Finding independence graphs for clinical trial adverse event data

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Contents:

Adverse events

Element of safety data collected in a clinical trial.

Adverse events:

E.g. MedDRA preferred terms.

Many terms (often several hundred) reported in any particular trial.

Can be represented as sparse binary data.

Interest in adverse events:

- High/low frequency,
- Possible relationship with treatment,
- Relationships with other adverse events,
- Time to an adverse event.

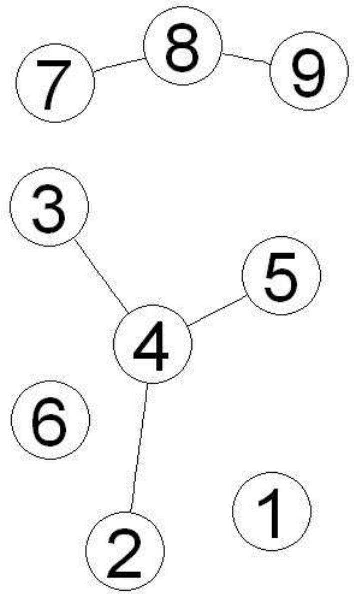
Focus here on interesting relationships,

building graphs in each treatment group,

separately and in combination.

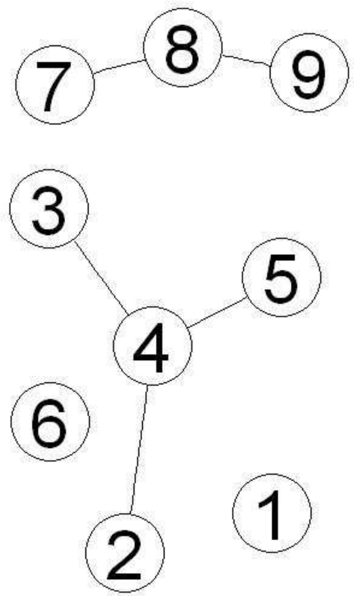
Some graph theory

- A graph consists of a set of vertices and a set of edges.
- In this example,
  $V = \{1, 2, 3, 4, 5, 6, 7, 8, 9\}$
  and
  $E = \{(2, 4), (3, 4), (4, 5), (7, 8), (8, 9)\}$.



Conditional independence graphs

- Each vertex, i is associated with a random variable X_i.
- An edge (i, j) is not in the edge set if and only if $X_i \perp\!\!\!\perp X_j \mid X_{V \setminus \{i,j\}}$.
- In example, $X_2 \perp\!\!\!\perp X_5 \mid X_{\{1,3,4,6,7,8,9\}}$.
- Equivalence of Markov properties give $X_2 \perp\!\!\!\perp X_5 \mid X_4$.



Mutual information, MI

Require a test statistic/measure of cond.indep.

Definition : the mutual information between discrete random variables X_1 and X_2 is

$$MI = \sum_{x_1,x_2} p(x_1,x_2) \log \frac{p(x_1,x_2)}{p(x_1)p(x_2)}.$$

MI measures the reduction in uncertainty in one random variable due to knowledge of the other.

- $X_1 \perp\!\!\!\perp X_2$ if and only if $MI = 0$.

The search algorithm

With 50 variables require 1225 tests of pairwise indep, and then more of cond.indep.

Variation on the PC algorithm:

- Start with the complete graph with edges between all vertices;
- remove edges from the graph using pairwise indep test;
- remove further edges using logistic regression of each variable on current neighbours;
- repeat until convergence.

Issues in search

- Alternative test statistics for conditional independence.
- Conditioning leads to sparse tables.
- Multiple testing (FDR procedure).
- Order of testing, through nodes, neighbourhoods, sequential updating.

Training data

Subset of data from a survival study in breast cancer

- 3000 patients in the training dataset.
- Three treatment groups, (A, B and A$+$B), with around 1000 patients in each group.
- 624 different adverse events.
- $1 =$ patient experienced adverse event,
  $0 =$ patient never experienced adverse event.
- 181 events have a frequency greater than 15 cases (0.5%),
  85 events have a frequency greater than 50.

