Assessment of Drug Prescriptions in Pregnancy with New FDA Standard

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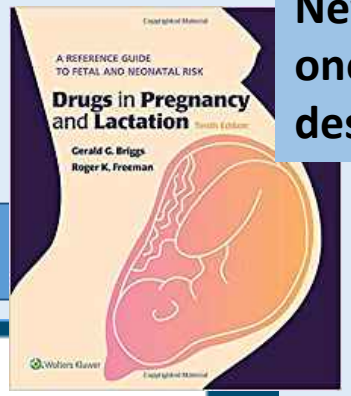
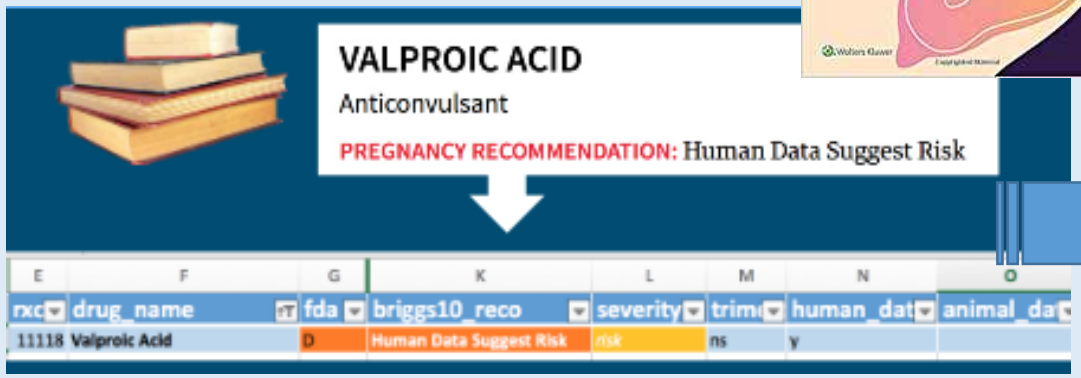
U.S. National Library of Medicine

Prior Work

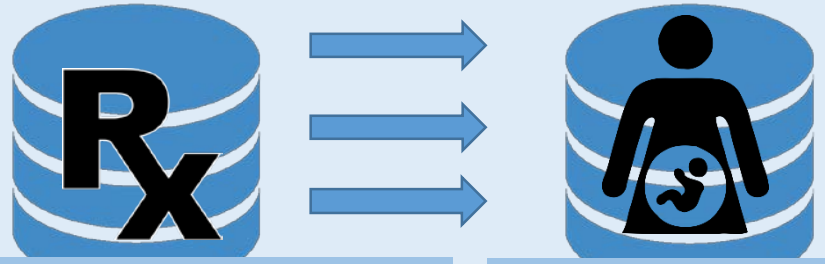


New FDA standard, one sentence description of risk

1. Reference risk categories



2. Large dataset of prescriptions in pregnancy



Mapped RxNorm IDs to risk descriptions and evidence dataset

Drugs prescribed during pregnancy

3. Characterizing the potential Risk in the prescription

Counts of Prescriptions
by categories of risk and level of evidence <270 days delivery code

