OPTIMAL SEQUENCING OF BIOLOGIC TREATMENT PROGRESSION IN CROHNS DISEASE BASED ON COMPUTATIONAL SIMULATION IN PYTHON

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ABSTRACT

Background: Crohn's Disease (CD) is a chronic autoimmune disorder with no known cure or cause. It necessitates lifelong management, commonly involving biologic therapies. However, patients often develop anti-drug antibodies (ADAbs), leading to diminished therapeutic efficacy and necessitating a switch to alternate biologic agents. Sequencing of therapies can have a significant impact on outcomes.

Objective: To investigate the impacts of treatment sequencing on CD outcomes, focusing on failure rates associated with various biologic treatments, and to explore the burden of the disease and its financial implications.

Methods: A linear compartmental model simulated Crohn's Disease progression and treatment efficacy over a 25-year period. Fifty treatment sequences were examined, alongside rates of CD incidence. Outcome variables included patient counts in each treatment category and in end-stage failure, as well as disability-adjusted life years (DALYs) and associated treatment costs.

Results: Treatment sequencing significantly affected patient outcomes, with sequences starting with TNF blockers (Humira or Remicade) and ending with IL-12 and IL-23 blockers (Skyrizi) identified as most effective. Conversely, sequences ending with JAK inhibitors (Rinvoq) were least effective. The disease burden was substantially higher during active treatment compared to post-failure (surgical intervention), with treatment costs vastly exceeding those of surgical maintenance.

Conclusion: Optimal sequencing of biologic treatments can profoundly influence the management of Crohn's Disease, potentially reducing both disease burden and treatment costs. Further research into sequential and inter-drug interactions, and the mechanisms of immunogenicity, could improve the clinical approach and patient quality of life.

1 INTRODUCTION

1.1 Background and Context

Crohn's Disease is an autoimmune disease that affects the gastrointestinal tract, causing chronic inflammation and ulcers primarily in the small intestine and large intestine. Crohn's Disease is a subset of inflammatory bowel disease (IBD) and is very similar in presentation and treatment to Ulcerative Colitis (UC); so much so that often, they are interchangeable. Diagnostic tests for Crohn's disease consist of bloodwork on red blood cells and white blood cells, and stool tests. Endoscopies and CT scans can also help with diagnosing Crohn's and are often used to differentiate between Chron's and UC. Crohn's usually develops in the early twenties, however, there is no known cause or cure (NIDDKD, 2016).

Common treatment forms for Crohn's amino salicylates, corticosteroids, immunomodulators, biologic therapies, and surgery. Biologic therapies are the most effective and most widely used at the end-stage of Crohn's disease to reach remission when symptom relief has not been achieved with other medications. Biologics block proteins or immune cells in the inflammatory pathway in the gut, reducing inflammation in the intestinal tract. There are four main categories of biologics: tumor necrosis factor (TNF) blockers, integrin blockers, interleukin blockers, and Janus Kinase (JAK) inhibitors. Anti – TNF biologics include Humira, Remicade, and Cimzia. The anti-integrin biologics are Tysabri and Entyvio. The IL-12 and IL-23 agonists are Stelara and Skyrizi. The main JAK inhibitor used in clinical treatment is Rinvoq. Biologics cause significant side effects, such as a high risk of infection, higher risks of cancers, and significantly decreased immune function (Healthline, 2020). However, they have been pivotal in helping patients achieve remission.

These therapies are highly effective; however, a large percentage of patients lose responsiveness to these biologics due to the formation of 'anti-drug antibodies' or ADAbs (Vermeire, 2018). Once this happens, patients are forced to move to a different biologic or another form of medication, possibly reducing the effectiveness or timeliness of the treatment and resulting surgery to remove the infected tissue.

1.2 Summary of Existing Topical Material

A review article published in the journal 'Therapeutic Advances in Gastroenterology' in 2018 aimed to study the formation of anti-drug antibodies (or immunogenicity) in six different biologic therapies (Vermeire et al., 2018). ADAbs resulted in an increase in adverse effects to the medication, a loss of response, and a reduction in primary efficacy. Little information was provided on the formation of the ADAbs and the timing of their development in the treatment timeline. ADAbs were found as early as 10 – 14 days and as late as 20 years. Immunogenicity is triggered due to the nature of biologics as large, complex proteins that act system wide. However, this loss of response is only specific to one agent, and other biologic agents can be attempted. Vermeire et al. found that immunogenicity was observed with all biologic agents investigated, but that there was a significantly large variation in the rate of development.

A subset of biologics called tumor necrosis factor (TNF) inhibitors are widely used as treatment for IBD and are often the first biologic attempt. A drawback to these biologics is that patients may lose responsiveness to the drug, or that they need escalating doses to be as effective. A systematic review and meta-analysis conducted in 2015 examined the immunogenicity of five TNF inhibitors to draw conclusions about the potential effect of anti-drug antibodies on the loss of clinical response to biologics (Thomas et al., 2015). All the treatment therapies studied exhibited the development of ADAbs. They found that the cumulative incidence of ADAbs was 12.7%, with the highest incidence of ADAbs reaching 25.3%. In all patients where they were observed, the clinical response was decreased by 67% and adverse effects to infusions and injections were reported more often. However, they found that the use of concomitant immunosuppressives (i.e. two medications taken at the same time) reduced the odds of immunogenicity by 74% (Thomas et al., 2015).

A systematic review in 2017 was conducted to 'explore the immunogenicity of biologic agents across inflammatory diseases and their potential impact on efficacy/safety' (Strand et al., 2017). This study looked at seven biologics and biosimilars and found that the highest incidence of ADAbs was found with infliximab (Remicade / Inflectra) at 83% (Strand et al., 2017). Almost 4 in 5 people developed immunity to these drug treatments, yet they are one of the most common biologic treatments available to those with autoimmune diseases.

