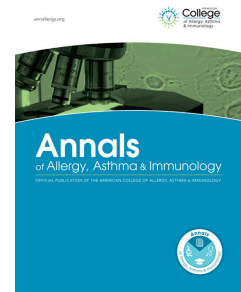


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Brittney M. Donovan, PhD, Lisa Bastarache, MS, Kedir N. Turi, PhD, Mary M. Zutter, MD, Tina V. Hartert, MD



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The Current State of Omics Technologies in the Clinical Management of Asthma and Allergic Diseases

Brittney M. Donovan, PhD¹; Lisa Bastarache, MS²; Kedir N. Turi, PhD¹; Mary M. Zutter, MD³;
Tina V. Hartert, MD¹

¹Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

²Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN

³Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN

Corresponding Author: Tina V. Hartert, MD, MPH, Department of Medicine, Vanderbilt University Medical Center, 2525 West End Avenue, Suite 450, Nashville, TN 37203; Phone: (615) 936-1010; Fax: (615) 936-1269; Email: tina.hartert@vumc.org

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Keywords: asthma, allergic disease, clinical management, genomics, epigenomics, transcriptomics, proteomics, metabolomics, lipidomics, microbiomics, exposomics, phenomics

Abbreviations/Acronyms: DNA, deoxyribonucleic acid; *FLG*, filaggrin; ICS, inhaled corticosteroid; *ADRB2*, adrenoceptor beta 2; *ALOX5*, arachidonate 5-lipoxygenase; *LTC4S*, leukotriene C4 synthase; *LTA4H*, leukotriene A4 hydrolase; *CYSLTR2*, cysteinyl leukotriene receptor 2; *FCER2*, fc fragment of IgE receptor 2; GWAS, genome-wide association study;

RNA, ribonucleic acid; EWAS, epigenome-wide association study; *FOXP3*, forkhead box P3; U-BIOPRED, Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes; CysLTR1, cysteinyl leukotriene receptor 1; HELIX, Human Early-Life Exposome; EHR, electronic health record; PheWAS, phenome-wide association study; *PNPLA3*, patatin-like phospholipase domain containing 3; OMIM, Online Mendelian Inheritance in Man; PheRS, phenotype-risk score; CLIA, Clinical Laboratory Improvement Act; eMERGE, Electronic Medical Records and Genomics; HIPAA, Health Insurance Privacy and Accountability Act; MeDALL, Mechanisms of the Development of ALLergy; ECHO-CREW, Environmental influences on Child Health Outcomes-Children's Respiratory and Environmental Workgroup; BMIC, Biologic Specimen and Trans-NIH BioMedical Informatics Coordinating Committee; CASyM, Coordinating Action Systems Medicine.

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Objective: To review the state of omics science specific to asthma and allergic diseases and discuss the current and potential applicability of omics in clinical disease prediction, treatment, and management

Data Sources: Studies and reviews focused on the use of omics technologies in asthma and allergic disease research and clinical management were identified using PubMed

Study Selections: Publications were included based on relevance, with emphasis placed on the most recent findings

Results: Omics-based research is increasingly being used to differentiate asthma and allergic disease subtypes, identify biomarkers and pathological mediators, predict patient responsiveness to specific therapies, and monitor disease control. While most studies have focused on genomics and transcriptomics approaches, increasing attention is being placed on omics technologies that assess the effect of environmental exposures on disease initiation and progression. Studies utilizing omics data to identify biological targets and pathways involved in asthma and allergic disease pathogenesis have primarily focused on a specific omics subtype, providing only a partial view of the disease process.

Conclusions: While omics technologies have advanced our understanding of the molecular mechanisms underlying asthma and allergic disease pathology, omics testing for these diseases are not standard of care at this point. Several important factors need to be addressed before these technologies can be effectively utilized in clinical practice. Use of clinical decision support systems and integration of these systems within electronic medical records will become increasingly important as omics technology becomes more widely utilized in the clinical setting.

