Mechanisms of the Development of Allergy (MeDALL): Introducing novel concepts in allergy phenotypes

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Asthma, rhinitis, and eczema are complex diseases with multiple genetic and environmental factors interlinked through IgE-associated and non–IgE-associated mechanisms. Mechanisms of the Development of ALLergy (MeDALL; EU FP7-CP-IP; project no: 261357; 2010-2015) studied the complex links of allergic diseases at the clinical and mechanistic levels by linking epidemiologic, clinical, and mechanistic research, including *in vivo* and *in vitro* models. MeDALL integrated 14 European birth cohorts, including 44,010 participants and 160 cohort follow-ups between pregnancy and age 20 years. Thirteen thousand children were prospectively followed after puberty by using a newly standardized MeDALL Core Questionnaire. A microarray developed for allergen molecules with increased IgE sensitivity was obtained for 3,292 children. Estimates of air pollution exposure from previous studies were available for 10,000 children. Omics data included those from historical genome-wide association studies (23,000 children) and DNA methylation (2,173), targeted multiplex biomarker (1,427), and transcriptomic (723) studies. Using classical epidemiology and machine-learning methods in 16,147 children aged 4 years and 11,080 children aged 8 years, MeDALL showed the multimorbidity of eczema, rhinitis, and asthma and estimated that only 38% of multimorbidity was attributable to IgE sensitization. MeDALL has proposed a new vision of multimorbidity independent of IgE sensitization, and has shown that monosensitization and polysensitization represent 2 distinct phenotypes. The translational component of MeDALL is shown by the identification of a novel allergic phenotype characterized by polysensitization and multimorbidity, which is associated with the frequency, persistence, and severity of allergic symptoms. The results of MeDALL will help integrate personalized, predictive, preventative, and participatory approaches in allergic diseases. (J Allergy Clin Immunol 2017;139:388-99.)

Key words: *Asthma, atopic dermatitis, allergy, rhinitis*

Asthma, rhinitis, and eczema are among the most common chronic diseases. One of the most challenging characteristics is their complexity, with multiple genetic and environmental factors interlinked through IgE-associated and non–IgE-associated mechanisms.[1] These diseases generally begin very early in life and can persist into adult life.[2] As in patients with other chronic

diseases, they often occur in the same subjects (multimorbidity) more often than expected by chance.[3]

During the last decade, increasing recognition of the challenges associated with the complexity of many chronic diseases has stimulated interest in applying ***systems biology*** approaches to biomedical research.[4] Personalized, predictive, preventative, and participatory (P4) medicine has been advocated to integrate personalized, predictive, preventative, and participatory approaches.[5]

An important milestone in this process was that the 7th Framework Programme of the European Union (EU) promoted research to develop systems medicine to better understand chronic diseases. Mechanisms of the Development of ALLergy (MeDALL; EU FP7-CP-IP; project no: 261357; 2010-2015)

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Terms in boldface and italics are defined in the glossary on page 390.

Abbreviations used

BAMSE: Barn/Children Allergy/Asthma Milieu Stockholm Epidemiologic
CHI3L1: Chitinase-3–like protein 1
CQ: Core Questionnaire
DARC: Danish Allergy Research Centre
ECA: Environment and Childhood Asthma
EDEN: Etude des Déterminants pré et post natals du développement et de la santé de l' Enfant
EGEA: Epidemiological study on the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness and Atopy
ENRIECO: Environmental Health Risks in European Birth Cohorts
EU: European Union
GA^{2}LEN: Global Allergy and Asthma European Network
GINIplus: German Infant Study on the Influence of Nutrition Intervention PLUS Environmental and Genetic Influences on Allergy Development
GWAS: Genome-wide association study
IL-1RL1: IL-1 receptor–like 1
INMA: Infancia y Medio Ambiente
LISAplus: Life-Style Factors on the Development of the Immune System and Allergies in East and West Germany PLUS the Influence of Traffic Emissions and Genetics
MAS: German Multicenter Allergy Study
MeDALL: Mechanisms of the Development of ALLergy
NIH: National Institutes of Health
P4: Personalized, predictive, preventative, and participatory
PARIS: Pollution and Asthma Risk: an Infant Study
PIAMA: Prevention and Incidence of Asthma and Mite Allergy
RHEA: Mother-Child Cohort in Crete
ROBBIC: Rome and Bologna Birth Cohorts

attempted to better understand the complex links of allergic diseases at the clinical and mechanistic levels.[1,6] Building on previous initiatives, MeDALL established a network of 14 European birth cohorts, including information from 44,010 participants in 160 cohort follow-ups between pregnancy and age 20 years, as well as information from 398 clinical and phenotypic attributes and more than 30,000 biological samples. MeDALL completed its project in May 2015.[7]

TABLE I. Steps of the MeDALL systems approach to allergic diseases

1. Identification of "classical" phenotypes using hypothesis-driven approaches and "novel" phenotypes using data-driven approaches in existing birth cohorts
2. Discovery of the relevant mechanisms in IgE-associated allergic diseases in existing longitudinal birth cohorts
3. Validation and redefinition of the "classical" and "novel" phenotypes of IgE-associated allergic diseases
4. Translational integration of systems biology outcomes by means of genomics, transcriptomics, epigenomics, and proteomics into health care, including societal aspects

This review updates the final MeDALL report[3,7] with new results and already reported data.

