or embargoed data are marked with a gray X. The two interaction networks generated from single, large-scale, high-throughput experiments are marked with red dots. Pairwise similarity of all evaluated networks reveal differences in network edges (red gradient, edge-wise Jaccard index) and network propagation behavior due to varying topologies (blue gradient). Network sizes are shown by numbers of nodes (genes, green bars) and edges (interactions, purple bars). See also Figure S1 and Table S1.

pathway of interest. Using this framework, we score 21 popular human gene interaction networks by their ability to recover gene sets that characterize a wide variety of diseases. We find that empirical evaluation of networks not only informs current genomic analyses, but can also inform the creation of future networks as the importance of various sources of network information becomes clear.

#### RESULTS

#### Human Gene Networks Are Numerous and Capture a Diversity of Data Types and Sources

We obtained the complete contents of 21 popular human genegene interaction network databases, each of which is available for public use and described in previous publications (Table S1). We noted high diversity among these resources in types of interactions and curation methods (Figure 1). Networks such as the Database for Interacting Proteins (DIP) (Xenarios et al., 2000) and the Human Protein Reference Database (HPRD) (Peri et al., 2003) focus wholly on physical protein-protein interactions. Networks such as ConsensusPathDB (Kamburov et al., 2009) and MultiNet (Khurana et al., 2013) concatenate protein interactions from multiple molecular networks with many additional interaction types, such as genetic interactions. Meanwhile, networks such as HumanNet (Lee et al., 2011) and Search Tool for Recurring Instances of Neighboring Genes (STRING) (Snel et al., 2000; Szklarczyk et al., 2017) quantitatively integrate different studies and interaction types into a single integrated score for each gene pair based on the total weight of evidence. We also examined two molecular networks each generated from a large-scale, high-throughput protein interaction screen (Huttlin et al., 2015; Rolland et al., 2014). Specific interaction content varied widely, even among repositories that appeared superficially similar (Figures 1 and S1). For example, HumanNet and STRING have less direct overlap in gene-gene interactions than might be expected given that they use similar data types and data integration methodologies. These differences in both interaction type and coverage can give rise to large differences in network size and topological structure (Figures 1 and S1).

# A Benchmark for Evaluating Networks Based on Gene Sets

To benchmark these networks, we developed an approach to score how well each network is able to recover a diverse collection of disease-associated gene sets (Figures 2A–2C and STAR Methods). Each gene set was randomly split into two subsets. We then calculated the ability of one subset to recover the other within the network, using the technique of network propagation under the random walk with restart model (Köhler et al., 2008). Models were constructed to select optimal parameter values



#### Figure 2. Set-Based Network Evaluation

(A) A gene set of interest is sub-sampled (with proportion p) on the molecular network. Each sub-sample of genes is then propagated over the network of interest (with network propagation coefficient *a*) to recover the remaining genes in the gene set.

(B) The area under the precision-recall curve (AUPRC) is calculated to measure the performance of this recovery task.

(C) For each network, a set of null models is created by shuffling network edges (while preserving node degree) and repeating steps (A) and (B). The final network performance metric on this gene set is the improvement over the distribution of the null models' AUPRCs.

(D) The sub-sampling rate p of each gene set was set by a function of the number of genes from the gene set also found in the network. We determined this relationship by fitting the  $\log_{10}$ -adjusted gene set coverage in the network versus the optimal sampling rate for recovering the MSigDB gene sets (Liberzon et al., 2011). The error bars are 95% confidence intervals on the average optimal sampling rate for each task across all networks and network propagation coefficients ( $\alpha$ ). (E) Similarly, the optimal amount of network propagation ( $\alpha$ ) was fit by a linear model on the  $\log_{10}$ -adjusted number of edges in the network. The error bars are 95% confidence intervals on the optimal  $\alpha$  for each network across all tasks.

For additional details see STAR Methods.

used in the sub-sampling and network propagation steps (Figures 2D and 2E; STAR Methods). The random walk with restart model is a common technique used for network propagation. While other variations of network propagation, such as heat diffusion, could be used to evaluate networks, previous studies have found that there is no appreciable difference between these variations for most tasks (Köhler et al., 2008; Lee et al., 2011; Paull et al., 2013; Vanunu et al., 2010). After network propagation, recovery was scored using the area under precision-recall curve (AUPRC). The average AUPRC over repeated trials was calibrated against a null distribution of AUPRC scores from networks in which individual edges had been shuffled, preserving node degrees. Comparison with this null distribution allowed the AUPRC to be expressed as a *Z* score (Rousseeuw and Croux, 1993), henceforth called the network's "performance score."

This framework was applied to evaluate the 21 networks for recovery of 446 disease-associated gene sets from the DisGeNET database (Piñero et al., 2015, 2016), which is based on text mining of MEDLINE abstracts (Figure 3A, henceforth

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#### Figure 3. Molecular Network Recovery Performance of Literature Gene Sets

(A) The network performance score (purple) on 50 selected literature gene sets.

(B) The proportion of all 446 literature gene sets versus the number of networks that performed significantly better than their null networks via the network performance score (Bonferroni corrected p value <0.05).

(C) Network performance gain for 50 literature gene sets as shown in (A). This value represents the effect size of the improvement in gene set recovery performance due to using real networks over scrambled null networks.

(D) The log<sub>10</sub>-adjusted network performance score of molecular networks compared with the log<sub>10</sub>-adjusted network performance score gain by the molecular networks over their respective null molecular networks recovering the literature gene sets.

(E) Network size-adjusted performance scores for 50 literature gene sets as shown in (A). The columns (networks) in heatmaps (A), (C), and (E) are sorted by the average rank of the metric being measured (green rows).

(F) The average ranked performance of each molecular network on the recovery of the literature gene sets compared with the log<sub>10</sub>-adjusted number of interactions in the molecular networks. The error bars are 1 SD of the ranked network performances across the tasks.

The methods used to calculate the described metrics (network performance score, network performance gain, network size-adjusted performance score, and average ranked performance) are described in the STAR Methods. See also Figures S3 and S4; Data S1.

called "literature gene sets," Data S1A). We observed that all networks significantly outperformed their corresponding null models on at least 220 of the literature gene sets (49%), while 118 gene sets (26%) were recovered (at Bonferroni corrected p value of <0.05) by all 21 networks (Figure 3B). For recovery of these literature gene sets, we found that STRING had the best overall performance (Figure 3A).

