Consent to Participate in Research

Study Title: Leveraging Pharmacogenomics in Asthma for Predication, Mechanism and Endotyping (EPIPHANY)

Principal Investigator:

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Sponsor and/or Funder: National Institutes of Health (NIH)

Summary of the Research

This is a consent form for participation in a research study.
Taking part in this research study is voluntary. This consent has important information about this study and what to expect if you decide to participate. Please consider the information carefully, and feel free to ask questions before deciding whether to participate.

The study aims to find the best treatments for people with moderate to severe asthma.
In this study, a new method will be used. Every person taking part will be given medications that are approved by the FDA and are based on established guidelines. The researchers will then assess how well you respond to each asthma treatment and will measure your responses using genetic and biologic measurements in your blood, saliva, and nasal secretions. The FDA approved medications used in this study are a corticosteroid (**triamcinolone acetonide**) and two biologics for moderate to severe asthma, **benralizumab** (also known as FASENRA®) and **dupilumab** (also known as DUPIXENT®). Biologic therapies target and prevent the body's immune response to asthma triggers. In asthma patients, biologics help prevent symptoms.

Participation will include an initial visit (screening visit) and an observation (also known as run-in) period to determine if you are eligible. If you qualify, there will be nine additional clinic visits and two 30-minute virtual visits. During the observation period you will be given standard asthma medications recommended in the asthma guidelines, and we will monitor your responses during the study. These study procedures include answering questionnaires; taking measurements, including your breathing capacity using a breathing machine (spirometer) and a peak flow meter; using an e-Diary to note daily symptoms and rescue inhaler use; providing blood samples; collecting sputum (a mix of saliva and mucus from coughing); checking fractional exhaled nitric oxide (FeNO) levels; and taking nasal cells with a brush.
The main risks of the study are from the procedures (as described below) and potential loss of confidentiality.

The main benefits include close monitoring of your asthma and possibly personalized recommendations for your asthma treatment. The knowledge gained from this study may help in choosing targeted biologic therapies more efficiently for people with moderate to severe asthma in the future.

Time commitment: This study involves a (4 week) screening and observation (eligibility) period, a corticosteroid period (8 weeks), two (12 weeks each) treatment periods, and one (16 week) wash-out period. In all, that is about 60 weeks, with nine in-person visits and two 30-minute virtual visits. The screening visit will last about 6-7 hours, the corticosteroid injection visit will last about 4 hours, and each of the other in-person visits will be about 2-3 hours per visit. You will also spend 15 minutes per day at home recording e-Diary (daily symptoms and rescue inhaler use) and peak flow measurements.

The University receives compensation from the sponsor of this study (National Institutes for Health: NIH) for the conduct of this study. If you have any questions, please discuss this with your study physician.

Why is this study being done?

Asthma has become an increasingly important healthcare problem in the US and in the world, affecting ~300 million individuals worldwide with more than 20% of asthma patients having severe or poorly controlled asthma. Measurable characteristics of the body are called biomarkers, and they may be used to evaluate the body's normal function, abnormal processes, or response to treatment medication. For example, abnormally high numbers of eosinophils (a type of white blood cell) in the blood is a biomarker for a specific type of severe asthma. This research study is designed to identify new biomarkers that could predict whether a treatment will work or not work for someone with asthma. To do this, we will study people who have moderate to severe asthma. These biomarkers will help us figure out if a person is likely to benefit from a particular treatment. We will look at their clinical characteristics and history of asthma as well as their clinical responses and changes in gene expression after each specific therapy given during this study. Changes in gene expression levels and clinical responses will then be used to develop biomarkers of how patients respond to asthma treatment. We will focus on corticosteroids and two biologics (antibodies that block immune proteins that cause asthma) that have been approved by the FDA. If this study is successful, doctors could use these biomarkers to identify the best therapy for their patients. This same approach could also be used to evaluate the response to other drugs that are available now or may be in the future.

Why am I being asked to be in this study?

You are being asked to be in this study because you have moderate to severe asthma.

What will happen if I take part in this study?

If you decide to participate and meet the requirements after the observation period, you'll go through three active treatment phases. There will be a 16-week break (referred to as a "washout period"), between the last two active treatment phases, where you will not receive any biologic treatments.

