Genetic Variation in Drug Transporter explains Side Effects in Pediatric Inflammatory Bowel Disease

Rishi Mehta
3rd Year Medical Sciences
University of Cincinnati – College of Medicine
mehtars@mail.uc.edu
Mentored by Dr. Laura Ramsey, PhD

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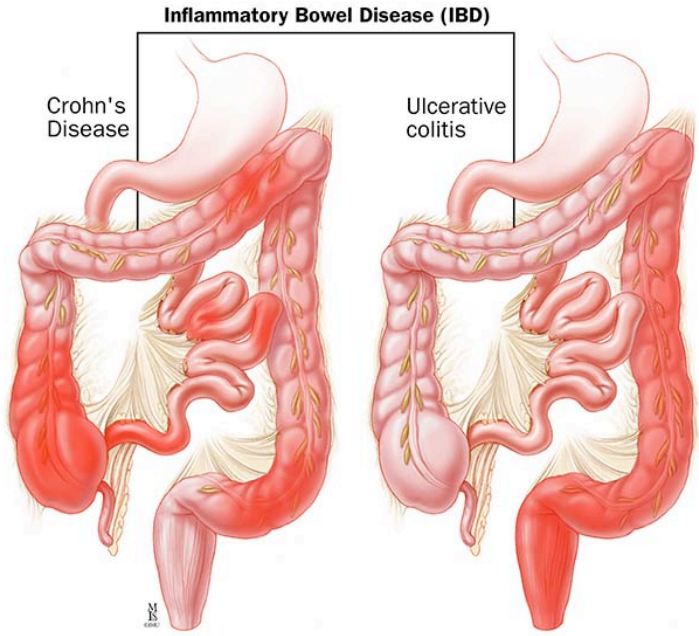
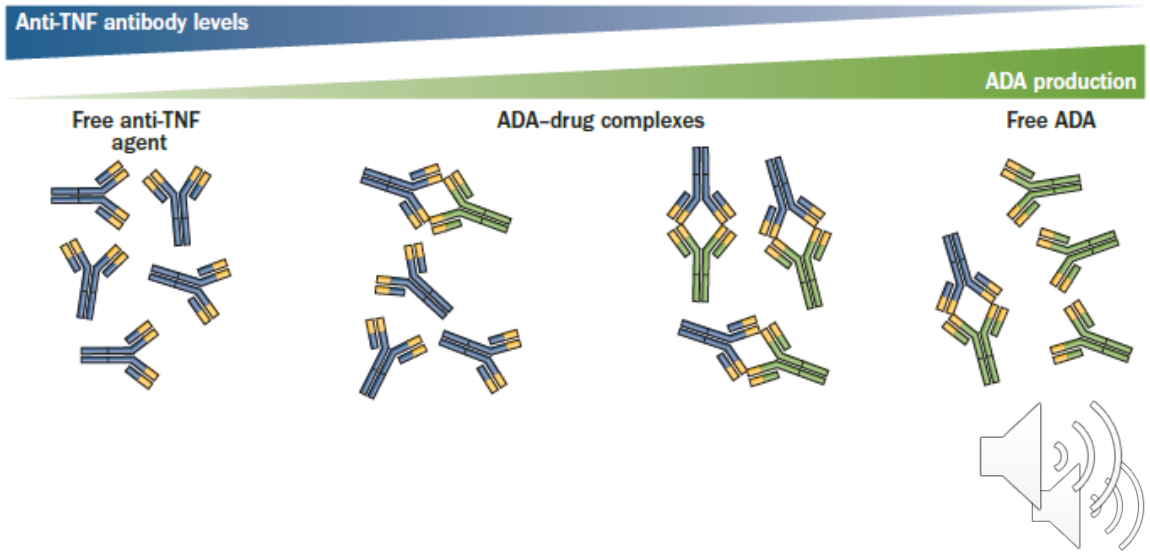
Antibodies neutralize biologic treatment needed for IBD