We also wanted to confirm that our network evaluation method was not simply scoring a network's ability to separate disease genes from non-disease genes, but rather its ability to recover specific gene sets. Therefore, we also measured network recovery of the literature gene sets when using a background of only disease genes. We found that these results using a different background were very similar to those obtained when using all genes (Figures S2 and S3). We were also concerned that the null models might have low variance, in which case a network's performance (Z score) could be high without a large effect size. Therefore, we also calculated an effect size metric, called the "performance gain," to address this concern (Figure 3C and STAR Methods). This metric was highly correlated with the performance score (Pearson's r = 0.88,  $p < 1.0 \times 10^{-16}$ ) with 58% of the tasks having performance gains of over 50%, confirming that many networks have large effect sizes on the gene recovery tasks (Figure 3D).

#### Larger Networks Have Improved Performance

In these results, we noticed that many of the larger networks appeared to be the best performing. We thus examined how performance rankings change when correcting each network's performance for the number of interactions in the network (Figure 3E and STAR Methods). We found that the smallest network (DIP) moved to the top of the network size-adjusted rankings, suggesting that, per edge, this network is most efficient. None-theless, the number of interactions in a network was strongly predictive of its overall average rank in recovery of the literature gene sets (Pearson's r = 0.88, p =  $1.7 \times 10^{-7}$ ) (Figure 3F). The full numeric results of network performance, performance gain, and size-adjusted network performance are given in Data S1B–S1D.

We also attempted to determine whether other network properties, such as the type of molecular interaction or method of network construction, were correlated with performance. For this purpose we encoded network type descriptors (columns in Figure 1) into a binary vector describing each network and performed ANOVA on the size-adjusted performance. Beyond network size, however, we did not find any additional network properties that significantly correlated with performance in recovery of disease gene sets (Table S2).

#### Assessing the Influence of Literature Bias

Although no particular type of molecular interaction significantly correlated with network performance, we next asked whether networks that used co-citation information have an unfair advantage over other networks on the literature gene set recovery task. Specifically, some of the co-citation information used in STRING and HumanNet had been determined by mining a compendium of MEDLINE abstracts (Lee et al., 2011; Szklarczyk et al., 2017), which we considered might be similar to how the literature gene sets were mined by DisGeNET (Piñero et al., 2015, 2016). To test the degree to which literature curation might bias our performance results, we removed all interactions in STRING and HumanNet that were based solely on text mining. This filter removed 634,062 of 5,135,768 interactions (12.3%) in STRING and 4,631 of 475,959 interactions (1.0%) in HumanNet. We found that this filtering greatly reduced the performance of HumanNet relative to other networks (Table S3), suggesting that co-citation of genes in MEDLINE abstracts were an important driver of its performance. In contrast, such filtering did not greatly affect the performance of STRING.

As additional controls, we also evaluated all networks on two collections of gene sets that had been constructed independently of literature mining or other information that could influence network construction. The first of these was a collection of nine expression-based cancer gene sets. These gene sets were derived from a single high-throughput mRNA expression profiling study in an unsupervised manner without any network or literature-based gene selection and were found to correspond with well-known oncogenic pathways (Kim et al., 2017). Furthermore, this study was published more recently than the download dates of the networks used, making it impossible for any of the networks to use information from these gene sets. While STRING had the best overall performance for recovering the literature gene sets, we found that GeneMANIA and GIANT (Genome-scale Integrated Analysis of gene Networks in Tissues) were the best performing networks on these expression gene sets, with STRING ranking third. In general, however, we found that the overall rankings of networks on the literature recovery tasks versus on the expression recovery tasks were correlated (Pearson's r = 0.60, p =  $3.7 \times 10^{-3}$ ) (Figure 4A). We also observed that performance gain was correlated with performance score (Figure S4A, Pearson's r = 0.89, p < 1.0 ×  $10^{-16}$ ) while network performance was correlated with network size (Figure S4B, Pearson's r = 0.62, p < 2.8  $\times$  10<sup>-3</sup>).

As a second control against literature curation bias, we evaluated each molecular network against 11 gene sets derived from the genome-wide association study (GWAS) catalog (MacArthur et al., 2017). We constructed these gene sets from experimental GWAS of a common disease or trait: nine gene sets were associated with a disease (e.g., Crohn's disease or type 2 diabetes) and two gene sets were associated with a complex trait (height or body mass index). The genetic loci discovered in these studies had been associated with disease phenotype without any prior expectation from the literature (although one cannot entirely rule out the possibility that literature may have been used to distinguish among multiple candidate genes at a locus). Nonetheless, we found that the performance of the 21 networks on the GWAS gene sets was highly correlated with performance on the literature gene sets (Pearson's r = 0.89, p =  $5.7 \times 10^{-8}$ ) (Figure 4B). Performance on the GWAS gene sets also correlated with the performance gain metric (Figure S4C: Pearson's r = 0.94, p < 1.0 ×  $10^{-16}$ ), as well as the network size (Figure S4D: Pearson's r = 0.74,  $p = 1.0 \times 10^{-4}$ ). The gene sets and full numeric results of network performance, performance gain, and size-adjusted network performance for the expression and GWAS gene sets are given in Data S1E-S1L.



Figure 4. Literature-Independent Gene Set Recovery Correlates with Literature Gene Set Recovery The average ranked performance of molecular networks recovering literature gene sets is correlated with their average ranked performance on the recovery of expression gene sets (red) (A) as well as their average ranked performance on the recovery of GWAS gene sets (green) (B). The calculation to determine the average ranked performance of a molecular network on a collection of gene sets is described in STAR Methods. See also Figure S4 and Data S1.

#### Integrating Networks Improves Gene Set Recovery

Given the good performance of molecular networks that are large and inclusive, we considered that these separate resources might be further improved by combining them to form a single composite network. We explored several approaches for creating this composite, as follows. First, we created a series of composite networks of increasing size, by progressively aggregating individual networks in order of their performance scores in literature gene set recovery (STAR Methods and Table S4). However, such composite networks did not increase performance, regardless of how many individual networks were added together (Figure 5A and Data S1M). Next, we created a series of composite networks of decreasing size, by requiring interactions to be present in ever greater numbers of individual networks (Table S5). By requiring a minimum of two networks supporting each interaction, the performance was significantly improved over the best individual network (STRING) despite having a much smaller network size (Figures 5B and 5C). This configuration was optimal, since further increasing the minimum number of supporting networks beyond two resulted in a degradation of performance (Figure 5B and Data S1M). We call this optimal configuration the "Parsimonious Composite Network" (PCNet).

Many of the interactions from the larger networks were not contained within PCNet, implying that these larger networks contain interactions not reproduced elsewhere (Figures 5D and 5E). On the other hand, several of the smaller networks had almost all of their interactions covered by PCNet (Figure 5F). Thus, while large networks generally associate with high performance in gene set recovery, carefully designed small networks can efficiently achieve equal or better performance.

