Universitatea *Transilvania* din Braşov

HABILITATION THESIS

Adult and pediatric asthma and related co-morbidities – from research to clinical practice and purposeful education

Domain: Medicine

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CONTENT

List of abbreviations

AAAAI	American Academy of Allergy, Asthma and Clinical Immunology
ACAAI	American College of Allergy, Asthma and Clinical Immunology
ACC	allergen challenge chamber
ACS	acute coronary syndromes
ACT	asthma control test
AD	atopic dermatitis
AHA	Active and Healthy Ageing
AHR	airway hyperreactivity
AIT	allergen specific immunotherapy
ANA	antinuclear antibodies
AR	allergic rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
BMI	body mass index
CARAT	Control of Allergic Rhinitis and Asthma Test
CART	capnometry-assisted respiratory training (CART)
CDSS	clinical decision support system
COPD	chronic obstructive lung disease
CS	corticosteroids
CLD	chronic lung disease
CRD	component resolved diagnosis
CRDs	chronic respiratory diseases
CRS	chronic rhinosinusitis
DB	dysfunctional breathing
DFS70/LEDGFp75	= dense fine speckled autoantigen of 70 kD/lens epithelium-derived growth factor p75
EAACI	European Academy of Allergy and Clinical Immunology
ED	emergency department
EDN	eosinophil-derived neurotoxin
EFA	European Federations of Allergy and Airways Diseases Patients Associations
EMA	European Medical Agency
EMTU	epithelial-mesenchimal trophic unit
ENDANA	Endotypes of Non-Eosinophilic Asthma
ERS	European Respiratory Society
EU	European Union
FACS	Fluorescence-activated cell sorting
FDA	Food and Drug Administration
FEF 25-75	forced expiratory flow at 25–75% of forced vital capacity
FeNO	Fractional concentration of exhaled nitric oxide
FEV1	volume exhaled during the first second of a forced expiratory maneuver started from the level of total lung capacity
GA^{2}LEN	Global Allergy and Asthma European Network
GARD	Global Alliance Against Respiratory Diseases
GINA	Global Initiative for Asthma
GRADE	Grading of Recommendations, Assessment, Development and Evaluation.
HCPs	healthcare professionals
iCAALL	International Collaboration in Asthma, Allergy and Immunology
ICON	International consensus document elaborated by iCAALL
ICPs	integrated care pathways
ICS	inhaled corticosteroids
ICT	information and communications technology
IFN	interferon
IL	interleukin
ILC	innate lymphoid cells
INS	intranasal corticosteroids
IP-10	IFN-gamma inducible protein

IPCRG	International Primary Care Respiratory Group
ITT	intention to treat
JACI	Journal of Allergy and Clinical Immunology
LABA	long acting beta 2 agonists
LF	lung function
LTRA	leukotriene receptor antagonists
MACE	major cardiovascular events
MASK	MACVIA-ARIA Sentinel NetworK for allergic rhinitis
MAUG	Molecular Allergology User's Guide
MCP-1	monocyte chemoattractant protein
MeDALL	Mechanisms of the Development of ALLergy
MEF50	maximal expiratory flow at 50% of vital flow capacity
MEP	member of the European Parliament
MIP-1α	macrophage inflammatory protein
MP-AzeFlu	azelastine+fluticasone propionate in a single device
NCDs	non-communicable diseases
NEA	non-eosinophilic asthma
NICE	National Institute for Health and Care Excellence
NK	neurokinin
NSAID	non-steroidal anti-inflammatory drugs
PRACTALL	Practical Aspects of Allergy
R&D	Research and Development
RCT	randomised control trial
REG	Respiratory Effectiveness Group
ROC	receiver operating characteristic
RV	rhinovirus
SAR	seasonal allergic rhinitis
SCIT	subcutaneous allergen immunotherapy
SCUAD	severe chronic allergic diseases
SIAF	Swiss Institute for Allergy and Asthma Research
SLIT	sublingual allergen immunotherapy
SLOW	slow breathing and awareness training
SNPs	single nucleotide polymorphism
SP	substance P
SR	systematic review
TARC	thymus- and activation-regulated chemokine
TGF	transforming growth factor
Th	T helper cell
TNF-α	tumor necrosis factor alpha
TNSS	total nasal symptom score
TRPV	vanilloid receptor–related transient receptor potential
TSLP	Thymic stromal lymphopoietin
UK	United Kingdom
VAS	visual analogue scale
VEGF	vascular-endothelial growth factor
WAO	World Allergy Organisation
WHO	World Health Organisation

Section A

Rezumat

Teza de abilitare "Astmul la adult și la copil și co-morbidități – de la cercetare la practica clinică și la educația ce își atinge obiectivele" este chintesența activității științifice și academice în ultimii 12 ani și include realizările majore științifice, profesionale și academice, cu obiectiv al activității de cercetare astmul la adult și la copil și co-morbidități.

Provocările în managementul astmului de la cercetarea fundamentală și clinică la activitățile educationale și de asigurare a sprijinului și angajamentului social și politic sunt deopotriva dificile și provocatoare. Le-am abordat cu entuziasm, tenacitate și dedicație, cu dorința de a dezvolta și implementa noi metode de analiză și a oferi soluții novatoare care să țină pasul cu mediul științific, academic și medical în continua schimbare. Dezvoltarea mea științifică, profesională și academică în ultimii 12 ani reflectă implicarea profundă în direcțiile de management ale astmului detaliate mai jos, cu realizări remarcabile:

a. ***Programe de cercetare și dezvoltare bazate pe prevenție, mecanismele bolii și biomarkeri, abordare personalizată și descoperirea de noi tratamente curative pentru astm***

b. ***Managementul integrativ al pacientului astmatic*** *la nivel global incluzând ghiduri de noua generație aplicabile la toate nivelele și în toate țările, registre pentru astm, facilitarea accesului la diagnostic precoce și îngrijire de calitate, controlul mediului și al co-morbidităților, educația pacientului și a societății, utilizarea cost-eficientă a resurselor și modele de îngrijire centrate pe pacient*

c. ***Recunoașterea astmului ca problemă majoră de sănătate*** *de către societate și factori de decizie politică, cu focus pe povara economica uriașă, afectarea calității vieții și impactul pe dezvoltarea copilului într-un adult sănătos valoros pentru societate*

d. ***Parteneriat strategic între toate părțile implicate*** *(pacienți și familiile acestora, profesioniști în domeniul sanitar, profesori, factori de decizie politică, industria farmaceutică și de dispozitive medicale) rezultând într-o* ***abordare comunitară pentru a rezolva o problemă comunitară*** *așa cum este astmul*

Partea I *prezintă realizările științifice, profesionale și academice*

Activitatea de cercetare*, descrisă în* ***Capitolul 1****, s-a concentrat în principal pe:*

1. *descrierea și validarea fenotipurilor, endotipurilor si biomarkerilor;*
2. *tratamentul astmului ghidat de endotip și noi metode de abordare terapeutica cu potențial curativ;*
3. *controlul mediului (infecții, poluare), a stilului de viață (dieta, efort fizic regulat) și a co-morbidităților astmului (rinita alergică, obezitate, alergia alimentară);*
4. *prevenția și controlul astmului;*
5. *dezvoltarea și implementarea de noi modele de management cost-eficient al astmului.*

Am publicat 58 articole, cu 2567 citări în ISI Web of Science și 8590 citări in Google Scholar. Am un h-index de 18 în ISI Web of Science și 20 în Google Scholar și i10-index de 32.

Capitolul 1.1 *detaliază contribuția personală în domeniul fenotipurilor și endotipurilor astmului. Definirea relației fenotip-endotip-biomarkeri a constituit o temă fundamentală de cercetare din 2009 reflectată prin publicarea a 12 articole cu 268 citări în reviste cu factor de impact semnificativ, conferințe, comunicări orale și postere susținute la manifestări internațional prestigioase și de proiectul PN II pe care îl conduc ce va endotipa pacienții cu astm non-eozinofilic.*

Prin cercetarea în acest domeniu am dezvoltat următoarele concepte-cheie:

1. *Necesitatea de a lega mecanismele patogenetice fundamentale (endotip) cu fenotipul clinic al astmului (proprietățile vizibile)*
2. *Validitatea unui endotip trebuie demonstrată prin replicare longitudinală în populații diferite și prin evidențierea diferențelor revelatorii între indivizi; endotipul trebuie să reflecte biologia și evoluția naturală a bolii și să prevadă răspunsul la tratament; endotipul trebuie să fie ușor de aplicat în practica clinică curentă și să fie cost-eficient*
3. *Conceptul de endotip simplu versus complex, utilizând ca prototip pentru endotip complex astmul de tip 2. Pe baza intervențiilor țintite în astm sunt descrise 3 căi majore în astmul de tip 2 mediate de IL-5, de IL-4/IL-13 și de IgE*
4. *Conceptul de endotip variabil ca răspuns la factorii modulatori externi și interni*
5. *Efectul disociat al terapiei țintite în astm reprezentând variabilitatea de răspuns la același individ și între indivizi în funcție de parametrii măsurați*
6. *Abordarea în trepte pentru clasificarea astmului ce încorporează fenotiparea de precizie, încorporarea datelor longitudinale cum ar fi rata exacerbărilor și analiza fluctuației funcției pulmonare sau a NO în aerul expirat, bazat pe cercetarea originală a autoarei, împreună cu identificarea de noi mecanisme și biomarkeri corespondenți (clasificarea astmului bazata pe endotip) și translatarea biomarkerilor în teste de diagnostic specific pentru fiecare mecanism patogenetic*
7. *Au fost descrise ariile insuficient acoperite de cercetarea fundamentală și clinică cum ar fi astmul non tip 2 și compartimentul celulelor rezidente (unitatea trofică epitelio-mezenchimală – EMTU)*
8. *Tratamentul astmului ghidat de endotip a fost descris pentru astmul de tip 2, non-tip 2 (neutrofilic, influențat de microbiom și de EMTU) și pentru astmul asociat cu obezitatea*
9. *Legătura dintre clasificarea și managementul astmului ghidat de endotip și conceptul de medicină de precizie în astm*
10. *Importanța descrierii și validării de noi fenotipuri: epigenetice, neurofenotipuri, etc și de endotipuri evolutive ce se adresează inițierii și progresiei bolii, necesitate majoră pentru a aplica măsuri de prevenție și strategii ce modifică evoluția bolii ca parte a principiului celor 4P din medicina de precizie*

Capitolul 1.2 *se concentrează pe cercetarea asupra biomarkerilor astmului. Fiind în strânsa legătura cu fenotipurile și endotipurile aceasta linie de cercetare a autoarei a completat realizările în descrierea fenotipurilor și endotipurilor bolii și a fost apreciată de către comunitatea științifică internațională prin articole înalt citate, invitații pentru lucrări de sinteză și conferințe și comunicări orale. În 2010 autoarea publică cercetarea de pionierat asupra valorii IL-17 seric ca biomarker pentru astmul sever, urmată de demonstrația recentă a valorii IL-5 și IL-13 serice ca cei mai buni marker predictivi ai eozinofiliei sanguine. În paralel sunt dezvoltate concepte-cheie cum ar fi legătura dintre biomarker și endotip (biomarkerul poate fi marker pentru endotip sau mecanism patogenetic fundamental al acestuia), validitatea (reproductibilitate, ușurința de mă-*

surare și accesibilitatea) și relevanța (specificitatea pentru endotip și relația cu end-point-urile clinic relevante).

Capitolul 1.3 *trasează contribuția autoarei la dezvoltarea de noi terapii țintite în astm, cum ar fi quilizumab și imunoterapia specifică cu alergen (AIT). AIT are potențialul de a modifica mecanismele fundamentale ale bolii și are un efect clinic susținut. Autoarea a evaluat recent beneficiile AIT în câteva lucrări de sinteză și consensuri internaționale și este lidera grupului de lucru asupra imunoterapiei specifice cu alergen în astm ca parte a ghidurilor internaționale dezvoltate de Academia Europeana de Alergologie și Imunologie Clinică (EAACI).*

Capitolul 1.4 *descrie contribuția la implementarea principiilor medicinei de precizie în astm ca o continuare convingătoare a cercetării de pionierat în domeniul fenotipurilor, endotipurilor și biomarkerilor începută în 2009. Ca o recunoaștere a realizărilor în acest domeniu autoarea a fost invitată în 2 Paneluri de Experți prestigioase ce au reunit academiile științifice din domeniul astmului și bolilor alergice – EAACI, Societatea Europeană de Boli Respiratorii (ERS), Societatea Europeană de Rinologie și Academia Americană de Alergologie, Astm și Imunologie Clinică (AAAAI).*

Capitolul 1.5 *cuprinde contribuțiile în domeniul co-morbidităților astmului. Fiind o co-morbiditate majoră a astmului rinita alergică a constituit un focus special de cercetare, de la autor al ghidului internațional ARIA, la cercetarea în domeniul epidemiologiei, factorilor de risc și noi tratamente pentru rinita alergică evaluate în studii internaționale multicelulare, la implementarea în viața reală și la dezvoltarea de noi modele de îngrijire. Ca secretar al Secțiunii de Astm a EAACI am inițiat și condus grupul de lucru ce a evaluat impactul stilului de viață asupra astmului, evaluare consolidată în documente de consens și luări de poziție bazate pe revizuirea sistematică a dovezilor publicate. Ca membră a Panelului de Experți ce a elaborat ghidul internațional EAACI de Alergie Alimentară și Anafilaxie am adus expertiza asupra astmului în legătura bi-direcțională cu alergia alimentară. Am condus grupul de lucru ce a elaborat recomandările pentru managementul anafilaxiei în comunitate și am fost membră în grupurile de lucru asupra epidemiologiei și prevenției alergiei alimentare. Ca membră a proiectului GA²LEN-DARE finanțat de Comunitatea Europeană am evaluat dovezile pentru rolul virusurilor și bacteriilor în exacerbarea astmatică.*

Capitolul 1.6 *furnizează informații asupra contribuțiilor autoarei la dezvoltarea de noi planuri de management ale astmului și noi modele de îngrijire. Aceasta direcție de cercetare a fost abordată în capitolul "Cele mai bune intervenții pentru prevenția și controlul astmului" inclus în Global Atlas of Asthma, pentru care am fost editor șef și co-autor. Sunt detaliate cele 10 puncte cheie ce trebuie incluse într-un plan de management eficient al astmului.*

Un diagnostic mai performant al astmului este o cerință esențială al unui plan de management eficient. Cercetarea pe care am condus-o asupra diagnosticului in vivo si in vitro al bolilor alergice și al astmului a condus la crearea și conducerea unui grup de lucru în cadrul EAACI ce e evaluat rolul și standardizarea testelor de provocare în astm și boli alergice și includerea ca autor în ghidurile EAACI de diagnostic molecular.

Un standard înalt calitativ de îngrijire al astmului și bolilor alergice în rețeaua de asistență primară are o influență majoră asupra prevenției și controlului bolii, calității vieții și satisfacției pacientului. Nivelul de cunoaștere asupra astmului și bolilor alergice și accesibilitatea la control regulat sunt esențiale. Am condus grupul de lucru EAACI asupra managementului astmului și bolilor alergice în rețeaua de asistență primară ce a avut ca scop dezvoltarea și implementarea de protocoale de îngrijire înalt calitative pentru medicii de medicina de familie și generaliști ca parte integrate a planului de management al astmului și al bolilor alergice.

Prioritatea anodină acordată astmului de către programele de sănătate publică datorită întâietății acordate altor boli și lipsei de cunoaștere a bolii de către societate și de către factorii de decizie politică este o barieră apreciabilă în implementarea eficientă a planurilor de management ale astmului. Două articole recent publicate reflectă activitatea autoarei în augmentarea percepției publice asupra importanței astmului și bolilor alergice ca procedură care facilitează acordarea de resurse pentru cercetarea și pentru managementul eficient al acestor boli.

***Capitolul 2** redă dezvoltarea profesională a autoarei. O scurtă prezentare a carierei profesionale este înfățișată în **capitolul 2.1** de la absolvirea facultății și teza de doctorat Magna cum laudae la o carieră de cercetare de succes (58 articole cu 2567 citari în ISI Web of Science și 8590 citări în Google Scholar, h-index 18 în ISI Web of Science, respectiv 20 în Google Scholar și i10-index 32), membră în Paneluri de Experți pentru ghiduri și documente de consens internațional, redactor și co-autor de cărți și atlase, referent înalt apreciat și editor asociat pentru reviste cu factor de impact semnificativ, Vice-Președinte și Președinte-Ales al Academiei Europene de Alergologie și Imunologie Clinică (EAACI). Țelul principal al carierei mele a fost dezvoltarea unei combinații unice de calități, de la un medic caritabil și bun dascăl la un cercetător științific de top. Contribuția științifică a tezei de doctorat este trasată în **capitolul 2.2** împreună cu aportul în programe de cercetare naționale și internaționale ca suport și apoi continuare a cercetării doctorale. Sunt prezentate în detaliu cu obiective și rezultate programul național PN-II-RU-TE-2014-4-2303 – Endotipurile astmului non-eozinofilic al cărui conducător sunt și participarea în proiectele finanțate de Uniunea Europeana, COST (COST BM 1201: Early Origins of Chronic Lung Disease) și programul GA-2LEN - DARE (Diary Card Piloting and Validation). Autoarea a fost invitată ca expert în proiectul EARIP (European Asthma Research and Innovation Partnership) și este membră a consorțiului AIRWAYS ICPs. **Capitolul 2.3** detaliază dezvoltarea profesională și aprecierea la nivel național și internațional cu descrierea realizărilor ca membră în comitetele directoare și editoriale ce au dezvoltat ghiduri și declarații de consens internațional, activitatea editorială și de referent, calitatea de autor de cărți și monografii și de lector la manifestări internaționale prestigioase. Calitățile de conducere și manageriale sunt discutate în **capitolul 2.4**.*

***Capitolul 3** prezintă dezvoltarea academică din 1996 până în prezent, de la Preparator Universitar la Universitatea Transilvania din Brașov la Conferențiar Universitar. În timpul carierei academice ținta a fost implicarea activă a studenților în procesul de învățare și motivarea pentru deprinderea de calități de raționament decizional, în paralel cu promovarea experienței de învățare cu însușirea temeinică a noțiunilor predate. Am implementat o nouă metodă de predare bazată pe învățământ interactiv ce încorporează mai multe obiective simultan. O altă abordare inovativă a fost conceptul de cercetare științifică creativă cu scopul de a stimula percepția studenților asupra succesului academic. Studenții au fost încurajați să abordeze un comportament pliat pe obiectiv, cu respectarea rigurozității și consistenței în demersul științific, cu aderență la principiile de etică în cercetare. Caracterul proactiv, simțul responsabilității, perspicacitatea și disciplina au fost reiterate ca principii fundamentale ale cercetării științifice creative. Am asigurat un mediu propice activității de cercetare de înalta calitate pentru a dezvolta punctele forte în cercetare ale studentului odată cu pregătirea lucrării de diplomă ca deschizător de oportunități pentru carieră.*

***Partea a II-a** elaborează asupra evoluției viitoare și a planurilor de dezvoltare ulterioare a carierei științifice, profesionale și academice.*

Realizările în carieră în ultima decadă mă poziționează favorabil în translatarea inovațiilor științifice de la cercetarea fundamentală la practica clinică oferind în paralel un program de instrucție și educație în cercetarea medicală de înalt nivel.

Pornind de la rezultatele proiectului PN-II-RU-TE-2014-4-2303 Endotipurile Astmului Non-eozinofilic (ENDANA) planurile viitoare de endotipare ale astmului non-eozinofilic vizează valida-

rea subendotipurilor prin intervenție terapeutică țintită și evaluare longitudinală a entităților descrise. Aceeași abordare este plănuită și pentru subendotipurile astmului de tip 2 folosind abordarea imparțială oferită de analiza topologică a datelor, analiza Bayeziană a rețelei generate și evaluarea longitudinală. Extinderea ariei de cercetare către endotipurile astmului pediatric este de asemenea anticipată. Beneficiul așteptat este translatarea cercetării fundamentale a endotipurilor în practica clinică curentă cu protocoale de decizie clinică ce permit selectarea pacientului ce răspunde cel mai bine la o intervenție țintită și cu predicția exactă a evoluției bolii pentru fiecare individ.

În paralel activitatea de cercetare va include biomarkeri și endotipuri pentru imunoterapia specifică cu alergen, elaborarea și implementarea de ghiduri și documente de consens internațional, programul Mobile Health/Allergy 2.0 și 3.0 și dezvoltarea de protocoale de intervenție educațională a comunității pentru managementul astmului.

Avem o datorie morală de a promova standarde înalte pentru educația medicală în facultate și ulterior. Voi continua să ofer studenților și profesioniștilor din domeniul sanitar instruire bazată pe obiective care să reflecte dinamica modificărilor în practica medicală, în nevoile pacienților și în sistemul de sănătate precum și modificările în perspectivele generale ale societății asupra modului în care profesioniștii în domeniul sanitar își exercită meseria.

În calitatea de clinician, cercetător și profesor voi continua să dezvolt un portofoliu variat de competențe care să cuprindă informații clinice de ultimă ora, comunicarea eficientă a rezultatelor cercetării, contextul multidisciplinar al îngrijirii pacientului, principiile de etică, calitățile de comunicare, management și comportamentale, lucrul în echipa, tehnologia informației, criteriile de audit, etc, cu scopul de a asigura rezultate mai bune și creșterea nivelului de satisfacție al pacienților, studenților și colegilor.

În Iunie 2017 voi deveni Președinte al Academiei Europene de Alergologie și Imunologie Clinică cu un mandat de 2 ani. În paralel cu recunoașterea internațională intenționez să promovez cooperarea dintre societățile internaționale și naționale ca eșafod pentru adaptarea locală și implementarea ghidurilor și a rezultatelor cercetării de top, a practicilor cele mai competitive de îngrijire a pacienților, a politicilor de sănătate eficiente și a acțiunilor de conștientizare a astmului ca problemă majoră de sănătate.

În următorii 4 ani este planificată dezvoltarea unui nou portofoliu educațional pentru student și tinerii profesioniști în domeniul sanitar ce facilitează deopotriva dezvoltarea profesională și a carierei ce îmbină practica clinică cu cercetarea. Voi introduce în practica academică conceptul de educație ce își atinge obiectivele bazat pe experiența directă din practică și beneficiul social. Vor fi dezvoltate noi metode de predare ce facilitează învățământul interactiv cum ar fi tutoriale pentru studenții la master și la scoală doctorală, programe de învățare multidisciplinară, brainstorming interactiv, buzz-sessions, Think-Pair share, incident process etc. Fiind certificată pentru instruirea didactică în limba engleză voi susține crearea de programe de studii în limba engleză pentru studenții străini în cadrul Facultății de Medicină Brașov.

Întemeierea sentimentului de apartenență la comunitate a studenților și profesorilor cu augmentarea participării în procesul de modelare al mediului academic și al promovării culturii organizaționale constituie de asemenea o prioritate.

Atât coordonarea de lucrări de doctorat cât și obținerea titlului de profesor universitar sunt luate în considerare pentru a progresa în activitatea academică în următorii 2 ani. Prin coordonarea de teze de doctorat voi sprijini activitatea de cercetare a tinerilor doctori și mediatizarea rezultatelor cercetării doctorale în mediul științific național și internațional. Cercetătorii debutanți vor fi sprijiniți în activitatea de pregătire a tezei doctorale prin proiecte de cooperare dezvoltate împreună cu colegii de la discipline înrudite.

Section B

Scientific and professional achievements and the evolution and development plans for career development

B-i

SCIENTIFIC AND PROFESSIONAL ACHIEVEMENTS

The habilitation thesis "Adult and pediatric asthma and related co-morbidities – from research to clinical practice and purposeful education" is the epitome of the academic activity in the last 12 years and encompasses the major scientific, professional and academic achievements, with the main research focus on adult and pediatric asthma and its co-morbidities.

This thesis aims to provide a valuable window of information on adult and pediatric asthma and co-morbidities highlighting the innovative and valuable contribution of the author in the field.

The challenges in asthma research, management and education are both difficult and interesting. I tackled them with enthusiasm, tenacity, and dedication to develop new methods of analysis and provide new solutions to keep up with the ever-changing threats. In this new age of global interconnectivity and interdependence, it is necessary to provide professionals, students, patients, policy makers and healthcare systems with state-of-the art knowledge on the frontiers in adult and pediatric asthma research while encouraging efficient management programmes and high level education. We must ensure that right people can access the right information at the right time.

Research is academia's favourite source of intelligence on funding opportunities and research policy. My research activity for my PhD Thesis in Internal Medicine "3 Years Evolution in Patients with Acute Coronary Syndromes and Chlamydia Pneumoniae Infection", appreciated "Magna cum laude", where I conveyed innovative aspects regarding the immune-inflammatory mechanisns in atherosclerosis, combined with the research and continuos education opportunities offered by the European Academy of Allergy and Clinical Immunology (EAACI) propelled my research and academic development in the field of immunology of allergic diseases. As any good research starts with the right question my observations were that there are several unmet needs regarding adult and pediatric asthma from bench (endotypes, biomarkers), to translational (precision medicine) and bedside management (lifestyle, healthcare system transformation, resource utilisation).

As a member of the medical profession, a senior specialist in Allergy and Clinical Immunology and a member of the Academia I have proved to posses special knowledge and skills in a widely recognised body of learning derived from research, education and training at a high level, and I was recognised by the my colleagues and reference bodies as such. As a professional I commited to competence, integrity and morality, altruism, and the promotion of the public good within my expert domain and I applied my knowledge and skills in the interest of my patients and my students.

Alongside cutting-edge scientific advancements I have also promoted educational programmes ensuring translation of knowledge to new generations of medical students and researchers. Driving standards in asthma and allergy education and raising awareness of these disease amongst all stakeholders is key to reach a better health status for asthma patients.

My entire career is dedicated to creation of new knowledge and/or the use of existing knowledge in a new and creative way so as to generate new concepts, methodologies and understandings to serve the wider purpose of translating asthma research into better clinical management and purposeful education.

B-i

Scientific and professional achievements

Main research area - development and results: Scientific achievements in adult and pediatric asthma and related co-morbidities

Chapter 1

FOREWORD

Asthma represents a major health problem, affecting the lives of 300 million people around the globe and with increasing prevalence in developing countries, with an overall projected increase in prevalence to 400 millions in the upcoming three decades (1, 2, 3, 4, 5, 6, 7). In European Union (EU) 30 millions citizens are diagnosed with asthma (10% of the EU population), the majority children and adults beyond 45 years old (8). Asthma prevalence is increasing especially for patients under 15 years old affecting up to 25% of the pedia-tric population in some European countries (1 in four children is asthmatic). Asthma is the most frequent chronic disease of childhood and is the leading cause for hospitalization and emergency department (ED) consultations for the pediatric population worldwide. Asthma imposes a significant burden to governments and to society in general due to significant direct and indirect costs (72.2 billion Euro annual), with major impact on the national macro-economy. Uncontrolled asthma with frequent exacerbations, hospitalisations together with medications costs are the leading determinants of asthma direct costs. 75% of the asthma economic burden is however due to indirect costs resulting from absenteeism and decreased productivity at the workplace (9, 10, 11, 12, 13).

There are significant unmet needs in the management of asthma patients as a consequence of insufficient support for basic, translational and clinical research in asthma and for the implementation of cost-efficient models for asthma management.

An efficient approach to tackle the "asthma epidemics" needs concerted efforts in the following directions:

1. **Research and development programmes focusing on prevention, disease mechanisms and biomarkers, personalised approaches and development of new treatments curing the disease.** The synergy between research centers and national/ regional and international research and development (R&D) programmes is of paramount importance (14, 15) together with prioritisation of R&D programmes targeting asthma prevention and cure and cost-effective management. Allergy and asthma are closely linked, with up to 90% cases of asthmatic children and 50% of asthmatic adults having the allergic asthma phenotype, thus a rational approach should include R&D programmes targeting both allergy and asthma.
2. **Integrative management of asthma patients** at a global level including next generation guidelines largely applicable at all levels (primary, secondary and tertiary care and self-management of the disease) and in any country, registries for asthma, improved access to early diagnosis and quality treatment, environment and co-morbidities control, patient and general public education, cost-efficient use of resources and patient-centered care models
3. **Recognition of asthma as a major health problem** by the society, governments, and policy makers (16) with emphasis on the huge economic burden, decreased quality of life and impact of the child development into a healthy adult valuable for the society (17)
4. **Strategic partnership between all stakeholders** (patients and caregivers, doctors and allied health, pharmacists, teachers, governments and policy makers, academia and pharmaceutical/devices industry) resulting in a **community approach to a community problem** targeting asthma. Such a model implemented in Finland ("Zero Tolerance for asthma") lead to a decrease with 86% of hospitalisations for asthma, no asthma deaths and decrease with 50% of the total asthma costs (18).

My research, professional and academic development in the last 12 years reflects the profound implication in the four pediatric and adult asthma management directions outlined above, with notable achievements

Research activity focused mainly on:

1. description and validation of pediatric and adults asthma phenotypes, endotypes and biomarkers;
2. endotype driven asthma treatment and new potential curative approaches;
3. tackling environment (infections, pollution), lifestyle (diet, exercise) and asthma co-morbidities (allergic rhinitis, obesity, food allergy);
4. asthma prevention and control;
5. development and implementation of new models for cost-efficient disease management.

Professional and academic development with international recognition in pediatric and adult asthma research and management lead to:

A. Leadership of national research programmes (PN-II-RU-TE-2014-4-2303 – Endotypes of Non-Eosinophilic Asthma - ENDANA) and partnerships in COST actions (COST BM 1201: Early Origins of Chronic Lung Disease)

B. Membership in steering committees and editorial boards for the development of international guidelines, international consensuses, books and monographs

- ARIA (Allergic Rhinitis and its Impact on Asthma) (19,20),
- MASK (MACVIA-ARIA Sentinel NetworK for allergic rhinitis) (21),
- Integrated care pathways for airway diseases (AIRWAYS-ICPs) (22), Working Package 10 of the European Innovation Partnership on Active and Healthy Ageing, Action Plan B3; Mechanisms of the Development of Allergy
- European Asthma Research and Innovation Partnership (EARIP), Working Package 4
- EAACI International Guidelines for Clinical Practice for Allergen Specific Immunotherapy (AIT) – Task Force Chair for AIT in asthma
- Coordinating Editor for EAACI Global Atlas of Asthma (2013) (23), Global Atlas of Allergy (2014) (24), Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis (2015) (25)
- Coordinating Editor for Implementing Precision Medicine In Best Practices Of Chronic Airway Disease published by Elsevier in November 2017
- Member of the expert panel of the iCAALL collaboration. Four of the most influential allergy/immunology professional organizations have joined forces to launch the International Collaboration in Asthma, Allergy and Immunology (iCAALL). Participating in iCAALL are the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma & Immunology (ACAAI), the European Academy of Allergy and Clinical Immunology (EAACI) and the World Allergy Organization (WAO). iCAALL is designed to collect and disseminate consensus-driven information about allergies, asthma and immunological diseases. Communicating this knowledge can positively impact diagnosis and treatment, as well as cost containment and policy decisions. A major focus of this initiative is the production of a series of International Consensus (ICON) reports. These documents offer general recommendations based on global challenges in caring for patients with allergic and immunologic diseases.
- Member of the expert panel of the PRACTALL collaboration. The PRACTALL program is a common initiative of EAACI and the AAAAI. It focuses on practical aspects of allergy to deliver updated and evidence based recommendations for clinicians

1.1. ASTHMA PHENOTYPES AND ENDOTYPES

A classification of asthma control and severity based on symptoms, lung function, exacerbations, limitation of physical activity and need for rescue medications guides asthma treatment today. This approach has significantly reduced asthma mortality and morbidity, however, all over the world; the disease continues to increase both in prevalence and severity. Current treatment has little or no effect on the natural history of asthma, and certainly does not cure the disease. The "one size fits all" approach to therapy and drug development has dominated the asthma field. With this model, epidemiologic and genetic research and development of effective targeted treatments has met limited success.

Discoveries from basic science research in the last decade have brought significant progress in knowledge of pathophysiologic processes of allergic diseases, with a compelling impact on understanding of the natural history, risk prediction, treatment selection or mechanism-specific prevention strategies. The view of the pathophysiology of asthma and allergic diseases developed from a mechanistic approach, with a focus on symptoms and organ function, to the recognition of a complex network of immunological pathways. Several subtypes of inflammation and complex immune regulatory networks and the reasons for their failure are now described, that open the way for the development of new diagnostic tools and innovative targeted-treatments.

The disease phenotype (26), describes observable and/or measurable visible properties of the disease without any implication of a mechanism (27), which is defined by the disease **endotype** (28, 29). The understanding of disease endotypes based on pathophysiological principles and their validation across clinically meaningful outcomes in asthma (exacerbations, lung function) is crucial for the success of precision medicine as a new approach to patient management, with the final aim to improve efficacy and safety for the patients.

A relevant endotype should reflect the corresponding phenotype via **biomarkers**. A biomarker measured and evaluated to examine any biological or pathogenic processes, including response to a therapeutic intervention (30, 31). The relation phenotype – endotype - biomarker is crucial for defining and validating the **precision medicine** and **precision health** approach for allergy and asthma (33, 34, 35).

Defining the relation phenotype – endotype - biomarkers has a been a constant research theme since 2009 and is reflected by original research and invited review papers in journals with high impact factor, by lectures, oral communications and abstracts presented at top level international meetings and by the ongoing PN II research project aiming to endotype patients with non-eosinophilic asthma.

In 2009 I published as first author the paper "***Antinuclear antibodies in asthma patients - a special asthma phenotype?***" where the value as independent risk factor of antinuclear antibodies (ANA) for severe exacerbations, lung function decline and high inhaled corticosteroid (ICS) doses to control asthma is proved in a cohort of 100 adults with asthma followed for 1 year (36). The paper is the continuation of a cross-sectional trial from 2007 communicated at the American Academy of Allergy, Asthma and Immunology (AAAAI) annual meeting evaluating adults with severe asthma identifying ANA as risk factors for asthma severity with the same impact as "traditional" risk factors for asthma severity such as blood and sputum eosinophils or association with obesity and chronic rhinosinusitis (CRS) (37). The 2009 prospective study identified ANA in 22% asthma patients with no signs of clinical or biological activity biologica – "silent" ANA. This study is one a few evaluating the relation between autoimmunity and asthma and is valuable by highlighting an unique

risk factor for severe asthma (silent ANA), less cited in the literature, and validated in a prospective observation. The confirmation of these published data came in the recent years when studies confirm the association between asthma and dense fine speckled ANA with specificity for the DFS70/LEDGFp 75 autoantigen. The emerging role of DFS70/ LEDGFp75 as a stress protein relevant to human acquired immunodeficiency syndrome, cancer, and inflammation points to the possibility that these autoantibodies could be sensors of cellular stress and inflammation associated with environmental factors in asthma (38). A unique new phenotype is thus described for severe asthma that might prove more responsive to immune modulation instead of classic anti-inflammatory treatment with ICS. The silent character of ANA points out to the need of screening for ANA in adults with severe asthma in order to identify this particular phenotype.

The research on asthma phenotypes continues with the evaluation of the impact of asthma co-morbidities, seasonal allergic rhinitis and dysfunctional breathing.

The paper "***Risk factors and asthma phenotypes in children and adults with seasonal allergic rhinitis***" published in 2010 evaluates the relation between asthma risk factors and phenotypes in adults and children with seasonal allergic rhinitis (SAR) (39). Asthma was diagnosed in 66.7 children and in 69.5% adults with SAR. Lack of AIT preceding asthma diagnosis was an independent risk factor both for children and adults, observation confirmed by several other prospective and retrospective trials (40, 41). This is the first study describing asthma phenotypes in adults and in children with SAR according to the associated risk factors for asthma: in children breastfeeding < 2 months and severe rhinitis and male, polysensitized and severe rhinitis; in adults polysensitization and severe rhinitis or male, exposure to pets and severe rhinitis or high total serum IgE and polysensitization. The study confirmed well known risk factors and phenotypic traits such lack of AIT, mixed sensitization (seasonal and perennial allergens), breastfeeding < 2 months, male sex in children, polysenzitization, and severe rhinitis and highlighted new risk factors and phenotypic traits for asthma in adults with SAR, such male sex and exposure to pets.

Abnormal breathing patterns such as dysfunctional breathing (DB) may be associated with asthma and impair asthma control and quality of life. Correct and prompt identification of abnormal breathing patterns in asthma offers the opportunity for treatment beyond pharmacology and for reducing unnecessary medication to control asthma symptoms. In the paper "***Dysfunctional breathing phenotype in adults with asthma - incidence and risk factors***" published in 2012 (42) we showed that the incidence of DB varies according to the test used (Nijmegen questionnaire versus progressive exercise testing diagnosing inappropriate ventilation in comparison with the baseline breathing pattern and in relation to objective parameters such as work load and lung function) highlighting the importance of use of objective methods to properly diagnose DB since some of the asthma symptoms such as breathlessness, chest pain, chest constriction and accelerated breathing overlap with DB symptoms as depicted by Nijmegen questionnaire. This study was the first to evaluate the relation between DB and other asthma co-morbidities. Except psychopathology, other asthma co-morbidities evaluated (obesity, moderate/severe rhinitis, gastro-esophageal reflux, atopy, high blood pressure) did not increase the risk for DB in the multiple regression analysis. However, there was increased incidence of moderate/ severe rhinitis and gastro-esophageal reflux in the DB group, suggesting a careful examination for DB in patients with asthma associated with these two co-morbidities. The increased incidence of moderate/severe rhinitis in asthmatic DB patients is not surprising considering the consequences of oral breathing and the link between rhinitis and asthma, which might involve common abnormal neural pathways. The major asthma co-morbidity increasing the risk for DB in asthma patients are the anxiety disorders, especially panic disorders and specific phobia of blood, injections, and injuries. Both panic disorders and specific phobias were related to asthma (43), and hyperventilation may provide an interesting link with asthma, based on sustained levels of hypocapnia (44, 45). In patients with

panic disorders raising CO2 levels by therapeutic capnometry proved superior to cognitive-behavior therapy (44). The method is not yet validated for asthma, since it was tested only in a small trial (46). Recently a larger clinical trial evaluated the benefits of therapeutic capnometry in 120 asthma patients randomly assigned to capnometry-assisted respiratory training (CART) for raising Pco2 or slow breathing and awareness training (SLOW) for slowing respiratory rate. Both interventions provided significant, sustained, and clinically meaningful improvements in asthma control however CART was associated with greater benefits on lung function and long-term symptom control (47). We also examined the relation between phenotypic traits of asthma and DB. In the multiple regression analysis lack of asthma control and the frequent exacerbator phenotype were independent predictors for DB. The association of the frequent exacerbator phenotype with DB in asthma is an interesting observation of this study, since we described this phenotype as an asthmatic with at least 3 severe exacerbations requiring systemic steroids and/or ER visit and/or hospitalization for asthma in the previous 12 months. The presence of DB should be carefully diagnosed in these patients in order to avoid over-treatment and to allow patient to benefit from non-pharmacological interventions. In the DB group there was significant increased incidence of severe asthma and of brittle asthma. These two asthma phenotypes could also benefit from non-pharmacological treatment and possible prevention of asthma attacks if DB is correctly and promptly identified. Since fast lung function decline was encountered more frequently in the DB group, the condition might prove important for evaluating asthma future risk. Another original aspect of this study was the evaluation of the link between DB and asthma medication. Asthma medication (long acting beta 2 agonists – LABA or leucotriene receptor antagonists - LTRA) or lack of ICS in the past six months, as a measure of under treatment of steroid-responsive asthmatic inflammation associated no increased risk for DB in the multiple regression analysis. Since in the non-DB group there was an increased usage of LTRA as a first line controller exploring the leukotriene pathway in the pathogenesis of hyperventilation syndrome might prove of interest.

The quest to describe severe or difficult asthma phenotypes continued with another paper published in 2012, "***Predictive value of lung function trend and FeNO for difficult asthma in children***" (48). Unlike in adults, little is known about risk factors or predictors of difficult asthma in children (49, 50). My hypothesis was that the combined use of clinical features with measurements of lung function and airway inflammation would provide the best characterization of the difficult pediatric asthma phenotype. However asthma is a dynamic disease, hence the fluctuating nature of the parameters used to describe asthma phenotypes. Fluctuation analysis is a research tool validated for use in other pathologies or biological processes with a fluctuating character (51, 52). Recent reports have highlighted the value of peak expiratory flow fluctuation analysis in characterizing asthma control during treatment with bronchodilators (53) and in predicting response to asthma treatment (54). At that moment no data were available on the relationship between lung function fluctuation and asthma severity, and furthermore, lung function fluctuation has not been evaluated yet in the pediatric population. In addition persistent airflow limitation is prevalent in adults with severe or difficult-to-treat asthma, with rates of 60% reported in the TENOR study (55) and of 49% in the European cohort (56). Thus, we considered a cumulative end-point merging lung function fluctuation and persistent airflow limitation. Exhaled NO, measured as fractional concentration of exhaled nitric oxide (FeNO), is a good surrogate for bronchial eosinophilic inflammation and has been used to identify steroid-responsive patients, adjust ICS doses, and predict relapse during medication tapering (57). Exhaled NO levels might predict changes in lung function and the risk of future asthma in wheezy infants and toddlers (58). We considered persistent high FeNO as a measure of asthma severity consistent with the observation that increased FeNO predicts accelerated lung function decline in adults with severe asthma (59) and set the cut-off at 45 ppb in line with a previous study showing that a cutoff of 46 ppb has the best positive

predictive value for asthma diagnosis (60). Children with difficult had a significantly increased frequency of severe rhinitis, psychopathology, unfavorable lung function trend, and persistent high FeNO, however in the logistic regression analysis, only obesity, severe rhinitis, and persistently high FeNO were independent risk factors for difficult asthma. Unfavorable lung function trend (high fluctuation and/or persistent airflow limitation) did not reach statistical significance, not surprising as, unlike in adults, spirometry is a poor predictor of severity in children. However, the prevalence of patients with high fluctuation was significantly higher in children with difficult to treat asthma. There are several innovative aspects of this study such as the use of the multidimensional approach to characterise the phenotype, evaluation of lung function and inflammation as dynamic traits using time trends and thus responding to the fluctuating nature of asthma and evaluating several domains of asthma severity: level of current prescribed treatment, asthma control over the preceding 3 to 4 months, and burden of asthma exacerbations. Phenotypes identified by a multidimensional approach combining clinical features with pathophysiologic features (lung function and inflammation) are more complex, but arguably more objective. In addition the multidimensional approach allows validation by replication across different populations and may contribute to a more reliable definition of asthma phenotypes.

By 2012 the experience accumulated from the original research on asthma phenotypes was summarized in the review paper "***Untangling asthma phenotypes and endotypes***" published as first author in 2012 (61), which reached **176 citations until today** by other papers published in high rank journals. Current concepts in asthma phenotyping are extensively explained, with a special focus on inflammometry, especially with the use of sputum cytology and on novel statistical and mathematical methods such as cluster or factor analysis, principal-component techniques and machine-learning used to phenotype asthma. The transition from phenotype to endotype is then explained, introducing two innovative concepts:

1. The necessity to link the key pathogenic mechanism with a clinical phenotype of asthma. An acceptable starting point to define endotypes would be the identification of corresponding molecular biomarkers for such a pathogenetic mechanism. Several asthma endotypes might be identified following this approach (Table 1)
2. The validity of the endotype demonstrated by:
   a) longitudinal replication across different populations should predict meaningful differences among individuals;
   b) observations implicated in such endotypes should reflect the diseases' biology, natural history and predict response to treatment;
   c) endotypes should be easily applicable and useful in daily clinical practice and cost-efficient.

Endotypes are detailed for major asthma phenotypes such as allergic asthma, intrinsic asthma, non-eosinophilic asthma, aspirin-intolerant asthma and extensive remodeling asthma. A special subchapter is dedicated to asthma endotypes and response to beta-2 agonists, inhaled steroids, antibiotics/antioxidants and targeted treatment. Advantages of endotyping asthma are also nicely explained (Figure 1).

