Utilizing CT Based Imaging Parameters of Body Composition to Understand Heterogeneity of Response to Biologic Therapies in Severe Asthma Cohorts

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Utilizing CT Based Imaging Parameters of Body Composition to Understand Heterogeneity of Response to Biologic Therapies in Severe Asthma Cohorts

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: **Utilizing CT Based Imaging Parameters of Body Composition to Understand Heterogeneity of Response to Biologic Therapies in Severe Asthma Cohorts**

Study Description: We plan to utilize University of Michigan EMR data to form a retrospective cohort of severe asthma patients on biologic therapies for asthma with CT imaging and known outcomes on therapy. We will then analyze these images using morphomics, a combination of high-throughput image analysis and deep learning techniques, to derive imaging biomarkers that will be able to predict therapeutic response to biologics. These biomarkers will then be tested in a second cohort from the University of Calgary to assess for validity.

Objectives:

Primary Objective:	To identify imaging biomarkers that are associated with the probability of any reduction in pre-treatment baseline exacerbation frequency in a severe asthma population on biologics
Secondary Objectives:	1. To identify imaging biomarkers that are associated with the probability of any post-treatment improvement of FEV1 of 5% or more 2. To identify imaging biomarkers that are associated with the probability of any post-treatment reduction in maintenance OCS use
Exploratory Objectives:	1. To identify imaging biomarkers that are associated with the probability of any reduction in pre-treatment baseline hospitalizations for asthma 2. To identify imaging biomarkers that are associated with the probability of any post-treatment improvement in ACT score 3. To identify imaging biomarkers that are associated with the probability of any subjective post-treatment reduction in symptoms described clinically

Endpoints:

Primary Endpoint:	Determine the cutoff value in chest wall muscle size/quality that optimally classifies patients that had and did not have any reduction in pre-treatment baseline exacerbation frequency (binary). Alternative (continuous): determine the strength of the linear/non-linear relationship

	between continuous chest wall muscle size/quality and continuous change in exacerbation frequency
Secondary Endpoints:	1. Determine individual and combinations of body composition measures (phenotypes) associated with a 5% or greater improvement in FEV1 when compared to baseline FEV1 2. Determine individual and combinations of body composition measures associated with any reduction in maintenance OCS use when compared to baseline OCS use
Exploratory Endpoints:	These endpoints may be limited in scope of analysis by the sample size within each of the outcome groups. 1. Determine individual and combinations of body composition measures associated with any reduction in hospitalizations when compared to baseline hospitalizations 2. Determine individual and combinations of body composition measures associated with any improvement in ACT score when compared to baseline ACT score 3. Determine individual and combinations of body composition measures associated with any subjective improvement of symptoms when compared to baseline symptoms

Study Population: Approximately 300 male or female subjects ages 18-85 with a diagnosis of asthma and on biologic therapy will be studied at the University of Michigan in Ann Arbor, MI, USA and approximately 200 male or female subjects over the age of 18 will be studied in the University of Calgary in Calgary, Alberta, CA.

Description of Sites/Facilities Enrolling Participants: University of Michigan in Ann Arbor, MI, USA is a tertiary academic medical center. Rockyview General Hospital, associated with the University of Calgary, Calgary, Alberta, Canada, is tertiary academic medical referral center for patients with severe asthma.

Study Duration: 1.5 years

1.2 SCHEMA

	Components	Year 1	Year 2

AIM 1	Identify all compatible patients at University of Michigan						
	Abstract EMR data to complete database						
	Collate University of Calgary cohort with database						
	Analyze pre-treatment characteristics						
AIM 2	Process CT data to derive morphomics values						
	Establish morphomics phenotypes						
	Assign clinical phenotypes						
	Assess for overlap in phenotypes to identify novel groups						
AIM 3	Perform analysis using University of Michigan data						
	Apply derived predictive variables to University of Calgary data						
	Perform analysis						
	Write final report						

2 INTRODUCTION

2.1 STUDY RATIONALE

DISEASE BURDEN IN SEVERE ASTHMA AND THERAPY SELECTION

Asthma is a highly prevalent disease that affects 33 million people in the United States and Canada. The vast majority of asthma patients are well controlled with conventional asthma therapies; however, 10% of patients have severe disease that is associated with significant comorbidity and exposure to high doses of OCS. OCS use increases the odds of developing co-morbid diseases such as diabetes, hypertension, cardiac disease and cataracts and is increasingly being recognized as a major contributor to severe asthma costs, making the development of alternative less harmful therapies paramount[1]. Fortunately, over the past three years there has been a rapid increase in the number of biologics approved for the management of severe asthma with type II inflammation, which is estimated to be present in up to 60% of this population. The term type II inflammation refers to an increase in the levels of type II cytokines including IL4, IL5 and IL13, which induce pathologic downstream production of IgE and eosinophils. Current clinical practice utilizes surrogate biomarkers, including peripheral and sputum eosinophils, FeNO and total IgE levels, to phenotype patients with severe asthma and guide biologic drug selection. Unfortunately, these surrogates are imperfect and prone to error from multiple sources, especially in the obese[2].