A SYSTEMS APPROACH TO ALLERGIC DISEASES

A new paradigm encouraging a convergence of omics, systems medicine, the digital revolution, and consumer-driven health care is P4 medicine, which aims at advancing medical care through adoption of a systems-based approach.[5] However, the P4 practical application is difficult in patients with multimorbid chronic diseases.[8,9] A general hypothesis underlying the application of systems approaches in medicine is that the interplay between multiple genetic and environmental factors results in deregulation of complex molecular networks. The ultimate goals of systems medicine are to understand this complexity by using an integrative approach and to identify directions to investigate more efficient clinical diagnostics and therapies.[10] Systems medicine approaches involve large-scale integration of existing knowledge with newly acquired multidimensional data, including biobanking and clinical, phenotypic, environmental, lifestyle, biologic, and omics data. There are opportunities and challenges for precision medicine in the treatment of allergic diseases.[11-13]

MeDALL has been a pioneer in adopting a systems medicine approach to understand allergic diseases from early childhood to young adulthood[1,6,7] by linking epidemiologic, clinical, and basic research (Table I)[14] and including genome-wide association studies (GWASs) as well as transcriptomic, epigenetic, and targeted proteomic studies. This approach was possible due to the multidisciplinary nature of MeDALL.

GLOSSARY

AIR QUALITY: A description of whether air is clean or polluted. In the United States the Environmental Protection Agency calculates an Air Quality Index, which measures 5 major air pollutants regulated by the Clean Air Act: ground-level ozone, particulate matter, carbon monoxide, sulfur dioxide, and nitrogen dioxide.

EXPLORATORY FACTOR ANALYSIS: Factor analysis is a statistical method used to describe variability among observed correlated variables in terms of a potentially lower number of unobserved variables called factors. Exploratory factor analysis is a type of factor analysis to be used when the researcher has no *a priori* hypothesis about factors or patterns of measured variables.

HIERARCHICAL CLUSTERING: Grouping of observations together (clustering) that share common features or lack certain features. When the grouping arranges observations together first that are the most similar and then continues arranging observations by their degree of similarity, the clustering is considered hierarchical. This analysis is often represented by a dendrogram (tree diagram).

IgE MICROARRAYS: Allergens obtained by using recombinant DNA technologies are tested in a multiplex system in which a serum sample is tested for reactivity to many individual allergens.

IN SILICO: The modeling of biological processes using computer software or simulation.

LAND USE MODEL: A multivariate regression model using monitored levels of the pollutant of interest as the dependent variable and variables such as traffic, topography, and other geographic variables as independent variables. Levels of pollution might then be predicted for specific locations.

SYSTEMS BIOLOGY: A field of investigation that uses quantitative systematic measurements of interactive components, as well as mathematic models to describe dynamic living systems.

The editors wish to acknowledge Daniel Searing, MD, for preparing this glossary.

TABLE II. Pooled MeDALL database (from Bousquet et al)[7]

- AMICS-M: Data from 482 integrated participants with up to 12 follow-ups
- BAMSE: Data from 4,089 integrated participants with up to 6 follow-ups
- BIB: Data from 13,565 (2,594 in MeDALL) integrated participants with up to 7 follow-ups
- DARC: Data from 562 integrated participants with up to 9 follow-ups
- ECA: Data from 3,754 integrated participants with up to 6 follow-ups
- EDEN: Data from 1,140 integrated participants with up to 6 follow-ups
- GINI: Data from 5,991 integrated participants with up to 8 follow-ups
- LISA: Data from 3,095 integrated participants with up to 9 follow-ups
- INMA-Gipuzkoa: Data from 406 integrated participants with up to 4 follow-ups
- INMA-Sabadell: Data from 772 integrated participants with up to 7 follow-ups
- INMA-Valencia: Data from 855 integrated participants with up to 6 follow-ups
- MAS: Data from 1,314 integrated participants with up to 19 follow-ups
- PARIS: Data from 1,549 integrated participants with up to 10 follow-ups
- PIAMA: Data from 3,963 integrated participants with up to 12 follow-ups
- RHEA: Data from 1,336 integrated participants with up to 6 follow-ups
- ROBBIC-Bologna: Data from 434 integrated participants with up to 5 follow-ups
- ROBBIC-Roma: Data from 694 integrated participants with up to 6 follow-ups

INNOVATIVE METHODOLOGICAL APPROACHES

Building on previous networks of birth cohorts

Long-term birth cohort studies are essential for understanding the life course and childhood predictors of allergy and the complex interplay between genes and environment (including ***air quality***, lifestyle, and socioeconomic determinants).[15] More than 150 cohorts focusing on asthma and allergy have been initiated in the world over the past 30 years.[14] Since 2004, several research initiatives funded under the EU Framework Program for Research and Technological Development FP6-FP7 have attempted to identify, compare, and evaluate pooling data from existing European birth cohorts (Global Allergy and Asthma European Network [GA^{2}LEN],[16,17] FP6; Environmental Health Risks in European Birth Cohorts (ENRIECO),[18] FP6; GABRIEL: A Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community [reference], FP7; CHICOS: Developing a Child Cohort Research Strategy for Europe, FP7; MeDALL, FP7; Early Genetics & Lifecourse Epidemiology [EAGLE]).[19,20] In the United Kingdom, the Study Team for Early Life Asthma Research (STELAR)[21] initiated a similar pooling of birth cohorts. The collaborative FP7 translational research project EuroPrevall started a multicenter birth cohort study, recruiting more than 12,000 newborns in 9 European countries in 2005-2009.[22,23] The information gathered by these birth cohorts has already made a significant advance in our understanding of allergy and asthma, particularly in the first years of life.