Part of the research on asthma phenotypes and endotypes I focused on the use of inflammometry evaluated via induced sputum. Starting with 2010 I started the collaboration for induced sputum immunologic examination with the Swiss Institute of Allergy and Asthma Research (SIAF) in Davos, where I was invited several times as visiting professor. Measurement of cytokines in induced sputum proved very difficult due to the combined effect of sputum composition (mucus, proteases) and sputum processing (DTT addition, filtration, and dilution). Thus, together with the SIAF team, we perfected a method using dialysis plus ultrafiltration (Figure 2), which improves significantly the rate of cytokine detection in induced sputum. The pilot small group results were communicated at the European Respiratory Society International Congress in Barcelona 2013, both the methodology (62) and

Table 1

Linking essential pathogenic mechanisms with phenotypes of asthma. *(Adapted from Agache I, et al. Untangling asthma phenotypes and endotypes. Allergy. 2012;67(7):835-46)*

Phenotype	Endotype
Allergic asthma	Eosinophilic
	Th2 driven inflammation
	Steroid-responsive
	Anti IgE responsive
	Anti IL-5 responsive
	Anti IL-4/IL-13 responsive
Intrinsic asthma	Eosinophilic
	Neutrophilic
	Associated with autoantibodies/ superantigens
	Steroid-responsive
	Steroid-resistant
Neutrophilic asthma	Activation of innate immune response
	HDAC2 abnormal recruitment
	Increased neutrophil survival
	Steroid-resistant
	Responsive to antioxidants/antibiotics
	Anti TNF-a responsive
	Responsive to HDAC regulators (theophylline)
Aspirin intolerant asthma	Eosinophilic
	Alteration in the eicosanoid metabolism/ sensitivity to leukotrienes C4, D4, and E4
	Steroid-responsive
	LTRA-responsive
Extensive remodeling asthma	Lack of inflammation/extensive remodeling
	Abnormal EMTU activation
	Abnormalities of ASM
	Defective repair mechanisms
	Steroid-resistant
	ASM-targeted treatment responsive
	MMP-targeted treatment responsive
	Antiangiogenic responsive

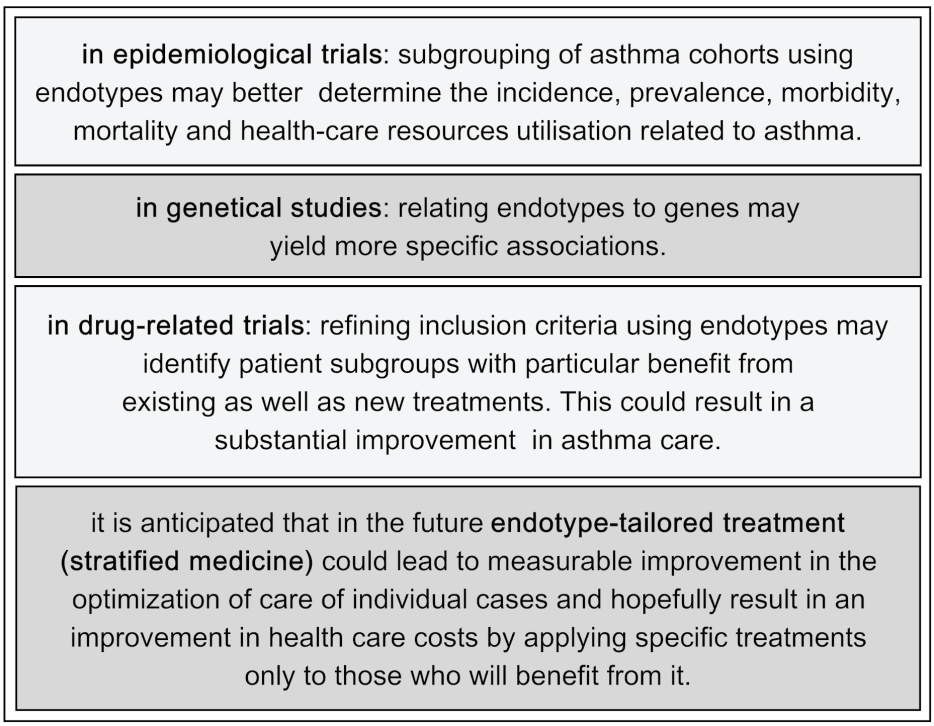

Figure 1

Potential advantage of asthma endotyping. *(reproduced from Agache I, et al. Untangling asthma phenotypes and endotypes. Allergy. 2012;67(7):835-46)*

the endotyping data (63). In 24 adult asthma patients we demonstrated that sputum and serum cytokine levels correlated, except for IL-9, IL-10 and IL-12. We also reported interesting correlations for sputum cytokines with asthma visible properties: IL-17, eotaxin and RANTES with smoker status; IL-13 and MCP-1 with atopic asthma; IL-5 and IL-10 with asthma associated with CRS; IL-6 with fast lung function decline; IL-10 with corticosteroid (CS) responsive asthma; IL-2 with brittle asthma, VEGF with near-fatal asthma; and IP-10 with the frequent exacerbator phenotype (63). The endotyping data were presented as an oral communication and the paper was highly appreciated and raised a lot of discussion and positive comments. The results were validated in a larger study group of 64 patients and the paper is in preparation.

In 2013 a new invited review (64) published in in Current Opinion on Allergy and Clinical Immunology "***From phenotypes to endotypes to asthma treatment***" an innovative concept is introduced regarding the response to a targeted intervention in asthma which may vary between individuals or for the same individual in relation to the outcome measures - the so called dissociated effect (Figure 3). This article is a critical review of the new approaches to classify asthma together with the

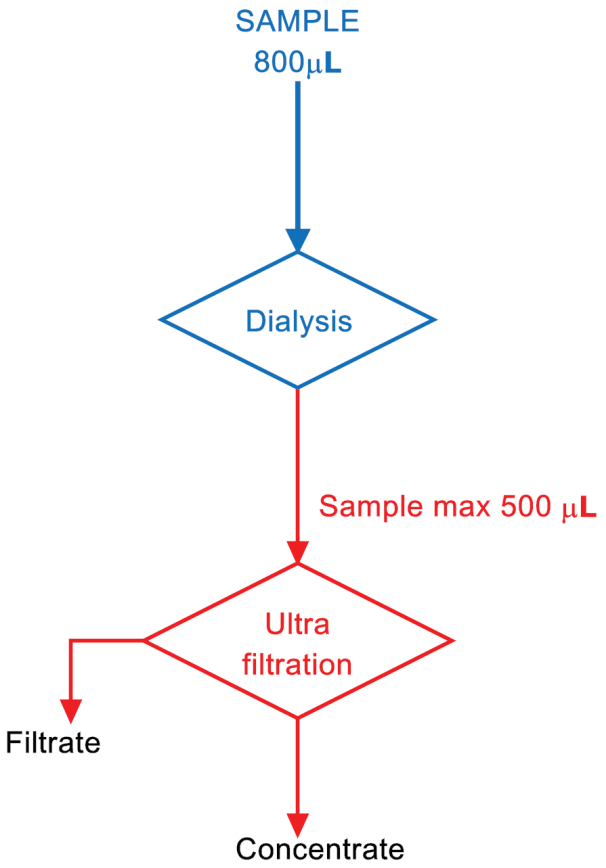

Figure 2

The dialysis-ultrafiltration method patented together with the SIAF asthma research team for measurement of sputum cytokines. *(reproduced from Agache C et al. European Respiratory International Congress, Barcelona, 2013)*

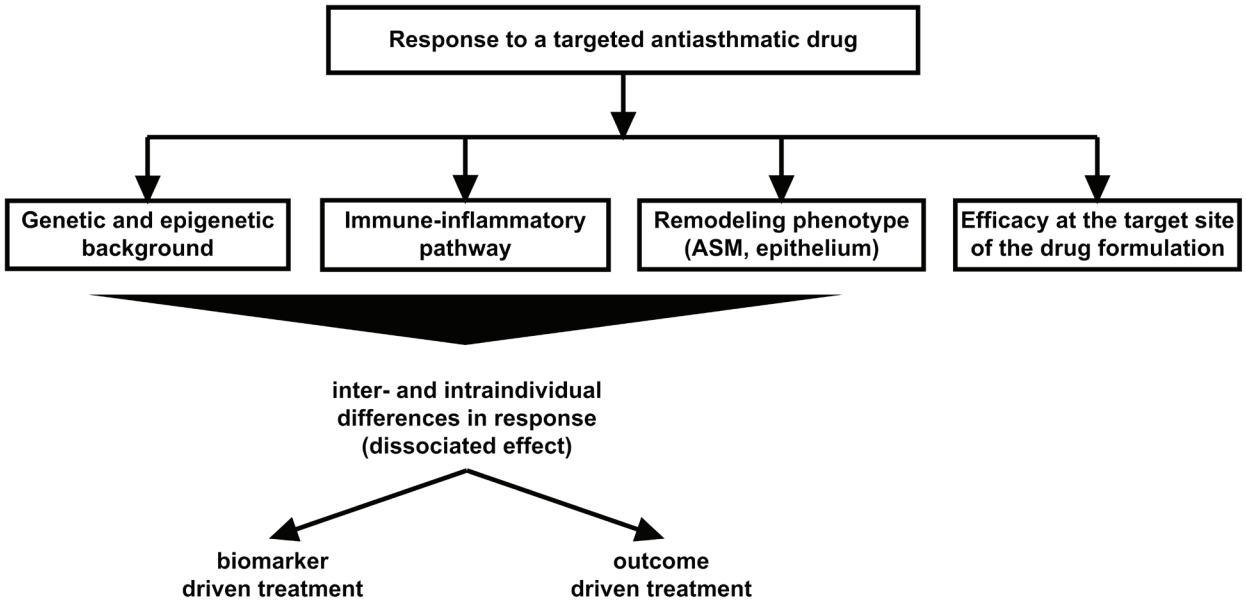

Figure 3

Main determinants influencing the response to a targeted intervention in asthma. Endotype-driven treatment of asthma has improved the response rate to targeted treatment but did not solve completely the dissociated effect of the intervention nor the variability in response due to drug efficacy at target site *(reproduced from Agache IO. From phenotypes to endotypes to asthma treatment. Curr Opin Allergy Clin Immunol. 2013;13(3):249-56)*

emerging endotype-driven therapeutic strategies. Several major unmet needs in asthma endotyping such as profiling the Th2 low and the resident cell compartment of asthma (the epithelial-mesenchimal trophic unit - EMTU) are highlighted and will be tackled in future papers of the author. New phenotypes, such as epigenetic phenotypes, asthmatic granulomatosis, or neurophenotypes are described. This review was **cited 30 times** since its publication including citations in articles from Nature Reviews Immunology, The Lancet Respiratory Medicine, Journal of Allergy and Clinical Immunology (JACI), Clinical and Experimental Allergy and Journal of Experimental Immunology.

A stepwise approach to classify asthma is proposed (Figure 4) incorporating precision (or deep) phenotyping, longitudinal data such as exacerbation rate, fluctuation analysis of lung function or exhaled NO, based on the author's previous original research (48) together with identification of novel causal pathways with corresponding biomarkers (endotype-driven asthma classification) and translation of biomarkers into pathways-specific diagnostic tests, which will represent the area of research of the author from 2013 onwards. Deep phenotyping can be defined as the precise and comprehensive analysis of phenotypic abnormalities based on stratification into disease subclasses with a common biological basis. Use of computational resources to capture, store, and exchange phenotypic data followed by sophisticated algorithms to integrate it with genomic variation, omics profiles, and other clinical information is essential (65) and will open the gate for precision medicine in asthma. In addition rapid advances in health information technology (HIT) have created unprecedented opportunities to collect, analyze and learn from vast amounts of "real-world" data that currently are locked away in unconnected servers and file cabinets. While clinical trials will likely remain the gold standard of evidence, crowdsourcing backed up by HIT advances promises to overcome the current limitations of observational data. By analyzing an immense body of observational data in real time physicians and researchers can identify trends and associations between myriad variables and generate new hypotheses and draw immediate practice-changing conclusions (66, 67). Advanced HIT tools, such as rapid learning systems, will structure the huge body of unbiased data by

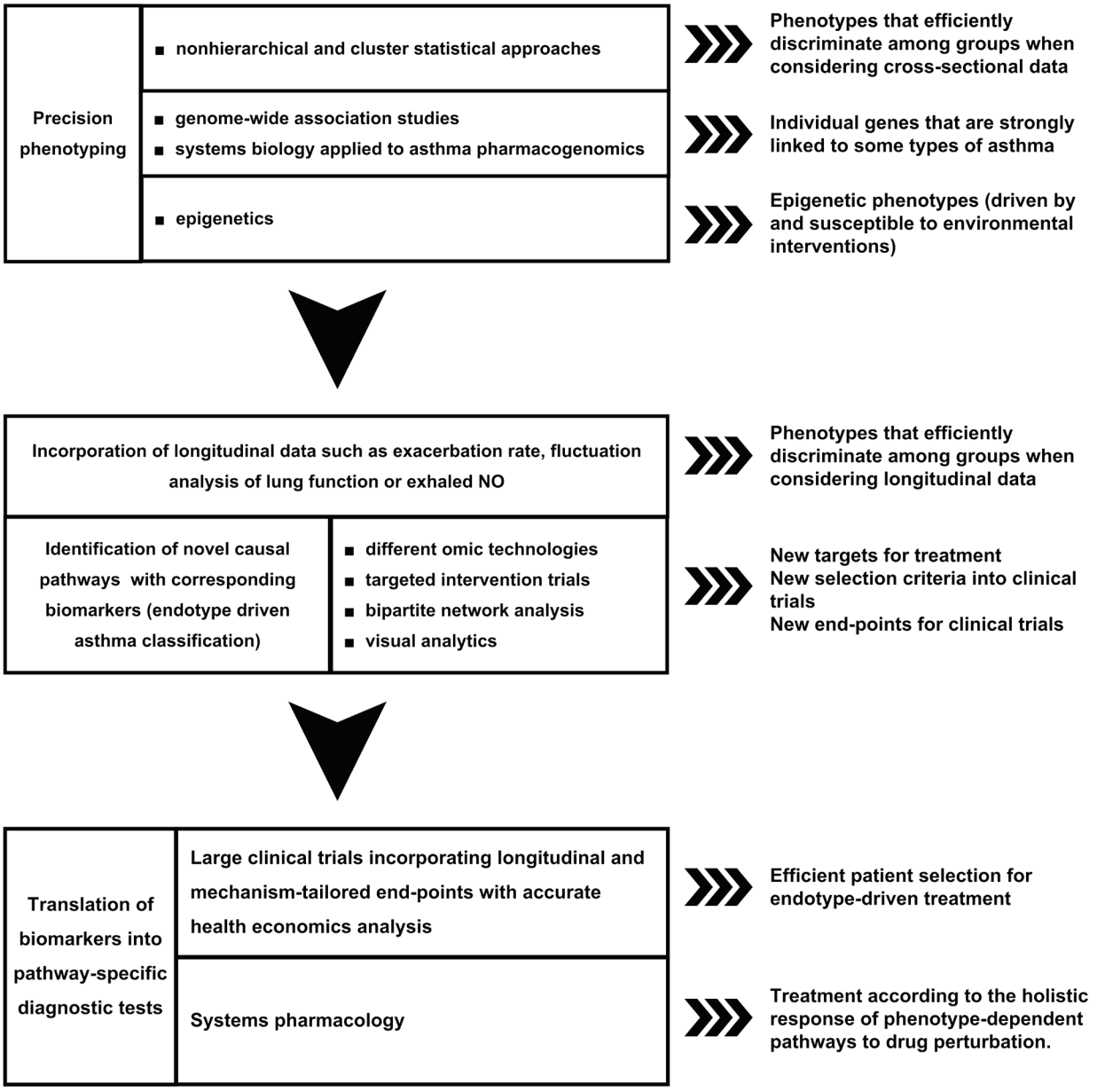

Figure 4

Step-wise approach to classify asthma. Several new approaches for classifying asthma are available, from precision and deep phenotyping to identification of novel causal pathways and translation of biomarkers into pathway-specific diagnostic tests. *(reproduced from Agache IO. From phenotypes to endotypes to asthma treatment. Curr Opin Allergy Clin Immunol. 2013;13(3):249-56)*

normalising similar information even if provided in different formats, correcting for the wide variation in data standards. Then data will be run through correlation and trend analysis tools, revealing connections that can be used to draw statistically valid conclusions and develop robust hypotheses (67, 68).

The step-wise approach is further developed into the concept of *endotype driven treatment of asthma* in the next review published in 2014 (69). The PRACTALL consensus report proposed several parameters for defining an asthma endotype: consistent clinical characteristics, biomarkers, lung physiology, genetic background, histopathology, epidemiology, and treatment response (29). Several endotypes are proposed for asthma, however none is validated across all the above-enumerated criteria. Translation of biomarkers into pathway-specific diagnostic tests is essential and should guide the design of future large clinical trials, incorporating both longitudinal and

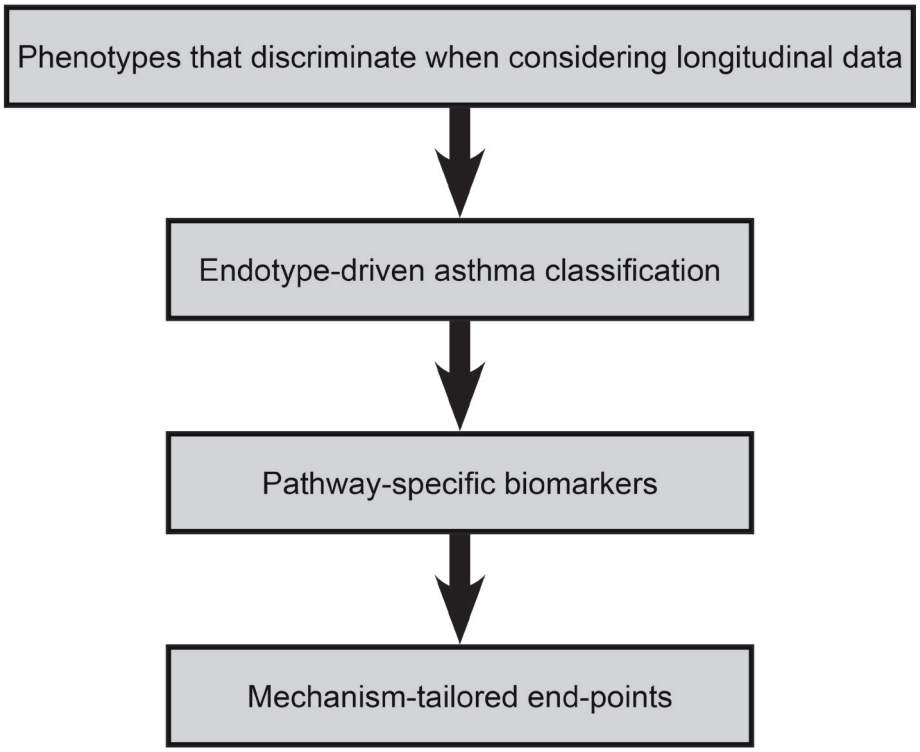

Figure 5

Essential steps to improve response to asthma treatment. The identification of corresponding molecular biomarkers for the individual pathogenic mechanisms underlying phenotypes or subgroups within a phenotype and incorporation of mechanism-tailored end-points into clinical trials are essential to improve the response rate to targeted treatment in asthma. *(Reproduced from Agache et al. presentation at the World Allergy Congress in 2011)*

mechanism-tailored endpoints (Figure 5). The selection of outcome measure is difficult, as it must reflect the mechanistic intervention and should be relevant for both the asthmatic population in general and the particular individual with asthma. The review provides detailed description of the evidence for endotype driven asthma treatment as derived from clinical trials. Endotype-driven treatment of asthma is described for Th2 high asthma and Th2 low asthma (neutrophilic, microbiome and EMTU driven) and for the obese asthma phenotype.

The next invited review published in 2015 (70) focuses on *non-eosinophilic asthma (NEA) endotypes* and prepared the application for funding by national research programmes finalized with winning the PN-II-RU-TE-2014-4-2303 project – Endotypes of Non-Eosinophilic Asthma – ENDANA. In this review pertinent arguments spanning from induced sputum to gene signature are described to argue for NEA as a distinct asthma phenotype with several relevant clinical features such as increased asthma severity, increased remodelling and lower response to bronchodilator and anti-inflammatory treatment. Two major mechanisms leading to neutrophilic inflammation were postulated and will be tested by the ENDANA project: the dysregulated innate immune response, including neutrophil intrinsic abnormalities, and the activation of the IL-17-dependent pathway. Several factors such as age, metabolic or epigenetic factors or the activation of the EMTU have been identified as modulators. The endotyping of NEA is far behind the eosinophilic asthma, and until now, no endotype driven interventions have been proved to be effective.

Another invited review (71) "***The Complex Type 2 Endotype in Allergy and Asthma: From Laboratory to Bedside***" published in 2015 in Current Allergy and Asthma Reports introduces the concept of simple versus complex endotype, using the type 2 asthma endotype as the prototype for a complex endotype.

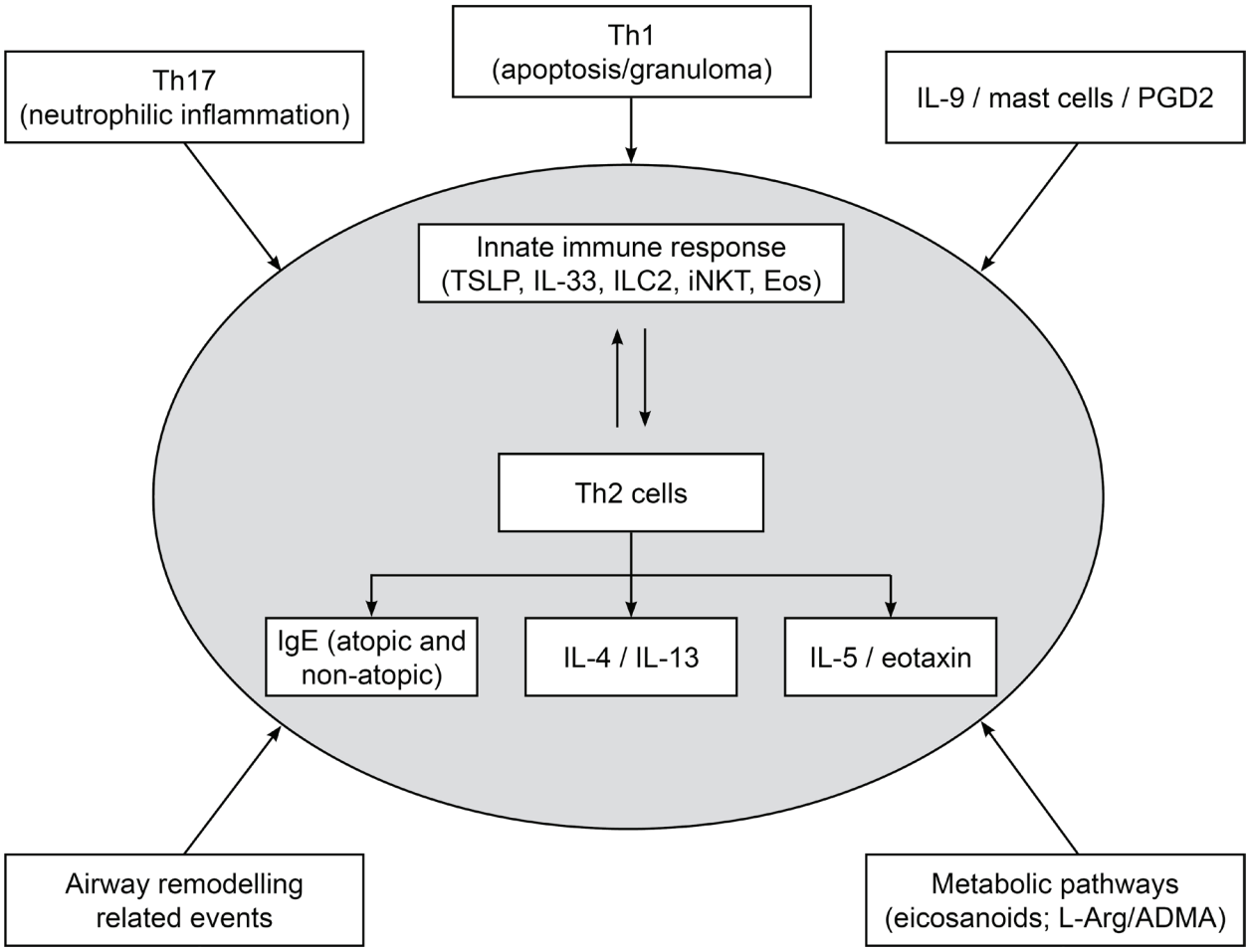

Figure 6

The complex network of Th2 endotype in allergic diseases involves the interaction between innate immune response and Th2 cells. Three major downstream effector pathways can be described: the IgE pathway, the IL-5/eotaxin pathway, and the IL- 4/IL-13 pathway. Additional modulators of the Th2 endotype can be described such as Th17 or Th1 cells, the IL-9/mast cell axis, activation of the metabolic pathways, or the degree of airway remodeling. (*Reproduced from Agache I, et al. The Complex Type 2 Endotype in Allergy and Asthma: From Laboratory to Bedside. Curr Allergy Asthma Rep. 2015;15(6):29)*

Three main pathways (IL-5, IL-4/IL-13 and IgE driven endotypes) are described, supported by targeted interventions in asthma, together with a thorough description of external factors modulating the expression of endotype (Figure 6). The type 2 endotype was described for all major allergic diseases: asthma, rhinitis, chronic rhinosinusitis, and atopic dermatitis. This complex endotype is mainly mediated by type 2 innate lymphoid cells (ILC2) and by Th2 cells, as well as Th2 cytokine-producing NKT cells, whereas their individual contribution is not known. The review was already **cited 20 times in one year** by papers published in high ranked journals.

In 2016 we published another invited review, "***Endotypes of allergic diseases and asthma: An important step in building blocks for the future of precision medicine***", linking the endotype driven disease classification and management with the concept of precision medicine in allergy and asthma (72). The article introduces the innovative concept of developmental endotypes addressing disease inception and progression highly needed for the outset of early prevention and disease modifying strategies as part of the 4Ps of precision medicine. Epigenetic mechanisms link gene regulation to environmental influences and developmental trajectories (73). Developmental program-

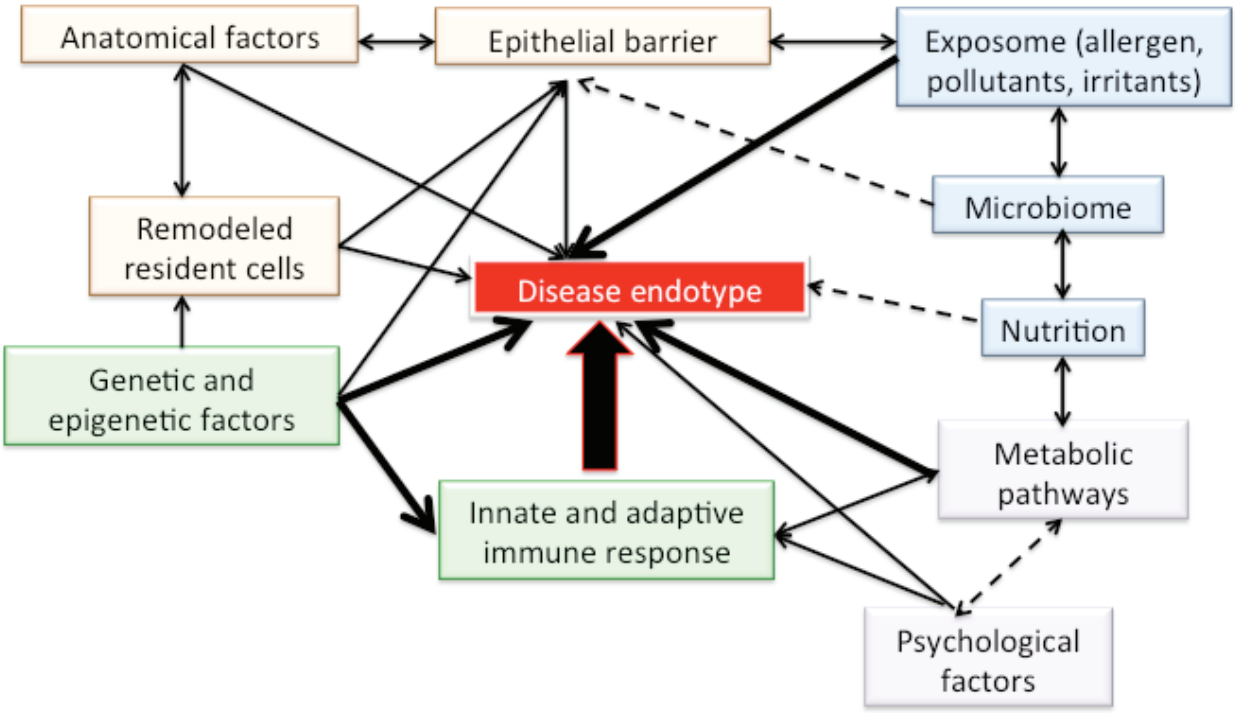

Figure 7

Factors that affect a disease endotype in allergic diseases. For precision medicine in allergic disease, more mechanistic approaches are needed, based on an integrated understanding of the individual patient's biological mechanisms, including the interplay between the immune response and the exposome, infections and microbiome, genetics, epigenetics, psychosocial factors, nutrition, anatomical factors and metabolic pathways. *(Reproduced from Agache I, Akdis CA. Endotypes of allergic diseases and asthma: An important step in building blocks for the future of precision medicine. Allergol Int. 2016;65(3):243-52)*

ming induced by the intrauterine environment (cigarette smoke, nutrition, and stress) affects the fetus and its germ line, with intergenerational epigenetic effects. Developmental programming can be transmitted across generations (trans-generational effects) and cannot be anymore attributed to direct environmental exposure. New bioinformatics tools to define multidimensional endotypes are detailed, together with data-driven unbiased approach as opposed to investigator-driven disease clustering. The mixed mixed Th17/Th2 endotype in asthma, CRS or atopic dermatitis (AD) is further described. Th2 cells can differentiate into dual-positive Th2/Th17 cells (74) and these cells were identified in the BAL fluid of asthmatic patients and related to glucocorticoid resistance in vitro and airway obstruction and hyperreactivity (75). In CRS IL-25 receptor (IL-17RB)-expressing Th2 effector cells were identified in NP tissue but not the healthy nasal mucosa or periphery, while abundant IL-17-producing T cells were observed in both healthy nasal mucosal and polyp populations, thus suggesting that the Th17 response might be important in healthy nasal mucosal immune homeostasis and the NP inflammation and remodeling occurs within the mixed endotype (76). A non-type 2 immune response mixing Th1, Th17 and Th22 driven inflammation and epithelial dysfunction is also described for AD in non-lesional skin and in the chronic remitting-relapsing form of the disease (77, 78, 79). The paper also highlights the importance of external modulators of an endotype (Figure 7). Crucial determining factors for complex immune regulation and barrier function include respiratory infections, microbiome, and nutrition. To further elaborate on the definition of an endotype one must recognize that one major pathogenic pathway such as type 2 immune response is highly complex, including several determinants with nonlinear dynamic interactions (Figure 7) and heterogeneous, since not all determinants are present in all patients

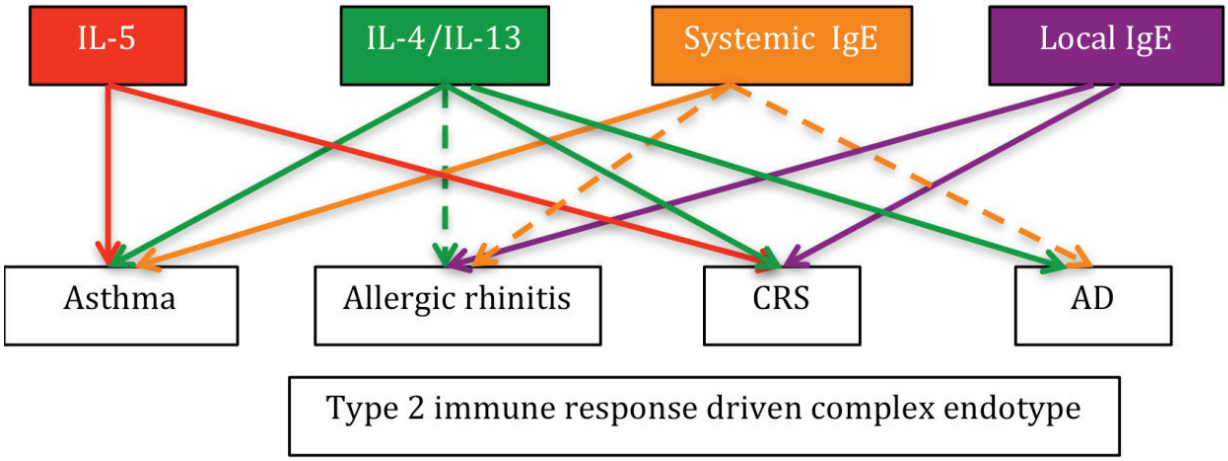

Figure 8

The complex type 2 immune response driven endotype consists of several individual pathways with different preponderance in major allergic diseases. The IL-5 pathway is a therapeutic target in asthma validated in major phase III clinical trials leading to regulatory approval of mepolizumab for severe asthma and was targeted in a proof of concept study in CRS with NP. The IL-4/IL-13 pathway seems similarly important for asthma, CRS with NP and AD: targeted intervention with dupilumab significantly reduced symptom burden. Targeting systemic IgE is a well-validated intervention in allergic asthma and new anti-IgE monoclonal antibodies are under clinical development. Anti-IgE treatment seemed less rewarding in AD. Local IgE production is a key pathogenic event driving the inflammation process both in AR and CRS. Up to now no targeted interventions were tested for AR as a primary disease phenotype. Continuous line: type 2 immune response endotypes with a beneficial response to targeted treatment and/or strong evidence for involvement in disease pathogenesis. Dashed line: evidence relating to disease pathogenesis. CRS = chronic rhinosinusitis; AD = atopic dermatitis *(Reproduced from Agache I, Akdis CA. Endotypes of allergic diseases and asthma: An important step in building blocks for the future of precision medicine. Allergol Int. 2016;65(3):243-52)*

or, in a given patient, at all time points (6, 7). We therefore must embrace the concept of a "complex endotype" consisting of several sub-endotypes as opposed to an endotype that encompasses a single molecular mechanism (67, 71). Based on the beneficial response to targeted treatment and/or strong evidence for involvement in disease pathogenesis the paper proposes two models of complex endotypes for type 2 (Figure 8) and non-type 2 allergic diseases (Figure 9). The concept of complex endotypes is supported further by studies showing differences in corticosteroid or anti IL-5 targeted treatment responsiveness in type 2 asthma pending on the localized or systemic inflammation or the innate or adaptive immune response arm predominant as pathogenetic mechanism (Table 2).

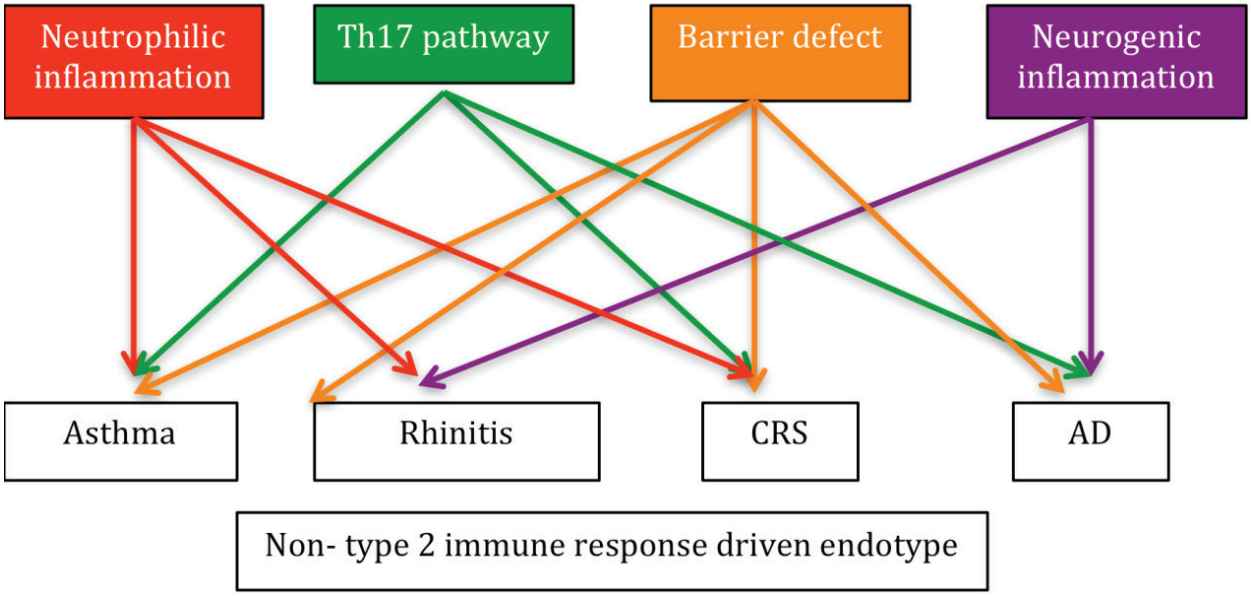

Figure 9

Multiple non-type 2-driven molecular sub-endotypes in major allergic diseases. Growing evidence supports a role for a dysregulated innate immune response promoting neutrophilic inflammation in asthma, rhinitis and CRS. The IL-17 pathway has been related to disease severity in asthma, CRS and AD. Tissue remodeling and barrier defects are major players modulating the non type-2 immune response in asthma and CRS, while barrier defect is central for all disease phenotypes. The neurogenic inflammation pathway appears of particular importance in rhinitis and AD. *(Reproduced from Agache I, Akdis CA. Endotypes of allergic diseases and asthma: An important step in building blocks for the future of precision medicine. Allergol Int. 2016;65(3):243-52)*

Table 2

The type and location of the immune-inflammatory responses influences the expression of a complex endotype. *(Reproduced from Agache et al presentation at the Hong Kong Allergy Convention 2016)*

Type 2 inflammation location	Localised	Predominance of the IL-4/IL-13-mediated pathway with eosinophilc inflammation localized in the bronchial mucosa
	Systemic	Driven by a strong chemokine signal (such as IL-5) More extensive eosinophilic airway inflammation involving the small airways and with fixed airway obstruction Increased risk of exacerbations Less responsive to ICS, requiring OCS and/or anti IL-5
Type 2 inflammation type	Driven by T helper 2 lymphocytes	Corticosteroid responsive
	Driven by innate type 2 lymphoid cells	Less responsive to corticosteroids; alternatives such as anti IL-5 or anti IL-4/IL-13 are needed

1.2. ASTHMA BIOMARKERS

Biomarkers, or biological markers, are measurable indicators used to examine any aspects of health or disease. Any type of analyses can be a biomarker and may provide information about the pathophysiology of an underlying disease, the course of an illness, and/or the response to treatment. They are expected to inform us if a disease is present or absent, define its severity, provide information about its progression, serve to select most effective treatment, and/or serve as guidance about the affected individual's survival.

A successful endotype should link the key pathogenic mechanism with a clinical phenotype of asthma via biomarkers (64). In relation to an endotype the biomarker can be a marker or the key mechanism itself (Figure 10). Both validity and relevance are important for a biomarker. **Validity** means that the biomarker should be both reproducible (pending on the inter- and intra- coefficient of variability) and usable as diagnostic test (easily measurable, affordable). **Relevance** refers to the quality of the biomarker to be pathway specific and to be related to the relevant clinical end point (pending on surrogate end points). It should be noted that most biomarkers are currently suited only for research settings and still need to be validated and qualified (80, 81, 82). Steps towards biomarker qualification are clearly delineated by regulators lead by the FDA (83).

Biomarkers in asthma are used at present to predict treatment response and very few to forecast disease risk and progression. However, they are not sufficiently specific to select the endotype specifically responding to a targeted treatment. For example, blood eosinophils predict response to anti-IL-4/IL-13, anti-IL-5, and anti-IgE antibodies, as well as CRTH2 antagonists and the clinician will face a challenge of how best to treat severe asthma patients with high blood eosinophils (83,84) (Table 3).

Being closely linked to asthma phenotypes and endotypes the biomarkers research line of the author complemented the achievements in describing disease phenotypes and endotypes acknowledged by the worldwide scientific community through highly cited research papers, invited review, lectures and oral communications.

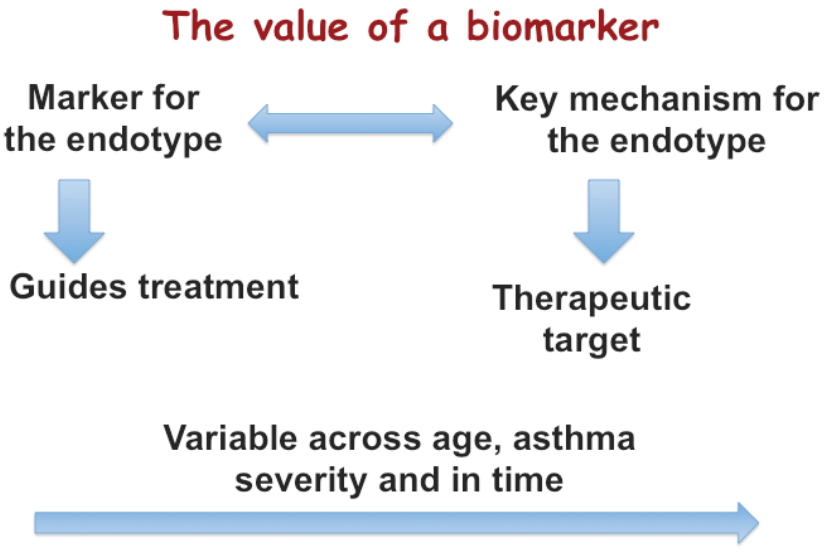

Figure 10

A successful endotype should link the key pathogenic mechanism with a clinical phenotype of asthma via biomarkers. Understanding the complex relation between biomarkers and endotypes is even more problematic given the fact that the same biomarker is variable across age, asthma severity and time. Longitudinal evaluation of the stability of an endotype is therefore essential for its relevance. *(Reproduced from Agache et al presentation at the EAACI annual meeting 2016)*

Table 3

Non-invasive biomarkers in asthma. None of the biomarkers are sufficiently specific to select the endotype specifically responding to a targeted treatment, they are subject to significant variability and none of them is validated and qualified. *(Adapted from Muraro A, et al. Precision medicine in patients with allergic diseases: airway diseases and atopic dermatitis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2016;137(5):1347-58)*

Biomarker	Treatment expected to produce a response	Surrogate end-point value	Comments
BLOOD			
Eosinophils	Anti-IL5 Anti IgE Anti IL-4/IL-13 Corticosteroids (CS)	Exacerbations LF decline Fixed airway obstruction	Easily available Significant fluctuation
Specific IgE	Anti-IgE AIT	Exacerbations	-
Periostin	Anti-IL13	LF decline	Research type Assay dependent
INDUCED SPUTUM			
Eosinophils	Anti IL-5 ICS	Exacerbations	Research type Significant fluctuation
IL-13	Anti IL-13	?	Research type
EXHALED BREATH			
FeNO	Anti IL-5 Anti IgE Anti IL-13 ICS	Exacerbations, LF decline	Easily available Point of care Significant fluctuation
Metabolomics (VOC)	ICS	Exacerbations in children	Research type

In 2010 the author publishes a pioneering research on serum IL-17 as a biomarker of severe asthma: "***Increased serum IL-17 is an independent risk factor for severe asthma***" (85). It was the first detailed study of the value of serum IL-17 in asthma and as such it was **cited 132 times** since its publication. In 2010 IL-17A was a newly described proinflammatory cytokine secreted by a subtype of T helper lymphocytes, Th17.1 Increased IL-17A expression was found to be associated with many chronic inflammatory diseases in humans, such as rheumatoid arthritis, asthma, systemic lupus erythematosus and allograft rejection (86). The role of IL-17/Th17 cells in asthma was unclear, with only murine models of asthma showing that IL-23 and Th17 cells not only induce Th17-cell-mediated neutrophilic airway inflammation, but also up-regulate Th2-cell-mediated eosinophilic airway inflammation (87). Evaluating 87 adult patients with mild, moderate and severe asthma the study demonstrates that it can be a non-invasive biomarker as serum IL-17 can be used to predict asthma severity since it is both increased in severe asthma compared to mild/moderate forms of the disease (Figure 11) and values > 20 pg/ml are independent predictor of severe asthma (Table 4). The results are in concordance with other

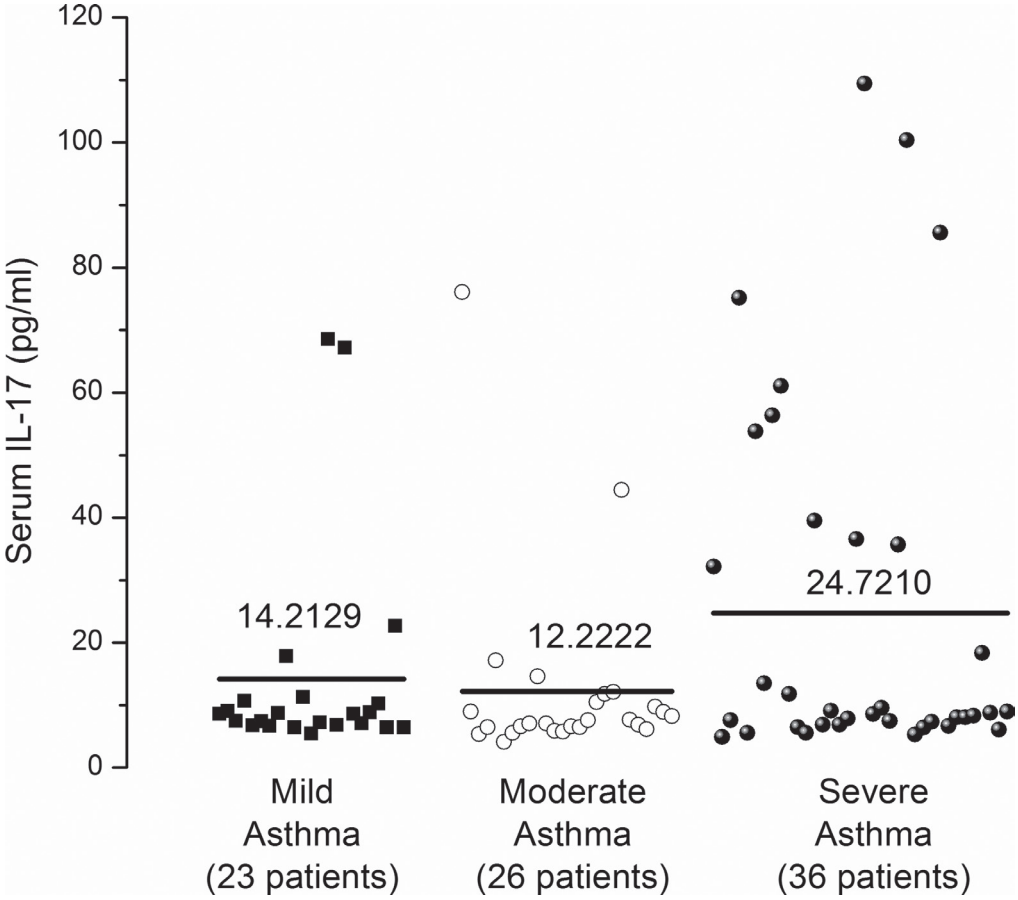

Figure 11

Serum IL-17 is increased in severe asthma compared to mild/moderate forms of the disease. Although median values of serum IL-17 were not discriminative for severe asthma compared to mild/moderate forms of the disease, there were significantly more asthma patients with values above 20 pg/ml in the severe asthma group compared to mild or moderate asthma patients. Very high values for serum IL-17 *(>100 pg/ml) were encountered only in the severe asthma patient's subgroup. (Reproduced from Agache I, et al. Increased serum IL-17 is an independent risk factor for severe asthma. Respir Med. 2010;104(8):1131-7)*

studies underlying the link between systemic inflammation and asthma severity (88, 89). The study evaluated in parallel tumor necrosis factor (TNF)-α as a biomarker for severe asthma. Increased serum IL-17 was more discriminative for severe asthma compared to serum TNF-a. Also, there was no correlation between increased serum IL-17 and serum TNF-a, thus both depicting separate phenotypes of asthma, with increased serum IL-17 more relevant for a subphenotype of severe asthma, non-smokers, without non-steroidal anti-inflammatory drugs (NSAID) intolerance, with preserved lung function (LF) and with normal serum TNF-α (Table 5). The study also showed an interesting relation between increased serum IL-17 and lung function is. There was an inverse correlation with small airways obstruction (as evaluated by FEF 25-75 and MEF50) and there is also a tendency towards inverse relation, although not statistically significant, with low lung function as depicted by an FEV1 value below 50% predicted. In the analysis of severe asthma patients subgroup FEV1 % predicted was significantly higher and the number of subjects with FEV1 <50% significantly lower in association with increased serum levels of IL-17A. It seems that IL-17 is increased in subgroup of severe asthma patients with more preserved LF. In another study sputum IL-17 was associated with increased bronchial hyperreactivity to methacholine (90). Increased IL-17 may thus characterize a peculiar lung remodeling with increased bronchial smooth muscle and less fibrosis. Unfortunately targeted anti IL-17 treatment with brodalumab in asthma did not preselect patients based phenotyp-

Table 4

Risk factor for severe asthma. Multiple regression analysis revealed as independent risk factors serum IL-17 > 20 pg/ml, non-steroidal anti-inflammatory drugs intolerance and low FEV1. *(Adapted from Agache I, et al. Increased serum IL-17 is an independent risk factor for severe asthma. Respir Med. 2010;104(8):1131-7)*

	Beta	Standard Error of Beta	B	Standard Error of B	t(73)	p-level
Smoke	0.010273	0.092371	0.010370	0.093245	0.11121	0.911746
NSAID intolerance	0.346923	0.097467	0.345615	0.097099	3.55940	0.000649
Atopy	-0.076304	0.098527	-0.075581	0.097593	-0.77445	0.441099
Obesity	-0.002673	0.104863	-0.002714	0.106457	-0.02549	0.979728
Moderate/severe persistent rhinitis/ chronic rhinosinusitis	-0.028323	0.097938	-0.041392	0.143129	-0.28919	0.773233
Blood eosinophilia	-0.094935	0.093798	-0.093847	0.092722	-1.01213	0.314731
FEV1 < 50% predicted	0.400498	0.092198	0.609701	0.140359	4.34388	0.000043
IL-17 > 20 pg/ml	0.352762	0.091920	0.442894	0.115406	3.83770	0.000257

NSAID = non-steroidal anti-inflammatory drugs

Table 5

Correlations between increased serum IL-17 and other phenotypic features of asthma. Serum IL-17 > 20 pg/ml was negatively correlated with increased blood neutrophils and with small airways and was not correlated with the presence of atopy, blood eosinophilia, smoker, obesity, moderate/ severe persistent rhinitis or chronic rhinosinusitis, non-steroidal anti-inflammatory drugs intolerance, FEV1 < 50% predicted or increased serumTNF-α. *(Adapted from Agache I, et al. Increased serum IL-17 is an independent risk factor for severe asthma. Respir Med. 2010;104(8):1131-7)*

Parameter	Coefficient	p value
Atopic status	0.1290	0.453
Moderate/severe persistent rhinitis or chronic rhinosinusitis	0.2345	0.169
Smoke	-0.1221	0.478
Obesity	0.0075	0.965
NSAID intolerance	-0.1706	0.320
FEV1 < 50% predicted	-0.3091	0.067
Small airways obstruction	-0.4526	0.006
Blood eosinophilia	0.0210	0.247
Blood neutrophilia	-0.3376	0.047
TNF-α>8.2 pg/ml	0.0606	0.729

ic traits and it was not successful, but, as a confirmation of our study observations, in the high-reversibility subgroup (post-bronchodilator FEV1 improvement ≥ 20%) the Asthma Control Questionnaire (ACQ) change with nominal significance was noted (91).