Unequal Response to Therapy Despite Similar Biomarkers

The response to targeted biologic therapies is heterogeneous despite the use of well-studied biomarkers to select potential responders. Unfortunately, even when patients with a high likelihood of response are selected, 10-15% have complete non-response in all clinical parameters, and only 40% have a robust and complete response to therapy. This is likely related to the presence of overlapping inflammatory pathways, co-morbid eosinophilic diseases that affect response to therapy, possible sub-optimal dosing of drug and the lack of highly specific biomarkers. Precision medicine approaches to severe asthma are in their infancy and the application of complex techniques to help guide therapy are urgently needed. Currently, patients that are partial responders or non-responders to given therapies are switched between available biologics as a means of identifying the best therapy—an inefficient approach that is both time consuming and costly to patients and payers (**Figure 1**).

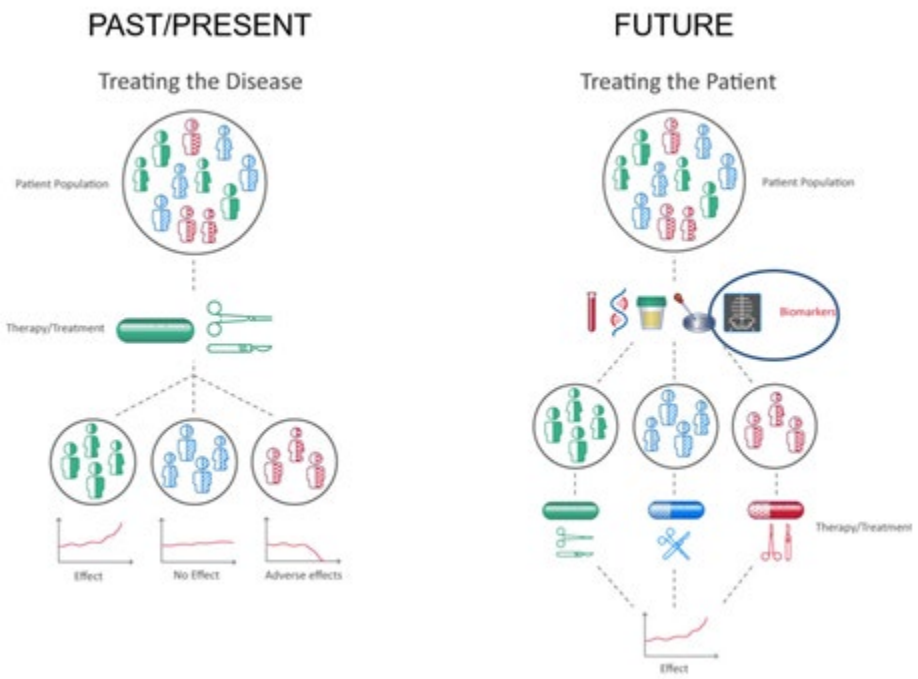

Figure 1: *Improving patient outcomes with Precision Medicine*

2.2 BACKGROUND

Innovation—Expanding on the Role of Body Composition

Nearly all research in severe asthma patients, including phase 3 trials for the current biologic therapies, has used BMI as a surrogate of body composition. Even when CT imaging has been used to better characterize body composition through relatively simplistic maneuvers such as calculation of total visceral and subcutaneous fat mass there have been no clinically usable predictive results from such analyses and no information about the role of the chest wall[3,4]. Morphomics is a combination of high-throughput image analysis and deep learning techniques that enable the segmentation of tissues to precise detail, enabling the characterization of body composition to an unparalleled degree[5,6]. Furthermore, the University of Michigan analytic morphomics group has an existing relational database of over 120,000 subjects that enables the generation of thousands of precise measurements, such as fat distribution, bone mineral density, and muscle density and size, and that can serve as a reference population for our asthma cohorts. This will allow for the accurate identification of extensive body composition patterns that differ from the norm utilizing an imaging population database on a scale that has never been done before.

