

## Monitoring all Drugs for a Specific Outcome in the Sentinel System

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#### **ICPE Disclosure Slide**

- Funding source: U.S. Food and Drug Administration
  - Mini-Sentinel Operations Center Response to Evaluation of Exposure/Outcome Associations, HHSF22301007T
  - Under contract: FDA HHSF223200910006I
- No relationships to disclose



#### What is

- A signal detection / data-mining method
- Scans electronic health data that are grouped into hierarchical tree

structures

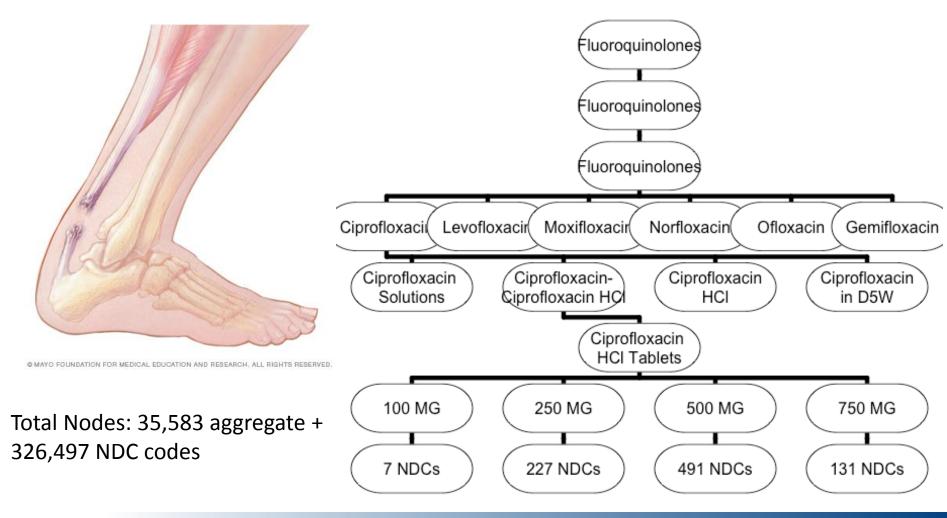
 Automatically adjusts for multiple hypothesis testing



http://www.treescan.org



# What is an Outcome-Oriented Scan / DrugScan (1 Outcome: M Exposures)?





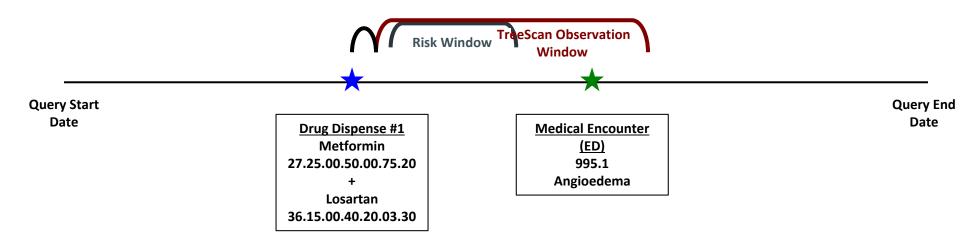
#### **Surveillance Population**

- Claims Data from 3 Data Partner Sites (2000-2014)
  - Not all sites had data back to 2000
- Males and Females >=18 years with medical and drug coverage and incident outcome of interest
- Outcome of Interest
  - Angioedema

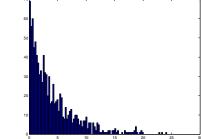


#### **DrugScan Analytic Design and Statistics**

- Case-Crossover Design (Self-Controlled)
- Incident Exposures or New "Starts" of Therapeutic
- Duration of Treatment Ignored
  - not "As Treated"
- Fixed and Variable Risk Window Scan Statistics







### **Conditional Tree-Based Scan Statistic** Hypotheses for Outcome-Oriented Scan

H<sub>0</sub>: The probability of an outcome after the dispensing of a drug is modified (conditioned) by the total number of events in the dataset across the observation window on that given day.

