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Assumptions and Consequences of Comparative Effectiveness Analysis Using Data Mining

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ABSTRACT

Comparative effectiveness analysis often results in the rationing of treatment due to cost considerations; the definition of futility care is similar. One of the unintended consequences of these concepts is to diminish successful treatment of patients on the margins. For example, the gestational age of neonates is decreasing as successful treatments are discovered in the course of practice. Similarly, treatments for HIV and cancer improved outcomes as newer medications were combined with older treatments. We want to examine trends in the use of treatments from their initial approval to see how the treatments spread through patient conditions and severities. We also want to examine whether a focus on medications results in higher treatment costs elsewhere. We will use the patient conditions datafile and the pharmacy database from the Medical Expenditure Panel Survey (MEPS) in order to investigate the spread of treatments as well as the AERS database of voluntary reporting of adverse events (Adverse Event Reporting System). The MEPS contains information concerning the use of pharmaceuticals from 1996 through 2008. We use the AERS reporting for 2009. SAS Enterprise Guide will be used to preprocess the data so that the spread of treatments can be identified. We will then use association rules to compare patient conditions in relationship to treatments by year. If such treatments are denied because they are not cost effective, such a spread in treatments will be discontinued and some medical advancements will not take place.

INTRODUCTION AND BACKGROUND

Once a comparative model has been defined, it usually becomes "locked in concrete" so that it is impossible to change results and decisions based upon a changing healthcare environment. Moreover, comparative models can be used to prevent changes because treatments are denied with no ability to treat patients on the margin where innovations frequently take place, resulting in a loss of medical advancement. This can be seen easily by the refusal of the British organization responsible for comparative effectiveness analysis to reconsider its model after it was judged in court to be seriously flawed. Moreover, the modeling defines the value of a human life in terms of remaining life and productivity without considering any moral issues surrounding the value of life.

Background in Comparative Effectiveness Analysis

The National Health Service in Britain has been using comparative effectiveness analysis for quite some time. The National Institute for Clinical Excellence (NICE) has defined an upper limit on treatment costs, and if the cost exceeds this pre-set limit, then the treatment is denied. It does not matter if the drug is effective or not. That means that there are many beneficial drugs that are simply not available to patients in Britain; fully 25% of cancer patients are denied effective chemotherapy medications. (Steinbrook 2008; Hope 2009)

NICE does not always compare drug A to drug B to see which is more effective at lower cost. Instead, the organization compares the cost of a drug to the value the organization places on your life. If it costs too much to keep you alive given your value, or to improve your life given your value, then you are denied treatment. While you may believe that such denial will not come to the United States, it already has. Oregon has become notorious in its Medicaid benefit, denying cancer drugs to patients, but making the same patients aware that assisted suicide is available. Currently, pharmaceutical companies have been subsidizing Oregon's Medicaid by providing these drugs to patients who have been denied by Medicaid. (Smith 2009) It has been suggested that euthanasia is cheaper than end of life care, and more cost-effective than treating many patients with terminal illnesses. (Sprague 2009) Just recently, the Food and Drug Administration has retracted approval of a chemotherapy drug for breast cancer on the basis of cost effectiveness rather than effectiveness. (Anonymous-WSJ 2010; Perrone 2010)

A comparative effective analysis starts with the perceived patient's utility given the disease burden. The QALY, or quality of life-adjusted years is an estimate of the number of years of life gained given the proposed intervention. Each year of perfect health is assigned a value of 1.0. A patient in a wheelchair is given a correspondingly lower value as is a patient who is elderly; this value is not clearly defined and is not always based upon patient input. The cost is then adjusted based upon this QALY, and if the cost exceeds a pre-determined threshold, the treatment is denied.

As an example concerning the use of comparative effectiveness analysis, we look at treatment medications for metastatic colorectal cancer as they were considered by the National Institute for Clinical Excellence (NICE). In

particular, there were six drugs considered; some were allowed while others were denied. We wanted to investigate the basis across these drugs for making these decisions, which were issued in two different reports.

The first report examined the drug, bevacizumab (Avastin). As discussed in the report, it was analyzed based upon a complete lack of data concerning a patient's quality of life. (Anonymous-bevacizumab 2009) Because of the lack of availability of such data, the model was completed based upon no knowledge of the quality of life, and it was assumed that there was no improvement in quality from the drug. The drug was rejected because the cost effectiveness based upon an additional 5 months of life was £39,136 to £69,439, beyond the limited threshold supported by the National Health Service. The report was based upon two clinical trials only. The actual cost was less than half the adjusted price, and this cost falls under the threshold value imposed by NICE. Therefore, the use of quality adjusted life years (QALY) essentially inflates the actual cost, given that the QALY cost is not one that is actually paid. Britain is the only western nation that disallows the use of Avastin for colorectal cancer.

In a similar fashion in the same report, a relatively new drug (cetuximab or Erbitux) that targets a specific gene marker was not approved, "No trials met the inclusion criteria for this systematic review. There is no direct evidence to demonstrate whether cetuximab plus irinotecan improves either health-related symptoms or OS [overall survival] in patients with EGFR-expressing metastatic CRC [colorectal cancer] who have previously failed on irinotecan-containing therapy." Nevertheless, it was estimated that the drug would provide an additional 4 months of life at a cost of £88,658 QALY, far beyond the threshold value imposed by NICE.

NICE revisited the drug, cetuximab in 2008 and 2009, changing their recommendation, "Cetuximab in combination with FOLFOX, or in combination with FOLFIRI, is recommended as an option for the first-line treatment of metastatic colorectal cancer where the metastatic disease is confined to the liver and the aim of treatment is to make the metastases resectable. " (Tappenden, Jones et al. 2007) FOLFOX and FOLFIRI are combination treatments for colorectal cancer. (Kohne 2010) However, there are some conditions that have to occur before Cetuximab can be prescribed, according to NICE: (Anonymous-NHS 2009)

- The primary colorectal tumour has been resected or is potentially operable.
- The metastatic disease is confined to the liver and is resectable.
- The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.
- The patient is unable to tolerate or has contraindications to oxaliplatin.

The average cost for the treatment is £22,796, which is considerably less than the QALY adjusted price assessed previously. The average survival was estimated to be 4.76 years rather than just a few months. This analysis reduced the QALY adjusted cost to £29,891, just below the NICE threshold. One of the reasons for this was that the patients who had a successful liver resection were given an estimated quality of life equal to that of the general population. In other words, by increasing the added survival and improving the definition of quality of life, the drug went from not acceptable to acceptable in terms of cost. It is highly problematic that the model outcome is so dependent upon the assumptions.

NICE is now considering an analysis for panitumumab, which is quite similar to cetuximab. (Saltz 2008) For this reason, NICE again revisited the drug, cetuximab. NICE also reconsidered bevacizumab. This third report is not yet copleted but NICE indicated that a final assessment would occur by June, 2011. (Anonymous-NICE 2010) The second assessment recommended cetuximab for a specific subgroup of patients but again recommended against bevacizumab. (Tappenden, Jones et al. 2007; Anonymous-NICE 2010)

It will be of interest to discover how NICE defines the quality of life assigned to panitumumab as its effectiveness is related to severe skin toxicity. (Nardone, Nicholson et al. 2010) Although temporary, this toxicity will lower the quality of life while on the drug. (Ouwerkerk and Boers-Doets 2010; Rother 2010) However, the improvement in overall and disease-free survival may be worth the temporary reduction in quality of life, as it has been shown to be very effective for those patients with the one gene marker in their cancer targeted by the drug, although it should not be combined with bevacizumab. (Morton and Hammond 2009; Cidon 2010; Mandrekar and Sargent 2010; Tombesi and Sartori 2010)

In contrast, the NICE report on Irinotecan, Oxaliplatin and Raltitrexed contained quite a bit of information concerning patient quality of life. All three drugs were approved for use. The report concluded with much lower QALY-adjusted costs and increased benefit for these drugs, resulting in a decision to fund their use for colorectal cancer. (Jones, Hummel et al. 2001)

METHODS

We want to work with health outcomes data, most commonly represented in the electronic medical record and in claims data. Many health outcomes databases are publicly available and we will work with those data sets in this study. These datasets require considerable preprocessing before they can be used to investigate outcomes, and we will give some of the preprocessing techniques briefly, referring the interested reader to a more complete discussion of preprocessing. (Cerrito and Cerrito 2010) Then, we demonstrate how market basket analysis, or how association rules can be used to examine comparative effectiveness parameters. We will work with the Medical Expenditure Panel Survey (MEPS), containing information concerning cost of treatment for a cohort of 30,000 individuals across 11,000 households. We will look at the impact of Medicare, part D as well as a comparison of costs of different medications for the chronic illness of COPD. The data are publicly available at http://www.meps.ahrq.gov/mepsweb/. In addition, we will look at the Adverse Event Reporting System (AERS) sponsored by the Centers for Disease Control. We will look at the voluntary complaints reported concerning medications used to treat colorectal cancer. The data set is located at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

Many-to-One Data Mergers

In claims data, prescriptions are separated from inpatient and outpatient treatments as well as office visits and home health care. Because all of this information is stored in different files in a one-to-many relationship with a patient's identification number, the most important aspect of using these databases is to convert them to a one-to-one relationship after filtering down to the condition under study. We take advantage of the data step and the use of summary statistics to do both. Each patient claim is identified by an ICD-9 code as to the primary reason for the medication or treatment. Osteoporosis, for example, is identified by the codes, 733.0x where x can be a digit from 0 to 9 (http://icd9cm.chrisendres.com/). Similarly, the code 496.xx represents COPD. Each of the datasets has a column for the primary code. We can use an if...then statement in a data step to isolate patients with a specific condition.