Analytic morphomics provides actionable quantification of patient heterogeneity for precision medicine.

Precision medical intervention requires granular, precise, and actionable data at the time of treatment. Supported by rapid advances in new high-throughput technologies, “omics” data provide a unique opportunity to better understand pathophysiology and to translate research findings to clinical practice. These data enable clinicians to shift from traditional one-size-fits-all

treatment toward more targeted and precisely individualized therapies. Over the past decade, research at the University of Michigan has demonstrated that **morphomics** is the “omics” data most proximate to a patient’s ultimate health outcome (**Figure 2**).

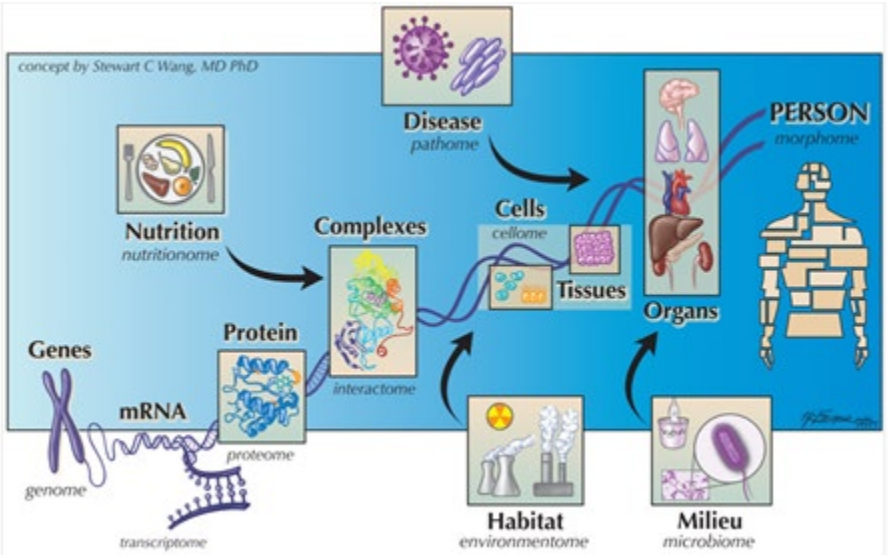

Figure 2: *Morphomics is the "omics" most proximate to treatment*

Recent studies have shown that these digital biomarkers extracted by analytic morphomics provide much better quantitative understanding of morphological features of the human body[7,8]. More importantly, morphomics has been shown to significantly and substantially improve the prediction of clinical outcome and cost in numerous patient populations[9,10]. By providing a quantitative measure of a patient’s body compartment dimensions and composition, near the time of treatment, morphomics can deliver tailoring variables for clinical decision-making.

More recently, morphomic measurements of rib length, density, shape, and angle have allowed a level of analysis of the chest wall that has never been studied in asthma patients [11,12,13]. Using adjacent ribs as a reference, we have then been able to measure intercostal muscle size and quality **(Figure 3**). Morphomics has previously demonstrated the role the chest wall can play in disease by linking rib angle and age to potentially explain the higher incidence of rib fractures in the elderly in motor vehicle collisions[14]. Since severe asthmatics typically have air trapping and are at risk for obesity, it follows that they would also have abnormal chest wall anatomy that could be mechanistically contributing to their disease in a way that could significantly impair their response to medical therapies. The specific characterization of chest wall anatomy in severe asthmatics has never been studied and represents an opportunity to identify novel biomarkers that could predict response/non-response to therapies and enrich the selection of patients in future targeted asthma studies of all levels of severity.