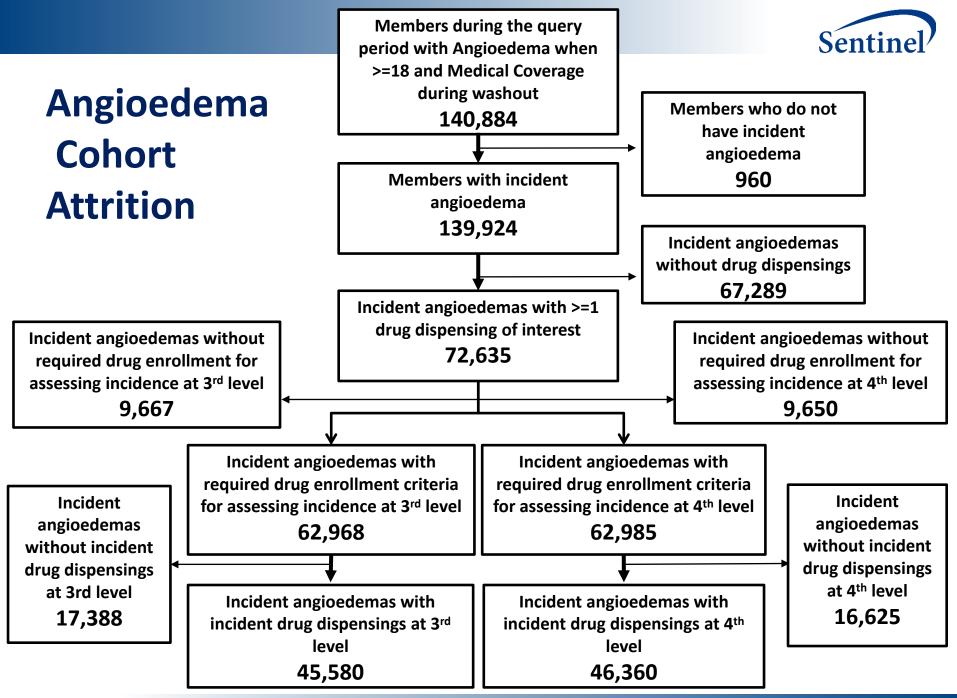
H<sub>A</sub>: There are at least some time periods in the observation window when the probability of an outcome is higher
 . . . after various adjustments



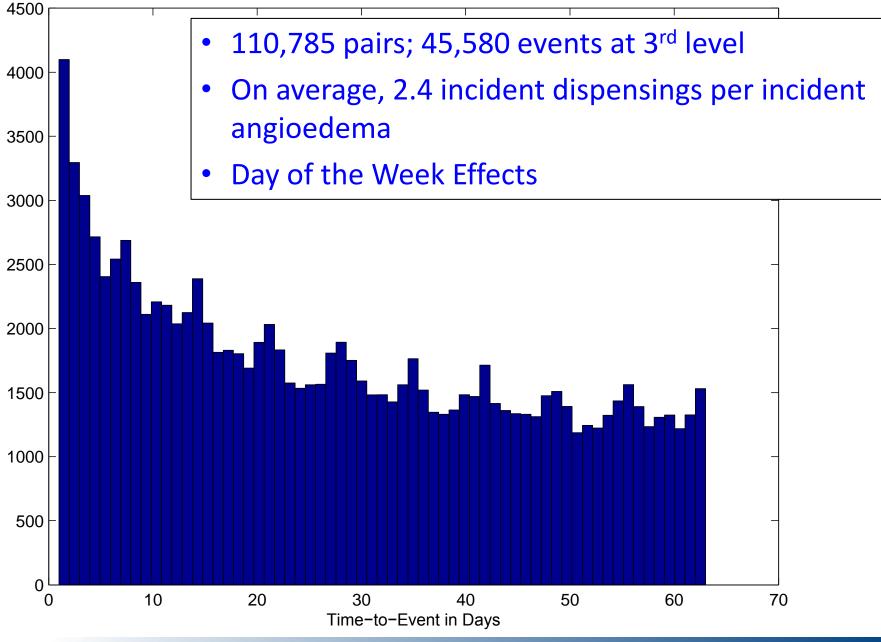
#### **Angioedema Takeaways**

#### 1) Manageable Total Number of Alerts 2) More Potential Misclassification of Disease Onset than Anticipated

Results







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#### **Angioedema Results**

- 28 unique alerts at 0.05 level, 20 meaningfully different
  - 9 were angioedema treatments
    - e.g., Glucocorticosteroids, Hydroxyzine, Diphenhydramine
  - Rest were known positives or likely positives
    - ACE inhibitors, Buproprion, Simvastatin, Antibiotics



#### **Angioedema Sensitivity Analyses**

- Pruned out all antihistamines and other angioedema treatments (e.g., hydroxyzine, glucocorticosteroids)
  - Strong known positives
    remain with slight
    adjustment of time-toevent
  - Lose some known positives (adjusted conditional analysis)
  - Some new alerts



#### **Tree-Temporal Alerts after Pruning**

- 13 unique at 3rd level, 9 meaningfully different
- Some new antibiotics, ACEI Combos are statistically significant.
- Some alerts become not statistically significant at 0.05 level (e.g., simvastatin)



#### **Angioedema Summary**

- 1. Misclassification of Disease Onset is present
  - DESIGN: Prune out anti-histamines from the tree *a priori* OR
  - DESIGN: Refine outcome definitions with MORE exclusions
    OR
  - ANALYSIS: Prune based at analysis phase
- 2. Detects known positives without too many false positives