1 Introduction

Most diseases are caused by a complex, multi-level combination of genomic, biological, and environmental factors, contributing to a high degree of variability in disease development, natural history, and response to therapy.¹⁻³ Disease subtyping has emerged as a way of identifying sub-populations of individuals with similar disease features for improved diagnosis and treatment.^{3,4} Traditionally, patients have been classified into groups according to their clinical characteristics (i.e., phenotypes). However, these classifications do not provide insight into the functional or pathobiological mechanisms of the disease within the individual (i.e., endotype).⁵ Omics is the comprehensive assessment of the molecules that comprise a cell, tissue, or organism.⁶ Integration of multi-omics data, such as genomics, proteomics, and metabolomics, along with clinical data allows for better understanding of disease pathogenesis and will be important for predicting, diagnosing, and treating diseases (**Figure 1**).^{7,8}

Asthma and allergic diseases, including allergic rhinitis and atopic dermatitis, are common diseases that often manifest early in life and persist into adulthood.⁹ The pathophysiology and expression of these diseases are influenced by interactions between susceptibility genes and exposure to environmental factors such as aeroallergens, secondhand smoke, and infections. Isolated use of traditional markers, such as lung function parameters and skin-prick testing, and clinical symptoms to diagnose specific subtypes and manage asthma and allergic diseases have been shown to be inadequate due to the heterogenous underlying pathophysiology of disease phenotypes.¹⁰ Integration of phenotyping and multi-omics endotyping can help differentiate asthma and allergic disease subtypes, identify biomarkers and pathological mediators, predict patient responsiveness to specific therapies, and monitor disease control.^{8,11,12}

We aim to briefly review the state of omics science specific to asthma and allergic diseases and discuss the current and potential applicability of omics in clinical disease prediction, treatment, and management. Previous reviews have focused on omics as they relate to specific allergic diseases, primarily asthma.^{5, 13-17} Our review will be uniquely framed to focus on omics subtypes, referencing current applications of each subtype within the field of asthma and allergic diseases, including research applications.

Applied Omics in Asthma and Allergic Diseases

Genomics

Genomics is the study of variations in the deoxyribonucleic acid (DNA) and their association with disease onset, severity, exacerbation, response to therapeutic agents (pharmacogenomics), or patient prognosis (**Table 1**).^{16, 18} A large portion of the susceptibility to asthma and allergic diseases is attributed to genomic contributions.¹⁹ Many genes have been identified as contributing to the development of asthma and allergic diseases, including the well-replicated 17q21 locus (associated with childhood-onset wheeze) and filaggrin (*FLG*) gene (associated with atopic dermatitis).^{13, 16} However, these genes account for only a small proportion of the disease heritability. The missing heritability may be attributed to rare variants, gene-gene, or gene-environment interactions. Lack of replication across studies and unknown functional implications of genes implicated in asthma and allergic disease pathogenesis have hindered the use of genetic risk factors in predicting disease onset and exacerbation in the clinical setting.^{19, 20} Further assessment of polygenetic scores of several genes may help in prediction and prognosis of such complex diseases.

The potential role of pharmacogenomics in the clinical management of asthma and allergic diseases is being increasingly recognized. As many susceptibility genes are shared

across allergic diseases, targeted therapeutics may be used to treat multiple diseases.^{20, 21} Most pharmacogenomics studies of asthma to date have focused on the clinical response to commonly prescribed medications, such as bronchodilators, leukotriene modifiers, and inhaled corticosteroids (ICSs), through candidate-gene approaches.^{20, 22} Studies assessing the role of short- and long-acting bronchodilators have mainly focused on *ADRB2* (adrenoceptor beta 2).²³ Asthmatic patients with a homozygous genotype for a variant substituting at amino acid 16 within *ADRB2* have been shown to have decreased lung function and increased exacerbation with regular short-acting beta agonist use. Studies assessing the response of these patients to long-acting beta agonists have been conflicting.^{22, 23} Variants in the arachidonate 5-lipoxygenase (*ALOX5*), leukotriene C4 synthase (*LTC4S*), leukotriene A4 hydrolase (*LTA4H*), and cysteinyl leukotriene receptor 2 (*CYSLTR2*) genes have been associated with response to leukotriene modifiers;^{22, 23} however, replication of these findings are needed.²³ Although a large number of studies have assessed the genetic contribution to ICS response, findings have been inconsistent. Variants within the *FCER2* (fc fragment of IgE receptor 2) gene have shown the most promising results, with asthmatic children with these variants showing poor ICS response.¹⁶ To increase clinical applicability or pharmacogenomic findings, research has shifted towards genome-wide association studies (GWAS). As a result, many novel therapies are being developed and evaluated.²⁰