The quest for molecular biomarkers for asthma continued and in 2016 the paper "***Serum IL-5 and IL-13 consistently serve as the best predictors for the blood eosinophilia phenotype in adult asthmatics***" published in Allergy as first author assessed the biomarker(s) that predict best the phenotype of blood eosinophilia in adult asthmatic patients. The results of this study were also presented in September 2016 as an oral presentation at the ERS annual congress in London. Several potential candidates were evaluated such as serum levels of periostin, eosinophil-derived neurotoxin (EDN), eotaxin, eNO, sputum eosinophils, total serum IgE as well as the Th2 cytokines IL-5 and IL-13. To better stratify the type 2-high complex endotype, additional serum cytokines were measured: interferon (IFN)-γ, IL-17A, IL-6, IL-7, IL-8, IL-10, IL-12, IL-15, IL-16, IFN-gamma inducible protein (IP)-10, macrophage inflammatory protein (MIP)-1α, monocyte chemoattractant protein (MCP-1), tumour necrosis factor (TNF)-α, thymus- and activation-regulated chemokine (TARC), vascular endothelial growth factor (VEGF). As secondary end-points, the study evaluated the relation between biomarkers and clinical significant asthma outcomes: night-time awakenings, exacerbation rate, LF decline, steroid resistance, brittle asthma (type 1 and 2), near-fatal asthma, AHR, asthma control and severity as defined by the Global Initiative for Asthma (GINA). In addition, the gained knowledge was used to further subgroup the asthma patients based on the molecular fingerprint. According to the receiver operating characteristic (ROC) curves IL-13 (AUC = 0.922) and IL-5 (AUC = 0.905) predicted best absolute blood eosinophil numbers at a cut-off value of > 350 eos/µl, followed by EDN and eNO (Table 6). In the regression tree model (Figure 12), blood eosinophilia was best predicted by IL-5 with a cut-off value of 341 eos/µl and a separation level of 0.57 pg/ml IL-5. The next important variables were EDN and eNO. Of note, the IL-5 and IL-13 levels remained stable over a period of 6 weeks with differences ≤3%, whereas blood eosinophils varied with -15.455% for absolute numbers. The subgroup analysis focused on the clinical relevant end-points in relation to the investigated biomarkers. After multiplicity correction, we observed a significant correlation between increased levels of MCP-1 and asthma severity (GINA) and fast LF decline. Serum IL-5 and IL-13 showed a strong correlation with airway hyperreactivity (AHR) (Figure 13). The correlation between IL-5/IL-13 and AHR seems interesting and supports our previous hypothesis that IL-13 reflects an inflammation type that is more localised into the lung and related to airway remodeling (71). IL-13 did not correlated with steroid resistance and therefore this subendotype might reflect a subgroup of blood eosinophilia asthmatics responding to topical ICS treatment. Asthma patients were clustered according to their

Table 6

Biomarkers predicting blood eosinophilia at a cut-off value for absolute blood eosinophil numbers > 350 eos/µl. Area under the curve (AUC) values for biomarkers are stated. According to the Receiver operating characteristic (ROC) curves IL-13 (AUC = 0.922) and IL-5 (AUC = 0.905) predicted best absolute blood eosinophil numbers followed by EDN and eNO. *(Adapted from Agache I, et al. Serum IL-5 and IL-13 consistently serve as the best predictors for the blood eosinophilia phenotype in adult asthmatics. Allergy. 2016;71(8):1192-202)*

Biomarker	Visit 1	Visit 2
IL-13	0.922	0.743
IL-5	0.905	0.730
EDN	0.826	0.720
eNO	0.713	0.643
VEGF	0.648	0.512
MIP-1b	0.647	0.524
IL-12	0.636	0.548
IL-16	0.615	0.590
Eotaxin-3	0.615	0.567
Sputum Eos	0.606	-

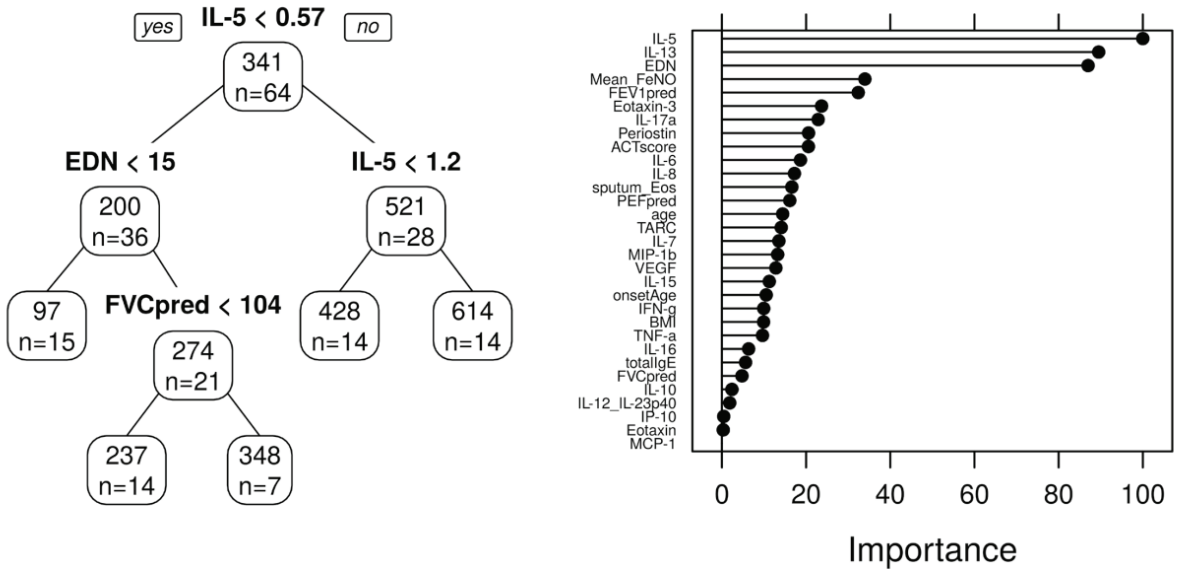

Figure 12

Regression tree model. Absolute blood eosinophils were best predicted by IL-5 with a cut-off of 341 eos/µl and a separation level of 0.57 pg/ml IL-5 (figure 4a). The next important variables were IL-13, EDN and eNO (figure 4b). *(Reproduced from Agache I, et al. Serum IL-5 and IL-13 consistently serve as the best predictors for the blood eosinophilia phenotype in adult asthmatics. Allergy. 2016;71(8):1192-202)*

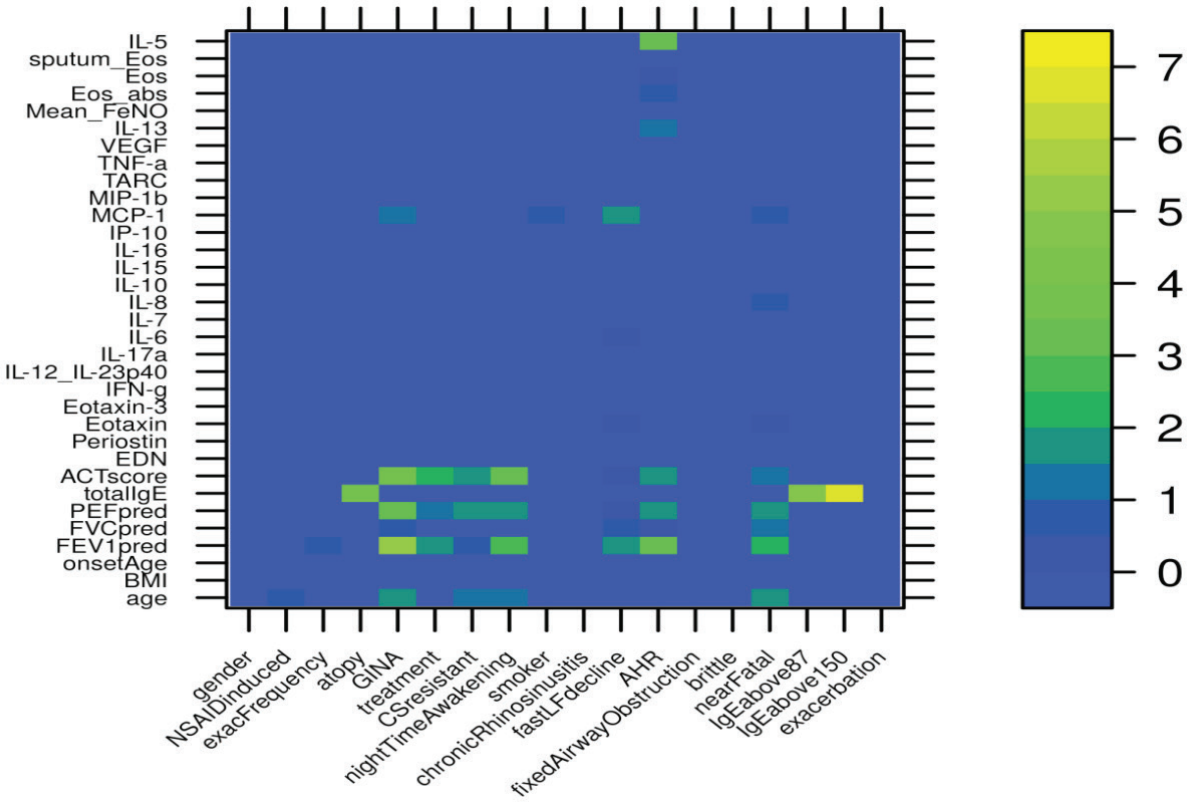

Figure 13

Correlation analysis between discrete clinical characteristics with continuous variables. Strength of the correlation is displayed on a scale from 0 (dark blue) to 7 (yellow). MCP-1 correlated with asthma severity (GINA) and fast LF decline. AHR correlated with serum IL-5 and IL-13. *(Reproduced from Agache I, et al. Serum IL-5 and IL-13 consistently serve as the best predictors for the blood eosinophilia phenotype in adult asthmatics. (Allergy. 2016;71(8):1192-202)*

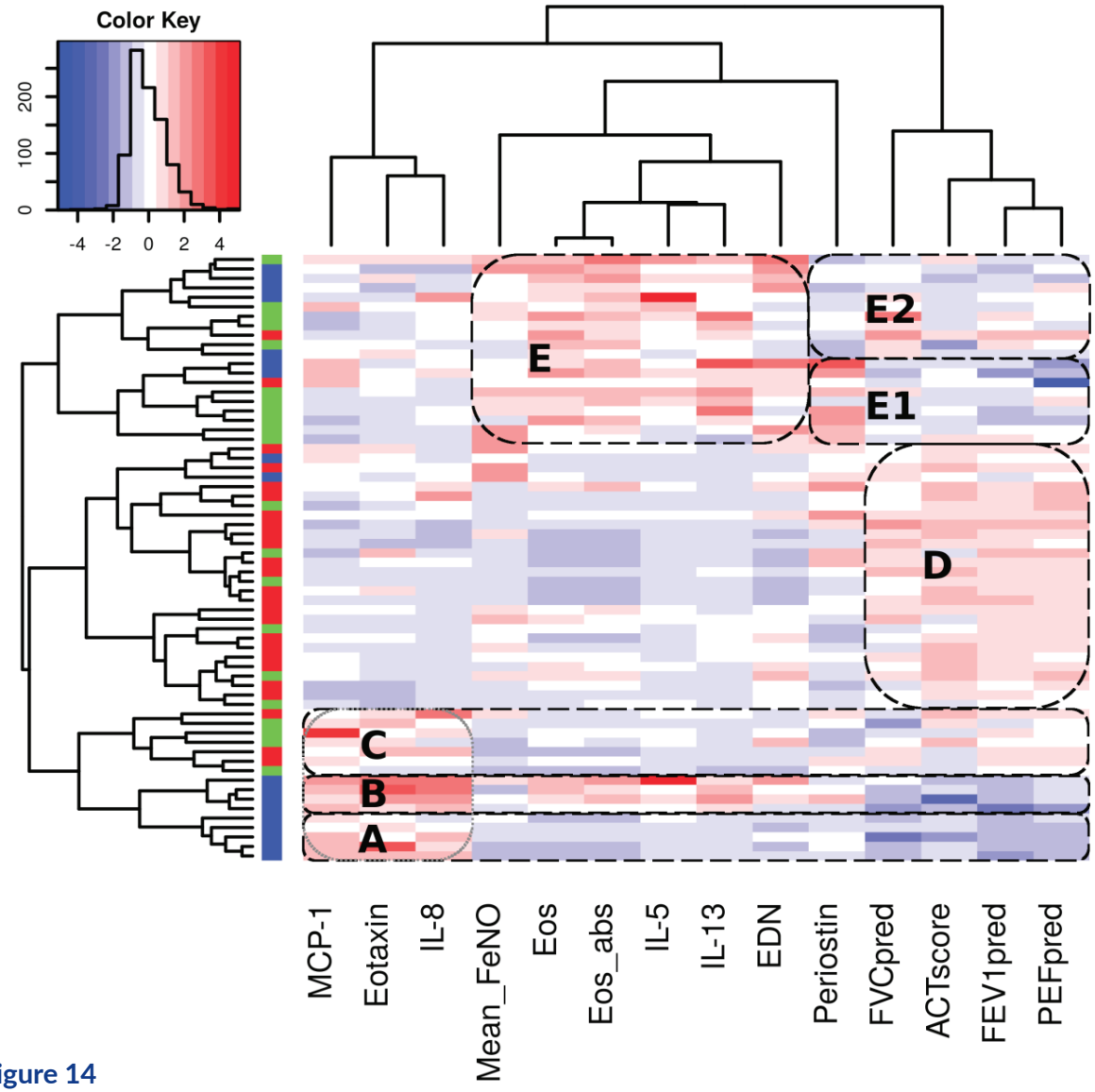

Figure 14

Hierarchical clustering including serum biomarkers identified by principal component analysis. Asthma patients were clustered according to their lung function (FVC, FEV1, PEF), ACT score, blood eosinophilia and correlated molecular biomarkers (IL-5, IL-13, EDN) and levels of MCP-1, IL-8, eotaxin. Asthma severity (GINA) is depicted on the vertical axis using a colour code: red for mild asthma, green for moderate asthma and blue for severe asthma. *(Reproduced from Agache I, et al. Serum IL-5 and IL-13 consistently serve as the best predictors for the blood eosinophilia phenotype in adult asthmatics. Allergy. 2016;71(8):1192-202)*

lung function (FVC, FEV1, PEF), asthma control test (ACT) score, blood eosinophilia and correlated molecular biomarkers (IL-5, IL-13, EDN) and levels of MCP-1, IL-8, eotaxin. Five main clusters can be identified (Figure 14). There are two clusters of patients with blood eosinophilia (B and E) that differ by their associated biomarkers. Cluster B includes four asthmatics with a severe mixed-type having both blood eosinophilia and increased levels of MCP-1 and IL-8. Cluster E includes 20 moderate-severe asthma patients with blood eosinophilia. Cluster A includes 5 severe patients without blood eosinophilia but high levels of MCP-1, eotaxin, IL-8. Cluster C contains 7 mild-moderate patients that show increased levels of IL-8, eotaxin and MCP-1. Cluster D includes 28 mild-moderate patients that show no particular endotype and good control of asthma. These results show that the subphenotype of eosinophilic asthma selected by serum IL-5 and IL-13 is divided into moderate-severe and very severe patients of mixed-type. The value of added biomarkers (MCP-1, IL-8) to stratify for asthma severity was also demonstrated.

1.3. NOVEL TARGETED TREATMENTS FOR ASTHMA

A. BIOLOGICALS

New and expensive biological therapies for asthma are emerging that are highly efficacious only for a selected group of patients. Selection of the target group of patients using an endotype driven decision guided by a biomarker directly involved in asthma pathogenesis together with a clever selection of outcome measures should be acknowledged as an essential scaffold for the design of successful clinical trials (69).

The knowledge accumulated on asthma phenotypes and endotypes was pursued in a multinational clinical trial with the results published in 2016 in the paper "***A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma***" (93). The trial evaluated the role of IgE in allergic asthma adult patients and tested the new humanized IgG1 monoclonal antibody, quilizumab, who targets the M1-prime segment of membrane-expressed IgE, leading to depletion of IgE-switched and memory B cells. Quilizumab may reset the IgE repertoire by targeting IgE production and provide a more sustained effect with a lower dose frequency compared to the other anti IgE monoclonal antibody that is in use for asthma, omalizumab. In a previous study Quilizumab abrogated the increase in challenge-specific IgE in patients with mild asthma following a whole-lung allergen challenge, and reduced the early and late asthmatic reactions, reliable surrogate end-points for IgE driven allergic asthma (94). The primary purpose of the study was to evaluate the efficacy (severe exacerbations, LF, asthma control, quality of life), safety, and pharmacokinetics of quilizumab after 36 weeks of treatment in adults with allergic asthma (at least one positive aeroallergen-specific IgE or a total serum IgE ≥75 IU/mL) inadequately controlled despite high-dose ICS and a second controller. The study also evaluated the ability of biomarkers (serum periostin, blood eosinophils, exhaled NO, and serum IgE) to predict benefit from quilizumab, using the previous models tested for omalizumab and lebrikizumab (95, 96). The study was terminated early because of the lack of efficacy for the primary end-point (asthma exacerbations) at Week 36, with the median time in the study at 72 weeks (Figure 15), although quilizumab demonstrated

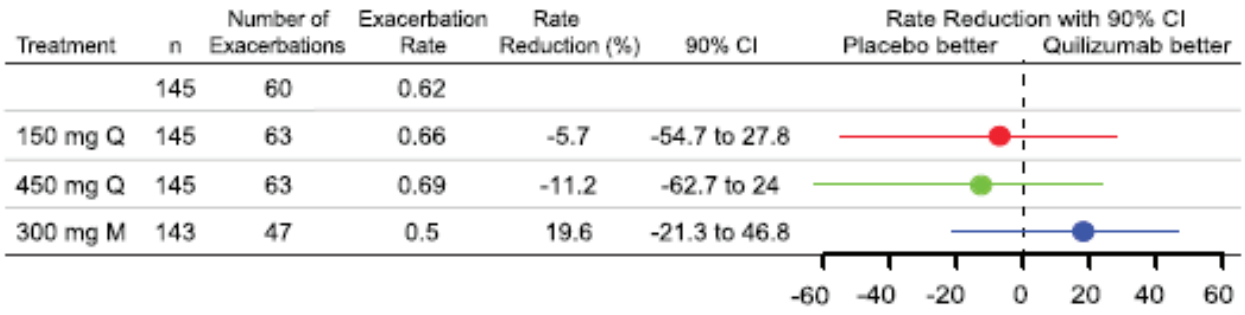

Figure 15

Rate of protocol-defined asthma exacerbations through Week 36 for all patients. M = monthly; Q = quarterly. Quilizumab treatment did not produce a clinically meaningful reduction of the rate of asthma exacerbations over the 36-week treatment period. In the ITT population, the reduction in the asthma exacerbation rate relative to placebo was 19.6 %. In the EXTRA study (95) that examined a similar patient population, omalizumab, the anti IgE antibody currently in use, significantly reduced asthma exacerbations by 25% in all patients group. *(Reproduced from Harris JM, et al. A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma. A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma. Respir Res. 2016;17:29)*

clear pharmacological activity by reducing both serum total and allergen-specific IgE an average of 30–40% from baseline in all three treatment arms (Figure 16). Subgroup analysis by baseline serum periostin (≥50 ng/ml, <50 ng/ml), blood eosinophils (≥300 cells/µl, <300cells/µl), FeNO (≥20 ppb, <20 ppb) and serum total IgE (≥200 IU/mL, <200 IU/mL) demonstrated no consistent effect of quilizumab on the exacerbation rate across all doses when compared to the intention to treat (ITT) population (Figure 17). No significant evidence of improved FEV1 at Weeks 12 and 36 was observed in quilizumab-treated patients compared to placebo and no meaningful differences were observed between the quilizumab dose groups compared with the placebo group for symptom scores and quality of life scores. Quilizumab prevents the formation of short-lived IgE plasma cells in the airway, while long-lived IgE plasma cells and the subpopulation of IgG1 memory B cells that undergo a secondary switch to IgE when reactivated, which lack IgE on the surface, are not targeted this monoclonal antibody. This mechanistic study challenges thus the role of local IgE production by short-lived IgE plasma cells for exacerbations and other clinical endpoints and showed that alternate sources of IgE play a more dominant role in allergic asthma. As for the surrogate marker itself (the allergen challenge model) used in the exploratory study with quilizumab it was shown to be less relevant for moderate/severe asthma compared to mild asthma.

B. ALLERGEN IMMUNOTHERAPY

Although current asthma pharmacotherapy is effective in mitigating the frequency of asthma exacerbations and the loss of disease control it does not offer any lasting benefit once treatment is stopped and shows quite limited intrinsic disease-modifying effects.

Allergen immunotherapy (AIT) has the potential of modifying the fundamental, underlying disease mechanisms and shows sustained clinical effect. Effective AIT triggers multiple immune-mediated mechanisms, which are sequentially activated, which lead to allergen-specific immune tolerance, suppression of allergic inflammation and multifaceted clinical improvement (97,98). ***Ioana Agache*** recently evaluated the benefits of AIT in a review paper "***Mechanisms of allergen-specific immunotherapy and novel ways for vaccine development***" (99) and two consensus documents "***International consensus on allergy immunotherapy***", developed by experts from the iCAAL initiative and published in JACI (97,98)

The review paper discusses the recent evidence providing a plausible explanation to AIT multiple mechanisms inducing both rapid desensitization and long-term allergen-specific immune tolerance, and suppression of allergic inflammation in the affected tissues. During AIT, peripheral tolerance is induced by the generation of allergen-specific regulatory T cells, which suppress proliferative and cytokine responses against the allergen of interest. Regulatory T cells are characterized by IL-10 and TGF-beta secretion and expression of important cell surface suppressive molecules such as cytotoxic T lymphocyte antigen-4 and programmed death-1 that directly or indirectly influence effector cells of allergic inflammation, such as mast cells, basophils and eosinophils. Regulatory T cells and particularly IL-10 also have an influence on B cells, suppressing IgE production and inducing the production of blocking type IgG4 antibodies. In addition, the development of allergen-specific B regulatory cells that produce IL-10 and develop into IgG4 producing plasma cells represent essential players in peripheral tolerance. These findings together with the new biotechnological approaches create a platform for development of the advanced vaccines. Moreover, reliable biomarkers could be selected and validated with the intention to select the patients who will benefit most from this immune-modifying treatment. Thus, AIT could provide a complete cure for a larger number of allergic patients and novel preventive approaches need to be elaborated. The paper highlights what is unknown in the mechanisms of AIT (Table 7), describes the characteristics of a good vaccine (Table 8) and offers possible solutions for new vaccines development (Table 9).

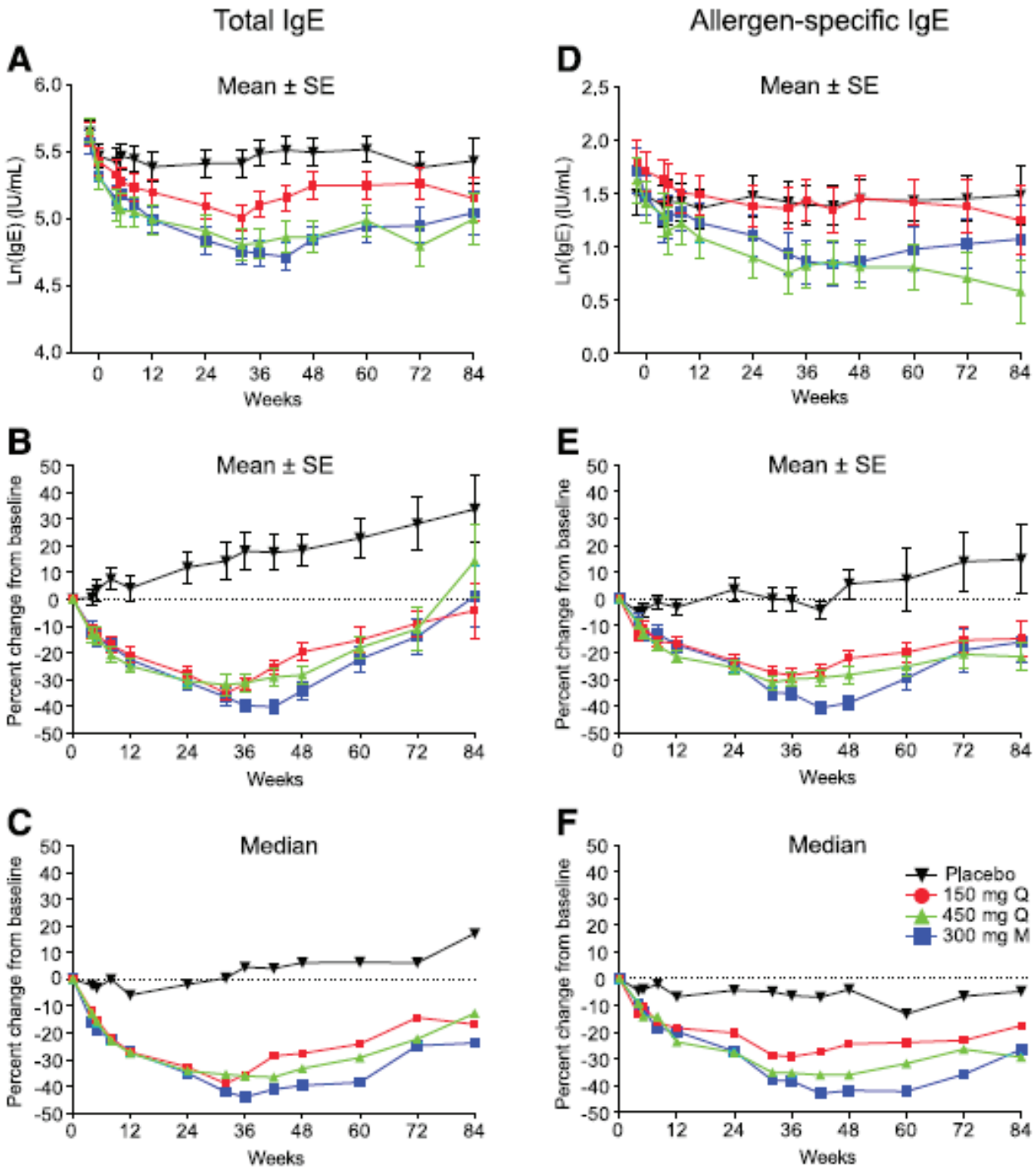

Figure 16

Effect of quilizumab on serum total (a-c) and allergen-specific IgE (d-f) from baseline to Week 84. IgE levels are represented as the mean ± standard error (SE) of the natural logarithm (a, d), the mean ± SE percent change from baseline (b, e), and median percent change from baseline (c, f). All IgE data analysis are based on observed values. M, monthly; Q, quarterly. Quilizumab demonstrated clear pharmacological activity by reducing both serum total and allergen-specific IgE an average of 30–40 % from baseline in all three treatment arms. *(Reproduced from Harris JM, et al. A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma. A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma. Respir Res. 2016;17:29)*

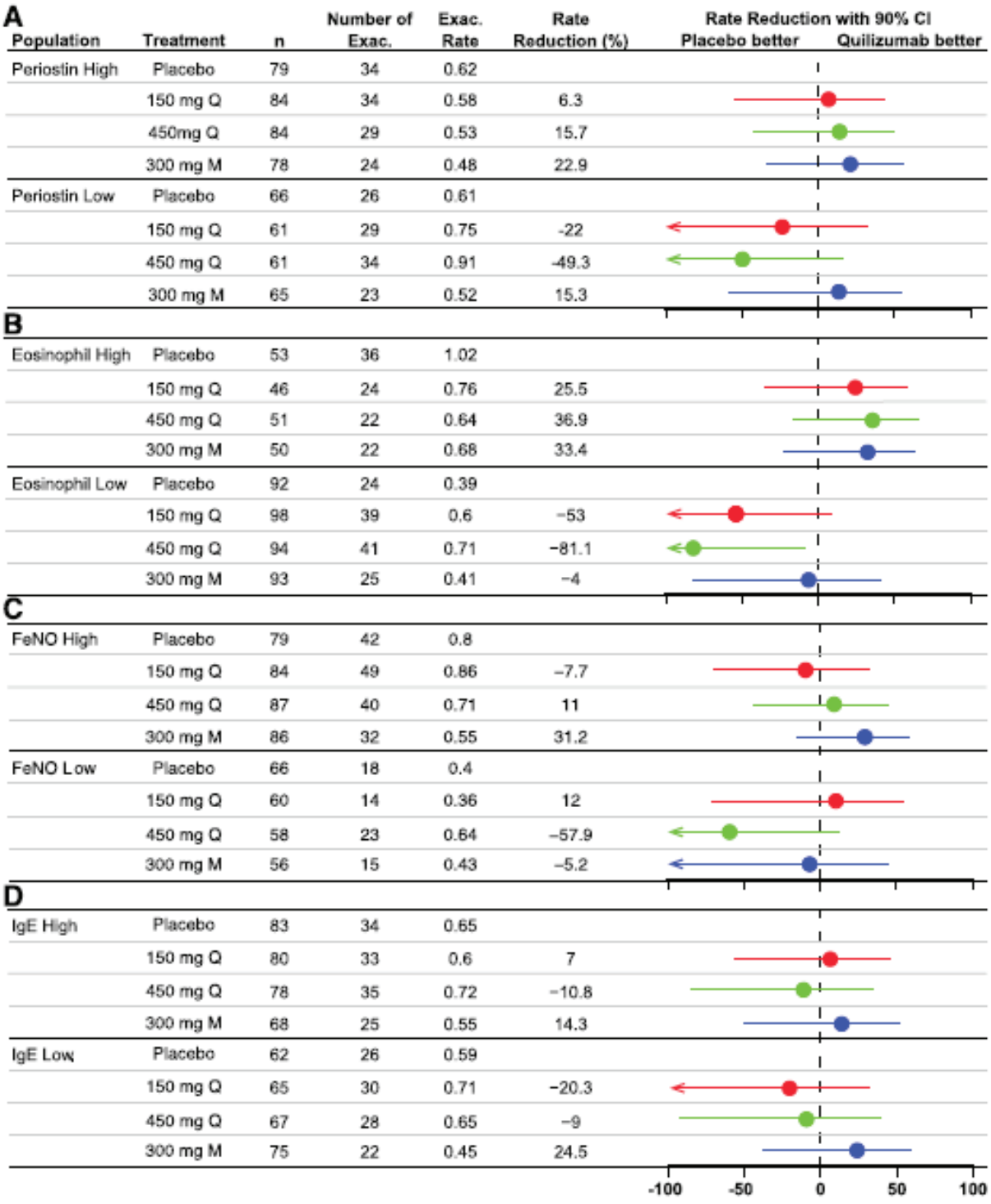

Figure 17

Rate of protocol-defined asthma exacerbations through Week 36 for patients stratified by biomarkers (a: periostin; b: blood eosinophils; c: FeNO; d: serum IgE). *Exac = exacerbation; M = monthly; Q = quarterly. The type 2 biomarkers, serum periostin, blood eosinophils, and FeNO, which identified patients with increased clinical benefit from anti IL-13 (lebrikizumab) (96) and anti IgE (omalizumab) (95), did not consistently enrich for increased benefit from quilizumab in this study. Similarly, patients with elevated serum IgE levels at baseline did not respond better to quilizumab nor was there a correlation between serum IgE reduction and exacerbation reduction or FEV1 improvement. (Reproduced from Harris JM, et al. A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma. A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma. Respir Res. 2016;17:29)*

Table 7

What is unknown in the mechanisms of allergen immunotherapy. Both Treg generation and maintenance and their role in other biological processes is yet to be discovered. Of equal importance the role of the tissue, including the barrier function is not explored enough. As for other targeted interventions the role of biomarkers, endotypes and drug efficacy pending on its pharmacological profile are key points for advancing the field forward. *(Adapted from Jutel M, et al. Mechanisms of allergen-specific immunotherapy and novel ways for vaccine development. Allergol Int. 2013;62(4):425-33)*

Molecular mechanisms of how Treg cells are generated *in vivo*
Better adjuvants that specifi cally induce Treg cells
In vivo life span of Treg cells induced by allergen-SIT
If there are deleterious roles of Treg cells, such as immune tolerance to tumor antigens and chronic infectious agents?
Role of resident tissue cells in immune tolerance
Molecular mechanisms of spontaneous healing, remissions and exacerbations of allergic disease
Local tissue events during SLIT and epicutaneous SIT
Early molecular markers and predictors to decide to start, stop and success
Is there differences in the mechanisms of high dose and low dose allergen-SIT?
Mechanisms of long term maintenance of allergen tolerance
Is there any role in defective barrier function in the successful response to allergen-SIT?

Table 8

Characteristics of a good AIT vaccine. The future needs of AIT include increased efficacy and patient's adherence, reduced side effects and costs and treatment duration. To achieve this aim better vaccines need to be developed. *(Adapted from Jutel M, et al. Mechanisms of allergen-specific immunotherapy and novel ways for vaccine development. Allergol Int. 2013;62(4):425-33)*

Should induce long term allergen tolerance (curative)
Should achieve clinical success in short time with few doses
Should target individuals with allergy to identifi ed allergens
Biomarkers should be identifi ed for patient selection and as-sessment on which population should be targeted, when to start and stop, and how to follow the patients
To use multiple allergens at the same time should be possi-ble
Same approach could be useful for the preventive vaccines

Table 9

New AIT vaccines development. Several approaches are currently under investigation to achieve better efficacy and safety of AIT: targeting T cells, recombinant allergens, the use of adjuvants and immune response modifiers and new routes of administration. *(Adapted from Jutel M, et al. Mechanisms of allergen-specific immunotherapy and novel ways for vaccine development. Allergol Int. 2013;62(4):425-33)*

Type of the vaccine/approach	Description and mechanism
Bypassing IgE binding and targeting T cells	
Fusion of major allergens and chimeric allergens	Major allergens or their fragments are fused and expressed as a single recombi- nant protein. T cell reactivity is preserved, IgE binding is attenuated. Preventive effect on development of IgE is demonstrated in mice.
Hypoallergenic hybrid molecules	Derived from Der p 1 and Der p 2, reduced IgE reactivity of hybrid proteins, in duce higher T cell proliferation responses.
Fragments of major allergens	NonIgE binding fragments of major allergen (Bet v 1). IgE binding is attenuated and T cell reactivity is preserved.
Peptide immunotherapy	T cell epitope peptides (Fel d 1, Api m 1) that do not bind IgE and induce T cell tolerance have been used in cat and bee venom allergy.
Unrefolded native or recombinant allergens	Major recombinant allergens (Api m 1, Bet v 1) are not refolded and lack the native conformation. IgE binding is abolished, T cell reactivity is protected.
Polymers of major allergens	Major allergen (Bet v 1) is trimerized. Mast cell, basophil degranulation is attenu ated, T cell reactivity is preserved in vitro.
Reconstitution of the natural extract with mixture of multiple recombinant allergens	
Mixture of several major recombinant allergens	Phl p 1, Phl p 2, Phl p 5a, Phl p 5b, Phl p 6 were used as a mixture of five recombinant grass pollen allergens.
Allergens coupled to adjuvants that stimulate various aspects of innate immunity	
GpG oligonucleotide-conjugated allergens	Toll-like receptor 9-triggering CpG oligonucleotide is fused to major ragweed allergen Amb a 1.
Allergens coupled to virus-like particles	Highly repetitive virus capside-like recombinant particles coupled to house dust mite major allergen Der p 1.
Carbohydrate-based particles	Carbohydrate-based particles-bound rPhl p 5b induced a stronger antibody and cytokine responses.
Hypoallergenic vaccine based on allergen- derived peptides fused to hepatitis B PreS	Recombinant fusion proteins show reduced allergenic activity in basophil activation and no IgE reactivity.
Monophosphoryl lipid A (MPL) formulated with allergoid	Th1-inducing adjuvant monophosphoryl lipid A (MPL) facilitates short-term SIT together with a grass pollen allergoid.
Novel routes of administration	
Intralymphatic vaccination	Allergen-SIT vaccines administered directly into inguinal lymph nodes with the aim to deliver high amounts of allergens into secondary lymphatic organs.
Epicutaneous vaccination	High numbers of antigen presenting cells (LCs), non-vascularized area, safe, needle-free, and potentially self-administrable.
Fusion of allergens with immune response modifiers	
Targeting FcγRII	Fusion of allergens with human Fcγ has been reported to inhibit allergen-induced basophil and mast cell degranulation by crosslinking Fcγ and FcεRI receptors.
Modular antigen trans-location (MAT) vaccines	The co-expression of major recombinant allergens together with transactivator of transcription (Tat) peptide and truncated invariant chain is able to target antigens to the MHC II molecules in the trans-golgi compartment.
Combination possibility with immune response modifiers	
Pre-treatment with anti-IgE mAb before SIT	To reduce SIT induced side effects. To enable relatively rapid dose increase. To use relatively high doses.