#### Acknowledgments

- DrugScan Team
  - Jeff Brown
  - Gerald Dal Pan
  - Inna Dashevsky
  - Martin Kulldorff
  - Andrew Petrone
  - Carolyn Balsbaugh
- DrugScan Protocol Reviewers
  - Mark Levenson
  - Rita Ouellet-Hellstrom
  - Simone Pinheiro



#### Q&A

# You Are (Not) Small



Angioedema, 3rd level,      Nade Name      D      Events      Start      End      Window      Cases      Expected      Statistic      P-value        3rd level, 3rd level,      **Glucconticosteroids***      2210004 500      11127      1      8      3526      2324.33      1.53      2279      1.00E-05        Tree-temporal, Conditional      Methylprednisolone      221000300      3893      1      8      1140      812.8      1.44      559.1      1.00E-05        Epinephrine      3890004000      3640      1      15      1925      1256.27      1.53      154.87      1.00E-05        -28 unique      mantidine      492000201      939      1      6      251      153.37      1.64      26.05      1.00E-05        -20 different      *Antianxiety Agents - Misc.***      572000402      2174      1      4      477      226.31      1.75      62.47      1.00E-05        Grey=Mis- Classification      *Midrowyine Pamoate      572004010      1931      1      4      472      25.97      1.75      62.47      1.00E-05	· ·		Node	Node	Window	Window	Cases in	Expected	Observed/	Test	intinci
S.* Level,    readisone    2210004500    7009    1    7    2145    1314.87    1.63    222.79    1.00E-05      Tree-temporal,    Methylprednisolone    22100030    3893    1    8    1141    813.21    1.4    59.12    1.00E-05      Conditional    Epinephrine    389000400    3840    1    15    1925    1256.27    1.53    154.87    1.00E-05      -28    unique    Famotidine    492003000    781    1    6    606    313.11    1.94    80.85    1.00E-05      -28    Infigure    Famotidine    492003000    781    1    6    251    1.53    37    1.64    26.05    1.00E-05      -20    different    Misc.***    57200040    2174    1    4    472    269.15    1.75    62.47    1.00E-05      Grey=Mis-    Misc.***    57200040    1931    1    4    472    269.15    1.75    62.47    1.00E-05      Grey=Mis-    Misc.***    57200402    243    1    10    104	Angioedema,								-	Statistic	P-value
Tree-temporal Conditional    Methylprednisolone    221000300    3893    1    8    1140    813.4.37    1.63    222.7    1.007-05      Conditional    Methylprednisolone    221000300    3893    1    8    1140    813.2.3    1.4    58.95    1.007-05      Conditional    Finephrine    38900000    3640    1    15    1925    1256.27    1.53    154.87    1.007-05      -28 unique    Famotidine    4920002010    939    1    6    606    313.11    1.94    0.076.55    1.007-05      -20 different    Hydroxyine    57200040    2174    1    4    467    257.99    1.81    6.831    1.007-05      Grey=Mis-    Hydroxyine Pamoate    572000400    243    1    10    104    60.23    1.73    13.04    0.00517      classification    Timethoprim    169900230    1812    3    13    641    431.96    1.48    44.16    1.00E-05      Green=Known    Diphenhydramine HCl    41200030    169    1    6    70    25.97	3 <sup>rd</sup> level										
Conditional      Methylprednisolone      2210003000      3891      1      8      1140      812.8      1.4      58.95      1.00E-05        Conditional      Epinephrine      33900000      3640      1      15      1925      125.27      1.53      154.87      1.00E-05        -28 unique      Famotidine      492000      971      1      6      206      127.56      2.32      80.85      1.00E-05        -20 different      Hydroxyine      572000      226      1      4      472      269.15      1.75      62.47      1.00E-05        Grey=Mis-      Hydroxyine Panoate      57200040      2174      1      4      407      229.15      1.75      62.47      1.00E-05        Grey=Mis-      Hydroxyine Panoate      57200402      243      1      10      104      60.23      1.73      13.04      0.00517        Classification      Mischwaines***      12000      169      1      6      73      27.6      2.64      2.651      1.00E-05        Green=Known      Diphenhydramine HCl	,				1						
Conditional      Methylprednisolone      2210003000      3891      1      8      1140      812.8      1.4      58.95      1.00E-05        Conditional      Epinephrine      33900000      3640      1      15      1925      125.27      15.31      154.87      1.00E-05        -28 unique      Famotidine      492000      971      1      6      296      127.56      2.32      80.85      1.00E-05        -20 different      Hydroxyine      572000      214      1      4      467      257.99      1.81      68.31      1.00E-05        Grey=Mis-      Hydroxyine Panoate      57200040      2174      1      4      407      229.15      1.75      62.47      1.00E-05        Grey=Mis-      Hydroxyine Panoate      57200402      243      1      10      104      60.23      1.73      13.04      0.00517        Classification      Mischwithereditamines-**      41200      169      6      73      27.6      2.64      2.561      1.00E-05        Green=Known      Diphenhydramine HCl      4	Tree-temporal,										