Example of an AE contingency table

Treatment Group A, 996 patients:

	Neck pain		
Nausea	No	Yes	
No	890	20	910
Yes	83	3	86
	973	23	996

	Vomiting		
Nausea	No	Yes	
No	903	7	910
Yes	67	19	86
	970	26	996

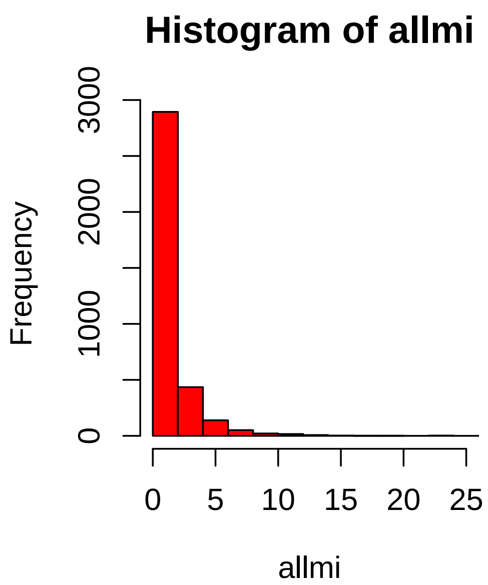
- (Chisq,MI) L$=(0.51, 0.38)$, R$=(67.97, 50.41)$.
- The (yes,yes) cells are relatively sparse.
- Further conditioning infeasible,

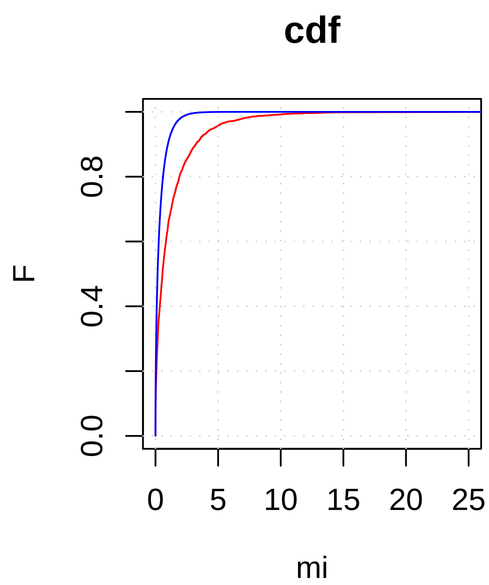
eg Nausea $\times$ Vomiting $|$ NeckPain$=$yes, has only 23 cases.

Are there any associations?

Consider combined AB data with 2020 cases and 85 AEs with at least 50 cases.