Biologic treatments remain some of the most used and most effective therapies for people with moderate to severe Crohn's disease, and there are many biologics available in the case of anti-drug antibody formation. A systematic review in 2015 investigated the literature of biologic therapies and their effectiveness. Their findings indicated that management of IBD with biologics is highly well validated. In the studies that were evaluated, a significant number of patients experienced endoscopic healing in the intestinal lining (Cote-Daigneault et al., 2015).

Clinical implications of anti-drug antibody formation are important not only for treatment plans, but also for the conception and implementation of a new drug. Due to the chronicity of IBD, effective treatments that do not lapse in time are needed. A systematic review conducted in 2016 published in the *American Journal of Gastroenterology* evaluated the evidence of ADAbs in common IBD biologics. They found that effective treatment depends on a decrease in levels of ADAbs in the system. The researchers in this study stated that biologics with the lowest rates of immunogenicity should be used for the treatment of IBD (Lula, 2016).

1.3 Current Literature Limitations and Knowledge Gaps

New treatments are approved constantly, and the guidelines surrounding combinations of therapies are dynamic as well. This leads to a constant lack of current research regarding these treatments, limiting provider's knowledge about the most recent therapy advances. There has only been limited study on the implications of the timeline of immunogenicity, both in rate and impact. The development of an immunogenic response to biological therapies is not well understood, and increased research into this area could provide major improvement to the clinical approach to Crohn's Disease treatment. It has been found that concomitant immunosuppressives have large dampening effect on immunogenicity (Thomas et al., 2015). Research is needed to find the effects of two biologics given at the same time, and if there are combinations of treatments that have a significant clinical and endoscopic effect.

Modeling of the failure rates (total surgery) for each treatment plan can help improve the current effort by identifying where the most room for improvement can be, and what sequences of biologics could be the most effective. Modeling is uniquely appropriate for this situation, as it is extremely difficult to track patients across their entire length of disease progression at a large enough scale to draw significant conclusions. Computational modeling can provide the insights needed to make informed decisions without the human burden of large-scale intervention.

1.4 Online Research

Digital research was conducted to collect failure rates of different biologics used in Chron's disease treatment. Numerous articles were analyzed for effective research rigor and result analysis. The most rigorous articles' failure rates were taken to be used in the model. If articles only reported success rates, the success rate was used to calculate the failure rate using the following equation:

$$Failure\ Rate = 1 - Success\ Rate \qquad (1)$$

2 METHODS

2.1 Structure

The modeling framework used was a linear compartmental model (see Figure 9), with each treatment option being a discrete compartment. Transition rates between compartments represented the probability of treatment failure. Once a simulated patient reached the 'failure' state – which signifies a surgical intervention (colostomy) – they were deemed to have reached an irreversible point in the disease and were not allowed to regress back to treatment in the simulation.

Each trial was run for 25 years, as this timespan is relevant in capturing long-term course of disease and reaching a treatment failure endpoint (Paramsothy, 2018). Each result was added as a DataFrame to a dictionary and used to analyze the performance of the treatment plans.

The structure of the model is dynamic to accommodate different inputs of treatment orders. Specific functions were defined for calculating the treatment plans to go into the model, the model simulation itself, and the calculation of associated costs.

2.2 Input Modeling

Treatments and their failure rates were recorded in a dictionary (see Appendix 1), and permutations of each treatment plan were simulated. This resulted in 719 possible treatment plans; however, this is computationally extensive and not realistic to practical Crohn's Disease treatment plans. Most patients are started with Mesalamine, and then moved to a TNF blocker as their first biologic (Bressler, 2023). Therefore, the list was cut to the first 50 permutations, with mesalamine first and either Remicade or Humira (both TNFs) as the second options (see Appendix 2). Additionally, 3 options with Entyvio (an anti-integrin) were included as a comparison. Table 1 shows the failure rates of each treatment mode.

There are approximately 340 million people in the US and the incidence of Crohn's Disease is 33,000 cases per 100,000 people. Therefore, the rate of developing Crohn's Disease in the US is 0.0009706% per year. To represent the initiation phase of Crohn's Disease within the model, the existing patient population was categorized under the 'mesalamine' treatment group (the first line of therapy). The assumption is that 340 million individuals start in the 'healthy' category, with the model reflecting the incidence rate of CD and effectively simulating the transition from a state of health to being diagnosed.

2.3 Outcome variables

The primary outcome variables of this model were focused on evaluating the burden and economic impact of Crohn's Disease treatment sequences. These outcomes include the number of people in each treatment, the number of people in failure, and the annual failure rates. The number of people in each treatment quantifies how many individuals are undergoing a specific treatment at any time within the model. The number of people in failure is the cumulative count of individuals for whom all treatments failed to identify the plans with the highest frequency of failure. The annual failure rates were used to find patterns or trends that might indicate the performance of treatment sequences. The aim of these variables was to identify which sequences resulted in the highest number of individuals experiencing failure by the end of the model simulation period to discern the performance of different sequences. When direct comparisons across treatment plans were not needed, an average across the fifty simulated treatment plans provided a general view of the outcomes.

Additionally, the concept of "people-years" was employed as a metric to gauge the cumulative time spent by individuals within each treatment phase or in the state of treatment failure. This allowed for the assessment of disease burden, which was further refined by extrapolating to the average lifespan of those diagnosed with Crohn's Disease—estimated to be around 70 years. This extrapolation provided a longitudinal perspective on the impact of the disease and treatments over a typical patient's life, rather than

just those in failure during the 25 years of simulation. Weights assigned to the condition states, 0.231 for treatment and 0.095 for failure were applied to the average years (Global Burden of Disease, 2024).