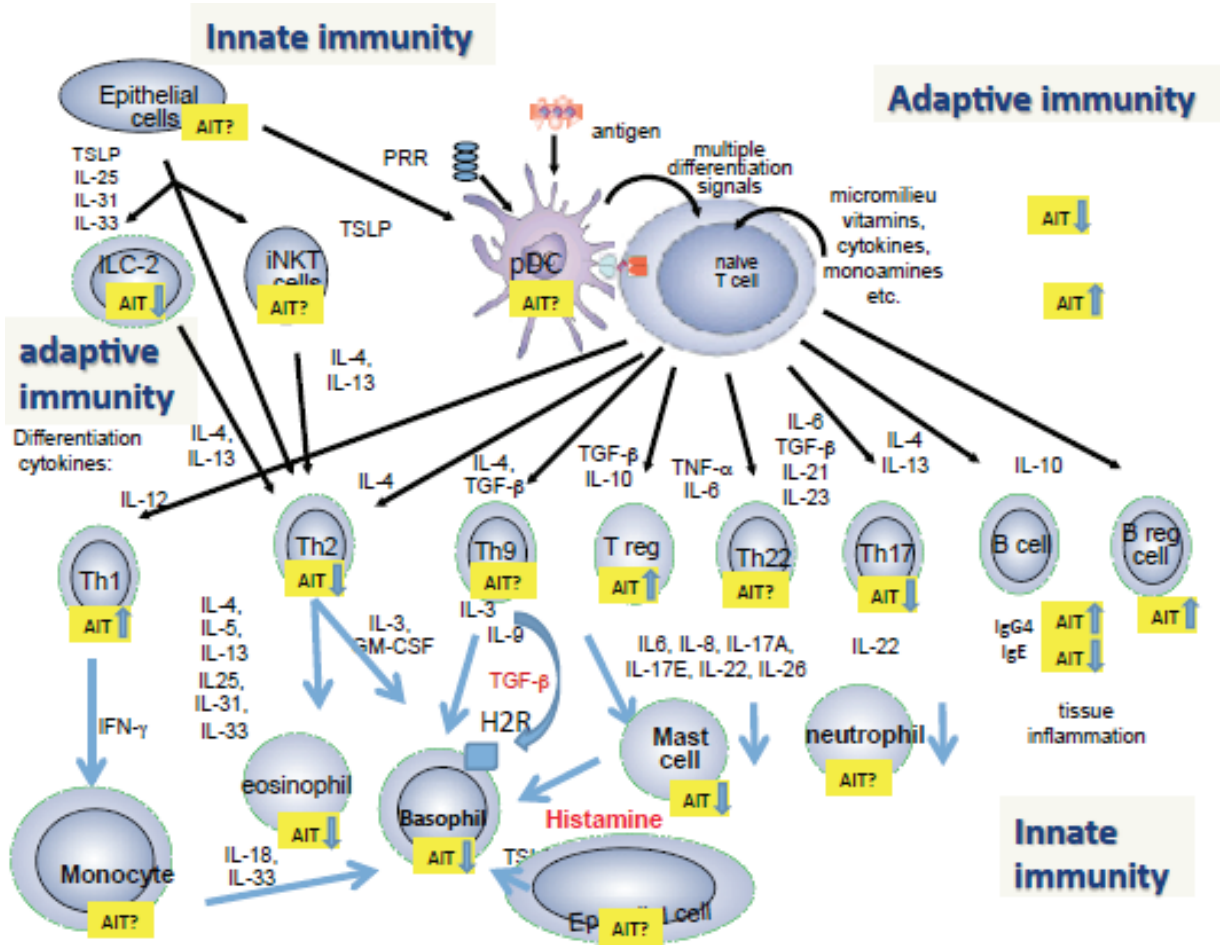

Figure 18

AIT targets both the innate and the adaptive immune response and the resident cells compartment. T and B regulatory cells are up-regulated, as well as Th1, while ILC2, basophils, mast cells, eosinophils, Th2, Th17 are downregulated. On B cells AIT shifts from IgE to IgG4 production. Arrows up: cells are upregulated by AIT. Arrows down: cells are downregulated by AIT. ?: possible effect *(Reproduced from Jutel M, Agache I et al. International Consensus on Allergen Immunotherapy II: Mechanisms, standardization, and pharmacoeconomics. J Allergy Clin Immunol. 2016;137(2):358-68)*

The International Consensus on Allergen Immunotherapy papers describe the current status of the AIT, mechanisms explaining the curative role (Figures 18 and 19), routes, schedules and duration of treatment and discusses in detail the role and challenges of AIT in the major allergic diseases: asthma, allergic rhinitis, food allergy and atopic dermatitis. Cost-effectiveness, safety of the intervention and regulatory guidance are thoroughly considered in balance with the efficacy and impact on patient's quality of life. The paper concludes that AIT is effective in reducing symptoms of allergic asthma and rhinitis. In addition, AIT modifies the underlying course of disease. However, AIT remains a niche treatment secondary to symptomatic drugs because of its cost, long duration of treatment, and concerns regarding safety and effectiveness. Worldwide the AIT "intention to treat" population is underserved. Further research is needed to develop novel therapies and optimize current ones and to accurate measure cost-efficacy. To these ends, having harmonized efficacy criteria, regulatory guidance, and reagent standardization would be of benefit. Also of benefit would be having biomarkers and phenotypes to predict the likelihood of response. As the mechanisms underlying disease continue to be elucidated, it is expected that novel strategies for AIT will continue to emerge. In spite of the progress in improving the efficacy and safety of AIT there is still the great potential for further modifications, which are hoped to broaden the pool of candidates for AIT, aiming at much better

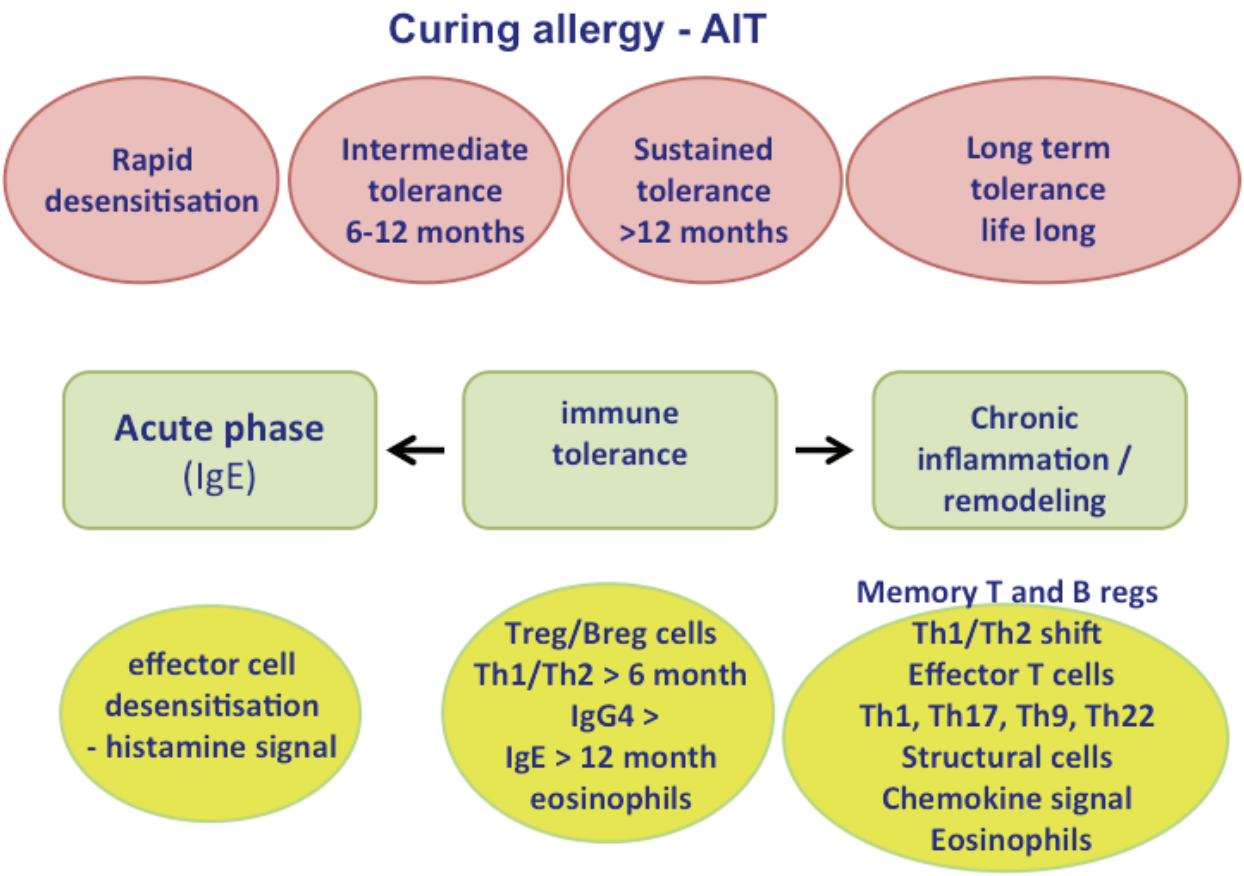

Figure 19

Effective AIT triggers multiple mechanisms, which are sequentially activated. AIT induced immune tolerance controls both the acute phase of the allergic reaction and the chronic inflammation leading to remodeling. Rapid desensitisation: A very early decrease in the susceptibility of mast cells and basophils to degranulation is observed. Mediators of anaphylaxis (histamine and leukotrienes) are released during AIT without inducing a systemic anaphylactic response. Several mechanisms have been proposed such as up-regulation of histamine type 2 receptors and decreased effector cell function as reflected by a decrease in allergen-stimulated surface expression of CD63. Early changes in basophil sensitivity predicts symptom relief with AIT. Immune tolerance involves the gradual increase in T and B regulatory cells and tolerogenic antibodies. Long term tolerance induced by AIT involves changes in memory T and B cell compartment, the Th1/Th2 shift, function of the effector and structural cells. *(Reproduced from Jutel M, Agache I et al. International Consensus on Allergen Immunotherapy II: Mechanisms, standardization, and pharmacoeconomics. J Allergy Clin Immunol. 2016;137(2):358-68)*

treatment and prevention of allergic diseases as well as other diseases related to immune dysregulation. However, the major barrier for the clinical application of these new technologies is the capacity to perform a large number of phase 3 confirmatory DBPC trials. Improvements of AIT vaccines are key for the progress in the allergy prevention and treatment. Research has focused on new vaccine formulations, which provide better efficacy and safety mainly by bypassing IgE responses and targeting T cells. Novel adjuvants, carrier proteins and new routes also show promising insights. The application of the advanced vaccines is limited by the high costs of clinical development. The paper also offers a balanced description of barriers and facilitators for effective implementation of AIT at a larger scale (Table 10).

Table 10

Barriers and facilitators in the application of AIT. AIT has been used to treat allergic disease since the early 1900s. Despite numerous clinical trials and meta-analyses proving AIT efficacious, it remains underused and is estimated to be used in less than 10% of patients with allergic rhinitis or asthma worldwide. In addition, there are large differences between regions, which are not only due to socioeconomic status. The international community of allergy specialists recognizes the need to harmonize, disseminate, and implement the best AIT practice. The elaboration of a wider consensus is of utmost importance because AIT is the only treatment that can change the course of allergic disease by preventing the development of asthma and new allergen sensitizations and by inducing allergen-specific immune tolerance. *(Adapted from Jutel M, Agache I et al. International consensus on allergy immunotherapy. J Allergy Clin Immunol. 2015;136(3):556-68)*

Barriers	
The application of AIT is limited in many areas due to the low awareness of AIT potential	World-wide acceptance and increased awareness that AIT reduces long-term costs and burden of allergies and potentially changes the natural course of the disease.
Regulations on AIT	Regulations on AIT have profound effects on allergy practice, allergen manufacturers, research programs. Especially in the EU allergy vaccines should undergo registration as all other drugs. There is a need for a standardized approach between regulatory agencies from different regions of the world.
Adherence to AIT	The demand of prolonged treatment over several years may impair patients' adherence
Facilitators	
Evidence-based documentation	Standardization, validation and consensus on the clinical outcome measures for clinical trials. Identification and validation of biomarkers for AIT monitoring. Environmental exposure chambers as suitable surrogates for natural allergen exposure (59,60). Validated tools for assessing effectiveness of AIT in real life – postmarketing studies.
Guidelines and recommendations	Standardization of guidelines and recommendations at the global and national society levels is necessary.
Better selection of patients	Diagnostic tools for better identification of clinically relevant patient's sensitization profile for a proper vaccine selection. Proper use of component-resolved diagnosis to identify potential responders and non-responders.
More convenient AIT regimens	Validation of different regimens (preseasonal, perennial), mode of updosing, duration of therapy, maximal dose, cumulative dose in terms of efficacy and safety.
Novel approaches	Existing evidence of efficacy and safety of novel approaches should be confirmed in independent phase 3 DBPC trials.
Pharmacoeconomics	More evidence on the overall cost-saving effects of AIT application. Limit the high costs of current treatment and clinical development.
Joint commitment	Coordinated actions among regulators, industry and the scientific environment to find solutions that properly answer the health expectations of the allergic patients

For allergic asthma AIT can be delivered either via the subcutaneous (SCIT) or sublingual (SLIT) route. Some alternative routes are under investigation. However, the efficacy of neither SLIT nor SCIT has been established for many allergens, especially the rare ones.

The current ARIA guidelines (100) give both SCIT and SLIT a conditional recommendation in allergic asthma due to moderate or low quality of evidence. According to the GINA report updated in 2016 (101) the efficacy of AIT in asthma is limited (level A evidence) and compared to pharmacological and avoidance options the benefit of both SCIT and SLIT must be weighed against the risk of side effects and the inconvenience and cost incurred by the prolonged course treatment, including the half on hour wait in the office for SCIT (level D evidence).

A limited number of studies has been specifically designed to evaluate AIT in asthma and only one with a formal sample size calculation. In addition no consensus exists on the optimal endpoints, with pulmonary function or asthma exacerbations assessed as primary outcome only sporadically. Yet, several double-blind, placebo-controlled trials and meta-analysis (potentially hampered by the heterogeneity of the trials included) confirmed that both SCIT and SLIT are of value in allergic asthma associated with allergic rhinitis by reducing symptom scores and medication use, improving quality of life and inducing favorable changes in specific immunologic markers.

Considering the unmet needs in AIT the European Academy of Allergy and Clinical Immunology is in the process of developing guidelines for public health using the AGREE II methodology for the AIT use in all allergic diseases. Ioana Agache is a member of the Steering Committee of the Guidelines Group and is leading the Task Force on AIT in asthma. The scope of the **AIT Asthma Guidelines** is to provide recommendations for indications and contraindications for AIT in asthma based on effectiveness, safety and cost-economic analysis and to identify gaps in knowledge and/or implementation, unmet needs and future perspectives. The AIT asthma Task Force included a wide range of countries, professional background (allergy, pediatrics, internal medicine, pediatric pulmonology, immunology, primary care, pharmacists) and patient representatives. Representatives of immunotherapy product manufactures were given the opportunity to review and comment on the draft guidelines, and, where appropriate, revisions were made. The AIT Asthma Guidelines are developed using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach (Agree Collaboration 2003; Brouwers 2010), a structured approach to guidelines for public health. The AGREE II methodology includes of a careful search for and critical appraisal of the relevant literature followed by a systematic approach to the formulation and presentation of recommendations while ensuring that the risk of bias is minimized at each step of the process. Appropriate representation of the full range of stakeholders, peer review and public comment and editorial independence, identifying gaps, barriers and facilitators are key features of the AGREE II approach. The AIT guidelines Task Force first met in April 2015 and an agreement was reached on the search strategy, key questions, formulating recommendations and the peer review process. Several other face-to-face meetings and webconferences followed including a broad representation of all stakeholders in each step of the guidelines. For a critical appraisal of the evidence published so far we performed both a systematic review (SR) and a narrative review. The protocol for the SR was published at the beginning of 2016 (102) and the results of the SR are currently under evaluation. Nine international databases were screened against predefined eligibility criteria (Table 11). The population of interest for the SR was allergic asthma of any age with a physician confirmed diagnosis of asthma and evidence of clinically relevant allergic sensitization as assessed by an objective biomarker (e.g., skin prick test or specific-IgE) in combination with a history of asthma symptoms due to allergen exposure. The intervention was AIT administered through subcutaneous (SCIT), or sublingual (SLIT) routes for the following allergens: pollens, house dust mites (HDM), animal dander, cockroach and mould with comparator placebo or active comparator. To assess effectiveness the SR included previous systematic reviews +/- meta-analysis and randomised controlled

Table 11

Primary and secondary outcomes considered in the SR for AIT in asthma. A limited number of studies have been specifically designed to evaluate AIT in asthma. In addition no consensus exists on the optimal endpoints. Most of the studies report on symptom and medication scores, thus these were considered as primary end-points, although secondary end-points such as exacerbations, asthma control and lung functions are more relevant to asthma. Unfortunately up until now they were assessed only sporadically and without a proper power calculation. *(Adapted from Dhami S, et al. Allergen immunotherapy for allergic asthma: protocol for a systematic review. Clin Transl Allergy. 2016;6:5)*

Primary outcomes	1. Effectiveness	Short term (during treatment)	Symptom score
		Long term (at least one year after discontinuation of treatment)	Medication score
			Symptom and medication score
	2. Cost-effectiveness		
	3. Safety		
Secondary outcomes	1. Asthma control		
	2. Asthma specific quality of life		
	3. Exacerbations		
	4. Lung function		
	5. Response to environmental exposure chamber or bronchial allergen challenge		
	6. Safety as assessed by local and systemic reactions		
	7. Health economic analysis from the perspective of the health system/payer		

trials (RCT). To assess health economics we used cost-effectiveness or cost-utility analysis. For assessing safety besides RCTs we included case series (>300 patients). In view of the co-morbidity with allergic rhinitis (AR), we included AR studies in the asthma SR if at least 80% of participants had asthma and/or if separate asthma outcomes were reported. Data were descriptively and, where possible and appropriate, quantitatively synthesised using random-effects meta-analyses. A subgroup analysis was conducted for children (<18) versus adults (≥18 years), SCIT versus SLIT; monosensitized/mono-allergic versus polysensitized; mild/moderate versus moderate/severe disease, treatment duration: ≤3 years versus >3 years. For studies and reports not included in the SR a narrative review was performed covering the following aspects: pediatric age groups (5-11 versus 12-18); rare allergens; the effect of background treatment (ICS vs no ICS); the effect of co-morbidities (nasal polyps/chronic rhinosinusitis/aspirin exacerbated respiratory disease, autoimmune diseases, food allergy, atopic dermatitis); the effect of smoking; AIT combination with biologics; adjuvants and alternative routes; recombinant allergens; AIT with multiple allergens; perennial versus preseasonal schedules; biomarkers for efficacy; provocation tests for patient selection.

1.4. PRECISION MEDICINE FOR ASTHMA

Precision medicine represents a novel approach, embracing four key features: personalized care based on molecular, immunologic and functional endotyping of the disease, with participation of the patient in the decision making process of therapeutic actions, and considering predictive and preventive aspects of the treatment (84, 103-106). The audacious goal of precision medicine is to deliver the right treatment, to the right patient at the right time (Figure 20).

Asthma, allergic rhinitis (AR), chronic rhinosinusitis (CRS), food allergy (FA) and atopic dermatitis (AD) are ideally suited for precision medicine, because they represent an umbrella of different diseases that partially share biological mechanisms (endotypes) and present similar visible properties (phenotypes) that require an individualized approach for a better selection of treatment responders, risk prediction and design of disease-modifying strategies (81, 84, 106). The precision in the clinic needs four main components: an improved disease taxonomy is a current unmet need because none of the disease endotypes in allergic diseases are included in the existing taxonomies; full patient monitoring using novel digital technology and the concept of endotypes and novel biomarkers is a must; improved understanding

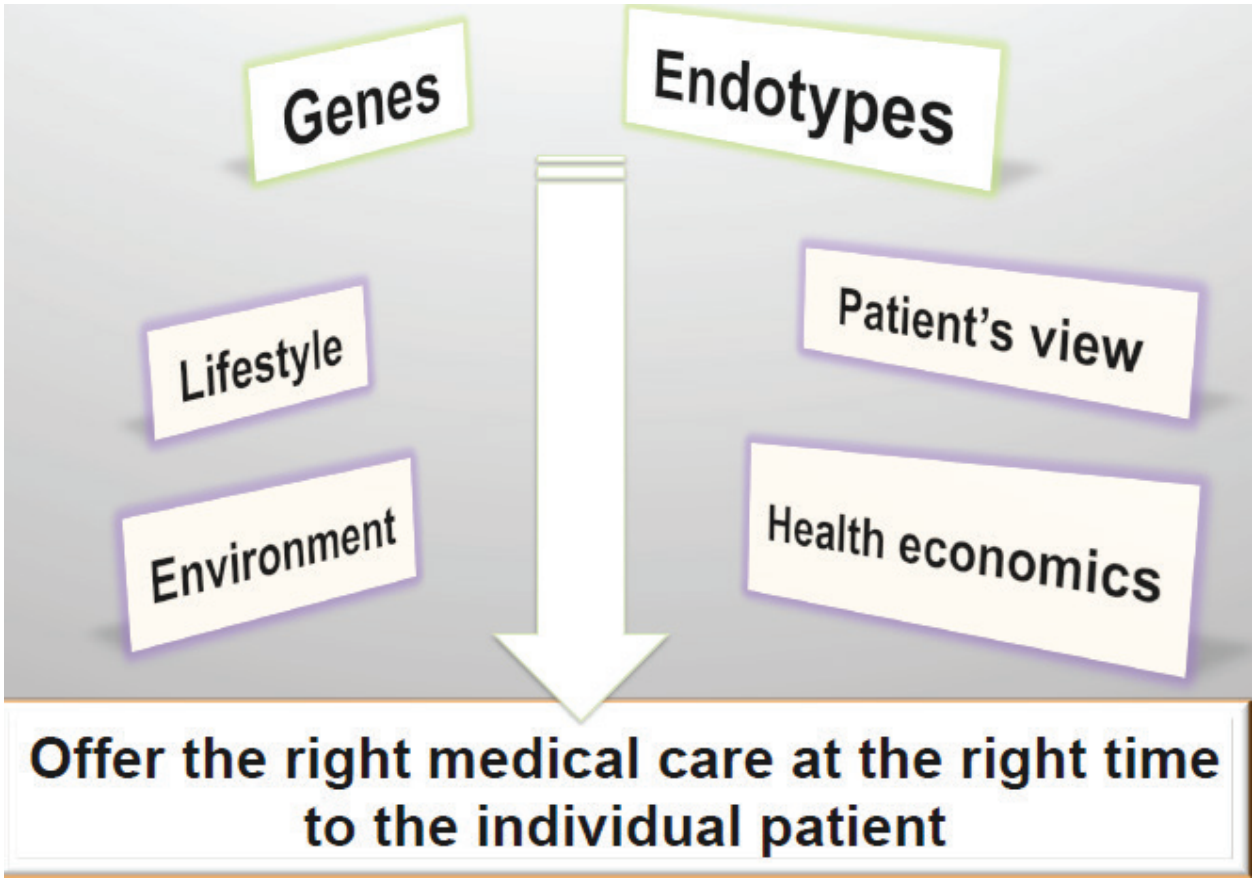

Figure 20

The audacious goal of precision medicine. Understanding the complex networks of molecular, genetic and environmental in combination with strong health economics data and in alignment with patients participation will open the door for prevention strategies and curative therapies for allergies and asthma. *(Reproduced from Agache I et al presentation at the European Rhinology Forum 2016)*

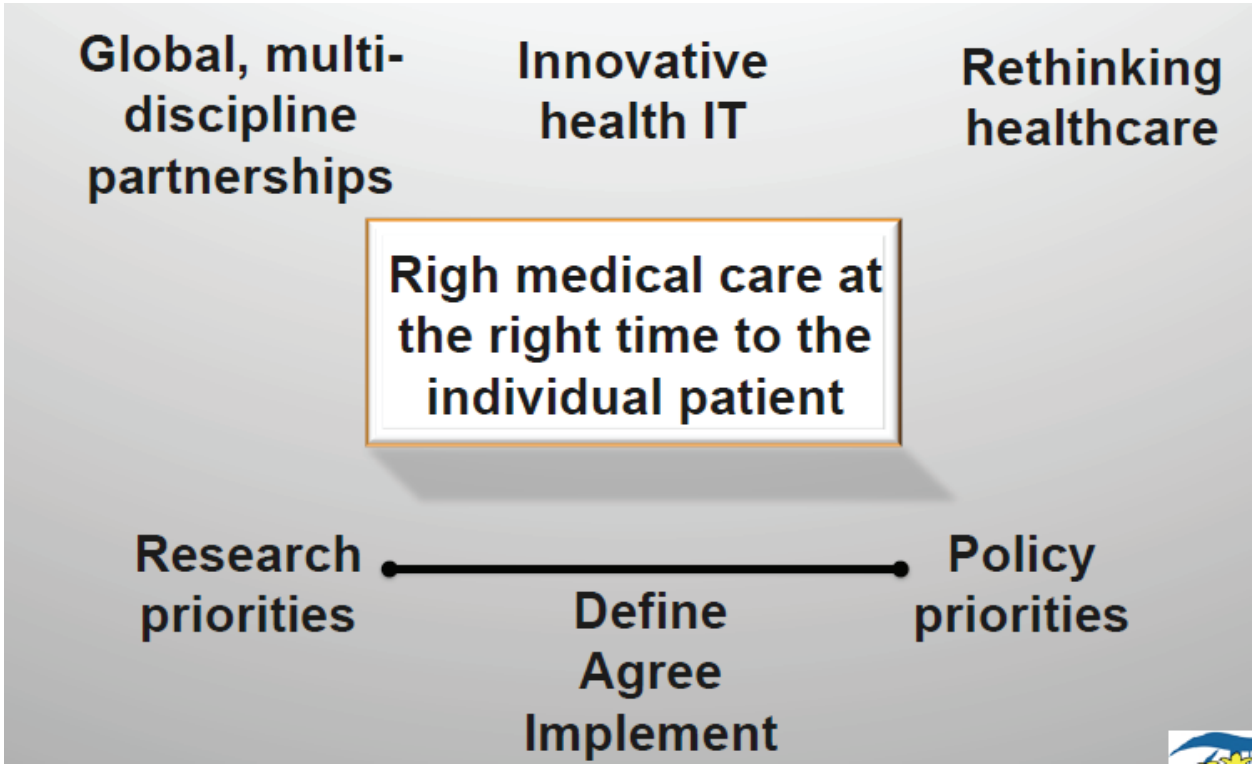

Figure 21

What we need to achieve the audacious goal of precision medicine. Harmonization between stakeholders and tools with agreement on a broad research program encouraging creative approaches and testing them rigorously both for robustness and for applicability for real life personalized care is needed to bring precision medicine to the clinic. *(Reproduced from Agache I et al presentation at the European Rhinology Forum 2016)*

and common usage of disease phenotypes, endotypes and biomarkers preferentially at the point of care; and finally biomarker and endotype-linked patient care and usage of precision therapies (103).

The Precision Medicine Initiative recently announced the need to move the field of precision medicine more rapidly into clinical care. As currently structured, it will primarily fund efforts in cancer genomics with longer-term goals of advancing precision medicine to all areas of health. This focused effort provides scientists, clinicians, and patients within the allergy community an opportunity to work together boldly to advance clinical care; the community needs to be aware and engaged in the process as it progresses (Figure 21).

To emphasize the importance of precision medicine in relation to endotyping of diseases, discovery of biomarkers, it will be good to quote a pioneer in precision medicine, Sir John Bell, Professor of Medicine at Oxford University, and Chairman of the Office for the Strategic Coordination of Health Research: "The best example of precision medicine in my opinion does not come from cancer, it comes from asthma. For this condition, we have gone more than 20 years without a new drug, because the disease was not defined very well." (http://www.pharmafile.com/news/.) As said, successful management of patients with severe asthma and allergic diseases continues to be a major unmet need. One of the barriers to successful management is the heterogeneity of the diseases with different phenotypes and endotypes. A revised paradigm for disease management, that entails categorization of patients via use of endotypes and multiomic biomarkers for prescribing targeted therapy, will replace the "one size fits all" approach to allergic diseases. The success of cytokine

inhibition defining the hierarchical position of distinct cytokines in allergic diseases pathogenesis with the description of meaningful clinical endotypes hold the promise to transform the therapeutic landscape in allergic diseases in a precision based fashion.

To move beyond a select few genes/drugs, the successful adoption of pharmacogenomics into routine clinical care and development of computational approaches and tools to effectively integrate multidomain data (such as cognitive IT-systems) are urgently needed for the development of newly targeted treatments. Real-time databases for molecular profiling data could become a pragmatic solution to several knowledge management problems in the practice and science of precision medicine. "Interventional informatics" approach can substantially improve human health and wellness through the use of data-driven interventions at the point of care of broader population levels. The collaborative medicine approach with open access to research databases worldwide will speed the discovery of new targets.

A major challenge for asthma researchers is to develop personalised approaches to treating patients with asthma because only then will we be able to treat patients as unique individuals rather than as a group (an approach called 'personalised medicine'). This approach will facilitate to select the responders to targeted treatment and to the implementation of a judicious cost-effectiveness strategy for the treatment of asthma patients. The following health indicators are expected to improve: number of asthma exacerbations, health-care utilisation including ER visits and hospitalisations, quality of life in parallel to decreased costs for asthma management both for the society and the patient.

The application of precision medicine to asthma comes as a compelling continuation of the phenotypes, endotypes and biomarkers field pioneered by Ioana Agache since 2009. In recognition of the achievements in the field the author was included in two prestigious Expert Panels reuniting the major scientific academies in the field of Asthma and Allergy – EAACI, ERS, European Rhinologic Society and AAAAI.

On October 14, 2015, EAACI, ERS and the European Medical Association (EMA) organized a symposium at the European Parliament in Brussels on Precision Medicine in Allergy and Airways Diseases, hosted by member of the European Parliament (MEP) David Borrelli and with active participation of the EU Commissioner for Health and Food Safety Vytenis Andriukaitis, the Interest Group on Allergy and Asthma of the European Parliament presided by MEP Sirpa Pietikainen, ERS, the European Federations of Allergy and Airways Diseases Patients Associations (EFA), the Global Allergy and Asthma European Network (Ga2len), ARIA, the Respiratory Effectiveness Group (REG), and the European Innovation Partnership on Active and Healthy Ageing. Participants discussed how precision medicine will increase the knowledge on chronic airway diseases, their prevention, early detection, and appropriate management in order to propose innovative solutions for improving the socioeconomic challenge across the life cycle and ultimately to promote active and healthy aging. A consensus document **European Symposium on Precision Medicine in Allergy and Airways Diseases: Report of the European Union Parliament Symposium (October 14, 2015)** was published both in Allergy and in Rhinology journals (105). The document highlights the current challenges of allergies and chronic respiratory diseases in Europe (Figure 22) and advocates for a joint and innovative action plan at the EU level, with precision medicine at its core (Figure 23). The concept of precision medicine is not new, as the analysis of the sensitization profile of allergic patients has been the diagnostic basis for the start of personalized, allergen-specific immunotherapy for decades (107). The prospect of broadly applying precision medicine in the field of allergy and chronic airways diseases is, however, novel. The 4Ps of precision medicine and their applicability to allergy and asthma are thoroughly described:

- **Personalized care** is a medical practice that proposes customization of health care, with medical decisions, practices, and/or products being tailored to the individual patient.

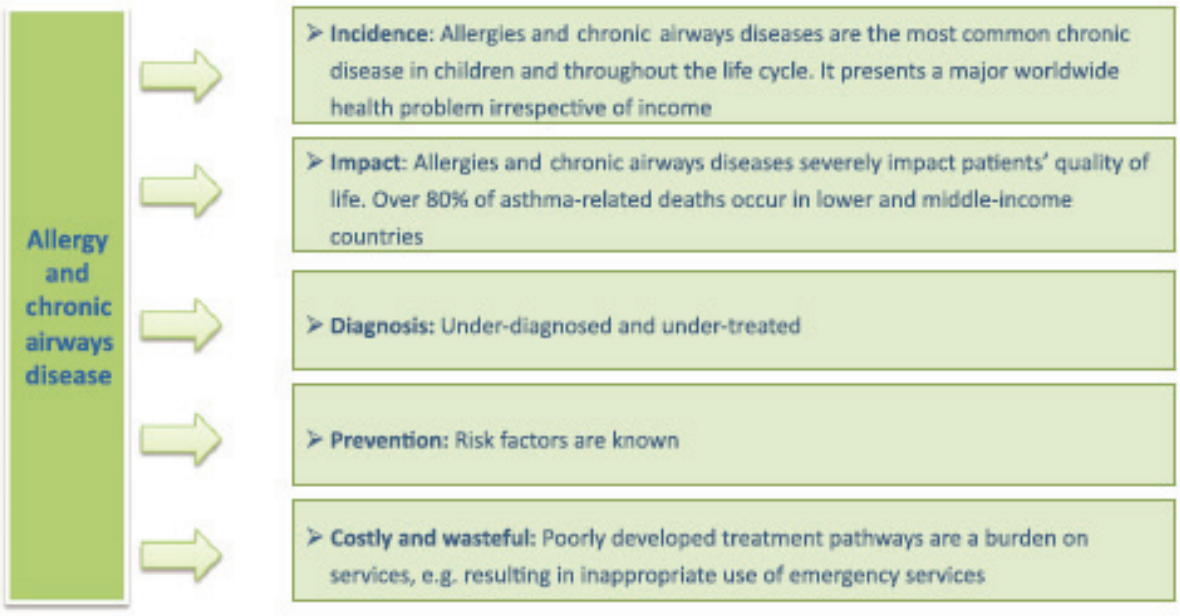

Figure 22

Current challenges in allergies and asthma. One-third of the population in Europe is suffering from allergies and asthma, with a prevalence reaching 40% in the population under the age of 60. These diseases often begin early in life and persist throughout the life cycle, affecting all age groups and have a heavy impact on productivity, quality of life and school performance. Modifiable risk factors are known, including allergens, tobacco smoke, and outdoor and indoor pollution *(air quality). Health promotion and prevention strategies should be better implemented across policy areas. (Reproduced from Muraro A, et al. European Symposium on Precision Medicine in Allergy and Airways Diseases: Report of the European Union Parliament Symposium (October 14, 2015). Allergy. 2016 71(5):583-7)*

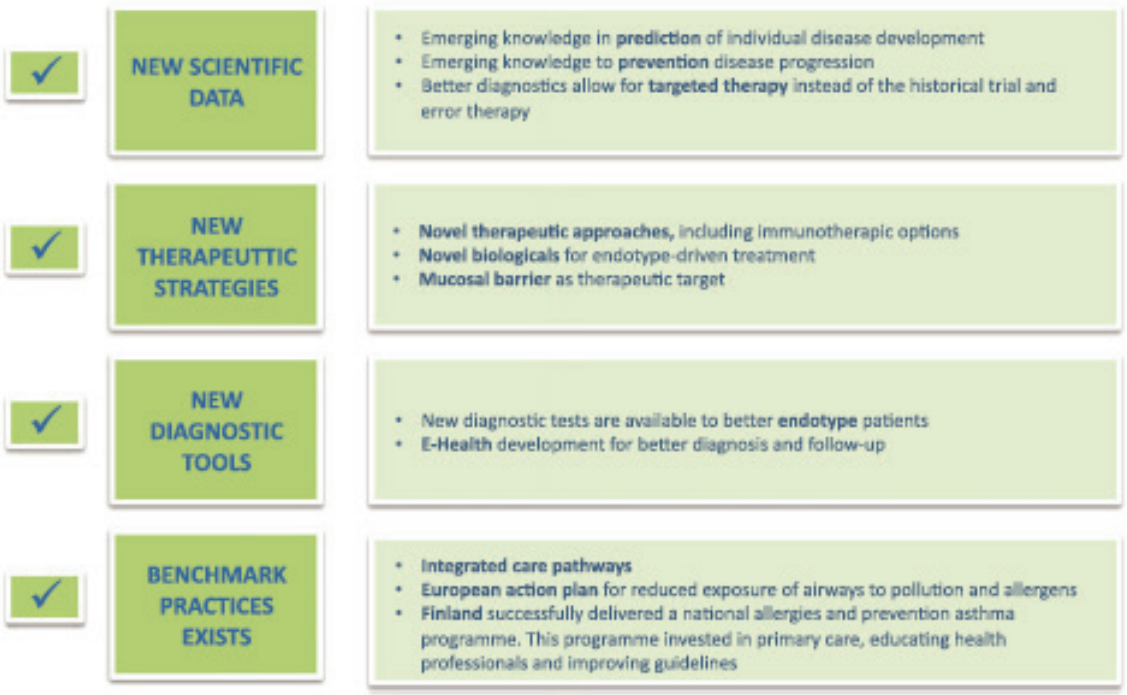

Figure 23

Top reasons for an action plan on precision medicine in allergy and asthma. *(Reproduced from Muraro A, et al. European Symposium on Precision Medicine in Allergy and Airways Diseases: Report of the European Union Parliament Symposium (October 14, 2015). Allergy. 2016 71(5):583-7)*

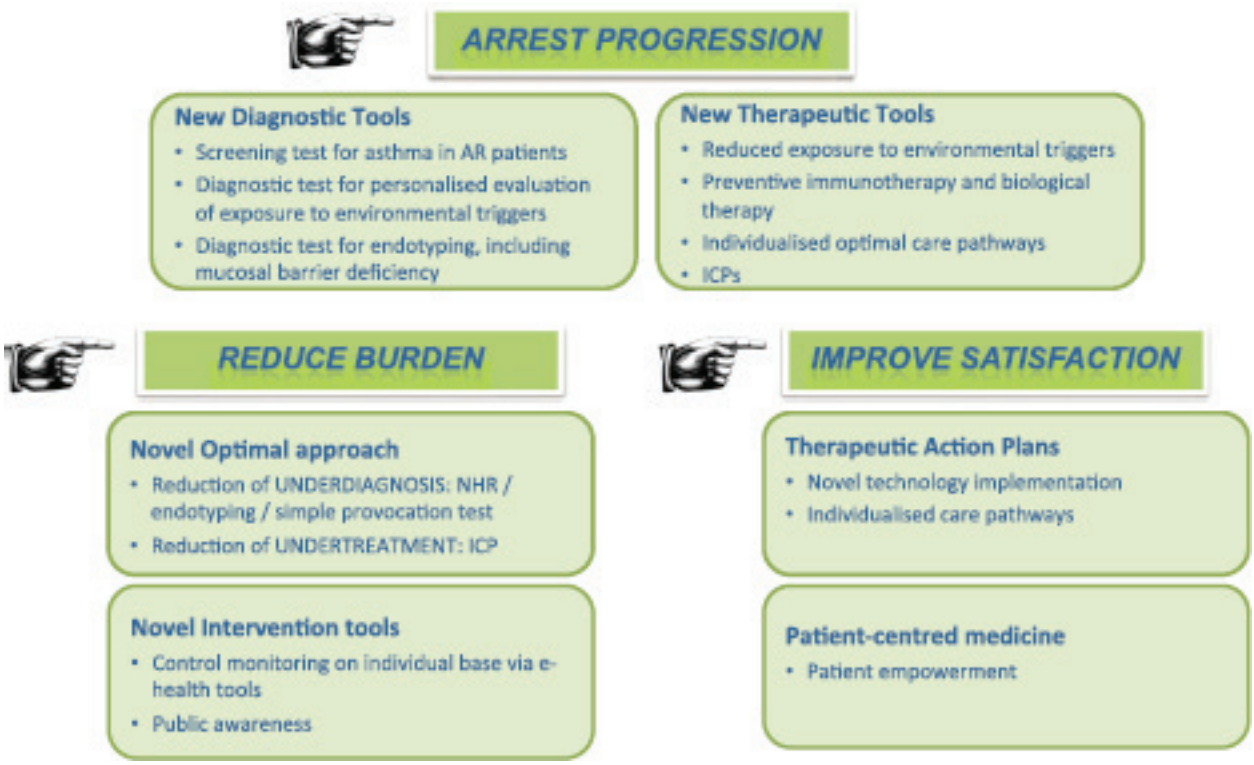

Figure 24

Aims of precision medicine in allergy and asthma. With the boost provided by new diagnostic and therapeutic tools the new model of patient-centered medicine intents to reduce the disease burden and improve satisfaction on multiple levels: the healthcare system, the regulators and payers and the patients. *(Reproduced from Muraro A, et al. European Symposium on Precision Medicine in Allergy and Airways Diseases: Report of the European Union Parliament Symposium (October 14, 2015). Allergy. 2016 71(5):583-7)*

- **Prediction of the natural progress of disease and of the success of treatment** allows the medical doctor as well as the patient to decide on the best therapeutic strategy.
- **Prevention of disease** should be distinguished in primary, secondary, and tertiary prevention. Preventive measures should be advised to prevent the disease from occurring (primary), to prevent the disease from becoming symptomatic (secondary), and to prevent from causing damage or disability (tertiary).
- **Participation of the patient** in the therapeutic plan is crucial for achieving good adherence and hence optimal efficacy of treatment.

The action plan proposed is based on emerging new scientific allowing prediction and prevention, novel diagnostic tools are emerging, allowing better immunologic and functional endotyping of the patient such as component-resolved diagnosis (CRD) allowing the evaluation of the individual sensitization pattern to environmental allergens (108), while novel e-health tools allow for better follow-up of patients. In addition novel therapeutic strategies, such as endotype-driven approach, are emerging allowing the design of novel therapeutic strategies, including allergen immunotherapy and biologicals. Elaboration and implementation of optimal care pathways (22) following the principles of precision medicine in allergology and chronic airways diseases may lead to arrest the epidemic and to reduce the socioeconomic burden of allergies and chronic airways diseases (Figure 24).

The second expert panel reunited representatives of the two top Allergy Academies, EAACI and AAAAI, under the PRACTALL (Practical Aspects of Allergy) initiative on precision medicine in allergy and asthma. Ioana Agache is the last author of the consensus document

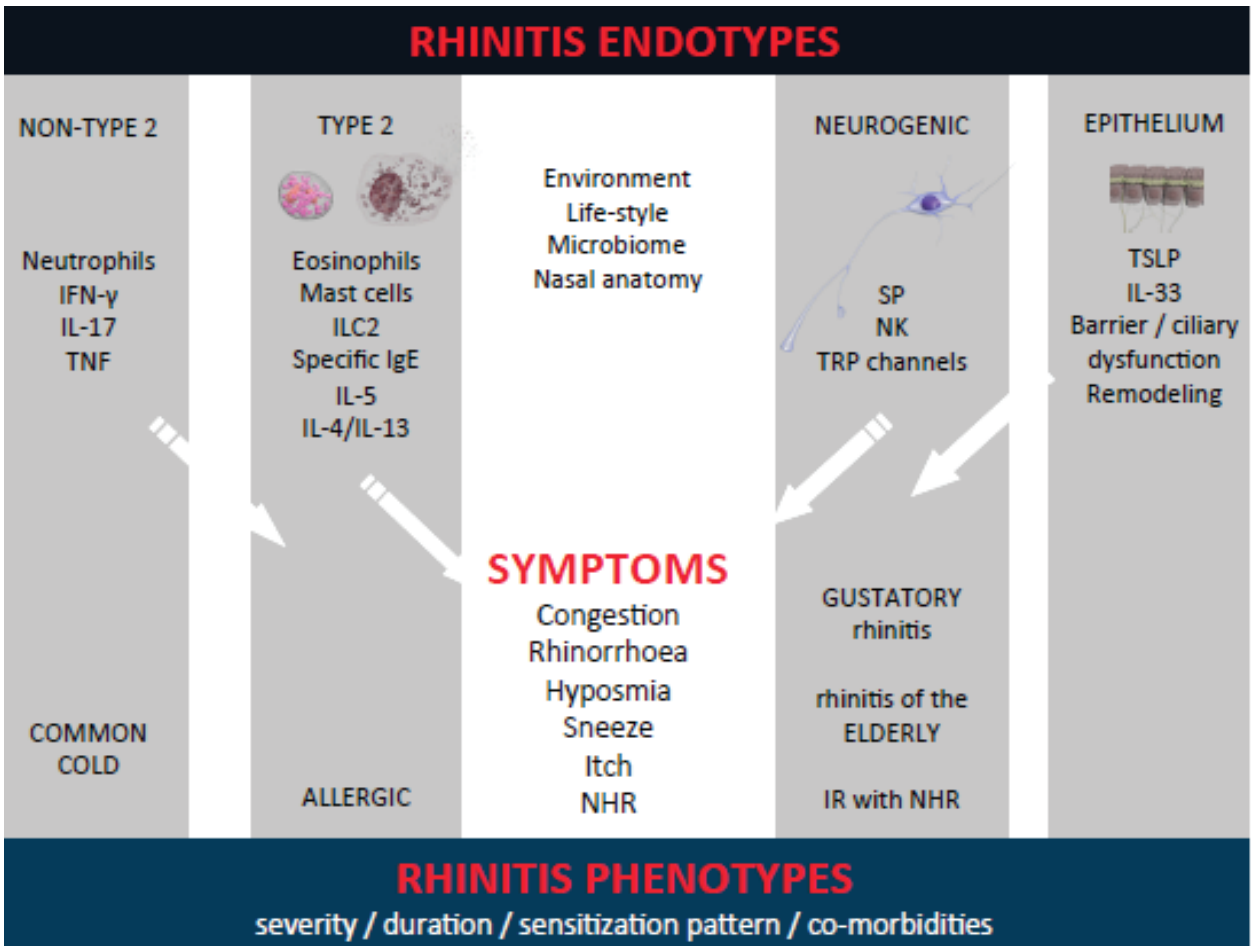

Figure 25

Overview of rhinitis phenotypes and endotypes Similar to asthma a type 2 immune response and non-type 2 immune response endotype can be described for rhinitis. Neurogenic and epithelial barrier dysfunction endotypes are particularly relevant for rhinitis. *(Reproduced from Muraro A, et al. Precision medicine in patients with allergic diseases: airway diseases and atopic dermatitis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2016;137(5):1347-58)*

(110) "***Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology***", published in a high impact journal (JACI) in 2016 and cited until now 14 times. The paper summarises the current knowledge on asthma, rhinitis and atopic dermatitis endotypes. Besides reinforcing the value of asthma endotypes and subendotypes, developed by Ioana Agache in the last decade into a strong validated concept, the paper describes innovative aspects on rhinitis and atopic dermatitis (AD) endotypes, building on the scaffold of asthma introduced by Ioana Agache. For rhinitis the following endotypes are being proposed (Figure 25): type 2 and type 1 immune response rhinitis, neurogenic rhinitis and epithelial dysfunction. In clinical practice, efforts can be made in endotyping rhinitis patients by measuring total and specific IgE, blood eosinophils, nasal eosinophils and neutrophils. Several other biomarkers are used in research settings such as serum IL-5, nasal total and specific IgE, eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP), IL-5, substance P (SP), neurokinin (NK)-1, IL-33, thymic stromal lymphopoietin (TSLP) and staining of mucosal biopsies for vanilloid receptor–related transient receptor potential (TRPV-1) channels, zonulla (ZO)-1 or occludin. These biomarkers should ideally be supplemented by nasal

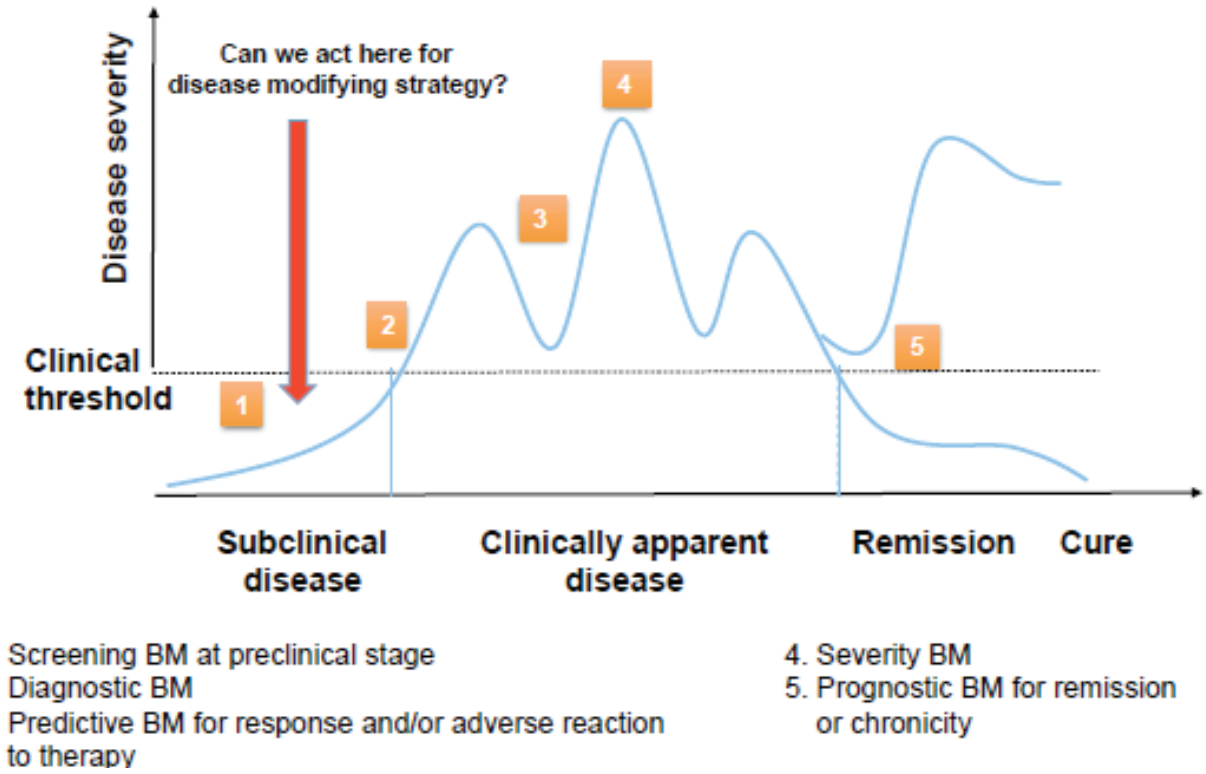

Figure 26

Biomarkers in the management of early-onset disease at different time points throughout the natural history of atopic dermatitis. *(Reproduced from Muraro A, et al. Precision medicine in patients with allergic diseases: airway diseases and atopic dermatitis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2016;137(5):1347-58)*

function measurements such as nasal flow measurement (to confirm nasal obstruction) and cold dry air provocation (to determine nasal hyperreactivity), nasal NO (to measure nasal inflammation), nasal allergen provocation (to confirm the clinical relevance of allergens), evaluation of smell performance (in patients mentioning reduced smell capacity). Following the example of endotype-driven treatment in asthma, another concept pioneered by Ioana Agache, the paper proposes increased focus on endotype-driven treatment in rhinitis exemplified by allergen-specific immunotherapy (AIT) in patients in whom an allergen-induced type 2 immune response endotype leads to clinically relevant exposure-symptom relation and by thehighly successful intervention with capsaicin for the neurogenic endotype. Precision medicine is of broad relevance for the management of AD, which is known to have a diverse natural history ranging from complete remission, relapsing flares to very severe and persistent forms, variably associated with comorbidities such as asthma and AR. Biomarkers could be useful in the management of early-onset disease at different time points throughout the natural history of AD (Figure 26). The paper introduces the innovative concept of prognostic biomarkers, valuable for primary and secondary prevention.

