

Developing Random Forest Models for Medication Response and Implementation in the Epic EMR

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Outline of Talk

- Background – IBD, IBD Therapies, Epic EMR
- Thiopurines and Patterns
- Building the Team
- Available Data in Clinical Data Warehouse
- ThioMon modeling and validation
- Missing Laboratory Data
- ThioMon implementation
- Challenges and Lessons Learned/Learning
- Vedolizumab

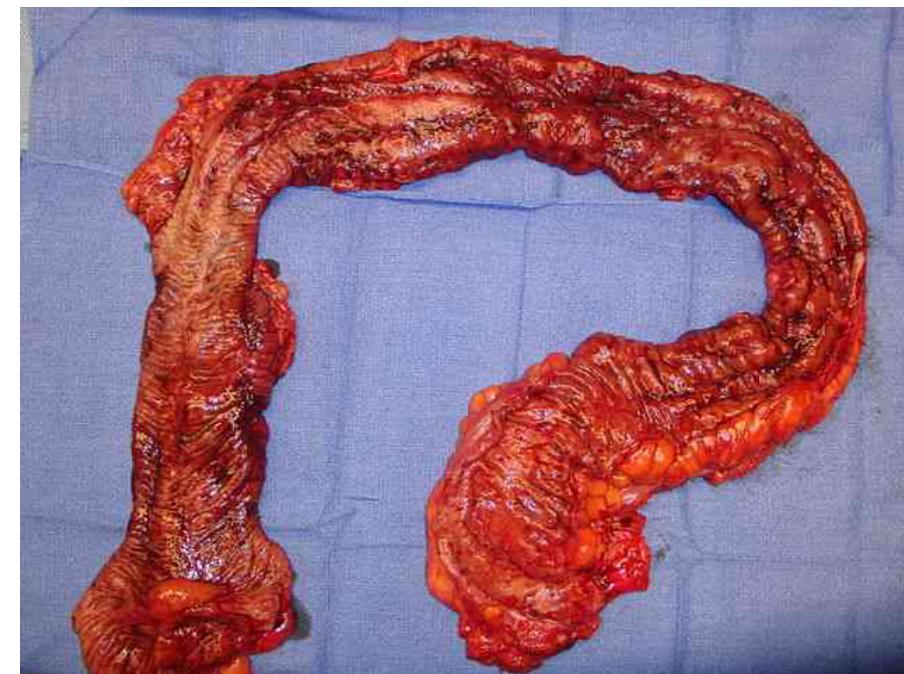


Inflammatory Bowel Diseases



Ulcerative colitis
Crohn's disease

Unpredictable, waxing and waning course of symptoms



IBD Therapies

Most patients will not respond to first therapy

Older Therapies

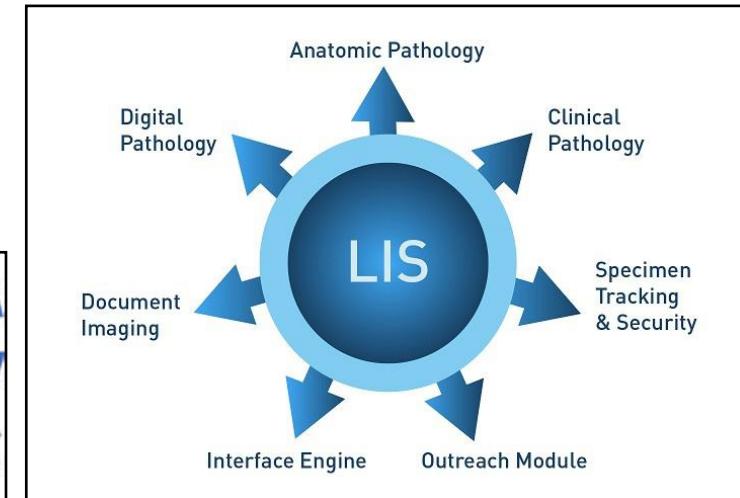
- Include
 - Azathioprine
 - 6-Mercaptopurine
 - Methotrexate
- Features
 - Small molecules, tablets
 - Remission in ~ 30%
 - ~ \$3K per year

Newer Therapies

- Include
 - Remicade
 - Humira
 - Stelara
- Features
 - Antibodies, injected
 - Remission in ~ 50%
 - \$20-120K per year

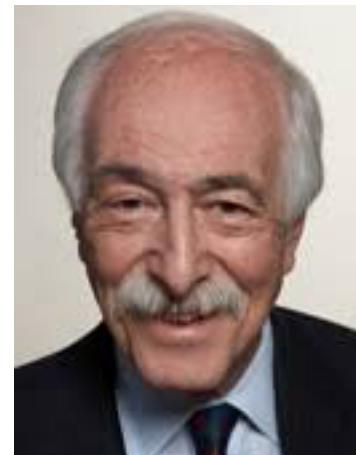
What is Epic?

- Epic is an Electronic Medical Record.
- Designed to optimize billing revenue.
- Implemented in many sites in US in response to IT mandate in ACA.
- Capable of more than billing, but many computing capabilities are underused.
- Laboratory Information System = Soft



Thiopurines and Patterns

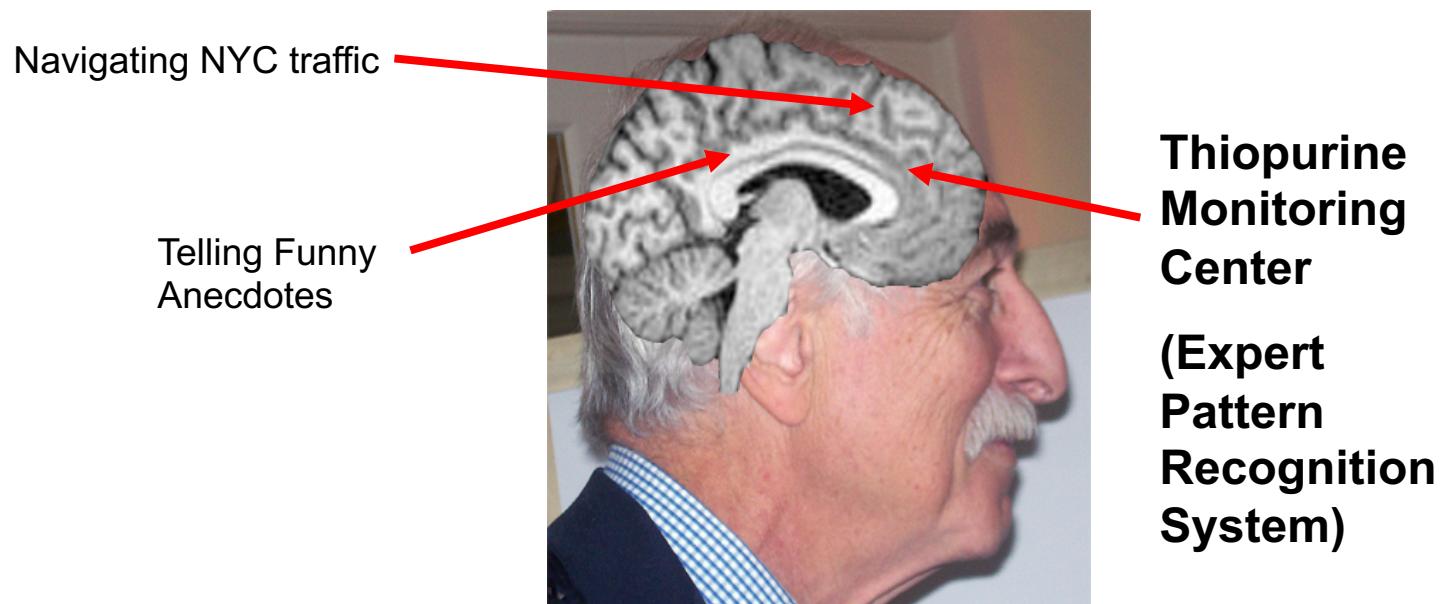
- Thiopurines are old chemotherapy drugs – generic, inexpensive
- At low doses, are very effective immune suppressants
- Work really well in IBD in ~ 30% of patients
 - Which patients?
 - How do you know if drug is working vs. spontaneous remission?
- Dan Present – I don't need expensive metabolite tests
- I can look at the patterns in the labs
 - Blood counts – white cells decreased, size of red cells increased
 - Chemistries – mild rise in alkaline phosphatase
 - Then I know it is working well.