- Clinical drug level
- Systemic drugs
- Multi-ingredient
- Market evolution

Previous Research

AMIA Annu Symp Proc 2016:45-46

Assessing the potential risk in drug prescriptions during pregnancy

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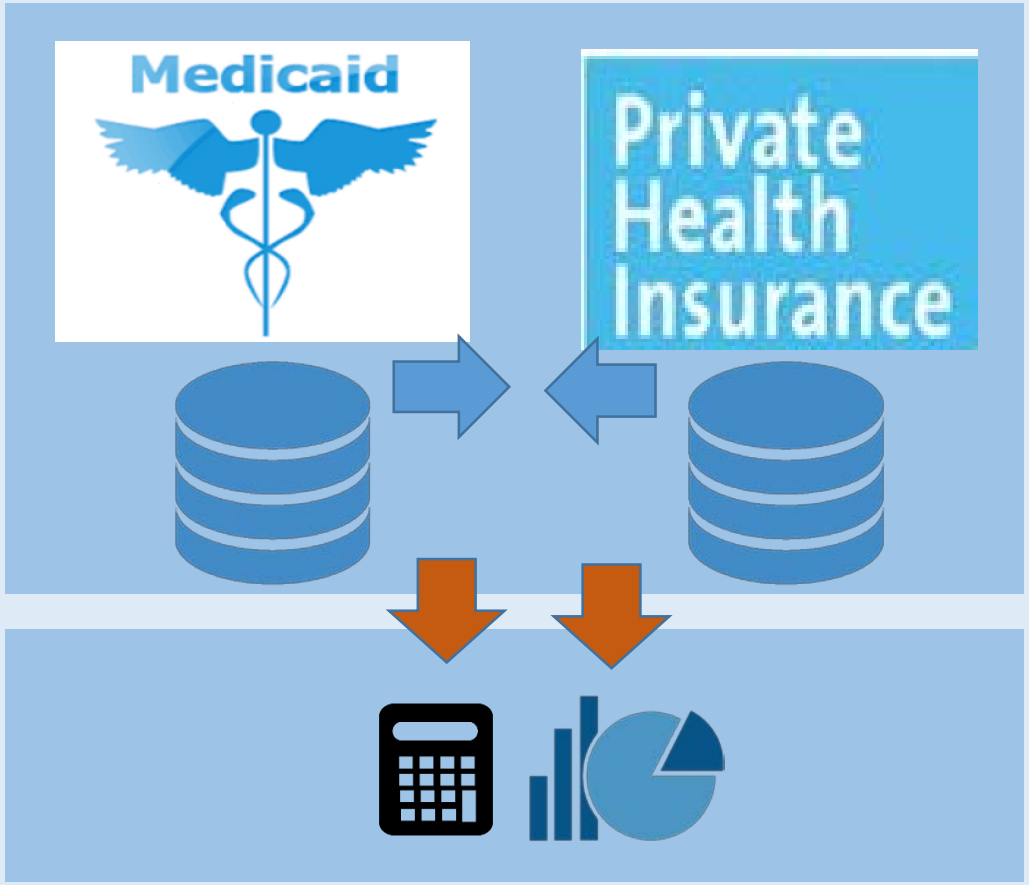
Introduction

Over eighty percent of pregnant women in the United States are prescribed at least one drug during pregnancy. The U.S. Food and Drug Administration (FDA) regulates the labeling of drug products and has established five risk categories for drug use during pregnancy. This classification was introduced in 1979. New FDA regulations (June 30, 2015) deeply revised the pregnancy and lactation labeling by eliminating these categories and replacing them with narrative summaries describing the risk of the drug and supporting evidence [1]. In a recent study on Medicaid data, 40% of pregnant women were dispensed at least one medication from categories D or X, for which there is positive evidence of human fetal risk [2]. In this work, our objective is to assess the potential risk in drug prescriptions during pregnancy, with respect to the new FDA standard. A secondary objective is to contrast risk assessment between the old FDA categories and the newly introduced narratives.

Objectives

- Characterizing prescription drugs dispensed during pregnancy according to the new FDA recommendations
  - Level of risk
  - Level of evidence
- Investigate differences between ★
  - Insurance ★
  - Age groups
  - Pregnancy period ★
- Specific contribution
  - Larger contribution
  - New FDA recommendation
  - Private vs. Public insurance ★



Prior Work Output

OUPUT

Private insurance aggregated data

- ccae_v5
- ccae_v5-C
- ccae_v5-C2
- ccae_v5-C4bWholePreg
- ccae_v5-C4ingredLevel
- ccae_v5-D2-evidence-trimester
- ccae_v5-D-evidence
- ccae_v5Eclass-FDA
- ccae_v5Eclassl-FDA
- ccae_v5Etrim-FDA
- ccae_v5Etriml-FDA
- ccae_v5-F2b-wholePregTopXinClass
- ccae_v5-F2-wholePregTopClassesVcols
- ccae_v5-Fb-byTrimTopXinClass
- ccae_v5-F-byTrimTopClassesVcols
- ccae_v5fout2-B.rds
- ccae_v5-G2Class-topIngredBySeverityWh...
- ccae_v5-G2Trim-topIngredBySeverity
- ccae_v5Gclass-bySevWholePreg
- ccae_v5Gclassl-bySevWholePreg
- ccae_v5-Gtrim-byTrimSeverity
- ccae_v5-Gtriml-byTrimSeverity
- ccae_v5-JbyAgeGrpTopIngred