A simple explanation for how a smaller network (e.g., PCNet) can lead to increased performance is that it concentrates interactions among genes of the same disease and, conversely, depletes interactions among unrelated genes. To test this hypothesis, we performed a case study of four different networks: a protein-protein interaction network derived from a single experimental study (BioPlex, Figure 6A), a much larger network integrating many different studies (STRING, Figure 6B), the maximal composite network containing the union of interactions from all 21 individual networks (Figure 6C), and, finally, the PCNet parsimonious composite network (Figure 6D). In each case, we examined the relationship between a network's interaction density within members of a disease gene set and the performance of recovering that gene set. For all four networks, we found that interactions were greatly enriched among known disease genes, with STRING and PCNet showing by far the greatest enrichment (Figure 6E). Moreover, this interaction enrichment was well correlated with performance in gene set recovery (Figure 6F). Thus, density of interactions among disease genes is indeed an important indicator of network performance.

#### DISCUSSION

Given that the compositions and topologies of popular molecular networks vary greatly (Figure 1), a key question is whether these differences affect downstream studies of disease and, if so, by how much. Here, we have found that the choice of network can matter greatly. A particularly revealing example is the case of the Lymphopenia gene set, for which the performance gap was a factor of >5,000× between the networks with highest and lowest performance (Data S1B). In other instances, the choice of network appears less important, such as in the Measles gene set where the gap in performance was  $<5\times$  (Data S1B). This variation highlights not only the importance of evaluating networks globally, but in matching the correct network to the disease of interest. When studying a particular disease, one might start with



#### Figure 5. Composite Networks Can Gain Performance Despite Smaller Size

(A and B) Composite network average performance gain across all 446 literature gene sets compared with STRING (blue line) and composite network size (red line) for additive composite networks (A) and parsimonious composite networks (B). All error bars are 95% confidence intervals on the average performance gain for a given composite network. PCNet, the parsimonious network with at least two networks supporting each edge, achieved the highest performance, despite having fewer edges than STRING. The blue dotted line in (A) and (B) represents the performance of STRING, and the red dotted line in (A) and (B) is the network size of STRING. See <u>STAR Methods</u> for additional details on how to construct the composite networks.

(C) The average performance gain of PCNet across all 446 literature gene sets compared with each of the 21 selected molecular networks. All error bars are 95% confidence intervals on the average relative gain in performance for PCNet against a given molecular interaction network.

(D) The percentage of interactions in PCNet that are found in each of the 21 selected molecular networks.

(E) The number of interactions from each of the 21 networks that are supported by exactly one other network in PCNet. The gray dotted line represents the total number of edges in PCNet supported by exactly two network sources (1,830,145 interactions).

(F) The percentage of interactions from each of the 21 selected molecular networks that can be found in PCNet.

See also Data S1.

the networks that performed best on that particular gene set, instead of or in addition to the networks that were the best performers overall (Data S1B).

The result that larger networks outperform smaller ones, as a general trend, supports the continued investment in highthroughput discovery of biological interaction networks. At the same time, we were able to derive a much smaller PCNet that outperformed a network twice its size on the literature gene set recovery tasks (Figure 5B). This observation suggests at least one straightforward method of contracting the size of a reference network without sacrificing performance: requiring multiple database support for interactions. Moving forward, the

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Figure 6. Increased Interaction Density in Relevant Network Neighborhoods Improves Gene Set Recovery

(A–E) Interactions among genes associated with the same disease, Pancreatitis, as contained in (A) BioPlex, (B) STRING, (C) the union of all networks, and (D) the Parsimonious Composite Network (PCNet). For each of these, the quantitative enrichment of interactions (E) is shown among genes associated with five representative diseases.

(F) Scatterplot of gene set recovery performance versus the within-disease enrichment for interactions.

principle of network expansion by introduction of new data, followed by network contraction by independent verification, may provide general guidance for network construction. This principle also highlights the importance of cooperation between multiple approaches to network creation and the continued need for community development of human molecular interaction maps.

While systematic, we acknowledge that the evaluation framework used here is but one of several that might have been employed. Random walk with restart, although common, is not the only network distance metric appropriate for molecular networks. Alternative possibilities include diffusion state distance (Cao et al., 2014; Vandin et al., 2011), among others. More broadly, one might employ completely different network analytical engines, such as using networks as priors or regularization constraints for machine learning approaches (Hill et al., 2016; Sokolov et al., 2016) or as the underlying structure for probabilistic graphical models (Vaske et al., 2010). Establishing the generality of our results across a broader selection of network analysis approaches remains for future work.

As ever greater numbers of protein interactions are mapped and verified across a range of biological contexts, database curators will continue making decisions on how and which molecular interactions should be incorporated. This work provides a proof-of-principle for how any network database, or interaction subset, may be evaluated and compared. We hope that the systems biology community will continue to develop other complementary, and especially data-driven, methods of network evaluation to accompany the present approach.

#### **STAR**\***METHODS**

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- CONTACT FOR REAGENT AND RESOURCE SHARING
- METHOD DETAILS
  - Raw Network Data Processing
  - Network Propagation
  - Gene Set Selection for Network Evaluation
  - Network Evaluation Method
  - Accounting for Literature Mined Interactions
  - Composite Network Analysis
- QUANTIFICATION AND STATISTICAL ANALYSIS
  - Calculating Network Topology Similarity
  - Propagation and Sub-sampling Parameters
  - Network Performance Ranks
  - Network Size-Adjusted Performance ANOVA Model
- DATA AND SOFTWARE AVAILABILITY

#### SUPPLEMENTAL INFORMATION

Supplemental Information includes four figures, five tables, and one data file and can be found with this article online at <a href="https://doi.org/10.1016/j.cels">https://doi.org/10.1016/j.cels</a>. 2018.03.001.

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#### **AUTHOR CONTRIBUTIONS**

Conceptualization, J.K.H., D.E.C., and T.I.; Methodology, J.K.H., D.E.C., and T.I.; Software, J.K.H., D.E.C., M.K.Y., and W.Z.; Formal Analysis, J.K.H. and D.E.C.; Investigation, J.K.H. and D.E.C., Resources J.K.H., and P.T.; Data Curation, J.K.H., D.E.C., W.Z., and J.F.K.; Writing—Original Draft, J.K.H., D.E.C., J.F.K., and T.I.; Writing—Review & Editing, J.K.H., D.E.C., and T.I.; Visualization, J.K.H. and D.E.C.; Supervision, J.K.H., D.E.C., P.T., and T.I.; Funding Acquisition, T.I.

#### **DECLARATION OF INTERESTS**

T.I. is co-founder of Data4Cure and has an equity interest. T.I. has an equity interest in Ideaya BioSciences. The terms of this arrangement have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies.