Cost considerations were integrated into the outputs of the model and used in analysis. The average cost of infusions, which are given every 2 months, was about $41,549 and the average cost of failure is the initial cost of a colostomy plus the maintenance costs, $47,114 and $3,000, respectively.

2.4 Assumptions

Crohn's disease is wildly variable, with individual outcomes being vastly different in terms of timeline, response, and outcome. Therefore, there were some assumptions made to ensure the model aligned as closely as possible with the average trends of Crohn's Disease patients. Additionally, assumptions were made in the model to ensure standardization across each treatment plan, so they could be better compared to each other. Namely, these assumptions were that medication turnover only occurred once per year and aligned with the time step of the model, every person starts with a common initial treatment, the rates of failure stay constant, and once someone moves on from one category to another, they do not regress. Table 2 outlines these assumptions and the justifications behind them.

3 RESULTS

3.1 Model Outputs

There were four distinct categories of performance that were revealed from the model output: top-tier performers, midrange performers split into higher and lower subcategories, and lowest performers (see Figure 1). Each category was characterized by consistent failure rates, so similar cumulative numbers of end-stage failures within respective groups are seen (see Table 3).

The best performers were plans 1, 4, 7, 10, 18, 20, 25, 28, 31, 34, 42, 44, and 49 and had cumulative failures of around 88,971 people (see Figure 2). The higher middle performing category consisted of plans 3, 5, 13, 16, 19, 22, 27, 29, 33, 35, 37, 39, 40, 41, 43, 45, 46, 47 and had around 434,000 people in failure (see Figure 4). The lower middle performing category consisted of plans 9, 11, 15, 17, 21, and 23 and had around 231, 500 people in failure (see Figure 4). The worst performing plans were 0, 2, 6, 8, 12, 14, 24, 26, 30, 32, 36, 38, 48, and 50 and resulted in over 600,000 failures (see Figure 3). Over time, across all trials, failure rates increased exponentially (see Figure 5), likely due to the growing population of people undergoing treatment following Crohn's diagnosis. There was a significant difference in the number of person-years in failure versus the number of person-years in treatment (see Figure 6), with the number of person-years in treatment being almost 72 times larger than those in failure. However, when adjusted for the fact that failure extends for the rest of the patient's life, that difference drops to only about 3 times as many people - years spent in treatment than in failure (see Figure 6).

Disability Adjusted Life Years (DALYs) were calculated to determine the burden of disease of Crohn's Disease. They are a measure of overall disease burden and are expressed as the number of years lost due to disease or disability (Global Burden of Disease, 2024). DALYs were calculated for both treatment and failure within the trials, and for failure extrapolated to the average lifespan of someone with Crohn's Disease, around 70 years (see Figures 7 and 8). The number of disability adjusted life years lost in treatment over 25 years are approximately 7 times higher than the number of disability adjusted life years lost in failure over the span of a patient's lifetime.

Cost was calculated based on person-years in treatment and person-years in failure. The cumulative cost for treatment was around $28 trillion whereas cumulative cost for failure maintenance over the patient's life was approximately $121 billion. This disparity underscored the economic implications of ongoing treatment for Crohn's Disease versus the long-term financial burden of managing treatment failure.

3.2 Output Analysis

The comparative analysis of different sequences of biologic therapies for Crohn's Disease within the study's model reveals significant variances in patient outcomes (see Table 3). Treatment plans exhibiting the lowest failure rates systematically integrated a sequence that concluded with Skyrizi, an IL-12 and IL-23 blocker. In charting the sequences of treatment plans, the placement of Skyrizi as the terminal intervention correlates with the most favorable prognoses. Conversely, treatment sequences concluding with a JAK inhibitor (Rinvoq) consistently rank as the worst performers, implying that their position as a final therapeutic option correlates with higher failure rates.

The findings of this model resonate with real-world implications. Clinicians' ability to discern and apply optimal sequencing of treatment can drastically reduce the likelihood of failures, reminding us that the chronological order of interventions possesses the potential to influence the trajectory of Crohn's Disease management significantly. Moreover, the assessment of people-years devoted to each treatment category versus failure informs our understanding of both the individual burden and the healthcare system's load as it pertains to managing chronic conditions. The human and economic costs accrued during treatment years cannot be overlooked, as they cumulatively amplify the disease's impact on patients' lives and the overall healthcare burden.

4 DISCUSSION

4.1 Conclusions

The strategic sequencing of treatments makes a pivotal impact on the clinical trajectory of Crohn’s Disease. Even with a limited scope such as the one in this model, where not all sequences were run, there were clear outliers in performance. Additionally, the sequencing observed in the best performing treatment plans aligned closely with current clinical practice.

Through the analysis of the DALYs lost, we can conclude that Crohn’s Disease has a large burden on those affected. When analyzing the results of the model (refer to Figure 6), it can be concluded that the burden during the course of treatment is noticeably greater than that encountered in post-treatment failure, with the latter being widely recognized as less favorable. The high burden of disease during treatment may be due to the side effects resulting from the different drugs, or from the symptoms resulting from the disease itself. Having Crohn’s Disease significantly impacts quality of life, and sequencing of treatment can be an effective tool to reduce its burden and improve the outcomes and quality of life of those with the disease.