Before and after receiving the treatments, clinical parameters will be measured and blood, sputum, and nasal brushings will be collected.

You will keep a diary twice a day to include details regarding any asthma symptoms as well as the results from testing your peak flow.

The duration of the study is approximately 60 weeks and includes the following:

Screening and Run-in (Observation) Period (Weeks 0-4): Will determine if you meet the criteria to qualify for enrollment into the study.

- Your current asthma medications will be standardized to medium or high dose inhaled corticosteroid (ICS)/ LABA (long-acting beta2-agonist) therapy; and you will remain on these throughout the study. Beta-agonists are commonly used to treat asthma; beta-agonists are used to relax airway muscles to widen/open the airways leading to better/easier breathing.

- Your adherence to taking controller medication (recommended target: ≥70% of scheduled doses) as well as completing e-Diaries and peak expiratory flow (recommended target: ≥70% on any 14 consecutive days during 21 days prior to visit 0) will be monitored.

Corticosteroid Treatment Period (Weeks 4-12): You will be administered a single intramuscular dose of triamcinolone acetonide 40 mg. This is an injection of a corticosteroid medication into a large muscle, like the shoulder, thigh, or buttocks.

Biologic Treatment Period (Starting at week 12): You will be randomly assigned (by chance like rolling dice) to either benralizumab (FASENRA®) or dupilumab (DUPIXENT®) biologic for three months. You will then receive the other biologic after a 16-week washout period in between. Both biologics are FDA approved for asthma.

Anti-IL-5 receptor treatment: Benralizumab (FASENRA®) is an anti-IL-5 receptor antibody, and it is administered once monthly as an under the skin injection. After being taught how to self-administer the medication, you will administer benralizumab (FASENRA®) to yourself.

Anti-IL-4 receptor treatment: Dupilumab (DUPIXENT®) is an anti-IL-4 receptor antibody, and it is injected under the skin every 2 weeks. After being taught how to self-administer the medication, you will administer dupilumab (DUPIXENT®) to yourself.

Study Visit Overview

STUDY OVERVIEW		
STUDY PERIOD	**WEEK (+/- 7 days)**	**VISIT DURATION**
SCREENING / RUN-IN (4 WEEKS)	Week 0-4: Screening	6-7 hours
CORTICOSTEROID TREATMENT (8 WEEKS)	Week 4: Corticosteroid Injection Visit	4 hours
	Week 6*: Post-Corticosteroid Injection Assesssment	2-3 hours
FIRST BIOLOGIC TREATMENT (12 WEEKS)	Week 12: Start of Biologic #1 (dupilumab or benralizumab)	2-3 hours
	Week 20: Mid-Treatment Visit	2-3 hours
	Week 24: End-of Treatment Visit	2-3 hours
WASHOUT (16 WEEKS)	Week 34: Mid-Washout (Virtual) Visit	30 minutes
SECOND BIOLOGIC TREATMENT (12 WEEKS)	Week 40: Start of Biologic #2 (dupilumab or benralizumab)	2-3 hours
	Week 48: Mid-Treatment Visit	2-3 hours
	Week 52: End-of Treatment Visit	2-3 hours
END OF STUDY	Week 60: End of Study (Virtual) Visit	30 minutes

*: Visit window +7 days

Study visits are described in more detail below.

Screening Visit (week 0): *[Can be completed over multiple visits if necessary]*

Before any study information is collected, a member of the study team will review the consent with you and will answer any questions that you may have about participation in this study. If you agree to participate, and sign the consent form, you will complete a screening visit to determine if you are eligible for the study. The screening visit will last about 7 hours and it can be split over two or three study visits.

During Screening you will be asked to complete:

- **Informed consent:** You will review and be asked to sign the study consent.
- **Physical exam:** Medical personnel will perform a physical exam on you. Your blood pressure, heart rate, respiratory rate, and temperature will also be measured.
- **Body measurements**: will include height, weight, as well as waist and hip circumference.

