Personalized Medicine in Asthma & Allergy

Canonica G.W.
Personalized Medicine Clinic
Asthma & Allergy

Milano Italy
GWC reports having received research grants as well as lecture or advisory board fees from:

- A. Menarini
- Alk-Abello’
- Allergy Therapeutics
- Anallergo
- AstraZeneca
- Boehringer Ingelheim
- Chiesi Farmaceutici
- Circassia
- Danone
- Faes
- Genentech
- Guidotti-Malesci
- Glaxo Smith Kline
- Hal Allergy
- Lofarma
- Meda
- Merck
- Merck Sharp & Dome
- Mundipharma
- Novartis
- Phadia
- Recordati-InnuvaPharma
- Roche
- Sanofi-Aventis
- Schering Plough
- Stallergenes
- UCB Pharma
- Uriach Pharma
- Teva
- Thermo Fisher
- Valeas
Personalized Medicine in Allergy

Matteo Ferrando, Diego Bagnasco, Gilda Varricchi, Stefano Bernardi, Alice Bragantini, Giovanni Passalacqua, Giorgio Walter Canonica

1Allergy & Respiratory Diseases, DIMI Department of Internal Medicine, IRCCS AOU San Martino-IST, University of Genoa, Genoa, Italy
2Division of Clinical Immunology and Allergy, Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy
Fig. 1. Evolution of treatment in asthma, from a therapy applicable to any patients to a precision medicine.
Clinical phenotypes in relation to sputum eosinophils

- **Discordant Symptoms**
  - **Early Symptom Predominant:** Early onset, atopic. Normal BMI. High symptom expression.
  - **Obese Non-Eosinophilic:** Later onset, female preponderance. High symptom expression.
  - **Benign Asthma:** Mixed middle-aged cohort. Well-controlled symptoms and inflammation. Benign prognosis.

- **Concordant Disease**
  - **Early Onset Atopic Asthma:** Concordant symptoms, inflammation & airway dysfunction.
  - **Inflammation Predominant:** Late onset, greater proportion of males. Few daily symptoms but active eosinophilic inflammation.

- **Monitoring Inflammation**
  - Allows down-titration of corticosteroids.
  - Allows targeted corticosteroids to lower exacerbation frequency.

- **Primary Care Asthma**
  - Symptom-based approach to therapy titration may be sufficient.

- **Secondary Care Asthma**

---

Haldar et al AJRCCM 2008; 178: 218-224
A Step toward Personalized Asthma Treatment

Jeffrey M. Drazen, M.D.

Drazen J.M. NEJM 2011
Asthma phenotypes

» Type 2

- TH2
- Allergic asthma
- EIA

» Non-type 2

- Non-TH2
- Very late-onset, (women)
- Obesity-associated
- Smoking-associated, neutrophilic
- Smooth-muscle mediated, paucigranulocytic

AERD = aspirin exacerbated respiratory disease; EIA = exercise-induced asthma

Transition from Phenotype to Endotype

Clinico-functional Phenotypes

Clinical physiologic biologic hereditary characteristics

Molecular phenotypes

Add pathobiologic processes at molecular level to clinical phenotype

Endotypes

Identifiable molecular pathway contributes to/causing clinical characteristics associated with molecular phenotypes
Asthma phenotypes: the evolution from clinical to molecular approaches

Sally E. Wenzel

Future of phenotyping: ‘Systems Medicine’

Patient reported
Clinical
Functional
Cellular
Molecular

Phenotyping

Genes → Gene expression → Airway histology → Lung Function → The patient

Severe asthma phenotyping
- Genetics: Epigenetics, Transcriptome, Proteome, Metabolome
- Microbiome: Immunity, Inflammation
- Remodeling: Bronchial hyperresponsiveness, Obstruction
- Symptoms: Comorbidity, Quality of life

FIGURE 1 Integration of factors, beginning with genetics, which may contribute to the ultimate phenotype of the severe asthma patient.

Chung et al ERJ 2014
Staton et al.
Biomarkers in Medicine
2015

Biomarkers in the clinical development of asthma therapies

Tracy L Staton¹, David F Choy² & Joseph R Arron*,³
Molecular phenotyping and biomarker development: are we on our way towards targeted therapy for severe asthma?

Expert Rev. Respir. Med. 00(00), 1-10 (2015)

Laura De Ferrari*, Alessandra Chiappori†, Diego Bagnasco, Anna Maria Riccio, Giovanni Passalacqua and Giorgio Walter Canonica*
Figure 1: Biomarkers discovery and phenotyping in severe asthma: actuality and perspectives
Fig. 2. Progression of personalized medicine and the necessity to expand the research to find molecular biomarkers able to predict patient’s response to therapy.
Systems Biology of Asthma and Allergic Diseases: A Multiscale Approach

Supinda Bunyavanich, MD, MPH\textsuperscript{1,2,*} and Eric E. Schadt, PhD\textsuperscript{1}

\textsuperscript{1}Department of Genetics and Genomic Sciences and Icahn Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

\textsuperscript{2}Division of Pediatric Allergy and Immunology, Department of Pediatrics, and Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Figure 1. Relationship between system-wide profiles in asthma and allergy

Bunyavanich & Schadt JACI 2015
From Bench to Bedside
Predictive Models

- **Computer modeling/simulation** – creation of software tools for constructing and simulating complex, multiscale biological processes