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#### SUPPORTING CITATIONS

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### **STAR**\***METHODS**

#### **KEY RESOURCES TABLE**

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited Data		
Network Evaluation Tools	This Paper	The software developed for this paper can be found at: https://github.com/ idekerlab/Network_Evaluation_Tools
BIND	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 04471cb3-86d3-11e7-a10d-0ac135e8bacf
BioGRID	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: becec556-86d4-11e7-a10d-0ac135e8bacf
BioPLEX	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: c060aff9-86d4-11e7-a10d-0ac135e8bacf
ConsensusPathDB	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 1a9d6d0f-86d5-11e7-a10d-0ac135e8bacf
DIP	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 1c363581-86d5-11e7-a10d-0ac135e8bacf
GeneMANIA	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: a5d6eb0e-86d9-11e7-a10d-0ac135e8bacf
GIANT	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 08ba2a31-86da-11e7-a10d-0ac135e8bacf
HINT	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 0f92ca13-86da-11e7-a10d-0ac135e8bacf
HPRD	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 1093e665-86da-11e7-a10d-0ac135e8bacf
HumanInteractome	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 110ce6f7-86da-11e7-a10d-0ac135e8bacf
HumanNet	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 18dc9109-86da-11e7-a10d-0ac135e8bacf
InBioMap	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 266efe30-86da-11e7-a10d-0ac135e8bacf
IntAct	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 295ef233-86da-11e7-a10d-0ac135e8bacf
iRefIndex	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 2ca3bcf6-86da-11e7-a10d-0ac135e8bacf
Mentha	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 326806a9-86da-11e7-a10d-0ac135e8bacf
MultiNet	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 359bba6c-86da-11e7-a10d-0ac135e8bacf
PathwayCommons	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 46b63cdf-86da-11e7-a10d-0ac135e8bacf
PID	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 47eb8891-86da-11e7-a10d-0ac135e8bacf
Reactome	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 4bc71515-86da-11e7-a10d-0ac135e8bacf
ReactomeFI	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 50cddb28-86da-11e7-a10d-0ac135e8bacf
STRING	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: cfcd4cdb-86da-11e7-a10d-0ac135e8bacf
HumanNet (Interactions from only text-mined sources removed)	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 1c363581-86d5-11e7-a10d-0ac135e8bacf

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Continued		
REAGENT or RESOURCE	SOURCE	IDENTIFIER
STRING (Interactions from only text-mined sources removed)	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: 959fe798-86d5-11e7-a10d-0ac135e8bacf
Parsimonious Composite Network (PCNet)	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: f93f402c-86d4-11e7-a10d-0ac135e8bacf
Full Composite Network (All molecular interactions)	This Paper	This network was converted to HUGO Symbols and deposited on NDEx with the following UUID: edaec0cb-86d8-11e7-a10d-0ac135e8bacf
Software and Algorithms		
Network Propagation	(Leiserson et al., 2015)	Our implementation of the network propagation method is available here: https://github.com/idekerlab/Network_Evaluation_Tools/blob/master/ network_evaluation_tools/network_propagation.py
statsmodels	(Seabold and Perktold, 2010)	http://www.statsmodels.org/stable/index.html
Other		
DisGeNET(BeFree gene-disease associations)	(Piñero et al., 2016)	http://www.disgenet.org/web/DisGeNET/menu/downloads#gdasbefree; RRID:SCR_006178
GWAS Catalog	(MacArthur et al., 2017)	https://www.ebi.ac.uk/gwas/; RRID:SCR_012745
Oncogenic Signatures	(Kim et al., 2017)	https://github.com/idekerlab/Network_Evaluation_Tools/blob/master/ Data/Oncogenic_Components_genesets.txt
Biomolecular Interaction Network Database (BIND)	(Alfarano et al., 2005)	http://www.pathwaycommons.org/archives/PC2/v8/PathwayCommons. 8.bind.BINARY_SIF.hgnc.txt.sif.gz; RRID:SCR_003576
Biological General Repository for Interaction Data Sets (BioGRID)	(Chatr-Aryamontri et al., 2015)	http://thebiogrid.org/downloads/archives/Release%20Archive/BIOGRID- 3.4.149/BIOGRID-ORGANISM-3.4.149.tab2.zip; RRID:SCR_007393
Biophysical Interactions of Orfeome-based comPLEXes (BioPLEX)	(Huttlin et al., 2017)	http://bioplex.hms.harvard.edu/data/BioPlex_interactionList_v4a.tsv
ConsensusPathDB	(Herwig et al., 2016)	http://cpdb.molgen.mpg.de/download/ConsensusPathDB_human_PPI.gz; RRID:SCR_002231
Database of Interacting Proteins (DIP)	(Salwinski et al., 2004)	http://dip.doe-mbi.ucla.edu/dip/File.cgi?FN=2016/tab25/Hsapi20170205. txt; RRID:SCR_003167
GeneMANIA	(Zuberi et al., 2013)	http://genemania.org/data/archive/2014-10-15/Homo_sapiens. COMBINED/COMBINED.DEFAULT_NETWORKS.BP_COMBINING.txt; RRID:SCR_005709
Genome-scale Integrated Analysis of gene Networks in Tissues (GIANT)	(Greene et al., 2015)	http://giant.princeton.edu/static//networks/all_tissues_top.gz
High-quality INTeractomes (HINT)	(Das and Yu, 2012)	http://hint.yulab.org/download/HomoSapiens/binary/hq/, http://hint.yulab. org/download/HomoSapiens/cocomp/hq/; RRID:SCR_002762
Human Protein Reference Database (HPRD)	(Prasad et al., 2009)	http://www.hprd.org/download; RRID:SCR_007027
Human Interactome Project (HumanInteractome)	(Rolland et al., 2014)	http://interactome.dfci.harvard.edu/H_sapiens/download/HI-II-14.tsv; RRID:SCR_015670
HumanNet	(Lee et al., 2011)	http://www.functionalnet.org/humannet/HumanNet.v1.benchmark.txt
InBio Map	<b>(</b> Li et al., 2017 <b>)</b>	https://www.intomics.com/inbio/map/api/get_data?file=InBio_Map_core_ 2016_09_12.tar.gz
IntAct	(Orchard et al., 2014)	ftp://ftp.ebi.ac.uk/pub/databases/intact/2017-06-03/psimitab/intact.txt; RRID:SCR_006944
iRefIndex	(Turner et al., 2010)	http://irefindex.org/download/irefindex/data/archive/release_14.0/ psi_mitab/MITAB2.6/9606.mitab.07042015.txt.zip; RRID:SCR_002085
Mentha	(Calderone et al., 2013)	http://mentha.uniroma2.it/doDownload.php?file=2017-06-12_MITAB- 2.5.zip
MultiNet	(Khurana et al., 2013)	http://homes.gersteinlab.org/Khurana-PLoSCompBio-2013/Multinet. interactions.txt

(Continued on next page)