Public insurance aggregated data

mdcd_v5	6/23/2016 6:45 PM
mdcd_v5-C	6/23/2016 6:44 PM
mdcd_v5-C2	6/23/2016 6:44 PM
mdcd_v5-C4bWholePreg	6/23/2016 6:44 PM
mdcd_v5-C4ingredLevel	6/23/2016 6:44 PM
mdcd_v5-D2-evidence-trimester	6/23/2016 6:44 PM
mdcd_v5-D-evidence	6/23/2016 6:44 PM
mdcd_v5Eclass-FDA	6/23/2016 6:44 PM
mdcd_v5Eclassl-FDA	6/23/2016 6:44 PM
mdcd_v5Etrim-FDA	6/23/2016 6:44 PM
mdcd_v5Etriml-FDA	6/23/2016 6:44 PM
mdcd_v5-F2b-wholePregTopXinClass	6/23/2016 6:44 PM
mdcd_v5-F2-wholePregTopClassesVcols	6/23/2016 6:44 PM
mdcd_v5-Fb-byTrimTopXinClass	6/23/2016 6:44 PM
mdcd_v5-F-byTrimTopClassesVcols	6/23/2016 6:44 PM
mdcd_v5ferdA-01-distinct-drugs	6/23/2016 6:40 PM
mdcd_v5fout2-B.rds	6/23/2016 6:44 PM
mdcd_v5-G2Class-topIngredBySeverityW...	6/23/2016 6:44 PM
mdcd_v5-G2Trim-topIngredBySeverity	6/23/2016 6:45 PM
mdcd_v5Gclass-bySevWholePreg	6/23/2016 6:44 PM
mdcd_v5Gclassl-bySevWholePreg	6/23/2016 6:44 PM

Milestones Overview

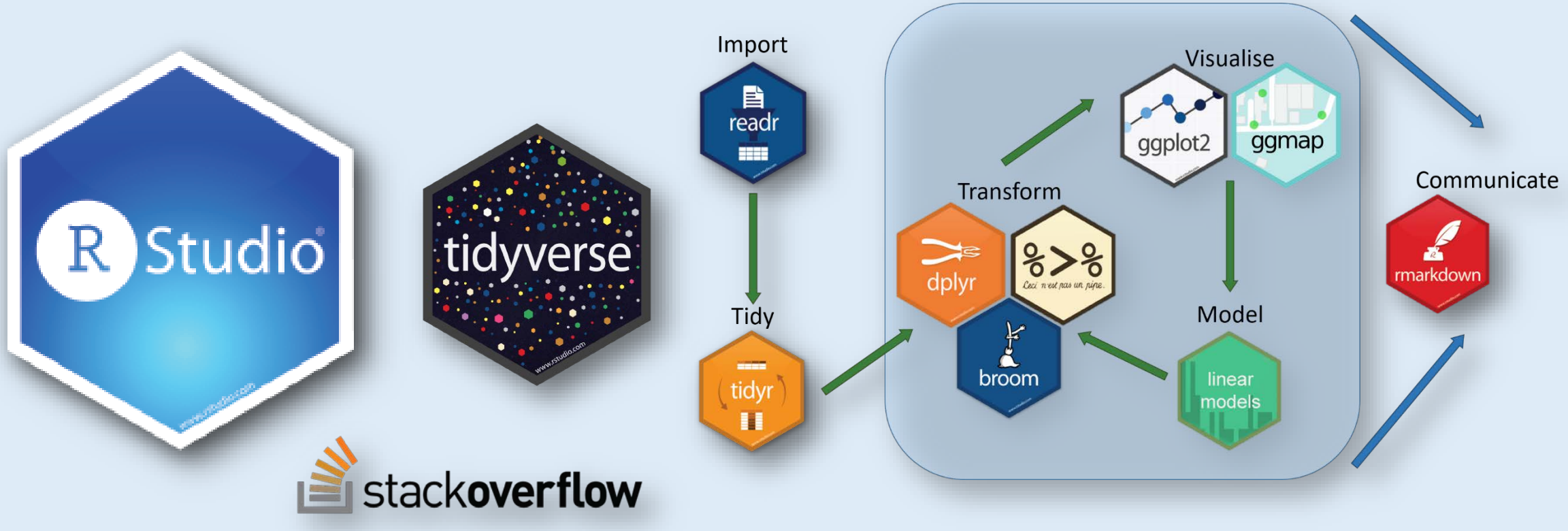
- Learn the Datasets
- Learn descriptive and inferential statistics in R
- Use R to produce descriptive and inferential statistics from the datasets

