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Asthma Biomarkers: Do They Bring Precision Medicine Closer to the Clinic?

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Measurement of biomarkers has been incorporated within clinical research of asthma to characterize the population and to associate the disease with environmental and therapeutic effects. Regrettably, at present, there are no specific biomarkers, none is validated or qualified, and endotype-driven choices overlap. Biomarkers have not yet reached clinical practice and are not included in current asthma guidelines. Last but not least, the choice of the outcome upholding the value of the biomarkers is extremely difficult, since it has to reflect the mechanistic intervention while being relevant to both the disease and the particular person. On the verge of a new age of asthma healthcare standard, we must embrace and adapt to the key drivers of change. Disease endotypes, biomarkers, and precision medicine represent an emerging model of patient care building on large-scale biologic databases, omics and diverse cellular assays, health information technology, and computational tools for analyzing sizable sets of data. A profound transformation of clinical and research pattern from population to individual risk and from investigator-imposed subjective disease clustering (hypothesis driven) to unbiased, data-driven models is facilitated by the endotype/biomarker-driven approach.

Key Words: Asthma; biomarkers; precision medicine

ASTHMA MANAGEMENT IN THE ADVENT OF PRECISION MEDICINE

Precision medicine (PM) is an emerging approach for disease prevention and treatment that takes into account individual variability in environment, lifestyle, and genes for each person. This is in contrast to a "one-size-fits-all" approach, in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals. The concept embraces 4 key features: personalized care based on molecular, immunologic and functional endotypes of the disease, with participation of the patient in the decision making process of therapeutic actions, and taking into account predictive and preventive aspects of the treatment.[1,2] PM is different from personalized medicine, and the terms should not be used interchangeably: in PM the focus is on identifying which approaches will be effective for which patients based on genetic, environmental, and lifestyle factors (individual risk) and on integrating research disciplines and clinical practice to guide individualized patient care (Fig. 1).

The concept of PM that takes individual variability into account is not new: starting with Archibald Garrod's pioneering research[3] in 1902 advancing the hypothesis of "chemical individuality" in alkaptonuria, to transfusion selected by blood typing, anemia treatment guided by its mechanism, and allergen immunotherapy driven by the relevant sensitizing allergen to genetically targeted therapies in cancer or cystic fibrosis. The prospect of applying this concept broadly has been dramatically improved by the recent development of large-scale biologic databases, powerful methods for characterizing patients (such as proteomics, metabolomics, genomics, diverse cellular assays, and health information technology [HIT]), and computational tools for analyzing large sets of data.[1,2,4,5]

The emerging framework of PM brings together a variety of stakeholders: Academia, patients, ethics committees, regulators/policy makers, and diagnostic/pharmaceutical industry in a precision-medicine 'ecosystem' using a variety of tools such as omics, biobanks/registries, bioinformatics, and HIT, which all need to be accounted for. What is needed now is harmonization between stakeholders with agreement on a broad research program encouraging creative approaches and testing them

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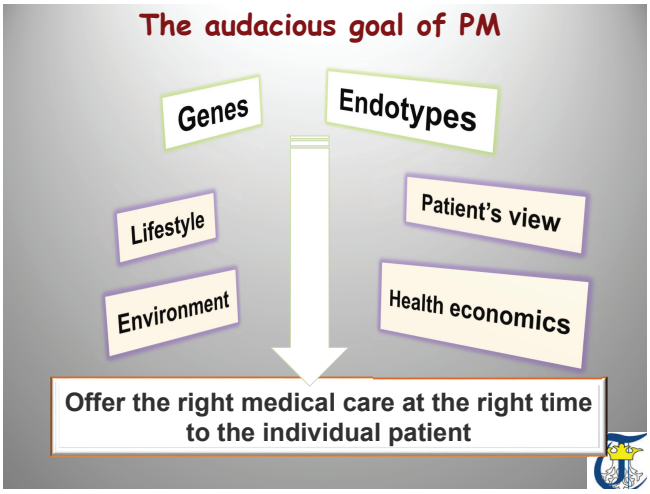

Fig. 1. The audacious goal of precision medicine. Understanding the complex networks of molecular, genetic and environmental in combination with strong health economics data and in alignment with patients participation will open the door for prevention strategies and curative therapies for asthma.