Dan Present, MD

Hypothesis

- There is a consistent pattern in blood counts and chemistries that indicates effective immunosuppression by thiopurines
- Can we find and define Dan Present's pattern?



Data in the Clinical Data Warehouse

- Patients on thiopurines are at risk of toxicity
 - Bone marrow (blood counts plus differential)
 - Liver (chemistry panel)
 - 31 distinct results
- Routine monitoring every 3 months while on drug
- Over 1,000 patients on thiopurines with lab data
 - Very high quality data – CLIA certified, regular QI
 - All available electronically
- Clinical data in EMR
 - Outcomes defined
 - Requires a *lot* of expert clinical grunt work to accurately classify success vs. failure
 - Some cases with inadequate documentation



A blue arrow points from the text "All available electronically" in the list above to the screenshot of the Epic EMR interface below, indicating that the data is accessible through the electronic medical record system.

Problems	Procedures	Results	Reports	Notes	Medications	Orders	Discharge	Transfusions
All Results	None	None	None	None	None	None	None	None
Blood								
Immunology								
U&G Creatinine	140	140	140	140	140	140	140	140
U&G Urea	200	200	200	200	200	200	200	200
U&G Alkaline Phosphatase	100	100	100	100	100	100	100	100
U&G Cholestrol	200	200	200	200	200	200	200	200
U&G Bilirubin	10	10	10	10	10	10	10	10
U&G BUN	100	100	100	100	100	100	100	100
U&G Creatinine kinase	100	100	100	100	100	100	100	100
U&G Lactate dehydrogenase	100	100	100	100	100	100	100	100
U&G Glutamyl transpeptidase	100	100	100	100	100	100	100	100
U&G Alanine transpeptidase	100	100	100	100	100	100	100	100
U&G Gamma glutamyl transferase	100	100	100	100	100	100	100	100
U&G Total protein	70	70	70	70	70	70	70	70
U&G Albumin	50	50	50	50	50	50	50	50
U&G Globulin	20	20	20	20	20	20	20	20
U&G Sodium	140	140	140	140	140	140	140	140
U&G Potassium	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
U&G Chloride	100	100	100	100	100	100	100	100
U&G Bicarbonate	25	25	25	25	25	25	25	25
U&G Urine Specific Gravity	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
U&G Urine pH	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0
U&G Urine Protein	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
U&G Urine Ketones	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
U&G Urine Nitrite	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
U&G Urine Leukocytes	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
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U&G Urine Urea Nitrogen	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
U&G Urine Creatinine	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
U&G Urine Uric Acid	0.0	0.0	0.0	0.0	0.0</			