- **Urine pregnancy test:** If you are a person who can become pregnant, you will be asked to provide a small amount of urine to make sure that you are not pregnant. You will not be enrolled if you are pregnant or breastfeeding.
- **Questionnaires:** You will complete several questionnaires, and you will be asked for basic information about yourself as well as about your medical and surgical history, past and current medications, and asthma symptoms and exacerbations (the worsening of a disease or an increase in its symptoms).
- **Peak Flow Meter**: You will be given a device called a *peak flow meter* and you will be asked to use it at home throughout your participation in the study. You will use the peak flow meter to perform peak expiratory flow measurement at home spirometry twice a day. We will show you how to use this device. Your adherence (on-schedule use and cooperation) to the use of this device is very important and will help determine your eligibility for the study.
- **Application (App) Installation on Smart Phone:** Study staff will help you install an app onto your electronic device (e.g. iPhone , iPad or iPod, or a smartphone or tablet). This app will be used as an electronic diary (e-Diary) to collect information about your symptoms. We will ask you to use the e-Diary two times a day, in the morning and evening. In order to participate in the study, you must own a device that will allow you to download and use this app. Please note that data charges may apply by using your device to record information in the diary. If your smartphone or tablet is unable to record your answers, we will give you paper forms to use as backup until your device is back up and running.
- **Pulmonary Function Testing** including medication withholding, spirometry, maximum bronchodilator response test (optional procedure if historical data are available/acceptable; at another visit if needed).

Medication Withholding: You will be asked to withhold some medications that you are currently taking to treat your asthma for 1 to 2 days before your visit. However, you may take your medications if you feel that you cannot withhold and tell us when you are at the visit.

Spirometry: You will be asked to take a deep breath in and blow your breath out as hard and fast as you can into a machine for at least 6 seconds. The machine measures the amount of air you can blow out and how fast you can blow it out. You will be asked to do this 3 or more times so we can get an accurate measurement of your lung function.

Maximum Bronchodilator Response Test: After you perform the baseline spirometry you will take 4 puffs of albuterol from a metered dose inhaler (MDI) to open your airways. You will then repeat spirometry 10-15 minutes later. The test will continue by having you take 2 more puffs of albuterol and then repeat spirometry 10-15 minutes

later to see if your airways have opened as much as possible. No more than 8 puffs total of albuterol MDI will be given.

Lifestyle Considerations*: In order to be eligible for the study, you will also have to comply with the following lifestyle considerations, throughout the whole study:*

- Do not use tobacco products or nicotine containing products (including e-cigarettes, patches).
- Do not use inhaled marijuana.
- Do not use any illegal drugs including abuse of prescription drugs.
- Persons who can become pregnant will have to take urine pregnancy tests throughout this study (at every visit) and must use a highly effective form of birth control. There have been no controlled studies of the use of asthma biologic therapies in pregnancy. Therefore, it is not known if these medications can cause fetal harm. Hormonal methods (birth control pill, etc.), double-barrier methods (condoms with spermicidal, sponge with spermicidal, or diaphragm with spermicidal), or abstinence (not having sex) may be used. Your study physician will discuss these with you.
- Contraception through any of the above-mentioned methods should be used for at least 1 month prior to start of study treatment, throughout study participation and for an additional 16 weeks after the end of the final test treatment.
- You cannot be breast-feeding; the effects of asthma biologic therapies in nursing infants have not been well studied.

Run-In (Observation) Period (Weeks 0-4): During this time, you will remain on a stable daily dose of a combination inhaled corticosteroid and long-acting beta agonist. This may require a change from your routine medication. You will also be asked to start completing your daily e-Diary with peak flow measurements.
Completing the Screening and Run-in procedures does not guarantee your eligibility for the study. Your eligibility will also depend on the results of the tests described above, whether you have consistently completed the daily e-Diary questions and assessments, and the medical opinion of the study physician.

Corticosteroid Injection Visit (Week 4): This visit will take approximately 4 hours.
During this visit, you will be asked to complete:

- **Eligibility assessment:** Your eligibility will be evaluated and confirmed, including whether you have been using your study e-Diary.
- **Physical exam**
- **Urine pregnancy test**
- **Questionnaires**
- **Peak-flow measurement and maintenance of an e-Diary:** Your adherence to

performing these tasks at home will be reviewed and discussed with you.