The goal of MeDALL was to use the wealth of already existing European birth cohort data and facilitate the integration of historical and newly generated data in a harmonized format for future research. MeDALL pooled 14 European birth cohorts, including AMICS-Menorca[24]; Barn/Children Allergy/Asthma Milieu Stockholm Epidemiologic (BAMSE)[25]; Born in Bradford (BIB)[26,27]; the Danish Allergy Research Centre (DARC)[28]; Environment and Childhood Asthma (ECA)[29]; Etude des Déterminants pré et post natals du développement et de la santé de l' Enfant (EDEN)[30]; German Infant Study on the Influence of Nutrition Intervention PLUS Environmental and Genetic Influences on Allergy Development (GINIplus)[31,32]; Infancia y Medio Ambiente (INMA) Gipuzkoa, Sabadell, and Valencia[33]; Life-Style Factors on the Development of the Immune System and Allergies in East and West Germany PLUS the Influence of Traffic Emissions and Genetics (LISAplus)[34]; the German Multicenter Allergy Study (MAS)[35-38]; Pollution and Asthma Risk: an Infant Study (PARIS)[39]; Prevention and Incidence of Asthma and Mite Allergy (PIAMA)[40]; Mother-Child Cohort in Crete (RHEA)[41]; and Rome and Bologna Birth Cohorts (ROBBIC).[42]

However, an important difficulty in data integration collected from the numerous existing birth cohort studies was the heterogeneity of questionnaires and data collection frameworks. Combining the data for a joint analysis in large international studies is not straightforward, and thus the harmonization of the available data to achieve comparability is one of the main challenges.

MeDALL approached this difficulty by following 2 steps. First, historical data from birth cohorts were harmonized to facilitate initial analysis at the beginning of the project. Second, a harmonized MeDALL Core Questionnaire (MeDALL-CQ) was developed to increase the number of questions that were identical in the questionnaires used by the different birth cohorts to guarantee the homogeneity of newly collected data.[43] After mapping existing databases in birth cohorts, MeDALL researchers agreed and evaluated 137 variable definitions for inferential compatibility. Two thirds of the definitions were evaluated as completely equivalent, 16% as only partially equivalent, and 16% as noncompatible. A major achievement of MeDALL was the development of the harmonized MeDALL-CQ, which has been used historically in the 14 cohorts and prospectively in 11 cohorts.[43] The questionnaire is available in paper form and in an electronic version.

Worldwide interest has been expressed in MeDALL-CQ, which will be included in future follow-up assessments of the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) birth cohort[44] and of the large Japanese national birth cohort Japan Environment and Children's Study (JECS), which recently recruited 100,000 parent-child pairs (www.env.go.jp/en/chemi/hs/jecs/).

Development of a database of pooled cohorts using a harmonized MeDALL-CQ

A MeDALL knowledge-management platform was developed to empower all partners with the means of open sharing and access to all the data and information collected, as well as to all the experimental and computational procedures used during the course of the project, and ultimately their dissemination in the scientific and biomedical community. The MeDALL knowledge base integrates historical and newly collected data from 44,010 participants on 398 clinical and phenotypic attributes (harmonized from 7,495 individual cohort variables) and 160 different follow-ups at 25 different time points between pregnancy and age 20 years, as well as information about available samples (>30,000 samples from blood, plasma, serum, DNA, RNA, and leukocytes;

Table II).[7,45] Samples are stored in individual biobanks of the different MeDALL partners.[1,6,7] Omics data produced or made available within MeDALL include 23,000 participants with historical GWASs, 2,173 with DNA methylations, 1,427 with biomarkers, and 723 with transcription experiments, ***IgE microarrays*** (3,292 IgE-chips) and individual estimates of ambient air pollution exposure (10,000 children) made by using the ***land use model*** (European Study of Cohorts for Air Pollution Effects [ESCAPE]).[46-49]

The availability of longitudinal samples of the same subject is a unique resource. The MeDALL database with its new central database is the starting point for future common and sustainable research initiatives in asthma and allergy. It can be extended with other epidemiologic studies, such as birth and patient cohorts.