Building a Team



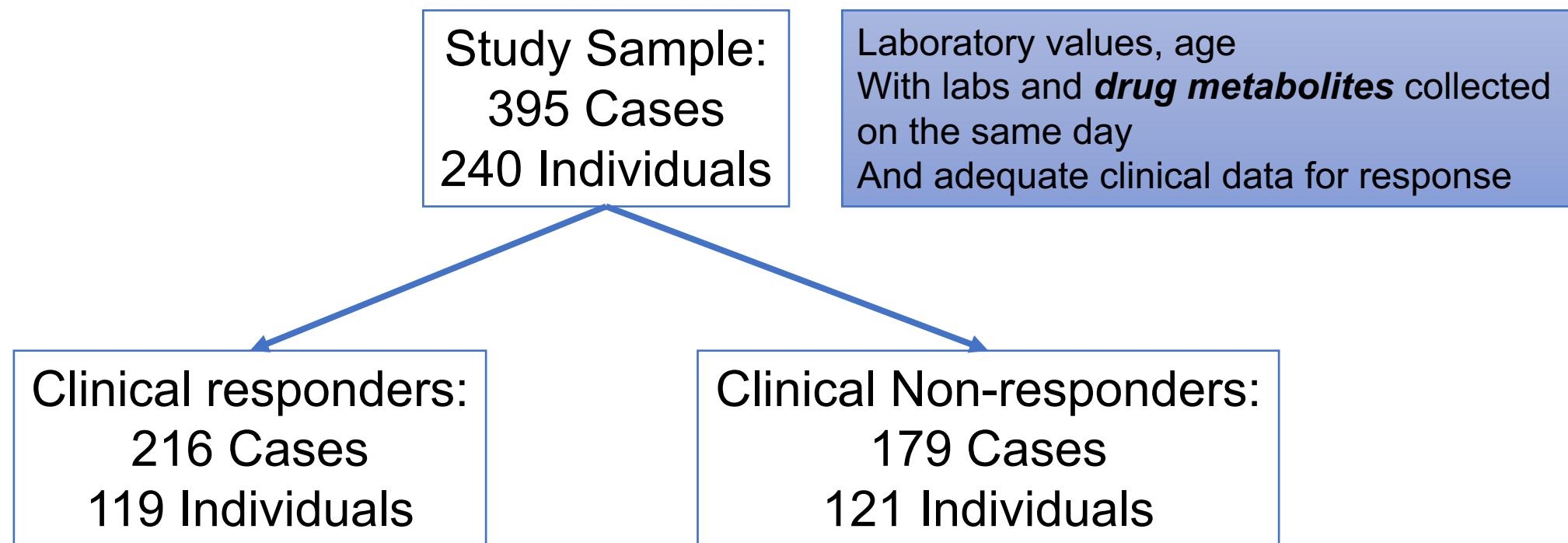
Ji Zhu, Statistics and ML



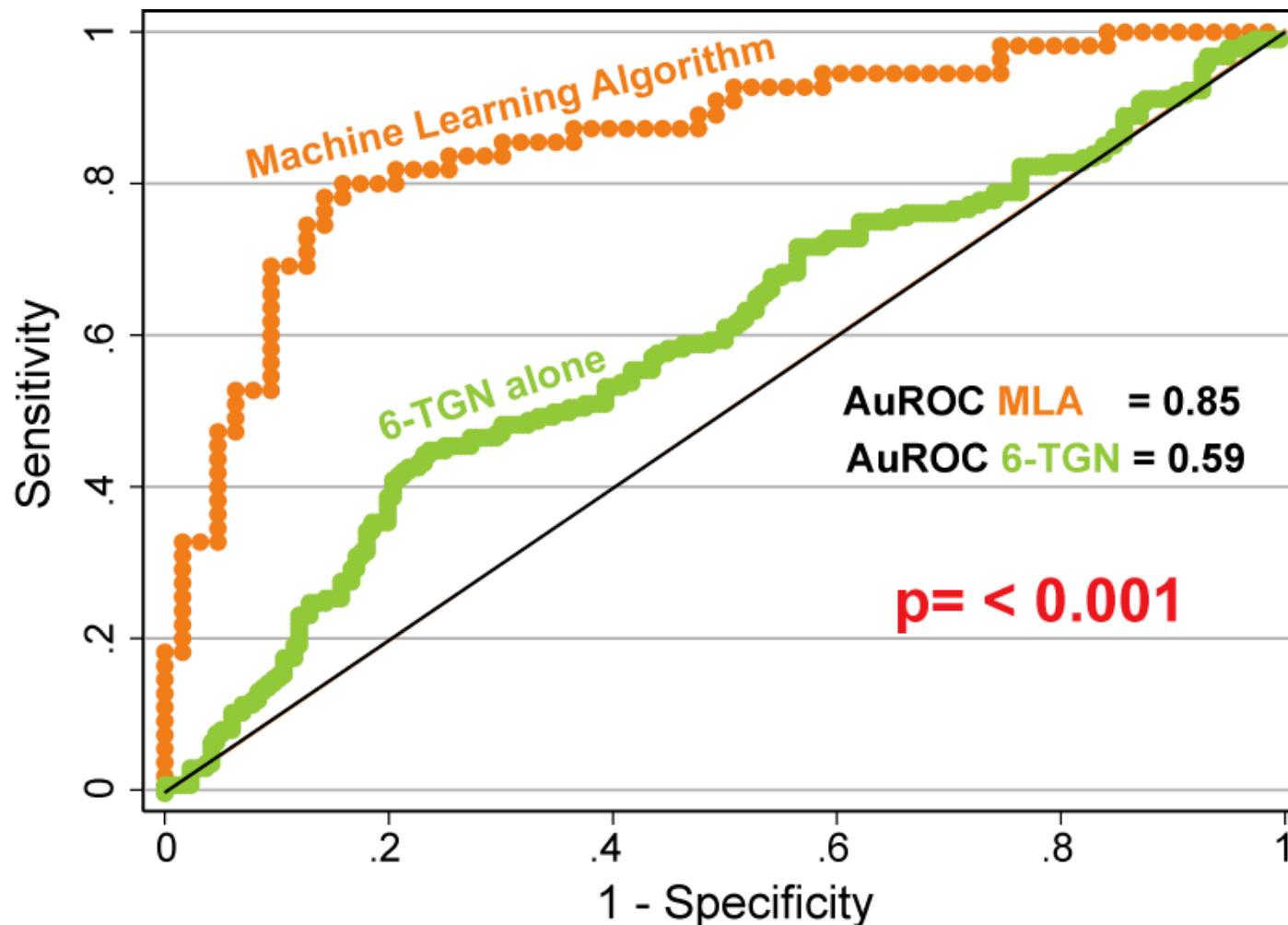
Ulysses Balis, Pathology IT

Thiopurine Modeling

- SVM vs Gradient boosting vs. Random Forest

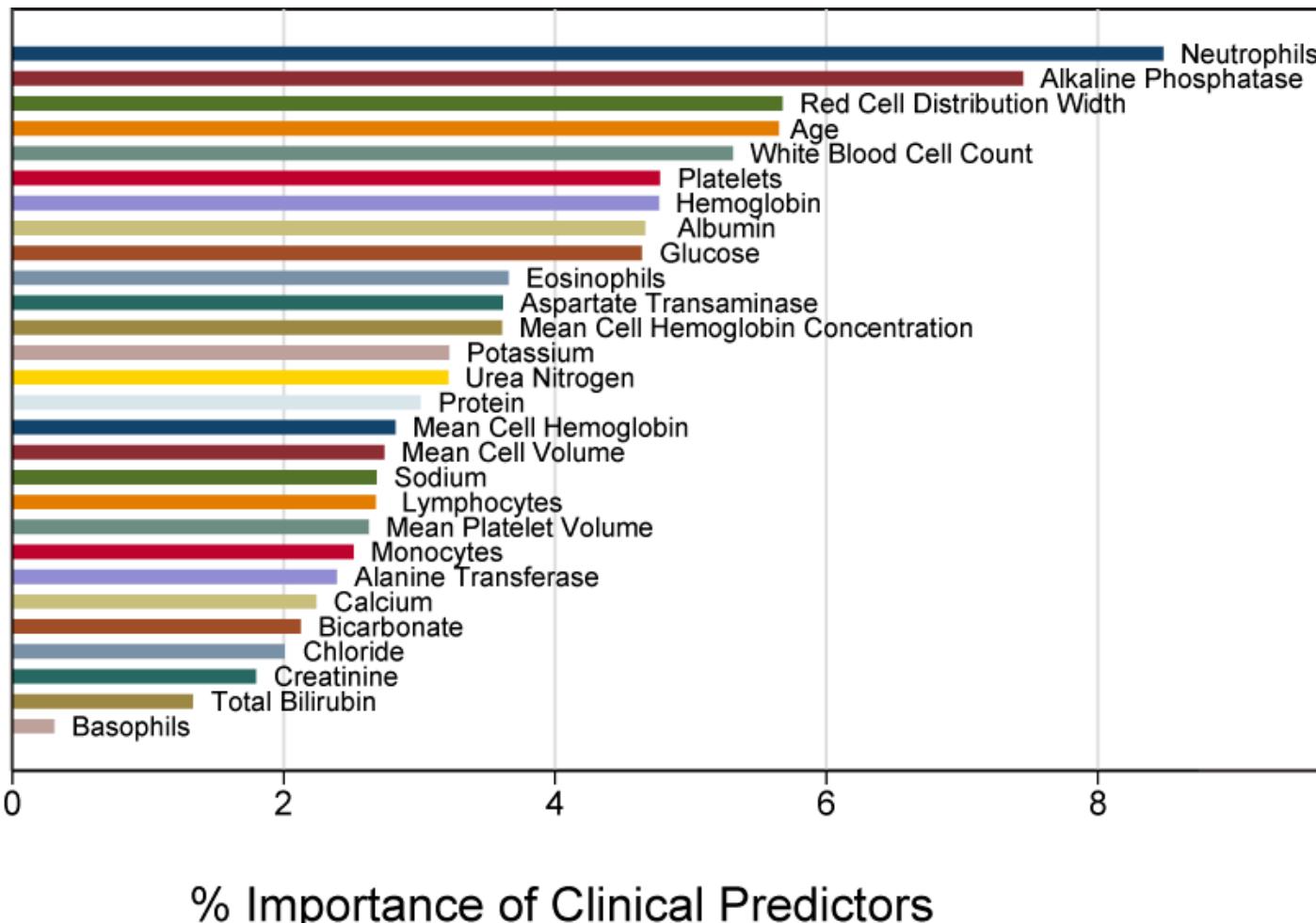


Clinical Response Model – Random Forest



Clin Gastroenterol Hepatol.
2010 Feb;8(2):143-50

Clinical Response Model - RF



[Clin Gastroenterol Hepatol.](#)
2010 Feb;8(2):143-50

Predicting Other Outcomes

- Shunting algorithm
 - AuROC of 0.80

Is drug being shunted to an alternative, toxic pathway (1 in 300 people) ?

- Non-adherence algorithm
 - AuROC of 0.81

Is the patient not actually taking the drug?

The Problem with Clinical Response as an Outcome

It is a mess

Clinical Response = ?

- Control of Irritable Bowel Syndrome?
- Several large RCTs in 2008-2012
 - Many “active” patients by symptom scores do not have
 - Elevated CRP (blood marker of inflammation)
 - Ulceration on endoscopy
 - These patients are unlikely to respond to anti-inflammatory Rx
- FDA ended symptom scores for therapeutic trials in IBD
- Field moving to BR = biologic remission

What is BR?

- Objectively measured absence of inflammation
 - ESR
 - CRP
 - FCP
 - Endoscopic ulcers
 - Histology of biopsies
 - CT enterography
 - MR enterography

