Provisionally accepted for publication

REVIEW

Exposome and pharmacogenomics: towards precision medicine in childhood asthma

Giuliana **Ferrante**[1], Giorgio **Piacentini**[1], Stefania **La Grutta**[2]

[1]Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Pediatric Division, University of Verona, Verona, Italy

[2]Institute of Translational Pharmacology, National Research Council, Palermo, Italy

*__Correspondence to:__

giuliana.ferrante@univr.it. ORCID ID: orcid.org/0000-0001-9917-2387

Doi: 10.56164/PediatrRespirJ.2023.37

ABSTRACT

Asthma is a complex and heterogeneous disease that requires individualized management. In childhood, poor asthma control can irreversibly compromise the children's lung function. Beyond asthma phenotypes, considering disease endotypes has been assumed a crucial issue in developing tailored therapies. The interaction between genome and exposome determines the emergence of several cellular and molecular mechanisms that contribute to different asthma endotypes and clinical phenotypes. The exposome concept was introduced as an innovative approach for simultaneously assessing environmental risk factors and their impact on human health, thus encompassing the totality of the environmental exposures occurring over a lifetime. Given that different types of environmental exposures occurring throughout life have a major impact on asthma, an exposome-based approach appears to be particularly suggested, as it provides a risk profile rather than individual predictors. Pharmacogenomics refers to the genome-wide study of variants in the deoxyribonucleic acid, which evaluates the effect of genetic variants on the individual's response to treatment. Though many genetic variants have been shown to influence response to asthma treatment, results are still inconsistent and/or effect sizes are small. Furthermore, it should be considered that epigenetic changes, gene–gene and gene–environment interactions could affect pharmacogenomic associations. Sustainability and large-scale population-based studies are needed in order to improve research in exposome and

pharmacogenomics. This review aims to discuss the latest developments related to childhood asthma in the fields of exposome and pharmacogenomics as well as challenges in integrating these innovative approaches into clinical practice and opportunities for future research.

IMPACT STATEMENT

Advances in the fields of exposome and pharmacogenomics research pave the way to precision medicine in pediatric asthma.

KEYWORDS

asthma; children; exposome; pharmacogenomics; precision medicine

INTRODUCTION

Asthma is a chronic respiratory disease of the airways affecting about 9% of children in the US and 15% of school-aged children in Europe (1), remaining a significant global health burden worldwide (2). The term "asthma" encompasses subgroups of patients characterized by considerable clinical variability, with some having persistent and some only transient or intermittent symptoms, some having eosinophilia and some not, some showing reduced and some normal lung function, some responding well to prescribed treatments and others with severe forms of therapy-resistant disease (3). Despite advances in understanding the mechanisms underlying the disease, the general principles of therapy have remained the same over time, being based on an approach calibrated on severity and exacerbations (4). Indeed, asthma guidelines have traditionally advocated a stepwise approach to treatment, in which uncontrolled patients are treated with higher doses or combinations of drugs. However, it is well recognized that patients with heterogeneous diseases comprising multiple phenotypes do not respond equally to the same treatment and have different prognoses. Therefore, such a traditional approach to asthma therapy may result in overtreating some patients, exposing them to adverse side effects from potentially harmful drugs, and undertreating others, putting them at risk of acute exacerbations. This suggests that patients with asthma need a more personalized and precise treatment approach (5).

The term "precision medicine" has been recently proposed to indicate “treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations” (6). Hence, this concept refers to the probability of responding (or not) to a certain therapeutic intervention and/or of suffering (or not) adverse effects, and can be adopted as an innovative strategy to guide asthma treatment (7). The challenge in achieving the concept of precision medicine is defining disease endotypes, that is identifying specific subtypes of a disease based on underlying molecular mechanisms, rather than on clinical features. Indeed, characterization of the endotype is crucial to ensure an optimal response to treatment (8).

It has been recently proposed that the interaction between the genetic background (genome) and the cumulative environmental exposures over a lifetime (exposome), through complex biological networks, determines the emergence of several cellular and molecular mechanisms that contribute to endotypes and clinical phenotypes (7).

Herein, the latest developments related to childhood asthma in the fields of exposome and pharmacogenomics are reviewed, describing their contribution to our current understanding of disease endotypes with regard to treatment response, and discussing challenges in integrating these innovative approaches into clinical practice as well as opportunities for future research.

THE EXPOSOME: AN INNOVATIVE APPROACH FOR ASSESSING ENVIRONMENTAL DETERMINANTS IN CHILDHOOD ASTHMA

Starting from the recognition that the genome alone explains only a small part of the variance observed in patients with chronic diseases, the exposome concept was introduced about 15 years ago as an innovative approach for providing a deep comprehension of the role that environmental risk factors have in disease etiology and pathophysiology, thus encompassing the totality of the environmental exposures occurring over a lifetime (9-11). Indeed, the exposome aims to cover the time frame of lifelong exposure history, providing an accurate assessment of the impact of environmental factors on human health, capturing the fluctuating dynamics of environmental exposures, the diversity in their

sources, and their interactions and also considering that body responses against these exposures can mediate the influence of these exposures on individual health (12).