New allergen microarray technology

The "MeDALL allergen-chip" is a collection of 170 allergen molecules used for the reliable detection of IgE and other isotypes of allergen-specific antibody signatures showing a higher sensitivity than the traditional ImmunoCAP system and skin prick testing. The MeDALL chip was used in more than 3,000 children and, as described in the following sections, allowed improvement in the understanding of the allergic nature of asthma, rhinitis, and eczema in children.[50-54]

Developing a systems medicine approach

An important advantage of the multidisciplinary nature of MeDALL was the integration of new bioinformatics methods with the classical epidemiologic and statistical ones. Unsupervised statistical models, such as portioning cluster analysis, were used as an unsupervised strategy to identify novel phenotypes, and an ***in silico*** model of multimorbidity was developed.[55] Another innovative approach in MeDALL was the use of omics data, including GWASs, DNA methylation, transcriptomics and targeted proteomics, with the advantage of expanding results from conventional cross-sectional analyses to longitudinal analyses at different ages in childhood. Systems medicine is evolving as a novel approach to understand the complex interplay between the environmental, genetic, molecular, and physiologic domains and how this interplay leads to complex chronic diseases. In MeDALL, we have contributed to paving the way to apply systems medicine to allergic diseases in children. MeDALL has included epidemiologic, clinical, and multiomics data together with cell and animal models to advance our understanding of allergic diseases in children. In MeDALL, we are still far from a complete integration of the different tools and data in a single model, but we have advanced in understanding the biological pathways that are related to the multimorbidity of asthma, eczema, and rhinitis, and how GWASs, epigenetics, and proteomics can be integrated to understand the role of some asthma genes (eg, chitinase-3–like protein 1 *[CHI3L1]* and IL-1 receptor–like 1 *[IL1RL1]*). The potential role of different disciplines in systems medicine is evolving, and expansion of the current epidemiologic methods to allow this type of integrative analysis is a current and future challenge.[56]

A NEW VISION OF MULTIMORBIDITY IN ALLERGIC DISEASES

The term multimorbidity is more appropriate than comorbidity because the primary allergic disease is poorly known and the classical allergic march does not apply to every child.[57] Several other allergy trajectories have been described since. The concept of multimorbidity of allergic diseases[58,59] and links between rhinitis and asthma in allergic and nonallergic patients[60] have been known for years. However, MeDALL has been the first population-based study to assess the allergic multimorbidity of eczema, rhinitis, and asthma by using a dual approach, hypothesis driven[61] and data driven (unsupervised cluster analyses),[55] quantifying the net excess of multimorbidity.[61]

Allergic phenotypes are highly heterogeneous. MeDALL carried out the first systematic review on allergic phenotypes and multimorbidity.[62] Studies reporting phenotypes of IgE-associated diseases in children are heterogeneous and often lack objective measures. The knowledge on multimorbidity was mostly restricted to links between asthma and rhinitis, indicating that a more global view of multimorbidity is needed.

MeDALL used classical cross-sectional and longitudinal epidemiologic methods to perform a precise analysis of allergic multimorbidity.[61] The study involved 16,147 children aged 4 years and 11,080 children aged 8 years in cross-sectional and longitudinal analyses from 12 MeDALL European birth cohorts. Coexistence of eczema, rhinitis, and asthma in the same child is more common than expected by chance alone, both in the presence and absence of IgE sensitization, suggesting that these diseases share causal mechanisms. Although IgE sensitization is independently associated with excess multimorbidity of eczema, rhinitis, and asthma, its presence accounted for only 38% of multimorbidity, suggesting that IgE sensitization can no longer be considered the only causal mechanism of multimorbidity for these diseases.

During the last years, unsupervised statistical learning techniques, such as ***exploratory factor analysis*** and ***hierarchical clustering***, have been used to identify asthma phenotypes, with partly consistent results.[63] However, there is less experience in using machine-learning methods to understand the interrelationships between different allergic phenotypes.[64] MeDALL also used machine-learning methods, allowing an unsupervised approach to identify novel phenotypes.[55] The study involved 17,209 children at age 4 years and 14,585 children at age 8 years from 7 birth cohorts. At variance with previous studies that applied these methods to a single disease,[6] we assessed asthma, rhinitis, and eczema together in the same models. At each age period, we performed partitioning cluster analysis, according to the distribution of 23 variables covering symptoms "ever" and "in the last 12 months", doctor's diagnosis, age of onset, and treatments of asthma, rhinitis, and eczema; IgE sensitization; weight; and height. The analysis used repeated latent class analysis and self-organizing maps.

Two groups were identified as the optimal way to cluster the data at both age periods and in all sensitivity analyses. The first (reference) group at 4 and 8 years of age (including 70% and 79% of children) was characterized by a low prevalence of symptoms and sensitization, whereas the second (symptomatic) group exhibited more frequent symptoms and sensitization. Ninety-nine percent of children with multimorbidities fell into the symptomatic group at both ages. At 4 and 8 years of age, at the population level, asthma, rhinitis, and eczema can be classified together as an allergic multimorbidity cluster. Future research, including time-repeated assessments and biological data, will help to understand the interrelationships between these diseases.[64] MeDALL use of machine-learning methods together