	SEVERITY_SCORE_MAX	INS_CNT
	2	4914341
	4	
3	5	
	8	
5	3	
6	6	

	CLASS	INST_CNT
16	any_contraceptive	9809
17	oral_contraceptive	8541
20	v10	1988
9	v12	267443

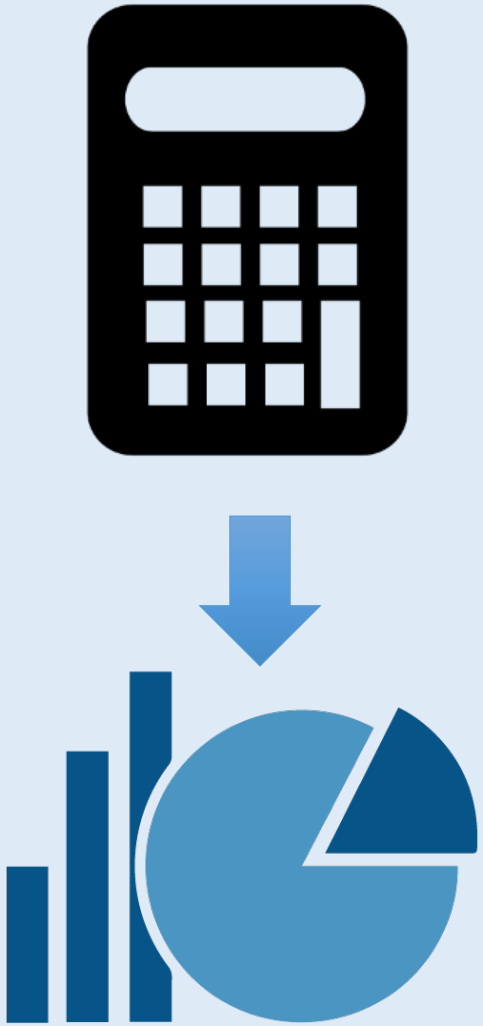
	RXN_ID	RLABEL	PREG_CNT	INS_CNT
1	73	Docosahexaenoate	21	32
2	99	6-Aminocaproic Acid	28	32
3	103	mercaptopurine	434	2053
4	149	Acebutolol	893	4099
5	161	Acetaminophen	104	135
6	167	Acetazolamide	532	1500
7	281	Acyclovir	29123	54548
8	376	Corticotropin	5	6
9	430	Albendazole	53	64
10	435	Albuterol	1604	3679
11	519	Allopurinol	127	344

Learning R


RStudio
tidyverse
stackoverflow
Import
readr
Tidy
tidyr
Transform
dplyr
%>%
broom
Visualise
ggplot2
ggmap
Model
linear models
Communicate
rmarkdown

Methods

1. Identify the most frequently prescribed drugs during pregnancy among both insurance datasets
   - Descriptive stats to compute the frequency of prescription of drug in both datasets
2. Compare the frequencies of prescription of specific drugs across datasets
   - Comparison of Two Proportions from Independent Populations Test
3. Compare the ranks of the top drugs in the two datasets
   - Wilcoxon Rank Sum Test