Infusions of treatment are very costly, with an average found at $41,549, and with rates increasing every year (Afzali et al., 2017). Treatment frequency differs from patient to patient, and can range from bimonthly to monthly, correlating with the disease severity and escalating aggregate healthcare spending. In comparison, the average cost of having a colostomy bag per year is around $3,000 with the additional initial cost of around $47,114 for the colostomy surgery (HMP Global, 2020). Analysis of the cost of treatment versus failure in average person-years across the trials run show that the cost of treatment is approximately 237 times the cost of failure, even when cost of failure is extrapolated across the lifespan of a Crohn’s Disease patient.

4.2 Implications

The methodology employed within this study sheds light on a critical facet of Crohn's Disease management: the strategic sequencing of biologic treatments could serve as a pivotal element in optimizing patient outcomes by minimizing treatment failures. This understanding should inspire healthcare professionals to reassess current protocols and, where feasible, restructure the order of biologic therapies to mirror sequences associated with reduced failure rates. Such readjustments could lessen the cumulative financial toll of managing Crohn's Disease, which, as indicated by the model, extends into trillions over the patients'

lifespans. Besides, given that individuals' quality of life is significantly affected during the treatment phase, finding strategies that can expedite the path to remission or reduce the need for successive interventions has the potential to alleviate the physiological and psychosocial burdens that patients bear when dealing with this disease.

As reflected in the disproportionate number of treatment and failure DALYs, the disease severity and interventions produce a pronounced decrement in quality of life. By controlling and anticipating the sequence of biologic therapies based on the most favorable outcomes, healthcare practitioners can more effectively utilize medical resources and move towards significantly enhancing the patient experience relative to living with Crohn's Disease.

4.3 Limitations

Crohn's Disease is highly variable and difficult to model computationally. Rates vary widely and are individualized, so one may reach failure of a certain treatment within 2 weeks, or as long as 20 years. Biologics reduce the effects of the disease, but they do not eliminate them, so success of treatment is hard to measure. Death does not occur from the disease, it only results in a reduced lifespan, so it is difficult to procure a model specific to Crohn's Disease that equivalates at a homeostasis point. Additionally, side effects from treatment are not considered, and may be another reason why a treatment does not work for a particular individual independent of its endoscopic failure rate.

There is limited research on drug interactions with each other, or in sequence. There are not a lot of studies looking at if drugs have different failure rates if they are used in sequence, or what that sequence might be. Additionally, there is not a lot of research on drug interactions when used in combination, although that is becoming a much more common implementation of treatment. The lack of understanding in this area necessitates that the model has fixed failure rates for individual treatment, but this may not fully capture the dynamic interactions between therapies.

4.4 Further Exploration

Recommendations for further exploration include more research on sequential and inter-drug interactions. More understanding of the cause is needed. It would be ideal to not need modeling of sequence at all, and for the first treatment to work (or at least have a higher success rate).

Additionally, modeling should be run on more permutations of drug sequencing to determine if current clinical practice is not the most effective. Future models can build upon this one, using varying failure rates and more individual tracking. This could be turned into an agent-based model where individualized time – to – failures are considered instead of using averages, making the model more accurate on a person – to – person basis. Death rates could be taken into account, and the model run over patients' lifespans to equivalate the model and gain more accurate understandings of economic and human burden of disease. In an agent-based model, side effects could be considered to make the model more accurate to patient experience.

Overall, although there are improvements that should be made, I believe this model is a good starting point in showing that there is a need for simulation – based modeling of Crohn's Disease treatment sequencing, and that future modeling projects could have a drastic impact on implementation of biologic therapies.

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APPENDICES

Table 1: Failure Rates of Biologic Treatments

Biologic Treatment		**Rate of Failure (%)**	**Source**
Clinical Name	*Colloquial Name*		
5-aminosalicylic acid	Mesalamine	60	Karagozian et al., 2007
Infliximab	Remicade	60	Buhl et al., 2017
Adalimumab	Humira	32	Gordon et al., 2015
Vedolizumab	Entyvio	60	Eriksson et al., 2021
Risankizumab-rzaa	Skyrizi	12.3	Ferrante et al., 2021
Upadacitinib	Rinvoq	86	Sandborn et al., 2020

Table 2: Model Assumptions and Justifications

Assumption	**Justification**
Medication turnover only happens once a year.	Rates of failure in the literature are determined per year, even though some people have timelines from 2 weeks – 20 years (Vermeire et al., 2018).
Every person starts on Mesalamine and then moves to a TNF blocker (either Remicade or Humira).	This closely follows current clinical practice due to TNF blockers having the least amount of side effects (Gisbert et al., 2020).
The rates of failure from the medications stay constant.	This helps to standardize rates across each treatment plan for more accurate analysis.
Once someone fails a biologic, they do not retry it.	This closely follows current clinical practice.
Once someone reaches failure, they do not reverse the colostomy.	Although this does happen occasionally, I was only interested in initial failure.

Table 3: Treatment Plan Performance and Characteristics

Category	**Cumulative Failures**	**Defining Characteristics**	
		Initial Treatments	*End-Stage Treatments*
Best Performers	88,971	Humira Remicade	Skyrizi
Middle Performer 1	434,004	Remicade	Humira
Middle Performer 2	231,468	Humira or Remicade	Remicade Entyvio
Worst Performers	622,072	Humira or Remicade Entyvio	Rinvoq

Appendix 1: Biologics and their rate of failure

```
treatment_rates = {'mesalamine': 60,
                   'remicaide': 60,
                   'humira': 32,
                   'entivyo': 60,
                   'skyrizi': 12.3,
                   'rinvoq': 86}
```

Rates were collected or calculated from the following articles: (Moss, et al. 2022), (Karagozian et al., 2007), (Buhl et al., 2017), (Gordon et al., 2015), (Eriksson et al., 2021), (Ferrante et al., 2021), and (Sandborn et al., 2020).