- **Genomics** – collection and analysis of data on gene expression, miRNA, epigenetic modifications, discovery of gene regulatory networks; in connection with CMB, experiments to connect signaling to gene expression prior to and in follow-up to modeling such connections

- **Cell/molecular biology** – HTS to discover new nodes and edges (molecules and interactions) in modular networks; testing of predictions from models using KD and related technologies

- **Bioinformatics** – development and application of statistical tools for extracting new data from literature, analyzing HTS data, microarray and next-gen sequencing data, construction of statistical inference network models

- **Proteomics** – protein modifications, number of molecules, Ka/Kd/Kcat … for parameterizing models

- **Immunology** – wet lab experiments at the cell and organism level to explore immune behavior and feed data into as well as test emerging models of immune function and host/pathogen interactions
Science observes phenomena and objects on multiple layers in a biological system:

- Chromosome
- Chr. scaffold
- Chromatin fiber
- Nucleosomes
- Genes
- RNA
- Primary amino acid chain
- Protein folding
- Post-translational modifications
- Transport, storage
- Protein function
- Degradation

Modeling in basic research

Epigenomics
Genomics
Transcriptomics
Proteomics
Metabolomics

Biological data
Clinical observations on population samples and patient cohorts on multiple layers:

- Risk factors, markers, *e.g.*
  - Chemical / molecular
  - Alimentary
  - Family history, social
  - Behavioral, physical activity
- Biomarkers of disease, *e.g.*
  - Phenotypic
  - Molecular
- Pharmacokinetics, ADME
- Pharmacodynamics, MOA
- Biomarkers of response

**Biological attributes of:**

- Epidemiology
- Etiology
- Diagnosis
- Treatment
- Response

**Clinical data**

**Biological data**
Information Commons
Organized Around Individual Patients

- Exposome
- Signs and Symptoms
- Genome
- Epigenome
- Microbiome
- Other Types of Patient Data
- Individual Patients
Preparing for Precision Medicine
Reza Mirnezami, M.R.C.S., Jeremy Nicholson, Ph.D., and Ara Darzi, M.D.
# Preparing for Precision Medicine

Reza Mirnezami, M.R.C.S., Jeremy Nicholson, Ph.D., and Ara Darzi, M.D.

## Health Care Stakeholders and Their Roles in Ensuring the Success of Precision Medicine.

<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>Recommended Actions</th>
</tr>
</thead>
</table>
| Government              | Generation of transparent privacy laws  
                          Identification of socioeconomic priority areas likely to benefit most from precision-medicine strategies  
                          Public consultation regarding “opt in–opt out” strategies for research participation |
| Research industry       | Development of effective clinical decision support tools for integration into electronic health records  
                          Setting up and conducting appropriate pilot studies for data collection in targeted precision-medicine areas |
| Biomedical community    | Changes to undergraduate training to develop improved understanding of molecular mechanisms involved in disease  
                          Development and contribution to an evolving new system of disease classification incorporating emerging molecular information  
                          Introduction of a more transparent, participatory role for patients considered for recruitment to clinical trials |
| Pharmaceutical industry | Development of effective diagnostic tests with or without tandem therapeutic agents for management of conditions identified as major socioeconomic burdens |
| Patient groups          | Increasing participation in health and well-being initiatives  
                          Use of novel means of providing data for research purposes, including social networks and mobile phone applications |
| Regulatory bodies       | Ensuring that regulatory frameworks are in place to safeguard patient safety, while ensuring that scientific progress is not hampered |

*Mirnezami et al. NEJM 2012*
Respiratory Proteomics: From Descriptive Studies to Personalized Medicine

Luis M. Teran,*,†,‡ Rosalia Montes-Vizuet,† Xinping Li,§ and Thomas Franz§

†Instituto Nacional de Enfermedades Respiratorias, Calz. de Tlalpan 4502, Distrito Federal 14080, Mexico
‡Biomedicine in the Postgenomic Era, Cuescontitla No. 5, Morelos 62515, Mexico
§Max Planck Institute for Biology of Ageing, Joseph-Stelzmann-Str. 9b, D-50931 Cologne, Germany
Figure 1. Typical SRM analysis of target proteins of bronchoalveolar lavage fluid. In the triple—quadrupole instrument, Q1 selects molecular ions of a specific analyte and Q2 fragments them into daughter ions, which are then selected in Q3 and guided to the detector.
Asthma severity in childhood and metabolomic profiling of breath condensate

S. Carraro¹, G. Giordano¹, F. Reniero², D. Carpi², M. Stocchero³, P.J. Sterk⁴ & E. Baraldi¹

¹Department of Women’s and Children’s Health, University of Padova, Padova, Italy; ²European Commission, Joint Research Centre, Institute for Health and Consumer Protection (IHCP), System Toxicology Unit (ST), Ispra, Italy; ³S-IN Soluzioni Informatiche, Vicenza, Italy; ⁴Department of Respiratory Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands
Biomarker discovery in asthma and COPD by proteomic approaches

Rossana Rossi¹, Antonella De Palma¹, Louise Benazzi¹, Anna Maria Riccio², Giorgio Walter Canonica² and Pierluigi Mauri¹