The exposome encompasses three different domains interacting closely with each other: the general external exposome, which includes the urban-rural environment, climate, socio-economic and psychological factors; the specific external exposome, which includes exposures from chemical (including environmental pollutants), biological (infectious organisms, diet), physical (radiation, noise) and lifestyle factors; the internal exposome, including internal biological factors, such as metabolic factors, gut microbiota, inflammation, oxidative stress and aging (**Figure 1**) (13). More recent definitions of the exposome have been formulated to include the application of omics sciences that can better characterize exposures and the molecular changes associated with exposures, introducing the concept of "precision exposomics" within the context of precision medicine (14).

Given that different types of environmental exposures occurring throughout life have a major impact on asthma, an exposome-based approach appears to be particularly indicated, as it provides a risk profile rather than individual predictors (15). The first study investigating childhood respiratory health through an exposome approach has been based on the Kingston Allergy Birth Cohort, a prenatally recruited cohort characterized by a wide variety in environmental exposures. Data about respiratory symptoms of 235 children at 2 years of age were obtained by parents. All the three exposome domains showed effects on the respiratory health of the study population. In particular, significant associations were observed between wheeze or cough without a cold and prenatal tobacco smoke exposure, mold/dampness in the house, and the use of air fresheners in the home environment. On the contrary, breastfeeding, older siblings, and increased gestational age were associated with decreased respiratory symptoms (16).

In the past years, some initiatives have been launched with the aim of expanding the current knowledge on the exposome approach in pediatric environmental health. In 2014, the "Health and Environment-wide Associations based on Large population Surveys" (HEALS) project (FP7-ENV- 2013- 603946 http://www.heals-eu.eu/) was funded by the European Commission with the aim to describe in a series of about 335,000 individuals the internal exposome by integrating omics and biomonitoring data through population studies taking into account different levels of environmental exposure, age-specific

windows of exposure, and genetic variability (17-19). Notably, the HELIX project (www.projecthelix.eu), involving six birth cohorts, has been already launched to investigate, with the aid of omics markers, the relationships between the early childhood exposome and health in 32,000 mother-infant pairs, as well as measure growth, development and children's health, including asthma and lung function (20, 21). In this context, the association between 85 prenatal and 125 postnatal environmental exposures and lung function has been investigated in 1,033 children aged 6–12 years. The authors reported that lower values of FEV1 were associated with prenatal perfluorononanoate and perfluorooctanoate exposures, as well as with 9 postnatal exposures (copper, ethyl-paraben, phthalate metabolites concentrations, house crowding, and facility density around schools), whereas the inverse distance to the nearest road during pregnancy was associated with a higher FEV1 (22). More recently, the PROMESA cohort study protocol aims to characterize the external exposome (ambient and indoor exposures) and its contribution to clinical respiratory and early biological effects in children under five in tropical countries (23).

Though promising, the study of the exposome is challenging both in terms of measuring it and analyzing its relationship to health. Exposure assessment should be “holistic”, with different assessment tools that are needed for different exposure domains. The exposome approach then involves the collection of cumulative measures of external and internal exposures since preconception. Measuring the “totality” of exposures also requires the use of wearable devices capable of evaluating personal exposures in real time. Therefore, being able to increase the volume of exposures without affecting the measurement accuracy is a major challenge in exposome research (24).

According to this vision, the “European Environmental Exposure Assessment Network” (EIRENE) project (https://www.eirene-ri.eu) was launched to support a comprehensive research on human health and the environment. Based on the Czech national research infrastructure RECETOX (https://www.recetox.muni.cz/en/ services/recetox-ri), EIRENE connects 50 research institutions from 17 countries around the world, with the mission of studying the effects of long-term exposures to various types of environmental stressors on human health and the roles played by such exposures in the development of chronic diseases. In addition, within the context of the “European Long-term Study of Pregnancy and Childhood” (ELSPAC) (https:// www.elspac.cz/index-en.php), a prospective study

launched by the World Health Organization (WHO) in the early 1980s in six European countries, the CELSPAC platform (https://www.recetox.muni.cz/en/services/celspac-population-studies/celspac-study) is continuing to expand data collection, build large databases, and create new protocols for addressing the exposome concept in environmental health (25).

These initiatives are expected to contribute to a better understanding of the relationships between environment and health through studies that will need to be continuously ongoing and systematically evaluated. Indeed, levels of environmental stressors usually vary during lifetime, and individual changes in lifestyle can result in increased or decreased exposures (26). Moreover, certain life stages are recognized to be more susceptible to environmental exposures with regard to specific health outcomes such as asthma (15). In this context, the use of prospective birth cohort studies has been advocated (11, 27). However, it should be pointed out that biomarkers of exposure might not be continuously recorded for a long time. Another issue to be considered is the risk of increasing exposure misclassification due to the increased number of time-varying exposures assessed (28). Additionally, other gaps in the research field of exposome need to be acknowledged, i.e. the ability to link exposome and genome data in order to investigate gene-environment interactions. Moreover, we lack validated criteria for selecting the best assay for assessing the chosen research question, as well as guidelines for sample collection, repositories and biobanks, data sharing and security (15). From a statistical point of view, methodologies combining omics and multiple exposures, mediators, confounders, and outcomes are needed, along with specific expertise to optimize the analyses of complex data and to facilitate transdisciplinary collaborations (29). Finally, exposome-based projects are highly expensive due to the large study sample sizes and to the use of innovative tools required to assess several exposome components, including environmental monitoring and omics technologies (30).