Continued		
REAGENT or RESOURCE	SOURCE	IDENTIFIER
PathwayCommons	(Cerami et al., 2011)	http://www.pathwaycommons.org/archives/PC2/v9/PathwayCommons9. All.hgnc.txt.gz; RRID:SCR_002103
PID	(Schaefer et al., 2009)	http://www.pathwaycommons.org/archives/PC2/v9/PathwayCommons9. pid.hgnc.sif.gz; RRID:SCR_006866
Reactome	(Croft et al., 2014)	https://reactome.org/download/current/interactors/reactome.homo_ sapiens.interactions.psi-mitab.txt; RRID:SCR_003485
ReactomeFl	(Wu et al., 2010)	http://reactomews.oicr.on.ca:8080/caBigR3WebApp2016/FIsInGene_ 022717_with_annotations.txt.zip
STRING	(Szklarczyk et al., 2015)	http://string-db.org/download/protein.links.v10.5.txt.gz; RRID:SCR_005223

#### **CONTACT FOR REAGENT AND RESOURCE SHARING**

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Justin K. Huang (jkh013@ucsd.edu).

#### **METHOD DETAILS**

#### **Raw Network Data Processing**

To normalize all networks for comparison, we filtered out all interactors that were not human protein coding genes. Then, the interactors were all mapped to HUGO Gene Symbols using MyGene.info (Wu et al., 2013; Xin et al., 2016). We kept only interactions where both interactors were mapped to a HUGO Gene Symbol. Many orthologous protein interactions and interactions between human proteins and small molecules/non-human proteins were also removed from analysis. We then removed redundant- and self-interactions in each of the 21 molecular networks. No other filters were applied to the networks except for the GIANT network. For GIANT, we downloaded the file of the top functional interactions across all tissues and filtered the network for only the top 10% of interactions by functional interaction score to extract a network that was comparable in size to the other networks.

#### **Network Propagation**

Network propagation requires a network and some nodes from that network as input. In this case those nodes represent a subsample of genes from a gene set of interest. These nodes were given some initial value (1 in this case), then a smoothing propagation process was applied to those initial values, passing some of the value to neighboring nodes. In this paper, the nodes are genes, and the edges represent various types of functional relationships between genes. These interactions include, for instance, protein binding interactions, transcriptional regulation and signaling by phosphorylation.

We employed a random-walk with restart model as our network propagation method. We used a closed-form version of the method as described by the HotNet2 paper (Leiserson et al., 2015):

$$F = (1 - \alpha)F_0 \cdot (I - \alpha A_{norm})^{-1}$$
 (Equation 1)

In this formulation,  $\alpha$  is the propagation constant, or random walk probability,  $A_{norm}$  is the degree-normalized adjacency matrix, and  $F_0$  is the initial binary vector over all genes indicating which genes in the network are in the initial subset of a gene set (Leiserson et al., 2015). Finally, F is a real-valued vector describing the network-smoothed values over all of the nodes in the network (called the "propagation score"). For the purpose of this paper, all networks were treated as undirected simple graphs. If there are multiple connected components in the network being smoothed, each connected component was propagated independently and the results of each connected component concatenated.

#### **Gene Set Selection for Network Evaluation**

Three collections of gene sets were downloaded as standards to evaluate networks against. The first collection of gene sets was downloaded from the DisGeNET website (http://www.disgenet.org). We used the "BeFree gene-disease associations," which is a collection of text-mined disease-associated gene sets mined from a collection of MEDLINE abstracts (Piñero et al., 2015, 2016). These gene sets were chosen to remove as much human curation bias as possible from the gene sets. The gene sets were then filtered to only the gene sets that contained less than 300 genes and contained at least 20 genes in each network studied. This yielded a collection of 446 gene sets from DisGeNET referred to as "literature gene sets".

We also evaluated the networks on two additional collections of gene sets that were constructed independently from the literature gene sets and molecular networks. The first literature-independent collection of gene sets were acquired from a recent Cell Systems paper that determined the pathways involved in treatment response in RAS-induced cancer cell lines (Kim et al., 2017). The authors in this paper defined 9 oncogenic transcriptional components ranging in size from 50-122 genes, each centered on different common cancer pathways. We refer to these sets as "expression gene sets".

The second literature-independent collection of gene sets was derived from the GWAS Catalog (MacArthur et al., 2017). The GWAS Catalog is a large database of significant SNP-trait associations. We defined each gene set as the genes mapped to significantly disease associated SNPs, with one gene set per trait. We kept only the gene sets that had between 20 and 500 genes present in all 21 networks. Of these, we eliminated gene sets that were unlikely to be generalized outside of the particular study context (e.g. blood cell count, resting heart rate), and kept the 9 gene sets associated with disease and 2 gene sets associated with easily observable quantitative traits: height and body mass index.

#### **Network Evaluation Method**

The set-based network evaluation method for a molecular network's ability to recover disease-associated gene sets was performed with the following steps:

- 1. Identify a gene set of interest on the molecular interaction network.
- 2. Sub-sample a proportion (~30-60%, see "Propagation and sub-sampling parameters") of the gene set of interest (Figure 2D).
- 3. Propagate this sub-sample of genes from (2) using the random walk model across the molecular interaction network (Hofree et al., 2013; Leiserson et al., 2015; Vanunu et al., 2010) (Figure 2E).
- 4. Sort all genes in the network by propagation score and then sweep this list to calculate a precision-recall curve of the list for recovering genes from (1) not contained in (2).
- 5. Calculate the area under the precision-recall curve (AUPRC) from (4).
- 6. Repeat (2-5) for 50 different sub-samples of the gene set of interest and average these values. This averaged AUPRC is the raw measure of performance for a given molecular network on clustering a gene set of interest.
- 7. Repeat steps 1-6 for 50 degree-preserved shuffles of the network on the same gene set of interest to construct a null distribution of average AUPRC values.
- 8. Calculate the robust Z-statistic (Rousseeuw and Croux, 1993) using the null distribution of average AUPRC values from (7) of the actual network's performance on the gene set of interest. This is the performance score of a network for a particular gene set.

#### **Accounting for Literature Mined Interactions**

Recognizing the possible effect of co-citation information in both STRING (https://string-db.org/) and HumanNet (http://www. functionalnet.org/humannet/about.html), we removed all interactions in these networks that were supported exclusively from textmined sources in human studies in these networks. However, we did keep edges with evidence from exclusively text-mined evidence in non-human studies since this evidence was not used for the literature gene sets. These filtered networks were then evaluated using our set-based evaluation method and re-ranked in the context of the performance of the other unmodified networks (Table S3). It is also important to note that the remaining network containing co-citation information, ReactomeFI, does not directly contain information mined from MEDLINE abstracts, nor does its publicly available database indicate which interactions are exclusively determined with literature text mining (Wu et al., 2010). Therefore, we did not perform any interaction filtering and re-evaluation on ReactomeFI.