-28 unique    *H-2 Antagonists***    492000    1    6    606    313.11    1.94    107.65    1.007-05      -28 unique    Famotidine    492000210    939    1    6    296    127.56    2.32    80.85    1.007-05      -20 different    Hydroxyine    5720004    2174    1    4    467    257.99    1.81    68.31    1.007-05      Grey=Mis-    Hydroxyine Pamoate    5720004    2174    1    4    472    269.15    1.75    62.47    1.007-05      Grey=Mis-    Hydroxyine Pamoate    5720004020    243    1    10    104    60.23    1.73    13.04    0.00517      classification    Timethogrin    169900220    1812    3    13    641    431.96    1.48    44.16    1.00F-05      Green=Known    Diphenhydramine HCI    412000301    159    1    6    70    25.97    2.7    25.39    1.00F-05      Minocycline HCI    412000301    159    1    6    70    2.5.97    2.7    25.39    1.00F-05	• •										
-28 unique -20 different    Famotidine Ranitidine HCl    49200300    781    1    6    296    127.56    2.32    80.85    1.00E-05      -20 different    Famotidine HCl    492002010    939    1    6    251    153.37    1.64    26.05    1.00E-05      -20 different    *Antianxiety Agents - Misc.***    57200040    2174    1    4    472    269.15    1.75    62.47    1.00E-05      Grey=Mis- classification    Hydroxyzine Pamoate    572000402    243    1    10    104    60.23    1.73    13.04    0.00517      Grey=Mis- classification    *Imethoxazole- Trimethoprim    169900230    1812    3    13    641    431.96    1.48    44.16    1.00E-05      Of onset    *Antihistamines - Ethanolamines***    412000    169    1    6    70    25.9    1.00    1.00    100    15    1.00    1.00E-05      Diphenhydramine HCl    412000300    159    1    6    70    25.13    1.30    2.024    1.00E-05      Misc.vinius    3610003000    160	Conuitional										
-28 unique -20 different      Ranitidine HCl Hydroxyzine      492002010 5720040      939 2174      1      6      251      153.37 257.99      1.64      26.05      1.00E-05        Grey=Mis- classification of onset      Hydroxyzine HCl Hydroxyzine HCl      572000402      2438      1      4      472      269.15      1.75      62.47      1.00E-05        Grey=Mis- classification of onset      Hydroxyzine HCl Hydroxyzine HCl      5720004020      243      1      10      104      60.23      1.73      1.64      2.60      1.00E-05        Greep=Mis- classification of onset      Suffamethoxaole- Trimethorim      169900230      1812      3      13      641      431.96      1.48      44.16      1.00E-05        Green=Known Positive      Diphenhydramine HCl Usinopril      412000310      159      1      6      73      27.6      2.64      25.61      1.00E-05        Winocycline HCl Usinopril      361000      2649      2      8      502      37.2      2.77      25.39      1.00E-05        Winocycline HCl      412000301      159      1      6      70      25.13 <th></th> <th>-</th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th>		-									
-20 different    Hydroxyzine *Antianxiety Agents - Misc.***    57200040    2174    1    4    467    257.99    1.81    68.31    1.00E-05      Grey=Mis- Grey=Mis- classification of onset    Hydroxyzine HCI Hydroxzole- Timethoprim    572000400    2181    1    4    407    229.15    1.78    56.09    1.00E-05      Grey=Mis- classification of onset    Sulfamethoxazole- Timethoprim    169900230    243    1    10    104    60.23    1.73    13.04    0.00517      Green=Known Positive    Diphenhydramine HCI Lisnopril    412000    169    1    6    73    27.6    2.64    25.61    1.00E-05      Minocycline HCI    4120003010    159    1    6    70    25.97    2.7    2.53    1.00E-05      Minocycline HCI    4120003010    159    1    6    70    25.13    1.00E-05      Minocycline HCI    412000300    2.169    2    8    502    372.83    1.35    20.24    1.00E-05      Minocycline HCI    400004010    199    12    3    63    22    8    502											
-20 different    *Antianxiety Agents - Misc.***    572000    2268    1    4    472    269.15    1.75    62.47    1.00E-05      Grey=Mis- Lydroxyzine Pamoate    5720004020    1931    1    4    407    229.15    1.78    56.09    1.00E-05      classification    Suffamethoxazole- Trimethoprim    169900220    1812    3    13    641    431.96    1.48    44.16    1.00E-05      of onset    *Antihistamines- Ethanolamines***    412000    169    1    6    73    27.6    2.64    25.61    1.00E-05      Green=Known    Diphenhydramine HCl    41200030    160    1    6    70    25.97    2.7    25.39    1.00E-05      Positive    361000300    160    1    6    70    26.44    25.61    1.00E-05      Burgopini    361000300    160    1    6    70    25.97    2.7    25.39    1.00E-05      Burgopini    361000300    2169    2    8    594    455.34    1.3    1.93    2.00E-05      Positive	-28 unique										
Grey=Mis- classification of onset      Misc.*** Hydroxyzine HCl Hydroxyzine Pamoate      572000      2268      1      4      472      269.15      1.75      62.47      1.00E-05        Grey=Mis- classification of onset      Hydroxyzine Pamoate Trimethoprim      572000402      243      1      10      104      60.23      1.73      13.04      0.00E-05        Of onset      *Anthistamines - Ethanolamines***      412000      169      1      66      73      27.6      2.64      2.561      1.00E-05        OphenhydramineHCl      412000301      159      1      66      73      27.6      2.64      2.561      1.00E-05        OphenhydramineHCl      412000301      159      1      66      70      25.97      2.7      25.39      1.00E-05        Ophenhydramine      412000301      159      1      6      70      25.97      2.7      25.39      1.00E-05        Ophenhydramine      412000300      2169      2      8      502      372.83      1.35      20.24      1.00E-05        Opositive      Exel Enhibitors***      3	20 difforant		57200040	2174	1	4	467	257.99	1.81	68.31	1.00E-05