Any of these
present
 $BR = 0$

All of these
negative,
 $BR = 1$

The ThioMon 2.0 Overhaul

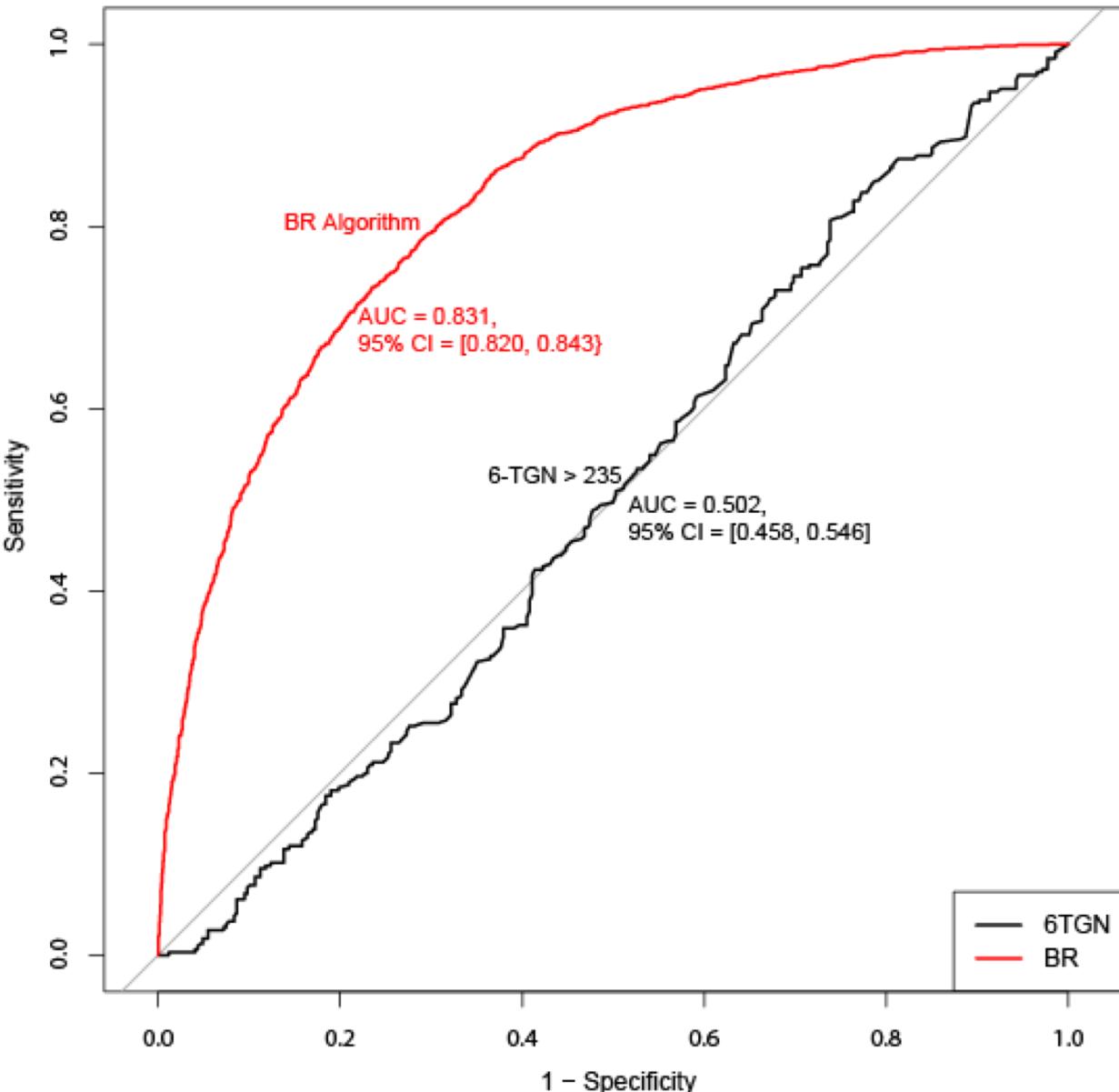
- Rebuild it, using BR as the gold standard
- MUCH higher bar
- N= 3300 subject evaluations
 - 1090 unique patients
 - Enormous chart review task
- Same Random Forest approach

ThioMon 2.0

- Metabolites don't work for BR
- Random Forest algorithm does work for BR

J Crohns Colitis. 2017
Jul 1;11(7):801-810.

ROC curves comparison



ThioMon 2.0

- Also upgraded Shunting algorithm
 - N = 509
 - AuROC = 0.84
- Also upgraded Non-adherence algorithm
 - N = 3012
 - AuROC = 0.78

[J Crohns Colitis.](#) 2017
Jul 1;11(7):801-810.

Clinical Outcomes

- Events present/absent during period:
 - Steroid prescriptions
 - Medication dose increases
 - Hospitalizations
 - Surgeries
- Count # of types of events – 0 to 4
- Convert to event rate per period
 - Events / year
- Divide subjects – sustained PBR, not PBR
 - Predicted Biologic Remission



Compare Clinical Outcomes

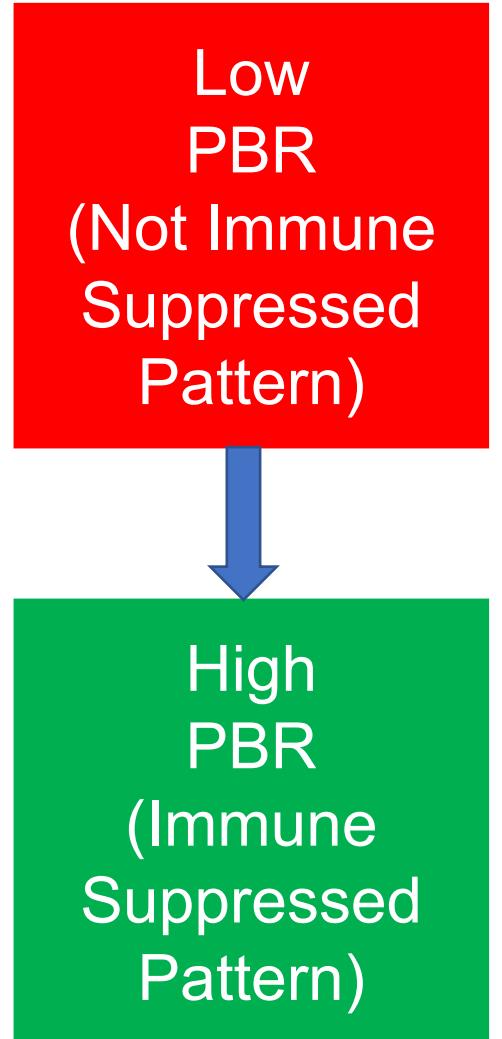
- Patients in Predicted BR (PBR) v. not PBR

	N=274	N=238	
Using Max=4	Sustained PBR	Not PBR	T test P=.0037
Events/year (mean)	1.23	3.38	
Events/year (median)	0.25	1.52	

	Unlimited	Sustained PBR	Not PBR	
Events/year (mean)				T test P=.0002
Events/year (mean)	1.52	4.69		
Events/year (median)	0.29	2.35		

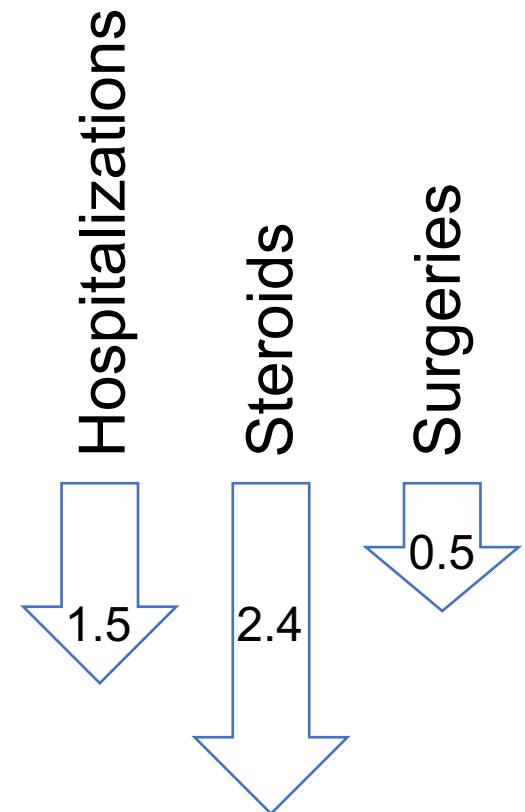
Can this Guide Dosing?