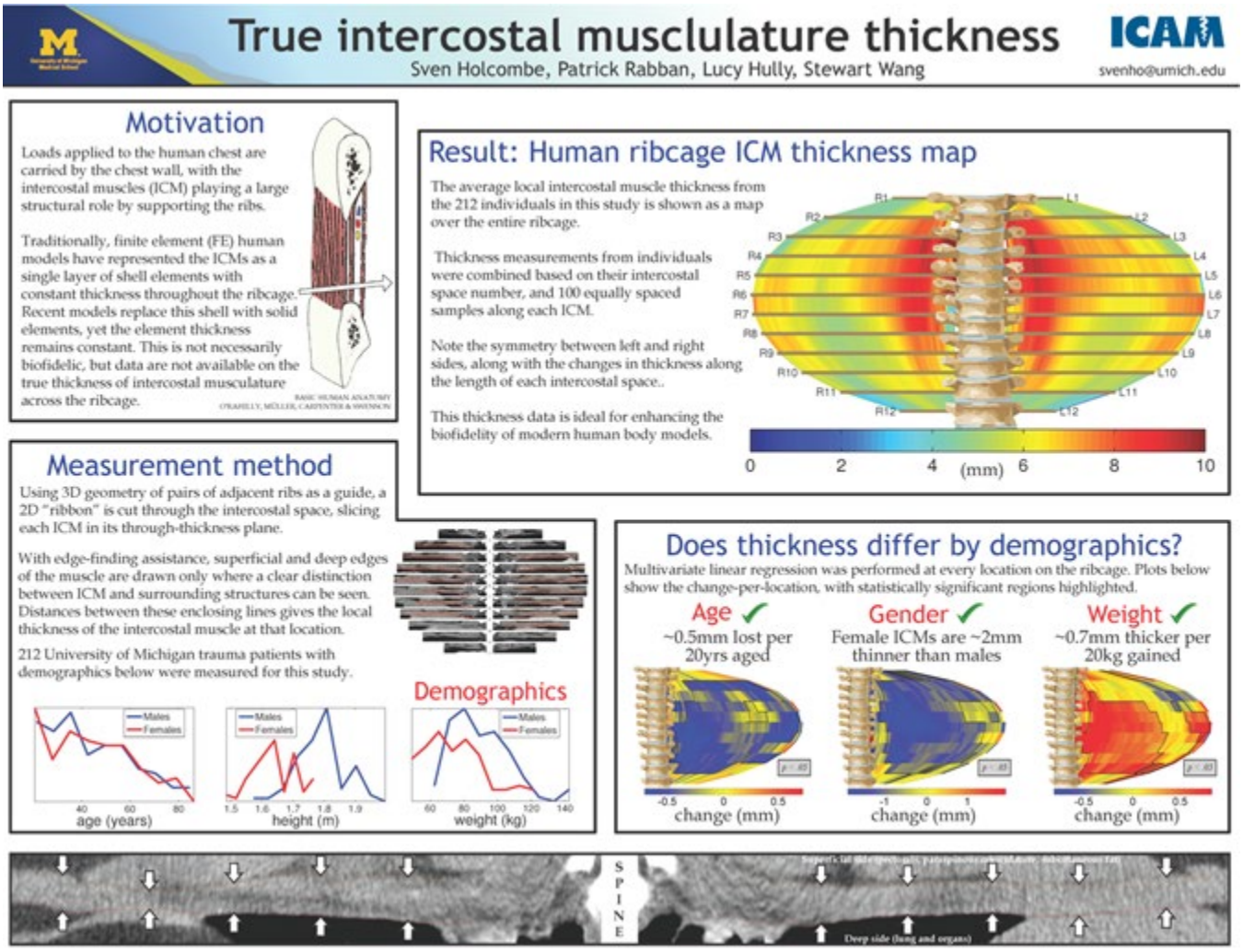

Figure 3: *Proof of concept of intercostal muscle measurements using morphomics*

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

As the study is retrospective, there is no known immediate or long-range risk to subjects besides risk of personal health information theft which is minimized by using only university computers for work, storing health information on university servers or hardware, and de-identification of data once abstraction is complete.

2.3.2 KNOWN POTENTIAL BENEFITS

There are no known immediate or long-range benefits to subjects.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