- **FeNO:** Measurement of exhaled nitric oxide will be performed.
- **Corticosteroid injection:** You will receive an injection of triamcinolone (corticosteroid).
- **Sample collection**: Blood, induced sputum, and nasal brushings will be collected.

  Sputum induction: Sputum (a mixture of saliva and mucus coughed up from the respiratory tract) cells and fluid will be collected for assessment of lower airway inflammation and presence of respiratory bacteria and viruses. An induced sputum sample will be collected following inhalation of hypertonic saline (salt solution with sodium chloride of greater than 0.85%). You will inhale 4 puffs of albuterol before this procedure to open the airways. You will then be asked to breathe in the salty mist for up to 12 minutes. Every two minutes you will be asked to cough deeply and vigorously to bring up a sample of sputum.

  Nasal brushes: We will use a nasal speculum (an instrument used to widen the opening of a nostril) and standard cytology (cell) brush to collect epithelial (surface) cells from the inferior turbinates (inside of your nose from both nostrils). For your comfort during this procedure, we will use "soft brushes". Two brushes will be rotated three times in each nostril. This is similar to being tested for COVID-19.

  Blood draw: Up to 35 mL (approximately 7 teaspoons) of blood will be drawn via venipuncture from a vein in your arm by needle stick.
- **Pulmonary function testing** including medication withholding and spirometry.

Post-Corticosteroid Visit (Week 6): This visit will take approximately 4 hours.
During this visit, you will be asked to complete:

- **Physical exam**
- **Urine pregnancy test**
- **Questionnaires**
- **Peak-flow measurement and maintenance of an e-Diary**: Your adherence to performing these tasks at home will be reviewed and discussed with you.
- **FeNO**: Measurement of exhaled nitric oxide will be performed.
- **Sample collection:** Blood, induced sputum, and nasal brushings will be collected.
- **Pulmonary function testing** including medication withholding and spirometry.

Biologic Medication Treatment Visits (Starting at Week 12):

Study visits will be scheduled at the beginning, middle, and end of the treatment period for each biologic. These visits are expected to take about 3 hours and may be divided into 2 visits for your convenience. The visits include the following:

- **Physical exam**
- **Urine pregnancy test**
- **Questionnaires**
- **Peak-flow measurement and maintenance of an e-Diary:** Your adherence to performing these tasks at home will be reviewed and discussed with you.
- **Pulmonary Function Testing** including medication withholding and spirometry
- **FeNO** – Measurement of exhaled nitric oxide will be performed.
- **Sample collection**: Blood sample will be collected at every in-person visit; induced sputum and nasal brushings will be collected (at the Start-of- and End-of-Treatment visits only).

Virtual Visits (Week 34 and Week 60): These visits will take approximately 30 minutes. During these visits, you will be asked to complete:

- **Questionnaires**
- **Peak-flow measurement and maintenance of an e-Diary**: Your adherence to performing these tasks at home will be reviewed and discussed with you.

How long will I be in this study?

The study will last approximately 60 weeks as described above.

How many people will take part in this study?

This is a multisite study, and we are planning to enroll 120 participants study wide. The goal is to enroll 40 subjects at each of the study sites: Mayo Clinic, Arizona, Yale University, and University of California San Diego.

What benefits can I expect from being in this study?

It is expected that you might receive a benefit from the close monitoring of your asthma, and general evaluation of your condition. Also, how you respond to the current targeted biologic treatments could help us better understand how asthma works in each person. This understanding may lead to personalized treatment suggestions in the future. It is also possible that the knowledge obtained from this study may help develop new asthma therapies in the future, which will benefit people with asthma like yourself.

Clinical test results and data that may influence your clinical care, such as spirometry reports and conventional biomarkers, will be shared with you and can also be shared with your physician with your permission.

You will be provided with a wallet card that contains contact information for the study team that can be shared with any of your physicians to allow them to ask any questions about the study that they may have. If you consent, we will also provide a summary of the study for your physician(s) and will actively coordinate your participation in the study with their clinical care. If you do not consent to share your participation in the study with your primary physician or if you do not have a primary physician, the study physician will discuss and provide referrals as needed for your asthma care. You will be provided with contact details of the study team and nurse.

What risks, side effects or discomforts can I expect from being in the study?