Top 20 Drugs

Commercial Insurance

	RXN_ID	RLABEL	PRCNT	INSR_PRCNT
1	18631	Azithromycin	7.929367	CCAE_PRCNT
2	26225	Ondansetron	7.182582	CCAE_PRCNT
3	723	Amoxicillin	5.632606	CCAE_PRCNT
4	8745	Promethazine	4.990360	CCAE_PRCNT
5	214182	Acetaminophen / Hydrocodone	3.046541	CCAE_PRCNT
6	2231	Cephalexin	3.026764	CCAE_PRCNT
7	10582	Thyroxine	2	
8	6922	Metronidazole	2	
9	8727	Progesterone	2.[illegible]	CCAE_PRCNT
10	4450	Fluconazole	2.241382	CCAE_PRCNT
11	73645	valacyclovir	2.046693	CCAE_PRCNT
12	10368	Terbutaline	1.961860	CCAE_PRCNT
13	19711	Amoxicillin / Clavulanate	1.938946	CCAE_PRCNT
14	817579	Acetaminophen / Codeine	1.811121	CCAE_PRCNT
15	6915	Metoclopramide	1.421372	CCAE_PRCNT
16	36437	Sertraline	1.259751	CCAE_PRCNT
17	39993	zolpidem	1.225248	CCAE_PRCNT
18	7417	Nifedipine	1.225106	CCAE_PRCNT
19	6902	Methylprednisolone	1.031569	CCAE_PRCNT
20	214183	Acetaminophen / Oxycodone	1.008567	CCAE_PRCNT

Public Insurance

	RXN_ID	RLABEL	PRCNT	INSR_PRCNT
1	8745	Promethazine	7.302233	MDCD_PRCNT
2	18631	Azithromycin	6.794953	MDCD_PRCNT
3	6922	Metronidazole	6.129653	MDCD_PRCNT
4	26225	Ondansetron	5.117727	MDCD_PRCNT
5	723	Amoxicillin	4.897023	MDCD_PRCNT
6	214182	Acetaminophen / Hydrocodone	4.070242	MDCD_PRCNT
7	[illegible]	Cephalexin	3.745473	MDCD_PRCNT
[illegible]	[illegible]	Acetaminophen / Codeine	3.507754	MDCD_PRCNT
[illegible]	[illegible]	Fluconazole	3.030999	MDCD_PRCNT
10	9143	Ranitidine	2.368291	MDCD_PRCNT
11	10368	Terbutaline	1.954115	MDCD_PRCNT
12	6915	Metoclopramide	1.697193	MDCD_PRCNT
13	5553	Hydroxyzine	1.497858	MDCD_PRCNT
14	19711	Amoxicillin / Clavulanate	1.385148	MDCD_PRCNT
15	10831	Sulfamethoxazole / Trimethoprim	1.256124	MDCD_PRCNT
16	73645	valacyclovir	1.237070	MDCD_PRCNT
17	214183	Acetaminophen / Oxycodone	1.216784	MDCD_PRCNT
18	71722	Docusate Sodium	1.174916	MDCD_PRCNT
19	82001	Docusate Calcium	1.174916	MDCD_PRCNT
20	82002	docusate potassium	1.174916	MDCD_PRCNT