Grey=Mis- classification      Hydroxyzine HCl Hydroxyzine Pamoate      5720004010      1931      1      4      407      229.15      1.78      56.09      1.00E-05        classification      Timethoxaole- Trimethor      Timethor      169900220      243      1      100      104      60.23      1.73      13.04      0.00E-05        of onset      *Antihistamines- Ethanolamines***      412000      169      1      6      73      27.6      2.64      25.61      1.00E-05        Oreen=Known      Diphenhydramine HCl      412000      169      1      6      70      25.97      2.7      25.39      1.00E-05        Opienhydramine      4120000      169      1      6      70      25.97      2.7      25.39      1.00E-05        Opienhydramine      4120000      169      1      6      70      25.13      1.35      22.04      1.00E-05        Opienhydramine      4120000      169      1      6      70      26.33      2.58      21.173      13.04      0.00270        Poistive      *AcE Inhibitors*	-20 unierent										
Grey=Mis- classification of onset      Hydroxyzine Pamoate Sulfamethoxacole- Trimethoprim      5720004020      243      1      10      104      60.23      1.73      13.04      0.00517        of onset      *Antihistamines- Ethanolamines***      169900230      1812      3      13      641      431.96      1.48      44.16      1.00E-05        Green=Known Positive      Diphenhydramine HCI Lisinopril      412000310      159      1      6      73      27.6      2.64      25.61      1.00E-05        Burpopin      *Acti Inhibitors***      412000310      159      1      6      70      25.97      2.7      25.39      1.00E-05        Burpopin      412000300      2169      2      8      502      372.83      1.33      20.24      1.00E-05        Minocycline HCl      412000300      2169      2      8      502      372.83      1.33      20.24      1.00E-05        Minocycline HCl      400004010      199      12      19      63      282.66      2.33      15.78      0.0002        Yellow=Likely      *											
Sulfamethoxazole- Trimethoprim      1699000230      1812      3      13      641      431.96      1.48      44.16      1.00E-05        of onset      Anthistamines - Ethanolamines***      412000      169      1      6      73      27.6      2.64      25.61      1.00E-05        Diphenhydramine HCl      412000301      159      1      6      70      25.97      2.7      25.39      1.00E-05        Diphenhydramine      412000301      159      1      6      70      25.97      2.7      25.39      1.00E-05        Diphenhydramine      412000300      2169      2      8      502      372.83      1.35      20.24      1.00E-05        Positive      Minocycline HCl      412000300      2169      2      8      502      372.83      1.35      20.24      1.00E-05        Burgorin      Minocycline HCl      400004010      199      12      19      63      282.66      22.3      15.78      0.00254        Positive      *Central Muscle      *S000340      1115      1      3											
Classification    Trimethoprim    169900230    1812    3    13    641    431.96    1.48    44.16    1.00E-05      of onset    *Antihistamines- Ethanolamines***    412000    169    1    6    73    27.6    2.64    25.61    1.00E-05      Green=Known    Diphenhydramine    41200030    169    1    6    70    26.13    2.68    25.11    1.00E-05      Minocycline HCl    41200030    169    1    6    70    26.13    2.68    25.11    1.00E-05      Minocycline HCl    3610003000    2169    2    8    502    372.83    1.35    20.24    1.00E-05      Minocycline HCl    400004010    199    12    19    63    28.26    2.23    15.78    0.0002      Yellow=Likely    *Central Muscle    *    *    751000    1243    54    63    222    15.31    1.45    13.60    0.00279      Positive    Levofloxacin    550003400    1115    1    3    161    104.99    1.53    12.84    0.00217	Grey=Mis-		5720004020	243	1	10	104	60.23	1.73	13.04	0.00517
of onset    *Antihistamines - Ethanolamines***    412000    169    1    6    73    27.6    2.64    25.61    1.00E-05      Green=Known Positive    Diphenhydramine    412000301    159    1    6    70    25.97    2.7    25.39    1.00E-05      Binnerking    Diphenhydramine    412000301    159    1    6    70    26.13    2.68    25.11    1.00E-05      Positive    Diphenhydramine    412000300    2169    2    8    502    372.83    1.35    20.24    1.00E-05      Minocycline HCI    400004010    199    12    19    63    28.26    2.23    15.78    0.00254      Yellow=Likely    *Central Muscle    751000    1243    54    63    222    153.14    1.45    13.60    0.00279      Positive    Levofloxacin    50000340    115    1    3    161    104.99    1.53    12.44    0.00619      Pink=Likely    *Benzodiazepines***    571000    1491    41    63    531    425.52    1.25    1.2	classification										