In summary, the main future research perspectives in the field of exposome include:

- to improve the identification of the target population according to the research question, the optimal study design, timing and duration of measurements;
- to establish standards for data collection and security, as well as for the use of emerging technologies for the exposome assessment;

- to develop advanced biostatistical approaches for linking a large number of exposures with biological and clinical outcomes.

PHARMACOGENOMICS: AN INNOVATIVE APPROACH FOR ASSESSING RESPONSE TO TREATMENT IN CHILDHOOD ASTHMA

The term "pharmacogenomics" refers to a subfield of genomics, i.e., the genome-wide study of variants in the deoxyribonucleic acid (DNA), which evaluates the effect of genetic variants on the individual's response to treatment (31). The relevance of pharmacogenomics has been recognized even by the European Medicines Agency, that described pharmacogenomics as an "integral part of the development and post-authorization (marketing) phase for a number of medicines, with significant impact on the management of their benefits and risks in clinical use" (32, 33). Indeed, the degree of the genetically determined variability in response to pharmacological treatment can vary considerably, from 20 to 95% depending on the drug (34). Therefore, the availability of a pharmacogenomic test would dramatically influence the choices made by the prescriber, detecting a genetic predisposition to an adverse drug reaction, or differentiating between drug responders and drug non-responders, or indicating that a different dose of the drug—or in some cases a different class of drug—is needed (**Figure 2**) (35).

With regard to asthma, there is evidence that individuals from different populations and ethnic groups respond differently to pharmacological treatment, likely due to genetic variants inherited from a specific ancestry associated with disease severity or response to treatment (36). This suggests that the inter-individual variation in drug response in asthmatic patients could be partly genetically determined (37). Despite the numerous genetic variants identified, the poor replication of the results obtained only partially explains the heterogeneity of the response to treatment in pediatric asthma. With regard to response to inhaled corticosteroids (ICS), the most consistent findings have been reported for DNA variants in chromosomes 5 (rs10044254), 6 (rs6924808), 11 (rs1353649) and 16 (rs2388639). Other genetic variants have been associated with response to ICS, though not reaching genome-wide significance. The most relevant results were reported for the FCER2 gene, encoding for a low-affinity IgE receptor (CD23). In particular, the DNA variant rs28364072 has been associated with asthma

symptoms and poor lung function, and the largest effect was reported with the risk of exacerbations (hazard ratio: 3.95, 95% CI: 1.64–9.51) (38). Genetic variation has also been associated with response to long-acting β-2 agonists (LABA) in children. According to a recent systematic review including eight studies on children (n=6051), the ADRB2 rs1042713 variant resulted more associated with LABA response in children than in adults. In particular, five studies and a meta-analysis reported an increased risk of exacerbations in children having one or two A alleles (OR: 1.52, 95% CI: 1.17–1.99), suggesting to investigate further the potential role of rs1042713 genotyping for personalized treatment in pediatric asthma (39).

Pharmacogenomic testing has recently become mainly available and less costly; however, challenges and evidence gaps have been associated with its use in childhood asthma research and practice (40). In addition, whereas the use of pharmacogenomics in pediatrics is currently limited to less common diseases, such as cystic fibrosis (41), international guidelines for asthma do not recommend it. In spite of this, a pilot prospective questionnaire-based study recently conducted in children and young people with asthma, their parents, and healthcare professionals at a secondary/tertiary children's hospital in the UK demonstrated that the use of genetic information to guide asthma management it is widely acceptable. In particular, 46% of participants were happy about sharing genetic data with healthcare providers, and 46% agreed to share solely to guide asthma management (42). A relevant issue to address in pharmacogenomics is the identification of genetic markers associated with treatment response in patients with different ethnicities to guide asthma treatment (43). Additionally, validation of the genes identified to date, as well as identification of the loci accounting for a large proportion of the variation in treatment response should be considered (40). International collaboration may be helpful in identifying genetic markers in large samples of well-phenotyped children with asthma. In this regard, the Pharmacogenomics in Childhood Asthma (PiCA) consortium was established as the first consortium focusing on pharmacogenomics in pediatric asthma. PiCA's main goals are developing a platform to discover new pharmacogenomic markers, replicating identified loci associated with treatment response, and ultimately establishing algorithms to guide asthma treatment (44).

Another potential limitation to the application of pharmacogenomics in the clinical management of asthma patients is the little functional evidence and the lack of experimental studies investigating the

link between genetic markers identified and biological pathways (45). Given the existence of many asthma pheno/endotypes, a promising approach in asthma pharmacogenomics is through applying phenome-wide association studies (PheWAS), which test for associations between genetic variants and a wide range of phenotypes in a given population (46). The application of pharmacogenomics in childhood asthma should also take into account the heterogeneous disease endotypes to improve the response to biological drugs (47). Genome-wide interaction studies (GWIS) might also provide novel insights into complex relationships between genetic background and the environment. Through this, Dahlin et al. have identified age-by-genotype interactions in several asthma candidate genes, suggesting that age-specific genetic mechanisms may be implicated in the response to ICS as measured by the occurrence of exacerbations. In particular, the top-ranked age-by-genotype association was found for the DNA variant rs34631960 in THSD4, a gene potentially involved in lung function, airway remodeling, and asthma severity, which could be protective against the risk of exacerbations in younger asthmatics on ICS treatment, or, conversely, may predict an increased risk of poor ICS response in older patients (48).