Epigenomics

While genomics is known to play a large role in susceptibility to asthma and allergic diseases, the increase in incidence and prevalence of these diseases observed globally over the past 70 years cannot be explained by genetic predisposition. Environmental and lifestyle factors must play an important role in the initiation and persistence of disease in predisposed

individuals.²⁴ Epigenomics is the study of potentially reversible modifications of the chromatin, measured by DNA methylation levels, histone modifications, or non-coding ribonucleic acid (RNA), due to normal cellular repair or environmental modifiers.^{24, 25} Epigenomics may be used to better understand the influence of environmental and lifestyle factors on the underlying mechanisms that contribute to the development of asthma and allergic diseases, which could aid in the development of preventive strategies for susceptible individuals.²⁴

While epigenomics technology and methodologies are less developed than genomics and transcriptomics approaches,¹⁷ studies aimed at identifying epigenomic signatures within asthmatic and allergic disease populations are on the rise. The value of DNA methylation signatures as biomarkers of diagnosis and/or therapeutic response has been illuminated in studies of other complex diseases, such as cancer and autoimmune diseases, suggesting its potential in understanding modifiable alterations in DNA that predispose to asthma and allergic diseases. Epigenome-wide association studies (EWAS) could be used to identify individuals who are allergy-prone prior to disease onset.²⁴ Epigenomic signatures can be inherited,¹⁷ and *in utero* exposure to farms, air pollution, and tobacco smoke have been shown to alter DNA methylation signatures associated with development of asthma and allergic disease early in life.^{16, 24, 26} DNA methylation signatures have also been shown to outperform conventional biomarkers, such as allergen-specific IgE levels and skin-prick tests, in the prediction of food allergy, suggesting that these signatures could potentially be used as a safe alternative to food challenges.^{24, 27}

A limited number of studies have assessed the effect of asthma and allergic disease treatment on the epigenome.^{16, 24} Demethylation of *FOXP3* (forkhead box P3), a gene that is only expressed by regulatory T cells and is reduced among allergic children, has been observed in children who develop tolerance for IgE-mediated cow's milk allergy after dietary intervention

and peanuts after oral immune-therapy.^{24, 28, 29} Epigenomic changes in response to ICS and biological agents have been identified but further replication is needed.^{16, 30} The use of DNA methylation inhibitors, such as 5-azacytidine, in patients with asthma and allergic diseases has been assessed; however, results are conflicting. In the future, the CRISPR/Cas9 gene-editing system could potentially be used to reverse environmentally-induced changes in the epigenome prior to disease onset.^{24, 30}

Transcriptomics and Proteomics

Gene expression is a dynamic process that is highly influenced by many factors including age, gender, developmental stage, health status, tissue/cell type, time of day, and exposure to allergens, infections, and medications.^{16, 31} Transcriptomics and proteomics investigate two important aspects of gene expression, RNA (i.e., the molecular intermediate between DNA and proteins) and proteins (i.e., the primary functional product of DNA).¹⁸ Omics technologies are currently being used to identify differential gene expression patterns between those with and without disease, leading to mechanistic hypotheses and biomarker development.^{20, 31}

In order to analyze the massive amount of data that is generated through gene expression analyses, sophisticated analytical methods are needed.¹⁶ Such techniques have been applied in large-scale projects such as the Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes (U-BIOPRED) consortium, which aimed to identify asthma endotypes through the characterization of gene expression profiles.^{16, 32} While transcriptomics approaches are now widely used in asthma and allergic disease research,^{13, 17} untargeted proteomics research has emerged more slowly which may be due in part to the diversity of technologies used.³¹

Transcriptomics and proteomics studies of asthma and allergic diseases have been most fruitful in identifying disease endotypes. Differences in gene expression patterns between

childhood and adult-onset asthma suggest that distinct mechanisms underly disease onset.¹⁶ Sputum proteomics has been used to identify multiple sub-endotypes of eosinophil- and neutrophil-mediated asthma.¹⁷ Transcriptomics has also been used to investigate mechanisms of asthma and allergic disease severity, exacerbation, and response to treatment. Genes involved in bronchodilation, reduction of inflammation, interferon response, and expression of CD8+ T cells have been shown to be differentially expressed in children with severe asthma compared to children with mild asthma.³¹ Increased expression of immune cytokines and chemokines have been shown to correlate with disease severity and progression in atopic dermatitis.¹⁵ Studies aimed at understanding the underlying mechanisms of asthma exacerbations in children have identified several differentially expressed genes during exacerbation related to immune responses against viral infections and potential environmental exposures, such as smoke, pollutants, or allergens.^{16, 33} A few studies have assessed transcriptomics response to glucocorticosteroid treatment;³⁴ however, further replication studies are needed. Although transcriptomics and proteomics studies in asthma and allergic disease have yet to yield new diagnostic tests or drugs, the growing sample size and robust design of ongoing studies show potential for clinical translation in the near future.³¹