There is no known risk exposure to subjects and thus the potential value of the knowledge gained from this study outweighs the minimal risk of loss of personal health information.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To identify imaging biomarkers that are associated with the probability of any reduction in pre-treatment baseline exacerbation frequency in a severe asthma population on biologics	Any reduction in exacerbations when compared to baseline exacerbations	Reduction in exacerbations is the primary clinical endpoint used in phase III trials to get many of the biologics used in asthma approved. Finding imaging biomarkers that associate with and possibly predict which patients will not have a reduction in exacerbations would be critical information for clinicians considering biologic initiation.
Secondary		
To identify imaging biomarkers that are associated with the probability of any post-treatment improvement of FEV1 of 5% or more	5% or greater improvement in FEV1 when compared to baseline FEV1	FEV1 is an important measure of lung function for patients with asthma, and any imaging biomarkers that predict a failure to improve this measure would be clinically useful.
To identify imaging biomarkers that are associated with the probability of any post-treatment reduction in maintenance OCS use	Any reduction in maintenance OCS use when compared to baseline OCS use	OCS are associated with multiple comorbidities, especially in the asthma population. Multiple phase III studies are currently underway to study maintenance OCS reduction in asthma due to this clinical concern and is a common reason for initiating biologics. Any imaging biomarkers that predict a failure to wean OCS after biologic initiation would be clinically useful.
Exploratory		
To identify imaging biomarkers that are associated with the probability of any reduction in pre-treatment baseline hospitalizations for asthma	Any reduction in hospitalizations when compared to baseline hospitalizations	Hospitalizations represent the most severe form of exacerbation and being able to find imaging biomarkers that associate with no improvement in hospitalizations would be clinically significant.
To identify imaging biomarkers that are associated with the probability of any post-treatment improvement in ACT score	Any improvement in ACT score when compared to baseline ACT score	Failure to improve symptoms after biologic initiation is a clinically frustrating scenario and finding imaging biomarkers that can predict this would be important for biologic initiation.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To identify imaging biomarkers that are associated with the probability of any subjective post-treatment reduction in symptoms described clinically	Any subjective improvement of symptoms when compared to baseline subjective symptoms	Given the retrospective nature of our study, there is a high likelihood some of the other endpoint data will be missing from clinical encounters for our cohort. Clinical impression of symptoms, however, is expected to be present in essentially every clinical encounter for asthma. In order to make use of this important information, we opted to include an endpoint designed to capture this subjective data since finding imaging biomarkers that predict no improvement with this subjective marker would be clinically important, since this is a common reason clinicians seek to start severe asthma patients on biologic therapies.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Over an 18-month period we plan to conduct our study in 3 parts as identified in the study timeline table above.

University of Michigan Cohort Discovery, Database Construction, and Baseline Analysis
We plan to utilize existing data analytic tools at the University of Michigan to search the EMR for eligible patients to include in a retrospective cohort as identified by the inclusion criteria in section 5. We estimate that approximately 300 subjects will meet our initial criteria based on a preliminary search. We will then abstract all available clinical information from the EMR, de-identify it (with coded key stored in a separate, secured location), and enter the resulting coded data into a database. Up to 2 years prior to biologic initiation or CT scan (whichever is earlier) and all post-biologic therapy information will be included. Clinical information we will abstract will include demographic information, heights, weights, comorbid illnesses (coded as malignancy, coronary artery disease, diabetes, stroke/TIA, cirrhosis, and CKD), non-biologic asthma medication dosage and frequency of use (OCS, ICS, SABA, LAMA, LABA, montelukast, zileuton, and theophylline), asthma biologic agent (benralizumab, reslizumab, mepolizumab, omalizumab, and dupilumab) start and (if applicable) end dates as well as reason for end date (coded as ineffective, cost, intolerance/allergy, non-compliance, lost to follow-up, and other), FeNO, ACT scores, serum and sputum eosinophil counts, IgE, pulmonary function test parameters (% predicted), hospital/emergency room/urgent care/unscheduled office visits and phone call encounters for asthma or breathing-related complaints, and subjective clinician assessment of asthma control (independently graded by 2 different clinicians interpretation of EMR data). Each subject will also be assigned a phenotype by the Severe Asthma Research Program criteria[15]. If a majority of subjects are missing post-bronchodilator data and unable to be clustered by these criteria, we will instead assign adopted clusters from this paper as follows: Cluster 3-Normal FEV1 (≥68% of predicted), eosinophils (<200 cells/μL), FeNO (<25 ppb), and IgE (<200 UI/ml) and no evidence of atopy; Cluster 4-Reduced FEV1 (≤68% of predicted) with abnormal elevation of eosinophils, FeNO, or IgE and/or evidence of atopy; Cluster 5--Reduced FEV1 (≤68% of predicted) with normal eosinophils, FeNO, or IgE and no evidence of atopy. We do not expect to have any Cluster 1 or 2 patients in our study but will assign them accordingly if present. We will perform similar abstraction procedures for approximately 200 patients in the University of Calgary cohort, and label the data with a tag for this cohort for analytical purposes.

For the purposes of our analysis, we will define baseline measurements as the average of all data obtained in the year prior to biologic initiation or, if only one clinical encounter (defined as an office or emergency room visit) is available in this time period, then the average of the 2 clinical encounters immediately prior to biologic initiation will be use with the time frame noted in the database. In order to assess our primary and secondary outcomes we will use the average of all data from 4 to 18 months after biologic initiation or, if only one clinical encounter is available in this time period, the average of the 2 clinical encounters closest to, but not before 4 months after, biologic initiation. If a second biologic is introduced or the initial biologic choice is

changed, we will use all clinical data prior to the change, even if it is before 4 months of use, then follow the above steps to collect new outcome data on the new drug (see **Figure 4**).