	RLABEL	Commercial	Public	pval	is_sig
1	Azithromycin	7.92936701	6.7949527	0.000000e+00	TRUE
2	Promethazine	4.99036038	7.3022328	0.000000e+00	TRUE
3	Ondansetron	7.18258245	5.1177274	0.000000e+00	TRUE
4	Metronidazole	2.34795872	6.1296535	0.000000e+00	TRUE
5	Amoxicillin	5.63260574	4.8970231	0.000000e+00	TRUE
6	Acetaminophen / Hydrocodone	3.04654077	4.0702422	0.000000e+00	TRUE
7	Cephalexin	3.02676356	3.7454733	0.000000e+00	TRUE
8	Acetaminophen / Codeine	1.81112092	3.5077542	0.000000e+00	TRUE
9	Fluconazole	2.24138154	3.0309989	0.000000e+00	TRUE
10	Thyroxine	2.58425738	0.4652846	0.000000e+00	TRUE
11	Ranitidine	0.70439470	2.3682911	0.000000e+00	TRUE
12	Progesterone	2.25770305	0.3781925	0.000000e+00	TRUE
13	valacyclovir	2.04669300	1.2370700	0.000000e+00	TRUE
14	Terbutaline	1.96186011	1.9541147	3.717263e-01	FALSE
15	Amoxicillin / Clavulanate	1.93894620	1.3851479	0.000000e+00	TRUE
16	Metoclopramide	1.42137168	1.6971928	9.531952e-281	TRUE
17	Hydroxyzine	0.79378202	1.4978580	0.000000e+00	TRUE
18	Sertraline	1.25975148	0.8405245	0.000000e+00	TRUE
19	Sulfamethoxazole / Trimethoprim	0.84912630	1.2561241	0.000000e+00	TRUE
20	zolpidem	1.22524770	0.8222139	0.000000e+00	TRUE
21	Nifedipine	1.22510593	1.0969578	1.911289e-81	TRUE
22	Acetaminophen / Oxycodone	1.00856676	1.2167839	9.855943e-224	TRUE
23	Docusate Sodium	0.01081012	1.1749159	0.000000e+00	TRUE
24	Docusate Calcium	0.01081012	1.1749159	0.000000e+00	TRUE
25	docusate potassium	0.01081012	1.1749159	0.000000e+00	TRUE
26	Methylprednisolone	1.03156928	0.4475901	0.000000e+00	TRUE

2) Compare the frequencies

All proportions are statistically significantly different except for the Drug **Terbutaline**

Statistical Test Used to Compare Two Proportions from Independent Populations

Azithromycin	Exposed	Not Exposed	Total
Commercial Insurance	P_A	T_A-P_A	T_A
Public Insurance	P_B	T_B-P_B	T_B

```
prop.test()
$p.value
```

Do NOT need to correct for conducting multiple tests because each test is independent from one another