- Look for patients with
 - Consistently low predicted BR that changes to
 - Consistently high predicted BR (N=32)
- Measure Events Pre/Post change
- Prediction – fewer events with high PBR
(Predicted Biologic Remission)
 - Paired t test



Clinical Outcomes Change After Achieving Predicted BR

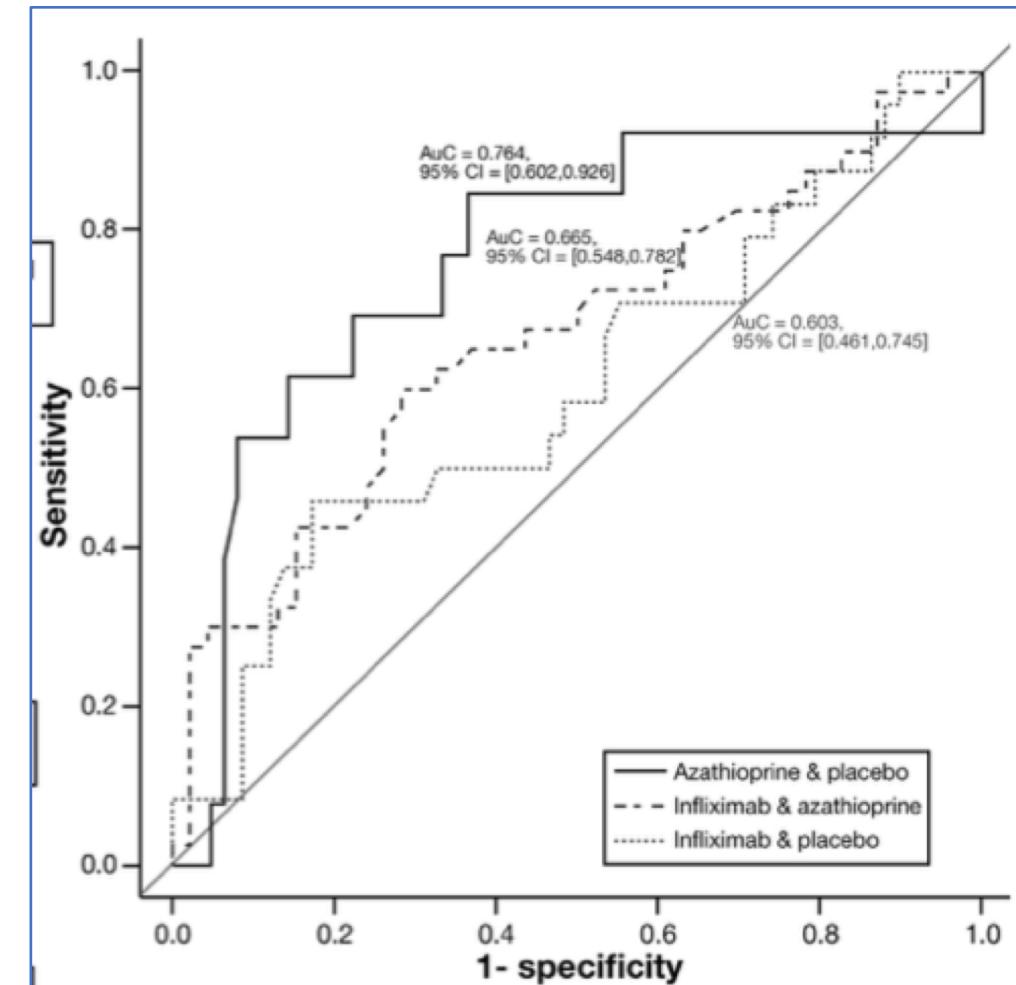
- Hospitalizations decrease $p=0.024$
 - By 1.5/year (95% CI: 0.26 to 2.73)
- Steroid prescriptions decrease $p =0.0003$
 - By 2.4/year (95% CI: 1.24 to 3.55)
- Surgeries decrease – trend $p=0.09$
 - By 0.5/year (95% CI: -0.06 to 0.98)
- Total events (H+S+S) decrease $p=0.0001$
 - By 4.3/year (95% CI: 2.5 to 6.1)



External validation of BR Model

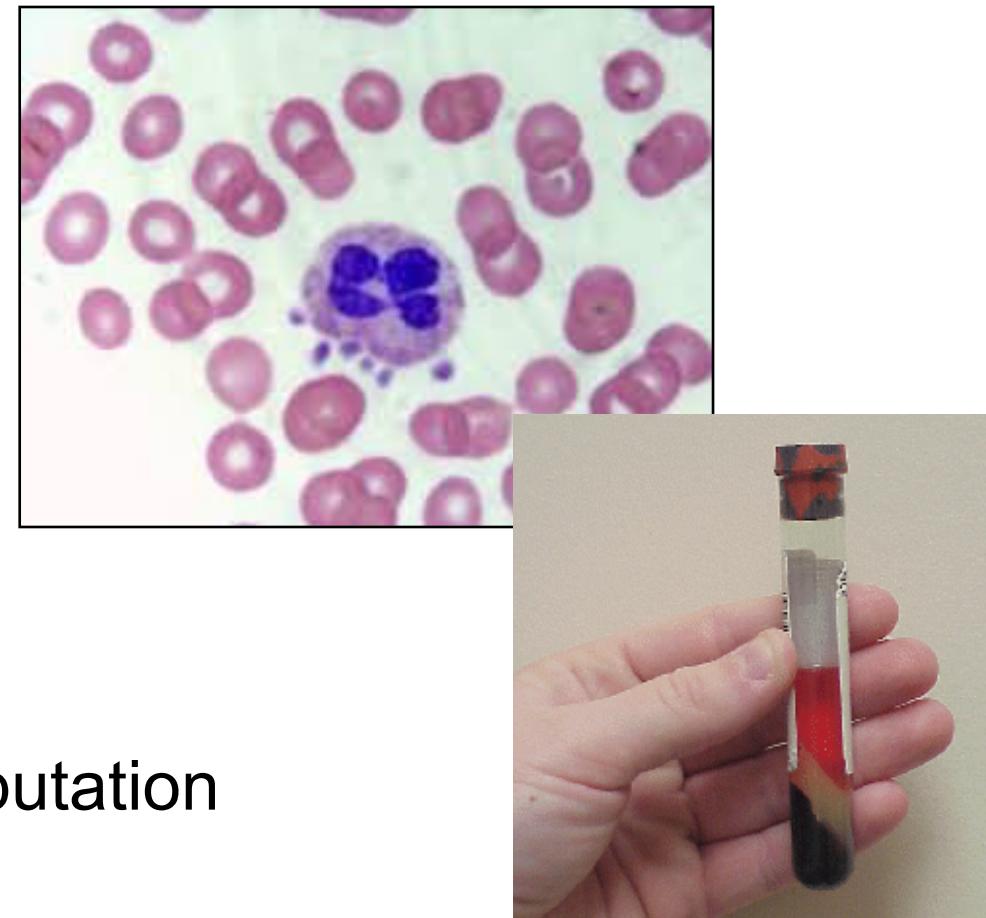
- Prospective RCT of thiopurine vs. Remicade vs. Combo (2010 NEJM)
- Data in YODA Repository
- Applied for access
- Applied BR Algorithm to predict outcomes
- Works well in Azathioprine alone
 - Less well in combo
 - ~ Coin flip in Remicade alone

[Clin Gastroenterol Hepatol.](#) 2018 Mar;16(3):449-451.