Appendix 2: First 50 permutations of treatment options.

```
0: ('mesalamine', 'remicade', 'humira', 'entyvio', 'skyrizi', 'rinvoq')
1: ('mesalamine', 'remicade', 'humira', 'entyvio', 'rinvoq', 'skyrizi')
2: ('mesalamine', 'remicade', 'humira', 'skyrizi', 'entyvio', 'rinvoq')
3: ('mesalamine', 'remicade', 'humira', 'skyrizi', 'rinvoq', 'entyvio')
4: ('mesalamine', 'remicade', 'humira', 'rinvoq', 'entyvio', 'skyrizi')
5: ('mesalamine', 'remicade', 'humira', 'rinvoq', 'skyrizi', 'entyvio')
6: ('mesalamine', 'remicade', 'entyvio', 'humira', 'skyrizi', 'rinvoq')
7: ('mesalamine', 'remicade', 'entyvio', 'humira', 'rinvoq', 'skyrizi')
8: ('mesalamine', 'remicade', 'entyvio', 'skyrizi', 'humira', 'rinvoq')
9: ('mesalamine', 'remicade', 'entyvio', 'skyrizi', 'rinvoq', 'humira')
10: ('mesalamine', 'remicade', 'entyvio', 'rinvoq', 'humira', 'skyrizi')
11: ('mesalamine', 'remicade', 'entyvio', 'rinvoq', 'skyrizi', 'humira')
12: ('mesalamine', 'remicade', 'skyrizi', 'humira', 'entyvio', 'rinvoq')
13: ('mesalamine', 'remicade', 'skyrizi', 'humira', 'rinvoq', 'entyvio')
14: ('mesalamine', 'remicade', 'skyrizi', 'entyvio', 'humira', 'rinvoq')
15: ('mesalamine', 'remicade', 'skyrizi', 'entyvio', 'rinvoq', 'humira')
16: ('mesalamine', 'remicade', 'skyrizi', 'rinvoq', 'humira', 'entyvio')
17: ('mesalamine', 'remicade', 'skyrizi', 'rinvoq', 'entyvio', 'humira')
18: ('mesalamine', 'remicade', 'rinvoq', 'humira', 'entyvio', 'skyrizi')
19: ('mesalamine', 'remicade', 'rinvoq', 'humira', 'skyrizi', 'entyvio')
20: ('mesalamine', 'remicade', 'rinvoq', 'entyvio', 'humira', 'skyrizi')
21: ('mesalamine', 'remicade', 'rinvoq', 'entyvio', 'skyrizi', 'humira')
22: ('mesalamine', 'remicade', 'rinvoq', 'skyrizi', 'humira', 'entyvio')
23: ('mesalamine', 'remicade', 'rinvoq', 'skyrizi', 'entyvio', 'humira')
24: ('mesalamine', 'humira', 'remicade', 'entyvio', 'skyrizi', 'rinvoq')
25: ('mesalamine', 'humira', 'remicade', 'entyvio', 'rinvoq', 'skyrizi')
26: ('mesalamine', 'humira', 'remicade', 'skyrizi', 'entyvio', 'rinvoq')
27: ('mesalamine', 'humira', 'remicade', 'skyrizi', 'rinvoq', 'entyvio')
28: ('mesalamine', 'humira', 'remicade', 'rinvoq', 'entyvio', 'skyrizi')
29: ('mesalamine', 'humira', 'remicade', 'rinvoq', 'skyrizi', 'entyvio')
30: ('mesalamine', 'humira', 'entyvio', 'remicade', 'skyrizi', 'rinvoq')
31: ('mesalamine', 'humira', 'entyvio', 'remicade', 'rinvoq', 'skyrizi')
32: ('mesalamine', 'humira', 'entyvio', 'skyrizi', 'remicade', 'rinvoq')
33: ('mesalamine', 'humira', 'entyvio', 'skyrizi', 'rinvoq', 'remicade')
34: ('mesalamine', 'humira', 'entyvio', 'rinvoq', 'remicade', 'skyrizi')
35: ('mesalamine', 'humira', 'entyvio', 'rinvoq', 'skyrizi', 'remicade')
36: ('mesalamine', 'humira', 'skyrizi', 'remicade', 'entyvio', 'rinvoq')
37: ('mesalamine', 'humira', 'skyrizi', 'remicade', 'rinvoq', 'entyvio')
38: ('mesalamine', 'humira', 'skyrizi', 'entyvio', 'remicade', 'rinvoq')
39: ('mesalamine', 'humira', 'skyrizi', 'entyvio', 'rinvoq', 'remicade')
40: ('mesalamine', 'humira', 'skyrizi', 'rinvoq', 'remicade', 'entyvio')
41: ('mesalamine', 'humira', 'skyrizi', 'rinvoq', 'entyvio', 'remicade')
42: ('mesalamine', 'humira', 'rinvoq', 'remicade', 'entyvio', 'skyrizi')
43: ('mesalamine', 'humira', 'rinvoq', 'remicade', 'skyrizi', 'entyvio')
44: ('mesalamine', 'humira', 'rinvoq', 'entyvio', 'remicade', 'skyrizi')
45: ('mesalamine', 'humira', 'rinvoq', 'entyvio', 'skyrizi', 'remicade')
46: ('mesalamine', 'humira', 'rinvoq', 'skyrizi', 'remicade', 'entyvio')
47: ('mesalamine', 'humira', 'rinvoq', 'skyrizi', 'entyvio', 'remicade')
48: ('mesalamine', 'entyvio', 'remicade', 'humira', 'skyrizi', 'rinvoq')
49: ('mesalamine', 'entyvio', 'remicade', 'humira', 'rinvoq', 'skyrizi')
50: ('mesalamine', 'entyvio', 'remicade', 'skyrizi', 'humira', 'rinvoq')
```