Fig. 2. 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.

rigorously both for robustness and for applicability for real life personalized care (Fig. 2).

We are coming to understand the complex networks of molecular pathways and characteristics of the asthma endotypes that interact to drive inflammation and remodeling that need to be targeted, in combination, to develop prevention strategies and curative therapies for asthma.[5-9] This subtle and highly complex architecture of disease-specific pathways (endotypes) steadily provides new targets for more efficient and tailored interventions.[5,10,11] However, although the progress in understanding the mechanisms of asthma has been so significant during the last decade, it does not yet mirror the number of submission dossiers for new medicinal products to regulatory agencies. Instead, it seems likely that the pipeline in successful drug development is rather slowing down.[12,13] The reasons for this declining trend could be the sluggish translational implementation of these discoveries and the uncertainty experienced by pharmaceutical companies due to the lack of guidance, which should be provided by the regulators. Expanding PM clinical trials in asthma is a must for moving the field forward, together with other initiatives, such as developing new laboratory models for research and national/regional and international asthma knowledge systems.[2,5]

The multilevel (clinical, functional, structural, and biological) and dynamic (*i.e.*, subjected to variability with time) heterogeneity of asthma challenges a personalized approach for treating these patients. Thus, asthma is ideally suited for PM requiring an individualized approach based on biological mechanisms (endotypes) for a better selection of treatment responders, risk prediction, and design of disease-modifying strategies.[2,4,5] A major critical step for this tailored, mechanistic approach will be the identification, validation, and qualification of pathways-specific biomarkers as companion diagnostics, which will ultimately enable the clinician to select 'the right treatment for the right patient at the right time.'[4,14,15] Therefore, the ultimate goal of the endotype/biomarker-driven approach in asthma is to develop the "magic bullet" linking drug response with the biological profile and to provide a safe and efficacious drug for a selected patient population. Besides the therapeutic purpose, the endotype/biomarker-driven approach should be able to open new avenues for prevention in high-risk individuals, early diagnosis and intervention, and disease modifying strategies.[4,5,7]

ASTHMA BIOMARKERS: A CRITICAL APPRAISAL

The ideal asthma biomarker links the disease endotype with the phenotype, predicts disease behaviors: exacerbation, severity, response to treatment, is stable over time or has a predictable variation pattern, and is easily replicated across populations with different genetic backgrounds.[7,10] Biomarkers can be associated with the mechanistic pathway and thus guide treatment (for example sputum or blood eosinophils or serum periostin) or is the key molecule of the pathway and thus the biomarker itself is the target of the intervention. The challenge with asthma biomarkers is their variability across age and asthma severity and in time, thus incorporating time trends as a hallmark of asthma as a variable disease is a must in biomarkers research and validation.[16] Another significant challenge is the complexity of a given endotype. We recently described the type 2 asthma as an example of a complex endotype with several major pathogenic pathways driven by interleukin (IL)-5, IL-4/IL-13, or immunoglobulin E (IgE) and with a multitude of modulators: genetic and epigenetic influences, barrier dysfunction,

the exposome, nutrition, and metabolic pathways, etc.[5,11,16] Last but not least, all biomarkers should be validated and qualified. Validation is the process of assessing the biomarker and its measurement performance characteristics, and determining the range of conditions under which the biomarker will give reproducible and accurate data. According to the Food and Drug Administration (FDA), a valid biomarker is defined as "measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results."[17] Qualification is the evidentiary process of linking a biomarker with biological processes and clinical end points.[14,15] The European Medicines Agency (EMA) offers scientific advice to support the qualification of innovative development methods for a specific intended use in the context of research and development into pharmaceuticals. The Committee for Medicinal Products for Human Use (CHMP) gives the advice on the basis of recommendations by the Scientific Advice Working Party. This qualification process leads to a CHMP qualification opinion or CHMP qualification advice. The opinion is based on the assessment of data submitted to the Agency. Before final adoption of qualification opinion, the CHMP makes its evaluation open for public consultation by the scientific community. The advice is based on the evaluation of the scientific rationale and on the preliminary data submitted to EMA and is meant to help develop future protocols and methods toward qualification. To facilitate parallel submissions of applications for biomarker qualification to EMA and to FDA, the 2 agencies launched in December 2014, a joint letter of intent allows the 2 agencies to share scientific perspectives and advice. The agencies are also able to provide the same response to submitters.[18]