¹ Proteomics and Metabolomics Unit, Institute for Biomedical Technologies (ITB)—CNR, Segrate, MI, Italy
² Allergy and Respiratory Diseases, Department of Internal Medicine, University of Genoa, Genoa, Italy
<table>
<thead>
<tr>
<th>References</th>
<th>Biomarkers</th>
<th>Sample source</th>
<th>Method</th>
<th>Verification</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Antibody-based methods</td>
<td>FOXP3, SP-A, MPO, sRAGE, NGAL</td>
<td>PBMC, Induced sputum, plasma</td>
<td>Real-time PCR, ELISA</td>
<td>Real-time PCR, ELISA</td>
<td>Asthma, control subjects, Asthma/COPD/COPD-asthma-smoker/nonsmoker</td>
</tr>
<tr>
<td>(B) Peak profiling MS-based methods</td>
<td>HNP1, HNP2, HNP3, three C-terminal amided peptides</td>
<td>Induced sputum</td>
<td>MSB (mesoporous silica beads) MALDI TOF/TOF</td>
<td>SELDI-TOF</td>
<td>Asthma/COPD</td>
</tr>
<tr>
<td>(C) Gel-MS based methods</td>
<td>Calgranulin A, calgranulin B, calgranulin C, CCSP, proline-rich salivary peptide</td>
<td>Induced sputum</td>
<td>SELDI-TOF</td>
<td>ELISA</td>
<td>Healthy control/asthma/COPD/CF/bronchiectasis</td>
</tr>
<tr>
<td>(D) LC-MS-based methods</td>
<td>Hemoglobin subunit-beta</td>
<td>Serum, nasal epithelial cell, lung tissue</td>
<td>SELDI-TOF</td>
<td>ELISA</td>
<td>Asthma/COPD/CF</td>
</tr>
<tr>
<td>Cell cultures of mesenchymal type from bronchial biopsies</td>
<td>2D gel MALDI TOF</td>
<td>Western blotting</td>
<td>Asthma patients with chronic cough</td>
<td></td>
<td></td>
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<tr>
<td>Plasma during exacerbation and stable period</td>
<td>2D gel MALDI TOF</td>
<td>ELISA and nephelometry</td>
<td>Asthmatic children</td>
<td></td>
<td></td>
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<tr>
<td>Nasal lavage fluid</td>
<td>2D-DIGE MALDI TOF</td>
<td>ELISA and immunoCAP</td>
<td>AERD</td>
<td></td>
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<tr>
<td>Plasma peripheral blood</td>
<td>2D gel MALDI TOF</td>
<td>Immunoassay</td>
<td>Nonsmoking asthma/nonsmoking COPD/healthy</td>
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Rossi et al Proteomics Clin Appl. 2014
Table 1. Continued

<table>
<thead>
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<th>References</th>
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<th>Sample source</th>
<th>Method</th>
<th>Verification</th>
<th>Subjects</th>
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<tr>
<td>[65]</td>
<td>426 proteins</td>
<td>Peripheral blood eosinophil</td>
<td>2D gel MALDI-TOF/TOF</td>
<td>Western blotting</td>
<td>Non-smokers donors who showed neither asthmatic nor allergies symptoms</td>
</tr>
<tr>
<td>[66]</td>
<td>Fibrinogen complement component C3</td>
<td>Plasma</td>
<td>2D gel MALDI-TOF</td>
<td></td>
<td>Non-smoking mildly asthmatic patients</td>
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<tr>
<td>[67]*</td>
<td>Calphosphine, surfactant protein A, transthyretin, ApoA1, S100A8</td>
<td>BALF</td>
<td>2D-PAGE MALDI-TOF</td>
<td></td>
<td>Healthy and sulfur mustard exposed</td>
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<tr>
<td>[68]</td>
<td>No</td>
<td>PBCMs</td>
<td>2D gel MS</td>
<td></td>
<td>Non-smoking asthma</td>
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<tr>
<td>[69]</td>
<td>No</td>
<td>PBCMs</td>
<td>2D-DIGE MALDI-TOF</td>
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<td>Healthy volunteers</td>
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<tr>
<td>(D) LC-MS-based methods</td>
<td></td>
<td></td>
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<tr>
<td>[78]</td>
<td>Galectin-binding glycoproteins</td>
<td>BALF</td>
<td>LC-MS/MS</td>
<td>Immunohistochemistry</td>
<td>Controls/asthma non-smokers</td>
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<tr>
<td>[79]</td>
<td>PDE7 and syntaxin</td>
<td>Plasma</td>
<td>LC-MS/MS</td>
<td>Multiplex immunoblot assay and WB</td>
<td>Asthma/NSCLC/healthy controls</td>
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<td>[80]</td>
<td>Secretoglobin S100A8/A9 complement component 3a</td>
<td>Induced sputum</td>
<td>LC-MS/MS</td>
<td>Western blotting</td>
<td>Healthy asthmatics</td>
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<tr>
<td>[81]*</td>
<td>42 protein spots, 22 upregulated and 20 downregulated</td>
<td>T-cell</td>
<td>nano-LC-MS/MS</td>
<td></td>
<td>Volunteers</td>
</tr>
<tr>
<td>[82]*</td>
<td>Panel of proteins</td>
<td>Nasal cells</td>
<td>2D LC MS/MS</td>
<td></td>
<td>Healthy controls/asthma children</td>
</tr>
<tr>
<td>[83]</td>
<td>Cytokeratin, albumin, actin, hemoglobin, lysozyme, dehydrogenase, and calgranul A</td>
<td>Exhaled breath condensate (EBC)</td>
<td>2D-nanoLC-TOF/TOF + MALDI-TOF</td>
<td></td>
<td>Non-smokers asthma/healthy smoking controls</td>
</tr>
<tr>
<td>[84]</td>
<td>Lamin, cyclophilin A, annexin 5, n2M, n2M, calgranul A,</td>
<td>Bronchial biopsies</td>
<td>iTRAQ labeling SCX off-line nano-LC-MS/MS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The references marked with asterisk (*) investigated both asthma and COPD. MPO, myeloperoxidase; sRAGE, soluble receptor for advanced glycation endproducts; NGAL, neutrophil gelatinase-associated lipocalin; CCSF, Clara cell secretory protein; HNP1, human neutrophil peptide 1; HNP2, human neutrophil peptide 2; HNP3, human neutrophil peptide 3; ApoA1, apolipoprotein A1; α2M, α2-macroglobulin; AERD, aspirin-exacerbated respiratory disease; AAT, α1-antitrypsin; VEGF-A, vascular endothelial growth factor A; Bk, bradykinin; EIA, enzyme immunoassay.
Fig. 3. New findings in asthma therapy increase possibility of therapy approach as well as costs.
Expert Review of Respiratory Medicine