The consensus document also provided essential precision medicine steps for the clinician and researcher (Figures 27 and 28). After a correct diagnosis and proper management of co-morbidities a crucial step is to unravel which pathophysiological mechanism(s) is driving the disease, thereby determining the endotype of the patient and provide validated pathway-specific diagnostic tests.

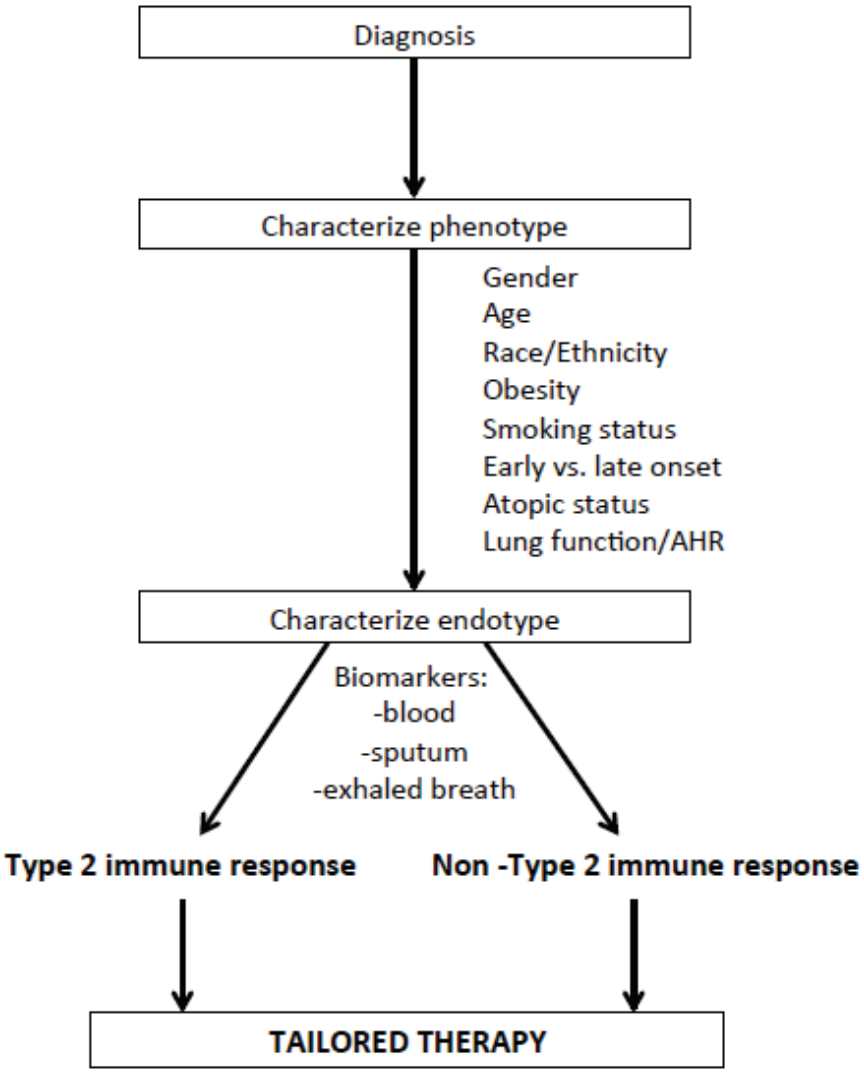

Figure 27

Suggested approach to precision medicine in asthma. First correct diagnosis of asthma should be verified and co-morbidities treated properly. In a second step phenotype is established based on visible properties. Further characterization of the patients' endotype is crucial to ensure the optimum response to treatment and risk prediction, especially for severe and uncontrolled disease. *(Reproduced from Muraro A, et al. Precision medicine in patients with allergic diseases: airway diseases and atopic dermatitis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2016;137(5):1347-58)*

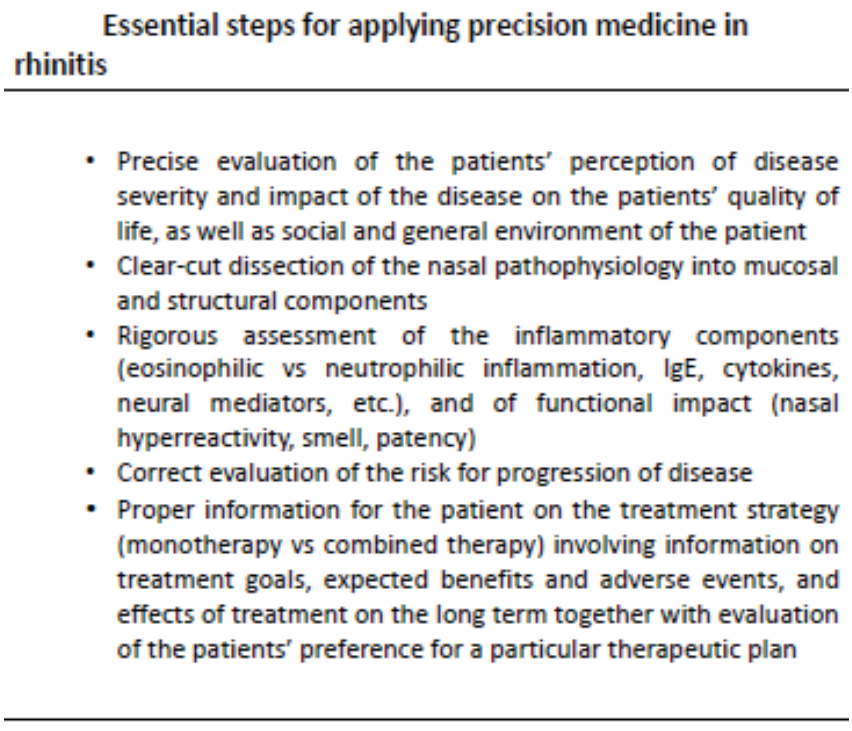

Figure 28

Suggested approach to precision medicine in rhinitis. The 4Ps principle of precision medicine is applied: personalised approach based on disease endotype and biomarkers, preventive and predictive aspects and participation of the patient. *(Reproduced from Muraro A, et al. Precision medicine in patients with allergic diseases: airway diseases and atopic dermatitis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2016;137(5):1347-58)*

1.5. ASTHMA CO-MORBIDITIES AND ENVIRONMENTAL INFLUENCES

The term comorbidity is frequently misapplied if one accepts the preferred definition, that is, a coexistent disease or condition. In this context, comorbid conditions occur together but do not necessarily influence one another. In contrast, clinicians frequently use the term comorbidity to describe conditions that mutually affect the other, as such interactions complicate diagnosis, management, and assessment more than coincident diseases.

Asthma comorbidity refers to a condition that influences asthma severity, management, or recognition or when referring to a disease affected by asthma. These relationships include increased severity of one or both diseases, an increased prevalence of one disease as a result of the other, a shared pathogenic process between the two, and misattribution of shared symptoms. Since asthma has a variable time of onset and clinical course its comorbidities will vary with age and clinical context.

Asthma control is based partially upon symptoms that are shared or influenced by many comorbid conditions. Surveys show in a variety of settings that achieving optimal asthma control varies from 30 to 70% (111, 112). Individuals who do not respond or respond inconsistently to asthma treatment often have comorbidity. These comorbidities may result in misdiagnosis, misinterpretation of symptoms, aggravation of one or both diseases, or decreased adherence. Recognition of these comorbidities facilitates more appropriate therapy or reduction of potentially risky therapies, such as systemic corticosteroids (113, 114). Comorbidities increase the likelihood of poorly controlled asthma as evidenced by a relatively small study by ten Brinke et al. Individuals with a confirmed diagnosis of asthma and frequent exacerbations were surveyed for coexisting conditions. The association was calculated for a specific comorbidity and the likelihood of more frequent asthma exacerbations. One hundred and thirty-six individuals completed the survey. The odds ratio (OR) of experiencing an asthma exacerbation was increased 10.8-fold by depression, 4.9-fold by GERD, 3.7-fold by severe sinus disease, and 3.4-fold by obstructive sleep apnea (115).

Several co-morbidities are described for asthma, such as allergic rhinitis, food allergy, atopic dermatitis, gatro-esophageal reflux, obesity. In addition, infections, particularly viral infections, are the major trigger of asthma exacerbations, both in adults and in children. Furthermore, lifestyle with diet, exercise and smoking, is a strong influencer of asthma control and is key to primary and secondary prevention of asthma.

Given the primary focus of Ioana Agache on pediatric and adult asthma research asthma comorbidities are an essential component of the scientific focus of the author.

A. ALLERGIC RHINITIS

Allergic rhinitis is a global health problem that causes major illness and disability worldwide. Patients from all countries, all ethnic groups and of all ages suffer from allergic rhinitis. It affects social life, sleep, school and work. The economic impact of allergic rhinitis is often underestimated because the disease does not induce elevated direct costs. However, the indirect costs are substantial.

Using a conservative estimate, AR occurs in over 500 million people around the world. The prevalence of AR is increasing in most countries of the world, and particularly in areas with low or medium levels of prevalence.

Both allergic rhinitis and asthma are systemic inflammatory conditions and are often co-morbidities. The prevalence of asthma in patients with rhinitis varies from 10% to 40%, and up to 98% of asthmatic patients have rhinitis. The concept of united airways or one airway disease is supported by experimental, clinical and epidemiological data (116-118).

The links between rhinitis and asthma are several folds:

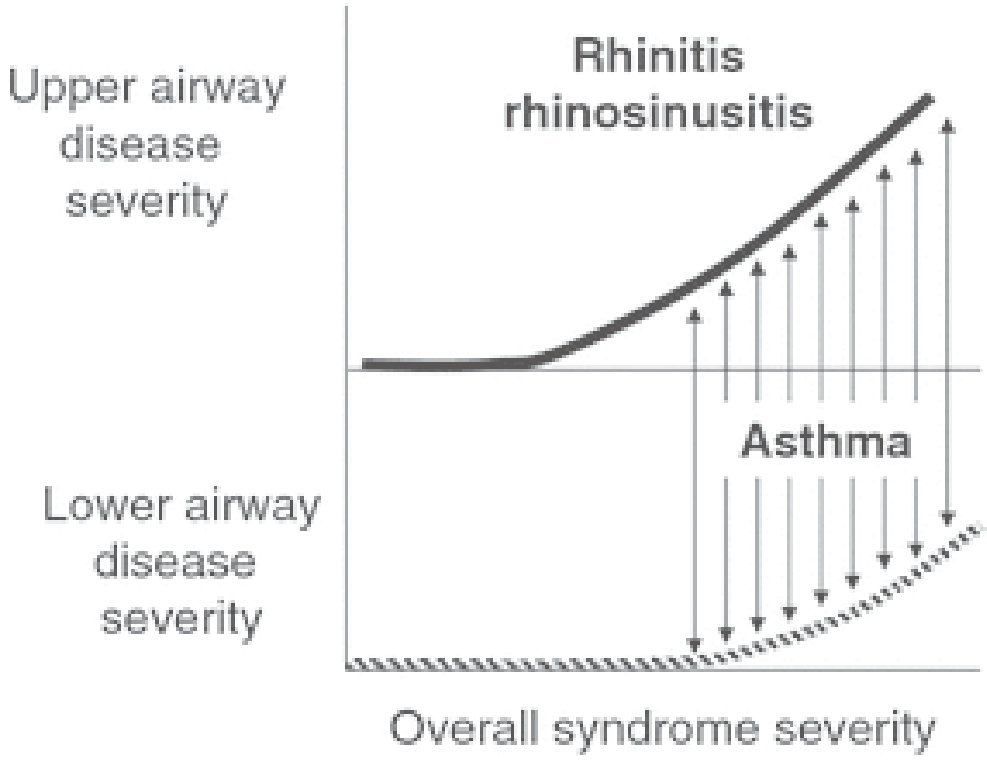

Figure 29

Links between asthma and rhinitis severity. A model has been proposed to illustrate the relationship between allergic rhinitis and asthma severity. The basic principle is that the two conditions are manifestations of one syndrome in two parts of the respiratory tract and that the more severe the rhinitis, the more severe the asthma. *(Reproduced from Bousquet J, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;63 Suppl 86:8-160)*

a. Both allergic and non-allergic rhinitis are risk factors for asthma (119) and proper rhinitis treatment could prevent the development of asthma (primary prevention)

b. The coexistence of rhinitis with asthma impairs significantly asthma control, thus rhinitis control prevents asthma worsening (120, 121) (secondary prevention) (Figure 29).

Thus, as a major co-morbidity of asthma, allergic rhinitis represented a special focus of the research of Ioana Agache, from international guidelines authorship to epidemiology of the disease and risk factors, new treatments for AR evaluated both in randomized control trials (RCT) and real-life scenarios and new models of care.

A1. Authorship of International Guidelines for AR

A first major achievement was the inclusion in the author panel of the Allergic Rhinitis and its impact on Asthma (ARIA). The Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update was published in 2008 in the Allergy journal (19) and was cited until now 7012 times.

The ARIA guidelines process started in 1999 and was intended to be a state-of-the-art for the specialist as well as for the general practitioner and other healthcare professionals (HCP):

- To update their knowledge of allergic rhinitis;
- To highlight the impact of allergic rhinitis on asthma;
- To provide an evidence-based documented revision on diagnostic methods;

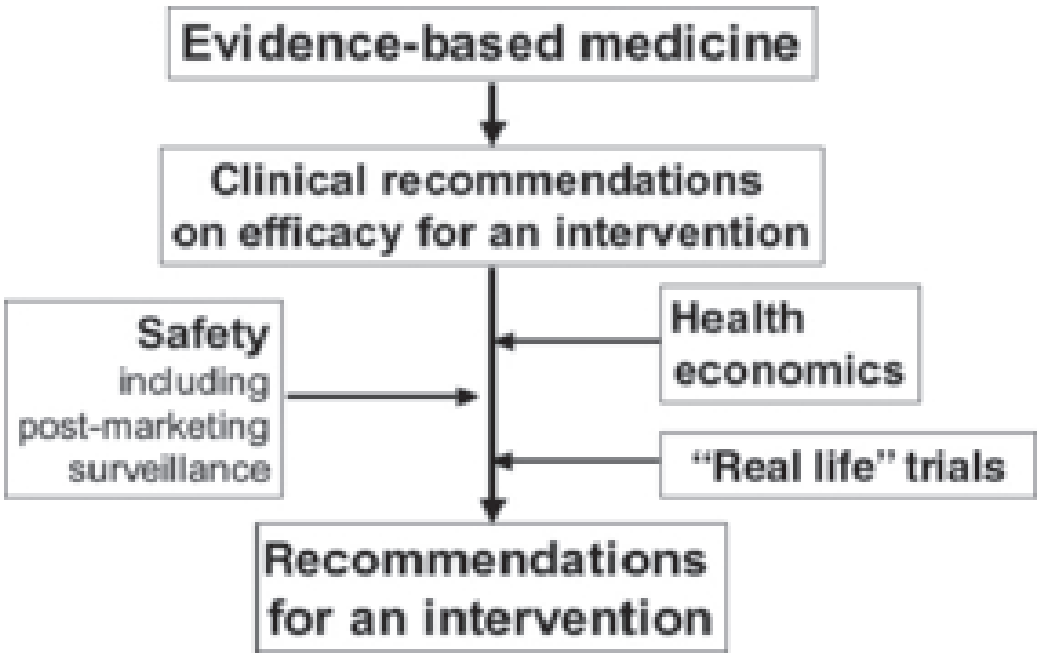

Figure 30

Development of guidelines. Clinical recommendations on efficacy are evaluated versus safety data, health economics and real life input (effectiveness) in order to formulate the final recommendation for an intervention. (Reproduced from Bousquet J, et al. MACVIA-ARIA Sentinel NetworK for allergic rhinitis (MASK-rhinitis): *the new generation guideline implementation. Allergy. 2015;70(11):1372-92)*

- To provide an evidence-based revision on treatments and
- To propose a stepwise approach to management.

In 1999, during the ARIA World Health Organization (WHO) workshop, the suggestions were made by a panel of experts and based on evidence using an extensive review of the literature available up to December 1999 (122). The statements of evidence for the development of these guidelines followed WHO rules and were based on those of Shekelle et al (123).

ARIA 2008 revision aimed to:

- Develop an evidence-based global document (Figure 30) on a key problem of respiratory medicine including diagnosis, epidemiology, common risk factors, management and prevention;
- Propose educational materials for HCP and patients
- Meet the objectives of the WHO Global Alliance against Chronic Respiratory Diseases (GARD; 29) in order to help coordinate the efforts of the different GARD organizations towards a better prevention and management of chronic respiratory diseases (CRDs), to increase CRDs awareness and also to fill some of the gaps in knowledge;
- Focus on the prevention of chronic respiratory and allergic diseases
- Highlight gaps in knowledge, particularly in developing countries and deprived areas
- Prepare an executive summary and pocket guide for doctors, patients and healthcare professionals

The author had a special focus in delivering the recommendations for evaluation and management of asthma in patients with AR. An easy to follow algorithm is provided (Figure 31).

ARIA is a guideline for public health. Guidelines are documents that synthesize current evidence on how to most effectively organize and deliver health services for a given condition. They inform healthcare decision-making and can serve as the basis for policy, planning, evaluation, and quality improvement.

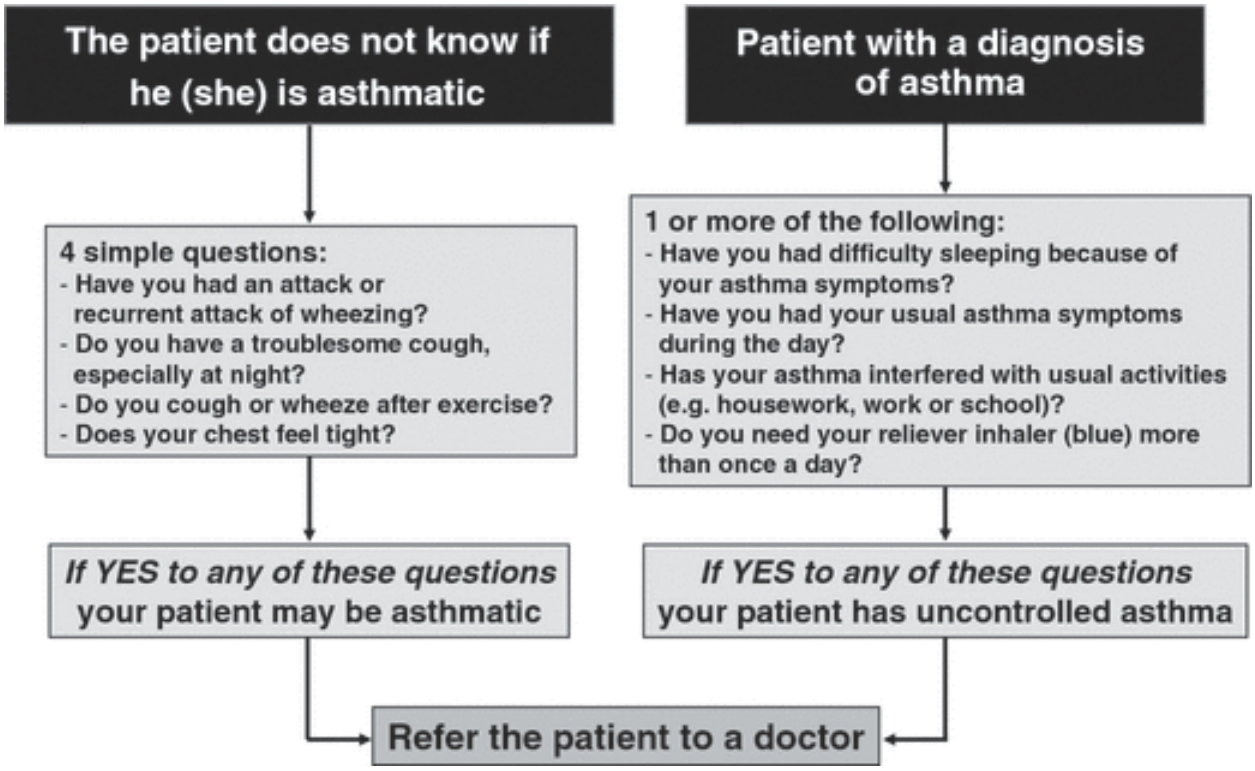

Figure 31

Diagnosis of asthma in patients with rhinitis. Two clinical scenarios (with or without an asthma diagnosis) are provided in order to assess the presence of asthma or the control of the disease impacted by the rhinitis association. (Reproduced from Bousquet J, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in *collaboration with the World Health Organization, GA(2) LEN and AllerGen). Allergy. 2008;63 Suppl 86:8-160)*

When newly developed, or when evaluation identifies suboptimal compliance, efforts are needed to promote awareness, acceptance, adoption, and adherence to guidelines. Such efforts include dissemination (posting on a web site, publishing in a journal, presenting information at a meeting) or implementation (purposeful strategies that employ educational, social, organizational, financial or technological means of promoting guideline use. Many issues challenge guideline implementation. A variety of contextual factors at the individual, institutional and system level often co-exist and pose significant challenges to guideline implementation and use. Promotional efforts by guideline developers may be constrained by lack of resources so implementation is often the responsibility of target users. Regardless of whether implementation is undertaken by developers or users, implementation is further complicated by two key factors. One, while instruments exist to assess barriers of guideline use, or organizational capacity or readiness to adopt guidelines, these do not reliably identify the most appropriate implementation strategy for a given guidelines. Two, implementation planning most often occurs upon guideline completion. Implementation could be more successful if planning were concurrent rather than consecutive to guideline development so that the recommendations were clear and useable, target users were primed for adoption, and their needs and preferences, and insight on contextual factors could inform implementation planning. This may also reduce the time required for guidelines to be adopted into policy or practice by avoiding a lengthy waiting period from guideline completion to implementation planning, and actual execution of implementation activities. Recently a checklist for guidelines implementation was published (124).

After its publication ARIA guideline was followed by tremendous efforts for dissemination and implementation. Immediately after its release, a local adaptation for Romania was published in 2009 by Ioana Agache as first author (125). A consecutive paper published in Allergy in 2010 (126), cited 89 times to present. In these papers the authors, including Ioana Agache, thoroughly describe how ARIA recommendations were formulated in order to improve understanding and acceptance by all stakeholders. Most patients with rhinitis and asthma consult primary care physicians and pharmacists and therefore these HCP are encouraged to understand and use ARIA guidelines. Patients should also be informed about these guidelines to raise their awareness of optimal care and increase control of the two related diseases. To apply these guidelines, clinicians and patients need to understand how and why the recommendations were made. The goal of the ARIA guidelines is to provide recommendations about the best management options for most patients in most situations. These recommendations should be based on the best available evidence. Making recommendations requires the assessment of the quality of available evidence, deciding on the balance between benefits and downsides, consideration of patients' values and preferences, and, if applicable, resource implications. Guidelines must be updated as new management options become available or important new evidence emerges. Transparent reporting of guidelines facilitates understanding and acceptance, but implementation strategies need to be improved.

The ARIA guideline was reviewed in 2010 and in 2016 and on both occasions Ioana Agache was part of the Expert Panel.

The 2010 review (100) presents recommendations about the prevention of allergic diseases, the use of oral and topical medications, allergen specific immunotherapy, and complementary treatments in patients with allergic rhinitis as well as patients with both allergic rhinitis and asthma. The guideline panel developed evidence profiles for each recommendation and considered health benefits and harms, burden, patient preferences, and resource use, when appropriate, to formulate recommendations for patients, clinicians, and other health care professionals.

Both the Executive Summary and the full text of the 2016 revision have been recently submitted (127). The objective of the 2016 document is to provide a targeted revision of treatment options in AR. The ARIA guideline panel identified new clinical questions and questions that required an update: nasal and ocular symptoms, quality of life, work/school performance, and adverse effects. We performed systematic reviews of health effects and reviewed the evidence about patient values and preferences, and resource requirements (up to June 2016). We followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence to decision frameworks to develop recommendations. We labeled the recommendations as either "strong" or "conditional" according to the GRADE approach. We used the words "we recommend" for strong recommendations and "we suggest" for conditional recommendations. Table 12 provides suggested interpretation of strong and conditional recommendations. The ARIA guideline 2016 revision provides recommendations about the use of 1) a combination of oral H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone, 2) a combination of intranasal H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone; 3) a combination of an intranasal H1-antihistamine and an intranasal corticosteroid vs. intranasal H1-antihistamine alone, 4) a leukotriene receptor antagonist vs. oral H1-antihistamine, 5) an intranasal H1-antihistamine vs. an intranasal corticosteroid, and 6) an intranasal H1-antihistamine vs. an oral H1-antihistamine in treatment of allergic rhinitis.

The impact of ARIA guidelines was evaluated in 2012 (20). Ten years after the publication of the ARIA WHO workshop report the guideline is disseminated and implemented in more than 50 countries of the world and its recommendations are included in several guidelines recommended by governments (e.g. Brazil and Singapore) or scientific societies. Global applicability of ARIA is highlighted in terms of management in clinical practice, personalised medicine, usability by all stakeholders (patients, primary care physicians, pharmacists,

Table 12

Strength of recommendation. *(Adapted from Brożek JL, Bousquet J, Agache I, Agarval A, Bachert C, Bosnic-Anticevich S et al. Allergic Rhinitis and its Impact on Asthma (ARIA) – 2016 Revision. Submitted)*

Strong recommendation	**For patients**: most individuals in this situation would want the recommended course of action, and only a small proportion would not.
	For clinicians: most individuals should receive the intervention. Adherence to a strong recommendation could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
	For health care policy makers: the recommendation can be adopted as policy in most situations.
Conditional recommendation	**For patients**: the majority of individuals in this situation would want the suggested course of action, but many would not.
	For clinicians: recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
	For health care policy makers: policy-making will require substantial debate and involvement of various stakeholders.

other HCPs), in all countries (including in developing countries), for research and clinical trials design, for public health planning, for developing new drugs and for registration of medicines and reimbursement. Unmet needs and future research are discussed, including disease phenotyping and endotyping in the context of united airways disease (rhinitis and asthma) and control of the disease. Control and severity are not well delineated in rhinitis as they are for asthma. Several tools were such as symptom scores, visual analogue scale (VAS) and patients' reported outcomes such as quality-of-life questionnaires. Scores with several items have been proposed (128). It appears in rhinitis that a simple measure such as VAS may be sufficient to appreciate the control of the disease (129) and is particularly relevant to primary (130) or pharmacy care (131) and to the follow up of patients. The level of control of allergic rhinitis is independent of the treatment step (132).

Unifying both the need to asses disease endotypes and severity/control assessment the author introduced in 2012 as part of a MeDALL–GA2LEN–ARIA consortium position paper (15) the concept of severe chronic allergic (and related) diseases (SCUAD). Concepts of disease severity, activity, control and responsiveness to treatment are linked but different. Severity refers to the loss of function of the organs induced by the disease process or to the occurrence of severe acute exacerbations. Severity may vary over time and needs regular follow-up. Control is the degree to which therapy goals are currently met. The SCUAD concept generalized the approach of the uniform definition of severe asthma presented to WHO for chronic allergic and associated diseases (rhinitis, chronic rhinosinusitis, chronic urticaria and atopic dermatitis) in order to have a uniform definition of severity, control and risk, usable in most situations. SCUAD concept is based on the appropriate diagnosis, availability and accessibility of treatments, treatment responsiveness and associated factors such as comorbidities and risk factors (Figure 32). This uniform definition allowed a better definition of the phenotypes of severe allergic (and related) diseases for clinical practice, research (including epidemiology), public health purposes, education and the discovery of novel therapies. The paper for cited 50 times since its publication.

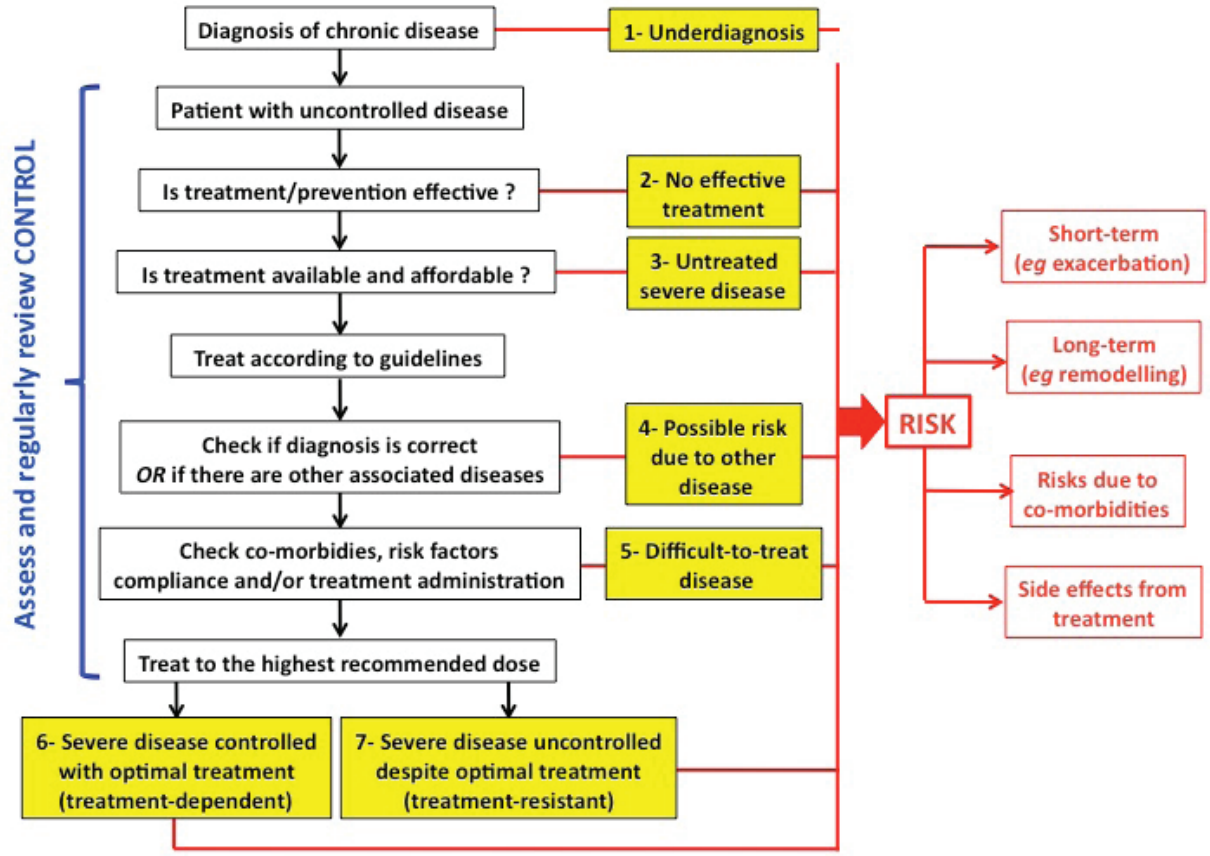

Figure 32

Uniform approach to the definition of severe allergic (and related) diseases. Severe allergic (and related) diseases include 7 groups (highlighted in yellow), each carrying different public health perspectives and challenges. (Reproduced from WHO Collaborating Center for Asthma and Rhinitis, Bousquet J, et al. Severe chronic *allergic (and related) diseases: a uniform approach--a MeDALL--GA-2LEN--ARIA position paper. Int Arch Allergy Immunol. 2012;158(3):216-31.)*

A2. New models of care for AR

Effective strategies are needed to reduce CRD burden. National programmes (e.g. the Finnish, Czech or Portuguese asthma or COPD programmes can be cost-effective (133), but they are insufficiently implemented in the EU. Integrated care pathways (ICPs) for COPD exist in the United Kingdom (UK) developed by the National Institute for Health and Care Excellence (NICE) (134), in France (Haute Autorité de Santé) and in the Netherlands (135), but ICPs for asthma or asthma and rhinitis co-morbidity do not exist. Asthma quality standards for asthma have been published by NICE. These are specific, concise statements that act as markers of high-quality, cost-effective patient care. Moreover, some initiatives are aimed at also incentivising good practice and improving implementation (i.e. remuneration based on performance indicators). In the UK, the Quality and Outcomes Framework has four asthma-specific performance indicators, which are explicitly linked to the subsequent remuneration of providers. In low-resource settings, some successful attempts to combine all non-communicable diseases (NCDs) into one single action plan have been developed (136) for the implementation of the WHO NCDs action plan. However, such combined plans are not available for the management of NCDs in high-resource settings.

The Polish Presidency of the EU Council (3051st Council Conclusions) has made the prevention, early diagnosis and treatment of asthma and allergic diseases a priority to reduce health inequalities (137, 138). The 3206th Cyprus Council Conclusions recommended that the diagnosis and treatment of chronic diseases should be initiated as early as possible to improve active and healthy

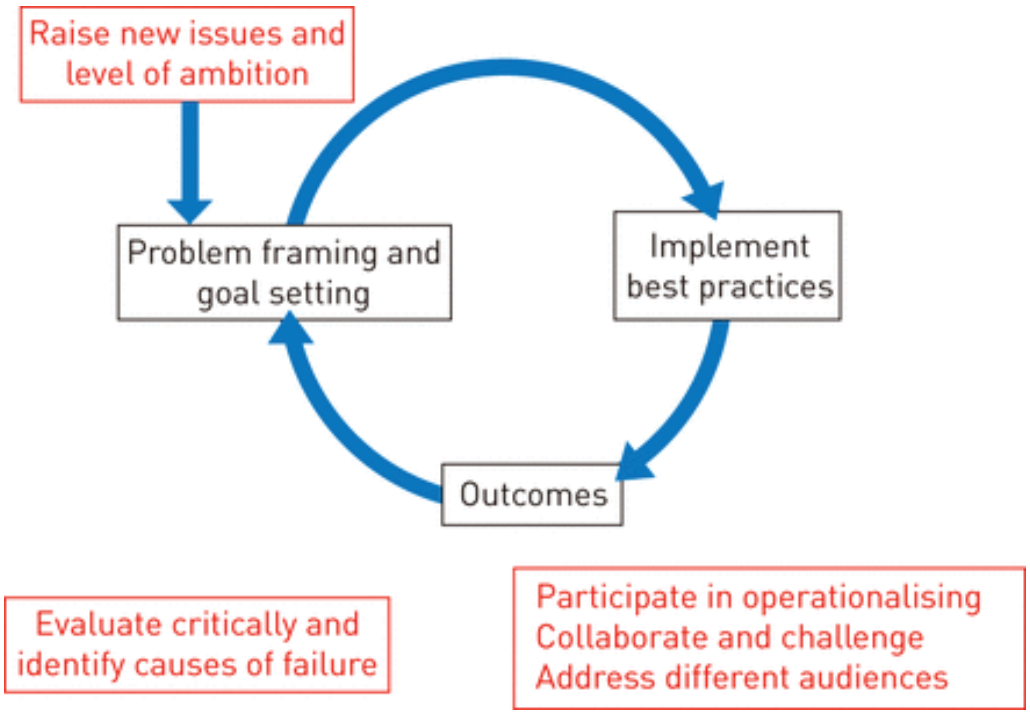

Figure 33

From science to guidelines and best practices using ICPs. ICPs are structured multidisciplinary care plans focusing on the quality and co-ordination of care which detail essential steps in the care of patients with a specific clinical problem. They promote the translation of guidelines into local protocols and their subsequent application to clinical practice and empower patients as well as their health and social carers. Clinicians are free to exert their own professional judgments as appropriate. However, any alteration to the practice identified within the ICP must be noted as a variance. Variance analysis may be used to optimise the ICPs linked with pay-for-performance, audit and feedback, and integration of recommendations with electronic medical records. *(Reproduced from European Innovation Partnership on Active and Healthy Ageing, Action Plan B3; Mechanisms of the Development of Allergy, WP 10; Global Alliance against Chronic Respiratory Diseases, Bousquet J, Addis A, Adcock I, Agache I, et al. Integrated care pathways for airway diseases (AIRWAYS-ICPs). Eur Respir J. 2014;44(2):304-23)*

ageing (139). A debate at the European Parliament (Cyprus Presidency of the EU Council, 2012) recommended early diagnosis and management of chronic respiratory diseases in children in order to promote active and healthy ageing (140).

Ioana Agache is a member of Expert Panel The European Innovation Partnership on Active and Healthy Ageing (EIP on AHA). This consortium developed the concept of integrated care pathways for airway diseases (AIRWAYS-ICPs). The paper (22), published in 2014 in the European Respiratory Journal was cited 45 times since its publication. The general objective of AIRWAYS-ICPs is to develop multi-sectoral ICPs for CRDs used across European countries and regions in order to 1) reduce the burden of the diseases, 2) promote active and healthy ageing, and 3) create a care pathways simulator tool which can be applied in older adults. AIRWAYS-ICPs will not duplicate existing EU prevention programmes in chronic respiratory diseases (e.g. anti-smoking) but will strengthen them where appropriate. The specific aim of AIRWAYS-ICPs is to propose central unifying themes and an overall potential to gain political leverage in the current environment and to better understand and manage the spectrum of care for patients with CRDs in European countries and regions. It will also aim to generalise the approach to the uniform definition of severity, control and risk of severe allergic diseases (131), in order to develop uniform risk stratification usable for CRDs in most situations. AIRWAYS-ICPs proposed a feasible, achievable and manageable project from science to guidelines (Figure 33) using existing networks and partners committed to Action Plan B3 of the EIP on AHA.

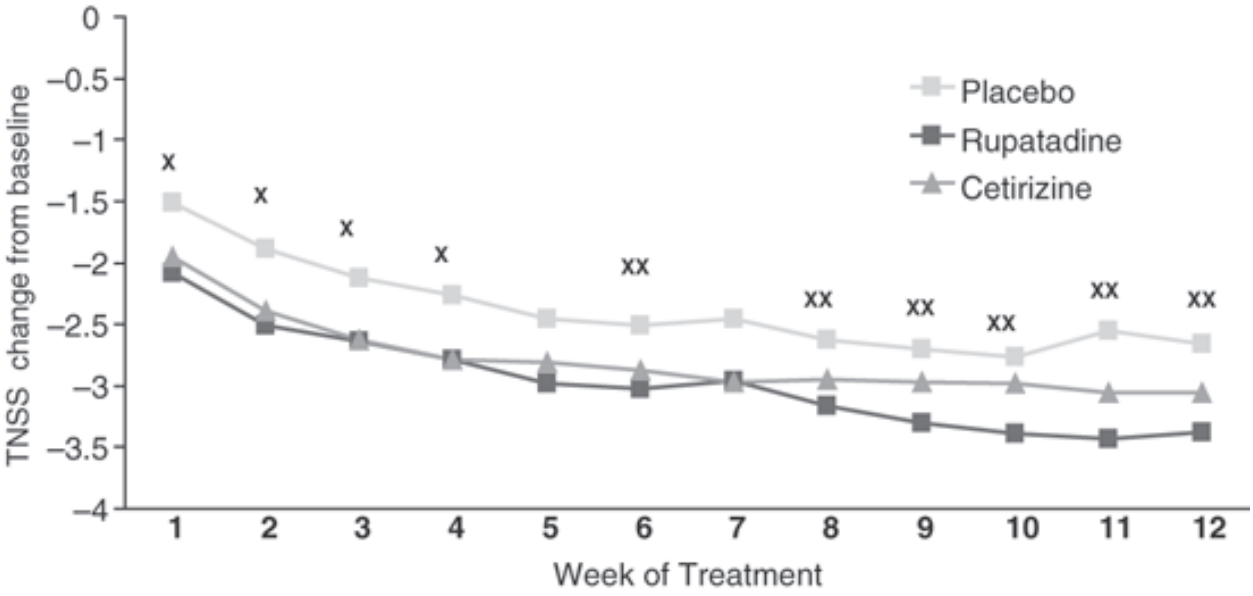

Figure 34

Serial time profile over 12 weeks of the instantaneous Total Nasal Symptom Score (iTNSS) mean change from baseline. *Significant improvements at p < 0.05 level were seen in both treatments (x) and only with rupatadine alone (xx) in comparison with placebo. (Reproduced from Fantin S, et al; international Rupatadine study group. A 12-week placebo-controlled study of rupatadine 10 mg once daily compared with cetirizine 10 mg once daily, in the treatment of persistent allergic rhinitis. Allergy. 2008;63(7):924-31)*

Several unmet needs have been identified in AR: identification of the time of onset of the pollen season, optimal control of rhinitis and comorbidities, patient stratification, multidisciplinary team for integrated care pathways, innovation in clinical trials and, above all, patient empowerment. A new consortium MASK (MACVIA-ARIA Sentinel NetworK for allergic rhinitis) study group was created (with Ioana Agache as a member of the Expert Panel) to tackle these unmet needs. One of the first deliverables (21) of the consortium (MASK-rhinitis) is a simple system centred around the patient which was devised to fill many of these gaps using Information and Communications Technology (ICT) tools and a clinical decision support system (CDSS) based on the most widely used guideline in allergic rhinitis and its asthma comorbidity (ARIA). Three tools are used for the electronic monitoring of allergic diseases: a cell phone-based daily VAS assessment of disease control, CARAT (Control of Allergic Rhinitis and Asthma Test) and e-Allergy screening (premedical system of early diagnosis of allergy and asthma based on online tools). These tools are combined with CDSS and are available in many languages. An e-CRF and an e-learning tool complete MASK. MASK is flexible and other tools can be added. It appears to be an advanced, global and integrated ICT answer for many unmet needs in allergic diseases which will improve policies and standards. The CDSS is currently being tested in clinical trials (141).

A3. New treatments for AR

Ioana Agache's interest in AR and asthma brought her research at the forefront of testing new drugs for these diseases.