Using RF models with Missing data

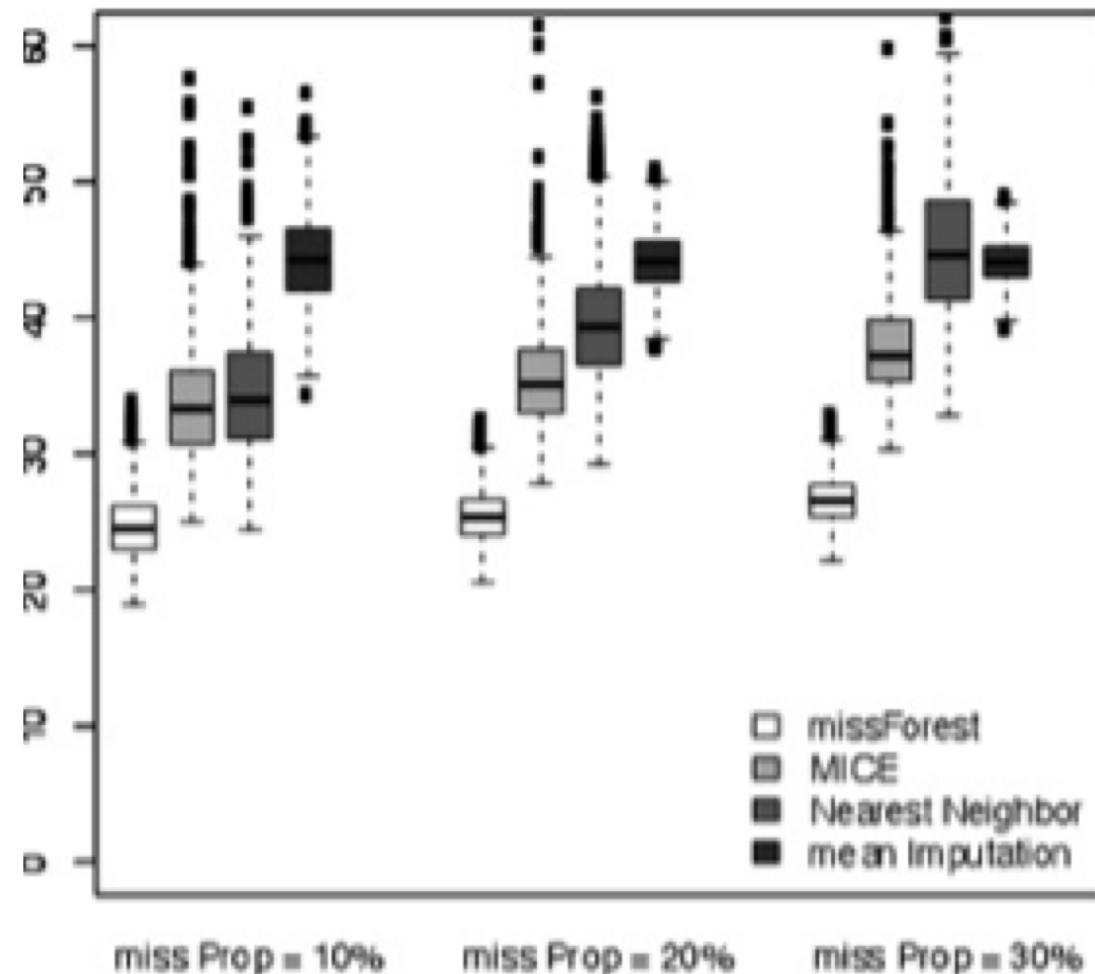
- Laboratory data is sometimes missing
- Largely phlebotomist error
 - Approximates MCAR
- Platelet clumping
 - Unreliable Platelet counts
- Hemolysis
 - Unreliable potassium values
- Missing data bake-off
- MICE vs. MissForest vs.
nearest neighbor imputation vs. mean imputation



Imputing Missing Laboratory Data

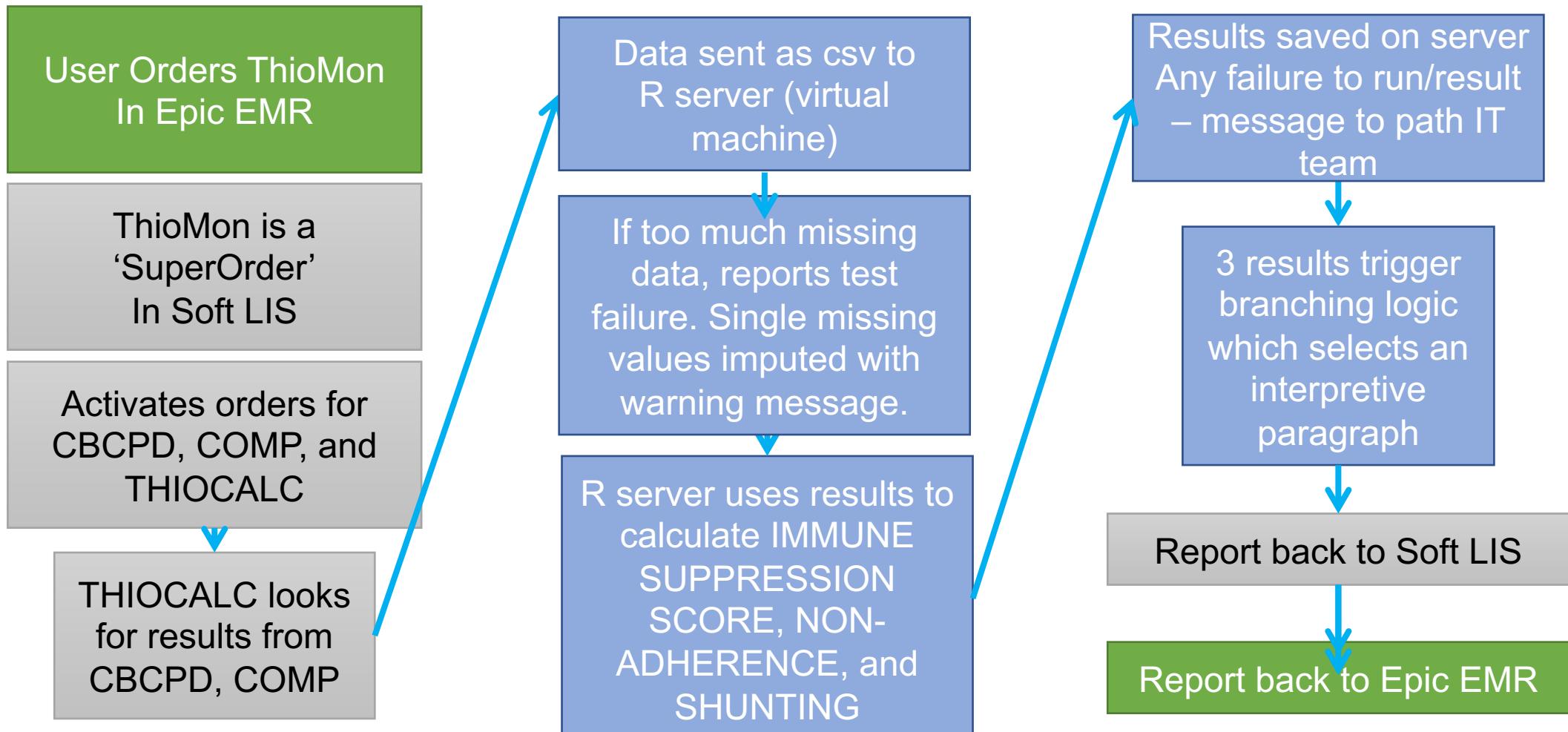
- Started with dataset of complete lab panels from 446 patients
- Pseudo-randomly replaced 10, 20, 30% with NAs in R
- Tested different methods of imputation to replace values
- Looked at degradation of random forest model accuracy
- MissForest wins – robust up to 30% MCAR

Imputation error Continuous variables LR



BMJ Open. 2013; 3(8)

ThioMon implementation



The Competition

- Metabolite testing from Prometheus Labs/Nestle
 - 6-TGN and 6-MMP are active and toxic metabolites
 - Measurable with HPLC, there is a CPT code
 - Mostly covered by insurance
 - NOT a good test
 - But marketed very well
- These are the same people who can sell billions of chocolate bars contaminated with stale rice.



Pathology dollars saved



- Previously ordered over 600 metabolite tests per year @ \$200 each
- Saved > \$120,000 per year in external costs
- Internal algorithm nearly free (virtual machine)
- Happy pathologists and accountants
 - A research project that actually **saved** money!



Dr. Jeffrey Myers
Vice Chair of Clinical Affairs and Quality

Challenges and Lessons Learned/Learning

- An algorithmic test requires repeated education
 - What does this mean?
 - Feels like a black box
 - Metabolites make sense to me.
- Show the data
- Walk through results in their specific patients
- Improve result reporting



Kim Turgeon MD
User Feedback

Result Reporting

- Recalibrate model scores
 - Initially model scores – negative #s
 - Then probabilities – uncertainty scary
 - Recalibrate - over 100 is good
- Limit complexity –
 - don't give more information than is needed
- Provide limited interpretation with branching logic
 - Some providers will use this test < 10 times per year
 - Education from a year ago will **not** stick.

Thiopurine Monitoring Test

Immunosuppression Score 102.3 (>100)

GOOD Result – patient has achieved effective immune suppression with thiopurines. If continued symptoms, consider infection, IBS, or drug failure necessitating a different class of therapy.