Once the different data sets have been filtered down to a specific condition, we need to convert them to a one-to-one relationship. We use the following code:

```
TITLE;
TITLE1 "Summary Statistics";
TITLE2 "Results";
FOOTNOTE;
FOOTNOTE1 "Generated by the SAS System (&_SASSERVERNAME, &SYSSCPL) on
%TRIM(%QSYSFUNC(DATE(), NLDATE20.)) at %TRIM(%SYSFUNC(TIME(), NLTIMAP20.))";
PROC MEANS DATA=WORK.SORTbyID
       FW=12
       PRINTALLTYPES
       CHARTYPE
       NWAY
       VARDEF=DF
              MEAN
              STD
              MIN
              MAX
              N      ;
       VAR TOTTCH06 OBTTCH06 OPVTCH06 OPOTCH06 AMETCH06 AMATCH06 AMTTCH06
AMTOTC06 ERDTCH06 ZIFTCH06 IPFTCH06 DVTOT06 DVOTCH06 HHNTCH06 VISTCH06 OTHTCH06
RXTOT06;
       CLASS cost_Sum /    ORDER=UNFORMATTED ASCENDING;

RUN;
```

We then choose one of the datasets to serve as the primary set and merge the datasets using a left join or a right join, depending upon the order of the data sets, using PROC SQL.

```
PROC SQL;
   CREATE TABLE SASUSER.QUERY_FOR_SUMMARYOFCONDITIONS_SA AS
         SELECT t1.patientID,
             t1.remaining variables from dataset,
             t2.variables from second dataset
```

```
FROM claims.summaryofconditions AS t1 RIGHT JOIN claims.h105 AS t2 ON
(t1.patientID = t2.patientID);
QUIT;
```

We will demonstrate how the results can be used for a direct comparison of costs. In addition, we have to be concerned about whether medication is discontinued, or if the patient switched to a different one. To find this information, we use the following code:

```
proc transpose data=medications out=medicationbyid
     prefix=med_;
    id patientid;
run;
```

Association Rules, or Market Basket Analysis

We use SAS Enterprise Guide to preprocess the data; we use SAS Enterprise Miner for the association rules. Because the data are in separate data files with one related to medications and another related to emergency department visits in considering the example of COPD, we will need to combine them in some way. Similarly, we will look at complaints from chemotherapy treatment, which have similar issues with separate data files.

An association rule is of the form X→Y, meaning that X and Y are related such that if a patient has treatment X, then that same patient will generally have treatment Y. We can use association rules in a different way to examine relationships between patient conditions, or relationships between different treatments. We will demonstrate how these association rules can be used to examine patient care.

In addition to the antecedent X and the consequent Y, an association rule has two numbers that express the degree of uncertainty about the rule. In association analysis, the antecedent and consequent are sets of items that are disjoint ($X \cap Y = \emptyset$). The first number is called the support for the rule. It is the number of times that the combination appears. The support is simply the number of transactions in the denominator with all items in the antecedent and consequent parts of the rule in the numerator. The other number is known as the confidence of the rule. Confidence is the ratio of the number of transactions that include all items in the consequent as well as the antecedent to the number of transactions that include all items in the antecedent.

The support is equal to the number in common divided by the total number of transactions. The rules X→Y and Y→X can have different confidence values, but will have the same support values. The expected confidence is equal to the number of consequent transactions divided by the total number of transactions. The last measure of the strength of an association is the lift, which is equal to the ratio of the confidence to the expected confidence; that is, lift=confidence / expected confidence.

RESULTS

Example of COPD Medications

For our first example using data summaries and association rules, the data are from the Medical Expenditure Panel Survey, and contain all encounters with healthcare providers for a cohort of over 30,000 individuals and 11,000 households. The data are publicly available from the federal government and are located at http://www.meps.ahrq.gov/mepsweb/. We specifically look at patients with a diagnosed condition of COPD and who are taking COPD medications. We first look at summaries of information for the years 2004-2008 for the prescriptions for COPD (Table 1).

Table 1. Average Total Medication Costs for Patients with COPD

Payer	2004	2005	2006	2007	2008
Self-Pay	465.77	334.41	303.79	430.93	206.66
Medicare	30.81	104.16	454.85	445.32	218.82
Medicaid	168.90	292.01	203.29	96.39	111.92
Private Insurance	207.66	122.99	80.58	157.63	215.42
Total Cost	903.83	901.77	1185.68	1257.27	853.03
Number of Patients	72	86	91	101	97

Note the increase in the costs to Medicare in 2006, the first year of Medicare, part D. Notice that there is a considerable drop in cost in 2008 that is not as readily explainable. The intervention of the federal government is quite apparent in the years 2006 and 2007 in terms of the shift from self-payment, Medicaid, and private insurance to the increase in Medicare costs. There is no obvious government intervention in 2008 that results in lower medication costs for that year. Because such a decrease can result from the market, the models used for comparative

effectiveness analysis cannot predict a market cost reduction. Denial of treatment based upon a non-changing medication cost can mislead and deprive patients of crucial medications that are effective and that are cost effective once the market has done its work. In addition, as Medicare represents a substantial proportion of the medication market, it could be that the government is leveraging the cost. We want to see if there is a reduction in costs in medications that might explain this difference. In order to do this, we first need to examine the specific medications, separating those used to treat COPD from those used to treat various co-morbidities. These are given in Table 2.

Table 2. Medications Used to Treat COPD

drug_names	Frequency	Percent	Cumulative Frequency	Cumulative Percent
albuterol	868	17.34	868	17.34
not copd	788	15.74	1656	33.09
advair	717	14.33	2373	47.41
spiriva	503	10.05	2876	57.46
combivent	354	7.07	3230	64.54
prednisone	222	4.44	3452	68.97
ipratropium	188	3.76	3640	72.73
theophylline	164	3.28	3804	76.00
singulair	141	2.82	3945	78.82
xopenex	135	2.70	4080	81.52
flovent	105	2.10	4185	83.62
atrovent	99	1.98	4284	85.59
serevent	92	1.84	4376	87.43
pulmicort	86	1.72	4462	89.15
duoneb	74	1.48	4536	90.63
proair hfa	55	1.10	4591	91.73
formoterol	40	0.80	4631	92.53
foradil	36	0.72	4667	93.25
qvar	35	0.70	4702	93.95
proventil	34	0.68	4736	94.63
mucinex	31	0.62	4767	95.24
azmacort	28	0.56	4795	95.80
vwnrolin	24	0.48	4819	96.28
symbicort	21	0.42	4840	96.70
mometasone	19	0.38	4859	97.08
nasonex	16	0.32	4875	97.40
rhinocort	11	0.22	4886	97.62
uniphyl	10	0.20	4896	97.82
zyrtec	10	0.20	4906	98.02
nebulizer	8	0.16	4914	98.18
sodium chloride	8	0.16	4922	98.34
ellipse compact spacer	7	0.14	4929	98.48
maxair	7	0.14	4936	98.62
optichamber	7	0.14	4943	98.76
asmanex	6	0.12	4949	98.88
budesonide	6	0.12	4955	99.00
flonase	6	0.12	4961	99.12
fluticasone	6	0.12	4967	99.24
guaifenex	6	0.12	4973	99.36
benzonatate	5	0.10	4978	99.46
alupent	4	0.08	4982	99.54
methylprednisolone	4	0.08	4986	99.62

drug_names	Frequency	Percent	Cumulative Frequency	Cumulative Percent
easivent	3	0.06	4989	99.68
montelukast	3	0.06	4992	99.74
salmeterol	3	0.06	4995	99.80
mytussin	2	0.04	4997	99.84
tessalon perles	2	0.04	4999	99.88
veramyst	2	0.04	5001	99.92
broncho saline	1	0.02	5002	99.94
guaifenesin	1	0.02	5003	99.96
promethazine with codeine	1	0.02	5004	99.98
tiotropium	1	0.02	5005	100.00

There is a considerable difference between the top ten or fifteen medications compared to those prescribed only occasionally. Moreover, there are 788 medications used to treat conditions other than COPD that are listed with the condition of COPD. We next examine the costs by year for these medications. Table 3 shows the average total cost for each of the most commonly prescribed medications.