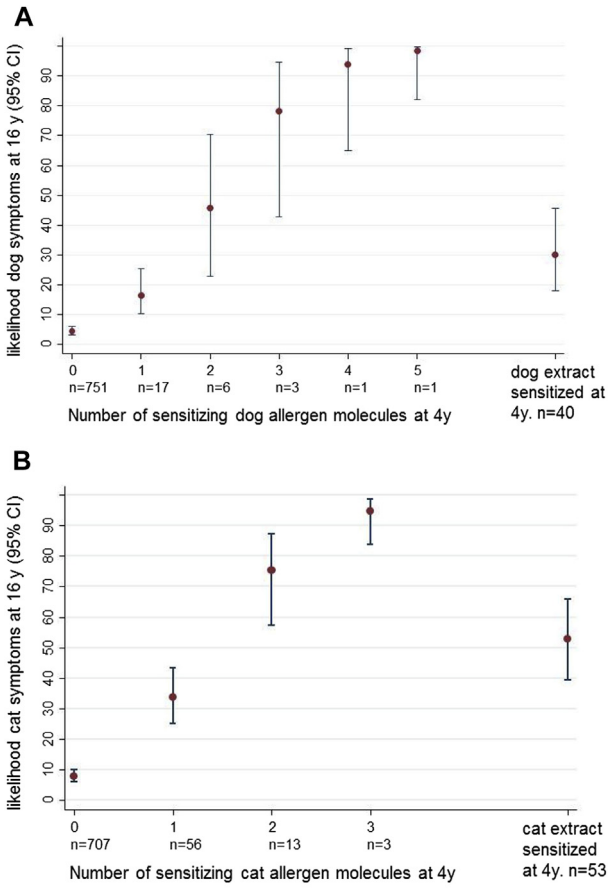

FIG 1. Likelihood of reporting symptoms to dog at 16 years of age depending on the number of IgE-reactive dog allergens and ImmunoCAP dog extract sensitizations at age 4 years **(A)** and to cat at 16 years depending on the number of IgE-reactive cat allergens and ImmunoCAP cat extract sensitization at age 4 years **(B)**. Used with permission from Asarnoj et al.[53]

with classical methods have contributed to show that efforts to elucidate more refined phenotypes should be integrated with a better understanding of multimorbidity.

MeDALL developed a bioinformatic model of multimorbidity of allergic diseases. An *in silico* study based on computational analysis of the topology of the protein interaction network was performed to characterize the molecular mechanisms of multimorbidity of asthma, eczema, and rhinitis. As a first step, proteins associated with either disease were identified by using data-mining approaches, and their overlap was calculated. Secondly, the functional interaction network was built, allowing the identification of cellular pathways involved in allergic multimorbidity. Finally, a network-based algorithm generated a ranked list of newly predicted multimorbidity-associated proteins. The results strongly support the existence of an allergic multimorbidity cluster between asthma, eczema, and rhinitis and suggest that type 2 signaling pathways represent a relevant multimorbidity mechanism of allergic diseases.

MONOSENSITIZATION AND POLYSENSITIZATION REPRESENT DISTINCT ALLERGY PHENOTYPES

The concept of monosensitization and polysensitization has been previously proposed[65-68] but never formally evaluated because of the lack of large numbers of samples in a population-based study and inadequate methods. This made it impossible to study a wide array of allergens, including cross-reactive molecules.[69] This became possible in MeDALL.

The BAMSE cohort (Sweden) was used as a model, and the same 779 children were tested at 4, 8, and 16 years of age.[70] Component-resolved diagnosis to birch proteins and cross-reactive pathogen-related class 10 protein by using the MeDALL chip allows the prediction of future allergy in young children.[52] There was an increased risk of incidence and persistence of asthma, rhinitis, or both induced by birch pollen up to age 16 years with increasing levels of Bet v 1–specific IgE or increasing numbers of IgE-reactive pathogen-related class 10 proteins at age 4 years.

Sensitization to individual cat and dog allergen molecules can contribute differently to the development of allergy in childhood.[53] Cross-sectionally, cat/dog-polysensitized children had higher IgE levels and more frequent symptoms to cat and dog than monosensitized children. Polysensitization to 3 or more allergen molecules from cat or dog was a better longitudinal predictor of cat or dog symptoms than monosensitization (Fig 1).[53]

Monosensitization and polysensitization represent 2 different phenotypes of IgE-associated diseases (Table III)[53,65,67,68,71-84] in the MeDALL cohorts,[3] in the PARIS cohort at 2 years of age,[81] and in patient cohorts in children with inhalant[82] or peanut[78] allergy.

In the Epidemiological Study on the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness and Atopy (EGEA), the monosensitized and polysensitized MeDALL phenotypes[3] were confirmed in adults.[54,71] It was found that multimorbid polysensitized subjects had an onset of the disease at preschool age. Onset was also found to occur earlier than in mono sensitized individuals or in those with asthma or rhinitis and no IgE sensitization (Siroux, personal communication).

IgE sensitization should be considered a qualitative (IgE response) and quantitative trait (monosensitization and polysensitization) because important clinical and immunologic differences exist between monosensitized and polysensitized subjects (Table III). The integration of multimorbidities and polysensitization has resulted in a new classification framework of allergic diseases[3,82] that could help improve the understanding of genetic and epigenetic mechanisms and pathways of allergy and improve the management of allergic diseases.

MeDALL identified a rare but severe allergy phenotype: the polysensitized multimorbid phenotype. Although multimorbidity is not always associated with allergy, studies in MeDALL[70] in children aged 2 years and in adults recruited in the PARIS[81] and EGEA cohorts,[54,71] respectively, as well as in subjects with peanut allergy from patient cohorts,[78] showed that subjects who are both polysensitized and multimorbid have a very high frequency of symptoms (persistent symptoms over time and more severe asthma symptoms) and higher total and specific IgE levels compared with other phenotypes.