Thiopurine Monitoring Test

Immunosuppression Score 92.7 (>100)

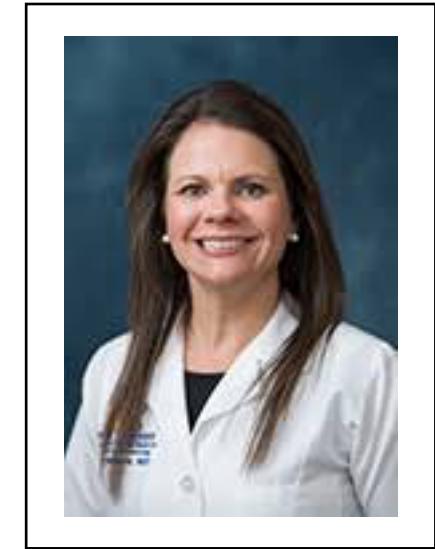
Shunting Score 91.1 (>100)

Non-adherence Score 94.4 (>100)

LOW Result – patient has not achieved effective immune suppression with thiopurines. No evidence of shunting or non-adherence. Consider increasing dose, adding allopurinol, or a different class of therapy.

Challenges and Lessons Learned/Learning

- A new test requires ongoing marketing
 - Especially with heavily-marketed competition
 - Slow but steady backsliding to using old test
 - 30% dropoff after 1 year
 - New faculty who missed original education
- Schedule regular education
 - Target new caregivers
 - Identify, target backsliders
 - Personalized approach to their patients
 - Out-market the chocolate rice sellers.



Jami Kinnucan, MD



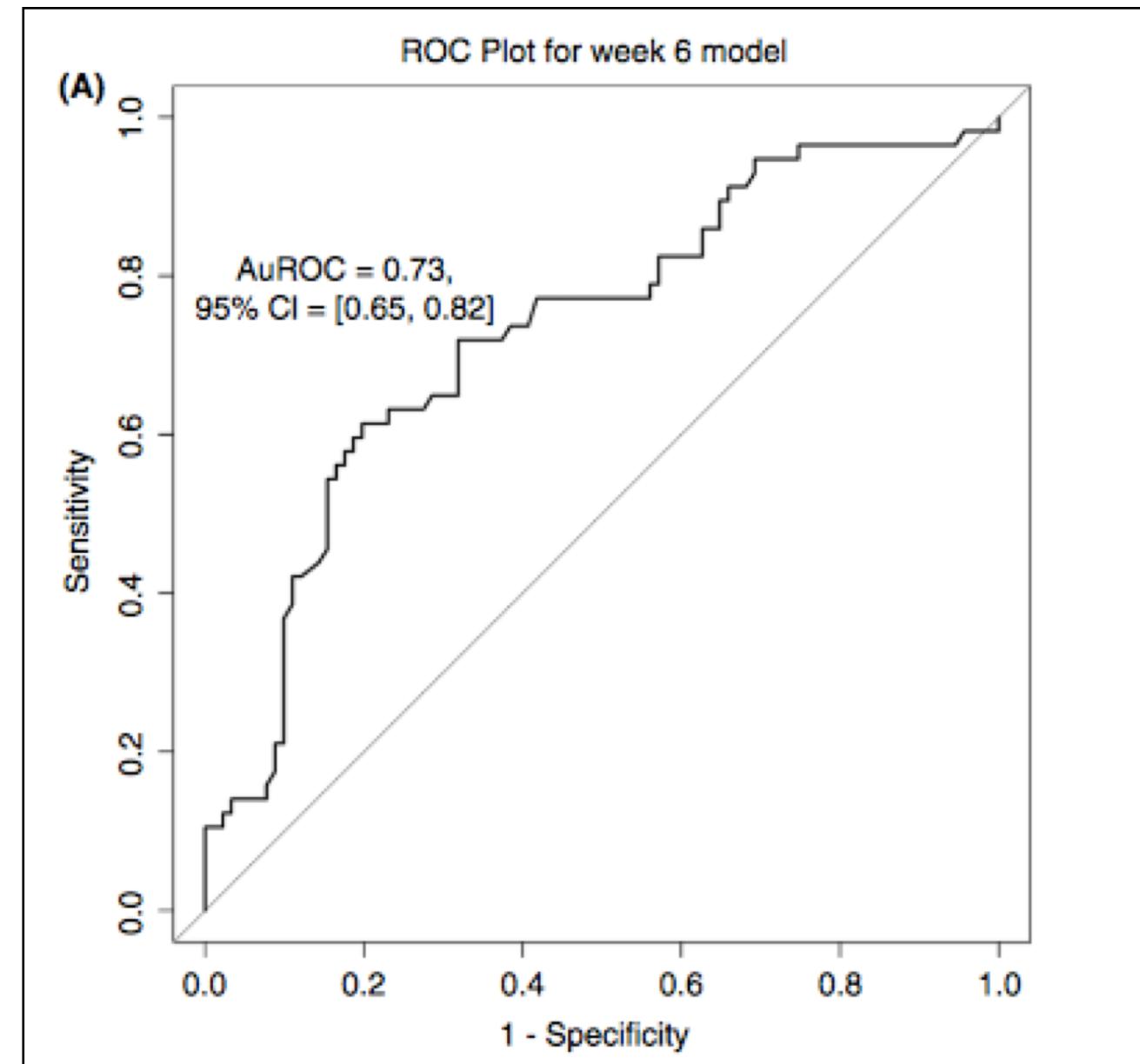
Vedolizumab in Ulcerative Colitis

- Expensive biologic therapy ~ \$20K per dose, q 8 weeks
- Phase 3 trial data at <https://www.clinicalstudydatarequest.com>
- Outcome – colon healed at week 52 AND off all steroid therapy.
- Predictors of response
 - All labs gathered, plausible clinical factors
 - At baseline – models are terrible—AuROC ~ 0.6
 - At week 6 (just before 3rd dose), RF models are reasonable.