Table 3. Average Total Cost of Medications by Year

drug_names	N Obs	Label	Mean	Std Dev	Minimum	Maximum
advair	717	Total Payment for 2004	150.9529167	73.7807743	2.7200000	521.3400000
		Total Payment for 2005	156.2967333	42.7729920	5.4400000	313.3400000
		Total Payment for 2006	152.2180588	118.3118609	4.4900000	454.7500000
		Total Payment for 2007	230.2320513	113.5926554	3.3500000	739.9200000
		Total Payment for 2008	212.6258537	76.9567573	138.7800000	572.8900000
albuterol	868	Total Payment for 2004	36.5801357	40.9133041	2.9000000	178.7400000
		Total Payment for 2005	35.5006627	38.5341329	3.0500000	159.8600000
		Total Payment for 2006	46.9564615	86.1687120	1.9100000	380.9900000
		Total Payment for 2007	34.5703727	28.5899895	4.0000000	184.0700000
		Total Payment for 2008	30.8788000	28.7350018	7.6500000	161.7900000
atrovent	99	Total Payment for 2004	88.0729545	34.7586735	35.0000000	125.1600000
		Total Payment for 2005	56.6365957	18.8148325	35.3800000	80.3000000
		Total Payment for 2006	.	.	.	.
		Total Payment for 2007	151.2580000	70.0914122	80.0000000	241.3900000
		Total Payment for 2008	202.6333333	99.1887762	88.1000000	259.9000000
azmacort	28	Total Payment for 2004	124.2600000	.	124.2600000	124.2600000
		Total Payment for 2005	91.6714286	0.7700742	90.1200000	92.4300000
		Total Payment for 2006	136.7978571	114.1526273	28.0000000	300.8800000
		Total Payment for 2007	122.0500000	0	122.0500000	122.0500000
		Total Payment for 2008	.	.	.	.
combivent	354	Total Payment for 2004	87.0571212	32.0007029	33.1300000	196.6500000
		Total Payment for 2005	85.0869880	32.9132361	68.1000000	224.1000000
		Total Payment for 2006	119.5557292	49.1174597	6.6400000	199.0600000
		Total Payment for 2007	129.4711538	44.0419276	78.2000000	186.4600000
		Total Payment for 2008	118.8342105	57.0055290	40.1400000	305.3000000
duoneb	74	Total Payment for 2004	137.3430769	35.3327203	124.8000000	254.6800000
		Total Payment for 2005	149.7471429	63.5943798	3.0000000	254.6800000
		Total Payment for 2006	62.6690000	59.6943214	5.0000000	153.7500000
		Total Payment for 2007	136.2142857	49.5975680	7.2300000	183.9400000
		Total Payment for 2008	38.0300000	0	38.0300000	38.0300000
flovent	105	Total Payment for 2004	99.1170968	40.3294271	15.0000000	132.7200000
		Total Payment for 2005	90.5700000	31.7648686	10.0000000	129.7500000
		Total Payment for 2006	103.2740000	25.5165541	82.7900000	134.0000000
		Total Payment for 2007	91.2725000	26.0587044	83.7500000	174.0200000
		Total Payment for 2008	184.5800000	15.8664692	173.7700000	228.5400000

drug_names	N Obs	Label	Mean	Std Dev	Minimum	Maximum
foradil	36	Total Payment for 2004	151.0533333	55.9567881	86.4400000	183.3600000
		Total Payment for 2005	179.7500000	0	179.7500000	179.7500000
		Total Payment for 2006	87.4384615	65.9508913	40.0000000	179.7500000
		Total Payment for 2007	113.9666667	0.3755884	113.2000000	114.1200000
		Total Payment for 2008	363.2400000	0	363.2400000	363.2400000
formoterol	40	Total Payment for 2004	7.0000000	0	7.0000000	7.0000000
		Total Payment for 2005	81.4200000	0	81.4200000	81.4200000
		Total Payment for 2006	157.3557143	59.2497108	22.9900000	179.7500000
		Total Payment for 2007	8.0000000	0	8.0000000	8.0000000
		Total Payment for 2008	245.2223077	65.7929903	26.2500000	263.4700000
ipratropium	188	Total Payment for 2004	38.0981250	32.3225210	7.0000000	129.0200000
		Total Payment for 2005	98.0536364	66.2309895	10.0000000	176.4000000
		Total Payment for 2006	80.3115789	46.2043961	1.0000000	123.0500000
		Total Payment for 2007	103.8059649	91.0024634	7.2400000	285.6000000
		Total Payment for 2008	102.4983871	90.0811710	20.1600000	331.5000000
mucinex	31	Total Payment for 2004	13.9425000	4.3559836	11.5900000	21.0000000
		Total Payment for 2005	11.5900000	.	11.5900000	11.5900000
		Total Payment for 2006	13.1900000	0	13.1900000	13.1900000
		Total Payment for 2007	20.9546154	7.4925481	14.2900000	28.7300000
		Total Payment for 2008	.	.	.	.
nasonex	16	Total Payment for 2004	.	.	.	.
		Total Payment for 2005	71.0816667	1.5390961	67.9400000	71.7100000
		Total Payment for 2006	.	.	.	.
		Total Payment for 2007	80.3500000	0	80.3500000	80.3500000
		Total Payment for 2008	84.8500000	0	84.8500000	84.8500000
not copd	788	Total Payment for 2004	56.0927807	159.9067646	2.2200000	1286.45
		Total Payment for 2005	39.7125735	26.6002198	4.3600000	103.8400000
		Total Payment for 2006	58.2003175	52.2658414	2.9700000	184.0000000
		Total Payment for 2007	45.7626351	53.4137812	1.0000000	379.6400000
		Total Payment for 2008	29.8967969	29.2189518	1.0500000	126.5200000
prednisone	222	Total Payment for 2004	6.8131111	3.2223924	1.3200000	12.5800000
		Total Payment for 2005	6.8401667	4.3540367	2.0000000	22.1900000
		Total Payment for 2006	8.2933333	7.3414355	1.8800000	32.5900000
		Total Payment for 2007	5.1909375	3.9959967	1.0000000	14.5200000
		Total Payment for 2008	4.1673684	3.4744797	1.1700000	10.0000000
proair hfa	55	Total Payment for 2004	.	.	.	.
		Total Payment for 2005	.	.	.	.
		Total Payment for 2006	36.7200000	0	36.7200000	36.7200000
		Total Payment for 2007	32.2315789	1.6136958	30.3800000	35.4100000
		Total Payment for 2008	32.0364706	22.3917946	3.1000000	137.6100000
proventil	34	Total Payment for 2004	86.8650000	15.7500000	78.9900000	110.4900000
		Total Payment for 2005	.	.	.	.
		Total Payment for 2006	.	.	.	.
		Total Payment for 2007	67.2100000	33.3637618	36.5100000	101.7700000
		Total Payment for 2008	25.7223529	15.2918261	7.2700000	41.1800000
pulmicort	86	Total Payment for 2004	269.0800000	.	269.0800000	269.0800000
		Total Payment for 2005	136.6931818	27.2703616	15.0000000	145.8200000
		Total Payment for 2006	134.4692000	115.2716745	2.6700000	308.2500000
		Total Payment for 2007	214.1432000	125.1348492	154.5500000	562.8100000
		Total Payment for 2008	277.2753846	167.0337554	157.7600000	559.3100000
qvar	35	Total Payment for 2004	.	.	.	.
		Total Payment for 2005	66.5500000	0	66.5500000	66.5500000
		Total Payment for 2006	74.2600000	0	74.2600000	74.2600000
		Total Payment for 2007	92.0366667	49.8856821	63.1000000	190.0200000
		Total Payment for 2008	86.9125000	53.0868522	63.1000000	200.5400000

drug_names	N Obs	Label	Mean	Std Dev	Minimum	Maximum
serevent	92	Total Payment for 2004	84.3076471	2.2450878	82.9400000	88.3500000
		Total Payment for 2005	182.0218182	118.0383094	40.0000000	368.6400000
		Total Payment for 2006	91.1274194	28.0455605	36.5500000	127.0000000
		Total Payment for 2007	151.4536364	53.3544059	114.2500000	258.9900000
		Total Payment for 2008	.	.	.	.
singulair	141	Total Payment for 2004	130.1766667	50.3359540	45.5600000	180.8900000
		Total Payment for 2005	89.7630435	3.0432615	85.1400000	93.2500000
		Total Payment for 2006	91.8921154	25.1095105	35.4600000	114.2400000
		Total Payment for 2007	130.6942857	70.3149260	49.1400000	272.0000000
		Total Payment for 2008	105.3822222	2.8792481	101.5100000	108.9400000
spiriva	503	Total Payment for 2004	130.3322581	40.8324759	104.9500000	277.2000000
		Total Payment for 2005	123.2941667	64.5479832	14.4500000	312.4600000
		Total Payment for 2006	146.9679646	77.7569150	40.0000000	408.2400000
		Total Payment for 2007	139.5695580	26.6962996	3.3500000	362.2900000
		Total Payment for 2008	158.1334746	49.8340750	102.5900000	463.6700000
symbicort	21	Total Payment for 2004	.	.	.	.
		Total Payment for 2005	.	.	.	.
		Total Payment for 2006	.	.	.	.
		Total Payment for 2007	157.7900000	2.1555510	156.9100000	162.1900000
		Total Payment for 2008	182.5160000	8.6480203	167.0400000	189.8000000
theophylline	164	Total Payment for 2004	25.5965217	23.9074714	4.7500000	95.1200000
		Total Payment for 2005	52.5860000	56.5902592	12.9400000	152.5700000
		Total Payment for 2006	31.3161111	11.8943723	11.0200000	63.8700000
		Total Payment for 2007	12.2487755	6.2207039	7.1200000	42.7100000
		Total Payment for 2008	5.0000000	0	5.0000000	5.0000000
vwnrolin	24	Total Payment for 2004	25.0200000	38.9681799	9.6900000	117.0000000
		Total Payment for 2005	58.9500000	0	58.9500000	58.9500000
		Total Payment for 2006	.	.	.	.
		Total Payment for 2007	55.6700000	29.3727057	36.7100000	93.5900000
		Total Payment for 2008	40.0000000	0	40.0000000	40.0000000
xopenex	135	Total Payment for 2004	.	.	.	.
		Total Payment for 2005	32.0358333	38.7902903	3.0000000	192.0000000
		Total Payment for 2006	83.2496667	106.1364171	15.0000000	380.9900000
		Total Payment for 2007	177.7068571	171.2485772	11.3000000	516.9400000
		Total Payment for 2008	165.7150000	157.5172608	78.1000000	446.1400000

Table 3 does not show any obvious reason for an overall reduction in costs for 2008. While some of the medications show an increase in cost, others show a decrease. Therefore, we need to examine the costs in more detail to determine why there is a difference overall in 2008.

We also want to examine other costs that are associated with COPD where the medications could have an impact. Table 4 gives the cost for visits to the emergency department. There appears to be a spike in cost for emergency care in 2007 followed by a considerable drop in cost for 2008; a drop that corresponds to a similar drop in 2008 for the cost of medications. The spike in costs was related to a significant increase in the cost for the facility. Again, the reason for this spike is not known and should be investigated. It could very well mean that the medications are becoming more effective for patients to avoid the emergency department.