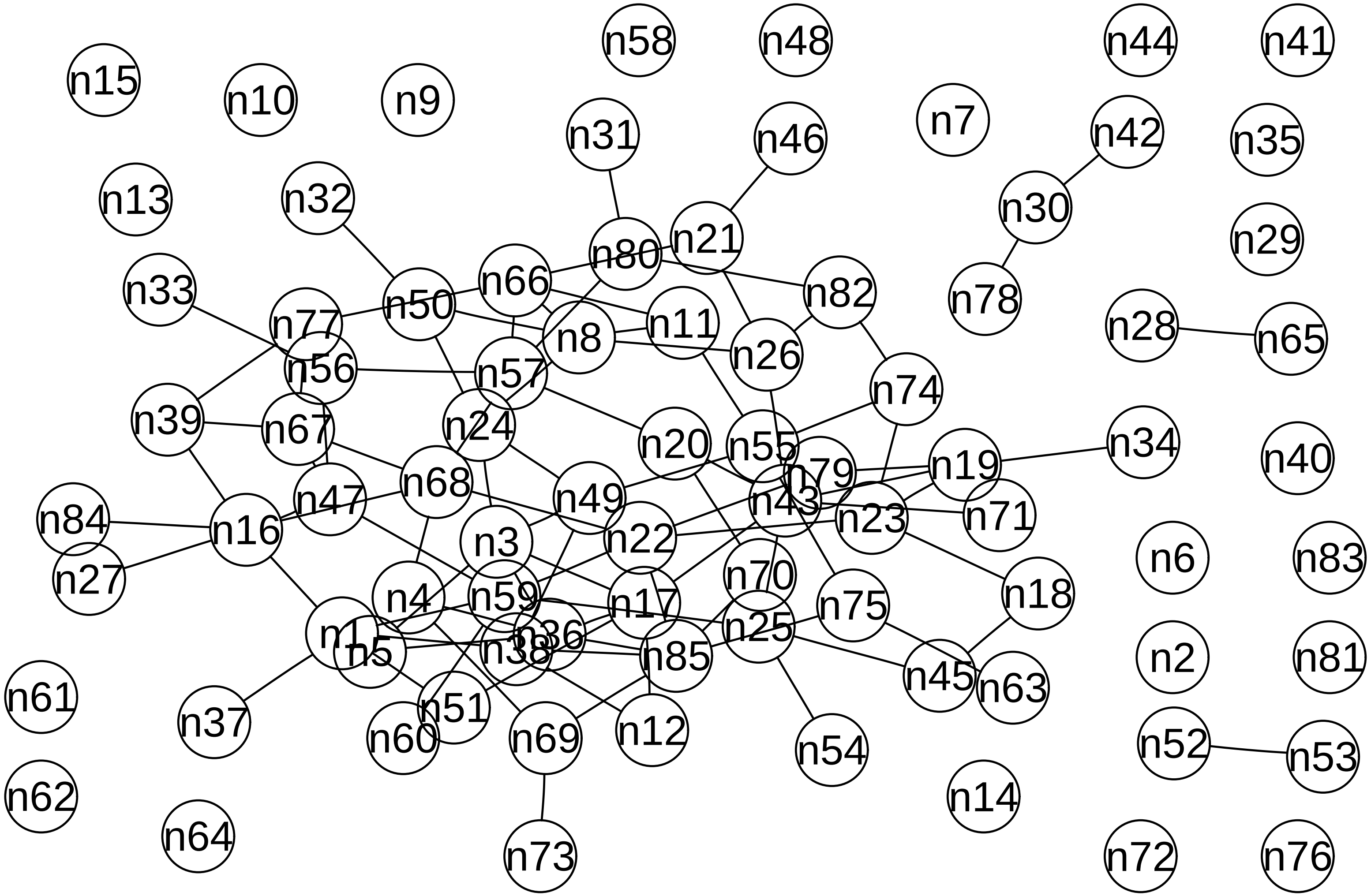
Associations between AE generally small, largest MI 50mbits (Vomiting,Nausea).