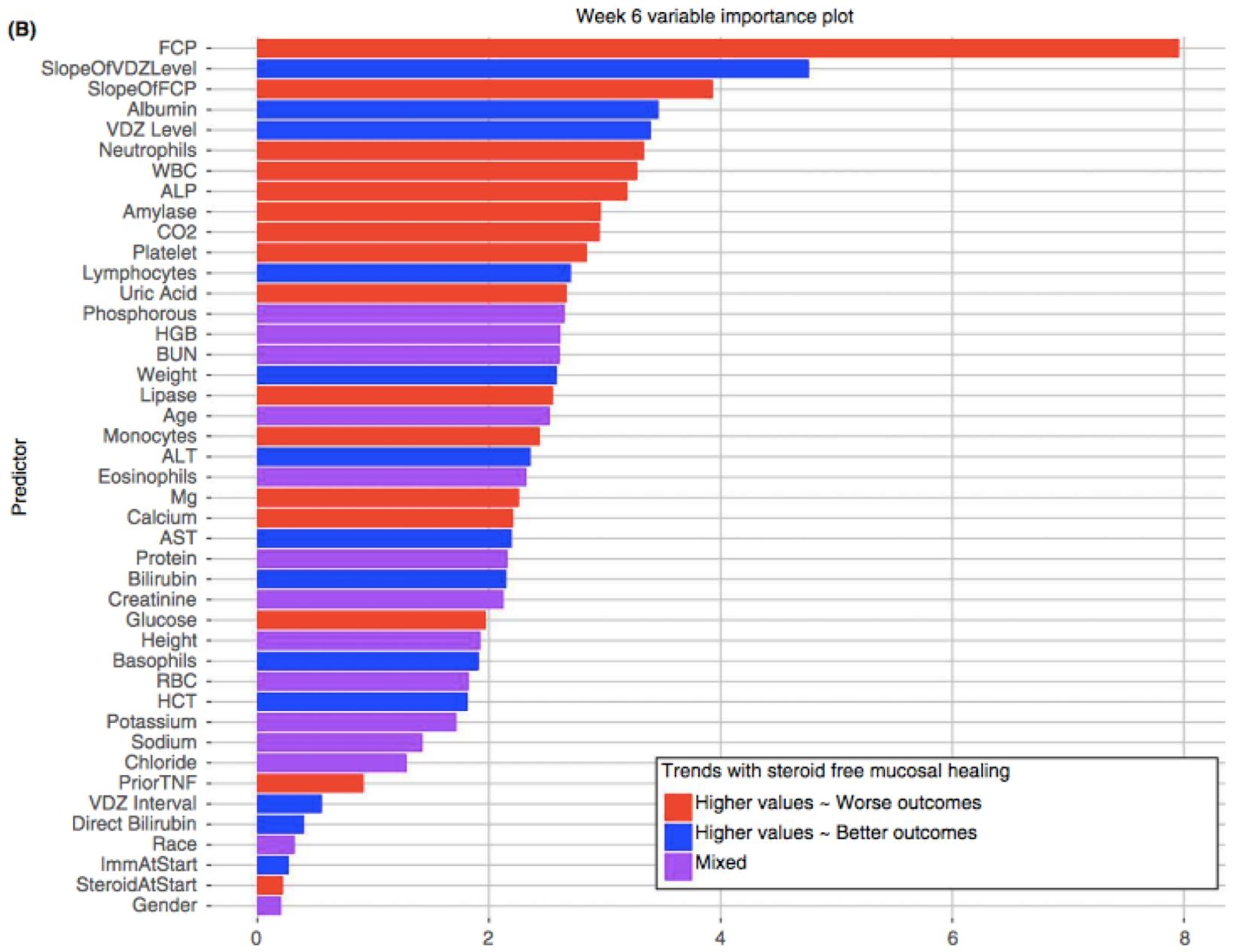
Week 6 Model

[Aliment Pharmacol Ther. 2018
Mar;47\(6\):763-772.](#)



Week 6 Model

Aliment Pharmacol Ther. 2018
Mar;47(6):763-772.



Clinicians want a Simple Model: Consider week 6 calpro/drug level ratio

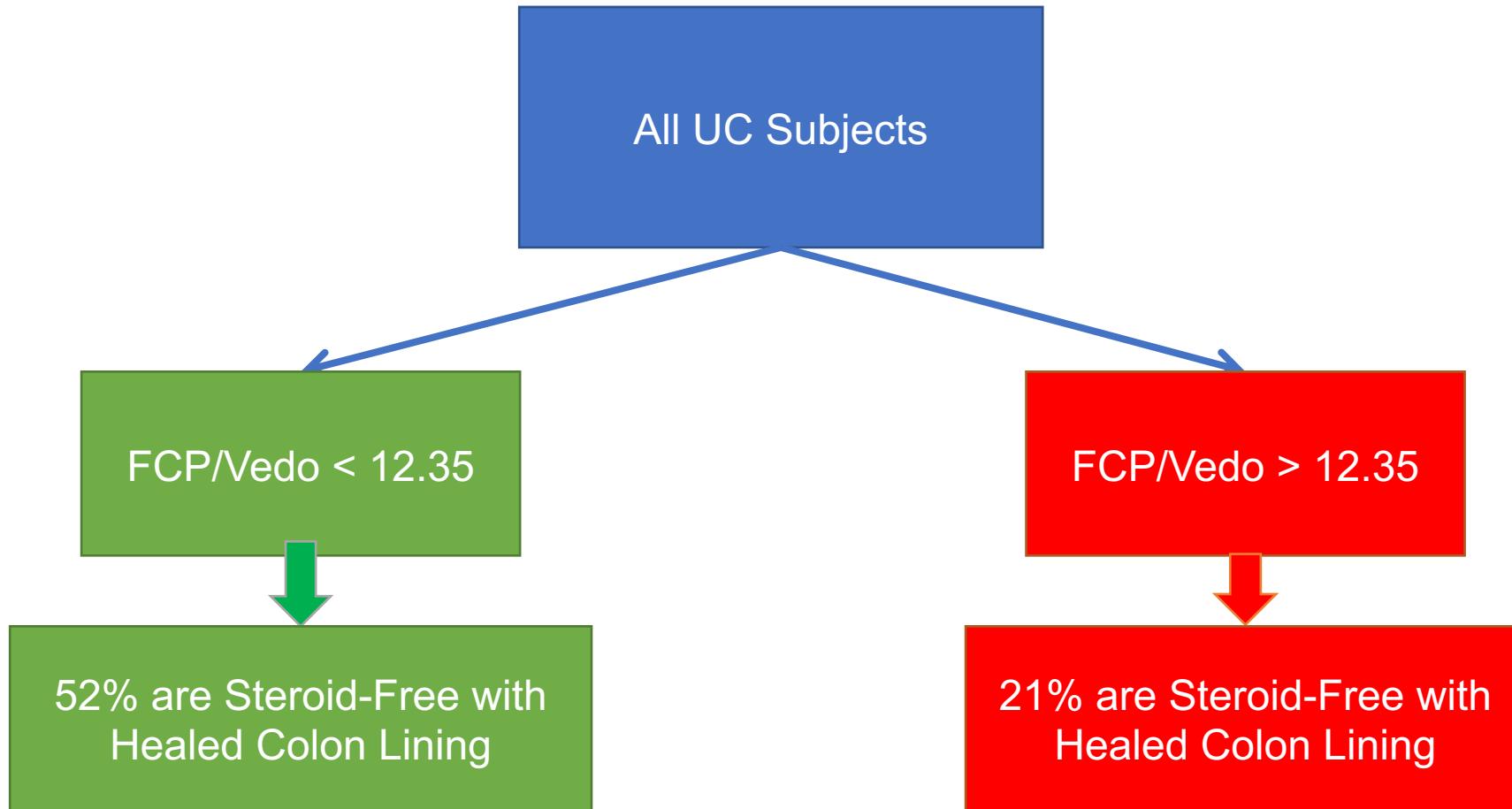
- Can we simplify this by just using the ratio of calprotectin and drug level at week 6?

Subjects with FCP/Vedo < 12.35
do well

Subjects with FCP/Vedo >12.35
do poorly

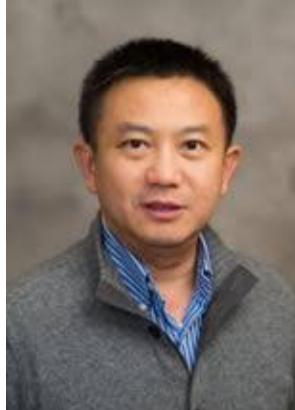


Outcomes at 52 weeks



Thanks To...

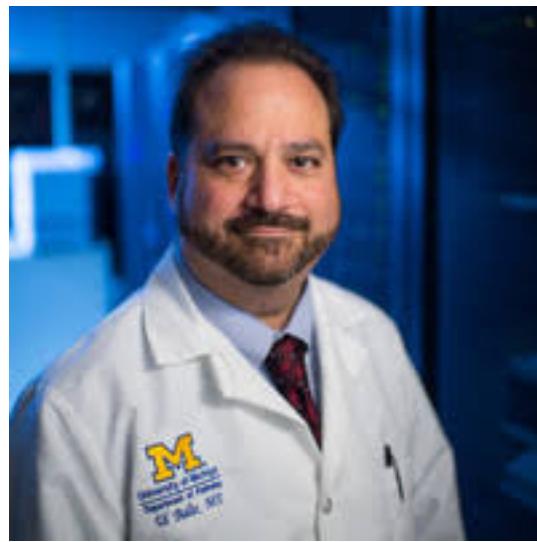
- Ji Zhu and his grad students
- UI Balis and his IT implementation team
- Clinicians for user feedback



Boang Liu

Sijian Wang

Ashin
Mukherjee



Conclusions

- Early response patterns in lab tests can predict long-term responses to drugs
 - Baseline data not very helpful in 3 different drugs
- Lots of rigorously collected lab data are out there
 - But plan ahead how you will deal with missing data
- Implementation requires IT insiders
- Talk to front-line users a lot, respond to their feedback
 - User experience matters



Questions?

Thanks for your interest!