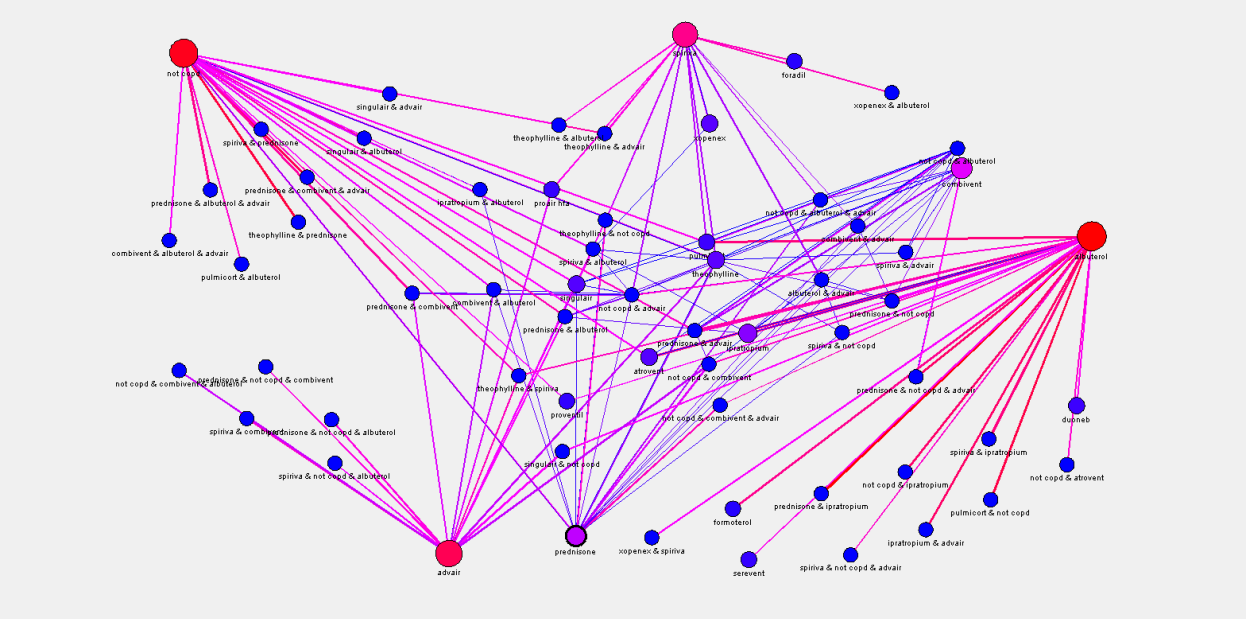
Table 4. Cost of Emergency Department Visits

Payer	2004	2005	2006	2007	2008
Self-Pay for Facility	67.88	23.69	46.81	38.46	62.59
Medicare for Facility	547.99	176.18	461.94	193.06	265.14
Medicaid for Facility	130.24	201.66	44.82	51.41	130.25
Private Insurance for Facility	95.47	99.57	61.63	1509.88	144.35
Total Cost for Facility	907.79	656.42	778.46	1863.20	860.54
Self-Pay for Physician	1.92	9.87	22.25	2.63	6.05
Medicare for Physician	91.93	75.22	120.28	52.94	61.69
Medicaid for Physician	29.10	69.41	8.38	28.30	21.38
Private Insurance for Physician	29.09	27.69	36.82	34.41	33.23
Total Cost for Physician	181.85	27.69	227.55	131.86	130.31

Payer	2004	2005	2006	2007	2008
Total Cost	1089.64	867.32	1006.01	1995.07	990.84
Number of Patients	43	44	46	32	33

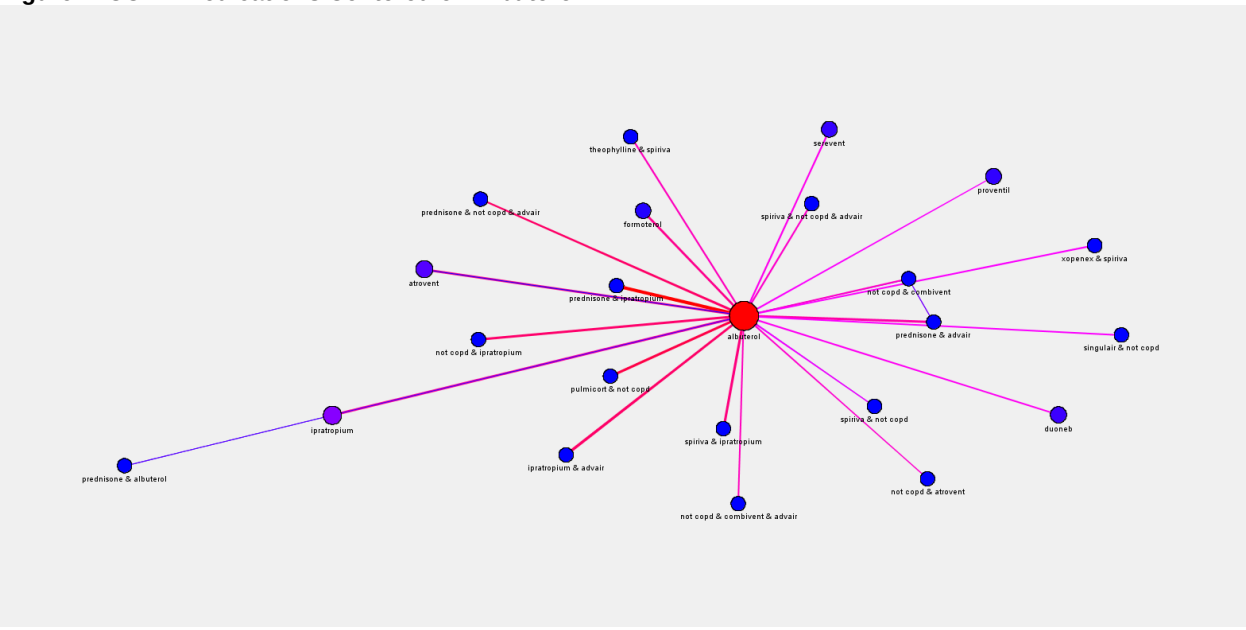
We next examine the prescription data using association rules. We can determine the relationship of multiple drugs, meaning that patients are taking drugs in combination or are switching drugs during the course of their treatment. Figure 1 gives the links between drugs as identified by patient identification number. There are four major centers located at Advair, Spiriva, Albuterol, and non-COPD drugs. Because of the difficulty in reading the complete link graph, Figure 2 focuses in on rules centered on the drug, Albuterol.

Figure 1. Link Graph for COPD Medications



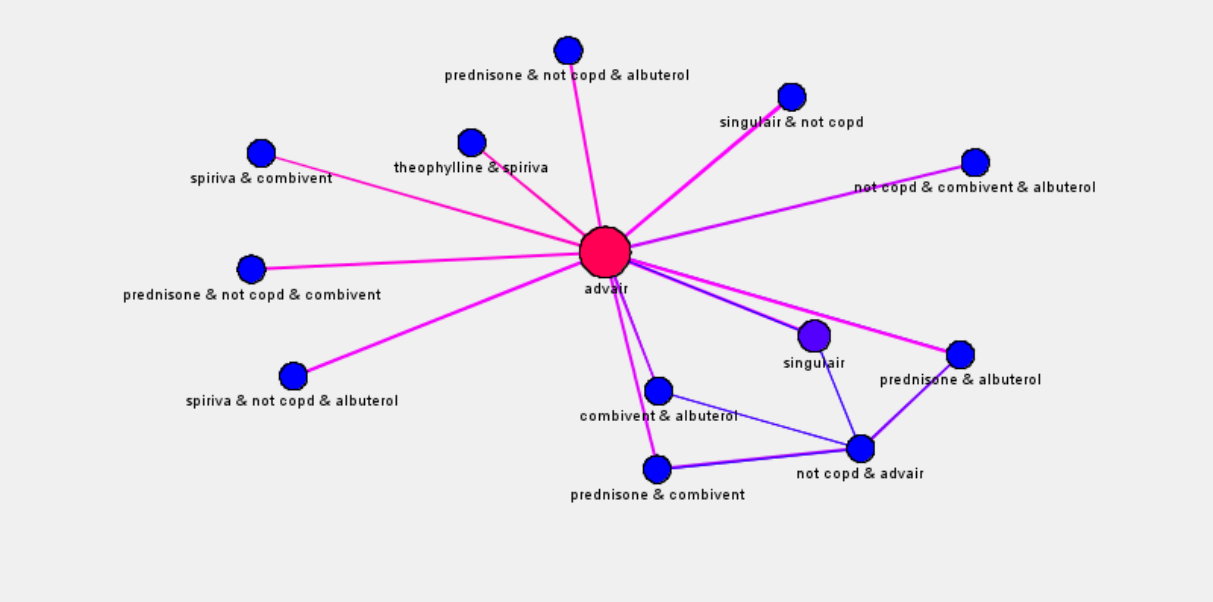
Albuterol is an emergency inhaler and should be used with some type of management medication; the drugs centered on Albuterol give the diversity and variety used by physicians for these management drugs.

Figure 2. COPD Medications Centered on Albuterol



Many of the nodes involve the use of Prednisone as well as Spiriva. Figure 3 shows the relationship centered at the drug, Advair.

Figure 3. COPD Medications Related to Advair



Advair has several connections to other management medications, suggesting that there is some switching going on because the initial medication is not working. Table 5 shows the combinations that are switched to Advair giving the rules table that accompanies the link graph; Table 6 shows the combinations switched from Advair. The different measures of the adequacy of the rule are defined by association rules that examine the strength of the treatment combinations.