Metabolomics

Metabolomics measures the total repertoire of low molecular weight products of cellular metabolism (e.g., amino acids, fatty acids, sugars, and lipids) present in cells, tissues, organs, and biological fluids.^{13, 17, 35} The identities, concentrations, and fluxes of these metabolites result from the complex interplay of the genome, gene expression, protein translation, and the environment.³⁵ As many cellular processes are regulated by metabolites, they can act as indicators of homeostatic imbalances.³⁶ Metabolomics can, thus, be used to improve our

understanding of disease pathogenesis, assess biological responses to risk factors, identify susceptibility biomarkers, and monitor disease progression.³⁵

Metabolomics approaches are particularly appealing for the study of asthma and allergic diseases, which are highly influenced by host-environment interactions.³⁵ Though limited in number, metabolomics studies have provided unique and novel insights into allergy and asthma profiling at the molecular level. Most metabolomics studies have focused on biomarker discovery to identify metabolites that distinguish between asthma/allergic disease and healthy phenotypes and asthma severity.^{13, 17, 35} Noninvasive biomarkers, such as volatile organic compounds in exhaled breath, have shown promising roles in the diagnosis, monitoring, and treatment of asthmatics and could be especially useful for the assessment of airway inflammation in young children.³⁷ However, validation of these biomarkers in independent cohorts of biological samples is needed to demonstrate clinical utility.^{17, 31} In addition to the global metabolic profiles of individuals with asthma and allergic diseases, metabolomics can provide deeper insights into the pathophysiology of distinct asthma and allergic disease phenotypes. Accurate prediction of phenotypes using metabolic biomarkers may have the greatest clinical impact, encouraging increased utilization of prospective study designs in metabolomics research.³⁸

Lipidomics

Lipids have both structural and functional roles, acting as the primary component of cellular membranes, energy reservoirs, and mediators in cellular mechanisms such as signal transduction, immunity, and inflammation.^{39, 40} Over 40,000 lipids have been documented to date.^{40, 41} Lipidomics, a sub-field of metabolomics, aims to understand the structure and function

of a given cell or organism's lipidome and how lipoproteins are affected by diseases and treatments.^{39, 40}

Although the emergence of more sophisticated techniques, such as mass spectrometry-based lipidomics, has facilitated the expansion of knowledge of the effects of lipids on asthma and allergic diseases, most studies have focused on targeted profiling of lipid mediators for treatment development. Lipid mediators, such as leukotrienes, platelet activating factor, prostaglandins, and sphingolipids, modulate the immune system in response to allergens and have, thus, been primary targets for therapeutic interventions. The leukotriene pathway, which promotes bronchial smooth muscle constriction and increases vascular permeability, has been the most successfully targeted, with two classes of drugs currently on the market, cysteinyl leukotriene receptor 1 (CysLTR1) antagonists and 5-lipoxygenase inhibitors.⁴² Clinical trials assessing the efficacy of antagonists of platelet activating factor, such as rupatadine which is not currently available in the United States, and prostaglandin receptor agonists/antagonists in patients with asthma and allergic diseases have been performed or are currently underway.⁴²⁻⁴⁴ While findings from animal studies assessing the efficacy of anti-sphingosine 1-phosphate compounds in allergic disease management have been promising, no clinical trials are currently underway.^{42, 45}

Microbiomics

The microbiome broadly describes the microorganisms (including bacteria, viruses, and fungi) colonizing the human body, their genes, and their interactions with each other and their host.^{18, 46} It is exceedingly complex, composed of trillions of microorganisms whose composition varies across body sites, time, and between individuals and is highly influenced by environmental and dietary factors.^{18, 47} Alterations in the composition or metabolic activity of

the microbiome can negatively impact immune function due to the intimate crosstalk between the two networks.⁴⁷ The immunomodulatory mechanisms of microbial dysbiosis are beginning to be elucidated using omics technologies, such as shotgun metagenomics sequencing and metatranscriptomics.^{47, 48} Whether alterations in the composition of the microbiome precede or follow immune responses in asthma and allergic diseases remains unclear; however, prospective birth cohort studies have begun to shed light on the temporal relationship.⁴⁷