Figure 1: Cumulative People in Failure after 25 years of treatment

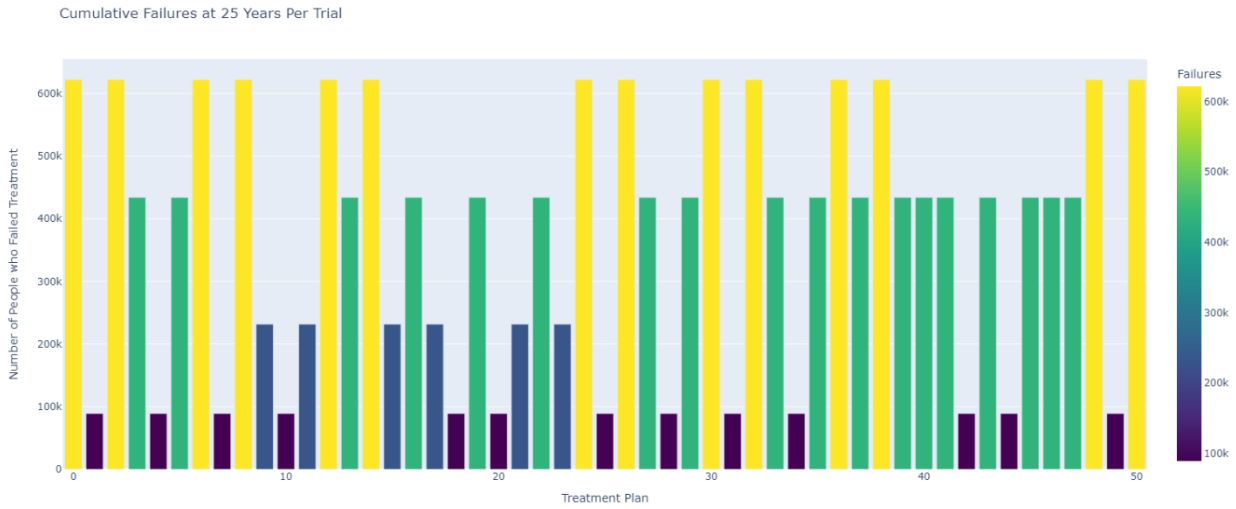

Figure 2: Failure Counts and Indices of Best Performing Treatment Plans

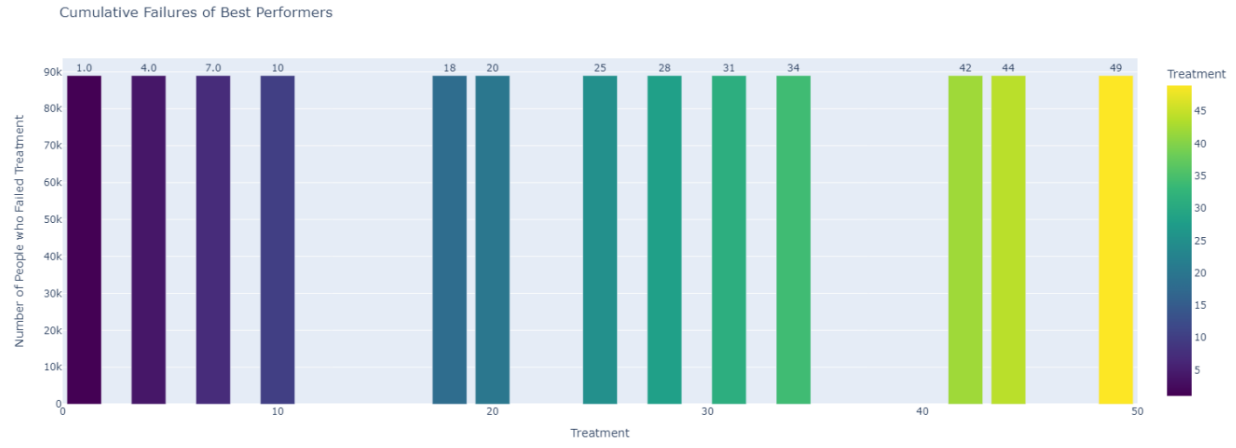

Figure 3: Failure Counts and Indices of Worst Performing Treatment Plans

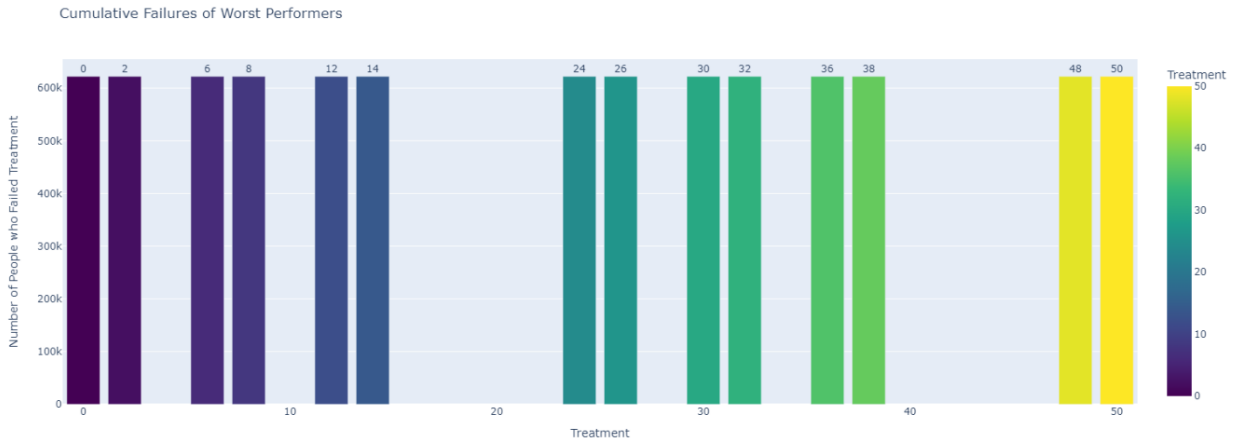