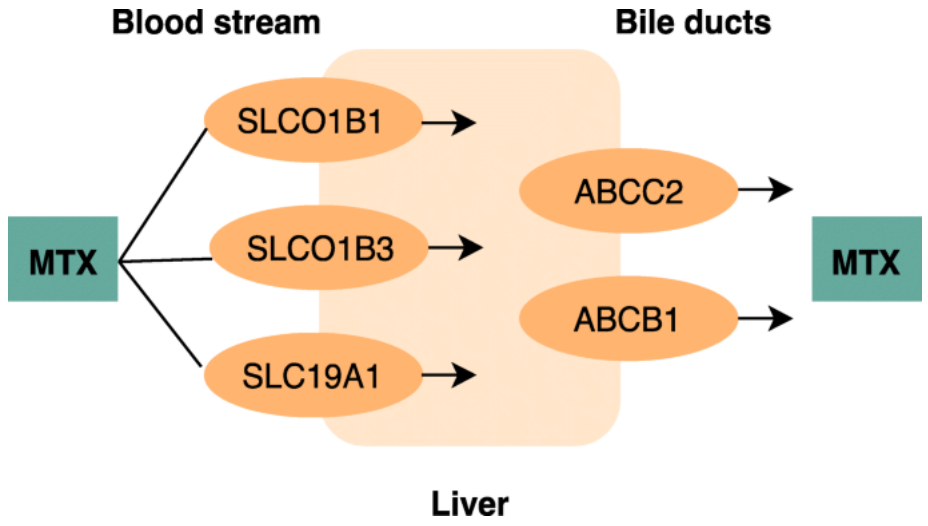
- Inflammatory bowel disease (IBD) includes two chronic diseases that cause swelling of the intestines
  - Crohn's disease and ulcerative colitis
  - Affects 1.6 million Americans (1 in 200 people)
- IBD is commonly treated with a combination of a biologic agent (ex. Infliximab) & an immunosuppressive agent
- Infliximab monotherapy causes high immunogenicity
  - Anti-drug antibodies (ADA) form against Infliximab
    - Infusion reactions
    - Shorter duration of response





MTX transport influenced by *SLCO1B1* pharmacokinetics

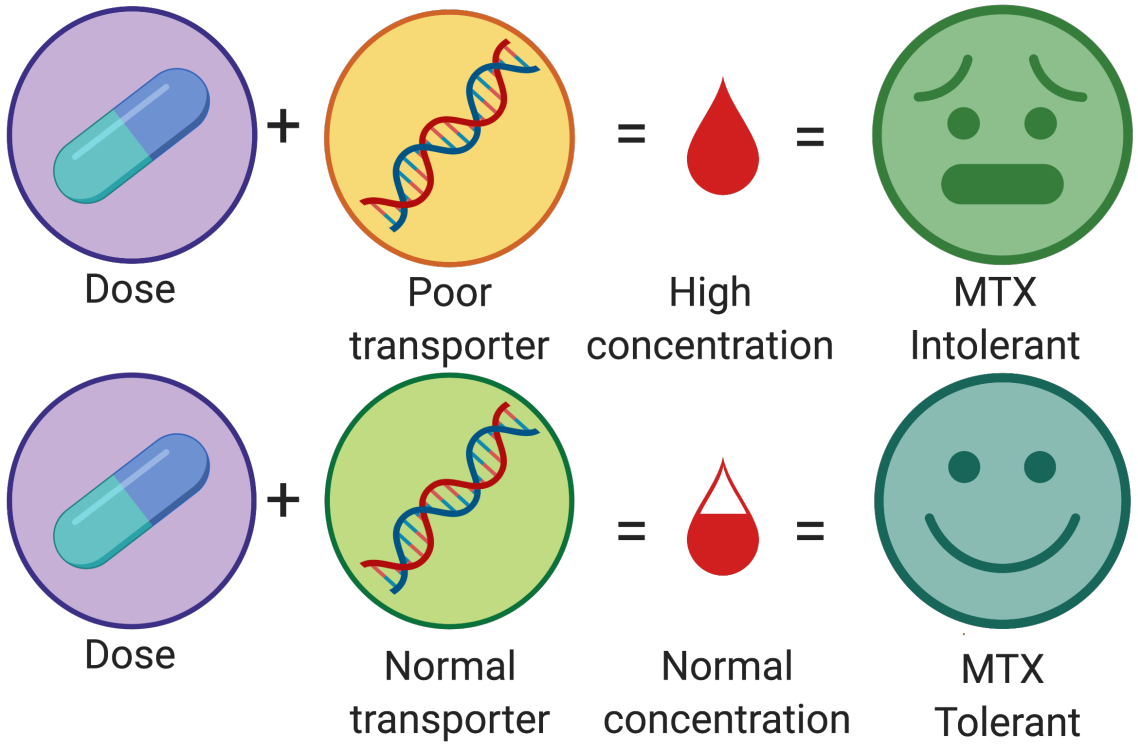
- Methotrexate (MTX):
  - Acts as an immunosuppressant
  - Reduces immunogenicity of infliximab
  - Increases levels of free infliximab
- MTX causes nausea and liver toxicity
- *SLCO1B1* transports MTX from blood to liver (→ kidney for excretion)
- The *5 & *15 reduced function alleles have been associated with:
  - Delayed MTX clearance
  - Increased side effects in adults