Microbiome-based strategies for prevention, treatment, and management of asthma and allergic diseases have focused on targets of innate immunity and therapies altering microbial communities, including prebiotics, probiotics, and microbial transplantation.⁴⁸ Drugs targeting lung inflammation, such as macrolide antibiotics and corticosteroids, have shown beneficial effects for treatment of certain asthma phenotypes. However, the airway microbiome may modulate the response to these therapies, suggesting that microbiome phenotyping of individuals prior to administration may be beneficial for treatment effectiveness.^{48, 49} While findings from studies assessing the effectiveness of prebiotic (non-digestible fiber that stimulates the growth of beneficial microorganisms) and probiotic (live microorganisms) use in preventing asthma and allergic diseases have been promising, particularly for prevention of eczema,⁴⁶⁻⁴⁸ no recommendations have been made to date for pre- or probiotic use in patients with asthma or allergic diseases.⁴⁷ Several clinical trials are currently underway to assess the effectiveness of microbiome transplants, including vaginal swabbing, skin creams, and oral encapsulated fecal microbiota, in preventing and treating asthma and allergic diseases.⁵⁰

Exposomics

The exposome defines the totality of an individual's external (e.g., climate, traffic, and pollutants) and internal (e.g., metabolism, inflammation, and aging) environmental exposures

throughout their life course.^{51, 52} Unlike epigenomics, which is used to assess modifications to the genome specifically, exposomics comprehensively assesses multi-omics responses to environmental exposures. These response patterns, ideally characterized from longitudinal biomonitoring, could then be used to provide an individualized disease risk profile for targeted prevention. Using a more holistic approach in assessing the effect of environmental exposures on disease will likely be more informative in predicting complex diseases like asthma and allergies than assessing the separate effects of individual exposures.⁵¹

While a growing number of studies have assessed the role of specific environmental exposures in the pathogenesis of asthma and allergic diseases, challenges related to measurement harmonization, feasibility of exposure assessment, integration of multifactorial data, and methods of discovery analysis have hindered exposome-wide analyses in this field.⁵¹ In an effort to overcome some of these issues, large-scale initiatives, such as the Human Early-Life Exposome (HELIX) and EXPOsOMICS projects, have been launched with the goal of refining exposomics characterization.^{53, 54} Additionally databases, such as the World Health Organization's Exposome-Explorer, can be used to identify biomarkers of environmental exposures for biomonitoring or studies of disease etiology.⁵⁵

Phenomics

Phenomics is the systematic study of a large set of phenotypes used to describe an organism. In biomedical informatics, the phenome is defined as symptoms, physical findings, and disease diagnoses that describe patients for the purposes of medical care. Phenomics can be used to identify and describe disease subtypes or study pleiotropy (i.e., multiple phenotypes arising from the same genetic alteration).⁵⁶

The electronic health record (EHR) is an important resource for the study of human phenomics. Compared to observational research cohorts that only capture a pre-specified set of phenotypes, the EHR contains information on a vast array of phenotypes that are pertinent to medical care.⁵⁷ Many health care systems now link EHR and genetic information, obtained through biospecimen collection, which has led to the development of phenome-wide association studies (PheWAS).⁵⁷⁻⁶¹ While originally designed to study the relationship between a large set of human phenotypes and a single genetic variant, PheWAS applications have since broadened to assess associations between phenotypes to identify comorbidities, subtypes, or health-service outcomes (e.g., length of hospital stay and treatment-related complications) related to a specific disease.⁵⁷

A mounting body of evidence has demonstrated the utility of EHR data in genomics research. EHRs have been used to replicate known genetic associations with asthma first discovered in observational cohorts.^{58, 62} PheWAS has been used to identify novel asthma risk loci and discover pleiotropy of asthma-associated genetic variants with atopy and leukemia and allergic rhinitis-associated genetic variants with metabolic disease and diabetes.⁵⁸⁻⁶¹ PheWAS has also been used to identify new therapeutic targets as well as predict adverse drug events. One study identified asthma as a potential side effect of drugs that inhibit *PNPLA3* (patatin-like phospholipase domain containing 3), a potential therapeutic for liver disease.⁶³

EHR-driven phenomics have also been used to study monogenic, or Mendelian, diseases. As variants within Mendelian disease-causing genes have been shown to contribute to complex diseases,⁶⁴ assessment of the association between these variants and asthma and allergic disease risk is warranted. The Online Mendelian Inheritance in Man (OMIM), a catalog of monogenetic diseases, describes many diseases that are characterized, in part, by traits related to asthma and

allergic diseases.⁶⁵ A method called the phenotype-risk score (PheRS) was recently developed to capture Mendelian phenotype patterns using EHR data and inform on the contribution of rare variants to common diseases.⁶⁴ Rare genetic variants may be used to link some patients' asthma to Mendelian diseases with targeted therapies.