In 2008 a novel, selective long-acting histamine H1 receptor inverse agonist with anti PAF activity, rupatadine, was evaluated in several clinical trials. The paper (142) published in Allergy in 2008 and **cited 46 times** since its appearance reports on a randomised, double-blind, parallel-group, placebo-controlled and multicenter study showing that rupatadine significantly relieves symptoms of perennial AR, providing a rapid onset of action and maintains its effects over a long period of 12-weeks (Figure 34). Rupatadine 10

mg presented a higher efficacy compared to cetirizine in all controls carried out (4, 8 and 12 weeks), which could be explained by the additional and sustained anti-inflammatory effect. A clear improvement in rupatadine 10 mg vs placebo was observed after 24 h of the first dose, indicating a fast onset of action of this drug in symptoms relief. This improvement was previously reported in patients with seasonal AR where the authors suggested a faster effect than cetirizine in the control of symptoms (143). In another randomised, double-blind, parallel-group, placebo-controlled and multicenter study Ioana Agache also investigated the efficacy of rupatadine versus desloratadine in seasonal AR (144) and showed that rupatadine is a very good choice for seasonal AR due to its contribution to the improvement of nasal and non-nasal symptoms to a similar degree as desloratadine.

Another novel antihistamine, bilastine, was tested versus cetirizine by Ioana Agache as part of a randomized, double-blind, parallel-group study, in adults with seasonal AR (145). Bilastine 20 mg once daily was significantly superior to placebo and comparable to cetirizine 10 mg in relieving symptoms of seasonal AR, although it demonstrated a significantly better adverse events profile than cetirizine. The paper was **cited 61 times** since its appearance.

Providing more effective pharmacological therapies is needed to achieve AR control. Second generation anti-histamines with little or no sedative effects were evaluated, and new intranasal corticosteroids (INS) with lower systemic bioavailability (compared to the older INS), but with comparable efficacy, provided. Increasing the dose of INS provided no additional symptomatic benefit due to the flat nature of their dose response curves. Indeed, an INS efficacy threshold has now been established (146). Although, multiple AR therapy usage is widespread throughout Europe (147) adding oral antihistamines or leukotriene receptor antagonists to INS provided little or no symptomatic benefit over INS monotherapy (148,149).

The combination between an intranasal anti-histamine (azelastine hydrochloride) and an INS (fluticasone propionate) delivered as a novel formulation in a single spray (MP-AzeFlu) is a new drug for AR. Results from well-designed RCTs showed that patients with moderate-to-severe seasonal AR treated with MP-AzeFlu experienced a rapid onset of relief (i.e. 30 mins) and twice the overall nasal and ocular symptom relief of an INS or intranasal anti-histamine (146). Moreover, more MP-AzeFlu patients experienced complete/near to complete symptom relief and many days faster than those on fluticasone propionate monotherapy (146, 150). In addition, MP-AzeFlu has a sustained effect, supporting continuous use with improved concordance and has established its effectiveness in a large multicenter non-interventional study (151). As part of the European investigators team Ioana Agache assessed the effectiveness of MP-AzeFlu on achieving AR control in routine clinical practice across Europe (152). AR control was assessed using a VAS, in line with MACVIA ARIA, REG and EAACI initiatives. 2988 patients (≥12 years) with ARIA-defined moderate/severe AR from Germany, Sweden, Romania, UK, Denmark and Norway were included. Patients assessed symptom severity using a VAS from 0mm (not at all bothersome) to 100mm (very bothersome) on Days 0, 1, 3, 7, and last visit (~Day 14) in the morning before MP-AzeFlu-use. Patients' perceived level of disease control was assessed on Day 3. A VAS score cut-off on Day 3 for 'well-controlled' AR was determined and the proportion of patients who achieved this response calculated. MP-AzeFlu treatment was associated with VAS score reduction from 73.7mm at baseline to 23.4mm by last visit. This reduction was significant ($p<0.001$) compared to baseline from Day 1 (fast relief of symptoms), and sustained until last day (Figure 33). By day 3, 50.3% of patients considered their symptoms 'well-controlled'. 18.2%, 40.0%, 66.6% and 75.9% of patients achieved the <38mm 'well-controlled' VAS score cut-off on days 1, 3, 7 and 14, respectively. The results were consistent across countries, age, AR phenotype and severity (Figures 35 and 36). These data are a valuable addition to the real-life evidence base, and confirm the rapid and sustained effectiveness of MP-AzeFlu under conditions of routine care around Europe, complementing the evidence gathered in RCTs. The effectiveness observed in this

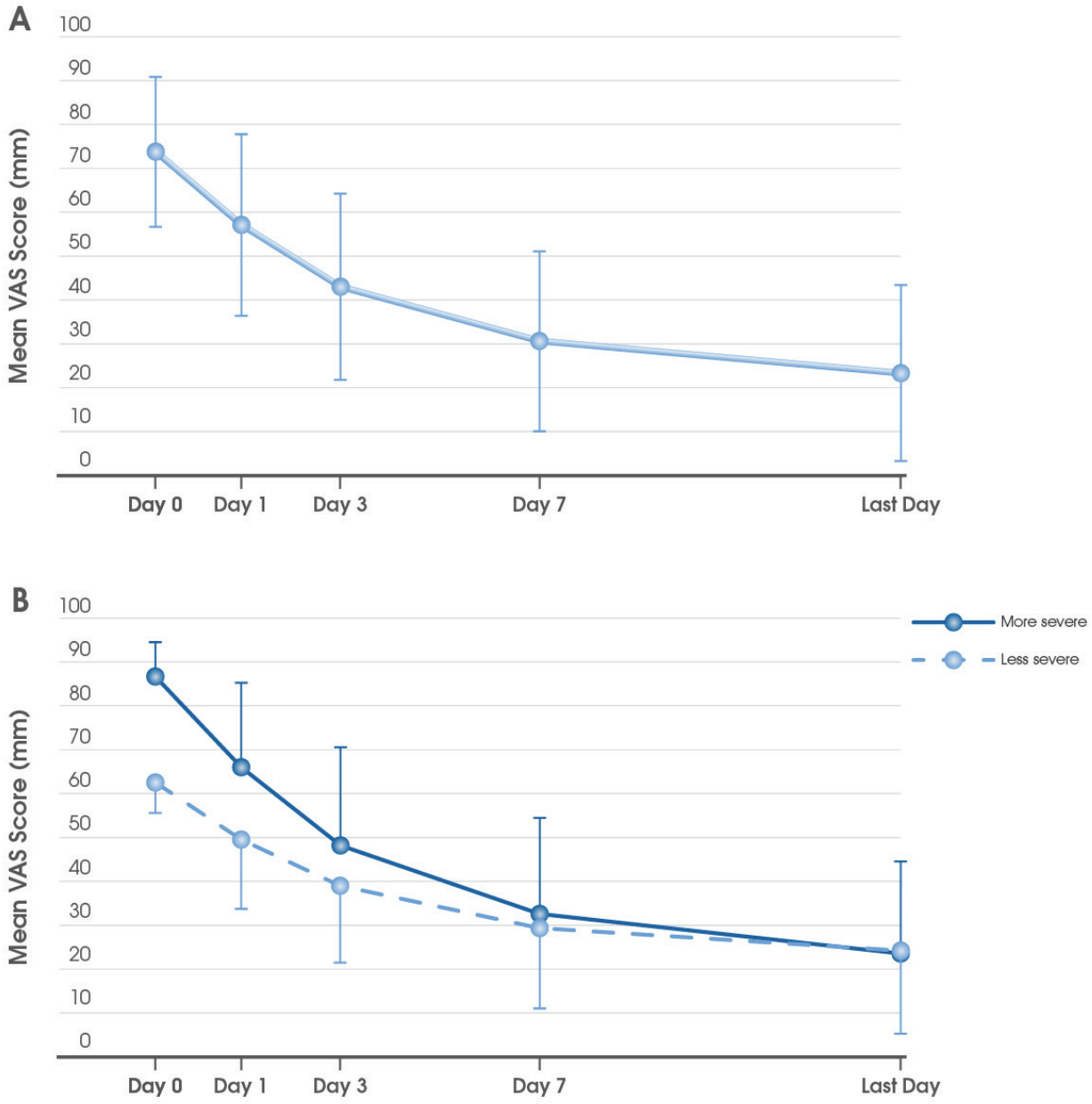

Figure 35

Effect of MP-AzeFlu on visual analogue scale (VAS) score over time in (A) the total population (n=2656) and (B) according to baseline severity. Less severe: baseline VAS score 50-74mm (n=1129), more severe: baseline VAS score 75-100 mm (n=1398). Data presented as mean and standard deviation for the pooled data. *(Reproduced from Klimek L, et al. MP-AzeFlu provides rapid and effective allergic rhinitis control in real life: A pan-European study. Allergy Asthma Proc. 2016;37(5):376-86)*

real-life study was better than the efficacy reported in RCTs, where MP-AzeFlu provided complete/near complete symptom control in 1 of 6 moderate/severe SAR patients by Day 14 and complete relief in 7 of 10 mild-to-moderate PAR patients in the first month, achieving these responses about a week faster than an INS.

The generalisability of MP-AzeFlu data derived from clinical studies to the Romanian population is unknown. The aim of the non-interventional study conducted by Ioana Agache (153) was to assess the effectiveness of MP-AzeFlu in achieving AR control in real-life clinical practice in Romania, using the VAS, in line with MACVIA-ARIA and EAACI

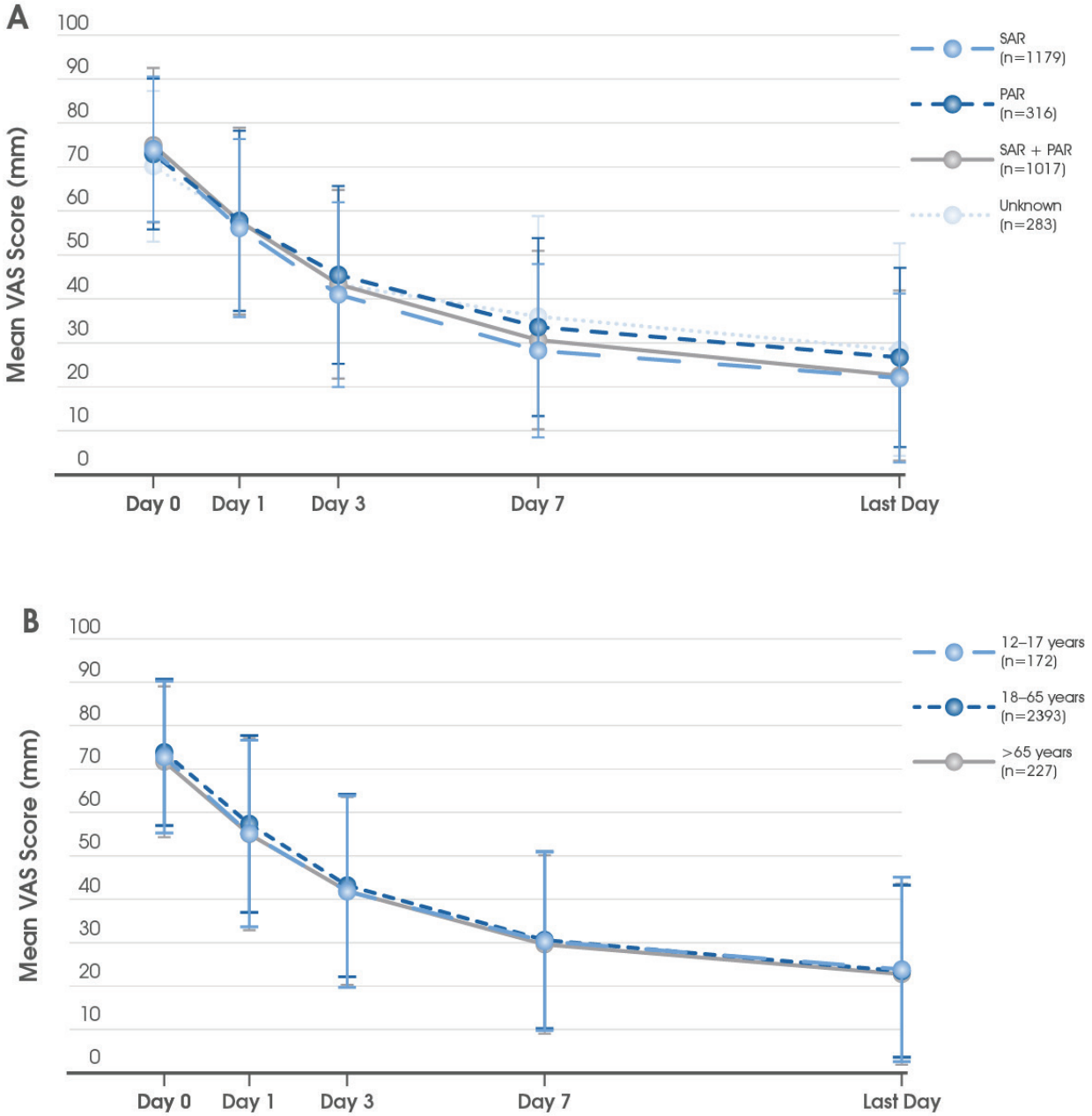

Figure 36

Effect of MP-AzeFlu on visual analogue scale (VAS) score over time according to (A) allergic rhinitis phenotype and (B) age. Data presented as mean and standard deviation for the pooled data. *(Reproduced from Klimek L, et al. MP-AzeFlu provides rapid and effective allergic rhinitis control in real life: A pan-European study. Allergy Asthma Proc. 2016;37(5):376-86)*

recommendations. The multicenter study included 253 patients ≥12 years old. MP-AzeFlu provided rapid, effective and sustained AR symptom control. Furthermore, 8 out of 10 patients treated with MP-AzeFlu in routine clinical practice crossed the well-controlled zone by end of treatment (i.e. VAS score ≤ 38 mm). Of note the results of this study in Romania showed a better symptom control compared to the other real-life studies with MP-AzeFlu conducted in Scandinavia and Germany. For example, the mean change from baseline in VAS score in our study was 63.6 mm, higher than that reported in Sweden (36.1 mm), Denmark (38.8 mm), Norway (30.8 mm) and Germany (54.1 mm).

A4. Epidemiology of AR

Data collected from patients during the Pan-European real life study (152) prior to MP-AzeFlu prescription highlighted the high burden of AR around Europe, and the need for a more effective pharmacological therapy. The societal burden of AR was evident from the high physician consultation rate (2.2 times/calendar year) and frequency of poly-pharmacy practices, with over two-thirds of patients reporting use of multiple therapies, which is neither recommended nor proven. Both of these practices inflate costs associated with the AR management and indicate dissatisfaction with therapy, a common finding from other AR surveys. The symptomatic burden of AR was evident not only from high baseline VAS scores reported despite multiple therapy use by many patients, but also the high frequency of troublesome symptoms, activity impairment, sleep disturbance, and incidence of ocular symptoms reported, which can impair patients' quality of life to a greater degree than nasal congestion. Nasal congestion was reported by 1 in every 2 patients, and associated with a high reported use of decongestants (oral or intranasal, both of which carry significant adverse effects). Another medication with potent side effects, systemic corticosteroids, was used previously in 1 of 8 subjects, to relieve severe symptoms and unblock the nose.

The burden of AR was also highlighted by the Romanian MP-AzeFlu study (153). As a secondary end-point the study collected data on the prevalence of moderate/severe AR in Romania (where the latest publications on AR epidemiology are from 1998) and the use of allergen specific immunotherapy (AIT). The mean VAS score at baseline was 78.4 mm, showing not only the high symptomatic burden experienced by these patients, but also the inadequate symptom relief provided by previously used AR treatments. The latter was confirmed by the high degree of polypharmacy noted (85.0%), higher that that reported in other countries, and the fact that over three-quarters of physicians prescribed MP-AzeFlu as other AR therapies were not sufficient in the past. Interestingly, almost 30% of physicians prescribed MP-AzeFlu first line, when they considered that other therapies would be insufficient to treat acute symptoms. Over 60% of patients had made multiple visits to their physician due to AR in the current calendar year emphasising the burden uncontrolled disease has on healthcare systems. The study also showed the very low usage of AIT for moderate/severe AR (n=30, 11.9%) highlighting the need to increase the knowledge of the physicians on the AIT disease-modifying benefits

A5. AR as a risk factor for asthma

Asthma and AR are comorbid conditions, with AR being a major risk factor for the occurrence of asthma and lack of asthma control (111, 113, 117). However, there are fewer and less convincing data on the risk of developing asthma in seasonal AR. Also, there are no data on the clinical phenotypes of asthma associated with SAR. These aspects were evaluated by Ioana Agache in the paper published in 2010 (39) and communicated at the AAAAI Annual Meeting (154). The study enrolled 33 children (mean age 8.27±1.77 years) and 82 adults (mean age 34.12 ± 10.59 years) with seasonal AR. Study subjects were evaluated for asthma (history, reversibility of bronchial obstruction, increased FeNO). The following asthma risk factors were considered in the multiple regression analysis: male sex, family history of asthma, breast feeding < 2 months, passive/active smoking, obesity, pets/moulds exposure, high total serum IgE, polysensitised (sensitised to 3 seasonal pollens with different structure), mixed sensitisation (seasonal and perennial allergens), severe rhinitis (ARIA) and lack of AIT for rhinitis preceding asthma diagnosis. Asthma phenotypes were characterised using the k-means clustering (silhouette method for cluster validation). Asthma was diagnosed in 22 (66.7%) children and in 57 (69.5%) adults with seasonal AR. Independent risk factors for asthma were lack of AIT preceding asthma diagnosis both for children (p=0.008132) and adults (p=0.000017) and mixed sensitisation for children (p=0.035694). Asthma phenotypes identified in children (Figure 37 A) according to the associated risk factors were: breastfeeding < 2 months and severe rhinitis in 16 (63.6 %) subjects; male, polysensitised and severe rhinitis in 8 (36.4%) subjects. Asthma phenotypes in adults (Fig-

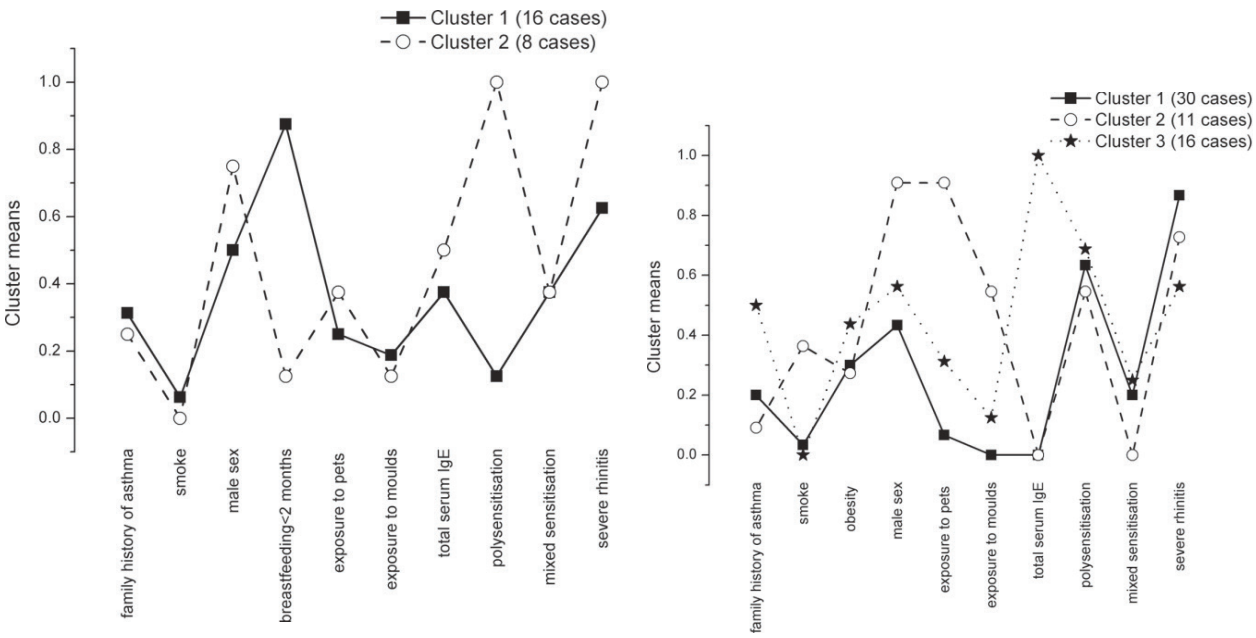

Figure 37

Cluster means for seasonal AR and asthma in children (A) and adults (B). Asthma phenotypes identified in children were: breastfeeding < 2 months and severe rhinitis in 63.6% subjects and male, polysensitised and severe rhinitis in 8 (36.4%) subjects. Asthma phenotypes in adults were polysensitised and severe rhinitis in 52.6% patients, male, exposure to pets and severe rhinitis in 19.3% patients, high total serum IgE and polysensitised in 28.1% patients. *(Reproduced from Agache I, Ciobanu C. Risk factors and asthma phenotypes in children and adults with seasonal allergic rhinitis. Phys Sportsmed. 2010;38(4):81-6)*

ure 37 B) polysensitised and severe rhinitis in 30 (52.6 %) patients, male, exposure to pets and severe rhinitis in 11 (19.3 %) patients, high total serum IgE and polysensitised in 16 (28.1%) patients.

This study demonstrated that asthma is frequently associated with seasonal AR, with seasonal AR preceding the development of asthma. The incidence of asthma in patients with seasonal AR observed in this study is highly significant (66.7% in children and 69.5% in adults) and very close to the incidence cited for asthma in patients with persistent AR (122). In all the cases seasonal AR preceded asthma appearance. Being a cross-sectional study we cannot however firmly conclude that seasonal AR is per se a risk factor for developing asthma. Our results clearly indicate lack of AIT is a risk factor for asthma both in adults and in children with seasonal AR. These results are in concordance with a prospective 10-year study, which proved the role of AIT in children with seasonal AR in preventing the appearance of asthma (155). Preventing asthma could be another benefit of AIT in treating AR apart from the potential for early and significant cost savings by reducing medication and healthcare resource utilization (156). Until this study no data existed on the potential of AIT of preventing asthma in adults with AR and our study proved that lack of AIT was an independent risk factor for asthma in adults with seasonal AR. This is a first study describing asthma phenotypes in adults and in children with SAR according to the associated risk factors for asthma. The presence of short or no breastfeeding as a phenotypic trait of asthma in children with seasonal AR is in concordance with other studies identifying breastfeeding as a protective factor for the appearance of asthma (157, 158, 159, 160, 161). The other phenotype of asthma in children with seasonal AR associates male sex and polysensitisation, both clearly demonstrated as risk factors for asthma in children (122, 158, 162, 163). Severe rhinitis is present in both phenotypes and is also demonstrated as a risk factor for asthma (122, 134). In adults severe rhinitis and polysensitisation are encountered in two out of three asthma

phenotypes. While severe rhinitis is clearly demonstrated as a definite risk factor for asthma in adults, polysensitisation is less clear cut related to the risk of asthma, as it is children, although a study showed that increased total serum IgE is a risk factor for asthma only in the presence of specific sensitisation (164). In another study atopy increased the risk of newly onset asthma in adults by 12 to 21%, with total serum IgE and sensitisation to cat being independent predictors for asthma (165). The presence of male sex as a risk factor describing an adult asthma phenotype is surprising since it is known that after puberty asthma is more frequent and more severe in females. However none of the studies demonstrating female sex as a risk factor for asthma included patients with seasonal AR and asthma. Exposure to pets as a phenotypic trait of asthma in adults with seasonal AR is also surprisingly. While in children there are many controversies (166, 167, 168), none of the studies evaluated exposure to pets as a risk factor for developing asthma in adults.

B. LIFESTYLE (DIET, OBESITY, EXERCISE) AND ASTHMA

In the last few decades, Europe has witnessed a dramatic increase in the burden of asthma (both metabolic and allergy-induced asthma), which has now reached pandemic proportions. Asthma currently affects 70 million citizens in the European Union, of whom 30 million are children or adults aged less than 45 years. The prevalence of asthma has particularly soared in children and youngsters under the age of 15. Today, asthma represents the leading chronic disease in childhood across Europe and is the principal cause of emergency hospital visits and admission among children (8). This trend has been accompanied by noticeable changes in lifestyle. Improved access to technology and development have led to a more sedentary life. Easier access to food and a shift in the eating patterns from naturally sourced to processed food have been accompanied by a reduced intake of fresh fruits and vegetables, less fibre, and an increased intake foods rich in refined sugar.

In parallel the proportion of children and youngsters who are overweight or obese in Europe is worryingly high and constantly increasing. According to the World Health Organization, around 1 in 3 children in the EU aged 6–9 years were affected by obesity or excess weight in 20102 compared with 1 in 4 children in 2008. Globally it is estimated that the number of children aged under 5 who are overweight will rise from 41 million today to 70 million by 2025. This constitutes a major public health concern as obesity is directly associated with an increased risk of numerous chronic diseases (169).

Numerous epidemiological studies have demonstrated the association between obesity and asthma. Obese children and adults are at an increased risk of asthma and asthma-like symptoms, with a proportionate relationship between increasing body mass index (BMI) and increasing asthma incidence (170, 171, 174, 175, 176). The frequent association between the 2 diseases has led to the concept of "twin epidemics" with interventions targeting lifestyle aiming to reduce both the incidence of obesity and asthma and improve asthma control

As a significant risk factor and co-morbidity of asthma, life style (diet, obesity, exercise) represented a special focus of the research of Ioana Agache. As secretary of the EAACI Asthma Section Ioana Agache initiated and chaired a Task Force on life style and asthma that produced several consensus documents and position papers based on systematic reviews derived data.

The consensus document (177) "***Weight loss interventions in asthma: EAACI evidence-based clinical practice guideline (part I)***" published in 2013 and **cited 42 times** since its publication is the latest systematic review (SR) of three large biomedical databases on obesity, weight loss and asthma. Studies were scrutinized and critically appraised according to agreed exclusion and inclusion criteria. Quality assessment of eligible papers was conducted using the GRADE method. Meta-analyses of comparable studies were carried out. The SR showed that weight increases above the obesity threshold significantly increase the risk of asthma: becoming obese increased the odds

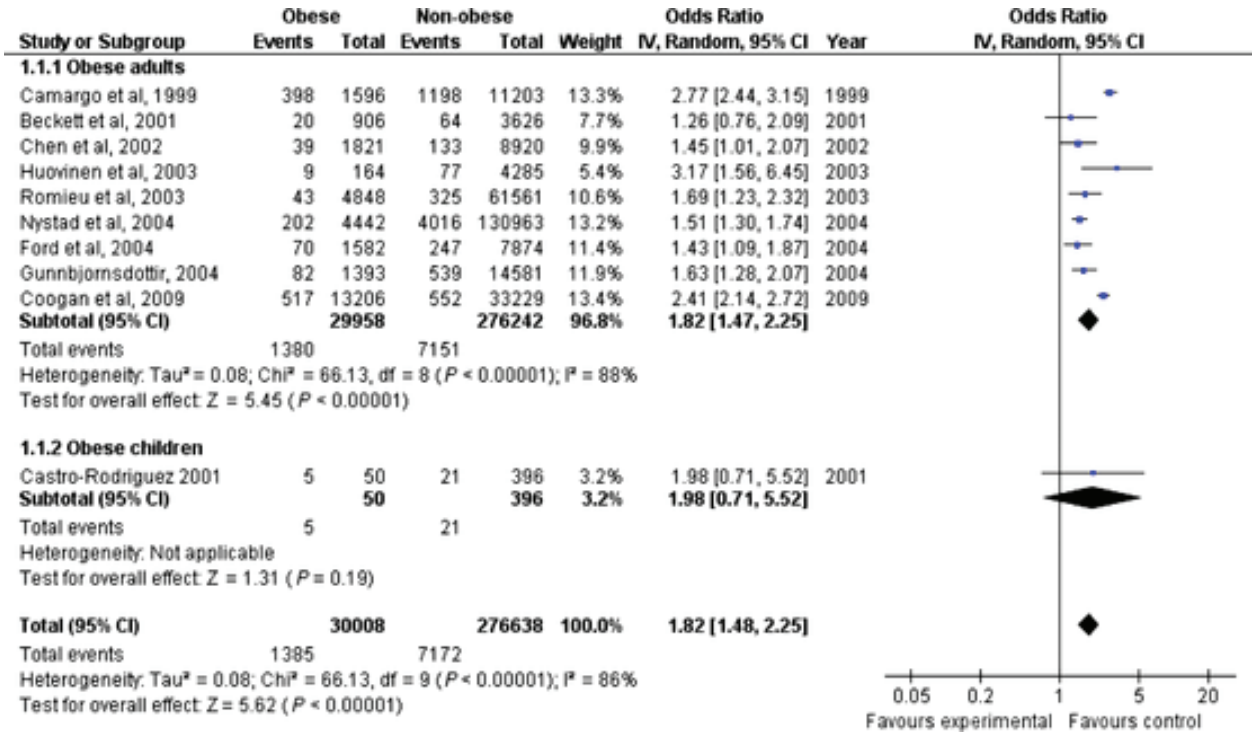

Figure 38

Forest plot showing meta-analysis of incident asthma risk comparing obese vs normal-weight subjects. Studies are ordered by year of publication, the center of each square represents study specific ORs, and horizontal lines represent 95% CIs; vertical vertex of the diamond represents the OR summary estimate, whereas the ends of the diamond (width) correspond to the 95% CI; vertical line indicates an OR of 1 (no difference). (Reproduced from Moreira A, et al. "Weight loss interventions in asthma: EAACI evidence-based clinical *practice guideline (part I)". Allergy 2013;68(4):425-39)*

for incident asthma by 1.82 (95% CI 1.47, 2.25) in adults and 1.98 (95% CI 0.71, 5.52) in children (Figure 38). The available studies show weak evidence of benefits from weight reduction on asthma outcomes: weight loss was associated with significant improvement in mean scores for symptoms, rescue medication score, and asthma exacerbations in the only randomized controlled trial. Similarly, evidence gathered from observational studies, with follow-up ranging between 8 weeks to 1 year, and from changes 1 year after bariatric surgery showed improvements in all asthma control-related outcomes. Changes in lung function were reported in one randomized controlled and eight observational studies of asthmatic subjects, with conflicting results. Either improvement after weight loss, decline with weight gain, or no effects at all were reported. Changes in airway inflammation and responsiveness were reported only by observational studies.

It is known that oxidative stress and airway inflammation are central features in the manifestation of asthma, which might be exacerbated by the poorer quality of the diet (178). The possible effect of diet on asthma, particularly in relation to the role of dietary antioxidants and polyunsaturated fatty acids has been investigated in numerous observational studies (179). Current evidence suggests that antioxidant vitamins C and E and a higher intake of fresh vegetables and fruits might have a protective effect on asthma, but most of the findings are still considered weak due to the cross-sectional design of the studies and the heterogeneity in diet assessment between them. Intervention trials have added little so far to understand the role of nutrients on asthma, which opens the question of whether the sources of nutrients matter (e.g. diet vs supplements).

A second position paper (180) of the Task Force **Asthma and dietary intake: an overview of systematic reviews** published in 2016 focuses on several components found in foods have proposed to have a protective effect against asthma risk through their antioxidant, anti-allergic and anti-inflammatory properties. In this overview of SR on dietary intake and asthma we found seven SR that met the AMSTAR score for high quality. The results show evidence of a negative association between asthma or wheeze and dietary intake of vitamins C, E and D, as well as intake of fruits and adherence to a Mediterranean diet. Objective measures of asthma were unrelated to variable levels of intake of salt in RCTs. With the exception of the evidence for vitamin D, the associations observed between asthma and dietary intake of foods and antioxidant nutrients come mostly from cross-sectional studies. Most of the evidence of a protective effect of dietary antioxidants and asthma was found in children, thus time of exposure would seem to be important. There are several strengths of this overview. First, it employed a comprehensive search strategy, developed and piloted to capture all available SR that met the eligibility criteria of this Task Force's review. We also used AMSTAR as a validated instrument to assess in detail the methodological quality of included reviews. In spite of the abundant scientific literature on asthma and diet, few systematic reviews meet the recommended cut-off score for high quality reviews. These are needed in order to produce adequate guidelines for health professionals, patients and patient-affiliated associations. This evidence supports recommendations in clinical practice to increase the net intake of fruits and vegetables as a way of reducing the risk of asthma, particularly in children. The current evidence comes mostly from observational studies and highlights the need for well-designed RCTs to investigate if such an effect has clinical benefits. The high prevalent rates of asthma in the general population, particularly in children, justify the implementation of such studies.

Following this overview of high quality SR the Task Force followed on its own SR aiming to comprehensively assess the existing scientific literature on the relationship between to dietary intake and the risk of asthma in children and adults, published in the last 5 years. The SR protocol (181) registered on PROSPERO on 3 March 2016 has been prepared following the new PRISMA-P guidelines. The scope of the SR is to provide evidence on dietary intake and dietary habits in relation to risk of asthma, wheeze (recurrent or persistent), and AHR. Our findings will serve as a reference to inform guidelines on dietary habits in susceptible and general population to reduce the risk and/or severity of asthma in children and adults. The SR will seek to answer the following questions:

- Does exposure to diet (as a whole or individual foods) during childhood influence the risk of asthma?
- Does exposure to diet (as a whole or individual foods) in adults influence their risk of asthma?

C. FOOD ALLERGY AND ASTHMA

Prevalence of both food allergy and asthma is on the rise, they are sharing the same risk factors and food allergy is a risk factor for asthma later in life. Moreover the association between food allergy and asthma is quite frequent: 4-8% of children with asthma have food allergy and asthma is present in 29–76% of all food-allergic people (182, 183). Due to the respiratory barrier defect in asthma the risk for being sensitized to milk, egg, peanut, shrimp, or multiple foods is higher in asthmatic patients (184).

The first SR review and meta-analyses that assessed the association between food sensitization and subsequent allergic diseases in 13 birth cohort studies proved that food sensitization in the first 2 years of life can identify children at high risk of subsequent allergic disease, including asthma, who may benefit from early life preventive strategies (185).

Both in children and in adult asthmatics food sensitization increases asthma morbidity, with high risk of hospitalisations and uncontrolled asthma (183, 186, 187). Food allergy is a risk factor for life-threatening asthma (188, 189). On the other hand uncontrolled asthma is a risk factor for severe reaction and even death in food-induced anaphylaxis: 85–96% of fatal food anaphylaxis occurs in people with asthma (190-192).

As a member of the Expert Panel of EAACI Food Allergy and Anaphylaxis Guidelines Ioana Agache brought her expertise on asthma in relation to food allergy and anaphylaxis. Ioana Agache led the Task Force on Food Allergy and Anaphylaxis Management in the Community and was part of the Food Allergy Prevention and Epidemiology Task Forces.

The SR performed in 2014 (193) examined ways to prevent the development of food allergy in children and adults. Seven bibliographic databases were searched from their inception to September 30, 2012, for systematic reviews, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-and-after studies, interrupted time series studies, and prospective cohort studies. Experts were consulted for additional studies. There were no language or geographic restrictions. Two reviewers appraised the studies using appropriate tools. Data were not suitable for meta-analysis due to heterogeneity, so were narratively synthesized. Seventy-four studies were included, one-third of which were of high quality. There was no good evidence to recommend that pregnant or breastfeeding women should change their diet or take supplements to prevent allergies in infants at high or normal risk. There were mixed findings about the preventive benefits of breastfeeding for infants at high or normal risk, but there was evidence to recommend avoiding cow's milk and substituting with extensively or partially hydrolyzed whey or casein formulas for infants at high risk for the first 4 months. Soy milk and delaying the introduction of solid foods beyond 4 months did not have preventive benefits in those at high or normal risk. There was very little evidence about strategies for preventing food allergy in older children or adults.

In 2015 the primary prevention LEAP (Learning Early about Peanut Allergy) study showed that early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts (194). Of note, since children with lesser risk factors for peanut allergy were excluded from enrollment in LEAP, there are no prospective, randomized data investigating the benefit or risk of early peanut introduction in the general to low-risk populations. Following this groundbreaking study the scientific community reacted with clear recommendation on how, when and to whom this primary prevention intervention is aimed to. Ioana Agache was a member of the Expert Panel that issued the **Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants** published (195) in all major journals of the Academies involved (American Academy of Allergy, Asthma & Immunology; American Academy of Pediatrics, American College of Allergy; Asthma & Immunology, Australasian Society of Clinical Immunology and Allergy; Canadian Society of Allergy and Clinical Immunology; European Academy of Allergy and Clinical Immunology; Israel Association of Allergy and Clinical Immunology; Japanese Society for Allergology; Society for Pediatric Dermatology; World Allergy Organization). Based on data generated in the LEAP trial and existing guidelines, the following interim guidance is suggested to assist the clinical decision-making of healthcare providers (Table 13).

The next SR systematic review (196) summarizes the evidence about the immediate management of reactions induced by food and longer-term approaches to minimize adverse impacts. Eighty-four studies were included, but two-thirds were at high risk of potential bias. There was little evidence about acute management for non-life-threatening reactions. H1-antihistamines may be of benefit, but this evidence was in part derived from studies on those with cross-reactive birch pollen allergy. Regarding long-term management, avoiding the allergenic food or substituting an alternative was commonly recommended, but apart from for infants with cow's milk allergy, there was little high-quality research on this management approach. To reduce symptoms in children with cow's milk allergy, there was evidence to recommend alternatives such as extensively hydrolyzed formula. Supplements such as probiotics have not proved helpful, but allergen-specific immunotherapy may be disease modifying and therefore warrants further exploration.

Table 13

Interim Guidance Regarding Early Peanut Introduction. The evidence for the benefit of early introduction of peanuts is limited to the high-risk infants from countries with a high prevalence of peanut allergy. There is currently no evidence that this intervention is suitable for low-risk infants or for countries with low prevalence of peanut allergy. The metabolic consequences of early peanut consumption need to be evaluated. *(Adapted from Fleischer DM, et al. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. J Allergy Clin Immunol. 2015;136(2):258-61)*

There is now Level 1 evidence from a randomized controlled trial that healthcare providers should recommend introducing peanut-containing products into the diet of "high-risk" infants early on in life (between 4 – 11 months of age) in countries where peanut allergy is prevalent
Infants with early-onset atopic disease, such as severe eczema, or egg allergy in the first 4-6 months of life, may benefit from evaluation by an allergist or physician trained in management of allergic diseases in this age group to diagnose any food allergy and assist in implementing these suggestions regarding the appropriateness of early peanut introduction. Evaluation of such patients may consist of performing peanut skin testing and/or in-office observed peanut ingestion, as deemed appropriate following discussion with the family. The clinician may perform an observed peanut challenge for those with evidence of a positive peanut skin test to determine if they are clinically reactive, before initiating at-home peanut introduction.
The LEAP study does not address use of alternative doses of peanut protein, minimal length of treatment necessary to induce the tolerogenic effect, or potential risks of premature discontinuation or sporadic feeding of peanut.
The LEAP trial only included high-risk infants with a minimal or negative SPT to peanut, and therefore does not address a strategy for those without these risk factors for developing peanut allergy

Ioana Agache led the **EAACI Food Allergy and Anaphylaxis Guidelines for managing patients with food allergy in the community** (197). These guidelines intend to provide guidance to reduce the risk of accidental allergic reactions to foods in the community addressing early-childhood and school settings as well as providers of non-prepackaged food (e.g., restaurants, bakeries, takeaway, deli counters, and fast-food outlets). Food allergy is the most common trigger of anaphylaxis in the community. Providing children and caregivers with comprehensive information on food allergen avoidance and prompt recognition and management of allergic reactions are of the utmost importance. Provision of adrenaline auto-injector devices and education on how and when to use these are essential components of a comprehensive management plan. Managing patients at risk of anaphylaxis raises many challenges, which are specific to the community. This includes the need to interact with third parties providing food (e.g., school teachers and restaurant staff) to avoid accidental exposure and to help individuals with food allergy to make safe and appropriate food choices. Education of individuals at risk and their families, their peers, school nurses and teachers as well as restaurant and other food retail staff can reduce the risk of severe/fatal reactions. Increased awareness among policymakers may improve decision-making on legislation at local and national level.

Table 14

Reported prevalence of individual microbial agents in acute asthma exacerbations. Percentage range and median value (in parentheses) are shown. Percentages referring to viral species are derived predominantly by PCR techniques that are applied in the majority of studies for viral detection. Bacterial (CP/MP) detection is usually by serology and/or PCR. Remarks in the last column are based on data from case–control studies. ? = Insufficient data. AAE, acute asthma exacerbation; CP, Chlamydophila pneumoniae; MP, Mycoplasma pneumoniae. *(Adapted from Papadopoulos NG, et al. Viruses and bacteria in acute asthma exacerbations-a GA²LEN-DARE systematic review. Allergy 2011;66(4):458-68)*

Pathogen	Prevalence (%) in AAE			Higher frequency in AAE than control populations
	Infants and pre-school-age children	Children (6–17 years)	Adults	
Rhinovirus	17–78 (33)	42–82 (55)	8–65 (29)	Yes
Enterovirus	12–25 (18)	5–16 (7)	?	?
Coronavirus	0–5 (2)	0–13 (1)	4–21 (12)	No
Influenza virus	1–20 (3)	0–7 (2.5)	8–25 (23)	Yes (adults only)
Parainfluenza virus	4–12 (7.5)	0–7 (2)	0–18 (0)	No
Respiratory Syncytial virus	2–68 (19)	1.5–12 (4)	0–39 (3)	Yes (infants only)
Metapneumovirus	1.5–9 (4)	4–7.5 (4.5)	7	?
Adenovirus	1.5–8 (4.5)	0–71 (0)	1–3 (2)	No
Bocavirus	7.5–19 (11)	?	?	?
Chlamydophila Pn	0–45 (4)	4–23 (11)	0–73 (13)	?
Mycoplasma Pn	1–10 (2)	0–50 (14)	0–8 (4)	Yes (children only)

D. INFECTIONS AND ASTHMA

In recent years, a growing number of observations have highlighted the importance of respiratory infections in acute asthma exacerbations. Respiratory viruses have repeatedly and consistently been associated with asthma exacerbations in different patient groups, with detection frequencies ranging from 40 to 90%. Bacteria, mostly *Mycoplasma* and *Chlamydophila pneumoniae*, are frequently identified in chronic asthma and may also precipitate exacerbations. Taking into account that a major proportion of asthma-related disease burden is caused by exacerbations (198), as well as that infectious agents are potential treatment targets, it becomes evident that the above associations require further attention.

As a member of the GA²LEN-DARE projected funded by EU under the 6th Framework Programme Ioana Agache evaluated in a SR the evidence for viruses and bacteria in acute asthma exacerbations.

The paper (199), cited 108 times until now, reports on the prevalence of individual microbial agents in acute asthma exacerbations in infants, children and adults (Table 14) and per geographical region (Table 15). The involvement and preponderance of rhinovirus (RV) is clear, and the plethora of data/studies associating this virus type with acute asthma exacerbations leaves little doubt about the importance of this pathogen, although the kinetics of RV infection in the community still requires attention, especially considering the newly identified RV-C. The relationship with different wheezing illnesses is also clear for

Table 15

Reported prevalence of microbial agents in acute asthma exacerbations sorted by geographical region. Percentage range and median value (in parentheses) are shown. Percentages referring to viral species are derived predominantly by PCR techniques that are applied in the majority of studies for viral detection. Bacterial (CP/MP) detection is usually by serology and/or PCR.? = Insufficient data. AAE, acute asthma exacerbation; CP, Chlamydophila pneumoniae; MP, Mycoplasma pneumonia. *(Adapted from Papadopoulos NG, et al. Viruses and bacteria in acute asthma exacerbations-a GA²LEN-DARE systematic review. Allergy 2011;66(4):458-68)*

Pathogen	Prevalence (%) in AAE (by region)					
	Children			Adults		
	Americas	Europe	Australasia	Americas	Europe	Australasia
Rhinovirus	26–77 (57)	17–82 (40)	33–78 (42)	29–36 (33)	35	8–65 (20)
Enterovirus	5	5–25 (9)	?	?	?	3.5
Coronavirus	0–3 (1.5)	0–13 (2.5)	1.5–2 (2)	12–21 (17)	?	4
Influenza virus	0–20 (10)	0–7 (3)	1–12 (6.5)	8–13 (11)	?	12–25 (23)
Parainfluenza virus	2–6 (4)	0–7 (4)	7.5–8 (8)	0–18 (9)	?	0
Respiratory syncytial virus	8–68 (40)	1.5–61 (12)	7.5–17 (16)	3	?	0–39 (2)
Metapneumovirus	7.5	2–8.5 (4)	1.5–8 (2.5)	7	?	0
Adenovirus	0–4 (2)	0–5 (4)	1.5	1	?	2.5–3 (3)
Bocavirus	?	7.5–19 (12.5)	11.5	?	?	?
Chlamydophila Pn	4	0–45 (6.5)	3–45 (24)	?	0–73 (18)	9–18 (14)
Mycoplasma Pn	0	1–50 (5)	3	?	0–4 (3.5)	8

respiratory syncytial virus, which is mostly prevalent in infants. The association with other respiratory pathogens is not as clear, possibly because of the relatively small proportion of cases for each, in addition to geographic and temporal variability. This is particularly true in regard to any possible involvement of bacteria in exacerbations, on which very little information is available. The paper also highlights several unmet needs that should be addressed in further research studies. Taking into account that respiratory pathogens may interact between themselves and with other factors, such as pollution, allergens, stress, nutrition, etc., in the induction of acute asthma exacerbations, large studies with comprehensive analysis of infectious agents and other possible precipitants are among research priorities to evaluate the relative contribution of respiratory pathogens in asthma exacerbations. As breakthroughs in microorganism detection become available for epidemiological use, in parallel to bioinformatics tools for their analysis, extensive virology and bacteriology should become a vital part of longitudinal cohort studies, aiming at better understanding the kinetics and natural history of microbial exposures, and reveal new targets for therapeutic intervention. Such interventions will also be needed to confirm causality behind the described associations.