FROM CLINICAL PHENOTYPES TO MECHANISMS

An important step in MeDALL was the study of the relevant mechanisms in patients with IgE-associated diseases. We developed a link with GWASs and transcriptomic, epigenetic, and

TABLE III. Differences between monosensitized and polysensitized subjects

	Monosensitized subjects	Polysensitized subjects	References
Symptoms			
Asymptomatic subjects	Often	Rarely	71
Common symptoms	Rhinitis (pollens) Asthma (mites)	Often multimorbid asthma and rhinitis	65,72
Family history of asthma or rhinitis	Often	Common	73
IgE			
Total IgE	Normal or increased levels	High levels, higher than in monosensitized subjects	65,72,74,75
Level of Specific IgE	Usually low (except for pollens)	High	53,67,72,76
T-cell response	Low IL-4 release	High IL-4 release	68,77
Severity of disease	Variable, can be severe	Often severe	78-80
Persistence of disease	Variable, can disappear	Often persistent	81-84

targeted proteomic studies. Although all analyses are not yet completed, some results are already available.

MeDALL omics data

Omics studies were completed by implementing a 2-stage approach (discovery plus validation) and optimizing completion of different omics measurements in the same participants to allow integrative analyses.

Among results published to date, a strong and consistent effect of maternal smoking on the child's whole-blood DNA methylome was observed from birth to 8 years in a large consortium, including MeDALL.[85] Another well-known environmental exposure associated with respiratory disease, traffic-related air pollution,[86] was also found to affect DNA methylation in offspring.[87] In the first published epigenome-wide air pollution study, NO_2 exposure during pregnancy was associated with differential offspring DNA methylation in mitochondria-related genes and in expression of genes involved in antioxidant defense pathways. Analyses of other traffic-related pollutants, such as particulate matter and soot, are ongoing. These studies underline the effect of early-life exposure to environmental factors, although it is currently not known whether these methylation changes and expression profiles are in the causal pathway toward asthma and lung function deterioration or just markers of exposure. Efforts are now directed to study the relevance of epigenetics and transcriptomics for disease development (asthma and allergy in particular). We also participated in a large international collaborative study on lung function maturation in childhood and found that circulating levels of club cell secretory protein at age 4 years predicted subsequent FEV_1 levels up to age 16 years,[88] supporting the value of this biomarker in lung health.

A targeted multiomics integrative analysis in childhood asthma was completed with genetic-epigenetic-protein data for the asthma biomarker YKL-40 *(CHI3L1)*, in which, using data from multiple birth cohorts, we showed that *CHI3L1* genetic variation affects circulating YKL-40 by regulating its gene methylation profiles. A similar study was conducted to assess the interrelationship between IL-1RL1-α polymorphisms, IL-1RL1-α methylation, serum IL-1RL1-α levels and asthma. SNPs in IL-1RL1-α strongly regulate IL-1RL1-α methylation, lung mRNA expression, and serum IL-1RL1-α levels, although no relation of these (epi)genetic effects were observed in asthmatic patients. Similar integrative analyses were conducted for the other protein biomarkers measured in MeDALL, for which we have determined the genetic and epigenetic loci associated with their circulating levels, identified their methylation quantitative trait loci, and, in turn, generated valuable information for integrative genomics studies.

Mechanistic experimental studies in animal studies and *in vitro* to complement MeDALL data

As part of the systems approach in the EU-FP7 program, MeDALL included *in vivo* and *in vitro* models to complement the epidemiologic and mechanistic studies in children. Transgenic mice, in which the T-cell receptor reacts to the relevant Der p 1 allergen of house dust mite, showed a novel IL-21–producing T-cell subset involved in asthma development.[89] Mice exposed to farm dust did not mount allergy and asthma to house dust mite because of a downregulation of epithelial cell activation and subsequent lack of dendritic cell activation. The pathway involved the ubiquitin-modifying enzyme A20. Genetic polymorphisms of A20 were associated with the risk of asthma in children and adults.[90]

In human subjects, *in vitro* studies are essential to confirm mechanisms suggested by cohort studies. In allergic patients, the immune profile of the tonsils might represent a suitable lymphatic organ for direct immune interventions.[91-93] Cytokine-producing memory B-cell subsets can have proinflammatory, anti-inflammatory, and immune effector and immunoregulatory functions during allergen tolerance, such as allergen immunotherapy and high-dose allergen exposure.[94-97] Regulatory T-cell counts are reduced during asthma exacerbations as markers of virus-induced asthma exacerbations.[98] The bronchial epithelial layer serves as the first site of exposure to inhaled allergens, dust particles, pollutants, or microorganisms. Tight junctions can be regulated by cytokines of the allergy pathways.[99,100] Administration of CpG-DNA could restore impaired epithelial barriers.[101]

CLINICAL TRANSLATION OF MeDALL OUTCOMES

A crucial aspect in asthma clinical practice is the early identification of children at risk of having asthma at school age. Thus far, efforts to develop predictive algorithms have proved to be of little use. MeDALL performed a systematic review of existing prediction models to identify preschool children with asthma-like symptoms at risk of asthma at school age and showed that the prediction of asthma development is difficult,[102] most likely because of interactions with viral infections. The experience of MeDALL suggests that opportunities to improve the performance and usability of asthma predictive models should be

explored further and that a more integrated use of biomarkers and multimorbidity is needed.