Figure 4: Failure Counts and Indices of Middle Performing Treatment Plans

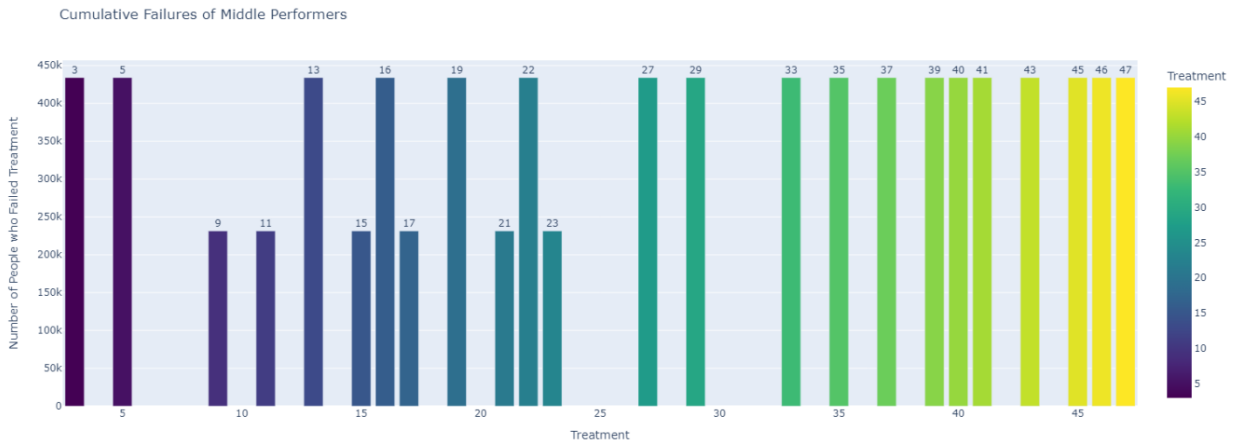

Figure 5: Failure Rates for Categories of Treatment Plans

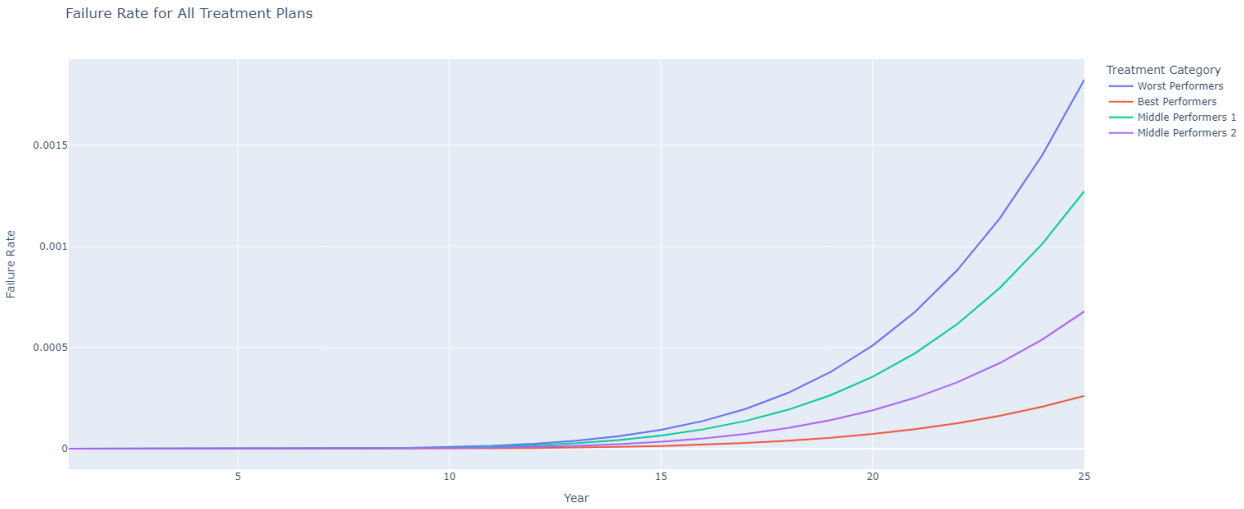

Figure 6: Average People-Years in Treatment and Failure vs. Extrapolated Failure

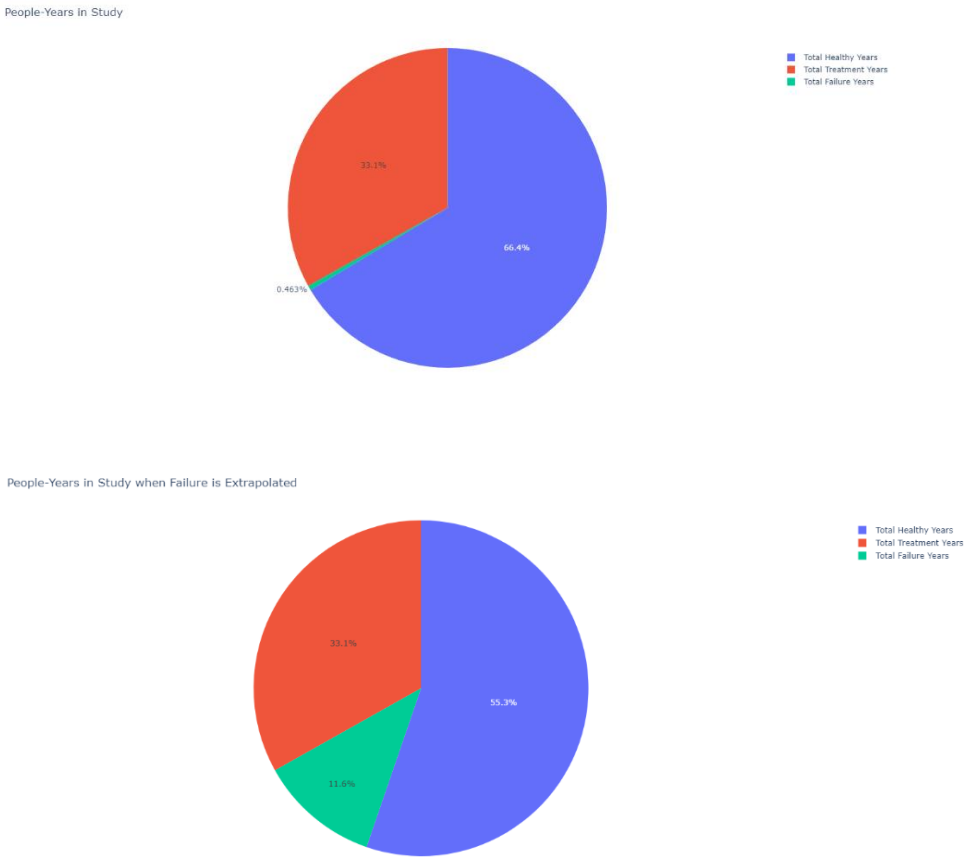