Participating in a research study has some potential risks. These risks include:

Risks of using medium to high dose corticosteroid (ICS) and long-acting beta agonist (LABA) during run-in and washout. All subjects will be treated with guideline-based standard of care throughout the entire study. However, the study does have a run-in and a washout period between therapies where patients will be taking only medium to high dose ICS/LABA/a combination of controller medications; this may require a change from your routine medication. To help reduce the risk, you will be counseled to use a short acting beta agonist (SABA) as needed and will be evaluated for the stability of your asthma control. Enrollment will be delayed or cancelled if an asthma exacerbation/attack (increased severity) occurs.

Questionnaires. You will complete questionnaires. There are no foreseen risks to answering these questionnaires, although they may be considered long because of some repeating of questions. There is potential that information from a study might be shared in a manner that could risk a person's privacy, leading to possible negative effects on their social and work life. However, this risk is not as great for a common condition such as asthma. Regardless, care will be taken to ensure confidentiality by keeping research records in locked cabinets or secure storage rooms when research staff are not in attendance. All sharing of data with the study co-investigators for analysis will be by a study ID code only (not using your name). Publication of results will involve group data only so that individual participants cannot be identified. On occasion it may be necessary, for legal reasons or for good clinical practice, for third parties such as the U.S. Food and Drug Administration (FDA), Institutional Review Board (IRB), or National Institutes of Health (NIH) to review medical records that might contain your name. However, this is not a common occurrence, and every effort will be made by the investigators to provide as much confidentiality as possible.

Peak flow meter. There are no significant risks associated with using a peak flow meter. At the advice of your health care providers, you should already have been using a peak-flow meter to monitor your asthma.

Spirometry and responses to short-acting beta-agonists (reversibility). Individuals with asthma routinely undergo spirometry and bronchodilator testing as part of usual clinical care, and you will also undergo these procedures as part of this study. To prepare for testing, you will be asked to **temporarily stop certain asthma medications** (and caffeine) prior to pulmonary function testing; however, if you feel that you are not able to temporarily stop the medication, you should take the medication and inform the study team at the time of your visit. Spirometry can cause you to become light-headed or dizzy and it can also make you wheeze, have shortness of breath or chest tightness, or worsening of these symptoms if they were already occurring. The chance of these symptoms occurring is rare, but treatment will be available if symptoms should occur.

Albuterol is given during the maximum bronchodilator response test. Side effects of albuterol may include nervousness, hyperactivity, increased heart rate, nausea, or headache. These side effects are temporary and should resolve within 15 to 30 minutes.

An increase in respiratory symptoms may occur because of these tests. If this occurs, you will be directed to resume the prior regimen and treatment is available, if needed.

Blood Collection via Venipuncture. Standard blood draws (venipuncture) will also be performed as part of the study. The risks of venipuncture include anxiety, brief pain during the needle insertion, local bruising at the collection site, chance of infection, and small hematomas (a solid swelling of clotted blood within the tissues). Rarely, people can get light-headed or even faint as a result of venipuncture. To minimize the risks and anxiety associated with this procedure, only experienced staff will perform venipuncture.

Genetic (gene) and genomic (gene expression) analyses on blood, sputum, and nasal brushings will be performed. To minimize risk and to protect privacy, only a numeric identifier will be used to label all genetic and genomic samples and data. These results will not be a part of your general medical record. Genomic results may be presented in publications and meetings, but your name will not be identified. However, there is an **extremely** small potential risk of loss of confidentiality.

Exhaled nitric oxide determination. Exhaled nitric oxide monitoring can cause similar risks as spirometry (including light-headedness) but these risks are less intense and more rare.

Hypertonic saline sputum induction. Induced sputum techniques can cause shortness of breath, wheeze, and chest tightness. Because inhalation of 3% sodium chloride (for sputum induction) can cause bronchospasm (narrowing of the bronchial smooth muscles), you will receive 4 puffs of albuterol prior to induction. Peak flows are monitored constantly during induction and the procedure is stopped if there is a 20% fall in peak expiratory flow (PEF). If any

respiratory symptoms occur, the symptoms usually are short-lived and treatment with a bronchodilator (a drug that causes widening of the airway) will be given. In addition, bronchodilators will be administered as needed to return forced expiratory volume (FEV1) to within 10% of the level prior to sputum induction.