The most scrutinized biomarkers in asthma are related to eosinophilic inflammation and/or type 2 immune response (Table 1). However, the available biomarkers cannot distinguish between the innate and adaptive immune responses generating the type 2 milieu, very few have been evaluated in targeted interventions and none is validated and qualified. In addition, there are few studies linking type 2 biomarkers to disease subendotypes. High-throughput profiling studies of well-characterized patients, including gene expression (microarrays) and omics, can help identify combined signatures for type 2 asthma as per system medicine.[19-21] One notable example of this approach using gene expression microarrays of bronchial epithelial cells obtained from patients with asthma has been the identification of periostin, an IL-13-responsive biomarker.[19,22,23] Additional studies have aimed to determine disease endotypes by exploring the transcriptome of the airway compartment, includ-

Table 1. Biomarkers linked to eosinophilic asthma and/or type 2 asthma

Biomarker	Experimental	Association	Intervention
IL-5 (serum, saliva)[27-35]	✓	✓	✓
IL-13 (serum, sputum)[27,36-38]	✓	✓	✓
IgE (serum)[39-41]	✓	✓	✓
IL-4 (serum, sputum)[38,42]	✓	✓	✓
Periostin (serum, lung biopsies, BAL, tears[43-45]	✓	✓	✓
Type 2 gene expression (periostin, serpin B2, CLCA-1) in bronchial biopsies/sputum cells[19,22,46]	✓	✓	-
DPP-4 (serum)[47]	✓	-	✓
Eotaxin, RANTES, GM-CSF (serum, saliva)[48,49]	✓	✓	-
IL-9 (serum)[50]	✓	✓	?
IL-25 (bronchial epithelium, serum)[51,52]	✓	✓	?
TSLP; CRTH2 and DP1 receptors[52-57]	✓	✓	Under investigation
CCR8; TARC; IL-31; IL-32 and T1/ST2; IL-19; NKT cells[58-60]	✓	✓	-
IL-33, proangiogenic BM precursors, osteopontin, galectin 9[61-63]	✓	✓	-
CD48, leptin, lactoferin, IL-23[64-66]	✓	-	-
IL-7 (serum, PBMCs)[67]	✓	✓	-
ICOS/ICOS-L; IL-22; H4 receptors[68-70]	✓	-	-
Il-5 and IL-13 producing Innate lymphoid cells in serum and sputum[71]	✓	✓	-
DNA methylation profile[72]	-	✓	-

Most of the biomarkers are only for research purpose and none of them is validated or qualified.
BAL, broncho-alveolar lavage; BM, bone marrow; CCR, C-C chemokine receptor; CLCA-1, chloride channel accessory 1; CRTH2, G-protein-coupled chemokine receptor homologous molecule expressed on Th2 lymphocytes; DNA, deoxyribonucleic acid; DP1, the prostaglandin D2 receptor 1; DPP4, dipeptidyl peptidase-4; GM-CSF, granulocyte-macrophage colony-stimulating factor; H, histamine; ICOS, inducible co-stimulator; ICOS-L, inducible co-stimulator ligand; Ig, immunoglobulin; IL, interleukin; NKT, natural killer T cell; PBMC, peripheral blood mononuclear cells; RANTES, regulated on activation, normal T cell expressed and secreted; TARC, thymus- and activation-regulated chemokine; T1/ST2, immunoregulatory protein of the IL-1 receptor family; TSLP, thymic stromal lymphopoietin.

ing the airway epithelium[24] and sputum.[25] Unfortunately, even gene signatures are not highly specific for type 2 asthma: a recent study showed airway gene expression alterations specific for type 2 asthma present in a subset of patients with chronic obstructive lung disease (COPD).[26] We have recently proposed a combination of biomarkers, such as IL-5 and IL-13, as the best predictor for blood eosinophilia in adult asthmatics.[27]