The path to personalized medicine in asthma

Diego Bagnasco, Matteo Ferrando, Stefano Bernardi, Giovanni Passalacqua & Giorgio Walter Canonica
THERE IS URGENT NEED

of well trained specialists to lead the process of PRECISION MEDICINE in ASTHMA in Clinical Practice
Interleukin-5 pathway inhibition in the treatment of eosinophilic respiratory disorders: evidence and unmet needs

Gilda Varricchi\textsuperscript{a}, Diego Bagnasco\textsuperscript{b}, Francesco Borriello\textsuperscript{a}, Enrico Heffler\textsuperscript{c}, and Giorgio W. Canonica\textsuperscript{b}
A Critical Evaluation of Anti-IL-13 and Anti-IL-4 Strategies in Severe Asthma

Diego Bagnasco\textsuperscript{a} Matteo Ferrando\textsuperscript{a} Gilda Varricchi\textsuperscript{b} Giovanni Passalacqua\textsuperscript{a} Giorgio Walter Canonica\textsuperscript{a}

\textsuperscript{a}Allergy and Respiratory Diseases, DIMI Department of Internal Medicine, University of Genoa, IRCCS AOU San Martino-IST, Genoa, and \textsuperscript{b}Division of Clinical Immunology and Allergy, Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy

\textit{Bagnasco et al. Int.Arch.All.Imm. 2016}
Allergens

Epithelial Cells

IL-33

TSLP

IL-25

IL-33R

TFLPR

IL-25R

IL-13

ILC2

TH2 cell

Mast cell

Basophil

Airway Smooth Muscle Cell Proliferation

Fibroblast Proliferation

Alternatively Activated Macrophage

Eosinophil

Mast cell

Cys-LTs

Histamine

PGD2

PAF

IgE

B cell

Basophil

Cytokines

Chemokines

IgE

IL-4

IL-13

IL-4α + γC

IL-4α + IL-13α1

IL-13α2

Identification of Molecular Mechanism of disease

Diagnostic Tool for the Molecular Mechanism

Treatment Blocking the Molecular Mechanism

Molecular mechanism:
IgE, arming effector cells, binds allergen/component: mediator release & symptoms

Diagnostic Tool:
IgE to causal allergen/component detection

Treatment Blocking the Molecular Mechanism
AIT- Allergen Immunotherapy (SCIT-SLIT)

Hamburg & Collins, NEJM 2010 [22]

Canonica et al. WAO J.2015 [18]
Passalacqua & Canonica, CMA 2015 [23]

Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: A randomized, double-blind, placebo-controlled trial

Holger Mosbech, MD, Regina Deckelmann, MD, Frédéric de Blay, MD, Elide Anna Pastorello, MD, Ewa Trebas-Pietras, MD, Luis Prieto Andres, MD, Inga Malcus, MD, Christian Ljørring, MSc, and Giorgio Walter Canonica, MD

Gentofte, Denmark, Leipzig, Germany, Strasbourg, France, Milan and Genoa, Italy, Lublin, Poland, Valencia, Spain, Malmö, Sweden, and Hørsholm, Denmark

(Mosbech et al., J Allergy Clin Immunol 2014;134:568-75.)

Composition of a new HDM SLIT-tablet

Der p 1
Der p 2 50/50 Der f 1
Der f 2
The primary efficacy endpoint was a significant reduction in inhaled corticosteroid dose compared to baseline after 1 year of daily treatment. A positive therapeutic effect on asthma was demonstrated by a reduction of more than 80 μg/day inhaled budesonide for a group receiving six developmental units daily compared to the placebo group.
Original Investigation

Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma: A Randomized Clinical Trial

J. Christian Virchow, MD; Vibeke Bækker, MD, DMSc; Piotr Kuna, MD; Luis Prieto, MD; Hendrik Nolte, MD, PhD; Hanne Hedegaard Villesen, MSc, PhD; Christian Ljørring, MSc; Bente Riis, MSc, PhD; Frederic de Blay, MD

Virchow et al. JAMA 2016
Figure 2. Probability of Having the First Moderate or Severe Asthma Exacerbation in the Full Analysis Set

- 50% ICS Reduction
- 100% ICS Reduction

<table>
<thead>
<tr>
<th>Time During ICS Reduction, d</th>
<th>Placebo</th>
<th>6 SQ-HDM tablet</th>
<th>12 SQ-HDM tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>257</td>
<td>237</td>
<td>248</td>
</tr>
<tr>
<td>30</td>
<td>228</td>
<td>224</td>
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<td>60</td>
<td>200</td>
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<tr>
<td>180</td>
<td>109</td>
<td>122</td>
<td>121</td>
</tr>
</tbody>
</table>