Hypothesis & Objective

Objective: Evaluate whether *SLCO1B1* alleles are associated with MTX-induced nausea and intolerance in children with inflammatory bowel disease

Hypothesis: Reduced function *SLCO1B1* alleles will result in MTX intolerance



Methods

- Retrospectively analyzed 278 patients ≤ 19 years of age who were prescribed MTX for IBD at Cincinnati Children's Hospital
- 202 patients had banked DNA and were genotyped for 3 *SLCO1B1* single nucleotide polymorphisms (SNPs)
  - rs2306283
  - rs11045819
  - rs4149056
- Diplotypes were determined by combining the SNPs into the *1a, *1b, *4, *5, *14, and *15 alleles
- Nausea and intolerance were abstracted from clinician notes
- Prescriptions and demographics were extracted from the medical record
- Regression and chi-square analyses were used with a $p < 0.05$ being statistically significant

SLCO1B1 Hyplotype	rs2306283	rs11045819	rs4149056	Function
1a				Normal
4				Possible increased
5				Decreased
14				Increased
15				Decreased
1b				Normal

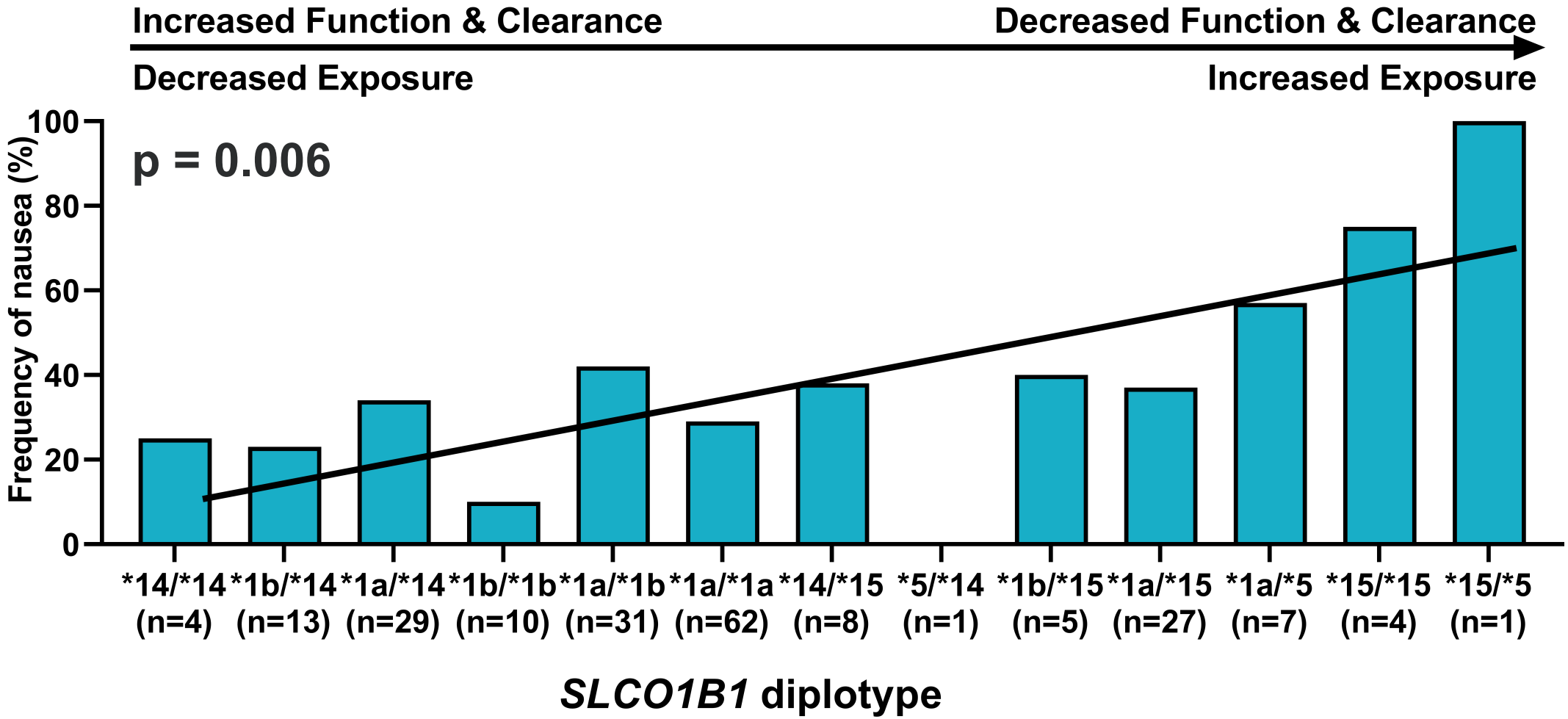
Our Patient Cohort

- The cohort was 69.8% male and 89.1% white with the median age of 16.04 (±3.9) years
- 51.7% of patients experienced MTX intolerance
  - Adverse drug reaction
  - Elevated liver enzymes
- 34.2% of patients experienced MTX-induced nausea
- 53.5% of patients discontinued MTX