Nasal brushing. The main risk of nasal brushing is epistaxis (bleeding from the nose). You may experience a brief discomfort at the time of brushing, but this is transient and soft brushes will be used.

ICS/LABA combination therapy. Most participants are already using combination therapy. Risks of side effects and adverse effects can include tremor, nervousness, insomnia (trouble falling or staying asleep) and tachycardia (abnormally rapid heart rate). Side effects are usually mild and resolve with treatment over time.

Triamcinolone Acetonide for Intramuscular Injection. Triamcinolone acetonide injectable suspension (Kenalog™, 40 mg/mL) provides a synthetic corticosteroid with marked anti-inflammatory action (reduces inflammation). This medication is used to obtain a prolonged anti-inflammatory therapeutic effect. Triamcinolone acetonide is FDA approved for the treatment of asthma exacerbations/attacks.

Adverse effects of a single triamcinolone injection are rare, but severe triamcinolone injection side effects can include signs of an allergic reaction including hives; difficulty breathing; swelling of face, lips, tongue, or throat. Other extremely rare possible side effects can be atrophy (a "dimple") or changes in skin color at the injection site. These side effects are kept low by placing the drug deep into the muscle. All injections will be given by experienced nurses. Side effects in the body after a single injection of triamcinolone are rare: in another NIH study (Serious Asthma Research Program), 714 people received similar triamcinolone injections with no significant side effects. However, with continuous or repeated use, which is not a part of this study, bone fractures, muscle weakness, ulcers, impaired wound healing, and growth suppression may occur. Despite rare risks, triamcinolone acetonide injection is thought to be generally safe, but there may be risks, discomforts, or side effects that are not yet known.

Anti-interleukin 5 (IL-5) receptor (anti-IL-5R) monoclonal antibody. Benralizumab (FASENRA®) is FDA approved and commercially available. It is administered subcutaneously (under the skin) with an injection. In general, it is well tolerated and has been shown to improve lung function and reduce asthma exacerbations (asthma attacks). The main reported side effects with Benralizumab (FASENRA®) are injection site reactions, and very rarely allergic reactions which would result in discontinuation of the drug. There might also be a reduction in blood eosinophil (a type of white blood cell) counts. Patients with known parasitic infections will be excluded from participation.

Anti-interleukin 4 receptor (anti-IL-4R) monoclonal antibody. Dupilumab (DUPIXENT®) is delivered subcutaneously with an injection. Generally, it is well tolerated although

hypereosinophilia (high number of a certain type of white blood cells) was observed in rare patients but decreased as treatment continued and was not associated with any other signs or symptoms. Additional risks include local injection site reactions and very rare systemic allergic reactions.

What other choices do I have if I do not take part in this study?

Your participation is voluntary. You can choose not to participate or to stop participating at any time without penalty or loss of benefits to which you are otherwise entitled.

The alternative to participating in this study is to get standard treatment from your doctor, participate in a different study, or you and your doctor can choose another approved asthma treatment instead of the treatments offered in this study.

Please note that ***you may not participate in other studies*** while you are enrolled in this study. Please inform the Investigator or study staff if you are thinking about enrolling in another study.

When may participation in the study be stopped?

You may be withdrawn from the study if you no longer meet the inclusion criteria, or if you become pregnant. You may be also withdrawn from the study for your safety as determined by the investigator. Your participation can also be stopped in the event that the study is cancelled. As a reminder, you may choose to end your participation at any time. Your data and samples collected before withdrawal will be used and stored according to this consent. No new data will be used or collected after the withdrawal.

What happens if I am injured because I took part in this study?

Side effects (injury) can happen in any research study. These effects may not be your fault or the fault of the researcher involved. Known side effects have been described in this consent form. However, side effects that are not currently known may happen and may require care. If you experience an injury or adverse event, please seek treatment and contact **(insert name of site investigator here)** at **(insert phone number of site investigator here).**

The study sites do not have funds set aside for payment if you are injured from being in the study. If you require medical care, you should seek medical treatment, and the costs for any treatment or hospital care you receive as the result of a study-related injury that are not covered by a health insurer will be billed to you. By signing this form, you do not give up any rights to seek compensation in the event of negligence.