Table 5. Medications Switched to Albuterol

Expected Confidence	Confidence	Support	Lift	Transaction Count	Left Hand of Rule
33.54	66.67	1.00	1.99	6.00	Theophylline & Spiriva
33.54	64.29	2.85	1.92	9.00	Spiriva & Combivent
33.54	60.00	2.85	1.79	9.00	Prednisone & not copd & Albuterol
33.54	60.00	1.90	1.79	6.00	Prednisone & not copd & Combivent
33.54	55.88	6.01	1.67	19.00	Spiriva & Albuterol
33.54	55.00	3.48	1.64	11.00	Singulair
33.54	54.55	3.80	1.63	12.00	Prednisone & Albuterol
33.54	54.55	1.90	1.63	6.00	Singulair & not copd
33.54	53.85	2.22	1.61	7.00	Theophylline & not copd
33.54	52.94	2.85	1.58	9.00	Spiriva & not copd & Albuterol
33.54	50.00	1.90	1.49	6.00	Proair HFA
33.54	50.00	2.22	1.49	7.00	Prednisone & Combivent
33.54	46.15	1.90	1.38	6.00	Not copd & Combivent & Albuterol
33.54	45.45	3.16	1.36	10.00	Theophylline
33.54	45.00	2.85	1.34	9.00	Not copd & Combivent
33.54	44.00	3.48	1.31	11.00	Combivent & Albuterol

Table 6. Medications Switched From Advair

Expected Confidence	Confidence	Support	Lift	Transaction Count	Right Hand of Rule
10.76	17.92	6.01	1.67	19.00	Spiriva & Albuterol
6.33	10.38	3.48	1.64	11.00	Singulair
6.96	11.32	3.80	1.63	12.00	Prednisone & Albuterol

Expected Confidence	Confidence	Support	Lift	Transaction Count	Right Hand of Rule
7.91	10.38	3.48	1.31	11.00	Combivent & Albuterol

This analysis suggests that there is some leveraging going on in terms of cost of the medications. We will continue to investigate these medications to find where the leveraging occurs.

Example of Colorectal Cancer Adverse Events

In this example, we use the AERS database (located at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm), which contains voluntary reports concerning adverse events related to various medications. Many attorneys have direct links to this reporting database and use it as a starting point for lawsuits. Since the reports are voluntary, the results of this analysis cannot be definitive; it will generate hypotheses that can be examined through claims databases and through the electronic medical record. In this analysis, we will focus on the medications used to treat colorectal cancer. In particular, we want to see if the complaints concerning Avastin are much more difficult than those of Oxaliplatin since NICE reports disallow Avastin while permitting Oxaliplatin based upon decisions concerning quality of life. We first look at the known side effects of the medications (Table 7). The list of side effects are located at http://www.chemocare.com/bio/oxaliplatin.asp for Oxaliplatin and http://www.chemocare.com/bio/avastin.asp for Avastin.

Table 7. Comparison of Side Effects of Oxaliplatin and Avastin

Side Effects of Oxaliplatin	Side Effects of Avastin
More Common	More Common
• Peripheral neuropathy- Numbness and tingling and cramping of the hands or feet often triggered by cold. This symptom will generally lessen or go away between treatments, however as the number of treatments increase the numbness and tingling will take longer to lessen or go away. Your health care professional will monitor this symptom with you and adjust your dose accordingly. • Nausea and vomiting • Diarrhea • Mouth sores • Low blood counts-Your white and red blood cells and platelets may temporarily decrease. This can put you at increased risk for infection, anemia and/or bleeding. • Fatigue • Loss of appetite	• Generalized Weakness • Pain • Abdominal pain • Nausea & vomiting • Poor appetite • Constipation • Upper respiratory infection • Low white blood cell count. (This can put you at increased risk for infection.) • Proteinuria (see kidney problems) • Nose bleed (see bleeding problems) • Diarrhea • Hair loss • Mouth sores • Headache
Less Common	Less Common
• Constipation • Fever • Generalized pain • Headache • Cough • Temporary increases in blood tests measuring liver function. (see liver problems). • Allergic reaction: a rare side effect, however, call for help immediately if you suddenly have difficulty breathing, your throat feels like it is closing, or chest pain. Other signs of allergic reaction include rash, hives, sudden cough, or swelling of the lips or tongue.	• Gastrointestinal perforation/ fistula formation/ wound healing complications • Hemorrhage (severe bleeding) • Hypertensive crisis (severe high blood pressure) • Nephrotic Syndrome - a condition marked by very high levels of protein in the urine (proteinuria), low levels of protein in the blood, swelling, especially around the eyes, feet and hands. This syndrome is caused by damage to the glomeruli (tiny blood vessels in the kidney that filter waste and excess water from the blood and send them to the bladder as urine). • Congestive heart failure in patients who have received prior treatment with anthracycline based chemotherapy, or radiation therapy to the chest wall.

Looking at these effects side by side, it is difficult to determine why one has a much lower disutility compared to the other. Many of the side effects are quite similar between the two drugs.

First line treatment for colorectal cancer generally consists of three drugs: 5-fluorouracil and folinic acid, and oxaliplatin. The three drugs in combination are abbreviated as FOLFOX. Avastin is added to this combination for metastatic colon cancer. If irinotecan is substituted for the oxaliplatin, the combination is identified as FOLFIRI. We will examine the first line treatment of FOLFOX in this analysis and include medications often administered to help to alleviate the side effects of the chemotherapy treatment. There are a total of 24,366 different complaints for 4,278 individuals in the AERS database for 2009. Table 8 summarizes the medications:

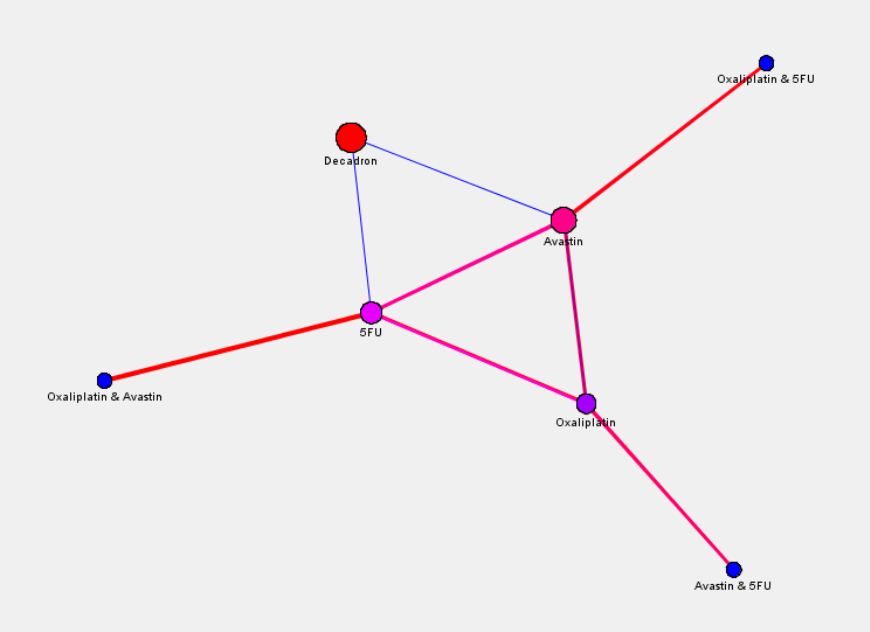
Table 8. Summary of First Line Colon Cancer Treatment

Drug	Frequency	Percent
5FU	4671	20.08
Aloxi	496	2.13
Avastin	6091	26.19
Decadron	9843	42.32
Leucovorin	1	0.00
Oxaliplatin	2155	9.27

Decadron is a steroid used for many different conditions, so the fact that it accounts for almost half of the complaints can be misleading; it is prescribed more often compared to the other drugs. Avastin also has a large number of complaints since it is used for multiple types of cancer. We will want to isolate the complaints for colorectal cancer.

We want to look at how the different drugs are connected in terms of complaints in the AERS database using association rules. Figure 4 shows the market basket analysis of complaints. It shows how complaints rather than treatments are linked together. It shows that Avastin is linked to both Oxaliplatin and 5FU, which suggests that it may be difficult to separate complaints concerning drugs that are given in combinations, and difficult to define the disutility of one drug over the combination of drugs. Yet comparative effectiveness analysis claims to do just that.

Figure 4. Link Graph of Market Basket Analysis of Voluntary Complaints



The link graph is a representation of the following association rules concerning the combination of drugs in the complaints. Table 9 gives these rules along with their transaction counts (number of complaints).

Table 9. Association Rules for Drug Combinations

Transaction Count	Rule
278	Avastin→5FU
278	5FU→Avastin
245	Oxaliplatin→5FU

Transaction Count	Rule
245	5FU→Oxaliplatin
238	Oxaliplatin→Avastin
238	Avastin→Oxaliplatin
152	Avastin→Decadron
104	5FU→Decadron
102	Oxaliplatin→Avastin & 5FU
102	Avastin & 5FU→Oxaliplatin
102	Oxaliplatin & Avastin →5FU
102	5FU→Oxaliplatin & Avastin
102	Oxaliplatin & 5FU→Avastin

Both the link graph and the table clearly demonstrate that it is very difficult to separate out complaints for just the one drug, Avastin, since the drugs are given in combination and the adverse events are experienced by patients who are taking these combinations.

We look now to the complaints of the various drugs. Figure 5 shows the overall complaints using a link graph. It shows four major centers and 3 minor centers in the link graph. Since the overall graph is difficult to read, Figures 6-9 show the four major centers.