Table 2. Patient Cohort

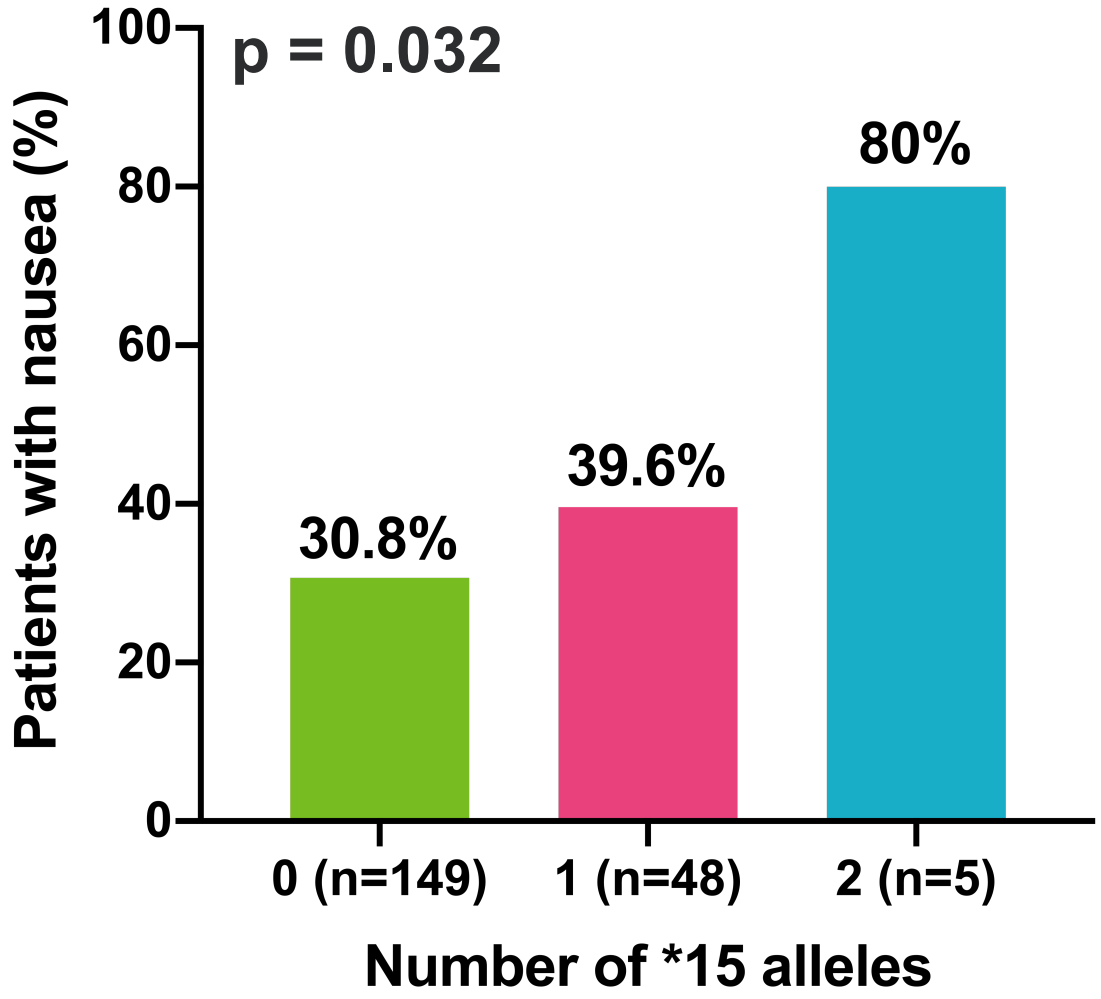
SLCO1B1 alleles	n = 404, n (%)
*1a (A-C-T)	209 (51.7%)
*4 (A-A-T)	0 (0%)
*5 (A-C-C)	8 (4.0%)
*14 (G-A-T)	59 (14.6%)
*15 (G-C-C)	50 (12.4%)
*1b (G-C-T)	69 (17.1%)