Chroniset      Ethanolamines***      412000      169      1      6      73      27.6      2.64      25.61      1.00E-05        Green=Known      Diphenhydramine      412000301      159      1      6      70      25.97      2.7      25.39      1.00E-05        Positive      Diphenhydramine      412000300      160      1      6      70      26.13      2.68      25.11      1.00E-05        Positive      *ACE Inhibitors***      361000      2649      2      8      502      372.83      1.35      20.24      1.00E-05        Minocycline HCl      361000      2649      2      8      594      455.34      1.3      19.33      2.00E-05        Minocycline HCl      361000      2649      2      8      594      455.34      1.3      19.33      2.00E-05        Vellow=Likely      *Central Muscle Relaxants***      751000      1243      54      63      222      153.14      1.45      13.60      0.00279        Positive      Levofloxacin      50000340      1115      1 <th></th> <th>•</th> <th>1699000230</th> <th>1812</th> <th>3</th> <th>13</th> <th>641</th> <th>431.96</th> <th>1.48</th> <th>44.16</th> <th>1.00E-05</th>		•	1699000230	1812	3	13	641	431.96	1.48	44.16	1.00E-05
Green=Known    Ethanolamines***    412000    169    1    6    73    27.6    2.64    25.61    1.00E-05      Diphenhydramine HCl    41200030    159    1    6    70    25.97    2.7    25.39    1.00E-05      Diphenhydramine    41200030    160    1    6    70    25.97    2.7    25.97    2.7    25.97    1.00E-05      Lisinopril    361000300    2169    2    8    502    372.83    1.35    20.24    1.00E-05      Minocycline HCl    400004010    199    12    19    63    28.26    2.23    15.78    0.0002      Yellow=Likely    *Central Muscle    751000    1243    54    63    222    153.14    1.45    0.00279      Positive    Levofloxacin    5000340    1115    1    3    161    104.99    1.53    12.84    0.00669      Levofloxacin    5000340    1115    1    3    161    105.09    1.53    12.79    0.00718      False Positive    Simvastatin    3940007500 <th>of onset</th> <th></th>	of onset										
Green=Known    Diphenhydramine    41200030    160    1    6    70    26.13    2.68    25.11    1.00E-05      Positive    *ACE Inhibitors***    361000 2649    2    8    502    372.83    1.35    20.24    1.00E-05      Minocycline HCl    400004010    199    12    19    63    28.26    2.23    15.78    0.0002      Wellow=Likely    *Central Muscle    *Ace inhibitors***    751000    1243    54    63    222    153.14    1.45    13.60    0.00279      Positive    *Central Muscle    *50000340    1115    1    3    161    104.99    1.53    12.84    0.00669      Positive    Levofloxacin    50000340    1115    1    3    161    104.99    1.53    12.84    0.00279      Pink=Likely    *Benzodiazeines***    571000    1243    54    63    531    425.52    1.26    0.1049      Pink=Likely    *Benzodiazeines***    5900034    1116    1    3    161    105.09    1.35    12.16    0.01492											
Green=known      Lisinopril      3610003000      2169      2      8      502      372.83      1.35      20.24      1.00E-05        Positive      *ACE Inhibitors***      361000      2649      2      8      594      455.34      1.3      19.33      2.00E-05        Minocycline HCl      400004010      199      12      19      63      28.26      2.23      15.78      0.0002        Winocycline HCl      800004010      390      19      30      122      72.96      1.67      13.69      0.00254        Yellow=Likely      8      62      22      153.14      1.45      13.60      0.00279        Positive      Levofloxacin      50000340      1115      1      3      161      104.99      1.53      12.84      0.00669        Levofloxacin      5000034      1116      1      3      161      104.99      1.53      12.84      0.00179        Pink=Likely      False Positive      Simvastatin      3940007500      802      42      54      188      129      1.46 <th></th>											
Positive    *ACE Inhibitors***    361000300    2165    2    8    502    572.83    1.33    20.24    1.00E-05      Positive    *ACE Inhibitors***    361000    2649    2    8    594    455.34    1.3    19.33    2.00E-05      Minocycline HCl    40004010    199    12    19    63    28.26    2.23    15.78    0.0002      Bupropion HCl    583004010    390    19    30    122    72.96    1.67    13.69    0.00279      Positive    Relaxants***    751000    1243    54    63    222    15.31    1.45    13.60    0.00279      Positive    Levofloxacin    50003400    1115    1    3    161    104.99    1.53    12.84    0.00669      Levofloxacin    5000340    1116    1    3    161    105.09    1.53    12.79    0.00718      Benzodiazepines***    571000    1491    41    63    531    425.52    1.25    12.16    0.01492      False Positive    Inhibitors***    3	Green=Known										
Minocycline HCl    400004010    199    12    19    63    28.26    2.23    15.78    0.0002      Yellow=Likely    *Central Muscle Relaxants***    *Contral Muscle Relaxants***    *75100    1243    54    63    222    153.14    1.45    13.69    0.00279      Positive    Levofloxacin    50003400    1115    1    3    161    104.99    1.53    12.84    0.00669      Positive    Levofloxacin    5000340    1115    1    3    161    105.09    1.53    12.79    0.00180      Pink=Likely    Simvastatin *Benzodiazepines***    571000    1491    41    63    531    425.52    1.25    12.16    0.01492      Pink=Likely    Simvastatin *HMG CoA Reductase    394000    2008    42    54    414    322.99    1.28    11.80    0.02207      False Positive    Inhibitors***    581600    1044    32    59    469    372.2    1.26    11.66    0.02514		•									
