Phenotyping Adverse Drug Reactions: Statin-Related Myotoxicity

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RATIONALE

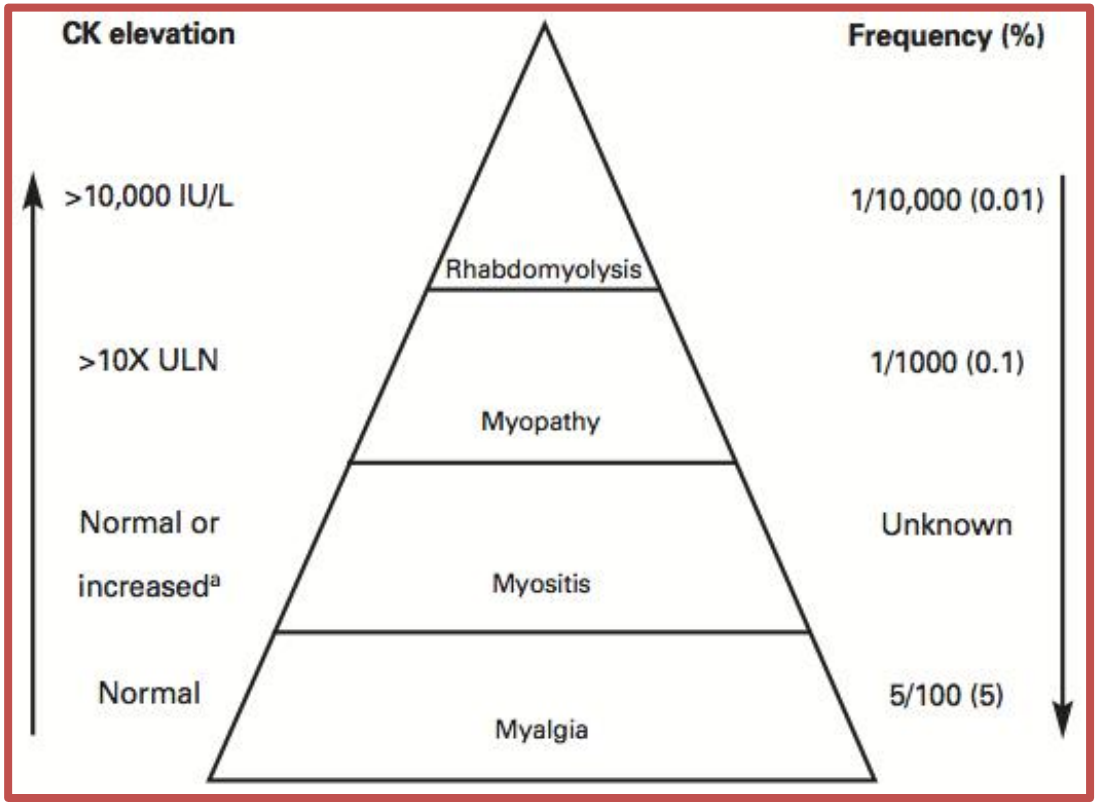
- It is unclear how well best practices for disease phenotyping translate to phenotyping adverse drug events
- Unique challenges
  - Ideally ADEs only occur once
  - Reaction severity may vary
  - May not be clear diagnostic criteria

Rationale – Why Statin Myotoxicity?

- Statins –
  - Widely used (~1/4 Americans > 45, circa 2010)
  - Myotoxicity side-effect leading cause of discontinuation

Unique Phenotyping Challenges

1) Single event
2) Reaction severity varies
3) May not be clear diagnostic criteria



Goal

Test a variety of phenotyping approaches against a *single, consistent definition* of statin myotoxicity.

Background – Who has done this before?