#### **Composite Network Analysis**

We constructed two sequences of composite networks to study the effect of combining networks on performance. The first sequence of composite networks increases in size starting with the best performing network across the literature gene sets, STRING. Each subsequent composite network was made by adding all unique edges from the next best performing network on the literature gene sets (Figure 5A and Table S4). Then we created a sequence of parsimonious composite networks of decreasing size by requiring increased support of each edge, starting with the additive composite network containing the union of all edges from the 21 networks (Figure 5B and Table S5). The performance of both sequences of composite networks were then evaluated on the same literature gene sets. We found that the network constructed out of edges with at least 2 network sources outperformed STRING on the literature gene sets, and we refer to this network as PCNet.

#### **QUANTIFICATION AND STATISTICAL ANALYSIS**

#### **Calculating Network Topology Similarity**

We compared the 21 molecular networks to each other with two similarity metrics, one based on the number of shared network edges and one based on the network topology by propagation (Figure 1). To determine the network similarity by shared network edges, we first took the intersection of nodes between the two networks being compared. Then all edges between this set of nodes in both networks were taken to create a subgraph of both networks. The Jaccard index of the number of shared edges between these two subgraphs was then taken as a the network edge similarity. In order to measure the similarity of network topology by propagation, we again took the intersection of nodes between the two networks. Then, each one of these nodes was propagated (Equation 1) across the entire network and we measured the similarity between the propagation scores across all shared nodes by Spearman correlation. The average similarity across all shared nodes between any two networks was the final network topology-by-propagation similarity measure.

#### **Propagation and Sub-sampling Parameters**

In order to calibrate the network propagation method, we constructed a model to estimate the optimal propagation constant ( $\alpha$ , Equation 1) as well as a reasonable sub-sampling proportion to use to optimize cohort recovery. In order to establish these parameters, we tested the performance of the 21 networks on recovering the 50 Hallmark MSigDB pathways (Liberzon et al., 2011) so as not to contaminate the parameter selection with the literature gene sets that were used in the actual benchmark. We examined a range of sub-sampling proportions and propagation constants to identify which values for these parameters yields the best results (Figures 2D and 2E). First, we averaged the resulting network performance scores for each propagation constant  $\alpha$  (from 0.05 to 0.95 in increments of 0.05) and fit a log-linear model to determine the best sub-sample proportion p for each gene set based on the coverage of that gene set in the network (Figure 2D). Then, using our model for determining p, we fit a second model to determine the optimal  $\alpha$  such that the networks had the best performance on recovering the MSigDB Hallmark gene sets. These  $\alpha$  constants for each network were then compared against various network properties. We found that a the optimal  $\alpha$  constant for each network was predicted by a linear model against the log<sub>10</sub>-adjusted number of interactions in the network (Figure 2E). These two models are then used to set the  $\alpha$  constant and sub-sample proportion for all subsequent network evaluation tasks. Note that the determination of these parameters was based on gene sets that were not used in any other evaluation, so overtraining of these parameters is not an issue in our evaluation framework.

#### **Network Performance Ranks**

Three network performance metrics are used here (Figure 3). In order to derive each of these metrics, we compared against a background of degree matched null networks that were created by shuffling the network edges while preserving node degree. We defined the performance score as the robust z-score of the true AUPRC of the gene set recovery task as compared to the background of AUPRCs from the degree matched null networks (Figure 3A). To determine the network rankings by an effect size metric, we defined the performance gain as the difference between the AUPRC of a given network and the median AUPRC of its null networks divided by the median AUPRC of its null networks (Figure 3C). In order to calculate the size-adjusted performance, a linear model was fit to the performance scores of each task against the log<sub>10</sub>-adjusted network interaction count. The residual values for each performance score were calculated against their respective size-adjusted performance models (Figure 3E).

All networks were ranked on each of these metrics individually for each task in each collection. The overall rankings were determined by the average rank of each network across all tasks in each collection. This value is described as the average ranked performance of a network. The average ranked performance gain as well as the average ranked network size-adjusted performance are calculated in the same manner as the average ranked performance using their respective metric.

#### **Network Size-Adjusted Performance ANOVA Model**

In order to determine if any specific network properties were correlated with network performance, we constructed an ANOVA model using the statsmodel package in Python (Seabold and Perktold, 2010). The construction method for each network, along with the types of interactions they contain were considered as independent categorical variables (columns marked with yellow in Figure 1, with the exception of column titled "Physical"). Each column where a network has a yellow indicator without a grey "X" in it was given 1 for that variable and given 0 otherwise. We then used all 14 of these variables to construct a model for predicting the averaged ranked network size-adjusted performance of each network. The formulation of the ANOVA model is as follows:

Size Adjusted Residuals  $\sim$  Low-Throughput + High-Throughput + Scored + Co-Citation + Co-Complex + Co-Expression + Genetic + Metabolic + Non-Protein + Orthologous + Pathway + Regulation + Shared Domain + Signalling.

The resulting ANOVA summary table then gave the significance of the explanation of the network size-adjusted performance by any of the network properties we examined (Table S2).

#### DATA AND SOFTWARE AVAILABILITY

Many of the functions written to perform the network evaluation are contained within an installable Python 2.7 package at https://github.com/idekerlab/Network\_Evaluation\_Tools. Documentation and examples of how to evaluate a molecular network for a given collection of gene sets are provided as both a Jupyter Notebook and as an executable command line script. All of the website links to the network source data and the Jupyter Notebooks used to process the network source data are also available in the aforementioned GitHub repository. The links to the network source data are also described in the Key Resources Table with the network version and reference information described in Table S1. The 21 molecular networks, the 2 filtered networks as well as PCNet and the union of all 21 molecular networks are available in a network set on the Network Data Exchange (NDEx) (Pillich et al., 2017; Pratt et al., 2015) at https://goo.gl/WVDznR.

Cell Systems, Volume 6

# **Supplemental Information**

# Systematic Evaluation of Molecular Networks

# for Discovery of Disease Genes

Justin K. Huang, Daniel E. Carlin, Michael Ku Yu, Wei Zhang, Jason F. Kreisberg, Pablo Tamayo, and Trey Ideker

### Supplementary Data

**Data S1. Gene Set Lists and Network Evaluation Performance Results.** *Related to Figure 3, Figure 4, Figure 5 and Figure S4*. The tabs in this file are a collection of spreadsheets presenting the gene sets in each of the three collections of gene sets (literature, expression and GWAS) as well as full numeric values of molecular network performance score, performance gain and size-adjusted performance across all gene sets (as presented in **STAR Methods**) for each collection of gene set recovery tasks. Composite network performance scores on the literature gene sets are also presented here.

