Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *Companion Diagnostics*

Personalized health care beyond oncology: new indications for immunoassay-based companion diagnostics

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Personalized health care (PHC) is an evolving field of medicine aimed at providing the right therapy to the right patient at the right time. This approach often incorporates the use of companion diagnostics (CDx) assays that provide information essential for the safe and effective use of the corresponding drug. In addition to oncology, many other therapy areas, such as cardiovascular, neurological, and infectious and inflammatory diseases, may benefit from PHC, owing to disease complexity and heterogeneity. Furthermore, although most U.S. Food and Drug Administration–approved CDx are based on molecular-based technologies, immunoassays can provide a significant contribution to the evolution of CDx in patient management. In this review we discuss how the incorporation of biomarker immunoassays into routine diagnostic testing may allow early and definitive detection of Alzheimer's disease and enable population enrichment in clinical trials. In addition, we will describe how biomarker-based CDx immunoassays have potential utility for stratifying patients with asthma based on their potential response to therapy and for selecting treatment according to phenotypic profile. Continued research into the underlying disease pathology and development of accurate and reliable diagnostic assays may ensure that PHC becomes the future standard for many indications.

Keywords: companion diagnostics; personalized health care; biomarker; periostin; asthma; Alzheimer's disease

Introduction

With the increasing availability of detailed patient profiles—through the use of novel techniques such as proteomics, genomics, metabolomics, and lipidomics—a paradigm shift from a one-size-fits-all approach toward personalized health care (PHC) is underway. The use of PHC enables treatment strategies to be tailored to individual patients through identification of the optimal drug and dosage, thereby potentially improving the benefit–risk ratio of treatment decisions. This approach can improve treatment efficiency both by reducing the number of patients receiving ineffective treatment and by potentially reducing the likelihood of adverse drugs reactions (ADRs) and their associated costs. For example, the use of *KRAS* testing before initiating cetuximab treatment has been estimated to result in cost savings of over $600 million per year compared to no testing. In addition, using a patient's thiopurine methyltransferase status to identify optimal dosage can help to minimize drug-induced morbidity in patients with rheumatologic and inflammatory bowel disorders.[1]

Biomarkers are becoming increasingly important for PHC, with uses ranging from prediction of disease course to treatment monitoring. Biomarkers can also be used to further understand the pathology of the disease, to differentiate patient populations, and to identify new treatment opportunities.[2] Ideally, a biomarker should be (1) a mediator of the disease pathology rather than an epiphenomenon of the disease; (2) present at low and stable levels in healthy individuals and measurably higher in individuals with the disease; and (3) simple and quick to measure, with minimal expense.[3] In addition, any assay for a biomarker should be validated to ensure that the results are reliable—that it delivers a high

doi: 10.1111/nyas.12754

level of precision, specificity, and sensitivity, with low lot-to-lot and interlaboratory variability.[4]

Biomarkers form the basis of accurate diagnostic tests, which are then used to stratify patients according to their underlying pathophysiological profile. If a drug is approved on the basis of the availability of a diagnostic test that provides information essential for the safe and effective use of the corresponding drug, the assay is known as a companion diagnostic (CDx).[5] In 2014, the U.S. Food and Drug Administration (FDA) published guidance on the development and approval of *in vitro* CDx devices, which stipulated that for a drug requiring use of a CDx, the test should be already/concomitantly cleared by the FDA. Therefore, ideally, a therapeutic product and its corresponding CDx device should be developed in parallel.[6]

Currently, most FDA-approved CDx assays are indicated in cancer and employ molecular-based technologies to detect various oncogene markers.[7] However, the potential to improve treatment efficiency in non-oncology indications on the basis of the presence of protein biomarkers is becoming increasingly apparent. This review[a] focuses on how the incorporation of biomarker immunoassays for diseases such as asthma and Alzheimer's disease (AD) may be used to improve diagnosis and treatment benefit, while reducing the likelihood of prescribing futile treatments and the risk of ADRs.

Approved and pipeline CDx technologies

Many CDx assays originate from pharmacogenomic biomarkers, which can be used to predict the differences in how individuals will metabolize drugs. Currently, 47 compounds approved by the FDA mention a pharmacogenomic biomarker within the indications and usage section of their label; among these, 36 drugs have oncology indications. These markers can provide information regarding risk of adverse events, drug mode of action, drug exposure, and clinical response.[8] Some of these biomarkers have been further developed into CDx to identify disease subtype or predict response to treatment based on stratification according to the drug's mode of action. As of November 2014, 19 *in vitro* CDx devices had been cleared (based on a premarket notification (510 k)) or approved (based on a premarket approval application) by the FDA; again, the majority (18 of 19) are focused on oncology (a full list is available on the FDA Web site).[7] The current focus on oncology for CDx development may be driven by the life-threatening nature and stigma of cancer, which drives investment in understanding not only the complexity and genetic heterogeneity of the disease, but also better prediction of patients more likely to respond to treatment. Minimizing the use of futile treatments could potentially focus treatment for those with the best chances of responding, thereby reducing overall healthcare costs.[9,10]