No. at risk
50 years of asthma pharmacotherapy

1972: Inhaled corticosteroid
1975: Montelukast (1998)
1980: Long-acting β2-agonists
1990: Combination LABA+ICS
1995: LABA/ICS for mx and relief (SMART)
2000: LAMA
2005: Anti-IL5 MAB
2010: Once-daily LABA/ICS
2015: AIT

- Bronchospasm
- Inflammation
- Remodelling
The most important PLAYER

PATIENT
So...we should not forget the starting point
Several terms including “personalized medicine”, “precision medicine”, “stratified medicine”, “targeted medicine” and “pharmacogenomics” are used interchangeably [1] but differ subtly. “Precision medicine” is similar to “personalized medicine” and is a new term encompassing one of the foremost examples of future disruptive innovation in healthcare. It is a medical model aiming at the customization of healthcare - with medical decisions, practices, and/or products tailored to the individual patient. It also
In this context my perception is:

**PRECISION MEDICINE**
is focused on the ENDOTYPE (or on the Mechanisms of patient’s disease)

**PERSONALIZED MEDICINE**
is focused on the PATIENT/PERSON not just on the mechanism
P4 Medicine
Dr. Hood created the technological foundation for the sciences of genomics (study of genes) and proteomics (study of proteins) through the invention of five groundbreaking instruments and by explicating the potentialities of genome and proteome research into the future through his pioneering of the fields of systems biology and systems medicine. Hood's
What is P4 Medicine?

P4 Medicine is a plan to radically improve the quality of human life via biotechnology.

P4 Medicine is a term coined by biologist Leroy Hood, and is short for “Predictive, Preventive, Personalized, and Participatory Medicine.” The premise of P4 Medicine is that, over the next 20 years, medical practice will be revolutionized by biotechnology, to manage a person's health, instead of manage a patient's disease.
From EBM to Clinical Recommendation

Evidence-based medicine

Clinical recommendations on efficacy for an intervention
A general process in guidelines evolution
Factors that influence the strengths of a recommendation

- Balance between desirable and undesirable effects
- Quality of evidence
- Patients’ values and preferences
- Costs
Two Examples

**DRUG A:**
- Effective
- Safe
- Cheap
- Administration: 18 shots a day

**DRUG B:**
- Effective
- Safe
- Fast Dissolving Tablet with a good taste
- Cost: 300,000 €/year
Third Example

DRUG C:
Effective
Cheap
Fast Dissolving Tablet with a good taste
Make the patient sleeping all day long

DIFFICULT to POSITIONING THOSE PRODUCT in CLINICAL RECCOMENDATIONS although there is Scientific Evidence of Efficacy
From EBM to recommendation

Evidence-based medicine

Clinical recommendations on efficacy for an intervention

Safety including post-marketing surveillance

Health economics

Patient’s views & Preference

recommendations for an intervention
PERSONALIZED TREATMENT
ASTHMA

Personalized Medicine is not just related to the new biologics.
PERSONALIZED TREATMENT

ASTHMA

A Step by Step approach
PERSONALIZED TREATMENT

ASTHMA

Nowadays this concept is including also the right choice of the DEVICE

..........Patient’s Preference and Value
The "least imperfect" inhaler

The inhaler which the patient can and will use effectively.
The poorer the device technique, the poorer the outcome

Giraud V, Roche N. Eur Respir J 2002;19:246–51

Asthma Instability Score AIS (0-best; 9-worst)

n= 3709

Misuser, poor coordinators

Misusers good coordinators

Good users
Improved inhalation technique affects outcome

Outpatient management in children with severe asthma improves inhalation technique from 65% to 95% with correct inhaler technique.


- Lower corticosteroid dose
- Improved asthma control
ERS/ISAM TASK FORCE REPORT

What the pulmonary specialist should know about the new inhalation therapies

**Recommendations**

Prescribers should:

1) Know the types of devices that are available to deliver specific drugs and classes of drugs (table 2).

2) Appreciate the advantages and disadvantages of each device (table 5).

3) Choose devices that the patient can and will use effectively (table 3).

4) Choose devices that have been approved by the appropriate authorities (table 2).

5) Train patients about the correct inhalation manoeuvre that is appropriate for the device being prescribed (table 4).

6) Check the patient’s inhaler technique regularly.

7) Review the patient’s adherence to treatment at each visit.