Nausea is associated with *SLCO1B1* diplotype



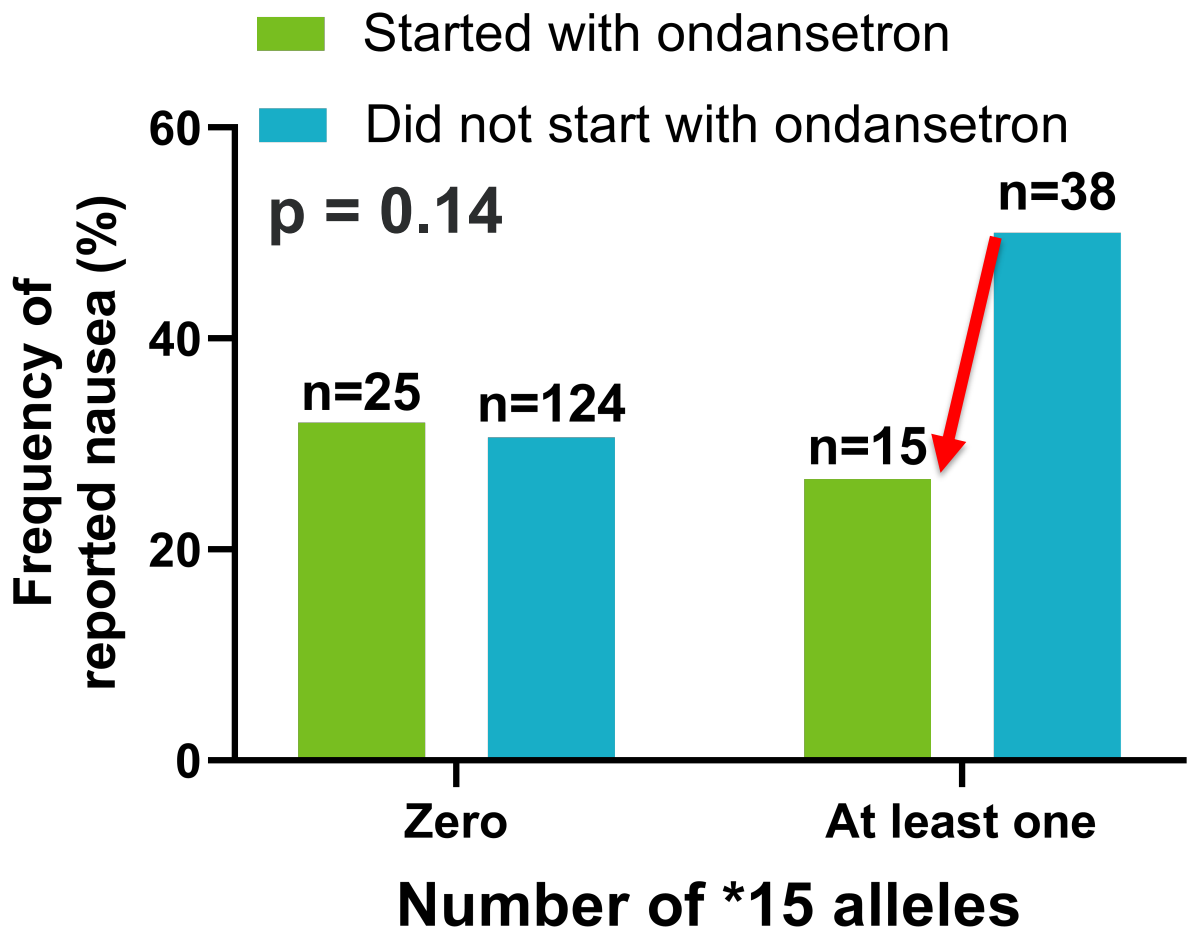
Data fitted by multivariate general linear regression

SLCO1B1 *15 carriers reported an increase in MTX-induced nausea



Chi-squared test for trend

Initiation with antiemetic reduced nausea in *15 carriers



Fisher's Exact Test

Conclusion

- Our data demonstrates that *SLCO1B1*15* allele is associated with MTX-induced nausea in pediatric patients with IBD
- Our study suggests that patients with at least one *15 allele could benefit from:
  - A dose reduction of MTX to reduce exposure
  - Initiating MTX treatment with concurrent ondansetron to reduce nausea

Limitations & Future Directions

Limitations:

- The retrospective nature of our study may have resulted in under-reported rates of nausea, d/c, and intolerance
- Adherence to medications was not able to be assessed

Future Directions:

- Look upstream at MTX metabolite levels in the blood
- Submitting a paper in *Clinical and Translational Science* by the end of the month

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Feel free to contact me with any questions!

Email: mehtars@mail.uc.edu

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