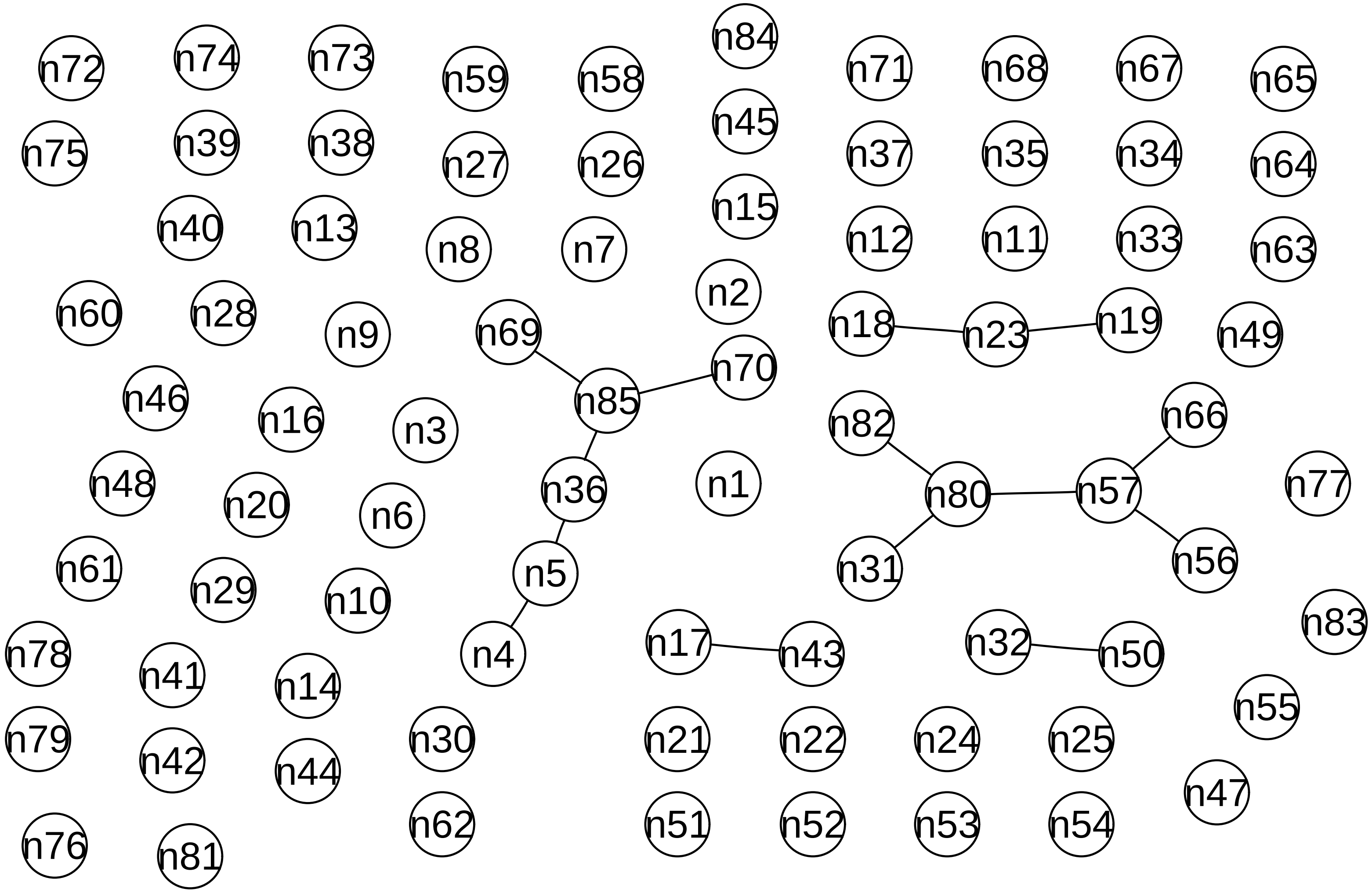


Empirical cdf overplotted with chisq$_1$ cdf (blue).