Data S1A: Literature gene sets

**Data S1B:** Molecular network literature gene set performance scores

**Data S1C:** Molecular network literature gene set AUPRC performance gains

Data S1D: Molecular network literature gene set network size-adjusted performance scores

**Data S1E:** Expression gene sets

**Data S1F:** Molecular network expression gene set performance scores

**Data S1G:** Molecular network expression gene set AUPRC performance gains

**Data S1H:** Molecular network expression gene set network size-adjusted performance scores

Data S1I: GWAS gene sets

**Data S1J:** Molecular network GWAS gene set performance scores

Data S1K: Molecular network GWAS gene set AUPRC performance gains

Data S1L: Molecular network GWAS gene set network size-adjusted performance scores

Data S1M: Composite network literature gene set performance scores

# Figure S1.

										Ν	etwo	ork									
	Q	GRID	pPlex	insensusPathDB	0	eneMANIA	ANT	NT	RD	ImanInteractome	imanNet	3io-Map	Act	efIndex	entha	ultiNet	0	thwayCommons	actome	actome-FIs	RING
Database	B	Β	Β	ပိ	D	Ğ	Ū	Ī	보	Н	Ъ	InE	Int	iRe	Me	Σ	PI	Ра	Re	Re	ST
BIND																					
BioCarta																					
BioGRID																_					
Co-Frac																					
CORUM																					
DIP												_									
						-		-		-				-		_					
GeneMANIA						-	-	-		-		-		-		-					
GeneWays																					
GEO																					
GO					-																
HINT																					
HPRD																					
HumanCyc																					
I2D																					
InnateDB																					
INOH																					
IntAct																					
iRefIndex																					
JASPAR																					
KEGG																					
Lit-BM-13																					
MatrixDB																					
Mentha																					
MINT																					
MIPS-MPPI							_														
mirTarBase																					
MPACT																					
MPIDB																					
							_					_									
NetPath BothwayCommono												_									
PDZBase																					
Pfam																					
PhosphoPOINT																					
PhosphoSitePlus																					
PID																					
PIG																					
PINA																					
PINdb																					
PrePPI-HC																					
Reactome																					
RECON X																					
SignaLink																					
SMPD																					
SPIKE																					
STRING																					
Tiger																					Щ
TRANSFAC																					Щ
TRED	<u> </u>		<u> </u>																		Щ
TTD					L						L										$\square$
VisANT																					$\mid \mid \mid$
WikiPathways																					

Systematic, direct mapping of interactions Computationally inferred Optional / Not-publicly available Validated against Figure S1. Molecular Interaction Network Underlying Database Sources. Related to *Figure 1 and Table S1.* The underlying molecular interaction databases (rows) for each molecular network evaluated (columns) is marked with various colors depending on how the data from the underlying database was used in the evaluated network. Networks developed from only manual literature curation or only high-throughput experiments have empty columns as they are not determined to have interactions mapped directly from other databases sources. The underlying interaction databases for networks that are compilations of other databases are marked in blue. The underlying interaction databases for functional interaction networks that derive their interactions from the information of multiple interaction databases are marked in green. Databases used as validation for evaluated networks are marked in orange, and interactions from networks that are not included in publicly available version of the evaluated networks are marked in red. The determinations of source databases was manually curated from websites and references of the evaluated networks in Table S1.

Figure S2.



**Figure S2. Comparison of Network AUPRCs on Disease Gene Set Recovery With Varied Background Genes.** *Related to STAR Methods.* Scatter plots comparing the Area Under the Precision-Recall Curve (AUPRC) values (**STAR Methods**) for each network on recovering literature gene sets when using the entire set of network genes or using only genes contained in the literature gene sets as the background of genes for recovery. Figure S3.



Figure S3. Disease Gene Set Recovery Performance With Varied Background Genes. *Related to Figure 3 and STAR Methods.* The average ranked performance (as calculated in the **STAR Methods**) of networks on recovering the literature gene sets when using a background of all network genes compared to using a background of only genes contained in the literature gene sets. The average ranked performance of networks on recovering literature gene sets is robust to changing the background of genes used in the performance calculation (**STAR Methods**).

# Figure S4.



**Figure S4.** Additional Literature-Independent Gene Set Recovery Network Performance **Correlations.** *Related to Figure 3, Figure 4 and Data S1.* (A) The log<sub>10</sub>-adjusted network performance score of molecular networks compared to the log<sub>10</sub>-adjusted network performance score gain by the molecular networks over their respective null molecular networks recovering the expression gene sets (B) The average ranked performance of each molecular network on the recovery of the expression gene sets compared to the log<sub>10</sub>-adjusted number of interactions in the molecular networks. (C, D) The same plots as as **Figure S4A** and **Figure S4B**, respectively, but instead evaluating networks on their recovery of the GWAS gene sets. The calculation to determine the average ranked performance of a molecular network on a collection of gene sets is described in the **STAR Methods**. Error bars in **Figure S4B** and **Figure S4D** are one standard deviation of the average ranked network performances across each collection of recovery tasks.

Network Name	Version Name	Approx. Version Date	Database Citations
BIND	Pathway Commons v9	December 15, 2010	(Alfarano et al. 2005; Bader et al. 2003; Bader et al. 2001; Gilbert 2005)
BioGRID	3.4.149	June 1, 2017	(Chatr-Aryamontri et al. 2015; Stark et al. 2006; Chatr-Aryamontri et al. 2013; Breitkreutz et al. 2008; Stark et al. 2011; Breitkreutz et al. 2003)
BioPlex		Jun 15, 2015	(Huttlin et al. 2015; Huttlin et al. 2017)
ConsensusPathDB	Release 32	January 11, 2017	(Herwig et al. 2016; Kamburov et al. 2009; Kamburov et al. 2013; Kamburov et al. 2011)
DIP Hsapi20170205		February 05, 2017	(Xenarios et al. 2000; Salwinski et al. 2004; Xenarios et al. 2001; Xenarios et al. 2002)
GeneMANIA		October 15, 2014	(Mostafavi et al. 2008; Zuberi et al. 2013; Warde-Farley et al. 2010)
GIANT		Spring 2015	(Greene et al. 2015)
HINT	Version 4	Early 2017	(Das & Yu 2012)
HPRD	Release 9	June 29, 2010	(Peri et al. 2003; Prasad et al. 2009; Mishra et al. 2006; Peri et al. 2004)
HumanInteractome	HI-II-14	2014	(Rolland et al. 2014)
HumanNet	v.1		(Lee et al. 2011)
InBioMap	2016_09_12	Sep 12, 2016	(Li et al. 2017)
IntAct	Release 207	September 12, 2016	(Hermjakob et al. 2004; Orchard et al. 2014; Kerrien et al. 2007; Aranda et al. 2010; Kerrien et al. 2012)
iRefIndex	Version 14.0	September 14, 2016	(Razick et al. 2008; Turner et al. 2010)
Mentha	06-12-2017	June 12, 2017	(Calderone et al. 2013)