- Mareedu et al. 2009
- Skentzos et al. 2011
- Khan et al. 2011, 2012
- Floyd et al. 2012
- Duke et al. 2012
- Sai et al. 2013
- Zhang et al. 2013
- Carr et al. 2013
- O'Meara et al. 2013
- Dube et al. 2013

ICD-9 Codes

CK Elevation

Natural Language Processing

Combination

Approach – Record Review

- Started with ~7000 person cohort
- 300 Records w/ Statins (from MedE)
  - 138 selected for "myopathy" keywords
    - cramp, muscle, pain, myo*, mya*, rha*, ache, weak, hold, dc
  - 162 selected at random
- Review every statin mention in MR
- "True Cases"
  - Any muscle symptom attributed to statin by care provider (anywhere in record)

Approach - Phenotyping Methods (1)

- ICD-9 Codes
  - Drug Side Effect (5)
    - e.g., 972.2 – poisoning by antilipemic & antiarteriosclerotic drugs
    - Any time in record
  - General Muscle Effects (7)
    - e.g., 359.9 – myopathy unspecified
    - Only after 1st statin mention

Approach - Phenotyping Methods (2)

- Creatine Kinase (CK) – after 1st Statin

  Previously in Literature

  1. CK > 3x Upper Limit Normal (ULN)
  2. CK (any value), not at same time as troponin
  3. CK > 3x ULN, not at same time as troponin

  New Approaches

  4. CK (any value), single measurement*
  5. CK > 3x ULN, single measurement*

* Only CK measurement within 5 day period.

Approach - Phenotyping Methods (3)

- Listed Drug Allergies

Problem List

Adverse & Allergic Drug Reactions
Atorvastatin (unknown)
~~Simvastatin (LFTs)~~

Medications
Metformin ER 500 mg
Pitavastatin 4mg
Niacin 250mg

Health Problems
Diabetes Mellitus
Hyperlipidemia

H&P Notes

HISTORY OF PRESENT ILLNESS: Mr. XXX is a pleasant 50 year old gentleman with a history of diabetes mellitus and hyperlipidemia who presents with unspecified muscle pains, possibly due to his statin.

ALLERGIES: Statins unkown; Atorvastatin causes myopathy
MEDICATIONS: Metformin, Niacin, Pitavastatin

All Code Available at: https://github.com/laurakwiley/StatinMyopathy

Approach - Phenotyping Methods (4)

- Keyword Searching

Clinical Comm.

NAME[STARUSER]: Mr. XXX called saying that he is having severe muscle **pain after increasing his dose of *atorvastatin* and would to know what to do.
**NAME[STARUSER]: Please call him back and tell his to stop taking the statin for 2 wks and see if his symptoms resolve.
**NAME[STARUSER]: Done.

High Value Docs

HISTORY OF PRESENT ILLNESS: Mr. XXX is a pleasant 50 year old gentleman with a history of diabetes mellitus and hyperlipidemia who presents with unspecified **muscle pains, possibly due to his *statin*.**

ALLERGIES: Statins unkown; Atorvastatin causes myopathy
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All Code Available at: https://github.com/laurakwiley/StatinMyopathy