TrA: no FDR, $\alpha = 0.01$ 94 edges



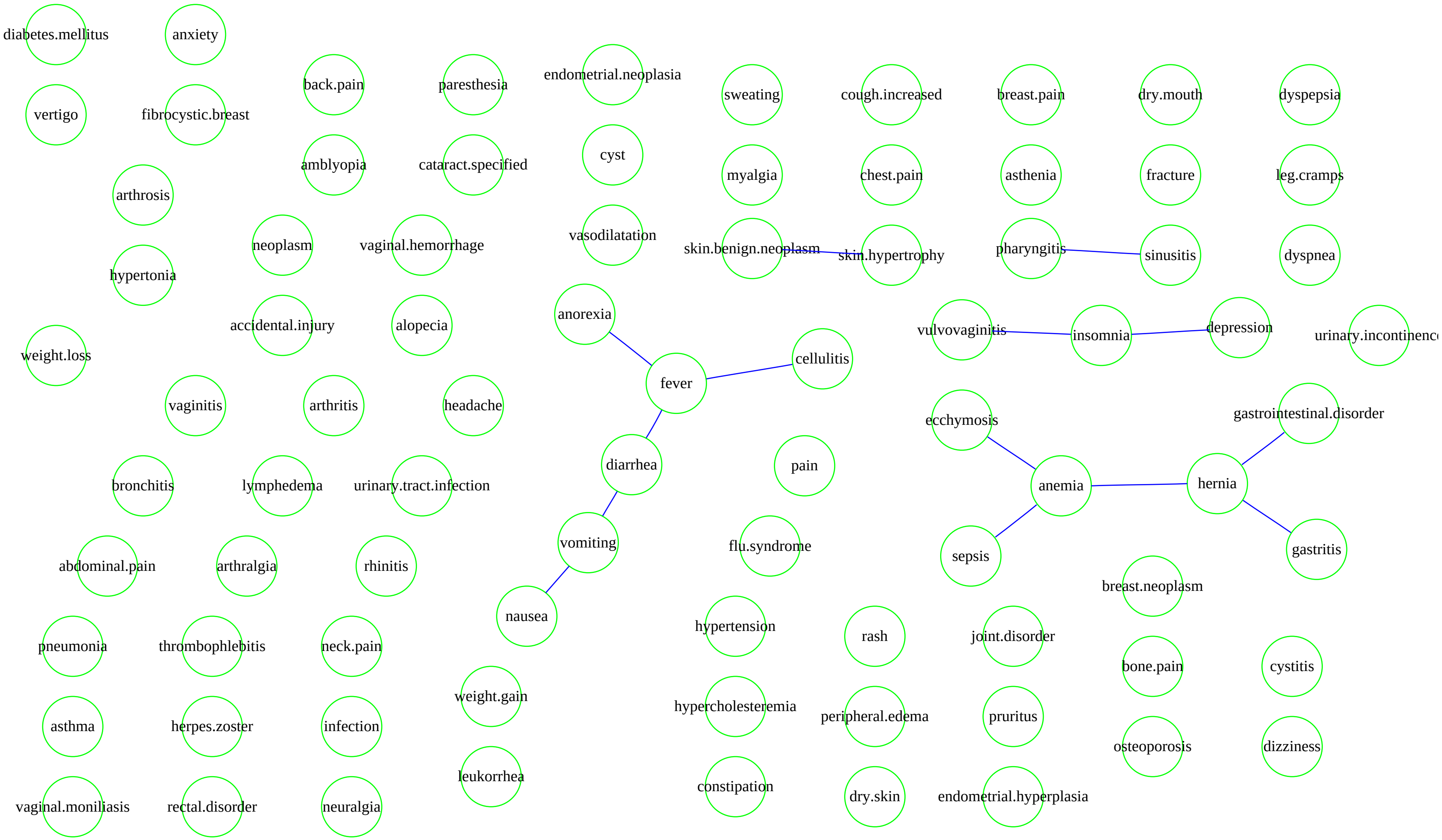
Tr A: with FDR $\alpha = 0.10$, 14 edges