Less is known about the biomarkers of non-type 2 asthma, a distinct asthma endotype with several relevant clinical features, such as increased asthma severity, increased remodeling, and lower response to bronchodilator and anti-inflammatory treatment. Based on data from Th2 high/low molecular signature studies and induced sputum evaluation, the incidence of adult non-type 2 asthma reaches 30%–50%.[19,20,73] The endotyping of non-type 2 is far behind the type 2 asthma, and until now, no endotype -driven interventions have been proved to be effective. Two major mechanisms leading to neutrophilic inflammation were postulated: the dysregulated innate immune response, including neutrophil intrinsic abnormalities, and the activation of the IL-17-dependent pathway.[4,74] Several factors, such as age, metabolic or epigenetic factors, or the activation of the epithelial-mesenchimal trophic unit, have been identified as modulators. Non-type 2 asthma has a distinct DNA methylation profile in peripheral blood mononuclear cells involving secreted frizzled related protein 1 (sFRP1) as a key node, over representing the Wnt signaling pathway.[72] Another example is the consumption of a high fat meal proven to increase neutrophilic airway inflammation in asthma subjects. This occurs through changes in expression of genes regulating airway inflammation and may provide useful therapeutic targets for immunomodulation, particularly relevant to obese asthmatics, who are habitually consuming diets with a high fat content.[75] Corresponding biomarkers can be described for each non-type 2 asthma subendotypes (Tables 2 and 3); however, very few were tested as a potential therapeutic target with equivocal results (IL-17, tumor necrosis factor [TNF-α], interferon [IFN]-β) and none of them is validated or qualified. Some of these biomarkers, such as IL-17, have prognostic value related to asthma severity.[76]

Biomarkers of defective resolution/repair (Table 4) are almost neglected in asthma research, although there are solid proofs that they can be linked to asthma severity and/or steroid responsiveness.[111-114] For example, children with severe asthma have decreased lipoxin A4 concentrations in induced sputum, and this coupled with increased levels of leukotriene B4 (LTB4) promoting neutrophilic inflammation might be involved in the reduced ability of inhaled corticosteroids to control airway inflammation.[115] Feeble attempts have been done to evaluate these biomarkers as therapeutic targets.[116]

Although airway remodeling is a prominent phenotypic trait of asthma and vast amounts of data accumulated from basic research, no attempt has been made to link a biomarker (Table 5) to a potential therapeutic intervention. Bronchial termoplasty (BT) trials, for example, were conducted in a population of severe asthmatic patients selected only based on positive methacholine challenge test as a surrogate for airway smooth muscle

Table 2. Biomarkers linked to neutrophilic inflammation in non-type-asthma

Biomarker	Experimental	Association	Intervention
IL-8, LTB4[77-79]	✓	✓	-
IL-12, IL-18[80]	✓	✓	-
IL-17/TRIF-1[76,81-84]	✓	✓	✓
BDNF, MIP-3a/CCL-20, IL-1 β[85-87]	✓	✓	-
IL-32; PAMPS, DAMPS, SDF[87-89]	✓	? (IL-32 in smokers)	-
Galectin-3 binding protein[90]	-	✓	-
DNA methylation profile[72]	-	✓	-

Less is known about the biomarkers of non-type 2 asthma. Neutrophil intrinsic abnormalities, and the activation of the IL-17-dependent pathway have been postulated as disease subendotypes.
BDNF, brain-derived neurotrophic factor; CCL, C-C chemokine ligand; IL, interleukin; LT, leukotriene; DAMPS, damage-associated molecular patterns; MIP, macrophage inhibitory protein; PAMPS, pathogen-associated molecular patterns; SDF, stromal cell-derived factor; TRIF, toll/IL-1 receptor (TIR)-domain-containing adapter-inducing interferon-β.

Table 3. Biomarkers linked to dysregulation of innate immune response in non-type-2 asthma

Biomarker	Experimental	Association	Intervention
TNF-α[91-93]	✓	✓	✓
IFNs[91,94,95]	✓	✓	✓
NK cells, TLRs[96-101]	✓	✓	-
Purinergic inflammation[102,103]	✓	✓	-
Chitinase-like proteins[104]	✓	✓	-
MBL, defensins, collectins, cathelidicin, granzyme, complement/C5L2[91,105-107]	✓	✓	-
IRAK-M; APRIL[108]	✓	-	-
TREM1[109]	✓	✓	-
Surfactant protein D[110]	-	✓	-

APRIL, a proliferation-inducing ligand; C5L2, C5a like receptor 2; IFN, interferon; IRAK-M, interleukin-1 receptor-associated kinase 3; MBL, mannan binding lectin; NK cell, Natural Killer cell; TLR, Toll-like receptor; TNF, tumor necrosis factor; TREM1, triggering receptor expressed on myeloid cells 1.