What are the costs of taking part in this study?

There is no cost for participation other than your time. The biologics, inhaled corticosteroids with long-acting beta-agonist medications, all study procedures, and services performed for research will be provided at no charge to you or your insurance company. Parking is also provided free of charge. Please note that data charges may apply by using your device to record information in the diary.
Routine medical care performed while participating in study will be billed to you and/or your insurance company. This will include (but is not limited to) non-research related lab-work, administration of non- research medications, and the treatment of side effects. Not all insurance companies are willing to pay for services performed in a research study (i.e., routine medical care services that are not covered under the research study). You will be responsible for any charges that your insurance does not cover including regular co-payments and deductibles for such routine medical care services. Please speak with your insurance company to find out what you may be financially liable for.

Will I be paid for taking part in this study?

You will receive **(insert site specific payment schedule here)**. Payment will be given to you after the visit is completed. If the visits are broken into several sessions, the total for that visit will be prorated, and you will receive partial payment at the conclusion of each session. You will also receive partial payment if you don't complete all tests and procedures during the visits. Mayo Clinic, Arizona participants will also receive free parking.

Compensation for participation in a research study is considered taxable income for you. If your compensation for this research study or a combination of research studies is $600 or more in a calendar year (January to December), you will receive an IRS Form 1099 to report on your taxes. For Mayo Clinic, Arizona participants: please note, if you are an employee of Mayo Clinic, Arizona any compensation from a research study is considerable taxable income.

For any compensation or reimbursement you receive, we are required to obtain identifiable information such as your name, address, and for amounts over $50, Social Security number for financial compliance purposes. Identifiable information collected for financial compliance purposes will not be linked to your research data.

Will my data or specimens be stored for future research?

Blood, nasal brushings, and induced sputum will be collected and stored for important biomarker analyses and for future studies, including unspecified future research, genomic analysis, and future asthma related research. Your de-identified data will also be used and shared for future research. During the study, you may withdraw permission for samples and/or your de-identified data to be stored for future research. However, this may not be possible after the study is completed.

Will my specimens be sold for commercial profits?

The information/specimens obtained in this study may be used in this research or other research and shared with other organizations but will not be sold for commercial profit. You will not receive share in any commercial value or other compensation from products developed using your information or specimens.

Will I hear back on any results that directly impact me?

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study. You will also receive any clinically relevant test results discovered during this study that may influence your clinical care, such as spirometry reports and biomarkers, such as eosinophil counts and exhaled nitric oxide concentrations. These results will also be shared with your treating physician(s) if you give permission. Please provide your initials below to give permission to share this information with your treating physician(s) and to acknowledge that you understand that we will be sharing this information with your treating physician(s).

Optional sharing of clinically relevant information with my physician/healthcare provider:

_____ YES, I agree to share clinically relevant information with my physician/healthcare provider.

_____ NO, do not share clinically relevant information with my physician/healthcare provider.

Will Whole Genome Sequencing be done with my specimen?

Genetic analyses will be performed as part of this study, including whole genome sequencing. All samples will be stripped of personal identifiers; however, there is a small chance that the genetic data can be linked back to you.

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Will my study-related information be shared, disclosed, and kept confidential?

We might ask you to provide medical records from other sources to evaluate your condition, outcomes, and adverse events with a (PHI/HIPAA release form) permission at the location where the information is located.

Your Personal Health Information (PHI) may no longer be protected under the HIPAA privacy rule once it is disclosed to the research team. After the PHI is disclosed to us, the study team will protect your information at the study site on encrypted computer drives and in locked cabinets/offices. In addition, your responses will be assigned a code number. The list connecting your name to this code will be kept in an encrypted and password protected file. Only the research team will have access to the file. When the study is completed and the data have been analyzed, the list will be destroyed. Samples and data will be coded at the sites and only de-identified samples and data will be shared among the study teams and during analysis.