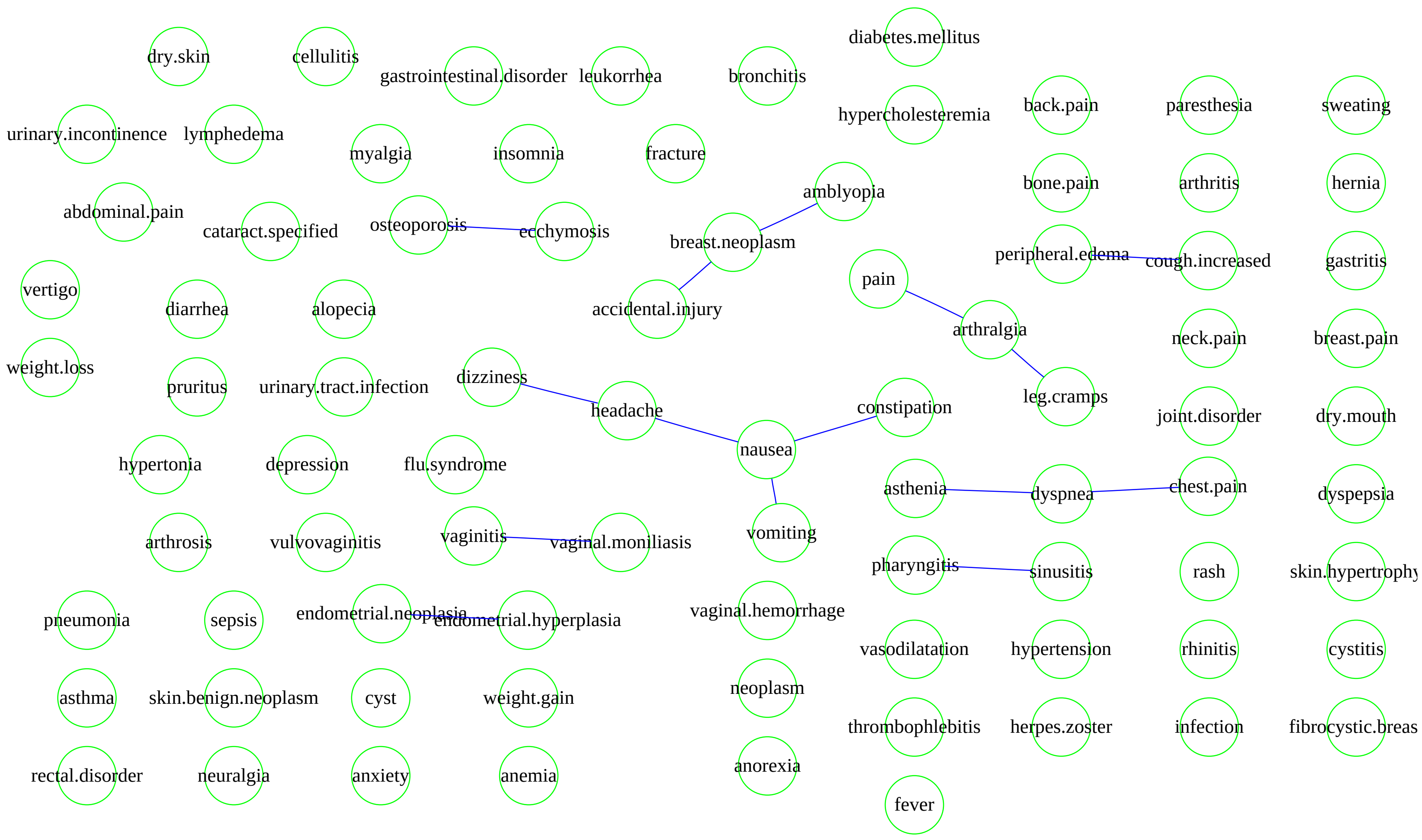
Remarks

The graphs differ substantially according to the settings of the Type1 error α and whether or not the FDR procedure is employed.