Conclusions and Future Perspectives

Clinical Decision Support Systems

Electronic Health Records

As omics technology becomes more widely utilized in the clinical setting, integration of omics data within EHRs will become increasingly important for interpretation and clinical decision support.^{66, 67} However, EHRs, which have traditionally been structured to provide a common workflow for health care providers and centralized documentation of billing and clinical monitoring and decisions, are not suited to accommodate omics data in their current form.⁶⁶ Next-generation EHRs will need increased storage capacity, structured data formats to allow return of omics results to physicians and patients, links to reference sources to aid in the interpretation of results from Clinical Laboratory Improvement Act (CLIA)-certified clinical laboratories and genetic counselors, and systems for reprocessing archived data and updating interpretations as new scientific knowledge becomes available.^{66, 67} To begin this transition, initiatives, such as the Electronic Medical Records and Genomics (eMERGE) network, have been established to develop methods and best practices for integrating omics data into the EHR system and returning results to patients.⁶⁸

Ethical, legal, and privacy considerations for data storage and sharing are also of concern with the integration of omics data in EHRs. While the federal Health Insurance Privacy and Accountability Act (HIPAA) imposed privacy standards on the use of protected health

information, such as names and birth dates,⁶⁹ omics data are not explicitly mentioned in the act and are, therefore, potentially vulnerable to privacy violations.^{66, 70} Frameworks for the storage and management of omics data and consent have not been widely implemented;⁶⁶ however, some institutions have established guidelines for physical and technological security controls to help protect omics data.^{70, 71} Further, issues related to recontact of potentially affected patients once new scientific knowledge becomes available and return of results, particularly from genomics testing, to potentially affected family members need to be carefully assessed and strategized.⁶⁶

Laboratory Formularies

The use of omics technologies in clinical care has been somewhat limited to those areas where data and validation have shown sufficient laboratory sensitivity, specificity, and reproducibility, as well as clinical validity and utility. The areas which have been brought forward as standard of care include cancer diagnosis and therapy, rare and/or inherited disease diagnosis and risk assessment, and pharmacogenomics.⁷² In an effort to provide more affordable, accessible, and high-quality healthcare in the United States, attention has been placed on reducing hospitalizations, readmissions, and therapeutic costs. However, management of diagnostic and screening testing is also important to healthcare reform as the number of these tests available to clinicians is rising and many are expensive and require extensive background knowledge for correct interpretation.⁷³ To promote the appropriate utilization of laboratory testing some institutions have implemented laboratory formularies.⁷⁴ These programs provide strategic guidance for ordering clinicians through evidence review and expert consultation of each test's clinical utility, cost, and interpretation. Successful implementation requires ongoing collaboration of hospital administrators, clinical and laboratory staff, and information technology developers.^{73, 74} Although omics testing for asthma and allergic diseases are not standard of care

at this point, use of a laboratory formulary structure to introduce and advance testing for these diseases would provide a structure to obtain strong evidence and appropriate utilization management.

Integrated Omics

The vast majority of studies utilizing omics data to identify biological targets and pathways involved in asthma and allergic disease pathogenesis have primarily focused on a specific omics subtype.^{13, 75} While important insights have been gained from these studies, they provide only a partial view of the disease process.¹³ Integration of multi-omics data provides a more comprehensive understanding of the underlying mechanisms of disease through identification of molecular interactions, intermediate phenotypes and processes, and upstream/downstream molecular targets.^{13, 76} However, amplification of issues related to data acquisition, harmonization, storage, quality, and analysis have slowed the integration and simultaneous assessment of multiple, multi-dimensional omics subtypes. As multi-omics approaches often require the collection and processing of larger volumes of multiple sample types, patient burden and cost-effectiveness also need to be weighed when performing these analyses.^{13, 18} Several large-scale consortia, such as the Mechanisms of the Development of ALLergy (MeDALL),⁹ U-BIOPRED,³² and Environmental influences on Child Health Outcomes-Children's Respiratory and Environmental Workgroup (ECHO-CREW),⁷⁷ have been established to study and develop approaches to facilitate clinical translation of multi-omics data for patients with asthma and allergic diseases.