MultiNet		Mar 17, 2013	(Khurana et al. 2013)		
PathwayCommons	Pathway Commons v9	July 21, 2017	(Cerami et al. 2011)		
PID	Pathway Commons v9	Jul 27, 2015	(Schaefer et al. 2009)		
Reactome	v60	April 20, 2017	(Fabregat et al. 2016; Joshi-Tope et al. 2005; Croft et al. 2014; Vastrik et al. 2007; Croft et al. 2011; Matthews et al. 2009)		
ReactomeFI	Version 2017	February 27, 2017	(Wu et al. 2010)		
STRING	v10.5	May 14, 2017	(Szklarczyk et al. 2017; Franceschini et al. 2013; Von Mering et al. 2005; Von Mering et al. 2003; Von Mering et al. 2007; Jensen et al. 2009; Szklarczyk et al. 2011; Szklarczyk et al. 2015; Snel et al. 2000)		

Table S2. P-Values of Molecular Network Interaction Property Association with Network-Size Adjusted Performance for Each Collection of Gene Sets via ANOVA. *Related to Figure 3.* 

Interaction Property	Disease Gene Sets
Low-Throughput	0.32
High-Throughput	0.15
Scored	0.09
Co-Citation	0.54
Co-Complex	0.68
Co-Expression	0.09
Genetic	0.21
Metabolic	0.80
Non-Protein	0.10
Orthologous	0.23
Pathway	0.06
Regulation	0.14
Shared Domain	0.22
Signaling	0.72

Table S3. Average Ranked Performance on DisGeNET Gene Sets With and Without Filtering Human-Only Co-Citation Exclusive Interactions From STRING and HumanNet. *Related to Figure 3.* 

Network Name	Filtered Networks	Full Networks
STRING	2.168	2.397
ConsensusPathDB	3.052	3.148
GIANT	5.132	5.296
HumanNet	7.760	5.439
GeneMANIA	5.213	5.442
InBioMap	6.300	6.561
ReactomeFI	7.031	7.249
Reactome	7.570	7.753
PathwayCommons	9.711	9.890
IRefIndex	11.052	11.202
MultiNet	11.969	12.058
HINT	13.090	13.164
BIND	13.271	13.388
BioGRID	13.655	13.711
Mentha	13.688	13.722
HPRD	15.063	15.110
IntAct	15.511	15.563
DIP	16.982	17.022
BioPlex	17.038	17.081
PID	17.637	17.664
HumanInteractome	18.108	18.141

 Table S4. Properties of Composite Networks Constructed By Adding Molecular

 interactions to Previous Composite Network. *Related to Figure 5.*

Composite Network Name	Network Added to Previous Composite Network*	Nodes	Edges	Avg Node Degree	Edge Density
CompositeNetwork+1	ConsensusPathDB	19,119	6,437,082	673.370	0.03522
CompositeNetwork+2	GIANT	20,175	9,437,208	935.535	0.04637
CompositeNetwork+3	HumanNet	20,299	9,681,620	953.901	0.04699
CompositeNetwork+4	GeneMANIA	20,557	14,577,547	1418.256	0.06899
CompositeNetwork+5	InBioMap	20,617	14,709,141	1426.894	0.06921
CompositeNetwork+6	ReactomeFI	20,989	14,741,927	1404.729	0.06693
CompositeNetwork+7	Reactome	20,991	14,764,475	1406.743	0.06702
CompositeNetwork+8	PathwayCommons	22,737	15,068,061	1325.422	0.05830
CompositeNetwork+9	IRefIndex	22,742	15,068,259	1325.148	0.05827
CompositeNetwork+10	MultiNet	24,566	15,114,254	1230.502	0.05009
CompositeNetwork+11	HINT	24,568	15,114,769	1230.444	0.05009
CompositeNetwork+12	BIND	24,571	15,154,676	1233.542	0.05021
CompositeNetwork+13	BioGRID	24,939	15,191,458	1218.289	0.04885
CompositeNetwork+14	Mentha	24,941	15,194,165	1218.409	0.04885
CompositeNetwork+15	HPRD	25,089	15,195,552	1211.332	0.04828
CompositeNetwork+16	IntAct	25,089	15,195,597	1211.335	0.04828
CompositeNetwork+17	DIP	25,089	15,195,597	1211.335	0.04828
CompositeNetwork+18	BioPlex	25,349	15,199,603	1199.227	0.04731
CompositeNetwork+19	PID	25,349	15,199,603	1199.227	0.04731
CompositeNetwork+20	HumanInteractome	25,355	15,199,639	1198.946	0.04729

\* Starting with STRING.

 Table S5. Properties of Parsimonious Composite Networks Constructed By Increasing

 the Threshold of Support for Each Edge. Related to Figure 5.

Composite Network Name	Network Support Count	Nodes	Edges	Avg Node Degree	Edge Density
CompositeNetwork-1	1	25,355	15,199,639	1198.946	0.04729
CompositeNetwork-2*	2	19,781	2,724,724	275.489	0.01393
CompositeNetwork-3	3	18,278	894,579	97.886	0.00536
CompositeNetwork-4	4	17,275	490,481	56.785	0.00329
CompositeNetwork-5	5	16,625	359,307	43.225	0.00260
CompositeNetwork-6	6	16,148	279,976	34.676	0.00215
CompositeNetwork-7	7	15,221	212,513	27.924	0.00183
CompositeNetwork-8	8	14,266	147,009	20.610	0.00144
CompositeNetwork-9	9	12,788	98,221	15.361	0.00120
CompositeNetwork-10	10	11,065	64,182	11.601	0.00105
CompositeNetwork-11	11	9,487	45,351	9.561	0.00101
CompositeNetwork-12	12	8,208	31,348	7.638	0.00093
CompositeNetwork-13	13	6,494	17,906	5.515	0.00085
CompositeNetwork-14	14	4,911	10,581	4.309	0.00088
CompositeNetwork-15	15	3,533	6,145	3.479	0.00098
CompositeNetwork-16	16	2,375	3,361	2.830	0.00119
CompositeNetwork-17	17	1,496	1,773	2.370	0.00159
CompositeNetwork-18	18	795	790	1.987	0.00250
CompositeNetwork-19	19	358	277	1.547	0.00433
CompositeNetwork-20	20	84	55	1.310	0.01578
CompositeNetwork-21	21	7	4	1.143	0.19048

\*CompositeNetwork-2 is also the parsimonious composite network referred to as PCNet