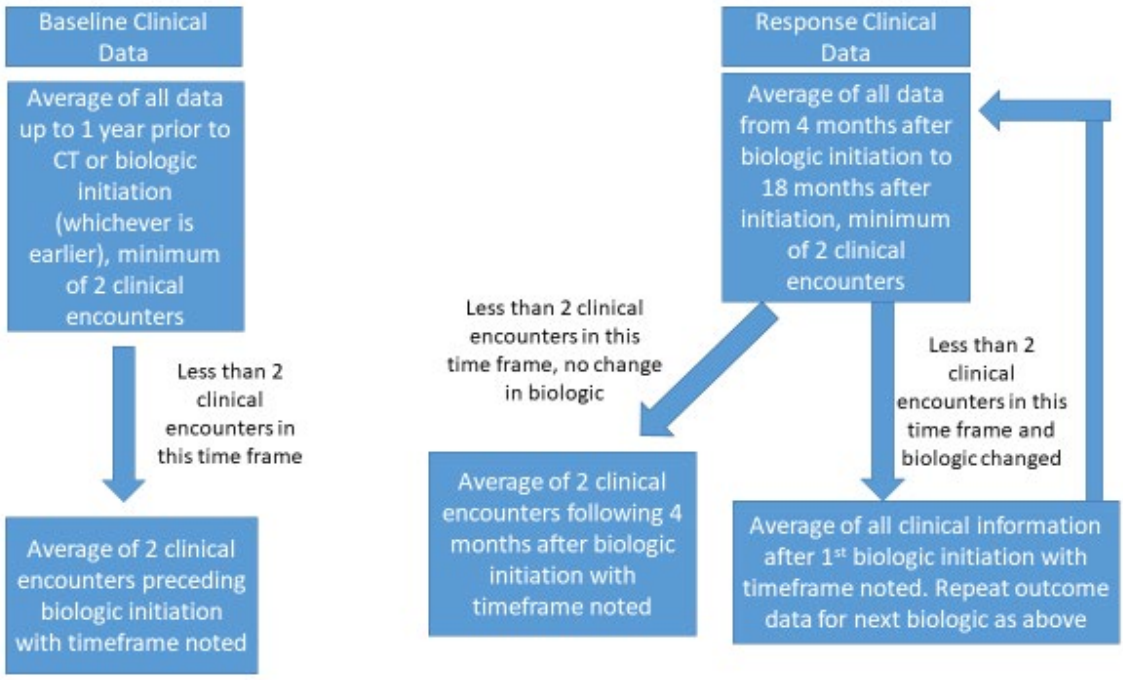

Figure 4. *Baseline and Response Clinical Data Plan.*

Since our interest is primarily in finding the ~15% of patients who do not respond to biologics, we have chosen to include partial and complete responders together in our endpoints in order to isolate the non-responder population. Table 1 below will represent the dichotomization of responders and non-responders for each endpoint using the baseline and post-biologic data as detailed above. An exacerbation will be defined as any hospitalization, urgent care, emergency room, or unscheduled office visit for asthma or a breathing-related complaint or a temporary increase of OCS or ICS dosing for 3 or more days with the intent of the increase to treat acute symptoms. For clinician response, clinical encounter notes will be read and interpreted by 2 independent physicians and graded as detailed in the table. Upon completion of all data abstraction the patient will be de-identified as described in data handling below.

	Responder	**Non-responder**
Exacerbations	Any decrease from baseline	No change from baseline
Hospitalizations	Any decrease from baseline	No change from baseline
Maintenance oral corticosteroid (OCS) use	Any decrease from baseline	No change from baseline

Change in FEV1	≥5% improvement from baseline	<5% improvement from baseline
ACT score	≥1-point improvement from baseline	No change from baseline
Clinician impression of response to therapy	Any improvement in symptoms from baseline	No change from baseline

***Table 1**. Outcome Response Grading.*

Morphomics CT Analysis and Clustering

After identification of all appropriate patients in the University of Michigan cohort, we will then identify all relevant CT scans in subjects. We will select pre-biologic CT data of the chest and, if available, abdomen/pelvis (or if no pre-biologic scans exist for a subject we will utilize CT imaging closest to the biologic start date and make note that the CT scan was obtained after biologic initiation) for analysis. Height-normalized measures will be computed to control for height-related correlation (e.g., Skeletal Muscle Index = Skeletal Muscle Area / Height^2). Morphomics analysis will be run with measures centered and scaled into standard deviation units, stratified by sex and age. In addition, the Reference Analytic Morphomics Population[16] will be used to generate additional variables that offer a population-based control for sex and age.