8) Not switch to a new device without the patient’s involvement and without follow-up education on how to use the device properly.
<table>
<thead>
<tr>
<th>Term</th>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labelled dose or nominal dose</td>
<td>TED</td>
<td>The mass of drug that is available within the aerosol generator per actuation. This is the dose that is metered.</td>
</tr>
<tr>
<td>Total emitted dose or delivered dose</td>
<td>TED</td>
<td>The mass of drug emitted per actuation that is actually available for inhalation at the mouth.</td>
</tr>
<tr>
<td>Fine-particle dose</td>
<td>FPD</td>
<td>The mass of particles &lt;5 μm in size within the total emitted dose.</td>
</tr>
<tr>
<td>Fine-particle fraction</td>
<td>FPF</td>
<td>The fine particle dose divided by the total emitted dose.</td>
</tr>
<tr>
<td>Aerodynamic equivalent diameter</td>
<td>dae</td>
<td>The diameter of a fictitious sphere of unit density (1 g·cm⁻³) that has the same gravitational (settling) velocity in the same gas as the actual particle.</td>
</tr>
<tr>
<td>Mass median aerodynamic diameter</td>
<td>dae,μm or MMAD</td>
<td>The MMAD divides the aerosol size distribution in half. It is the diameter at which 50% of the particles of an aerosol by mass are larger and 50% are smaller.</td>
</tr>
<tr>
<td>Geometric standard deviation</td>
<td>σg or GSD</td>
<td>The GSD measures the dispersion of particle diameter and is defined as the ratio of the median diameter to the diameter at ±1 sd (σ) from the median diameter. In a cumulative distribution plot of the aerodynamic diameter and mass of particles, the GSD is calculated as the ratio of the median diameter to the diameter at 15.9% of the probability scale, or the ratio of the diameter at 84.1% on the probability scale to the median diameter. Aerosols with a GSD ≥ 1.22 are considered polycisperse. Most therapeutic aerosols are polycisperse and have GSDs in the range of 2–3.</td>
</tr>
</tbody>
</table>

*: lung deposition can be presented as a percentage of the nominal or emitted dose. Note that these two parameters are not the same.
**Recommendations**

Prescribers should:

1) Know the types of devices that are available to deliver specific drugs and classes of drugs (table 2).

2) Appreciate the advantages and disadvantages of each device (table 5).

3) Choose devices that the patient can and will use effectively (table 3).

4) Choose devices that have been approved by the appropriate authorities (table 2).

5) Train patients about the correct inhalation manoeuvre that is appropriate for the device being prescribed (table 4).

6) Check the patient’s inhaler technique regularly.

7) Review the patient’s adherence to treatment at each visit.

8) Not switch to a new device without the patient’s involvement and without follow-up education on how to use the device properly.
Recommendations
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Let’s classify DPIs

Inhalation flow dependent
High - intermediate resistance
- Turbuhaler®
- Pulvinal®
- Novolizer®

Inhalation flow dependent
Low resistance
- Jethaler®
- Easyhaler®
- Clickhaler®
- Spinhaler®
- Gyrohaler®

Inhalation flow independent
High-intermediate resistance
- Cyclohaler®
- Aerolizer®

Inhalation flow independent
Low resistance
- Handihaler®
- Diskhaler®
- Aerohaler®
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Laube et al. ERJ 2011
**CHILDREN & ELDERLY**

*The elderly*

Those prescribing aerosol treatment for the elderly face similar problems to those which are confronted by physicians who treat children. Cognitive decline means that the more complex manoeuvres may be challenging for many elderly patients. The situation is compounded by dexterity issues. Once again, the clinician is obligated to prescribe a delivery system that a patient can and will use effectively. For many with limited abilities to adopt complex inhalation manoeuvres, the simplicity of a jet nebuliser may be a necessary compromise.

Laube et al. ERJ 2011
>250 inhaler devices and medications

Given the huge array of available devices:
- HCPs may not know all the inhaler key features and the way to use them
- Patients often make mistakes when using their inhalers

COPD, chronic obstructive pulmonary disease; HCPs, healthcare professionals; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; SABA, short-acting β-agonist;
Switching treatments in COPD: implications for costs and treatment adherence

41 different brands

13 different inhalers

HUNDREDS POTENTIAL SWITCHES!
Asthma and COPD: Interchangeable use of inhalers. A document of Italian Society of Allergy, Asthma and Clinical Immunology (SIAAIC) & Italian Society of Respiratory Medicine (SIMER)

Federico Lavorini a, *, Fulvio Braido b, Ilaria Baiardini b, Francesco Blasi c, Giorgio Walter Canonica b, on behalf of SIAAC-SIMER

a Department of Experimental and Clinical Medicine, Guglielmo University Hospital, Florence, Italy
b Respiratory and Allergy Diseases Clinic, DIM, University of Genoa, IRCCS AOI San Martino-UD, Genoa, Italy
c Department of Pathophysiology and Transplantation, Università degli Studi di Milano, IRCCS Foundation Ca’ Granda, Ospedale Maggiore Policlinico, Milan, Italy

ABSTRACT

Prescription cost-containment measures are increasing in many European countries and, as more inhaler devices become available, there may be pressure to switch patients from reference inhaler medication to cheaper generic inhaler devices. Indeed, in some countries, such a substitution is mandated by current regulations, and patients who do not accept the substitution have to pay the difference in cost. Generic inhalers are therapeutically equivalent to original branded options but may differ in their formulation and inhalation device. This new situation raises questions about the potential impact of switching from branded to generic inhaler medications in patients with asthma or chronic obstructive pulmonary disease (COPD), with or without their consent, in countries where this is permitted. Acquisition cost savings from a substitution could be offset by costs related to deterioration in asthma control or worsening in COPD outcomes if the patient is unable or unwilling to use the inhaler device properly. Non-adherence to therapy and incorrect inhaler usage are recognised as major factors in uncontrolled asthma and worsening of COPD outcomes. Switching patients to different inhaler device may exacerbate these problems, particularly in patients who disagree to switch. Where switching is permitted or mandatory, it is crucial that the reason for switching has been properly explained to the patient and adequate instruction for operating correctly the inhaler have clearly been provided.