Table 4. Biomarkers of defective resolution/repair

Biomarker	Experimental	Association	Intervention
Lipoxins[111-115]	✓	✓	?
Protectins[117]	✓	✓	-
Resolvins, marensins[118-123]	✓	-	-
Galectin-3[90]	-	✓	-
Tight junctions/epithelial barrier dysfunction[124-126]	✓	✓	?

Table 5. Biomarkers of airway remodeling

Biomarker	Experimental	Association	Intervention
MMP/TIMP, TGF-β, IL-13, ADAMTS, ADAM-8, ADAM-7[137-141]	✓	✓	-
VEGF/ADAM-33[141-146]	✓	✓	? (vitamin D)
Claudin, fibulin-1, endothelin-1, retinoid receptors[147-150]	✓	✓	-
COX-2, TMEFF2, TRPM-1[130]	-	✓	-
RELM-β, ICOS-L, relaxin, oncostatin M, decorin, amphiregulin, LIGHT, airway basal stem cells, CC/CXC chemokines[131,137,151]	✓	-	-
Serum chitotriosidase activity and chitinase-3-like protein 1 levels[152]	-	✓	-
Activin-A[153]	-	✓	-
Serum periostin, osteopontin[131,154]	✓	✓	-
Imaging biomarkers: HRCT airway wall thickening/wall area, MRI Sacin[132-136]	-	✓	-

ADAM, a disintegrin and metalloproteinase domain-containing protein; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; COX-2, cyclo-oxygenase-2; HRCT, high-resolution computed tomography; ICOS-L, inducible co-stimulator ligand; LIGHT, homologous to lymphotoxin, exhibits inducible expression, and competes with HSV glycoprotein D for binding to herpesvirus entry mediator, a receptor expressed on T lymphocytes; MMP, metalloproteinase; MRI, magnetic resonance imaging; RELM-β, resistin-like molecule-β; Sacin, acinar ventilation heterogeneity; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinase; TMEFF2, transmembrane protein with epidermal growth factor like and two follistatin like domains 2; TRPM-1, transient receptor potential cationic channel subfamily M member 1; VEGF, vascular endothelial growth factor.

(ASM) abnormalities.[127,128] Few clinics perform bronchoscopy with bronchial biopsies to substantiate ASM thickening. The intent of performing BT is to ablate ASM, but this response is variable—as was seen in the feasibility study—and there is a report of a patient who exhibited persistent smooth muscle hyperplasia following treatment.[129] Therefore, there are likely other mechanisms by which BT results in improved asthma symptoms, and better understanding of the precise role of ASM in the pathogenesis of asthma is thus required. Remodeling is of particular importance both in severe asthma where it can be demonstrated within the proximal airway wall despite suppressed tissue inflammation[130] and in steroid naïve asthma.[131] There have been significant advancements in imaging techniques (computed tomography, magnetic resonance imaging, and positron emission tomography) for the evaluation of asthmatic patients, both from clinical and research perspectives. Imaging biomarkers can be linked to specific asthmatic phenotypes and provide a more detailed understanding of endotypes. Airway wall thickening, as measured through high-resolution computed tomography (HRCT), was associated with asthma severity, airflow obstruction, airway reactivity, and lung volume.[132,133] Acinar ventilation heterogeneity (Sacin) was also associated with severe asthma.[134] Both HRCT and magnetic resonance imaging can identify small airway disease in asthma, a special phenotype and potential new endotype in asthma.[135,136]

Future perspectives

Key steps for moving the biomarkers field in asthma forward (Fig. 3) involve profiling asthma following the concept of complex endotypes and subendotypes linked to validated and qualified biomarkers resulting from the unbiased approach facilitated by the big data driven-models. Integrating HIT with systems medicine and with a patient centered environment is essential for coordination and alignment in translating the research data into functional clinical decision algorithms. A revised endotyp-