Figure 7: Comparison of DALYs for failure in the study and DALYs for failure extrapolated to average lifespan of someone with Crohn's Disease.

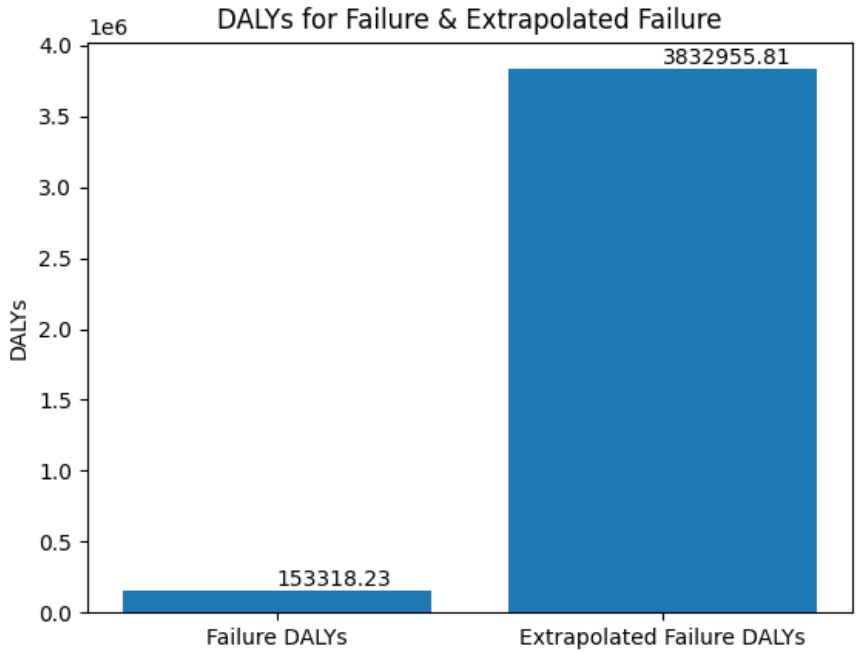

Figure 8: Comparison of DALYs for treatment in the model and extrapolated failure DALYs as an accurate view of burden of disease

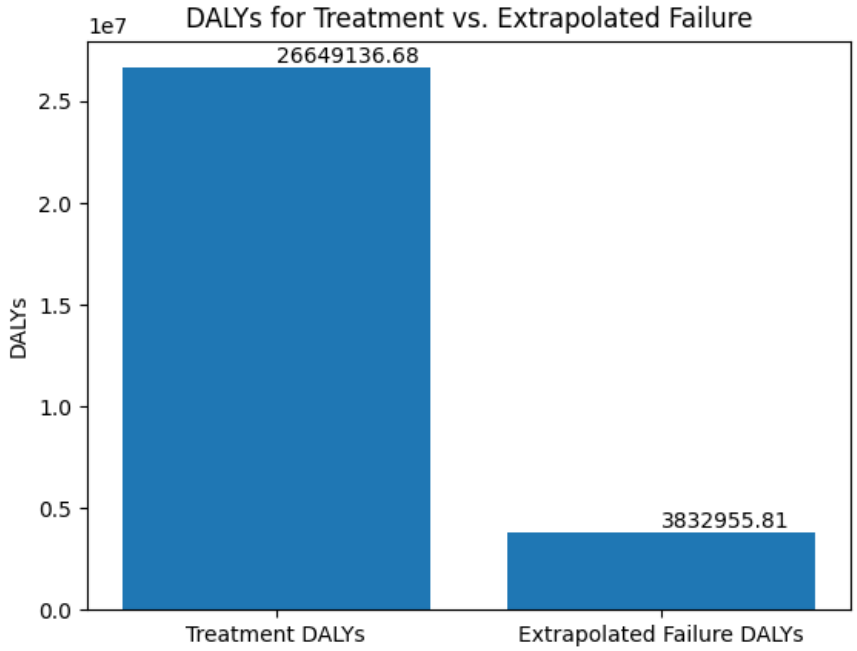

Figure 9: Flowchart of linear compartmental model