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Assessment of inhaler technique is crucial!
The device is "intrinsic" part of each inhaled product
DEVICE FEATURES in REAL LIFE
Need of education for dry powder inhaler storage and retention – a patient-reported survey

Birger Norderud Lærum¹,²*, Gunilla Telg³ and Georgios Stratelis³
### Table 1

Number of doses, shelf life and storage of the most commonly used multidose dry powder inhalers

<table>
<thead>
<tr>
<th>Inhaler</th>
<th>Doses</th>
<th>Shelf life (unopened)</th>
<th>Time in-use (opened)</th>
<th>Recommended storage conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diskus/Accuhaler</td>
<td>60</td>
<td>1.5–3 years (depending on drug strength)</td>
<td>1.5–3 years</td>
<td>Do not store above 30 °C. Store in a dry place. Inhaler is sealed in a foil overwrap, which should only be opened when it is to be used for the first time.</td>
</tr>
<tr>
<td>Easyhaler</td>
<td>200</td>
<td>3 years</td>
<td>6 months</td>
<td>Store in the original package. When in use, do not store above 30 °C and store protected from moisture.</td>
</tr>
<tr>
<td>Elipta</td>
<td>30</td>
<td>2 years</td>
<td>6 weeks</td>
<td>Do not store above 25 °C. Store in the original package in order to protect from moisture.</td>
</tr>
<tr>
<td>Genuair</td>
<td>60</td>
<td>3 years</td>
<td>90 days</td>
<td>Keep the inhaler protected inside the sealed pouch until the administration period starts.</td>
</tr>
<tr>
<td>Nexthaler</td>
<td>120</td>
<td>3 years</td>
<td>6 months</td>
<td>Do not store above 25 °C. Store in the original package in order to protect from moisture.</td>
</tr>
<tr>
<td>Novolizer</td>
<td>200</td>
<td>3 years</td>
<td>6 months</td>
<td>Store in the original package. When in use, keep the device tightly closed in order to protect from moisture.</td>
</tr>
<tr>
<td>Spiromax</td>
<td>120</td>
<td>3 years</td>
<td>6 months</td>
<td>Do not store above 25 °C. Keep the mouthpiece cover closed after removal of the foil wrapping.</td>
</tr>
<tr>
<td>Turbuhaler</td>
<td>200</td>
<td>2 years</td>
<td>2 years</td>
<td>Store in the original package. Do not store above 30 °C.</td>
</tr>
</tbody>
</table>

*a For further details reference to respective inhaler’s Summaries of Product Characteristics (SPCs)*
Patient reported device control frequencies

Fig. 1 Patient-reported (a) frequency of control of DPI expiry date; and (b) use after DPI expiry date (per cent of patients)

Spiromax, a New Dry Powder Inhaler: Dose Consistency under Simulated Real-World Conditions

Giorgio Walter Canonica, MD,1,* Jan Arp, MSc,2 Johan René Keegstra, MSc, PharmD,3 and Henry Chrystyn, PhD4,*
FIG. 1. Configuration of the Spiromax inhaler.
<table>
<thead>
<tr>
<th>Scheme</th>
<th>Inhaler strength</th>
<th>Dosing regimen</th>
<th>Duration (days)</th>
<th>Number of inhalers</th>
<th>Uniformity of dose delivery assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low&lt;sup&gt;a&lt;/sup&gt;</td>
<td>One inhalation twice daily</td>
<td>72</td>
<td>6 (three from each of the two batches)</td>
<td>Days 1–2 (3 doses) Days 36–37 (4 doses) Days 71–72 (3 doses)</td>
</tr>
<tr>
<td>B</td>
<td>Low&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Four inhalations twice daily</td>
<td>21</td>
<td>6 (three from each of the two batches)</td>
<td>Day 1 (3 doses) Day 10 (4 doses) Day 21 (3 doses)</td>
</tr>
<tr>
<td>C</td>
<td>Middle&lt;sup&gt;b&lt;/sup&gt;</td>
<td>One inhalation twice daily</td>
<td>90</td>
<td>9 (three from each of the two batches)</td>
<td>Days 1–2 (3 doses) Days 45–48 (4 doses) Days 87–90 (3 doses)</td>
</tr>
<tr>
<td>D</td>
<td>High&lt;sup&gt;c&lt;/sup&gt;</td>
<td>One inhalation twice daily</td>
<td>32</td>
<td>6 (three from each of the two batches)</td>
<td>Days 1–4 (3 doses) Days 15–18 (4 doses) Days 29–32 (3 doses)</td>
</tr>
<tr>
<td>E</td>
<td>High&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Two inhalations twice daily</td>
<td>16</td>
<td>6 (three from each of the two batches)</td>
<td>Day 1 (3 doses) Day 8 (4 doses) Days 15–16 (3 doses)</td>
</tr>
</tbody>
</table>