Tr A: labels, FDR $\alpha = 0.10$



Tr B: labels, FDR $\alpha = 0.10$



Remarks

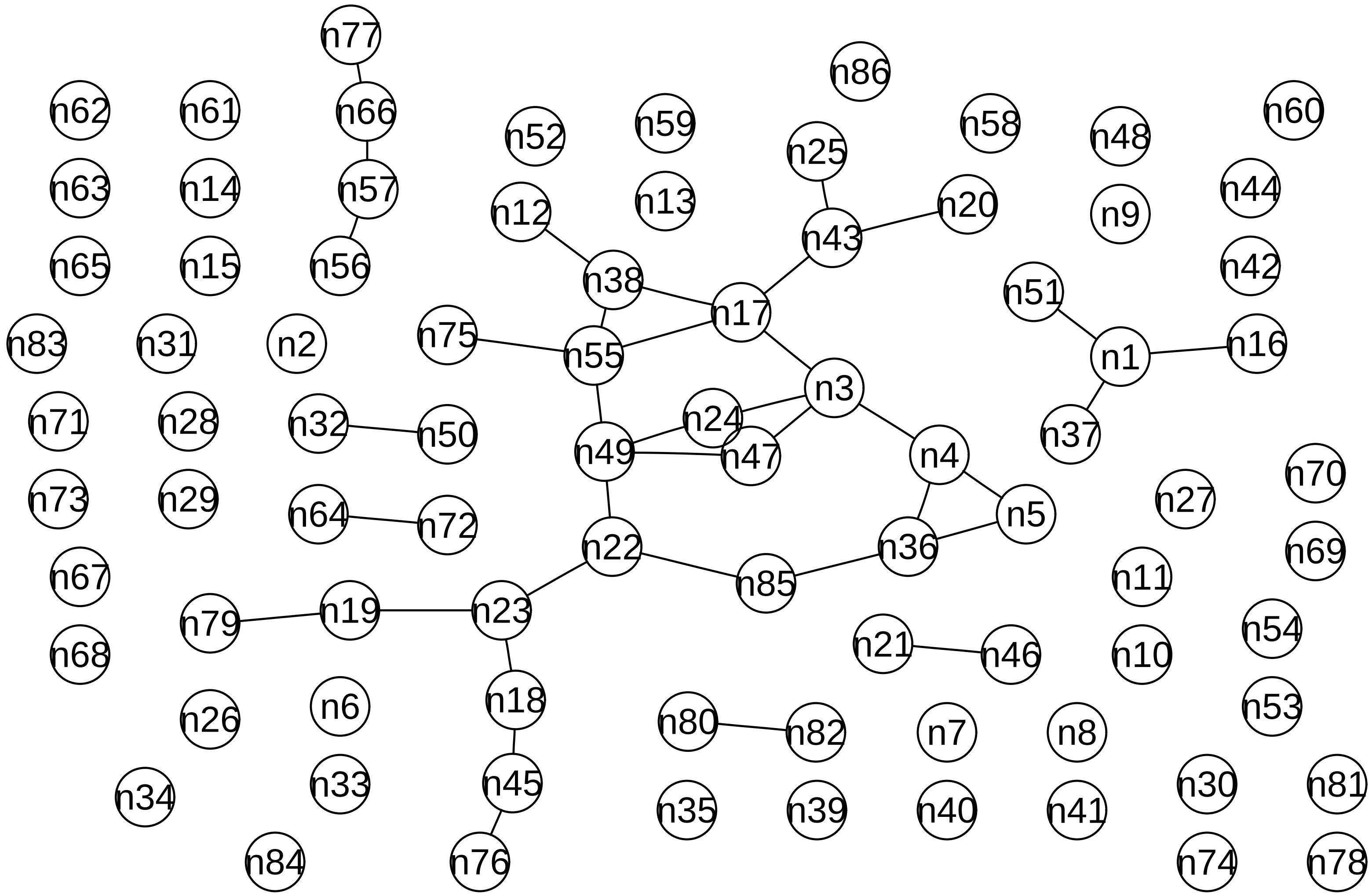
The graphs for both treatments are sparse.

There are similar number of edges, but different AEs are connected.

Some associations make sense e.g. Nausea and vomiting..., Pharyngitis and sinusitis.

Others are less obvious.