Analysis of Phenotypes, Training Data Set, and Assessing Model Robustness

Please see the statistical section for detailed statistical analysis plan.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We elected to approach this problem in a retrospective fashion due to the availability of existing data that is likely sufficient to answer our clinical question and the known risks of radiation from CT exposure. Many asthmatics undergo CT scans for various reasons; however, it is rare to obtain a CT scan in a stable asthmatic, even if symptoms are severe, since there is no known current clinical utility in this diagnostic test. Since our question relies on using CT data to assess body composition in severe asthmatics requiring biologics to find novel parameters that may be able to predict response more reliably than the current standard of care options (FeNO, sputum/serum eosinophils, and IgE), it follows that utilizing existing CT data while also having the concurrent retrospective benefit of known response to biologic therapy would allow this question to be most efficiently addressed without exposing any of the subjects to the harms of radiation solely for research purposes. Furthermore, our use of a learning cohort retrospectively constructed at the University of Michigan and a prospectively constructed validation cohort from the University of Calgary will allow us to generate more robust results than normally found in retrospective studies since we will be using a geographically distinct validation model.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Our population will include all adults 18 years or older with a diagnosis of asthma (defined as a positive methacholine test, supportive PFTs, or clinician diagnosis with appropriate supporting clinical context) who have been prescribed and taken an FDA-approved biologic medication for severe asthma (mepolizumab, benralizumab, reslizumab, omalizumab, or dupilumab) and have chest CT images in the University of Michigan radiology databases. All patients from the Calgary cohort will be screened in a similar fashion.

5.2 EXCLUSION CRITERIA

We will exclude patients with a > 10 pack year history of smoking and those with evidence of emphysema on CT imaging due to concerns that concurrent COPD may be attenuating the effects of the biologic. Those with some scattered bronchiectasis thought to be secondary to severe asthma will not excluded; however, severe bronchiectasis secondary to other causes will be excluded for the same reason. Furthermore, patients who do not have accessible adequate follow-up information (4 or more months from drug initiation with clear documentation of response) will be excluded from the final analysis in part 3 due to an inability to assess response but will be included in the initial analysis to help with cluster identification.

6 STATISTICAL ANALYSES

6.1 BASELINE DATA ANALYSIS

Tabulate summary statistics of baseline characteristics for each analysis cohort. Continuous variables will be summarized using mean, median, standard deviations, and interquartile range (IQR) of each baseline characteristic. Categorical variables will be summarized using class percentages. Perform exploratory data analysis (EDA) to identify potential outliers, assess the statistical distribution of data elements (e.g., Normal vs. Chi-square), and examine bivariate correlation matrix for potential non-linearity. Compare pre-treatment characteristics of University of Michigan and University of Calgary cohorts to assess similarity using Student's t (continuous, Normal), Fisher's Exact (binomial), Wilcoxon rank-sum (continuous, non-Normal), and Chi-Square/Tukey's Honest Significant Difference (Categorical) statistical tests.

6.2 MORPHOMICS ANALYSIS AND PHENOTYPING

Compute height-normalized measures to control for height-related correlation, e.g., Skeletal Muscle Index = (Skeletal Muscle Area / Height^2). Center and scale morphomics measures into standard deviation units, stratified by sex, to control for sex differences. (Optionally/additionally, convert morphomics measures into sex- and age-adjusted percentiles using the Reference Analytic Morphomics Population (RAMP), to simultaneously control for sex- and age-related correlation). The following analyses will be performed on both the UM and UC cohorts combined. Classification and regression tree (CART) will be utilized to develop individualized decision rule on SARP class based upon morphomic measures. In addition, Unsupervised learning techniques will be carried out to identify novel clusters for morphomic phenotypes in these cohorts.

6.3 IDENFITICATION OF BIOMARKERS FOR OUTCOMES

To incorporate high-dimensional morphomic parameters to better stratify patients in regard to their probability of complete response, we will leverage the regularization technique in machine learning to select important variables and develop risk predictive models. To be more specific, elastic net regularization will be utilized to address the high dimensional nature of data derived with analytic morphomics. Elastic net consists of a linear combination of L1 (lasso) and L2 (ridge) penalty to address over-fitting and co-linearity, respectively. In addition, to capture potential non-linear effects among variables, we will also apply random forest and gradient boosting, two highly utilized ensemble tree-based methods. Sample splitting will be used to assess model performance. We will evaluate the accuracy of developed predictive models by various performance measures, including Harrell's Concordance index, integrated cumulative area under the curve, and integrated brier score. The final developed predictive model will be evaluated on an independent dataset from the University of Calgary.