Actually, one of the main challenges for the implementation of pharmacogenomics in clinical practice is the lack of validated and useful biomarkers. High-throughput technologies approaching different -omics layers simultaneously, hold the promise of expanding our knowledge of molecular mechanisms underpinning asthma pathophysiology and may contribute to select and stratify targeted treatment strategies (49-51). Nevertheless, integrating multi-omics and clinical data needs large-scale databases, strong computational power, and close collaboration between clinicians and bioinformaticians (43). In this context, the Biobanking and BioMolecular resources (BBMRI-ERIC) infrastructure (https://www.bbmri-eric.eu/) (52), sustains the collection of biological samples that may be useful to detect new targets for therapy and may support drug discovery and development. In addition, the ELIXIR infrastructure (https://elixir-europe.org/) (53), which integrates and sustains bioinformatics resources across European life science organizations, may provide new insights from large data sets, particularly data from gene sequencers.

Finally, implementing a multidisciplinary team of healthcare professionals and stakeholders for the care of children with asthma will be a crucial aspect in the context of an innovative model of therapeutic management that also includes pharmacogenomics in the evaluation of response to treatment (35).

In summary, the main future research perspectives in the field of pharmacogenomics include:

- to investigate the associations between genetic variants and different asthma phenotypes;
- to study the interaction between the genetic background and the environment;
- to correlate endotype and response to treatment with biological drugs;
- to develop and validate genetic biomarkers that can help select and stratify personalized therapeutic strategies.

CONCLUSIONS

Asthma is a complex and heterogeneous disease that requires individualized management. Uncontrolled asthma is still an issue worldwide, particularly in low-resource settings (54). In childhood, poor asthma control can irreversibly compromise the children's lung function. Beyond asthma phenotypes, considering disease endotypes has been considered a crucial issue in developing tailored therapies (55). Looking at the concept of precision medicine in childhood asthma, we need validated biomarkers to identify the main drivers of morbidity, allowing the provision of the right treatment, at the right time to the right patient.

It has been suggested that the interaction between genome and exposome determines the emergence of several cellular and molecular mechanisms that contribute to different asthma endotypes and clinical phenotypes (7). The latest developments related to childhood asthma in the fields of exposome and pharmacogenomics may contribute to a identify disease endotypes with regard to treatment response. Indeed, an exposome-based approach is particularly suited to chronic diseases such as asthma as it provides a risk profile rather than individual predictors. On the other hand, advances in pharmacogenomics pave the way for investigating the association between treatment response and genetic variants. However, main challenges are associated with exposome and pharmacogenomics in childhood asthma research and practice (**Figure 3**). Though many genetic variants have been shown to influence response to asthma treatment, results are still inconsistent and/or effect sizes are small.

Furthermore, it should be considered that epigenetic changes, gene–gene and gene–environment interactions could affect pharmacogenomic associations (37). In this regard, Perez-Garcia et al., report novel associations of epigenetic markers with BDR in pediatric asthma identifying five differentially methylated regions and two CpGs genome-wide significantly associated with BDR in African Americans located in FGL2 (cg08241295, p=6.8x10-9) and DNASE2 (cg15341340, p=7.8x10-8) demonstrating that bronchodilator drug response (BDR) influencing DNA methylation (DNAm) and ultimately showing the applicability of pharmacoepigenetics in precision medicine of respiratory diseases (56).

Sustainability and large-scale population-based studies are needed in order to improve research in exposome and pharmacogenomics. In addition, huge efforts are required in terms of consortia building as well as development and validation of measurement devices and statistical tools. Furthermore, collaboration between experts from different fields (such as clinicians, pharmacologists, immunologists, and data scientists) is required to pave the way for more precise, personalized, and effective management of childhood asthma, and to identify endotypes/phenotypes that are predictive of therapy response. Integrating multi-omics and clinical data might improve the ability to predict treatment response in children with asthma and to build decision support tools potentially valuable for the selection of drugs, in particular emergent and expensive biologicals, and to predict adverse events as well as exacerbations and decline in lung function (40).

CONFLICTS OF INTERESTS

The Authors have declared no conflict of interests.

FINANCIAL SUPPORT

There were no institutional or private fundings for this article.

Compliance with Ethical Standards

Authorship

Drs. Giuliana Ferrante, Giorgio Piacentini, Stefania La Grutta

Author contributions

GF: conceptualization, writing - original draft. GP, SLG: writing – review, editing and supervision. All authors contributed to the article and approved the submitted version.

Ethical approval

Human studies and subjects

N/A.

Animal studies

N/A.

Data sharing and data accessibility

N/A.

Publication ethics

Plagiarism

N/A.