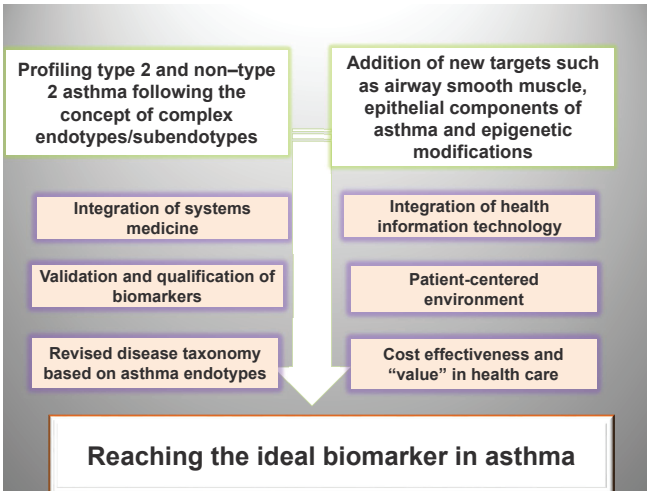

Fig. 3. Advancing the asthma biomarkers field. Profiling type 2 and non-type 2 asthma should follow the concept of complex endotypes/subendotypes in parallel with addition of new targets such as ASM, epithelial components of asthma and epigenetic modifications together with integration of systems medicine and advances in HIT. Validation and qualification of asthma biomarkers is an essential step for facilitating regulatory approval and acceptance into the health system. Improved understanding and common usage of disease phenotypes, endotypes, biomarkers, and precision therapies at the point of care is key for bringing the precision medicine into asthma clinic. Both full patient monitoring using novel digital technology and the concept of endotypes/novel biomarkers/patient centered care need to be reinforced as part of the healthcare system transformation. Development and implementation of a new asthma taxonomy including disease endotypes is highly needed. ASM, airway smooth muscle; HIT, health information technology.

ic taxonomy of asthma can stimulate targeted research and interventions to identify biomarkers predicting the implication of distinct endotypes in disease pathogenesis. Policy makers feel threatened by analytical outputs and find reasons to reject them, unless they develop high levels of trust in their pedigree and provenance, thus healthcare systems need to adapt based on cost-effective delivering value grounds.

Emerging technologies have generated a new wealth of knowledge that needs to be analyzed and translated into clinical decision algorithms, personalized asthma prevention, and management. Big data analytics, computer vision, image processing, sensors, and robotics with medical science are expected to benefit personalized asthma diagnosis and monitoring. Data mining as well as profiling and techniques for big data analytics are key tools used to discover and communicate meaningful patterns in personalized health data to promote early and instant disease diagnosis and personalized management. These advances are starting to improve the quality of health care and reduce costs. However, we should proceed on this pathway with care, and data mining should always be subjected to meaningful clinical interpretation and external validation.[155-157]

Rapid advances in 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.[158-161]

In the near future, asthma practices will participate in HIT-based systems that securely compile and analyze information from individual electronic health records (major clinical endpoints, comorbidities, symptom scores, objective measurements, treatments, side effects, molecular profiles, and quality of life, etc.). The data collected will not be biased by any preselection criteria. Advanced HIT tools, such as rapid learning systems, will structure the huge body of unbiased data by normalizing 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.[162-165]

Global HIT systems will allow physicians anywhere in the world to benefit from the latest, best available knowledge.[166] Asthma biomarkers research goes global, as HIT systems link researchers, patients, biobanks, registries, and research procedures, even in the most remote locations, so endotyping—a central element of PM—becomes affordable and universal.

CONCLUSION

There are several arguments strongly supporting the asthma biomarkers as valuable tools to bring precision medicine closer to the asthma clinic: the evidence for endotype/biomarkers-driven treatment of type 2 asthma is accumulating, the unbiased data-driven models allow for a shift from investigator-driven hypothesis research to hypothesis-generating research, health information technology is quickly advancing and there is significant pressure and support from patients and society to implement precision medicine for asthma. On the other hand, several challenges need to be overcome in the near future, including biomarkers validation and qualification as pathway specific, translation of big data into clinical decision algorithms, variation between countries in IT resources, and limits of patient expertise in population subgroups. In addition, regulators and policy makers need strong economic arguments to implement the changes. Failure to balance data volume and quality to support material and measurable decisions in asthma care will undermine the success of big data initiatives.

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