Figure 5. Link Graph of Complaints for All Medications

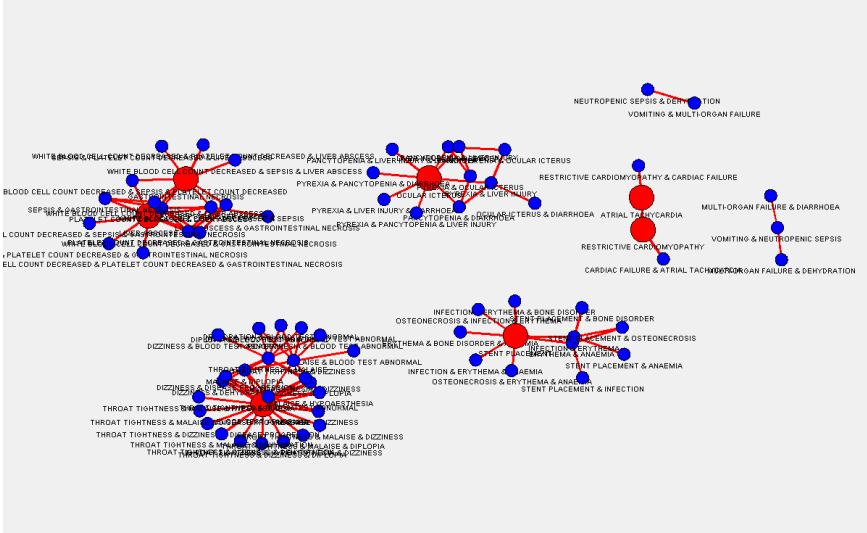
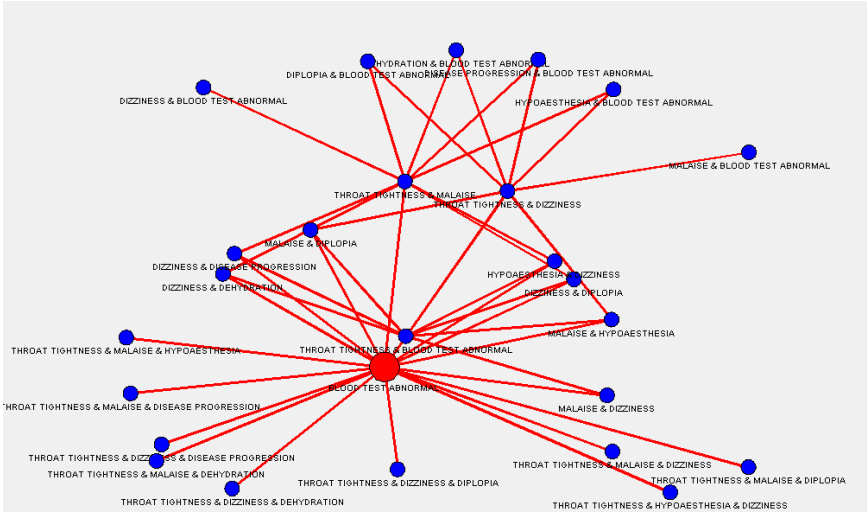


Figure 6. Pattern 1- Abnormal Blood Tests and Throat Tightness



The first pattern deals mostly with low blood counts, particularly low platelet counts and throat tightness. These are not unusual side effects of chemotherapy generally. (Castells, Tennant et al. 2008) The second pattern is for stent placement and infection; neither are unusual for medical procedures generally and these are not specific to chemotherapy. Therefore, they should not contribute to the disutility of any one drug. (Castells, Tennant et al. 2008)

Figure 7. Pattern 2-Stent Placement and Infection

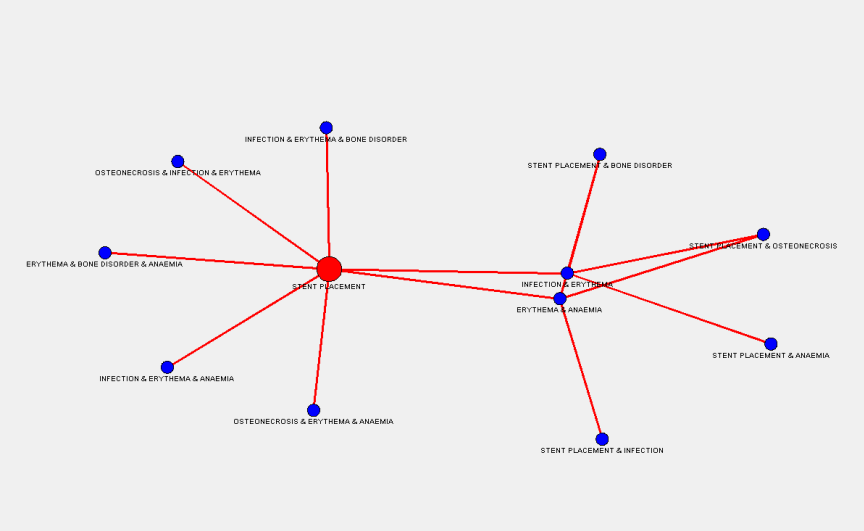


Figure 8. Pattern 3-Cell Counts and Sepsis

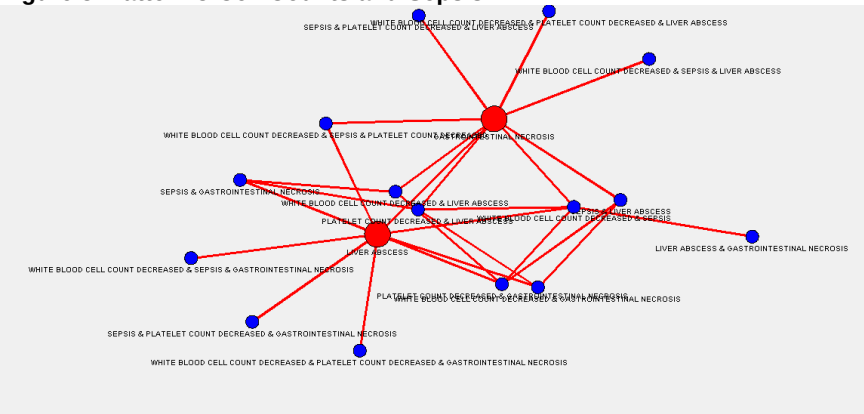
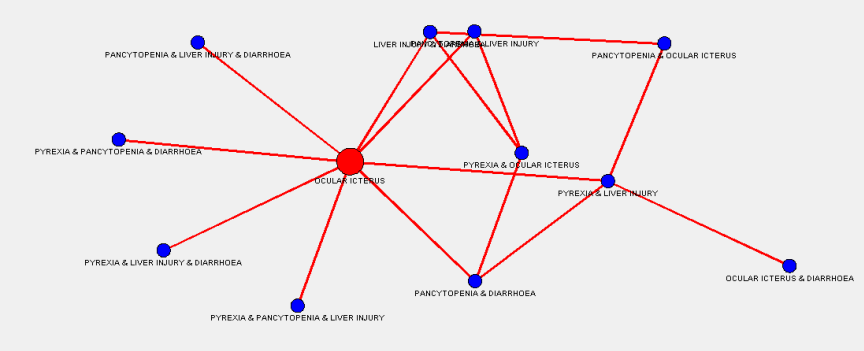


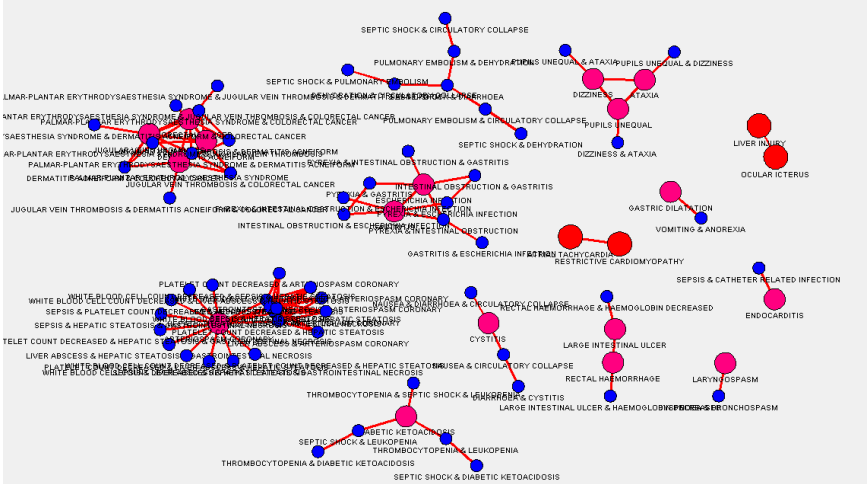
Figure 8 is very similar to the pattern shown in Figure 5 as it has to do with cell counts and infection. However, the infection of sepsis is much more severe than just general infections. The cell counts also focus on white cells rather than platelets as in Figure 5. While platelets are related to injury and blood clotting, white cells are related to the susceptibility to infection. These problems are very typical with chemotherapy generally and are specifically identified as side effects for both Oxaliplatin and Avastin.

Figure 9. Pattern 4-Jaundice



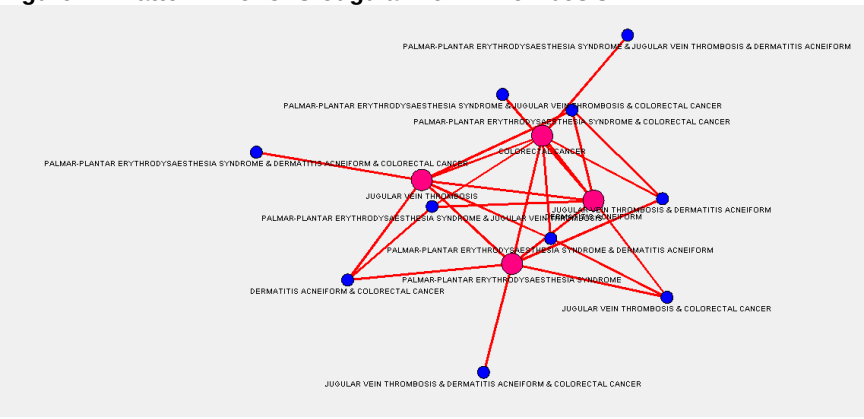
Many with colon cancer have metastasizes in the liver, so a complaint of jaundice is not so much from the chemotherapy but from progression of the disease. We next isolate the drug, 5FU to see if there are some complaints specific to the drug. Figures 10-14 show the results.