Most diagnostic devices in oncology are designed to measure the expression of specific proteins or genetic mutations, many of which result in activation of key mitogenic signaling pathways. A notable target is HER2 receptor expression or overexpression; as of November 2014, 10 CDx devices were available for detection of HER2 expression profiles. These devices are indicated for use with the breast cancer drugs trastuzumab (Herceptin®), pertuzumab (Perjeta®), and ado-trastuzumab emtansine (Kadcyla®).[7]

Various types of assays are available for measuring gene expression, including qualitative, semi-quantitative, and quantitative tests. The technology employed in the assays includes RNA- or DNA-based technologies such as real-time reverse transcription polymerase chain reaction; *in situ* hybridization, including either fluorescent or chromogenic signal detection; and microarray technology.[7] More recently, the advent of next-generation (or high-throughput) sequencing approaches has played a prominent role in diagnostic research. These technologies allow a high number of DNA strands to be sequenced in parallel, enabling comprehensive genome-wide sequencing.[5] One of these systems, Illumina's MiSeqDx platform, was cleared by the FDA as a class II device[b] in November 2013.[5] Two diagnostic assays that use the MiSeqDx platform to detect mutations in the cystic fibrosis (CF) transmembrane

[a]Related to a presentation given in April 2014 at the New York Academy of Sciences conference "Companion Diagnostics: From Biomarker Indentifcation to Market Entry."

[b]The MiSeqDx platform was classified as a class II (moderate-to-high risk) device with a premarket notification (510 k).

Ann. N.Y. Acad. Sci. 1346 (2015) 71–80 © 2015 The Authors. *Annals of the New York Academy of Sciences* published by Wiley Periodicals Inc. on behalf of The New York Academy of Sciences.

conductance regulator (CFTR) gene were also approved contemporaneously.[5]

In addition to changes in the DNA sequence, epigenetic mechanisms that result in changes to gene expression or cellular phenotype play a key role in oncogenesis.[11] Gene–environment interactions are also thought to contribute to the pathogenesis of noncancerous conditions, including inflammatory bowel disease and rheumatoid arthritis.[11,12] For example, DNA methylation is associated with gene silencing and affects many cellular processes.[11,12] Moreover, changes in methylated DNA can be detected in a range of body fluids; thus, the potential to use DNA methylation and other epigenetic biomarkers to stratify and monitor diseases is an active area of diagnostic research.[11,12]

Protein biomarkers are also reliable predictors of disease pathology and clinical outcome, since they reflect the end point of biological processes.[13] Assay technologies that measure protein biomarkers are generally based on well-established techniques such as immunohistochemistry, Western blot analysis, or enzyme-linked immunosorbent assays (ELISAs), although various high-throughput proteomic technologies are in development.[13]

Biomarker use beyond oncology

Although oncology has been the primary therapeutic area for CDx development historically, the focus of biomarker research is now widening to include other therapy areas such as metabolic and cardiovascular diseases, infectious diseases, neurological disorders, and inflammation and airway diseases. There is increasing understanding that these diseases are heterogeneous and require further separation of patients into subgroups (phenotypes) based on their signaling and effector pathways. Difficulties with diagnosis using currently available methods and safety concerns with the use of existing treatments also contribute to a high unmet need to identify putative biomarkers in some of these conditions. In clinical trials, biomarkers enable enrichment strategies, aimed at providing homogeneity to the defined enrollment population and improving the potential for detecting clinical efficacy.[14] Biomarker-based diagnostic tests may also be used to reduce the risk of ADRs, potentially improving the overall health gain with a given treatment.[1] Furthermore, post hoc stratification using biomarkers can help to monitor treatment responses and safety in patient subgroups.[15,16] Finally, identification of new biological pathways involved in disease pathology may be useful to identify new treatment opportunities, as described further below.