1.6. ASTHMA MANAGEMENT PLANS AND NEW MODELS OF CARE

The burden of asthma around the world is of sufficient magnitude to warrant its recognition as a priority disorder in government health strategies. The prevalence of asthma has been increasing dramatically mainly in the last decades both in industrialized and developing countries. The rate of asthma increases as communities adopt western lifestyles and become urbanized. With the projected increase in the proportion of the world's population that is urban from 45% to 59% in 2025, there is likely to be a marked increase in the number of asthmatics worldwide over the next two decades. It is estimated that there may be an additional 100 million persons with asthma by 2025, adding to the existing world asthma population of 300 million people.

A. ASTHMA PREVENTION AND CONTROL

An important part of the integrated management programme for asthma this research direction was approached in the chapter "***Best buys for asthma prevention and control***" from the Global Atlas of Asthma (23), where Ioana Agache is both Editor in Chief and author. The author describes 10 key points to be tackled by an efficient asthma management plan (Table 16). An example of an asthma management plan focusing on prevention and control is also provided (Figure 39).

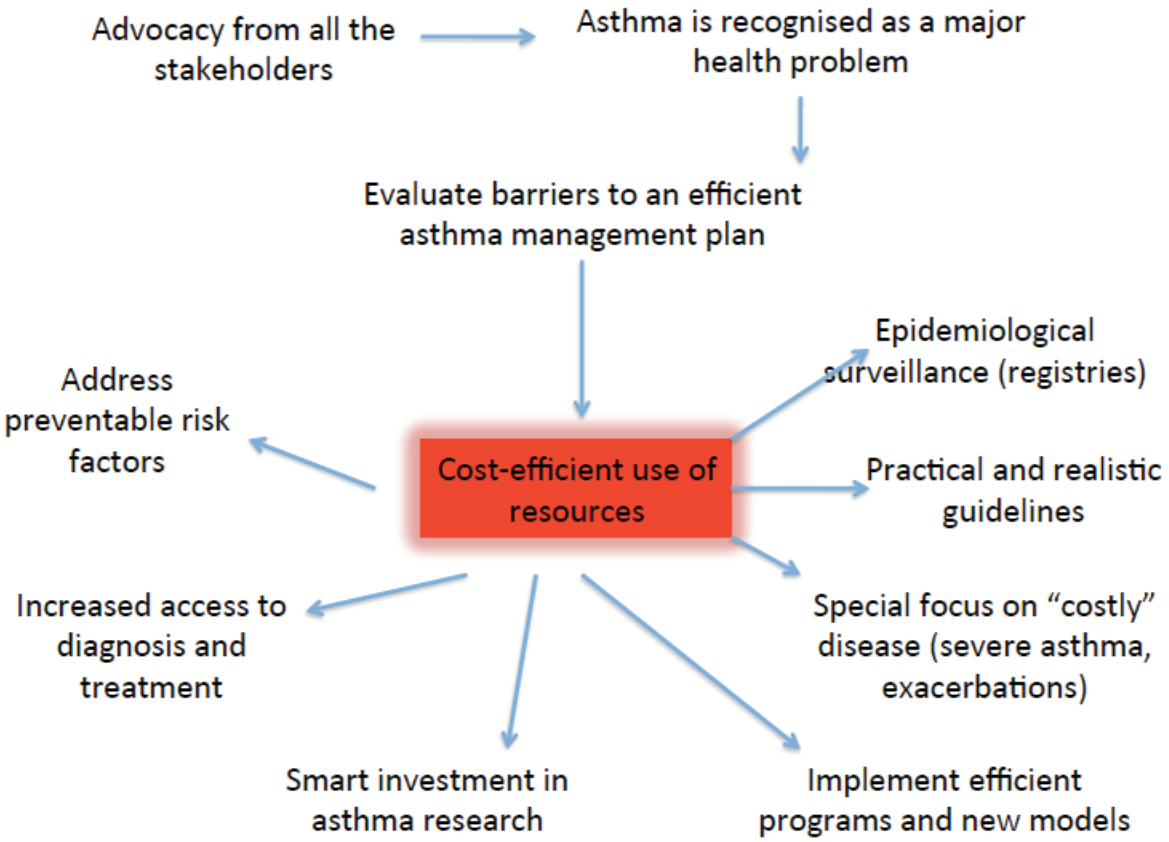

Figure 39

Asthma "best-buys" management plan. Special targets are adherence to treatment; low income countries/hard-to-reach populations; registries; efficient implementation of guidelines; cost-efficiency studies and smart investment in asthma research, increased awareness; well defined short and long-term outcomes; focus on special needs: exacerbations/severe asthma/phenotypes-endotypes. *(Reproduced from Agache I. Global Atlas of Asthma, EAACI 2013)*

Table 16

Ten "best buys" for asthma prevention and control. There are many economic and political factors conditioning the efficiency of asthma prevention and control strategies. Examples include poverty, poor education and infrastructure, low public health priority and the lack of good worldwide valid data on morbidity and mortality from asthma. Guidelines used to prevent and control asthma should be practical and realistic in terms of different health care systems. Usually, due to differences across cultures and health care systems management international guidelines developed in high-income countries are difficult to implement in low and middle-income countries. *(Adapted from Agache I. Global Atlas of Asthma, EAACI 2013)*

Identify and address barriers limiting the efficiency of interventions aiming to prevent and control asthma.
Position asthma as an important cause of morbidity, economic cost, and mortality worldwide.
Well-controlled epidemiological description and surveillance of asthma. National, regional and international asthma registries are urgently needed to continuously monitor the prevalence, morbidity and mortality of asthma at a global scale.
Cost-efficient use of available resources. Particular resources are needed for asthma research, which should provide effective prevention, accurate and rapid diagnosis and a curative treatment of asthma.
Improve accessibility to asthma diagnosis and to essential drugs for the management of asthma in low- and middle-income countries and for hard-to-reach populations
Control the preventable environmental factors increasing asthma prevalence and morbidity by using standardised decision support tools
Adapt international asthma guidelines for developing and low income countries and use realistic dissemination and implementation strategies
Promote cost-effective asthma management approaches which have been proven to reduce morbidity and mortality in parallel with disease-related costs and invest in innovative models for chronic diseases
Smart investment in asthma research - key priority areas • unveiling the risk factors and mechanisms that cause asthma, including detailed phenotyping/endotyping • novel biotechnological innovations and patient-oriented diagnostic and treatment protocols • well designed primary and secondary intervention strategies for asthma prevention and control, with reproducible short and long-term deliverables and fully applicable in developing and low income countries
Special focus on difficult-to-manage and costly severe disease forms and/or exacerbations of asthma. A multidisciplinary approach within specialist centers with experience and wider access to national and international severe asthma networks is needed
involvement of all stakeholders, including the Primary Care Network, Patient Organizations and policy makers

The low public health priority of asthma due to the importance of other illnesses and to the lack of awareness of the general public and policy makers is an important barrier to efficient implementation of asthma management plans. Until asthma is recognised as a novel major public health problem and pharmacological measures become available to reduce the prevalence of asthma, resources need to be prioritised to address asthma preventable risk factors, such as air pollution or tobacco smoke, to improve the care of disadvantaged groups with high morbidity, including certain racial groups and those who are poorly edu-

cated, live in large cities, or are poor and to ensure that cost-effective management approaches which have been proven to reduce morbidity and mortality are available to as many persons as possible with asthma worldwide. Even if asthma control is not achieved, improvements in quality of life can still be obtained with appropriate treatment. Therefore, treated patients with partly controlled asthma, and even uncontrolled asthma, could contribute to lessen asthma-associated disability.

Current information on the cost effectiveness of interventions in asthma is limited to randomised trials results conducted in developed countries. A sectoral cost effectiveness analysis using a lifetime population model evaluated asthma interventions in two WHO epidemiological sub-regions, in Africa (countries with high child and very high adult mortality), and South East Asia (countries with high child and adult mortality). If resources are available, the results indicate that policy makers in both regions should prioritise first the implementation of low dose inhaled corticosteroids for mild persistent asthma. This intervention is relatively inexpensive but averts a sizable number of DALYs, avoiding exacerbations, which are an important source of damage to quality of life and increased mortality. In the sub-Saharan African region policy makers should focus on the provision of low dose inhaled corticosteroids plus long acting β agonists for moderate persistent asthma as the next most cost effective intervention. Medium dose inhaled corticosteroids for moderate persistent asthma cases would make a further important contribution to asthma control but is a less cost effective option.

Most of the lifestyle-related risk factors for asthma (poor hygiene or diet, obesity and psychosocial stress) are prevalent among the poor. In many areas of the world asthma sufferers do not have access to diagnosis or to basic asthma medications. Increasing the economic wealth and improving the distribution of resources between and within countries represent important priorities to enable better health care to be provided.

The “Yes We Can Urban Asthma Partnership” was created by local organisations in San Francisco and reaches out to high-risk children from underserved urban areas in different clinical settings: urgent visits, the hospital, a comprehensive specialty asthma clinic, and through an expanded community health worker programme. Programme evaluation demonstrated significant increases in prescribing controller medications, use of action plans, use of mattress covers and together with a significant decrease in asthma symptoms. Additional changes occurred within the local system of asthma care to support ongoing efforts to improve asthma management. We conclude that pediatric asthma programs can effectively target the social and medical needs of children in a sustainable manner.

The La Red intervention in the selected Puerto Rican communities experiencing a disproportionately high level of asthma burden combined the key components from the “Yes We Can” and the Inner-City Asthma Study interventions. The program significantly reduced asthma symptoms and exceeded reductions of the original US based interventions. Asthma-related hospitalizations and emergency department use, and their associated high costs, were also significantly reduced.

A variety of decision support tools (DSTs) are used at various levels and by various stakeholders, both researchers and decision makers. A recent survey showed that more than 25% of the DSTs address only one pollution source or only one environmental stressor, while almost 50% of the DSTs are only applied to one chronic disease and 41% of the DSTs can only be applied to one decision making area. In the same survey 60% of the DSTs’ results are used only by national authority and/or municipality/urban level administration and almost half of the DSTs are used only by environmental professionals and researchers. This survey indicates the need to develop standardised DSTs covering an increasing number of pollution sources, environmental stressors and health end points.

Telemanagement of asthma includes key components of asthma management, such as education, self-monitoring, goal setting, written action plans and regular medical review. An increasing number of studies showed that a comprehensive telemanagement approach

is effective in improving quality of life and clinical outcomes, especially in adult patients with moderate to severe asthma. The intervention is tailored to the individual patient needs. However, more research is needed on the long-term effectiveness and cost-effectiveness under real-world conditions.

Community pharmacies have the potential to make a greater contribution to promoting public health. A new concept, called the Healthy Living Pharmacy (HLP) was designed to meet public health needs through a tiered commissioning framework delivering health and well being services through community pharmacy, tailored to local requirements for tackling health inequalities. Some good evidence exists for the introduction of specific community pharmacy services, targeted at customer groups, both with and without pre-existing diseases, for interventions on asthma.

The Chronic Care Model advocates a multi-component remodelling of chronic disease services to improve patient outcomes. Integrated at the point of care in primary care practices is a promising innovation expected to improve patient self-efficacy and empowerment in the short-term and an improvement in health behaviour, functional health status, quality of life and psychological well-being in the mid-term. At the organizational level, the project should lead to coordinated service delivery, improved patient follow-up mechanisms and enhanced interprofessional collaboration.

B. IMPROVED DIAGNOSIS OF ASTHMA

Better asthma diagnosis is a prerequisite of an efficient management plan. Ioana Agache's research focused on the in vivo and in vitro diagnosis of allergies and asthma, leading an EAACI Task Force focusing on provocation tests in asthma and allergic diseases and being an author of a guideline for in vitro molecular diagnosis.

In most of the cases the standard diagnosis of an allergic disease is done based on a detailed clinical history and demonstration of sensitisation (either by skin test or in vitro testing) to a relevant allergen concordant with the history. The allergen challenge test is rarely required. However, the history of allergy diagnosis started with a 'functional skin test', named the patch test in 1894, which is essentially a provocation test. Systematically applied provocation tests followed with the introduction of conjunctival provocation (1907), followed by nasal and bronchial provocation with allergens (1914 and 1925).

The allergen provocation test is a long-standing model for studying and diagnosing allergic diseases such as rhinitis, conjunctivitis, asthma or food allergy. Due to safety issues and lack of standardisation in conjunction with increased availability of high quality reagents for skin tests or in vitro diagnosis the allergen provocation test was almost abandoned from daily practice and reserved for research purposes.

The position paper published by Ioana Agache as first author provides a critical appraisal of allergen challenge methods (bronchial, nasal, conjunctival, food, venom) together with recommendations on indications, procedure and safety (200). A special subchapter is dedicated to a novel diagnostic test – the allergen challenge chamber (ACC) - targeting several locations where a type I allergic reaction occurs (eyes, upper- and lower respiratory tract and even skin). The use of a stable and reproducible allergen load leads to an even symptom score. Challenge sessions are possible all over the year, with no regard to seasons. In contrast to field or park studies it is possible to report additionally objective assessments such as slit lamp investigation, rhinomanometry, spirometry, endoscopy with the opportunity to crosscheck the validity of the subjective scoring. Furthermore it is possible to take blood samples, lavages and scrapings on several time points of the challenge session for pharmacodynamics and pharmacokinetic investigation. The ACC is not usually used for individual diagnosis and is indicated for assessing the efficacy of anti-allergic treatments, for studies in occupational allergy and basic research. The ACC model is approved and accepted by the FDA and EMA for phase II trials (proof of concept or dose finding) and

for further supporting phase III trials. EMA suggests ACC trials for conducting dose finding trials of immunotherapeutic products. Since they require significantly less time than field studies and smaller numbers of individuals per trial the potential of ACC trials could be extended to monitor AIT and to reduce the cost of drug development substantially. The paper highlights the value of challenge testing is the mainstay of allergy diagnosis since it directly proves the clinical relevance of the tested allergen. Once a research tool, challenge tests are slowly making their way into daily practice, mainly due to an increased safety profile and better standardisation. The use of recombinant allergens and modern techniques to objectively quantify and compare the biological modifications induced by allergen challenge are highly promising. However, proper use of clinical judgment in recommending a challenge test, selection of the appropriate allergen for testing and interpretation of results, as derived of a thorough training as an allergist, are essential to ensure the deserved value of allergen challenge test.

The availability of allergen molecules ('components') from several protein families has advanced our understanding of immunoglobulin E (IgE)-mediated responses and enabled 'component-resolved diagnosis' (CRD). Ioana Agache was a co-author of the EAACI Molecular Allergology User's Guide (MAUG), a comprehensive book that provides detailed information on important allergens and describes the diagnostic options using CRD (108). IgE-mediated reactions and allergic diseases, including allergic rhinoconjunctivitis, asthma, food reactions, and insect sting reactions, are discussed from a novel molecular perspective. The EAACI MAUG documents the rapid progression of molecular allergology from basic research to its integration into clinical practice, a quantum leap in the management of allergic patients. Part A of the EAACI MAUG introduces allergen molecules, families, composition of extracts, databases, and diagnostic IgE, skin, and basophil tests. Singleplex and multiplex IgE assays with components improve both sensitivity for low-abundance allergens and analytical specificity; IgE to individual allergens can yield information on clinical risks and distinguish cross-reactivity from true primary sensitization. Part B discusses the clinical and molecular aspects of IgE-mediated allergies to foods (including nuts, seeds, legumes, fruits, vegetables, cereal grains, milk, egg, meat, fish, and shellfish), inhalants (pollen, mold spores, mites, and animal dander), and Hymenoptera venom. Diagnostic algorithms and short case histories provide useful information for the clinical workup of allergic individuals targeted for CRD. Part C covers protein families containing ubiquitous, highly cross-reactive panallergens from plant (lipid transfer proteins, polcalcins, PR-10, profilins) and animal sources (lipocalins, parvalbumins, serum albumins, tropomyosins) and explains their diagnostic and clinical utility. Part D lists 100 important allergen molecules.

C. THE ROLE OF PRIMARY CARE IN ASTHMA

The standard of care for asthma and allergic diseases within a primary care setting has a strong influence on disease prevention and control, quality of life, and patient satisfaction. The level of knowledge of asthma and allergic diseases and the accessibility to regular follow-up are essential. Ioana Agache led an EAACI Task Force on Allergy and Asthma Management in Primary Care aiming to deliver the best care pathways for the general practioners as part of the integrated management of asthma and allergic diseases

The Task Force started with a survey (201) in collaboration with the International Primary Care Respiratory Group (IPCRG) aiming to evaluate the actual status of care for allergic diseases in primary care. Access to allergy and asthma specialist treatment was identified as the greatest 'unmet need'. The average waiting time between a referral and being seen in a public health service is usually >6 weeks. Referring the patients to an 'organ' specialist is much easier compared with referral to an allergist. Most general practitioners have access to blood tests for total and specific IgE. Skin prick testing is available in only half of the cases, while provocation tests, allergen

quantification in homes, and a dietician service are even less available. 20.6% of practices do not have access to allergy tests at all. Other issues raised by the survey were low political or general public awareness, lack of understanding by the patients of their allergic disease, the need to invest in primary care, and to achieve sufficient competence at the appropriate level of care.

The dominant model of allergy care within Europe is at the moment specialist-based. This model will become unsustainable and undeliverable with increasing disease prevalence. One solution to increase provision of allergy services is to diversify the providers. A new model for the provision of allergy care in the community with the general practitioner at the forefront is proposed by the Task Force lead by Ioana Agache (202). Pre- and postgraduate allergy education and training, implementation of pathways of care, allergy specialization and political will to generate resources and support are essential to achieve this new model. In parallel the holistic view of allergic diseases should be maintained, including assessment of severity and risk, psychological factors and health-care related costs in the context of the patient-centered decision making process.

In most of the European countries, the majority of patients who seek medical advice for allergic diseases are first seen in a primary care setting, partly because relative ease of access but also because of the paucity of trained allergists to meet the ever growing demand. Correct diagnosis with identification of all offending allergens is an absolute prerequisite for appropriate management of allergic disease by the general practitioner. One of the aims of the EAACI Task Force for Allergy Management in Primary Care was to critically review the diagnostic tests and to provide management pathways for the most common allergic diseases seen and treated in primary care (203). Management pathways for asthma and major allergic diseases within the primary care network are recommended (Figure 40). Key recommendations for allergy management in primary care are as follows:

1. Specific IgE measurement can be performed in primary care or referred (depending on local conditions), but only in light of a precise patients history
2. Skin prick tests are not recommended without a proper training and the risk of anaphylaxis should be considered
3. Total IgE as a single parameter measurement is not recommended
4. IgG measurement is not recommended
5. Seasonal and easily responsible to treatment allergic rhinitis should not be IgE tested
6. Use of management pathways adapted for PC is strongly recommended

D. INCREASING AWARENESS ON ALLERGIES AND ASTHMA

Since more than 30% of the total European population suffers from airways allergies and asthma, reaching a higher level of awareness and elaboration of an active prevention plan is mandatory.

Independent of incidence, age group or nationality, it is important to realize that asthma and allergic diseases have a detrimental impact on the quality of life of patients and their families, affecting their personal development, career plans and lifestyle choices. These diseases may affect sleep and mood, school or work competence, and social interaction. The impact of asthma and allergies on quality of life can be as high or even higher than that of diseases commonly perceived as being more ‘serious’ (8, 204, 205)

At the society level, the rising prevalence of allergic diseases poses a multifaceted, major socioeconomic burden on national and European budgets. The increased use of health services, hospitalization and pharmaceutical costs, in addition to the billions of days of lost productivity through absenteeism or presenteeism (people going to work but being unable to perform), reveal a worrying prospect for public health when it comes to asthma and allergies (8, 206). Given the nature of current lifestyles, the ageing population and continuing environmental changes, these costs are likely to increase, unless a concerted effort is devised to understand the causes and mech-

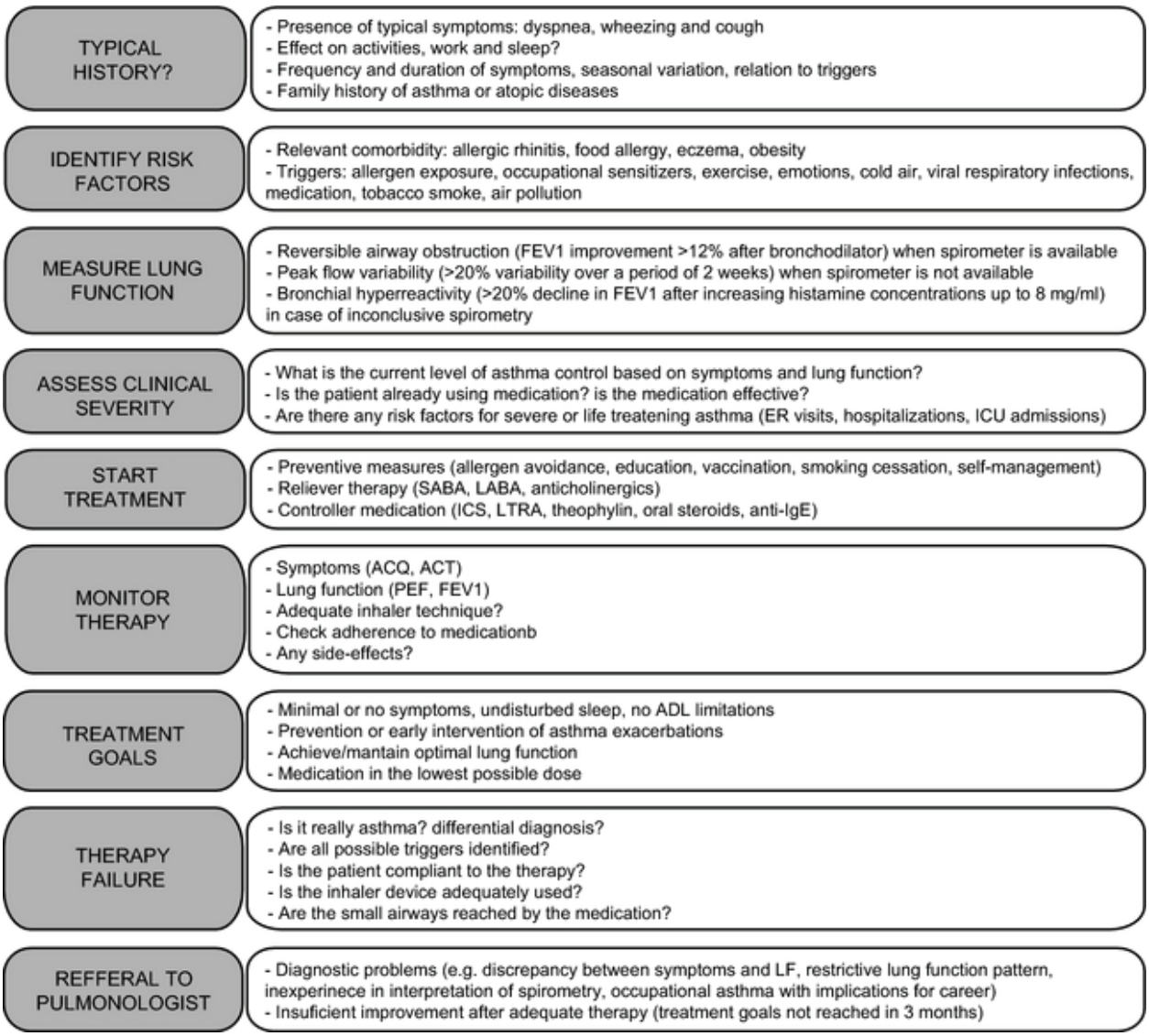

Figure 40

Pathway for asthma diagnosis and management in primary care. Objective tests to measure airway obstruction are recommended as the correlation between pulmonary symptoms and lung function is poor. Measuring lung function in primary care is needed for the diagnosis of asthma and for guiding subsequent management. Patients with inconclusive spirometric results should be referred for additional tests, such as nitric oxide *(NO)* measurement and/or bronchial provocation. After the recent introduction of small, portable analyzers, NO measurement is also feasible in primary care. Inhaler medication is the cornerstone of asthma treatment. There are several types of inhalers that vary in dose delivery, deposition and particle size, flow dependency and convenience. Several aspects need to be considered when prescribing an inhaler: asthma severity, cooperation, inspiratory flow, hand-mouth coordination, type of medication (bronchodilators, anti-inflammatory) and location of the disease process and receptors in the lung. Teaching optimal inhaler technique requires repeated visits and guidance by experienced health care workers. *(Reproduced from Jutel M, et al. Recommendations for the allergy management in the primary care. Allergy. 2014;69(6):708-18)*

anisms of allergy and design effective strategies for prevention and/or treatment.

The low public health priority of asthma due to the importance of other illnesses and to the lack of awareness of the general public and policy makers is an important barrier to efficient implementation of asthma management plans.

Two recently published papers highlight Ioana Agache's activity in increasing awareness on asthma and allergic diseases in order to ensure proper funding for research and efficient management of these diseases.

The paper ***Research needs in allergy: an EAACI position paper, in collaboration with The European Federation of Allergy and Airways Diseases Patients' Associations (EFA)***, (207) cited 85 times since its publication, highlights the most important research needs in the field of allergy and asthma to serve as key recommendations for future research funding at the national and European levels.

There are several common themes that need to be prioritized in research efforts.

1. As in many other chronic diseases, effective prevention, curative treatment and accurate, rapid diagnosis represent major unmet needs. Detailed phenotyping/endotyping stands out as widely required in order to arrange or re-categorize clinical syndromes into more coherent, uniform and treatment-responsive groups. Research efforts to unveil the basic pathophysiologic pathways and mechanisms, thus leading to the comprehension and resolution of the pathophysiologic complexity of asthma and allergies will allow for the design of novel patient-oriented diagnostic and treatment protocols.
2. Asthma and allergic diseases require well-controlled epidemiological description and surveillance, using disease registries, pharmacoeconomic evaluation, as well as large biobanks.
3. There is a need for extensive studies to bring promising new biotechnological innovations, such as biological agents, vaccines of modified allergen molecules and engineered components for allergy diagnosis, closer to clinical practice.
4. Particular attention should be paid to the difficult-to-manage, precarious and costly severe disease forms and/or exacerbations. Nonetheless, currently arising treatments, mainly in the fields of immunotherapy and biologicals, hold great promise for targeted and causal management of asthma and allergic conditions.
5. Active involvement of all stakeholders, including Patient Organizations and policy makers are necessary to achieve the aims emphasized herein.

From 26th to 28th of April 2016, an allergy awareness campaign was organized by EAACI and EFA in the European Parliament in Brussels, with support of the European Parliament's Interest group on Allergy and Asthma and was co-hosted by the Members of the European Parliament David Borrelli, Sirpa Pietikainen and Nessa Childers. Skin prick tests were performed to gain attention for the increasing prevalence of allergic airways diseases in Europe. The results of the intervention were recently published (208): of the 406 individuals tested in the European Parliament, 211 participants (52%) reported to have suffered from an allergy in the past, with allergic symptoms being present in the nose and eyes (40% and 36% respectively), the skin (27%), lower airways (14%) and the gut (8%). Of the 381 skin prick tests with reliable results, sensitization to at least one aeroallergen was found in 201 (53%) participants. Of those, 70 participants (35%) were monosensitized while 131 participants (65%) were polysensitized. The positive skin reactions were found mostly for grass pollen (n=108), followed by Dermatophagoides pteronyssinus (n=105), Dermatophagoides farina (n=96) and birch pollen (n=85). This paper provides evidence that chronic respiratory diseases are a major and growing health problem in Europe and highlights the need for a joint preventive action plan needs to be developed for a better health status of European citizens.

B-i

Scientific and professional achievements

Professional developments

Chapter 2

2.1. CAREER OVERVIEW

The foundation of a career plan needs to be driven by your professional goals, always balancing short-term with long-term considerations, creative research with self-development, being both an efficient problem-solver and problem-creator by asking interesting new questions, pose old problems in a new way, or by demonstrating a simple but fruitful connection that no-one previously realized existed.

Developing a unique combination of abilities such as being a compassionate medical doctor, a good teacher and top researcher was the main goal of my career development. Developing a unique combination of abilities such as being a compassionate medical doctor, a good teacher and top researcher was the main goal of my career development.

I graduated in 1994 Carol Davila" University in Bucharest as a Medical Doctor, in 1998 I started my residency in Allergy and Clinical Immunology and became in 2000 Specialist and in 2004 Senior Specialist in Allergy and Clinical Immunology at the "Carol Davila" University, Bucharest.

I finalised in 2005 my PhD Thesis in Internal Medicine *Magna cum laude*. The thesis evaluated a very original facet of the pathogenesis of atherosclerosis with the hypothesis that the immune-inflammatory mechanisms precede and potentiate the well-known metabolic pathways that lead to atheroma lesions formation and progression. At that time the research theme was considered absolutely leading-edge and was appreciated via publications and oral communications, including a lecture as the guest speaker at the prestigious Swiss Allergy and Clinical Immunology Society Annual Meeting.

My research pathway was always at the forefront of the innovative and cutting-edge science focusing on asthma, allergic rhinitis and food allergy. As an appreciation I was invited to be a member of the Expert Panels for several international guidelines such as ARIA (Allergic Rhinitis and its Impact on Asthma), a famous WHO project referenced all over the world, the Food Allergy and Anaphylaxis Guidelines recently published by the European Academy of Allergy and Clinical Immunology (EAACI) and the Allergen Immunotherapy Guidelines currently developed by EAACI.

I published 58 papers with 2567 citations and h-index 18 in ISI Web of Science. In Google Scholar my activity is reflected by 8590 citations (4644 since 2012). My h-index is 20 and i10-index 32 (figure 41).

I edited recently three very successful Global Atlases, on asthma, allergic diseases and rhinitis/chronic rhinusinusitis and was involved in several Expert Panels of the World Allergy Organisation.

I am a highly appreciated reviewer of high impact scientific journals such as Journal of Allergy and Clinical Immunology and Allergy and the Associate Editor of the open-journal Clinical and Translational Allergy.

I was a member of several Scientific Committees organizing international conferences with > 8000 participants for several years in a row and I am at present the Vice-President and President Elect of the European Academy of Allergy and Clinical Immunology (EAACI).

In the last five years my research focused on the area of asthma and allergic diseases phenotypes and endotypes with the aim to identify new treatment targets and better select the responders to the treatment options available for these diseases. I am the first/last author of 6 original papers and reviews published in highly ranked ISI journals highlighting the need and the modality of endotype-driven approaches for the management of asthma. The research on asthma and allergic disease endotypes is performed since 2010 in cooperation with the Swiss Institute for Allergy and Asthma (SIAF), Davos, where I was Visiting Professor.

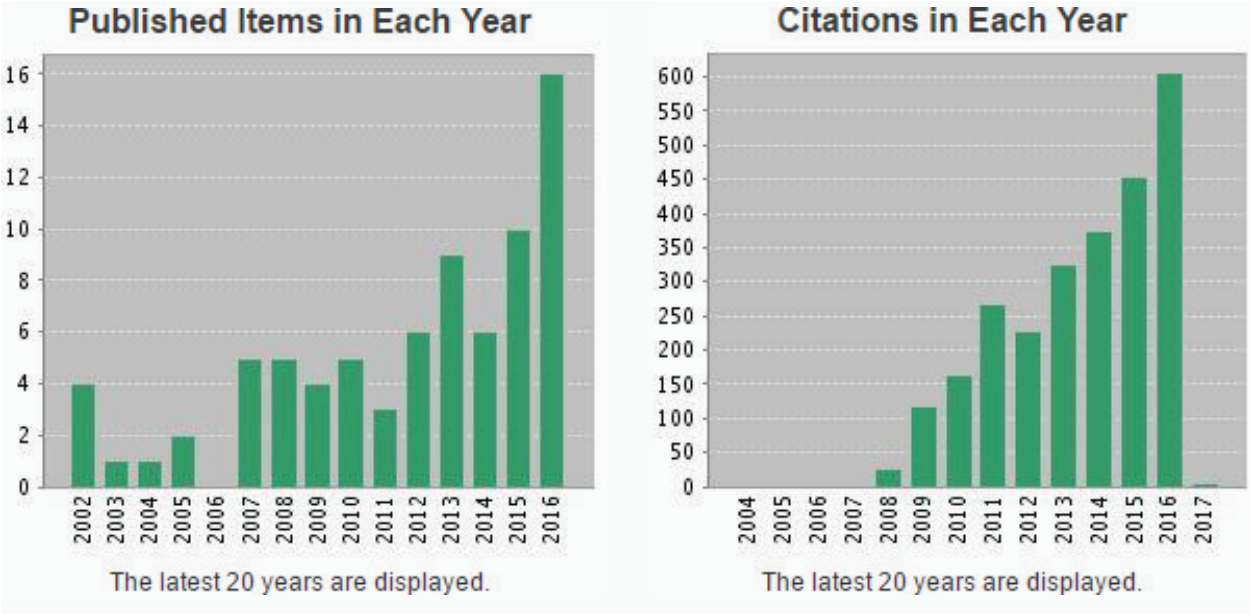

Figure 41

Scientific and professional achievements achievements – Web of science and Google scholar citation index.

2.2. PhD THESIS AND PROJECTS

A. PhD THESIS

I defended in 2005 my PhD Thesis in Internal Medicine "**3 Years Evolution in Patients with Acute Coronary Syndromes and *Chlamydia Pneumoniae* Infection**" and I graduated *Magna cum laude*. The background of my research was based on several novel publications at that time underlining the association, however controversial, between increased titres of anti *Chlamydia Pneumoniae* (CP) antibodies and coronary heart disease, stroke and peripheral obstructive artery disease (209, 210), while endovascular CP markers expression demonstrated through immunohistochemistry, electronic microscopy, in situ hybridisation and cultivation of the bacteria from the atherosclerotic plaque supported the relation between the CP infection and coronary atherosclerosis by a risk ratio of 20 (211). Animal models and in vitro experiments have implicated CP pathogenically in the initiation and accelerated progression of the atherosclerotic lesions and in plaque activation (212). The impact of macrolide or chinolone treatment on the incidence of cardiovascular events in patients with coronary heart disease was largely controversial (213).

The PhD research was part of my engagement between 2000-2003 in the CNCSIS programme, contract 3993/14.06.2000, "*Chlamydia Pneumoniae* infection as a risk factor for acute coronary syndromes, stroke and peripheral artery disease", coordinated by Prof. Dr. Mariana Radoi. My specific assignments were CP detection via immunohistochemistry and serology and the immunologic evaluation of acute coronary syndromes and stroke.

The main aim of the PhD research was the evaluation of the incidence of major cardiovascular events (MACE) - cardiovascular death, non-fatal myocardial infarction, unstable angina with readmission – after 30 days, 6 month, 1 year, 2 years and 3 years of evolution in patients with acute coronary syndromes (ACS), with or without CP infection, as appreciated serologically. Secondary aims were: 1) Evaluation of the relation between CP infection and systemic inflammation (fibrinogen, C reactive protein, IL6, TGF-β), serum concentration of T troponin, the titre of anti oxLDL antibodies and of the relation between CP infection and traditional atherosclerotic risk factors; 2) study of the CP infection incidence in unstable atherosclerotic lesions and the correlation of CP infection with the severity of atherosclerotic lesions and with the cellular events implicated in plaque instability; 3) evaluation of the impact of macrolide treatment association to the conventional treatment of ACS on MACE incidence after 3 months, 6 months and 4 years of evolution in patients with ACS. Several major findings deserve to be highlighted: 1) The incidence of CP infection in patients with ACS was significantly increased, both by serological evaluation and by immunohistochemistry evaluation; 2) The presence and the persistence of anti CP antibodies at 30 de days and the IgG anti CP titre >1/1024 UI/ml at the initial moment have the highest prognostic value for the short, medium and long term evolution with MACE 3) Histological markers of CP infection are implicated in the promotion of atherosclerotic lesions instability, independent of the expression of histological markers for cellular activation, and in direct relation with myocardial necrosis; 4) Treatment with Rovamycine ® 12 or 24 de days added to the conventional therapy of acute coronary syndromes is beneficial for the medium and long term evolution by reducing the MACE incidence at 6 months and at 4 years.

There are several strengths in the results of my PhD research: while serologic and immunohistological data supporting the increased incidence of CP infection in ACS were perfectly aligned with other studies published at the same time, thus showing consistency and reproducibility of the research, I found and published new data supporting the prognostic value of CP serology and its relation the with dislipidemia as an indirect mechanism by which CP promotes systemic inflammation. The significantly increased incidence of CD14

expression in grade V and VI atherosclerotic lesions was reported for the first time here and then confirmed by numerous successor studies. The research also added high quality evidence for the long-term beneficial effect of macrolide treatment in ACS.

Besides being appreciated "*Magna cum laudae*" the PhD thesis the value of the results was acknowledged by several publications and lectures delivered by Ioana Agache (Table 17).

Table 17

Scientific accomplishments during my PhD thesis.

Full text articles in ISI/BDI journals	• **Ioana Agache**, Mariana Rădoi, T. Leaşu; "Infecţia cu Chlamydia Pneumoniae - implicaţii în patogenia aterosclerozei"; Revista Medicală Naţională, 2001, vol. V, nr. 1-2, ISSN 1453-2506; pg.49-54, 6 pagini; • Mariana Rădoi, **Ioana Agache**, Alina Pascu; "Reacția imun-inflamatorie în ateroscleroză"; British Medical Journal 2002 - ediţia în limba română, http://www.bmj.ro/revista/martie-2002-nr-2 • Mariana Rădoi, Elena Bobescu, **Ioana Agache**; "Rovamycine as add-on treatment in unstable angina and 4 year evolution with major cardiovascular events"; Romanian Journal of Internal Medicine 2003, 41, 3; pg.237-246; 2003
Book chapters	• Mariana Rădoi, **Ioana Agache**. "Reacţia inflamatorie în ateroscleroză – date actuale". Progrese in cardiologie" sub redactia L. Gherasim, 2002, Editura Infomedica, ISBN 973-9394-89-2; pg.377-399 ; 2002 • Mariana Rădoi, **Ioana Agache**, Mariana Anghel, Marius Penciu, Florin Leasu; "Expression of CD14 receptor and Chlamydia Pneumoniae membrane antigens in coronary atherosclerotic lesions grade V and VI – study on 46 patients"; „Frontiers in Coronary Artery Disease" edited by B. L. Lewis, DA Halon, MY Flugelman, GF Gensini; 2003, Monduzi Editore, ISBN 88 – 323 -3161-6; pg. 215-217; 2003
Oral communications at international conferences	• Elena Bobescu, Mariana Rădoi, **Ioana Agache**, A. Burducea; "Correlation between oxidative stress, inflammatory syndrome and prognosis in patients with acute coronary syndromes"; 11th International Conference on Advances in Prostaglandin and Leukotriene Research: Basic Science and New Clinical Application, Florence, Italy, June 4 –8, 2000 • **Ioana Agache**, Mariana Rădoi; "Infection with Chlamydia Pneumoniae and atherosclerosis – is there a link?"; EAACI Summer School, Rome-Cagliari, 2000 • Mariana Rădoi, Elena Bobescu, **Ioana Agache**, Claudia Timu; "Serological status for Chlamydia Pneumoniae, systemic inflammation and one month evolution of patients with unstable angina"; First International Symposium on PPARs: from basic science to clinical applications. Florence, April 4-7, 2001 • Mariana Rădoi, Elena Bobescu, **Ioana Agache**, Mariana Anghel; "TGF β plasma level and evolution of patients with unstable angina at one and six months." Heart, vol. 87, suppl.1, pg. A11; 2002 • Mariana Rădoi, **Ioana Agache**, Elena Bobescu, Mariana Anghel; Serological status for Chlamydia Pneumoniae in patients with acute coronary syndromes in correlation with IL6 and TGF beta serum level; 1st International Conference on Cytokine Medicine, Manchester; pg.16; 2003 • Mariana Rădoi, Elena Bobescu, **Ioana Agache**, Florin Leasu; Rovamycine as add-on treatment in unstable angina and 4 year evolution with major cardiovascular events"; 12th International Congress on Cardiovascular Pharmacotheraphy; Abstract Book, pg.4; 2003 • Mariana Rădoi, **Ioana Agache**, Mariana Anghel, Marius Penciu, Elena Bobescu, Florin Leasu; Expression of CD14 receptor and Chlamydia Pneumoniae membrane antigens in coronary atherosclerotic lesions grade V and VI – study on 46 patients"; The Journal of Coronary Artery Disease, 5; 1: pg 118; 2003 • Mariana Rădoi, Elena Bobescu, **Ioana Agache**, Mariana Anghel; Antibodies against oxLDL, CRP and IL6 serum levels an one and six months evolution of 54 patients with acute coronary syndromes; Clinical and Experimental Rheumathology 22; pg. 21, 2004

	• Mariana Rădoi, **Ioana Agache**, Mariana Anghel, Marius Penciu, Elena Bobescu, Claudia Timu, Diana Tant; "CD 14 receptor expression in unstable coronary atherosclerotic lesions"; Clinical and Experimental Rheumathology 22; pg. 21; 2004
Oral communications at national conferences	• Mariana Rădoi, **Ioana Agache**; "Immune-inflammatory mechanisms in atheroslerosis", Annual Conference of the Romanian Society of Allergology and Clinical Immunology with international participation, Bucharest 2002, vol. rez. pg. 53; 2002 • Mariana Rădoi, Elena Bobescu, **Ioana Agache**, Mariana Anghel, Liliana Eftimie; "Antibodies against ox LDL in correlation with IgG and IgA anti Chlamydia Pneumoniae serum titers in 54 patients with acute coronary syndromes"; First Romanian Symposium with International Participation - Inflammation 2004. April 20-23, 2004, Sâmbata de Sus Academy, Braşov County, Romania; pg. 53; 2004 • Mariana Rădoi, Elena Bobescu, Diana Ţânţ, Mirela Şerbănoiu, **Ioana Agache**, Claudia Timu, T. Alexandru, Maria Anghel, Ioana Rusu; "Incidenţa infecţiei cu Chlamydia Pneumoniae în sindroamele coronariene acute"; Revista Naţională de Cardiologie, 2000 • Mariana Rădoi, Elena Bobescu, **Ioana Agache**, Claudia Timu, Mirela Serbanoiu; "Status-ul serologic pentru Chlamydia pneumoniae, inflamaţia sistemică şi evoluţia la o lună a pacienţilor cu angină instabilă" Revista Română de Cardiologie,2001, vol. XIV, nr.3, pg. 54-55 • Elena Bobescu, **Ioana Agache**, Mariana Rădoi, Claudia Timu, Diana Tînţ. "Persistenţa infecţiei cu Chlamydia Pneumoniae şi valorile plasmatice ale colesterolului, PCR, fibrinogen, IL6, TGF beta, status-ul antioxidant total şi sindroamele coronariene acute"; Revista Română de Cardiologie, vol. XVII, nr.3 ; pg.69; 2002 • Elena Bobescu, Mariana Rădoi, **Ioana Agache**, Mariana Anghel, Gabriela Ifteni; "Titrul anticorpilor anti oxLDL, nivelele serice ale PCR si IL6 si evolutia la 1 si 6 luni a 54 pacienti cu sindroame coronariene acute"; Revista Română de Cardiologie, vol. XVII, nr.3 ; pg.75; 2002 • Elena Bobescu, Mariana Rădoi, **Ioana Agache**, Alina Tudose, A. Burducea. "Corelatiile dintre status-ul antioxidant total si prognosticul pacientilor cu sindroame coronariene acute"; Revista Română de Cardiologie, vol. XVII, nr.3 ; pg.132; 2002 • Mariana Rădoi, **Ioana Agache**, Mariana Anghel, Marius Penciu, Elena Bobescu, Claudia Timu, Diana Tânţ; "Aterotromboza coronariană în relaţie cu activarea celulară evaluată imunohistochimic prin expresia receptorului CD14"; Revista Română de Cardiologie, vol. XVIII, nr. 3; pg. 110; 2003
Invited lectures	• **Ioana Agache**, Mariana Rădoi; Immune inflammatory mechanisms in atherosclerosis. 5th Course: Allergy and Immunology Update (AIU), Swiss Society of Allergology and Immunology; 2003 • **Ioana Agache**; „Mecanisme imun-inflamatorii în ateroscleroză"; al VII-lea Simpozion Naţional "Prof. Dr. Dimitrie Gerota", 27-29 oct.2004

Following the PhD Thesis the experience accumulated with the immunological evaluation of cardio-vascular diseases was engaged into another research programme" the IMPACT program, CERICARD project 908/13 June 2007 – Research and integrated management in heart failure, Project Coordinator Prof. Dr. Mariana Rădoi. My specific appointment was to coordinate the fundamental research in heart failure.

B. PROJECTS

Leadership of national research programmes (PN-II-RU-TE-2014-4-2303 – Endotypes of Non-Eosinophilic Asthma - ENDANA), and partnerships in EU projects: COST actions (COST BM 1201: Early Origins of Chronic Lung Disease) and GA2LEN program, DARE – diary card piloting and validation are detailed below.