Improved prediction of asthma and its relationships with rhinitis and eczema could be achieved by a better understanding of the sex switch in prevalence during puberty. There seems to be a clear male predominance of asthma prevalence in children, switching to a female predominance in adolescence. Similarly, this has been confirmed for rhinitis prevalence in a recent worldwide systematic review of cross-sectional studies. The longitudinal sex-specific MeDALL analyses of 18,852 children participating in PIAMA, BAMSE, LISAplus, GINIplus, DARC, and MAS showed similar but less pronounced puberty-related changes in the sex-specific prevalence of asthma and allergic rhinitis. However, the hypothesis that further into adulthood the sex imbalance in the prevalence is switching to a clear female predominance of asthma and rhinitis will be examined with the next follow-up data collected by the MeDALL cohorts in adulthood.

Patient stratification is an important goal of the P4 medicine approach. Patient stratification aims at grouping patients into disease subgroups, where the specific pathologic processes involved are better defined (clinical/molecular phenotypes). This will lead to the development of targeted therapies optimizing the intervention to individual patients, thus achieving greater success in treating or curing the patient. Many phenotypes of asthma, rhinitis, or both exist. MeDALL has refined allergy phenotypes and showed that polysensitization and multimorbidity need to be considered together. However, the allergic phenotype is maturing from early childhood to puberty and beyond, in which associations between allergic diseases and risk factors change over time.[103] Thus it is important to assess the allergic phenotype across the lifecycle and to investigate stratification when allergic diseases will be fully developed between late adolescence and early adulthood.

Emerging technologies have been used successfully to stratify allergic patients. In the follow-up of birth cohort studies in young adults, the combination of a clinical decision support system for rhinitis[104] and asthma based on information technology (App and tablet)[105,106] might provide an improved stratification of allergic patients. Moreover, the molecular sensitization profiles determined with the MeDALL chip might be the basis for stratification for allergen immunotherapy.[107]

TRANSLATION OF MeDALL OUTCOMES INTO POLICIES

A specific focus of MeDALL was to translate research into political action through the World Health Organization Global Alliance Against Chronic Respiratory Diseases (GARD),[108-110] which was the model of AIRWAYS ICPs (Integrated Care Pathways for Airway Diseases),[105,111-115] a new initiative of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA; Directorate General DG Santé, and DG CONNECT, EU).

The leading priority for the Polish Presidency of the Council of the EU (2011) was to reduce health inequalities across European societies, and, within its framework, to concentrate on the prevention and control of respiratory diseases in children to promote active and healthy aging.[116,117] The clinical implications of MeDALL reinforce the priority of the EU and suggest solutions for implementation.

The first results of "the Finnish Allergy Programme 2008-2018,"[118] which are supported by MeDALL data, indicate that allergy burden can be reduced with relatively simple means. This has been endorsed by the Norwegian Allergy Health Programme and, along with the Finnish program, will serve as a platform for other countries (Oslo, November 2014).[119]

LESSONS LEARNED AND CONCLUSIONS

The MeDALL project reinforced previous collaborations among most of the largest and oldest ongoing European birth cohorts, enhancing harmonized population-based asthma and allergy research activities in Europe instead of continuing with fragmented individual approaches often lacking sufficient statistical power. The MeDALL project with its new central database is the starting point for conducting future common and sustainable asthma and allergy research initiatives. It can be extended easily by including other epidemiologic studies involving birth and patient cohorts.

A joint National Institutes of Health (NIH)–MeDALL workshop on birth cohorts in allergy and asthma was organized in September 2012 to update the knowledge provided by asthma/allergy birth cohorts, to identify the knowledge gaps and inconsistencies, and to suggest strategies for moving forward, including potential new study designs and the harmonization of existing asthma birth cohort data from both European and non-European countries.[14]

Strength of birth cohorts covered by MeDALL

Birth cohort pooling[14] has strengthened the capacity of developing harmonized research protocols and multilingual instruments. MeDALL has achieved a certain number of goals (Table IV).*

Unmet needs of birth cohorts

There is no consistent evidence that clinical phenotypes correspond to genuine biological entities that reflect specific interactions between genetic susceptibility and environmental exposures. Exploration of new phenotypes is a useful task that might eventually result in a more refined classification of phenotypes that closely reflects the relevant pathogenic mechanisms. Future research needs were discussed during an NIH (National Heart, Lung and Blood Institute–National Institute of Allergy and Infectious Diseases)–MeDALL meeting and were proposed to include some issues already covered by MeDALL[14]:

1. A better characterization of phenotypes is required, including (I) a unique agreement on classification of asthma that can be applied to research, diagnosis, and treatment; (II) a better understanding of the interplay between asthma, allergy, and multimorbidity; (III) how allergic phenotypes interrelate across the lifecycle; and (IV) how respiratory allergy interacts with food allergy.[121]
2. Assessment of natural history and its determinants during and after childhood must be made. There is a well-established relationship between lung function impairment and chronic wheezing and asthma. The development of allergic diseases and trajectories of sensitization or lung function during childhood and adolescence depends on allergenic and nonallergenic exposure modulated by early-life events and puberty, as shown in birth[122] and

*References 6,14,15,19,20,43,46,50-53,55,61,70,86,88,102,120.