Data falsification and fabrication

N/A.

Manipulation of images

N/A.

REFERENCES

1. Global Initiative for Asthma. GINA guidelines. Global strategy for Asthma Management and Prevention. Available from: https://ginasthma.org. Accessed: Jan 12, 2023

2. Asher MI, Rutter CE, Bissell K, Chiang CY, El Sony A, Ellwood E, et al. Worldwide trends in the burden of asthma symptoms in school-aged children: Global Asthma Network Phase I cross-sectional study. Lancet. 2021;398(10311):1569–80. doi: 10.1016/S0140-6736(21)01450-1

3. Custovic A, Henderson J, Simpson A. Does understanding endotypes translate to better asthma management options for all? J Allergy Clin Immunol. 2019;144(1):25-33. doi: 10.1016/j.jaci.2019.05.016

4. Martin MJ, Beasley R, Harrison TW. Towards a personalised treatment approach for asthma attacks. Thorax. 2020;75(12):1119–1129. doi: 10.1136/thoraxjnl-2020-214692

5. Agustí A, Barnes N, Cruz AA, Gibson PG, Heaney LG, Inoue H, et al. Moving towards a Treatable Traits model of care for the management of obstructive airways diseases. Respir Med. 2021;187:106572. doi: 10.1016/j.rmed.2021.106572

6. Jameson JL, Longo DL. Precision medicine – personalized, problematic, and promising. N Engl J Med. 2015;372(23):2229–2234. doi: 10.1056/NEJMsb1503104

7. Agustí A, Bafadhel M, Beasley R, Bel EH, Faner R, Gibson PG, et al. Precision medicine in airway diseases: moving to clinical practice. Eur Respir J. 2017;50(4):1701655. doi: 10.1183/13993003.01655-2017

8. Proper SP, Azouz NP, Mersha TB. Achieving Precision Medicine in Allergic Disease: Progress and Challenges. Front Immunol. 2021;12:720746. doi: 10.3389/fimmu.2021.720746

9. Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev. 2005;14(8):1847–50. doi: 10.1158/1055-9965.EPI-05-0456

10. Wild CP. The exposome: from concept to utility. Int J Epidemiol. 2012;41(1):24–32. doi: 10.1093/ije/dyr236

11. Vrijheid M. The exposome: a new paradigm to study the impact of environment on health. Thorax. 2014;69(9):876–8. doi: 10.1136/thoraxjnl-2013-204949

12. Buck Louis GM, Smarr MM, Patel CJ. The Exposome Research Paradigm: an Opportunity to Understand the Environmental Basis for Human Health and Disease. Curr Environ Health Rep. 2017;4(1):89–98. doi: 10.1007/s40572-017-0126-3

13. Vineis P, Robinson O, Chadeau-Hyam M, Dehghan A, Mudway I, Dagnino S. What is new in the exposome? Environ Int. 2020;143:105887. doi: 10.1016/j.envint.2020.105887

14. Zhang P, Carlsten C, Chaleckis R, Hanhineva K, Huang M, Isobe T, et al. Defining the Scope of Exposome Studies and Research Needs from a Multidisciplinary Perspective. Environ Sci Technol Lett. 2021;8(10):839–852. doi: 10.1021/acs.estlett.1c00648

15. Agache I, Miller R, Gern JE, Hellings PW, Jutel M, Muraro A, et al. Emerging concepts and challenges in implementing the exposome paradigm in allergic diseases and asthma: a Practall document. Allergy. 2019;74(3):449–63. doi: 10.1111/all.13690

16. North ML, Brook JR, Lee EY, Omana V, Daniel NM, Steacy LM, et al. The Kingston allergy birth cohort: exploring parentally reported respiratory outcomes through the lens of the exposome. Ann Allergy Asthma Immunol. 2017;118(4):465–73. doi: 10.1016/j.anai.2017.01.002

17. Baldacci S, Maio S, Cerrai S, Sarno G, Baïz N, Simoni M, et al. Allergy and asthma: effects of the exposure to particulate matter and biological allergens. Respir Med. 2015;109(9):1089–104. doi: 10.1016/j.rmed.2015.05.017

18. Parmes E, Pesce G, Sabel CE, Baldacci S, Bono R, Brescianini S, et al. Influence of residential land cover on childhood allergic and respiratory symptoms and diseases: evidence from 9 European cohorts. Environ Res. 2020;183:108953. doi: 10.1016/j.envres.2019.108953

19. Fasola S, Montalbano L, Cilluffo G, Cuer B, Malizia V, Ferrante G, et al. A critical review of statistical methods for twin studies relating exposure to early life health conditions. Int J Environ Res Public Health. 2021;18(23):12696. doi: 10.3390/ijerph182312696

20. Vrijheid M, Slama R, Robinson O, Chatzi L, Coen M, van den Hazel P, et al. The human early-life exposome (HELIX): project rationale and design. Environ Health Perspect. 2014;122(6):535–44. doi: 10.1289/ehp.1307204

21. Maitre L, de Bont J, Casas M, Robinson O, Aasvang GM, Agier L, et al. Human Early Life Exposome (HELIX) study: a European population-based exposome cohort. BMJ Open. 2018;8(9):e021311. doi: 10.1136/bmjopen-2017-021311