Clinical Implementation: Current Challenges and Progress

While omics technologies have advanced our understanding of the molecular mechanisms underlying asthma and allergic disease pathology, these technologies are primarily

being used as research tools at this time and several important factors need to be addressed before they can be effectively utilized in clinical practice. Validation and replication of findings from previous studies is essential, necessitating standardization of data collection, processing, and analysis.^{13, 18} Large-scale initiatives and data repositories, such as the UK Biobank⁷⁸ and the Biologic Specimen and Trans-NIH BioMedical Informatics Coordinating Committee (BMIC),⁷⁹ have facilitated the generation of robust biomedical datasets to improve research efficiency, increase collaboration, and facilitate validation of findings.^{67, 80} Institutions, such as the Food and Drug Administration⁸¹ and the American College of Medical Genetics and Genomics,⁸² have created guidelines for collection and processing of biospecimens and development of standard data storage formats and data interpretations.⁸⁰ Additionally, standardized clinical diagnostic codes and phenotypic terminology have been established to allow consistent information exchange and comparability of diseases across populations.⁸⁰

Infrastructures for clinical informatics and increased cross-disciplinary training for health professionals are also key for the successful application of omics technologies and have been highlighted in projects such as CASyM (Coordinating Action Systems Medicine).⁸³⁻⁸⁵ Many online and offline courses are now being offered to improve the analysis and interpretation of omics data.⁸⁰ With a concerted collaborative effort from patients and experts with diverse backgrounds, including clinicians, bioinformaticians, medical laboratory scientists, lawyers, ethicists, and hospital administrators, it is possible for omics technologies to transform and improve patient health and the healthcare system.^{83, 84}

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Table 1. Features of omics data.

Omics Subtype	Measured biomarker	Sample type	Data collection technologies
Genomics	DNA	Any tissue that has a nucleus ^a ~~(blood and saliva are the most common)~~	Genotyping arrays NGS Exome sequencing
Epigenomics	DNA methylation levels, post-translational histone modifications, ~~non-coding RNA (e.g., microRNAs (miRNAs))~~	Tissue-specific (sera, other bodily fluids, or tissues may be used)	NGS DNA methylation analysis with arrays Small RNA sequencing
Transcriptomics	RNA	Tissue-specific (sera, other bodily fluids, or tissues may be used)	Probe-based arrays RNA-Seq
Proteomics	Proteins	Tissue-specific (sera, other bodily fluids, or tissues may be used)	MS
Metabolomics	Metabolites ~~(molecules weighing <1,500 Da)~~	Tissue-specific (sera, other bodily fluids, or tissues may be used)	MS NMR Semiconductor metal oxide
Lipidomics	Lipids	Tissue-specific (sera, other bodily fluids, or tissues may be used)	MS NMR
Microbiomics	Microorganisms ~~(bacteria, viruses, and fungi)~~	Tissue-specific (sera, other bodily fluids, or tissues may be used)	NGS
Exposomics	Any biomarker of exposure ^{ab}	Dependent on the biomarker(s) ~~assessed^c used (e.g., sera, urine, saliva, exhaled gas, tissue, predictive index using clinical features)~~	Dependent on the biomarker(s) ~~assessed^c used~~
Phenomics	Disease states, symptoms, lab measurements, vitals	N/A ^{ab}	Extraction from electronic health record, surveys, physical exams, ~~and measurements, etc.~~

DNA, deoxyribonucleic acid; NGS, next generation sequencing; RNA, ribonucleic acid; MS, mass spectrometry; Da, Dalton; NMR, nuclear magnetic resonance spectroscopy; N/A, not applicable.

^aBlood and saliva are commonly used.

^bExamples of biomarkers of environmental exposures include vitamins (diet), polycyclic aromatic hydrocarbons (pollutant), and organohalogens (pesticide).

^cSamples types may include sera, urine, saliva, exhaled gas, tissue, etc. ^aDatabases, such as Exposome Explorer (<http://exposome-explorer.iarc.fr>), can be used to identify biomarkers of exposure to environmental risk factors.

^{db}Phenomics studies utilize patient-level data extracted from electronic health records, surveys, physical exams, measurements, etc. This data is sometimes linked with genetic information.