7 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

7.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

7.1.1 INFORMED CONSENT PROCESS

Both the University of Michigan and University of Calgary sites will apply for exemption of informed consent through their respective local IRBs given the retrospective nature of the study and intent to store all information in a de-identified fashion.

7.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

N/A

7.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

N/A

7.1.2 STUDY DISCONTINUATION AND CLOSURE

This study will be discontinued in approximately 18 months or at completion of the final analysis as detailed above.

7.1.3 CONFIDENTIALITY AND PRIVACY

Both University of Michigan and University of Calgary sites will obtain institutional authorization to share clinical information for the purposes of this study

7.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

All finalized CT and chart data will be stored in a de-identified fashion on University of Michigan servers for future research use.

7.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigators	**Sub-Investigators**
Stewart Wang, MD PhD	Jon Grace, MD
Njira Lugogo, MD	Patrick Mitchell, MD

7.1.6 SAFETY OVERSIGHT

N/A

7.1.7 CLINICAL MONITORING

N/A

7.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Chart data abstraction will be carried out by research staff and overseen by the principal investigator and co-investigators. For areas where clinical judgement is required (such as identification of an exacerbation or scoring subjective clinical response to therapy), 2 physicians with a pulmonary background will adjudicate the clinical data to ensure quality control.

7.1.9 DATA HANDLING AND RECORD KEEPING

7.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Study oversight will be performed by the principal investigators and the co-investigator and the University of Michigan data analysis team. The study database will be developed on servers managed by MICHR (the CTSA supported clinical research infrastructure) at the University of Michigan. Web-based data entry and management, as well as the creation and export of study reports for the safety committee will be provided by the University of Michigan under the guidance of the data management core. The study will use the REDCap clinical trial software platform for electronic data capture and clinical data management, as the basis for our custom-designed data entry and management system. Protocols for the transfer of data, with careful attention to data integrity, will be written by experienced programmers and stored in the database. Data collection is the responsibility of the research staff. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

CT scans anonymization will be performed through existing processes in the analytic morphomic group. Scans will be selected using software that connects directly to the institution's existing PACS system. Once an appropriate scan is identified, it will be downloaded and processed through the morphomic lab's anonymization software. This system removes the patient information stored in each image file's DICOM header, which contains attributes such as name, patient ID, date of birth, etc. All patient identifying data is removed, and a unique identifier (UI) is created and stored in the Patient ID attribute. The UI takes place of the medical record number (MRN) throughout the life of the project. The key connecting this UI with the patient MRN will be maintained and controlled by the project PIs.

7.1.9.2 STUDY RECORDS RETENTION

Data obtained from the study will be retained in a de-identified fashion for a minimum of 3 years after completion of study or longer if required by local regulations.

7.1.10 PROTOCOL DEVIATIONS

Please see additional considerations for anticipated changes to the protocol as described above that may occur once data is obtained.

7.1.11 PUBLICATION AND DATA SHARING POLICY

An explicit goal of this study is to present the primary and related outcomes of this study at Scientific Meetings and to publish, as possible, in peer-reviewed Scholarly Journals to assure dissemination of the findings. The authority to do so resides with the subject investigators and not with any sponsor.

7.1.12 CONFLICT OF INTEREST POLICY

Applicants will certify the absence of certain financial interests and arrangements of clinical investigators that could affect the reliability of data, or alternatively disclose those financial interests and arrangements to the agency and identify steps taken to minimize the potential for bias.

7.2 ADDITIONAL CONSIDERATIONS

None

7.3 ABBREVIATIONS

ACT	Asthma Control Test
AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CKD	Chronic Kidney Disease
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CT	Computed Tomography
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EMR	Electronic Medical Record
FeNO	Fraction of Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in One Second
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator’s Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroid
IDE	Investigational Device Exemption
IgE	Immunoglobulin E
IL	Interleukin

IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LABA	Long-Acting Beta Agonist
LAMA	Long-Acting Muscarinic Antagonist
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OCS	Oral Corticosteroid
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SABA	Short Acting Beta Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
TIA	Transient Ischemic Attack
UP	Unanticipated Problem
US	United States

8 REFERENCES

REFERENCES

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