Figure 10. Link Graph of Associated Complaints for 5FU



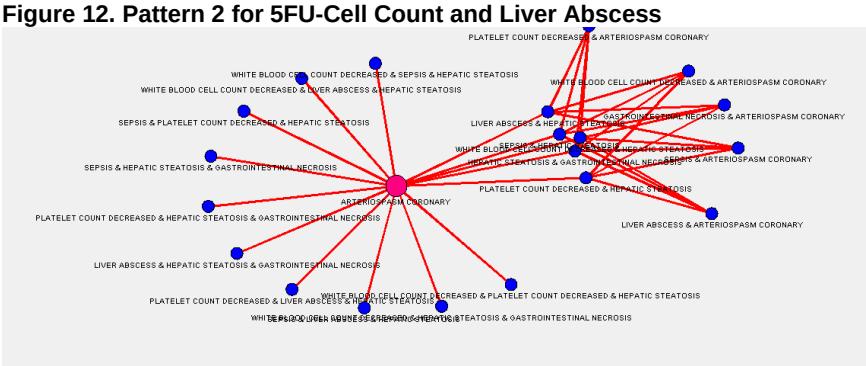
This graph shows two large centers and several smaller centers. Again, because the overall link graph is difficult to read, we next show some of those centers.

Figure 11. Pattern 1 for 5FU-Jugular Vein Thrombosis



Jugular vein thrombosis is not very common. Interestingly enough, there are indications that it can be prevented by the use of Avastin, which could increase utility rather than to decrease it. (Togashi, Kim et al. 2010)

Figure 12. Pattern 2 for 5FU-Cell Count and Liver Abscess



As cell counts are a major problem with chemotherapy (as sometimes opposed to targeted treatments), this is not unusual. For colon cancer, spread to the liver resulting in a liver abscess is also not unusual. It is a disease progression rather than a side effect of treatment.

Figure 13. Pattern 3 for 5FU-Gastritis and Intestinal Problems

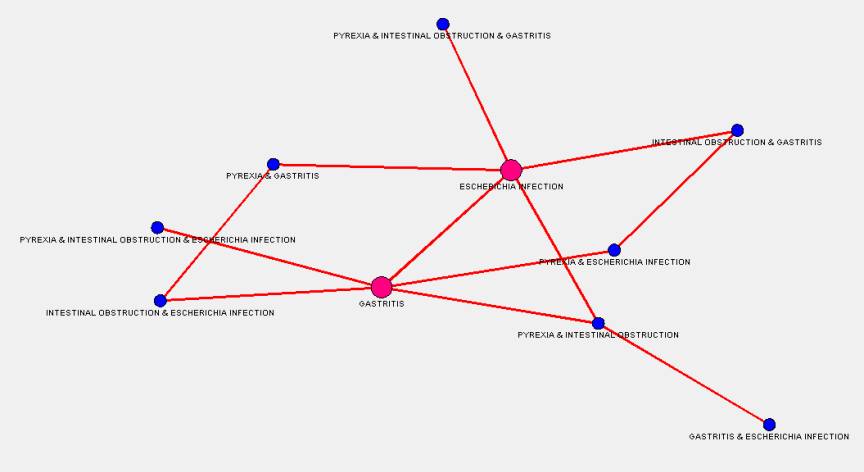
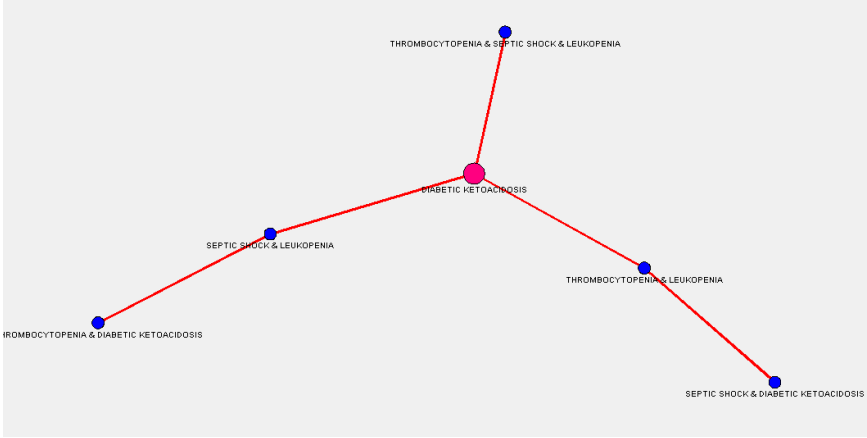


Figure 13 shows patient complaints regarding gastritis and intestinal problems, both of which are fairly typical for 5FU, and for chemotherapy in general. Patients generally receive medications to counter these side effects.

Figure 14. Pattern 4 for 5FU-Diabetes and Severe Complications



It appears that the complications result from patients with diabetes and who are at risk for diabetic ketoacidosis; otherwise, sepsis and thrombolytic are also included.

Figures 15-17 show the links for the drug, Oxaliplatin. There are very few discernible patterns in the data; it shows that the complaints are very scattered and may be attributed to Oxaliplatin when they should be attributed to the chemotherapy treatment in general.

Figure 15. Links Connecting Complications Listed for Oxaliplatin

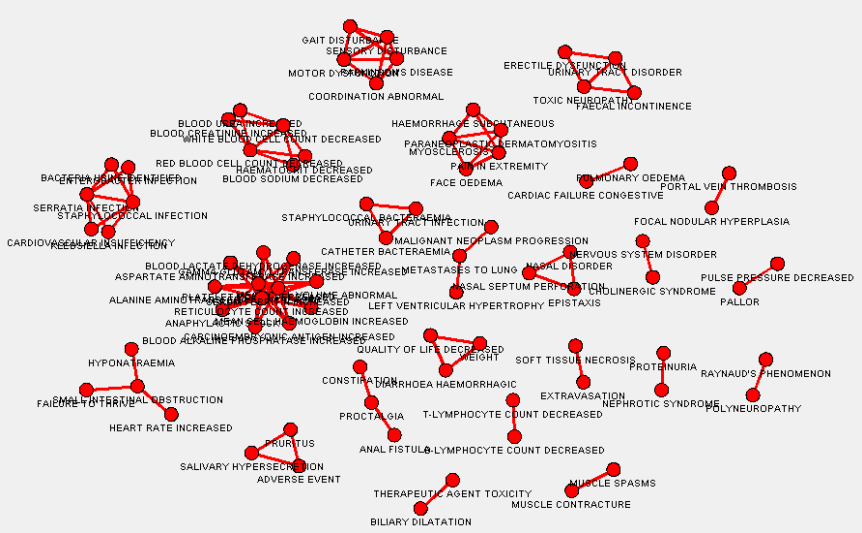


Figure 16. Pattern 1 for Oxaliplatin Complications

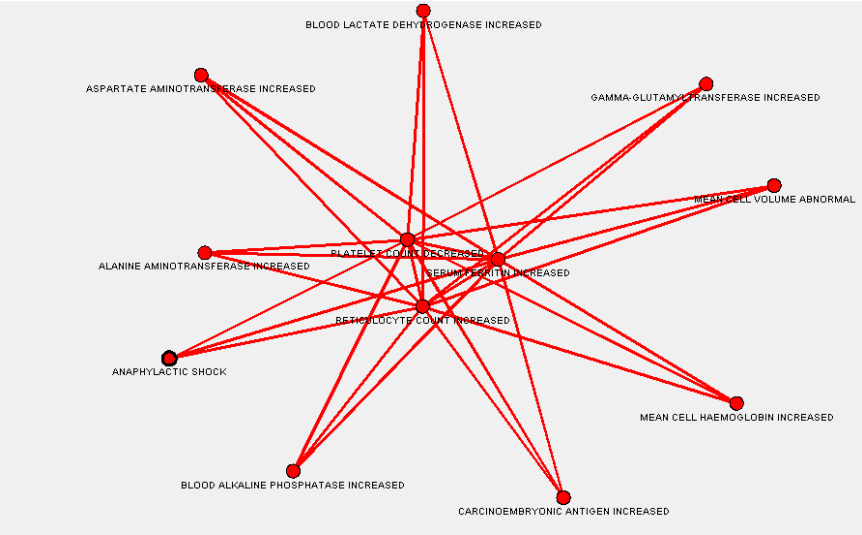


Figure 16 shows a problem with cell counts as well as some severe complications that are known concerning Oxaliplatin. These include anaphylactic shock. Because of the risk, patients are often given a steroid and an anti-histamine to prevent this shock.