Top 20 drugs ranked

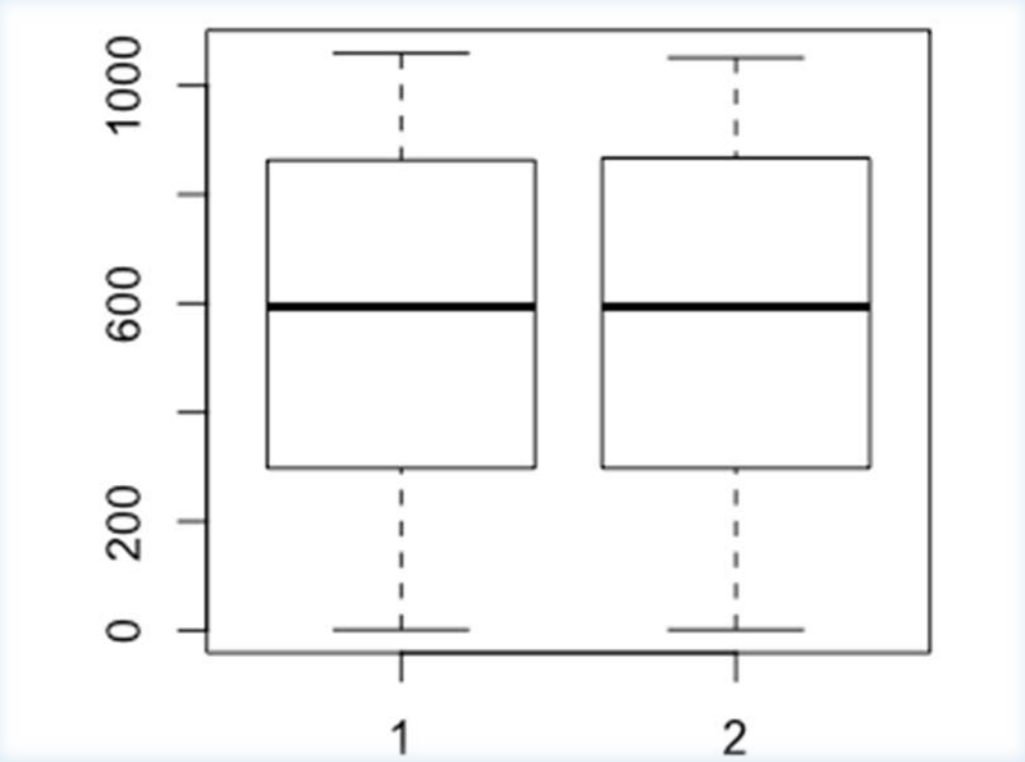
Commercial Insurance

	RLABEL	RANK
1	Azithromycin	1
2	Ondansetron	2
3	Amoxicillin	3
4	Promethazine	4
5	Acetaminophen / Hydrocodone	5
6	Cephalexin	6
7	Thyroxine	7
8	Metronidazole	8
9	Progesterone	9
10	Fluconazole	
11	valacyclovir	
12	Terbutaline	12
13	Amoxicillin / Clavulanate	13
14	Acetaminophen / Codeine	14
15	Metoclopramide	15
16	Sertraline	16
17	zolpidem	17
18	Nifedipine	18
19	Methylprednisolone	19
20	Acetaminophen / Oxycodone	20

Public Insurance

	RLABEL	RANK
1	Promethazine	1
2	Azithromycin	2
3	Metronidazole	3
4	Ondansetron	4
5	Amoxicillin	5
6	Acetaminophen / Hydrocodone	6
7	Cephalexin	7
8	Acetaminophen / Codeine	8
9	Fluconazole	9
	e	10
	ne	11
12	Metoclopramide	12
13	Hydroxyzine	13
14	Amoxicillin / Clavulanate	14
15	Sulfamethoxazole / Trimethoprim	15
16	valacyclovir	16
17	Acetaminophen / Oxycodone	17
18	Docusate Sodium	18
19	Docusate Calcium	18
20	docusate potassium	18

Wilcoxon Rank Test



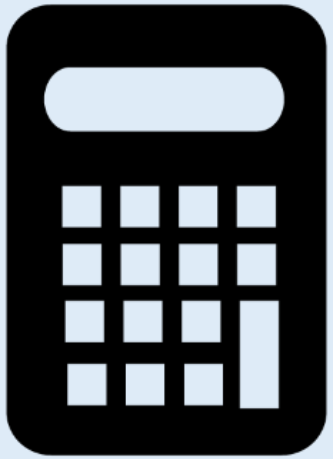
- If p-value is a little less than 0.05, may conclude the medians of these two distributions differ
- H_A = true location shift is not equal to 0

Results

- W = 716000
- **P-value = 0.4904**
- 95% confidence interval:
  - -20.99996 23.00002
- Sample estimates in location
  - 7.999986
- **P-value > alpha : H_0 = True & H_A = False**

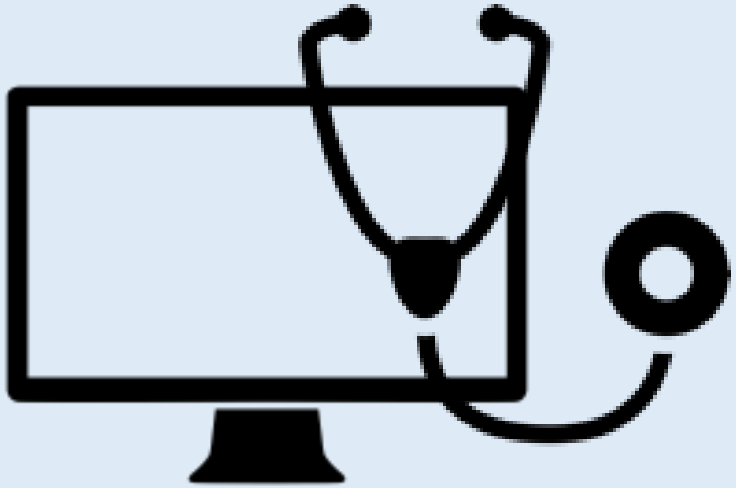
Future Work

- Only a small part of what we need to do
  - The different tasks, i.e. risk and evidence
- There’s a significant amount of work left
- I plan to continue contributing to the research



Thank you all for your time!

Special thanks to Dr. Bodenreider, Dr. Fontelo, and Dr. McDonald for providing fellowship & mentorship opportunities for students and myself to learn and be immersed in such a work place that distinguishably drives biomedical research and further knowledge!



Thank you

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