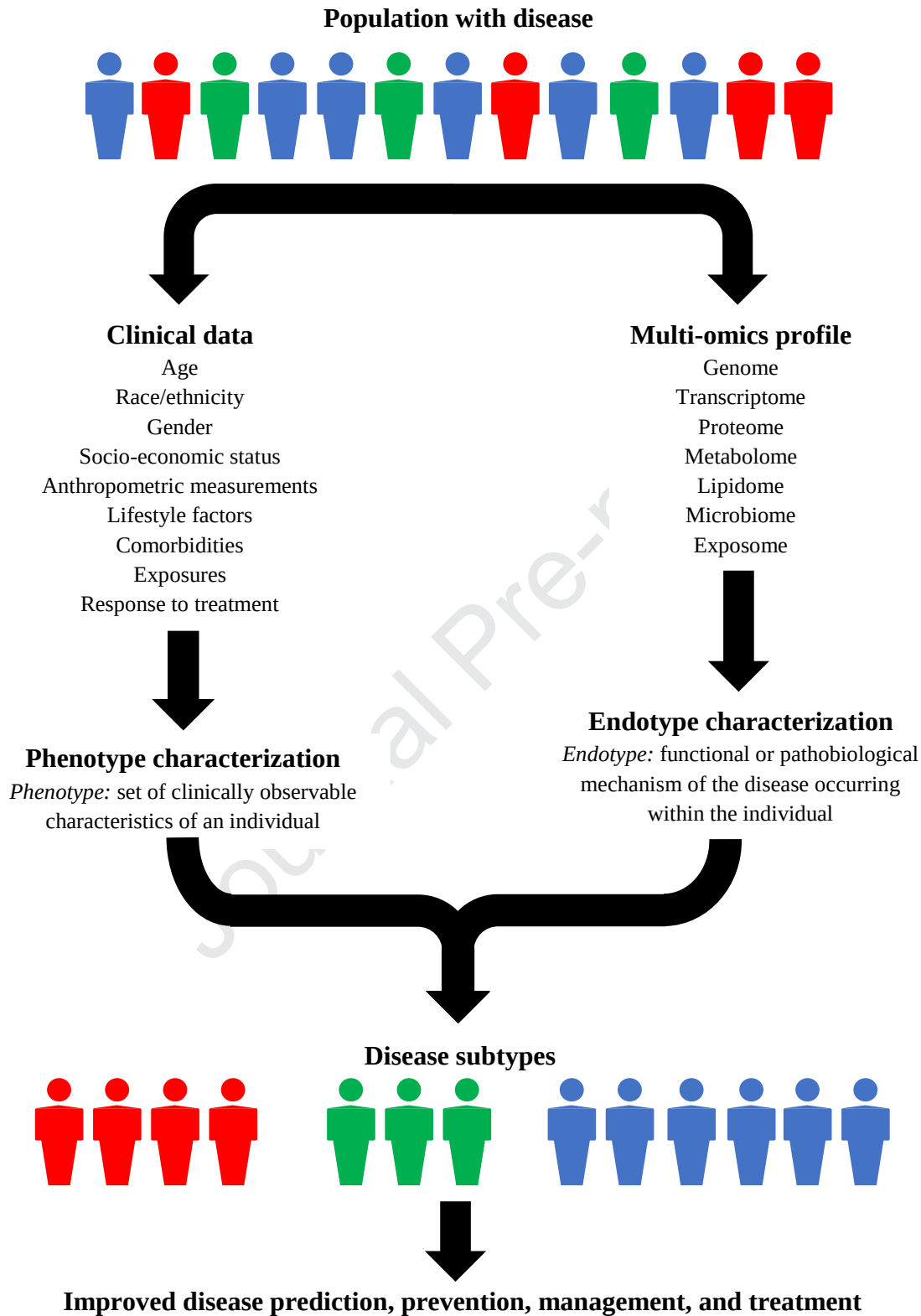


Figure 1. Framework for integration of clinical and multi-omics data for improved disease subtyping within the disease population.

Key Messages

- Integration of phenotyping and multi-omics endotyping can help differentiate asthma and allergic disease subtypes, identify biomarkers and pathological mediators, predict patient responsiveness to specific therapies, and monitor disease control.
- Most omics studies of asthma and allergic diseases to date have focused on genomics and transcriptomics approaches; however, increasing attention is being placed on omics technologies that assess the effect of environmental exposures on disease initiation and progression.
- Integration of multi-omics data may provide a more comprehensive understanding of the underlying mechanisms of disease through identification of molecular interactions, intermediate phenotypes and processes, and upstream/downstream molecular targets.
- While omics technologies have advanced our understanding of the molecular mechanisms underlying asthma and allergic disease pathology, these technologies are primarily being used as research tools at this time and several important factors need to be addressed before they can be effectively utilized in clinical practice.
- Use of clinical decision support systems, such as laboratory formularies, and integration of these systems within electronic medical records will become increasingly important as omics technology becomes more widely utilized in the clinical setting.