22. Agier L, Basagaña X, Maitre L, Granum B, Bird PK, Casas M, et al. Early-life exposome and lung function in children in Europe: an analysis of data from the longitudinal, population-based HELIX cohort. Lancet Planet Health;2019:3(2):e81–92. doi: 10.1016/S2542-5196(19)30010-5

23. Marı´n D, Orozco LY, Narva´ez DM, Ortiz-Trujillo IC, Molina FJ, Ramos CD, et al. Characterization of the external exposome and its contribution to the clinical respiratory and early biological effects in children: The PROMESA cohort study protocol. PLoS ONE 2023;18(1):e0278836. doi.org/10.1371/journal.pone.0278836

24. Ferrante G, Fasola S, Cilluffo G, Piacentini G, Viegi G, La Grutta S. Addressing Exposome: An Innovative Approach to Environmental Determinants in Pediatric Respiratory Health. Front Public Health. 2022;10:871140. doi: 10.3389/fpubh.2022.871140

25. Palát J, Kukucˇka P, Codling GP, Price EJ, Janku P, Klánová J. Application of 96-well plate SPE method for analysis of persistent organic pollutants in low volume blood serum samples. Chemosphere. 2022;287(Pt 3):132300. doi: 10.1016/j.chemosphere.2021.132300

26. DeBord DG, Carreón T, Lentz TJ, Middendorf PJ, Hoover MD, Schulte PA. Use of the "Exposome" in the practice of epidemiology: a primer on -Omic technologies. Am J Epidemiol. 2016;184(4):302–14. doi: 10.1093/aje/kwv325

27. Baluch N, Gallant M, Ellis AK. Exposomal research in the context of birth cohorts: what have they taught us? Ann Allergy Asthma Immunol. 2020;125(6):639–45. doi: 10.1016/j.anai.2020.09.006

28. Siroux V, Agier L, Slama R. The exposome concept: a challenge and a potential driver for environmental health research. Eur Respir Rev. 2016;25(140):124–9. doi: 10.1183/16000617.0034-2016

29. López-Cervantes JP, Lønnebotn M, Jogi NO, Calciano L, Kuiper IN, Darby MG, et al. The exposome approach in allergies and lung diseases: is it time to define a preconception exposome? Int J Environ Res Public Health. 2021;18(23):12684. doi: 10.3390/ijerph182312684

30. Burbank AJ, Sood AK, Kesic MJ, Peden DB, Hernandez ML. Environmental determinants of allergy and asthma in early life. J Allergy Clin Immunol. 2017;140(1):1–12. doi: 10.1016/j.jaci.2017.05.010

31. What Is Pharmacogenomics? Available from: https://ghr.nlm.nih.gov/primer/genomicresearch/pharmacogenomics. Accessed: Jan 23, 2023

32. Ehmann F, Caneva L, Papaluca M. European Medicines Agency initiatives and perspectives on pharmacogenomics. Br J Clin Pharmacol. 2014;77(4):612-617. doi: 10.1111/bcp.12319

33. European Medicines Agency (EMA). Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products. 2011. EMA/CHMP/37646/2009. Available from: https://www. ema.europa.eu/documents/scientific-guideline/guideline-use-pharmacogenetic-methodologies-pharmacokinetic-evaluation-medicinal-products_en.pdf. Accessed: Jan 23, 2023

34. Arwood MJ, Chumnumwat S, Cavallari LH, Nutescu EA, Duarte JD. Implementing pharmacogenomics at your institution: establishment and overcoming implementation challenges. Clin Transl Sci. 2016;9(5):233-245. doi: 10.1111/cts.12404

35. Barker CIS, Groeneweg G, Maitland-van der Zee AH, Rieder MJ, Hawcutt DB, Hubbard TJ, et al. Pharmacogenomic testing in paediatrics: Clinical implementation strategies. Br J Clin Pharmacol. 2022;88(10):4297-4310. doi: 10.1111/bcp.15181

36. Ortega VE, Meyers DA. Pharmacogenetics: Implications of race and ethnicity on defining genetic profiles for personalized medicine. J Allergy Clin Immunol. 2014;133(1):16–26. doi: 10.1016/j.jaci.2013.10.040

37. Kersten ET, Koppelman GH. Pharmacogenetics of asthma: Toward precision medicine. Curr Opin Pulm Med. 2017;23(1):12–20. doi: 10.1097/MCP.0000000000000335

38. Farzan N, Vijverberg S, Arets HG, Raaijmakers JAM, Van Der Zee AHM. Pharmacogenomics of inhaled corticosteroids and leukotriene modifiers: A systematic review. Clin Exp Allergy. 2017;47(2):271–293. doi: 10.1111/cea.12844

39. Slob EMA, Vijverberg SJH, Palmer C, Zazuli Z, Farzan N, Oliveri NMB, et al. Pharmacogenetics of inhaled long-acting beta2-agonists in asthma: A systematic review. Pediatr Allergy Immunol. 2018;29(7):705–714. doi: 10.1111/pai.12956