It is anticipated there will be circumstances where your study related information will be released to persons and organizations described in this form. If you sign this form, you are giving permission to the research team to use and/or disclose your study related information for this study. Your information might be shared or disclosed with others for the purpose of conducting the study, following regulations, and making sure the study is carried out correctly. These other groups may include:

- Office for Human Research Protections, Food and Drug Administration, or other federal, state, or international regulatory agencies
- The University of Arizona (UA) and the UA Institutional Review Board
- The sponsor and/or funder supporting the study, their agents or study monitors
- Investigators and regulators at collaborating sites including Data Coordinating Center, UA; the University of California, San Diego (UCSD); Yale University; Mayo Clinic, Arizona; and Channing Laboratory, Harvard University/Brigham and Women's Hospital

Demographic information may include, but is not limited to, your name, address, phone number, or social security number. If you receive compensation for participating in this research study, information identifying you may be used or disclosed as necessary to provide that compensation.

Your existing health records may include information related to the diagnosis or treatment of sexually transmitted disease (STD), acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV), other communicable diseases, genetic information (e.g., genetic testing), and/or alcohol and/or drug abuse. The study staff and study sponsor's monitor may see this information while reviewing your regular health records for this study, but they WILL NOT create, collect, or disclose this type of information for the purposes of this research study.

Genetic and Genomic Data: Genetic data refers to your genes themselves, and genomic data refers to how activated those genes are. All of your genetic and genomic data will be shared with investigators at the University of Arizona; Mayo Clinic, Arizona; Harvard University/Brigham and Women's Hospital; University of California San Diego; and Yale University through study ID codes and not by name. Genetic and genomic results may be

presented in publications and meetings but individual names will not be identified. The U.S. Department of Health and Human Services has the right to inspect medical records relating to this research for the purposes of verifying data, and your general demographic information and de-identified genomic data will be released to the National Institutes of Health. As required by NIH, de-identified genomic data will be submitted to the Gene Expression Omnibus (GEO) and other required national databases, but you will not be identified.

Peak Flow Meter: In addition, a peak flow meter will be used to measure peak expiratory flows (PEF) and an e-diary will be used to record PEF measurements.

Certificate of Confidentiality:
This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to your health insurers, medical providers, or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

When will my authorization expire?
There is no expiration date for your authorization to use and disclose your study related information. Therefore, unless you cancel this authorization (as instructed below) this authorization will continue to be in effect.

Also, by signing this form you are authorizing and permitting uses and/or disclosures of your study related information for future research purposes (e.g., future studies) as described in this document.

What do I need to know if I decide to cancel my authorization?

After signing the authorization, you may decide to cancel it so the research team will no longer be able to use your study related information. If you cancel the authorization, you will no longer be able to stay in this research study. Please note that any PHI that we received through your previous authorization and study related information collected before you cancel the authorization may still be used. You may revoke the authorization by contacting the Principal Investigator in writing. Contact information is under "Who can answer my questions about the study" at the end of this document.

Will access be limited to my research study record during this study?

Other than the clinically relevant test results that we will shared with you and your physician (upon your authorization), you may not have access to the research information developed as part of this study until it is completed. Genetic information will not be shared with you, your physician, or your family.

Who can answer my questions about this study?

If at any time you feel you have had a research-related injury, or for questions, concerns, or complaints about the study you may contact **(insert name of site investigator here) at (insert phone number of site investigator here) or the study team at (insert site study team number here).** For non-medical questions, you may contact the University of California San Diego at 619-431-0995.

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the Human Subjects Protection Program Director at 520-626-8630 or online at https://research.arizona.edu/compliance/human-subjects-protection-program.

To cancel your authorization for access to study related information you must notify the site in writing at **(insert site investigator address here).**
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by the National Institutes of Health (NIH) who is funding this study. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Signing the consent form

I have read (or someone has read it to me) this form, and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them

answered to my satisfaction. I voluntarily agree to participate in this study, and I authorize the use and/or disclosure of my study related information. I am not giving up any legal rights by signing this form. I will be given a signed copy of this form**.**

Printed name of subject	Signature of subject	Date

Investigator/Research Staff

I have explained the research to the participant or the participant's representative before requesting the signature(s) above. There are no blanks in this document. A signed copy of this form has been given to the participant or to the participant's representative.

Printed name of person obtaining consent	Signature of person obtaining consent	Date