Tr AB: FDR $\alpha = 0.01$

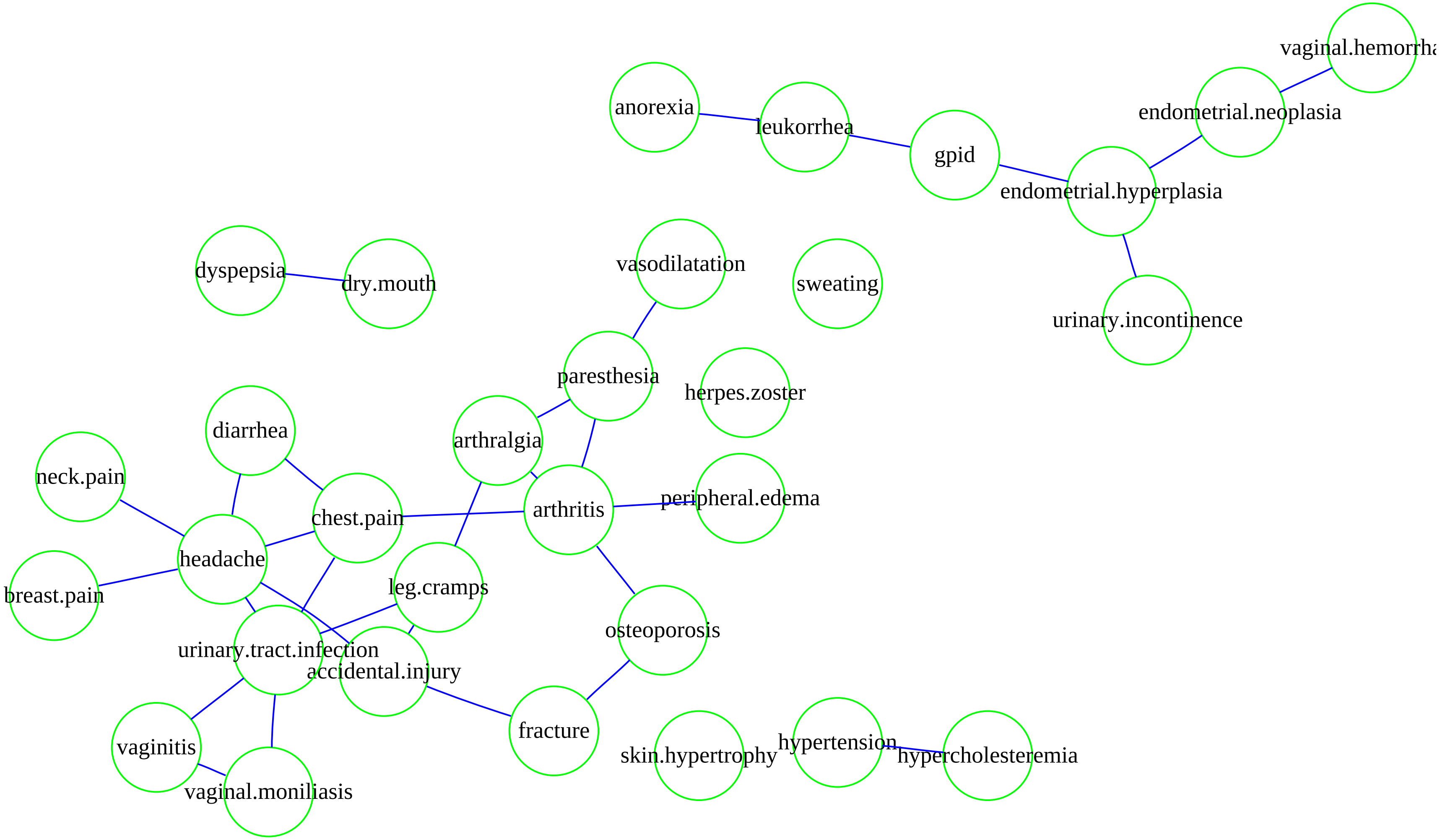


This last graph combined treatments A and B, together with a treatment indicator.

With $\alpha = 0.10$ it has 408 edges, so have used $\alpha = 0.01$.

However the treatment indicator is gpid=n86 is not connected, as its edges are swamped.

Tr AB: AEs associated with gpid, FDR $\alpha = 0.10$



Concluding remarks

- Independence graphs grants some insight into relationships between treatments and AEs, and between different AEs.

- Graphs are sensitive to algorithmic settings, so potentially unstable.

- Intuitively, identifying how AEs cluster together (i.e. syndrome detection) should be useful, but empirically, its clinical value yet unproven:
  some associations are obvious (nausea + vomiting) and uninteresting... others difficult to interpret and easy to dismiss as spurious.

- Further investigation of these issues underway.