40. Ferrante G, Fasola S, Malizia V, Licari A, Cilluffo G, Piacentini G, et al. Pharmacogenomics: A Step forward Precision Medicine in Childhood Asthma. Genes (Basel). 2022;13(4):599. doi: 10.3390/genes13040599

41. Trust CF. Life-Saving Drugs. 2020. Available from: https://www.cysticfibrosis.org.uk/the-work-we-do/campaigning-hard/ life-saving-drugs. Accessed: Jan 24, 2023

42. Parry CM, Seddon G, Rogers N, Sinha IP, Bracken L, King C, et al. Pharmacogenomics and asthma treatment: Acceptability to children, families and healthcare professionals. Arch Dis Child. 2022;107(4):394–399. doi: 10.1136/archdischild-2021-322396

43. Vijverberg S, Farzan N, Slob EMA, Neerincx AH, Van Der Zee AHM. Treatment response heterogeneity in asthma: The role of genetic variation. Expert Rev Respir Med. 2017;12(1):55–65. doi: 10.1080/17476348.2018.1403318

44. Farzan N, Vijverberg SJ, Andiappan AK, Arianto L, Berce V, Blanca-López N, et al. Rationale and design of the multiethnic Pharmacogenomics in Childhood Asthma consortium. Pharmacogenomics. 2017;18(10):931–943. doi: 10.2217/pgs-2017-0035

45. Ober C. Asthma Genetics in the Post-GWAS Era. Ann Am Thorac Soc. 2016;13 Suppl 1(Suppl 1):S85–S90. doi: 10.1513/AnnalsATS.201507-459MG

46. Bush W, Oetjens MT, Crawford D. Unravelling the human genome–phenome relationship using phenome-wide association studies. Nat Rev Genet. 2016;17(3):129–145. doi: 10.1038/nrg.2015.36

47. Chen S, Tao A. The Pharmacogenomics of Asthma Beyond its Endotypes. Curr Drug Metab. 2018;19(14):1206–1212. doi: 10.2174/1389200219666180628170113

48. Dahlin A, Sordillo JE, McGeachie M, Kelly RS, Tantisira KG, Lutz SM, et al. Genome-wide interaction study reveals age-dependent determinants of responsiveness to inhaled corticosteroids in individuals with asthma. PLoS One 2020;15(3):e0229241. doi: 10.1371/journal.pone.0229241

49. van der Schee MP, Palmay R, Cowan JO, Taylor DR. Predicting steroid responsiveness in patients with asthma using exhaled breath profiling. Clin Exp Allergy. 2013;43(11):1217–1225. doi: 10.1111/cea.12147

50. Wysocki K, Conley Y, Wenzel S. Epigenome Variation in Severe Asthma. Biol Res Nurs. 2014;17(3):263–269. doi: 10.1177/1099800414553463

51. Brinkman P, Van De Pol MA, Gerritsen MG, Bos L, Dekker T, Smids BS, et al. Exhaled breath profiles in the monitoring of loss of control and clinical recovery in asthma. Clin Exp Allergy. 2017;47(9):1159–1169. doi: 10.1111/cea.12965

52. BBMRI-ERIC®. Available from: https://www.bbmri-eric.eu/ Accessed: Jan 24, 2023

53. ELIXIR. Available from: https://elixir-europe.org/ Accessed: Jan 25, 2023

54. García-Marcos L, Chiang CY, Asher MI, Marks GB, El Sony A, Masekela R, et al; Global Asthma Network Phase I Study Group. Asthma management and control in children, adolescents, and adults in 25 countries: a Global Asthma Network Phase I cross-sectional study. Lancet Glob Health. 2023;11(2):e218-e228. doi: 10.1016/S2214-109X(22)00506-X

55. Licari A, Manti S, Castagnoli R, Parisi GF, Salpietro C, Leonardi S, et al. Targeted therapy for severe asthma in children and adolescents: current and future perspectives. Paediatr Drugs. 2019;21(4):215–237. doi: 10.1007/s40272-019-00345-7

56. Perez-Garcia J, Herrera-Luis E, Li A, Mak ACY, Huntsman S, Oh SS, et al. Multi-Omic Approach Associates Blood Methylome with Bronchodilator Drug Response in Pediatric Asthma. J Allergy Clin Immunol. 2023 Feb 14:S0091-6749(23)00206-3. doi: 10.1016/j.jaci.2023.01.026