Results – Review Population

Review Population

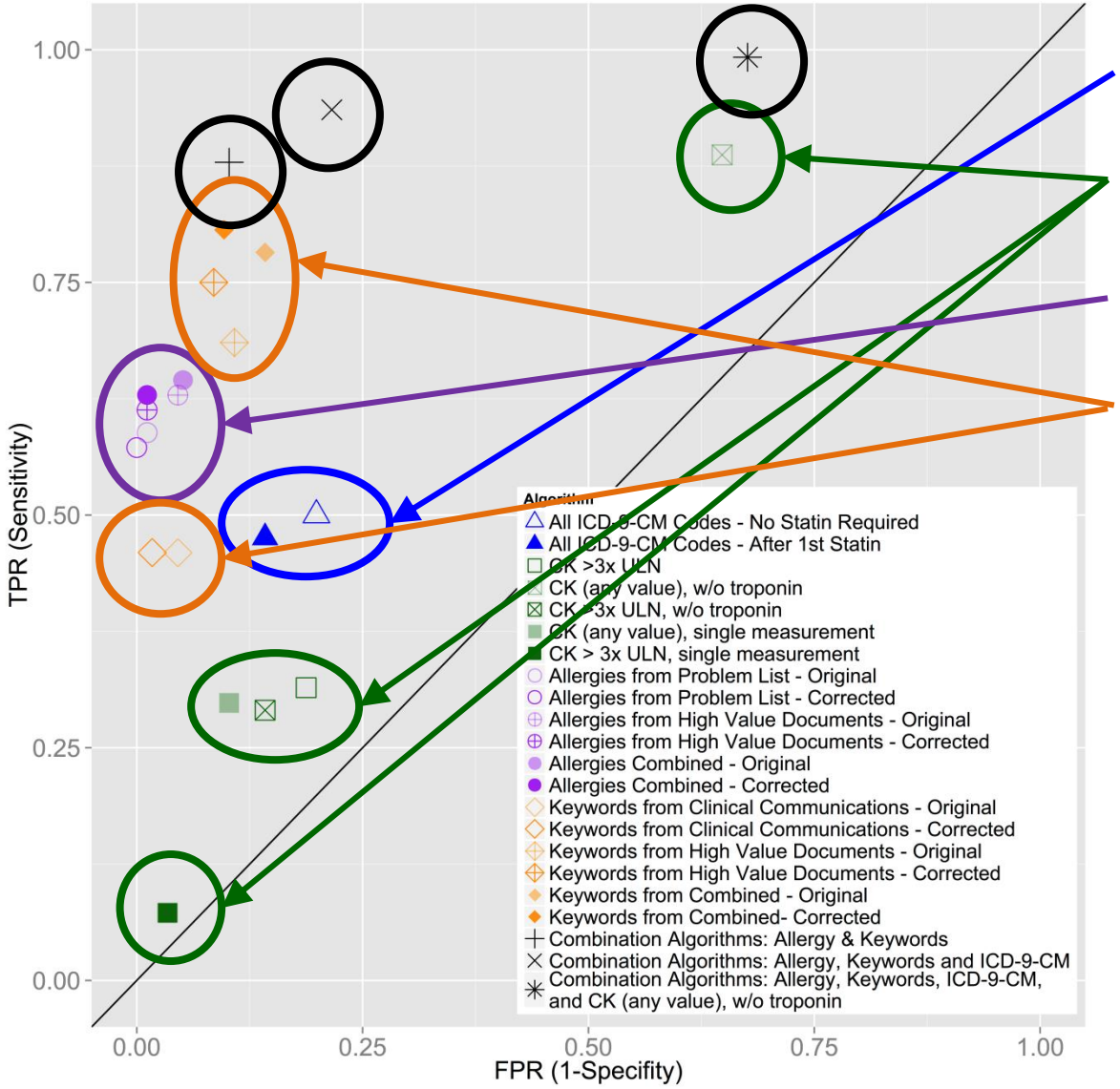
- 300 Records w/ Statins
  - 138 selected for "myopathy" keywords
  - 162 selected at random

	Statin Ever Prescribed[1] (n=300)	Attributed to Myotoxic Event[1,2] (n=124)
Atorvastatin	150 (50%)	64 (51.6%)
Fluvastatin	25 (8.3%)	5 (4%)
Lovastatin	42 (14%)	11 (8.9%)
Pitavastatin	1 (0.3%)	0
Pravastatin	99 (33%)	31 (25%)
Rosuvastatin	60 (20%)	19 (15.3%)
Simvastatin	235 (78.3%)	74 (59.7%)
Not Specified	0	8 (6.5%)

[1]Includes overlap (i.e., patients on multiple statins)

[2]Percentages of 124 myopathy events.

Results – Algorithm Performance



ICD-9 Codes

CK Elevation

Allergies

Keywords

Combined

- **Allergy+Keyword**
- **Allergy+Keyword+ ICD-9**
- **Allergy+Keyword+ ICD-9 + CK (any value) no troponin**

LIMITATIONS

- Selection Method for Review Population
  - May improved performance of text approaches
  - May have inflated PPV due to higher case proportion
- Reviewed 50 additional, independent records (randomly selected statin exposed individuals)
  - *Manual Review:* 8 cases, 42 controls
  - *Text-Only Combined Algorithm:* 3 cases, 47 controls

    PPV = 100% Sensitivity = 38%

    NPV = 89% Specificity = 100%

Conclusions & Discussion

- **Conclusions**
  1. ICD-9 codes or Creatine Kinase measurements alone are insufficient for phenotyping statin myotoxicity.
  2. Text Mining provides the most balanced results and are not strongly improved by addition of multiple data types (ICD-9, CK measurements, etc.)
- **Discussion**
  - "Best" algorithm depends on study design
  - Important to tailor text algorithms to study population

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  - https://github.com/laurakwiley/StatinMyopathy