<sup>a</sup>80/4.5 μg per dose; <sup>b</sup>160/4.5 μg per dose; <sup>c</sup>320/9 μg per dose.
FIG. 3. Mean* (SD) total emitted doses of budesonide and formoterol at the beginning (BOL), middle (MOL), and end (EOL) of inhaler life, with low-, middle-, and high-strength DuoResp Spiromax. *Mean of three batches. Low strength: 80/4.5 μg per dose; middle strength: 160/4.5 μg per dose; high strength: 320/9 μg per dose. BOL, beginning of life; EOL, end of life; MOL, middle of life; SD, standard deviation.
FIG. 4. Effects of flow rate on emitted dose of budesonide and formoterol delivered by low-, middle-, and high-strength DuoResp Spiromax. Low strength: 80/4.5 µg per dose; middle strength: 160/4.5 µg per dose; high strength: 320/9 µg per dose. Colored lines represent results from different batches.
<table>
<thead>
<tr>
<th>Batch</th>
<th>Test Condition</th>
<th>Budesonide</th>
<th>Formoterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low</td>
<td>Middle</td>
</tr>
<tr>
<td>1</td>
<td>Low</td>
<td>98</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>Standard</td>
<td>104</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>101</td>
<td>104</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>100</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>Standard</td>
<td>102</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>101</td>
<td>105</td>
</tr>
<tr>
<td>3</td>
<td>Low</td>
<td>103</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>Standard</td>
<td>101</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>101</td>
<td>105</td>
</tr>
</tbody>
</table>

Dose after temperature cycling (stored wrapped, tested at standard laboratory conditions)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Standard</th>
<th>Low</th>
<th>Middle</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>102</td>
<td>105</td>
<td>97</td>
<td>100</td>
</tr>
</tbody>
</table>

*Test condition Low: 20°C–21°C, 25%–31% RH; Standard: 21°C–23°C, 46%–54% RH; High: 23°C–27°C, 72%–79% RH; 80/4.5 μg per dose; 160/4.5 μg per dose; 320/9 μg per dose; Low strength: Batch 2 (stored 3–6 months at 25°C ± 2°C, 60% ± 5% RH); Middle strength: Batch 3; High strength: Batch 1 (both stored 9–12 months at 25°C ± 2°C, 60% ± 5% RH). Values are mean percent relative to the label claim and relative standard deviation (%). RH, relative humidity.
Table 4. Effects of Different Orientations on Doses of Budesonide and Formoterol Delivered by Spiromax

<table>
<thead>
<tr>
<th>Orientation ('tilt')</th>
<th>Budesonide</th>
<th>Formoterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low(^a)</td>
<td>High(^b)</td>
</tr>
<tr>
<td>45° orientation study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (upright inhalation and actuation)</td>
<td>102 (5)</td>
<td>102 (5)</td>
</tr>
<tr>
<td>+45° (inhalaion)</td>
<td>102 (6)</td>
<td>104 (5)</td>
</tr>
<tr>
<td>+45° (actuation)</td>
<td>102 (7)</td>
<td>103 (5)</td>
</tr>
<tr>
<td>-45° (inhalaion)</td>
<td>102 (6)</td>
<td>101 (8)</td>
</tr>
<tr>
<td>-45° (actuation)</td>
<td>104 (6)</td>
<td>103 (6)</td>
</tr>
<tr>
<td>90° orientation study</td>
<td>95 (5)</td>
<td></td>
</tr>
<tr>
<td>Control (upright inhalation and actuation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+90° (inhalaion)</td>
<td></td>
<td>97 (4)</td>
</tr>
<tr>
<td>+90° (actuation)</td>
<td>98 (5)</td>
<td></td>
</tr>
<tr>
<td>-90° (inhalaion)</td>
<td>99 (5)</td>
<td></td>
</tr>
<tr>
<td>-90° (actuation)</td>
<td>101 (4)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean percent relative to the label claim and relative standard deviation (%).
\(^a^{80/4.5 \mu g per dose}; ^b^{320/9 \mu g per dose}.\)
Delivered doses of budesonide and formoterol after dropping the Spiromax inhaler.
In conclusion, these results indicate that Spiromax delivers consistently accurate doses throughout inhaler life under controlled laboratory conditions. Consistency of overall dose is maintained when this inhaler is exposed to variations in temperature, humidity, inspiratory flow rate, and orientation during actuation/inhalation, or when it is dropped or knocked. Comparison of the flow rates achieved by patients with asthma and COPD with the in vitro dose delivery results suggest in vitro findings may also be applicable to clinical practice.
Figure 6  Chronic obstructive pulmonary disease control panel for personalised medicine in the clinic. Each of the three modules (severity, activity and impact) provides information on an actionable (ie, treatable) component of the disease. CAT, COPD Assessment Test; FEV$_1$, forced expiratory volume in 1 s; IC, inspiratory capacity; mMRC, modified Medical Research Council dyspnoea score; 6MWD, 6 min walk distance; PaO$_2$, arterial oxygen tension; TLC, total lung capacity. For further explanation, see text. Reproduced with permission from Agusti and MacNee.
Modules, networks and systems medicine for understanding disease and aiding diagnosis


Gustafsson et al Genome Medicine 2015
Figure 4 An idealized systems medical approach to personalized treatment. (a) All factors that influence a disease can potentially be described by networks. For example, symptoms and signs that tend to co-occur can be linked and form a module that corresponds to a disease (pink oval). That module may be linked to underlying modular protein changes (blue oval). Similarly, the disease module may be linked to co-occurring environmental factors (green oval). (b) Each of the modules in (a) can be further divided to represent different sublayers, from which (c) predictive markers from the different sublayers can be identified, and used for (d) personalized treatment. MLDM, multilayer disease module; nc-RNA, noncoding RNA; PPI, protein-protein interaction; SNPs, single-nucleotide polymorphisms.
BAL BIOMARKERS

EXHALED BIOMARKERS

INFLAMM BIOMARKERS

OUTDOOR BIOMARKERS

INDOOR BIOMARKERS

BLOOD BIOMARKERS

URINE BIOMARKERS

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