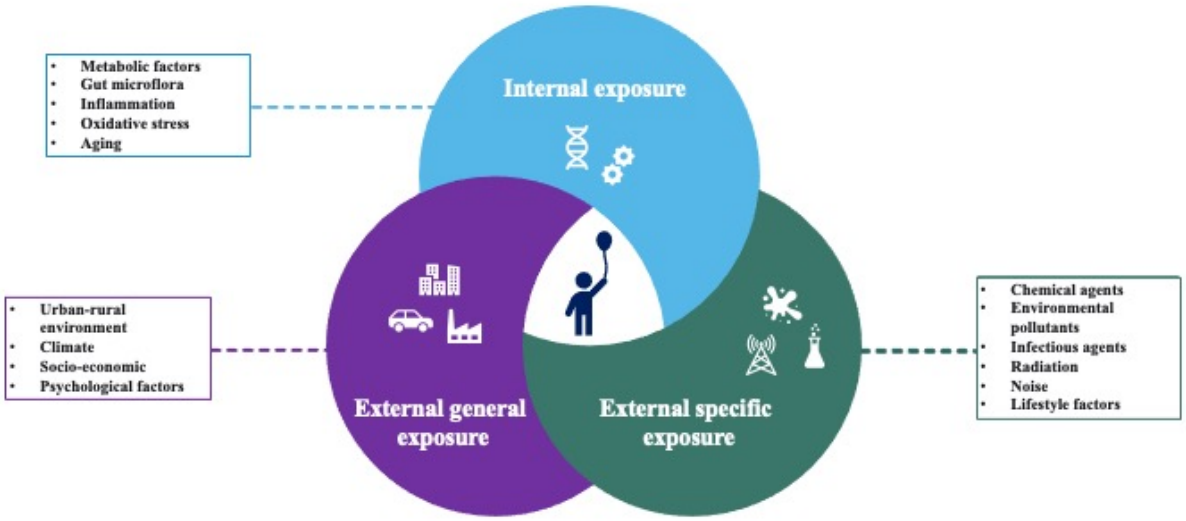


Figure 1. The three exposome domains: general external, specific external and internal.

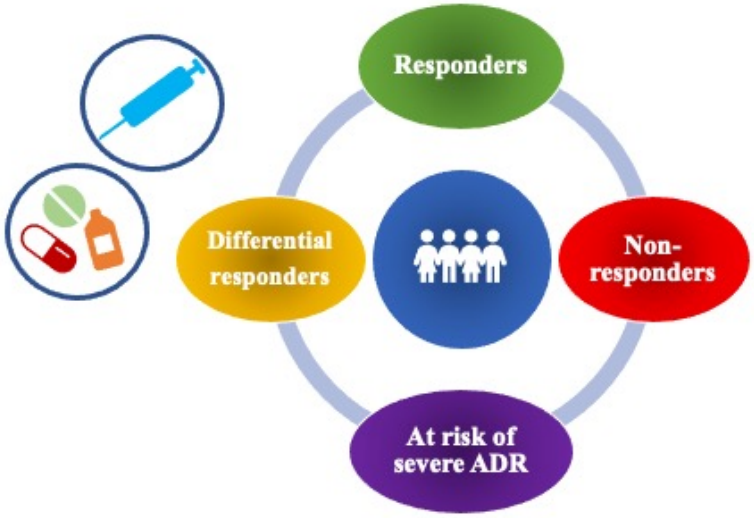
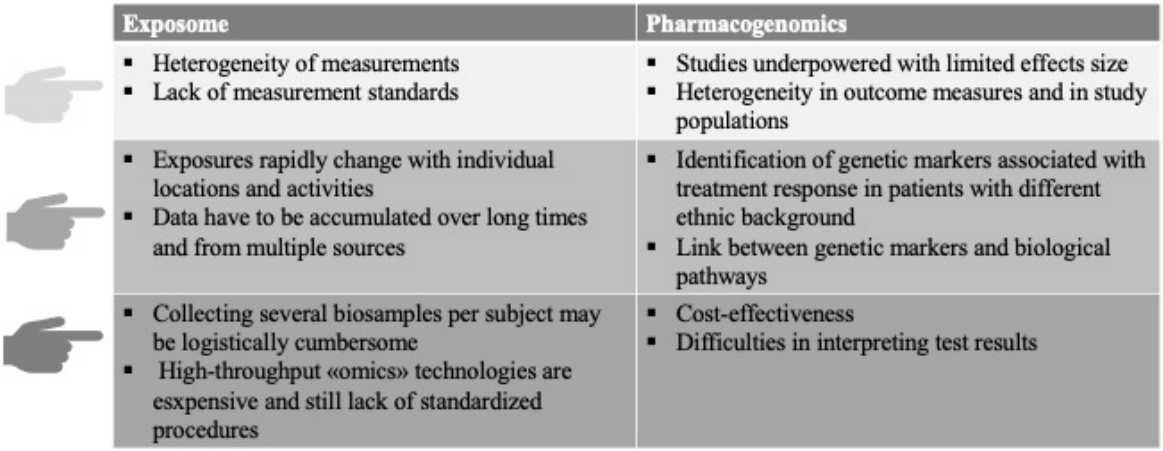


Figure 2. Stratification of patient groups according to treatment response. ADR: adverse drug reaction.



Exposome	Pharmacogenomics
▪ Heterogeneity of measurements ▪ Lack of measurement standards	▪ Studies underpowered with limited effects size ▪ Heterogeneity in outcome measures and in study populations
▪ Exposures rapidly change with individual locations and activities ▪ Data have to be accumulated over long times and from multiple sources	▪ Identification of genetic markers associated with treatment response in patients with different ethnic background ▪ Link between genetic markers and biological pathways
▪ Collecting several biosamples per subject may be logistically cumbersome ▪ High-throughput «omics» technologies are esxpensive and still lack of standardized procedures	▪ Cost-effectiveness ▪ Difficulties in interpreting test results

Figure 3. Main challenges associated with exposome and pharmacogenomics in childhood asthma research and practice.