B1. PN-II-RU-TE-2014-4-2303 – Endotypes of Non-Eosinophilic Asthma - ENDANA

Non-eosinophilic asthma represents approximately 50% of the adult asthma cases and is characterized by a modest response to the therapeutic intervention with inhaled steroids (70, 214, 215), which is the mainstay of

asthma treatment as reflected by the current guidelines. Thus, profiling the non-eosinophilic (Th2 low) and the resident cell compartment of asthma are major unmet needs in the field of asthma endotyping.

In the PN-II-RU-TE-2014-4-2303 project lead by Ioana Agache we hypothesise that non-eosinophilic asthma is not a single disease, but a syndrome resulting from several distinct underlying pathological processes known as endotypes. Since non-eosinophilic asthma represent in adults approximately 50% of all cases many novel investigational therapies directed against Th2 targets (IL-5/IL-13/CRTH2), are likely to have efficacy in only 50% of subjects with severe disease. There is currently a lack of hypothesised specific novel therapeutic targets for non Th2-mechanisms and the focus of this project is to characterise these alternative drivers of asthma pathophysiology. We anticipate that these approaches will identify potential therapeutic targets in subsets of non-eosinophilic asthma patients, leading to endotype-specific personalised therapies.

The main objective of the ongoing research project are to describe and validate non-eosinophilic asthma endotypes using complementary approaches such as detailed immunological and molecular analysis of induced sputum cells and of sputum and serum cytokines and chemokines in extensively characterised (visible properties) adult non-eosinophilic asthma patients (mild/moderate/severe) together with unbiased bio-statistical tools such as cluster analysis to identify putative immunopathological non-eosinophilic asthma endotypes. Secondary objectives are aligned with the professional and academic development and target capacity building with new skills or qualifications gains by staff involved in the project in the field of bioinformatics, molecular biology and sputum cell flow-citometry with FACS-analysis, acquirement of leadership, managerial and communication skills by young researchers, the project aiming to develop a stable team of young researchers, which is anchored in specific organisational needs and standards. In addition we aim to set up an interdisciplinary framework for basic, translational and clinical research, benefiting from pooled knowledge and resources leading to new product development in the field of asthma biomarkers and other diagnostic techniques and new treatments for asthma and more resources (both funding and high qualified researchers) for the personalized approach to asthma management

There are several elements of originality and innovation in this project, related to the state of the art in the field and to the previous projects developed by the project leader, Ioana Agache. Non-eosinophilic asthma was not endotyped previously so this is a first ever attempt to delineate the mechanistic pathway, their biomarkers and the potential therapeutic targets. Innovative diagnostic techniques will be employed such as sputum dialysis and ultrafiltration for cytokine concentration, while the incorporation of longitudinal data such as asthma exacerbations and lung function into the clusters will add to the validity of the construct. The project aims to improve clinical guidelines and clinical practice by modelling the behaviour of healthcare professionals or providers by reinforcing the concept of personalized medicine and is likely to identify potential novel targets and biomarkers for non-eosinophilic asthma. This pathway was successful for the development of biomarkers of eosinophilic asthma and subsequent selection of responders to targeted treatment. This project will thus support product development such as new treatments and new diagnostic techniques

The impact expected for this project can be systematized as follows:

- Knowledge production, such as journal articles and presentations that add to or confirm existing knowledge to the area of research of asthma endotypes and personalized treatment
- Capacity building, such as new skills or qualifications gains by staff involved in the project in the field of bioinformatics and sputum cell FACS-analysis
- Health sector benefits, such as improved health economics via reduced costs and improved asthma care with reduced morbidity and better quality of life

The project will be finalised in 2017. Preliminary results reported in December 2016 on the in-depth characterization on the patients based on visible properties (phenotype) show

specific traits for non-eosinophilic asthma in comparison with eosinophilic asthma such as increased frequency of nocturnal symptoms, increased AHR both of large and small airways, increased resistance of the airways, decreased diffusion coefficient, prominent remodeling and parenchymal abnormalities. As for the biomarkers evaluated until now, half (57.14%) of the patients had increased serum levels of total IgE providing evidence for an "allergic" sub-endotype of non-eosinophilic asthma that might be responsive to targeted anti IgE treatment. This observation is in line with the data reported on the serum IgE induced airway smooth muscle cell remodeling independent of allergens and prevented by omalizumab (216).

B2. COST BM 1201: Early Origins of Chronic Lung Disease

Recent studies indicated that the risk to develop chronic lung disease (CLD) is modified by early exposures during critical developmental windows. This concept opens unique opportunities for the pre- or early postnatal modification of later disease risks, but the underlying molecular mechanisms are largely unexplored. To close this gap, a highly cross-disciplinary approach involving scientists from basic and clinical research is required. Several European institutions study early origins of CLD with adequate national funding, but these efforts are not integrated and lack a comprehensive platform for synergistic collaboration. This COST Action created a coordinated and highly translational research program and brought forward a novel understanding of CLD pathogenesis while building the prerequisites for the successful development of early interventions and/or innovative therapies. The COST Action BM1201on Early Origins of Chronic Lung Disease involved partners from 21 European countries and two partners from the United States to pool their resources and expertise to investigate effects of early life exposures on chronic lung diseases in later life. The consortium included internationally acknowledged leaders in key areas of epidemiology, lung morphogenesis, lung physiology and biology, immunology, cell signaling, lung biology, stem cell biology, genetics, and clinical research from major research centres across Europe and the United States. Many partners have a proven track record in collaborative research and have participated in other large scale EU projects e.g. such as EU IMI, UBIOPRED on Severe Asthma, FP7 iFAAM Programming food allergy, FP7 RESOLVE, FP7 MeDaLL or ECRHS III, Medical Research Council and others. Ioana Agache was a member of the Management Committee, the coordinator of the Short Term Scientific Missions programme and member of the Working Group 1 Infant Lung Development. Activities of WG1 included

- Census of existing birth cohorts with both early life exposure data and respiratory outcomes. Expert assessment of existing cohorts with infant lung function data to establish the validity of pooling data between cohorts.
- Meta analysis of relationship between anthropometric measures at birth and adult lung function and lung function decline. While observations have been previously made in individual cohorts regarding the relationship between fetal growth and respiratory outcomes in adult life, combining analyses across cohorts will strengthen the evidence. Furthermore, this also allows the investigation of pre- and early post-natal risk factors for poor adult lung function
- Meta analysis of the effect of SNPs identified in genome-wide studies of adult lung function on their association with infant lung function measurements

B3. GA2LEN Working Package 2.2.3 on virus-induced exacerbations of respiratory allergy

The DARE Cohort ('Definition And Risk factors of acute Exacerbations of respiratory allergy: a longitudinal cohort') has been designed to assess the definition and risk factors of acute exacerbations of respiratory allergy. It will use diary cards, focusing on common colds and/or asthma exacerbations. Similar cards have been used in several studies before but most of them have not been formally validated. Ioana Agache participated in the pilot study including few selected centers that validated the diary cards to be used in the DARE cohort. Diary cards allow patients to report their

symptoms and the medication they took day after day. In the DARE study, diaries will be an essential tool to help describe what happens during an asthma exacerbation and compare with clinical definitions from both the patient and physician perspectives. The observations in the diary cards in combination with for instance peak flow rates, bronchial inflammation measures, will be the basis of an optimal definition of an asthma exacerbation. The DARE study will also evaluate the relative contribution of exacerbation risk factors and compare symptom variability between upper and lower airway disease - rhinitis and asthma – in the context of respiratory allergy. The Working Packed also delivered a highly cited systematic review (199) on the role of viruses and bacteria in acute asthma exacerbations where Ioana Agache is co-author.

B4. European Asthma Research and Innovation Partnership (EARIP)

The European Asthma Research and Innovation Partnership (EARIP), supported by European Commissions FP7 programme, aims to identify the investment required in different areas to bring about significant improvements in asthma outcomes in Europe. Ioana Agache was involved EARIP Work Package 4 Expert Workshop organised by the European Federation of Allergy and Airways Diseases Patients' Associations (EFA) in close collaboration with Asthma UK. The key objective of this workshop was to evaluate existing national, regional and European asthma programs and to develop recommendations and gaps for research in healthcare system change in asthma. The report was recently published (217) and provided the following recommendations: development of preventive interventions; adoption of minimum asthma standards across Europe; the establishment of mechanisms to measure public health performance; boost structural changes, focus more on personalised medicine and extend education of both healthcare professional and patients.

B5. INTEGRATED CARE PATHWAYS FOR AIRWAY DISEASES (AIRWAYS-ICPS) (22)

Working Package 10 of the European Innovation Partnership on Active and Healthy Ageing, Action Plan B3; Mechanisms of the Development of Allergy

The objective of Integrated Care Pathways for Airway Diseases (AIRWAYS-ICPs) is to launch a collaboration to develop multi-sectoral care pathways for chronic respiratory diseases in European countries and regions. AIRWAYS-ICPs has strategic relevance to the European Union Health Strategy and will add value to existing public health knowledge by:

1. proposing a common framework of care pathways for chronic respiratory diseases, which will facilitate comparability and trans-national initiatives;
2. informing cost-effective policy development, strengthening in particular those on smoking and environmental exposure;
3. aiding risk stratification in chronic disease patients, using a common strategy;
4. having a significant impact on the health of citizens in the short term (reduction of morbidity, improvement of education in children and of work in adults) and in the long-term (healthy ageing);
5. proposing a common simulation tool to assist physicians; and
6. ultimately reducing the healthcare burden (emergency visits, avoidable hospitalisations, disability and costs) while improving quality of life.

In the longer term, the incidence of disease may be reduced by innovative prevention strategies. AIRWAYS ICPs was initiated by Area 5 of the Action Plan B3 of the European Innovation Partnership on Active and Healthy Ageing (AHA). All stakeholders are involved (health and social care, patients, and policy makers). Eight proposals for synergies have been approved by the Task Force: Five cross-cutting synergies which can be used for all current and future synergies as they consider overarching domains (appropriate polypharmacy, citizen empowerment, teaching and coaching on AHA, deployment of synergies to EU regions, Responsible Research and Innovation), and three cross-cutting synergies focussing on current Action Group activities (falls, frailty, integrated care and chronic respiratory diseases). Ioana Agache is a member of the AIRWAYS ICPs consortium and co-author of two papers in highly ranked journals (22, 218).

2.3. PROFESSIONAL DEVELOPMENT AND NATIONAL AND INTERNATIONAL RECOGNITION

A. MEMBERSHIP IN STEERING COMMITTEES AND EDITORIAL BOARDS FOR THE DEVELOPMENT OF INTERNATIONAL GUIDELINES, CONSENSUSES AND STATEMENTS

1. **ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines** (19,20) - Member of the Scientific Advisory Board

   The ARIA guidelines process started in 1999 and was intended to be a state-of-the-art for the specialist as well as for the general practitioner and other healthcare professionals. Ioana Agache is co-author of the 2008, 2010 and 2016 revisions and first author of the ARIA 2008 adaptation for Romania (125). Unifying both the need to asses asthma and allergic rhinitis endotypes and severity/control assessment Ioana Agache co-authored the MeDALL–GA2LEN–ARIA consortium position paper (15) introducing the concept of severe chronic allergic (and related) diseases (SCUAD).

2. **MASK (MACVIA-ARIA Sentinel NetworK for allergic rhinitis)** (21)

   Several unmet needs have been identified in AR: identification of the time of onset of the pollen season, optimal control of rhinitis and comorbidities, patient stratification, multidisciplinary team for integrated care pathways, innovation in clinical trials and, above all, patient empowerment. A new consortium MASK (MACVIA-ARIA Sentinel NetworK for allergic rhinitis) study group was created (with Ioana Agache as a member of the Expert Panel) to tackle these unmet needs. One of the first deliverables (21) of the consortium (MASK-rhinitis) is a simple system centred around the patient which was devised to fill many of these gaps using Information and Communications Technology (ICT) tools and a clinical decision support system (CDSS) based on the most widely used guideline in allergic rhinitis and its asthma comorbidity (ARIA). Three tools are used for the electronic monitoring of allergic diseases: a cell phone-based daily VAS assessment of disease control, CARAT (Control of Allergic Rhinitis and Asthma Test) and e-Allergy screening (premedical system of early diagnosis of allergy and asthma based on online tools). These tools are combined with CDSS and are available in many languages. An e-CRF and an e-learning tool complete MASK. MASK is flexible and other tools can be added. It appears to be an advanced, global and integrated ICT answer for many unmet needs in allergic diseases which will improve policies and standards. The CDSS is currently being tested in clinical trials (141).

3. **EAACI International Guidelines for Clinical Practice for Allergen Specific Immunotherapy (AIT)** – Member of the Steering Committee and Chair Task Force for AIT in asthma

   Considering the unmet needs in AIT the European Academy of Allergy and Clinical Immunology is in the process of developing guidelines for public health using the AGREE II methodology for the AIT use in all allergic diseases. Ioana Agache is a member of the Steering Committee of the Guidelines Group and is leading the Task Force on AIT in asthma. The scope of the AIT Asthma Guidelines is to provide recommendations for indications and contraindications for AIT in asthma based on effectiveness, safety and cost-economic analysis and to identify gaps in knowledge and/or implementation, unmet needs and future perspectives. The AIT asthma Task Force included a wide range of countries, professional background (allergy, pediatrics, internal medicine, pediatric pulmonology, immunology, primary care, pharmacists) and patient representatives. For a critical appraisal of the evidence published so far we performed both a systematic review (SR) and a narrative review. The protocol

for the SR was published at the beginning of 2016 (102) and the results of the SR are currently under evaluation.

4. **EAACI International Guidelines for Food Allergy and Anaphylaxis** – Member of the Steering Committee and Task Force Chair on Managing patients with food allergy in the community.

   The EAACI Food Allergy and Anaphylaxis Guidelines Group has undertaken this unprecedented project over 2 years. Within the group, six task forces have comprehensively reviewed food allergy and anaphylaxis in children, adolescents and adults. The activity has been grounded in evidence with the use of comprehensive systematic reviews and, where appropriate, meta-analyses of the literature. The work was carried out by a wide range of health care professionals and scientists along with the involvement of both patient groups and regulators. Ioana Agache was a member of the Task Forces on Epidemiology and Prevention and led the Task Force on Managing patients with food allergy in the community. Ioana Agache is first author and co-author of several papers on guidelines recommendations (197) and systematic reviews supporting the recommendations (193,196).

5. **Member of the expert panel of the iCAALL collaboration**. Four of the most influential allergy/immunology professional organizations have joined forces to launch the International Collaboration in Asthma, Allergy and Immunology (iCAALL). Participating in iCAALL are the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma & Immunology (ACAAI), the European Academy of Allergy and Clinical Immunology (EAACI) and the World Allergy Organization (WAO). iCAALL is designed to collect and disseminate consensus-driven information about allergies, asthma and immunological diseases. Communicating this knowledge can positively impact diagnosis and treatment, as well as cost containment and policy decisions. A major focus of this initiative is the production of a series of International Consensus (ICON) reports. These documents offer general recommendations based on global challenges in caring for patients with allergic and immunologic diseases.

   Ioana Agache was member of the ICON on Allergen Immunotherapy. Two consensus documents were published in JACI (97,98)

6. **Member of the expert panel of the PRACTALL collaboration.** The PRACTALL program is a common initiative of EAACI and the AAAAI. It focuses on practical aspects of allergy to deliver updated and evidence based recommendations for clinicians.

   Ioana Agache was member of the PRACTALL on Precision Medicine. The consensus document was recently published in JACI with the Ioana Agache as last author

7. **Chair of the EAACI-European Respiratory Society Task Force "Understanding of and Adherence to International Guidelines in the Management of Stable Asthma by Non-Specialists. Indications for Specialist Referral"**.

   This task force intends to:

   1. Systematically review the literature in order to identify:
      a. Previous studies and audits assessing the understanding of and adherence to the international asthma guidelines and whether any interventions were suggested in order to improve the quality of care;
      b. Studies assessing whether different thresholds of referral to the respiratory team improved the quality of care.
   2. Develop, validate and distribute a short online questionnaire to assess the understanding of and adherence to international guidelines among the different specialties across Europe.

   Multiple-choice questions will be used to assess the approach to simple and frequent clinical scenarios in patients with asthma. The approach to the diagnosis, assessment

and management of stable asthma, as well as the management of acute asthma exacerbations will be assessed.

All data will be combined and analysed and if significant diversity is highlighted, it will be decided whether these differences could be narrowed by further training or whether an earlier input by respiratory physicians may be considered.

Outcomes of the Task Force will be published as an official ERS/EAACI Statement.

8. Chair of EAACI Task Force on "**Lifestyle Interventions in Allergy and Asthma**"

   The focus of this Task Force was a systematic review of the effects of nutrition, physical activity and obesity on asthma and allergies related outcomes both in children and adults. One SR on weight gain and loss was published, one overview on diet was published as well, together with the protocol for the second SR on diet, which is ongoing.

9. Secretary of the EAACI Task Force on "**Allergy Management in Primary Care**"

   This Task Force outlined and proposed the optimal work up and diagnostics to be performed in patients visiting primary care, including standardization of tests, suggested health economy considerations of available tests and provided an up-to-date guideline on what to do in primary care, interpretation of the tests and when to refer allergy patients to secondary care. The final aim was to ensure that allergy patients are investigated at the lowest appropriate economic level at the minimum appropriate cost for society. Three papers were published in Allergy with Ioana Agache as first or last author.

10. Secretary of the EAACI Task Force on "**In vivo allergy diagnosis**"

    The allergen challenge test has been the mainstay of diagnosis of allergic diseases for a long time since it offers a direct proof of the clinical relevance of a particular allergen for the allergic disease symptoms and severity. Standardisation and availability for daily practice (including safety issues) are still to be refined but most of the challenge tests have safely crossed the border from research tools to diagnostic tests available for daily practice for a well trained clinical staff. The use of recombinant allergens and modern techniques to objectively quantify and compare the biological modifications induced by allergen challenge are highly promising. Proper use of clinical judgement in recommending a challenge test, selection of the appropriate allergen for testing and interpretation of results, as derived of a thorough training as an allergist, are essential to ensure the deserved value of allergen challenge test. The EAACI TF on "In vivo allergy diagnosis" provided a critical appraisal of allergen challenge methods, together with recommendations on indications, procedure and safety. The paper was published in Allergy by Ioana Agache as first author.

11. Secretary of the EAACI Task Force for "**Allergy Nomenclature**"

    The aims of this TF are to develop an updated of allergy, to include the missing new diseases, such as eosinophilic osephagitis and new concepts such as endotypes, immune tolerance, to cover hypersensitivity reactions under the umbrella of our specialty, to have international dissemination and acceptance and aligned veterinary terminology. Besides the revised terminology an Encyclopedia of Allergy will be published

12. Member of the EAACI Task Force on "**Guidelines on Pediatric Clinical Trials**". The Belmont Report justified research involving children, as it would help find better ways of treating childhood illnesses and promote their healthy development. (6). The Report categorized children as a vulnerable population with diminished autonomy and hence entitled for additional protection from undue influence and coercion. The protective approaches such as requirement of careful scrutiny of pediatric research protocol for the level of risk, entrusting the responsibility of permitting the child to enroll with parents and demanding steps for minimi-

zation of risk are some of the protective approaches described in that report.

Considering the importance of drug trials in children, the US and European countries enacted several legal provisions to encourage, entice or compel pharmaceutical companies to undertake pediatric trials. The European Regulation of Pediatric Medicines has three major initiatives for ensuring that children will receive drugs that are safe and efficacious: the adoption of incentives for industry, the implementation of a mandatory Pediatric Investigation Plan considering all age ranges and the creation of a Pediatric Committee.

Responding to the needs to address asthma and allergy in children EAACI started this Task Force aiming to offer regulary agencies the scientific recommendations ensuring both the efectiveness of the trials and the safety of the subjects included.

13. Member of the EAACI Task Force on "**Diagnosis and Management of NSAIDs-Exacerbated Respiratory Disease**". This TF aims to collect and analyse available data on the clinical features and heterogeneity of asthma/CRS phenotype associated with hypersensitivity to NSAIDs, to summarize novel information on the pathomechanism of NSAIDs-induced hypersensitivity reactions as well as on the pathophysiology of the underlying eosinophilic tissue inflammation (endotype, biomarkers), to assess performance and propose recommendations for diagnostic methods to confirm NSAID hypersensitivity (oral , bronchial challenges and in vitro tests) , to review the effectiveness of currently available, phenotype-specific treatment modalities and to agree on algorithm(s) for diagnosis and management and unmet needs
14. Member of the EAACI Task Force on "**The role of nutritional factors in immunomodulation"**. Optimal functioning of the immune system is crucial to human health, and nutrition is one of the major exogenous factors modulating different aspects of immune function. Currently, no single marker is available to predict the effect of a dietary intervention on different aspects of immune function. Nutrition may modulate the immune system of both health and compromised people. A number of factors may play a role, including, milk, breastfeeding, enteral feeding, prebiotics, and probiotics. The goal of this task force is to collectively develop and publish updated, authoritative and evidence based position papers in this important field.
15. Member of the EAACI Task Force on "**Standardization of nasal allergen challenges**. The last standardization is more than a decade ago, with the last position paper published in 2004. The aim of this Task Force is to evaluate and critically discuss all subsequent technical improvements and scientific findings that were made during the last 12 years.
16. Member of the EAACI Task Force on "**The Harm Of Long-term Use Of Systemic Steroids In Rhinitis And Rhinosinusitis**". This TF will gather evidence to demonstrate that use of systemic corticosteroids or depot-steroid injections is harmful both short term and long term and provide support for the recommendation that the use of systemic corticosteroids should be abandoned as standard long term treatment for rhinitis and rhinosinusitis.

B. EDITORIAL ACTIVITY

- Associate Editor of Clinical and Translational Allergy since 2014
- Editorial board Polish Journal of Allergology
- Editorial board of the Romanian Society of Allergy Journal
- Coordinating Editor for EAACI Global Atlas of Asthma (2013) (23), Global Atlas of Allergy (2014) (24 (2015) (25)
- Editorial board of Food Allergy and Anaphylaxis Guidelines (2014) (213)
- Coordinating Editor for Implementing Precision Medicine In Best Practices Of Chronic Airway Disease due to be published by Elsevier in November 2017

C. BOOKS, MONOGRAPHS

- **Ioana Agache**. Phenotypes and endotypes of allergic rhinitis. Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis 2015, published by EAACI, pg. 268-270
- **Ioana Agache**, Cezmi Akdis. Endotypes of allergic diseases. Global Atlas of Allergy 2014, published by EAACI, pg. 104-107
- Muraro A, **Agache I**, Clark A, Sheikh A, Roberts G, Akdis CA, et al; European Academy of Allergy and Clinical Immunology (EAACI) food allergy and anaphylaxis guidelines: managing patients with food allergy in the community, published by EAACI, pg.239-259 (219)
- **Ioana Agache**. Best buys for asthma prevention and control. Global Atlas of Asthma 2013, published by EAACI, pg. 132-134
- **Ioana Agache**. Astmul-de la noi mecanisme patogenice până la noi metode de terapie, 2008, Editura Lux Libris, Braşov,
- Mariana Rădoi, **Ioana Agache**, Diana Ţînţ, Patologia Trombotică. Date actuale, 2007, Editura Lux Libris, Braşov, 209 pag
- Mariana Rădoi, **Ioana Agache**, Reacţia inflamatorie în ateroscleroză – date actuale, în "Progrese in cardiologie" sub redactia L. Gherasim, 2002, Editura Infomedica, pg. 337-399
- Mariana Rădoi, **Ioana Agache,** Astmul în "Pneumologie Clinică" sub redacţia M. Rădoi, Vol I, 1999, Ed. Concordia, pg. 75-138
- **Ioana Agache**, Mariana Rădoi Boli pulmonare interstiţiale în "Pneumologie Clinică" sub redacţia M. Rădoi, Vol I, 1999, Editura Concordia, pg. 139-200
- Mariana Rădoi, **Ioana Agache**, T. Alexandru, Pneumologie Vol I, 1999, Reprografia Universităţii "Transilvania" Braşov, 200 pag
- Emanoil Gheorghiţă, **Ioana Brumaru**, Imunologie. Vol I, 1998, Reprografia Universităţii "Transilvania" Braşov, 105 pag

D. REVIEWER ACTIVITY

- Reviewer board of Journal of Allergy and Clinical Immunology (impact factor 12.485) since 2010
- Reviewer board of Journal of Allergy and Clinical Immunology in Practice (impact factor 6.335) since 2014
- Reviewer board of Allergy (impact factor 5.429) since 2009
- Reviewer for the European Commission, DG Research & Innovation, E4 Non-communicable Diseases and the Challenge of Healthy Ageing
- Reviewer for Asthma UK
- Reviewer for National Science Center, Poland
- Reviewer for Respiratory Research (impact factor 3.751), PlosOne (impact factor 3.234), International Archives of Allergy and Clinical Immunology (impact factor 2.677), Respiratory Medicine (impact factor 3.036)

E. LECTURER AT INTERNATIONAL MEETINGS IN ASTHMA AND COMORBIDITIES (SELECTED LIST)

- Microbiome and Asthma: An Obvious but Often Overlooked Parameter – March 2017, AAAAI Annual Meeting
- Precision medicine in asthma – November 2016, European Rhinology Forum
- Precision medicine in allergy and asthma - October 2016, Joint Congress of APAAACI & APAPARI 2016
- Appraising the Evidence: Is Precision Medicine Ready for the Clinic? – October 2016, 9th Hong Kong Allergy Convention
- The Complexity of Type 2 Asthma Endotype - October 2016, 9th Hong Kong Allergy Convention
- Serum IL-5 and IL-13 consistently serve as the best predictors for the blood eosinophilia phenotype in adult asthmatics – September 2016, European Respiratory Society Annual Meeting
- Food allergy and asthma – September 2016, XLIII Congresso Brasileiro de Alergia e Imunologia

- Use of biomarkers in personalized medicine – June 2016, EAACI Annual Congress
- Can we afford a system change to prevent disease progression? – January 2016, Allergy Think Tank
- Type 2 asthma endotype – October 2015, World Allergy Congress
- The asthma epidemic: How did we come to worldwide 300 Million patients? – October 2015, Global Risk Forum
- Asthma phenotypes and endotypes – implications for AIT – October 2015, Polish Allergy Society Annual meeting
- New tools in asthma: biomarkers – June 2014, EAACI Annual Meeting
- Lessons from the lower airways – June 2014, European Rhinology Society Annual Meeting
- Induced sputum cytokines and chemokines and mechanistic pathways in adult asthma phenotypes – September 2014, European Respiratory Society Annual Meeting
- Mechanism-guided treatment for asthma – June 2013, EAACI Annual Meeting and World Allergy Congress
- Molecular markers of asthma phenotypes and endotypes – December 2011, World Allergy Congress
- Immune pathogenesis of asthma exacerbations – June 2011, EAACI Annual Meeting
- Is anti-microbial therapy an option to treat asthma/allergy? – November 2008, World Congress of Asthma
- Asthma management in Eastern Europe – November 2008, World Congress of Asthma

F. INTERNATIONAL RECOGNITION

I am currently involved in several leadership boards and committees of international professional organisations

- 2017-2019 – President of the European Academy of Allergy and Clinical Immunology (EAACI)
- 2017-2019 - WAO (World Allergy Organisation) Nominating Committee
- 2013-2017 - Vice-President Communication & Membership of EAACI
- 2009-2013 - EAACI Executive Committee Member at Large
- Since 2008 - WHO project ARIA (Allergic Rhinitis and Impact on Asthma) Advisory Committee Member
- 2005-2009 - Secretary of the EAACI Asthma Section
- 2005-2009 - EAACI Scientific Program Committee
- 2009-2011 - WAO Asthma Special Committee
- 2008-2009 - WAO Communication Council
- 2009-2011 - WAO Congress Council
- 2008-2009 - WAO Allergy Diagnosis Special Committee
- 2000-2005 - EAACI Junior Members and Affiliates Working Group

2.4. LEADERSHIP AND MANAGERIAL SKILLS

Between 2004-2007 I was Head of the Allergy and Clinical Immunology Department, Brasov County Hospital and since 2006 I am the Medical Manager and Head of Allergy and Clinical Immunology Department, National Centre of Allergy and Asthma Theramed HealthCare Brasov

Since 2003 I am leading the Immunology Discipline at Transylvania University Brasov, Faculty of Medicine and since 2010 I am also leading the Physiology Discipline

On the international side since 2013 I am leading the Communication and Membership Department of the European Academy of Allergy and Clinical Immunology, a professional organization with 10.000 members worldwide

I am also leading the PN-II-RU-TE-2014-4-2303 project, Endotypes of Non-Eosinophilic Asthma (ENDANA)

B-i

Scientific and professional achievements

Academic development

Chapter 3

My academic development combined teaching activities with creative research as an extension of the self-development process.

Teachers are integral portions of a student's ability to succeed in life.

Teaching involves an opened-minded plan for helping students and young doctors to meet and exceed educational goals. Teaching styles may differ from teacher to teacher, class to class and school to school. Yet every teaching objective must include a structured but flexible process for student advancement. My academic career started in 1996 as a Junior Assistant Professor at Transylvania University from Brasov, where I am at present an Associate Professor. Through my academic career I focused on engaging students in the learning process and motivating them to practice higher-level critical thinking skills, while promoting meaningful learning experiences.

A. **1996-2000, Junior Assistant Professor,** Transylvania University from Brasov, Faculty of Medicine, Internal Medicine Department, Clinical Immunology Discipline

   As Junior Assistant Professor I delivered practical lessons in the field of clinical immunology to the medical students in the 4th year and lectures in internal medicine to the students in the 4th and the 5th year. To achieve these tasks I developed the curriculum for practical lessons in clinical immunology and respiratory diseases for medical students (also published as a reference guides, see below) and the curriculum for lectures in asthma, chronic obstructive lung diseases (COPD), interstitial lung diseases and anaphylaxis.

   I supervised together with the Head of the Discipline 5 dissertation thesis and wrote two practical reference guides for students use:

   1. Emanoil Gheorghiţă, **Ioana Brumaru,** Imunologie. Vol I, 1998, Reprografia Universităţii "Transilvania" Braşov, 105 pages
   2. Mariana Rădoi, **Ioana Agache**, T. Alexandru, Pneumologie Vol I, 1999, Reprografia Universităţii "Transilvania" Braşov, 200 pag

B. **2000-2006, Assistant Professor**, Transylvania University from Brasov, Faculty of Medicine, Internal Medicine Department, Clinical Immunology Discipline.

C. As Assistant Professor I continued the practical lessons in the field of clinical immunology to the medical students in the 4th year and to the students attending the 2nd year at the General Nursing specialization together with lectures in internal medicine to the students in the 4th and the 5th year. To accomplish these tasks I developed a new curriculum in allergy and clinical immunology adapted to the needs of General Nursing focusing on practical aspects such as recognition and treatment of emergencies (anaphylaxis, severe drug induced reactions, severe asthma attack, acute hemolysis, acute respiratory failure, etc) together with preventive measures (anaphylaxis and anaphylactoid reactions, drug hypersensitivity, immune induced tissue and blood incompatibility, latex and food allergy, etc)

   In 2003 I became Head of Clinical Immunology Discipline and started the lecture programme in clinical immunology for the medical students in the 4th grade. To achieve this assignment I implemented a **new teaching approach based on the interactive teaching styles** incorporating a multitude of goals beneath a single roof. Interactive classes were designed around a simple principle: without practical application, students often fail to comprehend the depths of the study material. Interactive training styles provided four basic forms of feedback:

   - Measurable student accomplishments: several students choose after graduation to specialise in Allergy and Clinical Immunology and one joined the discipline as Junior Assistant Professor. In addition the grades at the final examination improved considerably
   - Flexibility in teaching: applying training methods that involve two-way communications enabled quick adjustments in how the information was delivered and the lectures were modified each year according to the input received from students

- Practice makes perfect: interactive instruction enhanced the learning process with students acquiring practical skills valuable for their further career development.
- Student motivation: two-way teaching and constructive feedback dispelled student passivity and engaged them in lectures and practical lessons design, research projects and in volunteering activities at the hospital (night rounds in the emergency department or in the general department, home visits to check on critically ill patients, etc)

Variability in teaching methods and materials, learning aids and multiple level questions were also used.

I continued to supervise dissertation thesis while implementing a new approach for **creative scientific research** to improve students' perception of academic success. The students were stimulated to approach a task-oriented behavior, exactness and consistency in the scientific quest while respecting the ethic principles of research. Proactivity, personal responsibility, vision, and discipline were enforced as basic principles of creative scientific research. A high quality research environment was ensured in order to develop research strengths of the student with the dissertation as a key opener for future career development.

2006-2007, Lecturer, Transylvania University from Brasov, Faculty of Medicine, Internal Medicine Department, Clinical Immunology Discipline.

Between 2006 and 2007 I continued to lecture in clinical immunology to the 4th year medical students and to 2nd year students in General Nursing. In parallel I coordinated the activity of residents in Allergy and Clinical Immunology from different years of their residency.

2007-present, Associate Professor, Transylvania University from Brasov, Faculty of Medicine, Internal Medicine Department and since 2008 Fundamental Science Department, Immunology Discipline and since 2010 both Physiology and Immunology Disciplines.

In 2008 the profile of the Discipline that I lead changed from Clinical Immunology to Immunology and I started a new curriculum for the 3rd year medical students with extended focus on basic immunology.

In 2010 I was assigned the Physiology Discipline for medical students in the 2nd year. I developed a new curriculum while keeping the new teaching approach based on the interactive teaching styles. The new curriculum implemented novel concepts such as physiologic systems temporal behaviors and structural patterns in health and disease together with the application of biomedical research with concepts and computational tools derived from the contemporary study of complex systems such as the respiratory or the cardiovascular system. In parallel the new curricula incorporated cross-sectional information from related disciplines such as functional genomics and gene-environment interactions, cell signaling and the role of cytoskeleton, lung and heart stressors, etc. A thorough practical lesson curricula teaching methods for exploring lung, heart, circulation, endocrine and nervous system was developed

In 2014 I was appointed the Physiology Discipline for 1st year students from Physical-Kinetic-Therapy specialisation. I developed a new curriculum addressing the special needs of their specialisation such as biomechanics, respiration in exercise, or cardiopulmonary exercise testing

Addressing the needs of early career researches and young doctors was also part of my Academic development.

In 2008 I was a lecturer in the master programme for Emergency Medicine with lectures on asthma and anaphylaxis management and since 2014 I am a lecturer in research methodology and science for the master programme of Palliative Care Strategies and for the master programme Management of preventive strategies and health policies.

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THE EVOLUTION AND DEVELOPMENT PLANS FOR CAREER DEVELOPMENT

My career achievements in the last decade offer me a position at the forefront in translating bench-to-bedside innovations while offering the best education and research training.

The modern research and learning environment, much more complex and challenging than before, new models of care, a sufficient pipeline for our clinical and academic workforce, international recognition through strong partnerships are "key-shapers" of the changing landscape to which my future career needs to adapt. The challenge is to develop relevant and practical deliverables and to grow steadily in a sustainable way

My career focus is personalized medicine in asthma from endotypes and biomarkers to new patient centered models of care. "Team care" is the center of my practice. Medicine requires passionate, supportive, collaborative providers. In my clinic and at the university we embrace an interdisciplinary model that capitalizes on patients and students' engagement while delivering high-level education. I'm proud to have trained graduate students, and undergraduates, many of whom have attained academic positions or reached the level of independent investigator.

Based on the SWOT analysis of my career development the following aspects should be considered to pursue further achievements my scientific, professional and academic development

***Strenghts**: professional, scientific and didactic abilities developed in the last 12 years of my career; strong partnerships and the national and international level; interdisciplinary joint effort to develop curricular activities*

***Weaknesses**: small research team that can be developed by incorporating PhD students as their coordinator*

***Opportunities**: improved collaboration with professional and allergy networks from the perspective of the EAACI 2017-2019 Presidency*

***Threats**: incoherency in legislation and declining human and economic resources*

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The evolution and development plans for career development

Scientific development future plans

Chapter 1

A. ASTHMA ENDOTYPES

Building on the results from the PN-II-RU-TE-2014-4-2303 project, Endotypes of Non-Eosinophilic Asthma (ENDANA) project my future research plans for non-eosinophilic asthma focus on validation of the subendotypes both through therapeutic targeted intervention and by longitudinal evaluation of the stability of the clusters described. The same approach will be undertaken for type 2 asthma subendotypes using and unbiased approach such as topological data analysis, Bayesian network analysis and longitudinal evaluation. Expansion of endotype research into the pediatric asthma population is also anticipated.

Expected benefit is translation of endotype research into bedside, clinically meaningful decision protocols for selecting a targeted intervention into a given asthma patient and for a better prognosis of disease evolution.

B. BIOMARKERS AND ENDOTYPES FOR ALLERGEN IMMUNOTHERAPY

A new project that is about to start in cooperation with the Swiss Institute for Allergy and Asthma Research (SIAF) will evaluate the biomarkers for the efficacy of allergen immunotherapy in adult and pediatric patients with allergic rhinitis and asthma.

Objectives

1. to validate the biomarkers across clinical efficacy end-points such as decrease in the symptom and medication score, decrease in asthma exacerbations, improved lung function, decreased steroid load for rhinitis and asthma control, decrease in the nasal provocation test score, improved quality of life, improved disease control
2. to link biomarkers to the endotypes of responders to AIT

The study will evaluate the AIT biomarkers in two data sets:

1. A retrospective analysis will correlate the responder status with biomarkers measured from blood and nasal samples from adults and children after 2-3 years of AIT
2. A prospective analysis will use serial blood and nasal samples from adults and children at the beginning, after one month of AIT, after reaching the stable maintenance dose of AIT and at the end of AIT. The second set will allow the identification of early predictors of response to AIT.

Expected benefits are the identification of responders to AIT based on their endotype and reshaping the allergy vaccine adapted to target the responder pathways.

C. INTERNATIONAL GUIDELINES AND CONSENSUS DOCUMENTS DEVELOPMENT AND IMPLEMENTATION

Several items are in preparation following the ARIA guidelines in 2016 and the AIT guidelines in 2017. Food Allergy and Anaphylaxis guidelines launched in 2014 are in the process of dissemination and implementation within the primary care network across Europe. EAACI will engage starting with 2017 in the Atopic Dermatitis International Guidelines and consensus documents in collaboration with AAAAI and ERS are envisaged for biologics and exposome in asthma.

D. MOBILE HEALTH/ALLERGY 2.0 AND 3.0

Rapid advances in health information technology (HIT) have created unprecedented opportunities to collect, analyze and learn from vast amounts of “real-world” data that currently are locked away in unconnected servers and file cabinets. While clinical trials will likely remain the gold standard of evidence, crowdsourcing backed up by HIT advances promises to overcome the current limitations of observational data. By analyzing an immense body of observational data in real time physicians and researchers can identify trends and associations between myriad variables and generate new hypotheses and draw immediate practice-changing conclusion.

The project will develop an IT-based system for asthma clinics that securely compile and analyze information from the individual electronic health records (major clinical endpoints, comorbidities, symptom scores, objective measurements, treatments, side effects, molecular profiles, quality of life, etc). The data collected will not be biased by any

pre-selection criteria. Advanced HIT tools, such as rapid learning systems, will structure the huge body of unbiased data by normalising similar information even if provided in different formats, correcting for the wide variation in data standards. Then data will be run through correlation and trend analysis tools, revealing connections that can be used to draw statistically valid conclusions and develop robust hypotheses

In addition the system will provide real-time, robust and truly informative clinical decision support at the point of care. Decision support at the point of care is a must in the advent of precision medicine in the clinic. As a result of this real-time guidance, most asthma care will harmonised and based on guidelines, practice parameters and quality criteria. Other providers will play a larger role in routine asthma care. For less complex cases and in follow-up care primary care physicians, community pharmacists and allied health workers will be equipped to provide care based on the IT-system feedback and consultation with specialists. The increased involvement of non-specialists will counteract the asthma specialists' shortage that is projected as the population ages and allergy and asthma incidence increases. Specialists freed up from activities that do not capitalize on their unique expertise will be able to guide or oversee care for larger numbers of patients and can focus on developing better prevention and treatment plans and highly qualified managing care teams.

Through personalized, patient-friendly HIT tools, patients will have a much greater opportunity to serve as well-informed advocates for their own care and to stay connected with the healthcare provider in real time. A significant shift in the doctor-patient relationship is expected with the patient better informed on allergy and asthma when he arrives at the consultation and the doctor provided with personalized information from patient portals. The patients are expected to contribute to all important decisions about their care with increased confidence that treatment plans will work since they truly reflect their patients' wishes. They will take an active role in their care by reporting their health status, side effects and other experiences as they happen and thus the majority of patients will participate in clinical research with greater understanding and appreciation of clinical research as a part of routine allergy care, in part because enrollment procedures will become simpler and more patient- and provider-friendly.

Global HIT systems will allow physicians and patients anywhere in the world to benefit from the latest, best available knowledge, helping to reduce today's noticeable global disparities in allergy and asthma care. Low-resource countries will contribute to, and benefit from, global cooperation networks. The benefits of clinical decision support will be greatest in countries or regions where allergists are in short supply. At the same time, collecting the experiences of patients in these countries will lead to the development of meaningful international clinical guidelines for allergy and asthma care. Allergy research go global, as HIT systems link researchers, patients, biobanks, registries and research procedures, even in the most remote locations, so endotyping—a central element of precision medicine— becomes affordable and universal.

E. DEVELOPMENT OF PROTOCOLS FOR EDUCATIONAL INTERVENTION IN THE COMMUNITY FOR ASTHMA MANAGEMENT

The community pharmacy is a new milieu for asthma care. The project will develop a care protocol with the important ingredients of asthma education on medications, triggers, self-monitoring and an asthma plan, with pharmacists taking responsibility for outcomes, assessment of a patient's readiness to change and tailoring education to that readiness, compliance monitoring and physician consultation to achieve asthma prescribing guidelines.

Expected benefits while using the pharmaceutical care-based protocol are significant improvements in clinical, economic and humanistic outcome measures in asthma patients as an incentive for the health care system to support such care.

B-ii

The evolution and development plans for career development

Professional development future plans

Chapter 2

We have a moral duty to promote high standards of both medical undergraduate and postgraduate medical education. I will continue to offer medical students and healthcare professionals (HCPs) purposeful training to reflect changes in practice, changes in the needs of patients and the service, and changes in society's expectations of the way HCPs work.

Both as clinician, researcher and teacher I will continue to develop a wide-ranging competencies encompassing clinical update, research and scientific writing, multidisciplinary context of patient care, ethical practice, communication, management and behavioral skills, team building, information technology, audit, and appropriate attitudinal change to ensure improved outcomes and satisfaction for my patients, my students and my colleagues

In 2017 I will take over the Presidency of the European Academy of Allergy and Clinical Immunology (EAACI), with a 2-year mandate. EAACI, is an association including over 50 National Allergy Societies, more than 9,500 academicians, research investigators and clinicians, from 121 different countries, aimed at:

- Promoting basic and clinical research
- Collecting, assessing and disseminating scientific information
- Functioning as a scientific reference body for other scientific, health and political organisations
- Encouraging and providing training and continuous education
- Promoting good patient care in this important area of medicine

My vision for my Presidency is for EAACI to inspire the way towards sustainable health policies for allergy and asthma ensuring higher quality care at affordable costs. The Academy should continue its journey as international leader in allergy, asthma and clinical immunology. Clinicians, researchers, and educators choose EAACI as their professional home. We must continue to train, mentor and enroll the next generation of leaders by demonstrating the value of membership. And we need to understand who we are and what our members need.

Besides the international recognition I aim to facilitate the cooperation between international and national societies as a scaffold for local adaptation and implementation of guidelines and cutting-edge research, best practices and efficient health policies and advocacy for promoting asthma as a major health problem.

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The evolution and development plans for career development

Academic activity future plans

Chapter 3

I plan to develop in the next 4 years a new educational portfolio for students and young HCPs that facilitate both professional and career development with a clinical and a research track. The concept of purposeful education including key-concepts such as work-experience and social service will be introduced. New tools facilitating interactive learning are envisaged, such as tutorials for the faculty master programmes and for the doctoral school, multidisciplinary learner programmes, interactive brainstorming, buzz-sessions, Think-Pair share, incident process, etc. Being certified for my English literacy for teaching purposes I will actively support the creation of a new Department with English teaching for foreign students.

In addition I will support the inception of interdisciplinary teams in our university in cooperation with the coordinators of licence and master programmes in ensure that the majority of our students engage in research during or after medical school. A wide choice of subjects for research should be encouraged. Students may choose basic laboratory projects or may investigate clinical, epidemiologic or sociologic (including medicine and humanities) topics.

Building the community feeling for students and teachers with increased engagement in shaping the academic landscape and the organizational culture is also a priority. A close working relationship between the student and faculty research mentor is a major goal and is strongly encouraged. When laboratory research is performed, it is the responsibility of the faculty advisor to provide all necessary space, equipment and supplies. If the project is concerned with clinical or epidemiological investigation, the same commitment to guidance and support is expected. Weekly conferences between student and advisor are encouraged during the course of the research. The research must be designed and specifically performed by the student with the advice of the faculty mentor.

Both PhD coordination and achieving full professorship are envisaged in order to progress with my academic activity in the next 2 years. Through my involvement in coordination of doctoral thesis I will continue to support the young doctors to perform their own researches and to communicate the results of their research in the national and international scientific environment. Early career researches should be strongly supported in preparation of their doctoral thesis through cooperative projects developed with colleagues from related disciplines.

B-iii

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