Yellow=Likely Positive      Bupropion HCI *Central Muscle Relaxants***      5830004010      390      19      30      122      72.96      1.67      13.69      0.00254        Positive      Econfloxacin Levofloxacin      751000      1243      54      63      222      153.14      1.45      13.60      0.00279        Pink=Likely False Positive      Simvastain *HMG CoA Reductase Inhibitors***      571000      1115      1      3      161      104.99      1.53      12.84      0.00679        Pink=Likely False Positive      Simvastain *HMG CoA Reductase Inhibitors***      394007500      802      42      54      188      129      1.46      11.82      0.0217        Simvastain      3940007500      802      42      54      188      129      1.46      11.82      0.02207        False Positive      Inhibitors***      394000      208      42      54      414      322.99      1.28      11.80      0.02207        Selective Serotonin Reuptake Inhibitors (SSRIs)***      581600      1044      32      59      469      372.2      1.26      11.66	Positive										
Yellow=Likely    *Central Muscle    *Central Muscle    *Central Muscle    *Central Muscle      Relaxants***    751000    1243    54    63    222    153.14    1.45    13.60    0.00279      Positive    Levofloxacin    50003400    1115    1    3    161    104.99    1.53    12.84    0.00669      Pink=Likely    *Benzodiazepines***    571000    1491    41    63    531    425.52    1.25    12.16    0.01492      Simvastatin    3940007500    802    42    54    188    129    1.46    11.82    0.0217      *HMG CoA Reductase    1nhibitors***    394000    2008    42    54    414    322.99    1.28    11.80    0.02207      *Selective Serotonin    Reuptake Inhibitors    581600    1044    32    59    469    372.2    1.26    11.66    0.02514		•									
Yellow=Likely    Relaxants***    751000    1243    54    63    222    153.14    1.45    13.60    0.00279      Positive    Levofloxacin    50003400    1115    1    3    161    104.99    1.53    12.84    0.00669      Levofloxacin    5000034    1116    1    3    161    105.09    1.53    12.79    0.00718      Benzodiazepines***    571000    1491    41    63    531    425.52    1.25    12.16    0.01492      Pink=Likely    Simvastatin *HMG CoA Reductase    3940007500    802    42    54    188    129    1.46    11.82    0.02207      False Positive    Inhibitors***    394000    2008    42    54    414    322.99    1.28    11.80    0.02207      Keuptake Inhibitors (SSRIs)***    581600    1044    32    59    469    372.2    1.26    11.66    0.02514		· · ·	5830004010	390	19	30	122	72.96	1.67	13.69	0.00254
Positive    Relating ***    131000    1243    54    63    222    133.14    1.43    13.00    0.00279      Positive    Levofloxacin    500003400    1115    1    3    161    104.99    1.53    12.84    0.00669      Levofloxacin    5000034    1116    1    3    161    105.09    1.53    12.79    0.00718      Pink=Likely    Simvastatin    3940007500    802    42    54    188    129    1.46    11.82    0.0217      False Positive    Inhibitors***    394000    2008    42    54    414    322.99    1.28    11.80    0.02207      Keidating    Simvastatin *Selective Serotonin Reuptake Inhibitors (SSRIs)***    581600    1044    32    59    469    372.2    1.26    11.66    0.02514	Yellow=Likely										
Levofloxacin    5000034    1116    1    3    161    105.09    1.53    12.79    0.00718      *Benzodiazepines***    571000    1491    41    63    531    425.52    1.25    12.16    0.01492      Simvastatin    *MG CoA Reductase    3940007500    802    42    54    188    129    1.46    11.82    0.0217      False Positive    Inhibitors***    394000    2008    42    54    414    322.99    1.28    11.80    0.02207      Keuptake Inhibitors    581600    1044    32    59    469    372.2    1.26    11.66    0.02514	,										
*Benzodiazepines***    571000    1491    41    63    531    425.52    1.25    12.16    0.01492      Pink=Likely    Simvastatin    3940007500    802    42    54    188    129    1.46    11.82    0.0217      False Positive    Inhibitors***    394000    2008    42    54    414    322.99    1.28    11.80    0.02207      Keuptake Inhibitors    581600    1044    32    59    469    372.2    1.26    11.66    0.02514	Positive										
Pink=Likely    Simvastatin *HMG CoA Reductase Inhibitors***    3940007500    802    42    54    188    129    1.46    11.82    0.0217      False Positive    Inhibitors***    394000    2008    42    54    414    322.99    1.28    11.80    0.02207      Selective Serotonin Reuptake Inhibitors (SSRIs)***    581600    1044    32    59    469    372.2    1.26    11.66    0.02514											
PTITK-LIKETy    *HMG CoA Reductase      *HMG CoA Reductase    394000    2008    42    54    414    322.99    1.28    11.80    0.02207      False Positive    Inhibitors***    394000    2008    42    54    414    322.99    1.28    11.80    0.02207      Keuptake Inhibitors    581600    1044    32    59    469    372.2    1.26    11.66    0.02514		-									
False Positive    Inhibitors***    394000    2008    42    54    414    322.99    1.28    11.80    0.02207      Selective Serotonin    Reuptake Inhibitors    581600    1044    32    59    469    372.2    1.26    11.66    0.02514	Pink=Likelv		3940007500	802	42	54	188	129	1.46	11.82	0.0217
*Selective Serotonin Reuptake Inhibitors (SSRIs)*** 581600 1044 32 59 469 372.2 1.26 11.66 0.02514											
Reuptake Inhibitors      581600      1044      32      59      469      372.2      1.26      11.66      0.02514	False Positive		394000	2008	42	54	414	322.99	1.28	11.80	0.02207
(SSRIs)*** 581600 1044 32 59 469 372.2 1.26 11.66 0.02514											
		•									
Triazolam 6020104000 35 51 52 8 0.77 10.41 11.51 0.02985											
		Triazolam	6020104000	35	51	52	8	0.77	10.41	11.51	0.02985