TABLE IV. Goals of birth cohorts set during an NIH-MeDALL meeting[14]

	Goals	MeDALL achievements
1	Promote and facilitate harmonization of existing questionnaires and clinical data of ongoing birth cohorts	Harmonized questionnaire[43] Clinical and biological data in database[7,15]
2	Propose future common questionnaires for different age groups and a common clinical study protocol to be used in new birth cohorts, as well as in new follow-ups of ongoing birth cohorts, which could facilitate interoperability and a better comparison with historical data	Deployment to Japan and the United States
3	Analyze pooled data from ongoing birth cohort studies in large databases to complement newly developed birth cohorts	In process
4	Broaden the diversity of environmental exposures in Europe (dietary, inhalant, and socioeconomic factors)	Several studies using pooled analyses[46,86]
5	Achieve statistical power needed to assess clinical or biological phenotypes, genetic or environmental determinants, and their interactions	Achieve the statistical power needed to assess clinical[55,61,102] or biological[50-53,70,88] phenotypes, genetic[19,20,88,120] or environmental[46,86] determinants, and their interactions
6	Assess the life course of subgroups of allergic and asthmatic phenotypes, including economic burden and quality of life of most phenotypes	Life course up to 16 y; plan for study in young adults
7	Determine sex-specific differences across different cultures and regions in Europe	Achieved (in preparation)
8	Facilitate research on underlying mechanisms explaining heterogeneous results among the cohorts	In process

patient[82,84] cohorts. Moreover, links to new-onset and chronic asthma in adults and to chronic obstructive pulmonary disease are of great interest but need more integrated data.[123]

3. Disease stratification that cannot be simply derived from birth cohorts alone must be addressed because patients with severe disease are insufficiently represented and severe patient cohorts need to be complemented by population-based cohorts.
4. Risk prediction of allergic diseases is required because current models lack sufficient accuracy to be of clinical use at the individual level.[102]
5. Understanding the mechanisms of asthma and allergies from early life to those in elderly patients (ie, across the lifecycle) is an important requirement for a better understanding of phenotypes and their natural history (ie, expression, progression, and remission).[103] There is a close interaction between clinical and epidemiologic research, and research on mechanisms is of crucial importance.
6. Integration of all omics techniques with clinical, lifestyle, environment, and societal factors is needed in longitudinal ways to establish underlying mechanisms of allergic comorbidities.Omics data and identified genes and pathways need to be evaluated beyond association to understand disease causation and enable clinical implications.

Moreover, new studies should include novel concepts, such as biodiversity[124] or the microbiome,[125-128] and new methods, such as next-generation sequencing, which has ignited an unprecedented pace of discovery in the biomedical sciences.[129,130]

THE FUTURE

The European Commission considers MeDALL to be a success story. A summary can be found on the Horizon 2020 Web site. It will also be present in the future "Health Success Stories Brochure," which is scheduled to be launched within the next few months.

As in other similar projects, MeDALL has involved a huge multidisciplinary effort by a large international network of partners. MeDALL has been made possible thanks to previous consortiums (eg, GA^{2}LEN, ENRIECO, and CHICOS),[15] which have paved the way for pooling and integrating single-center and multicenter birth cohorts. Each of these consortiums has experienced the challenge of sustaining the network. MeDALL includes more than 44,000 participants recruited at birth for study of the most common chronic disease (allergy). The project is sufficiently powered for the assessment of primary diseases (asthma, rhinitis, and eczema) but limited for the study of multimorbidity (in particular at the early stages, 4 years)[61] and, in turn, for the discovery of its molecular determinants. In studies of multimorbid noncommunicable diseases (eg, chronic obstructive pulmonary disease, cardiovascular diseases, and diabetes), the power of population cohorts will be sufficient to assess established diseases. However, cohorts are likely to fail in the identification of early multimorbid diseases and their causality and discovery of their biomarkers. Thus the MeDALL data are generalizable to multimorbid noncommunicable diseases across the lifecycle. Funding from the EU Structure and Cohesion Funds has been obtained by the Région Languedoc Roussillon in the MACVIA-LR frame[114,115] to maintain the database until new funding from the EU or other sources is available for other projects.

The "severe" allergic phenotype is rare in the MeDALL birth cohorts, and it is possible that patients with the most severe disease will not be found (eg, those with severe corticosteroid-dependent asthma). It is likely that the phenotypes of allergic patients in population-based cohorts differ from those seen in primary or specialist care. The "mild" allergic phenotype is common in population-based cohorts, whereas it is exceptional in clinical care.

Despite the successful experience of MeDALL to integrate birth cohorts of asthma and allergy, we do need to escalate the level of integration. A new methodology should be proposed to combine the strengths and weaknesses of the birth cohorts, possibly enriching them with patient cohorts,[82,131,132] registered

data in primary care,[133] clinical trial databases,[134] and/or Internet-based studies. In very young children, similar severe asthma phenotypes exist in patient cohorts of persistent recurrent wheezers[131] and in cohorts in the general population,[135] suggesting the possibility of pooling both types of cohorts. However, ethical and legal issues are of great importance in pooling such studies.

Developing a systems medicine approach to complex diseases is a phenomenal challenge. MeDALL was used as a model of systems medicine and has initiated a common language for the assessment of all noncommunicable diseases.[8]

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