Figure 17. Pattern 2 for Oxaliplatin Complications

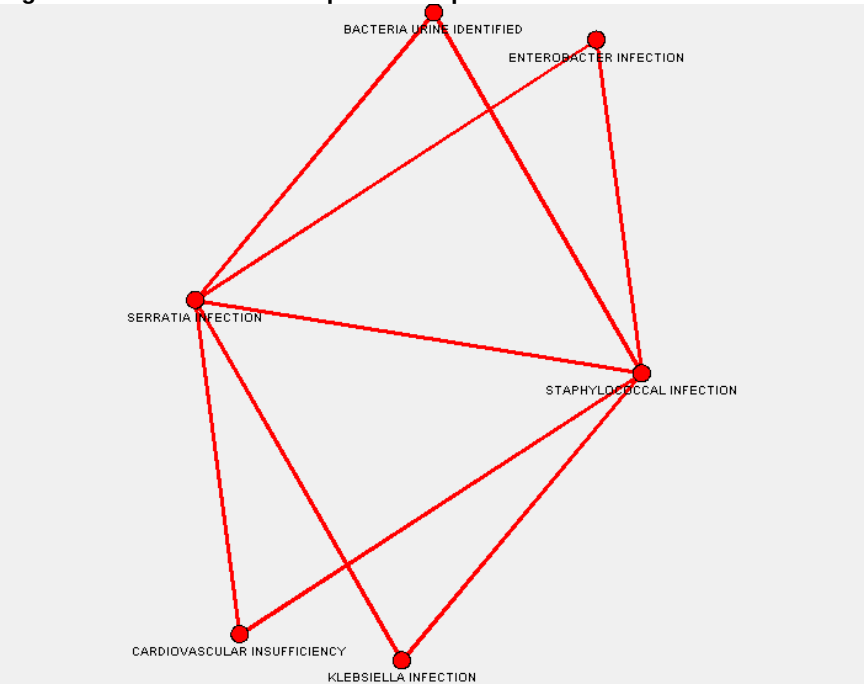


Figure 17 indicates the risk of infection that can occur because of low white cell counts. It is not known if Oxaliplatin aggravates the problem of infection in terms of severity, or if the risk is generally related to chemotherapy. Figures 18-21 show the connections between complaints related to the drug, Avastin. Figure 18 clearly shows that there is no discernable pattern to the complaints, again suggesting that the complaints are related to chemotherapy generally rather than to just the one drug, Avastin. We will look at three of the small patterns to examine specifics.

Figure 18. Associations for Avastin

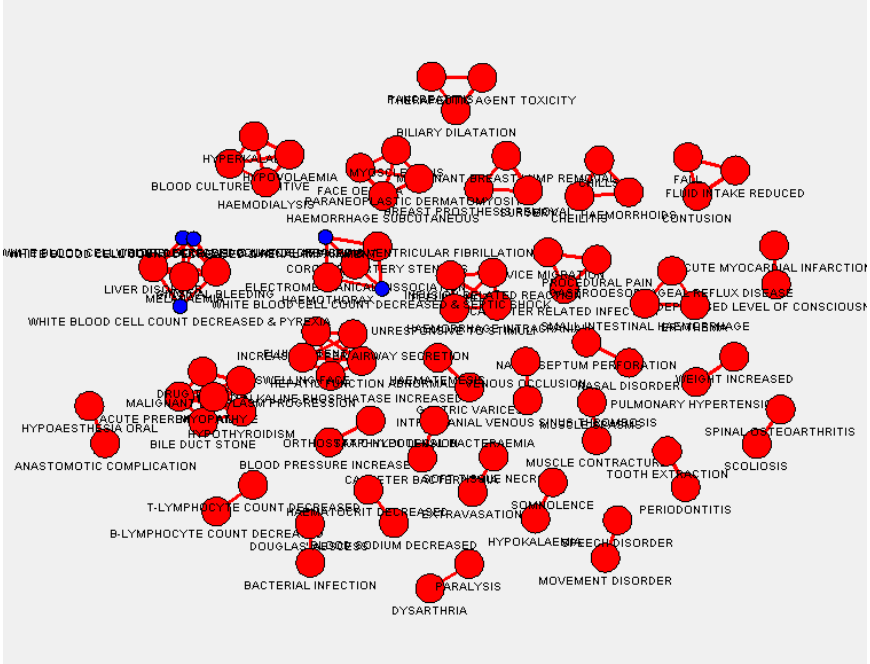
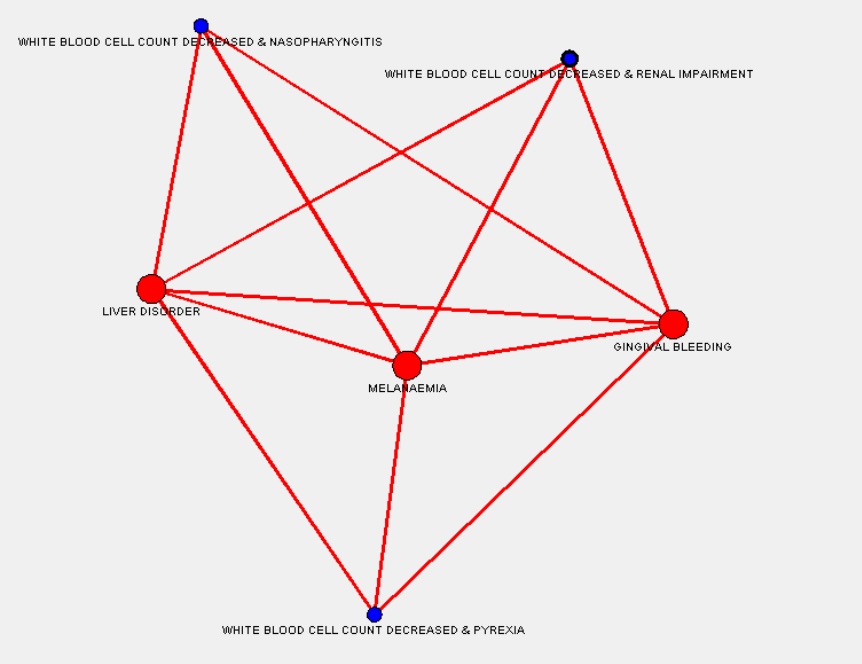
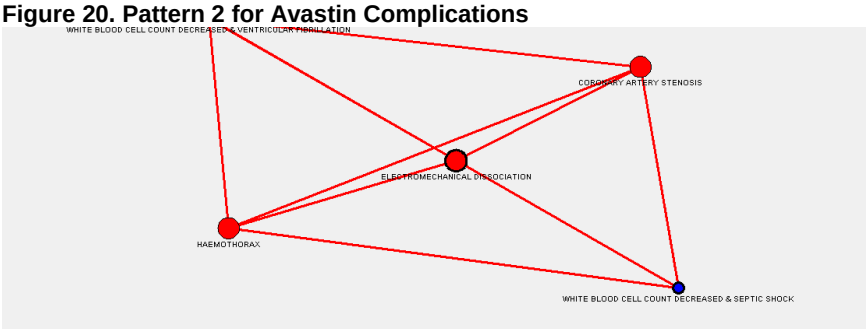


Figure 19. Pattern 1 for Avastin Complications



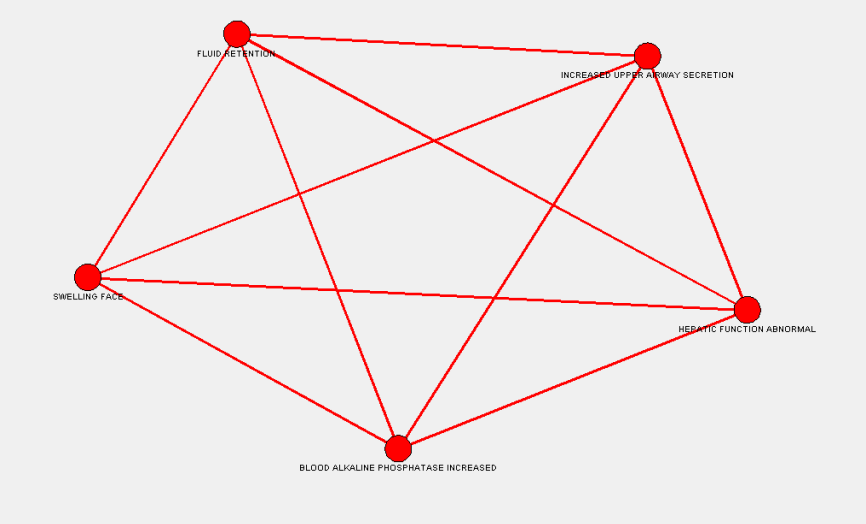
Most of the complications in Figure 19 are related to low cell counts, which are more likely from systemic chemotherapy rather than from targeted therapy such as Avastin. Two complications are related to Avastin and are known, gingival bleeding and melamaemia (The presence of dark brown or black granules of insoluble pigment in the blood).

Figure 20. Pattern 2 for Avastin Complications



The complications shown in Figure 20 center on problems of the heart along with the white cell count problem that is known for chemotherapy in general. It suggests that these complications can be attributed to patients with heart disease of some type, including coronary artery stenosis.

Figure 21. Pattern 3 Complications for Avastin



Fluid retention and swelling face (Figure 21) are likely because of the medications provided to deal with the side effects of the chemotherapy generally (ie, Decadron). Increased upper airway secretion is also a complication of chemotherapy generally. Abnormal hepatic function occurs in colon cancer patients with metastasizes in the liver. Generally, then very few of the problems shown here with Avastin can be directly attributed to Avastin other than some mild bleeding. It suggests that adding Avastin to another regimen, (FOLFOX, FOLFERI) does not significantly enhance the side effects. Because it is rarely given alone, it should be considered as an add-on to that treatment when defining quality of life rather than as a stand-alone quality.

DISCUSSION

Because the consequences of comparative effectiveness analysis can be severe, we need to examine the consequences very carefully. We also need to examine the assumptions used to define comparative effectiveness models. This paper has shown that the basic terminology that is essential to the modeling has questionable validity since it can mean different things to different individuals. Moreover, we need to examine just how threshold values are obtained, and how many individuals have shortened survival because treatment is denied.

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