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#### **Tree-Temporal Alerts after Pruning**

			Window	Window	Cases in	Exp	ected	Observed/	Test	
Node Name	Node ID	Node Cases	Start	End	Window	Cas	es	Expected	Statistic	P-Value
Sulfamethoxazole-Trimethoprim	1699000230	1812	2	3	12	598	373.06	1.6	5 57.51	1.00E-05
Lisinopril	3610003000	2169	)	1	8	590	402.72	1.4	7 38.23	1.00E-05
*ACE Inhibitors***	361000	2649	)	2	8	594	407.13	1.40	5 37.71	1.00E-05
Levofloxacin	500003400	1115	5	1	6	249	158.23	1.5	7 22.18	1.00E-05
Levofloxacin	5000034	1116	5	1	6	249	158.39	1.57	7 22.08	1.00E-05
*Fluoroquinolones***	50000	3159	)	1	6	588	447.95	1.3	L 20.02	1.00E-05
Minocycline HCl	400004010	199	)	15	19	44	15.95	2.70	5 16.60	3.00E-05
Clindamycin	16220020	770	)	1	7	189	127.28	1.48	3 13.02	0.0012
Clindamycin HCl	1622002010	769	)	1	7	188	127.1	1.48	3 12.71	0.0018
Bupropion HCl	5830004010	390	)	18	31	136	85.58	1.59	) 12.59	0.00199
Lisinopril & Hydrochlorothiazide	3699180255	748	3	2	9	188	128.84	1.40	5 11.90	0.00465
ACE Inhibitors & Thiazide/Thiazide-Like	36991802	814	1	2	9	201	139.95	1.44	11.74	0.00571
Triazolam	6020104000	35	5	51	52	8	0.94	8.48	3 10.05	0.0463

- 13 unique at 3<sup>rd</sup> level, 9 meaningfully different
- Some new antibiotics, ACEI Combos are statistically significant.
- Some alerts become not statistically significant at 0.05 level (e.g., simvastatin)