Cystic fibrosis

CF is caused by mutations that lead to dysfunction of the CFTR protein; therefore, drugs that directly interact with CFTR have therapeutic potential in this disease.[17] In 2013, two assays developed to detect CFTR mutations became the first *in vitro* diagnostic devices to be cleared by the FDA based on a next-generation sequencing platform.[5] Illumina's MiSeqDx Cystic Fibrosis Clinical Sequencing Assay sequences all the medically relevant regions of the CFTR gene and is intended to be used as an aid in the diagnosis of individuals with suspected CF. MiSeqDx Cystic Fibrosis 139-Variant Assay is more specific than the Clinical Sequencing Assay and is designed to detect all 139 variants of the CFTR gene.[5] Notably, the MiSeqDx CF assays have not been cleared specifically as CDx;[7] however, they will still be useful for identifying patients who are most likely to respond to treatment with CFTR-targeted therapies. Ivacaftor (Kalydeco®) is currently the only FDA-approved CFTR modifier, indicated for the treatment of CF patients with the G551D mutation in CFTR; however, other CFTR-targeted treatments are in development.[17]

Hepatitis B

Hepatitis B is a complex disease in which infected patients can be separated into subgroups according to on-treatment predictors of response to immune-based therapy. These markers include quantitative measurements of serum hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) DNA, two biomarkers that provide different (but complementary) information regarding prognosis and treatment response.[18] During a time-limited course of pegylated interferon therapy, a reduction in the level of serum HBsAg can be used as a surrogate marker to predict treatment response in patients with chronic hepatitis B, and is used as a stopping rule in clinical practice.[19] Furthermore, the combination of low HBV DNA and low HBsAg levels can predict inactive carrier status with a one-time measurement.[18] Thus, serum HBsAg quantification represents a novel diagnostic tool for characterization of HBV patients and for therapy guidance.[18]

Alzheimer's disease

AD is a progressive neurodegenerative disorder associated with a distinctive pathology that is characterized by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein. Eventually, neuronal damage leads to neurotransmitter deficits and cognitive defects.[20] The underlying neuropathology of AD begins decades before the disease manifests in terms of cognitive impairment.[20] AD progresses slowly from the presymptomatic stage, in which neurodegeneration has begun but does not have noticeable effects, to a prodromal phase (associated with mild cognitive impairment (MCI) and sometimes known as MCI due to AD). More rapid progression to dementia then occurs, with increasingly severe cognitive symptoms.[20]

The diagnosis of early stages of AD is challenging using clinical criteria alone.[20] However, potentially disease-modifying treatments may be most effective when administered very early in the disease course.[20] In addition, in the absence of approved disease-modifying therapies, patients and caregivers may benefit from early diagnosis of AD in terms of advanced care planning.[21] From an ethical perspective, there is ongoing discussion regarding whether patients in the early stages of AD should be offered the choice of knowing their biomarker-based diagnosis, despite the current lack of effective treatments.[22] It is, therefore, important to identify and validate biomarkers that reflect the underlying pathology of the disease process. Incorporation of these biomarkers into routine diagnostic testing will depend on ensuring that the corresponding tests exhibit good performance and are reliable, reproducible, noninvasive, simple to perform, and cost effective.[20,23–25]

An additional challenge is that progression of AD is not well understood; thus, the use of biomarkers may help to define subgroups with faster progression and different therapeutic needs. Lessons from previous studies suggest that clinical trials should target patients earlier in the disease course and employ robust tools capable of identifying earlier stages of amyloid pathology. For example, recent phase III studies of the anti-amyloid therapies solanezumab and bapineuzumab failed to meet their primary end points. In the first of two phase III, placebo-controlled trials of the anti-Aβ antibody solanezumab (EXPEDITION 1), no improvement was noted for either of the primary outcome measures. However, in a planned subgroup analysis of patients with mild AD, there was an improvement in the 14-item cognitive subscale of the AD Assessment Scale (ADAS-Cog14) and in the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) score. The primary outcome measure for the second phase III trial, EXPEDITION 2, was subsequently revised to changes in ADAS-Cog14 scores in patients with mild AD, although this outcome was also not reached.[14] A finding common to these two trials, and to two trials of bapineuzumab, was that approximately 25% of enrolled patients were amyloid negative and therefore unlikely to have AD.[14] A further phase III trial of solanezumab, EXPEDITION 3 (NCT01900665), will employ an enrichment strategy by enrolling only patients who show evidence of amyloid pathology based on the results of florebetapir positron emission tomography (PET) imaging (reflecting brain Aβ content) or a cerebrospinal fluid (CSF) Aβ1-42 assay.[14,26] Combining early intervention with the use of biomarkers to improve the accuracy of AD diagnosis may greatly increase the potential to demonstrate clinical efficacy.[14,20]

Several completed or ongoing clinical trials evaluating other treatments for AD have included imaging and/or biochemical markers, either within the inclusion criteria or as outcome measures. The results of these studies will be useful for validating each type of biomarker both as potential CDx and for predicting and monitoring disease progression.

According to New Research Criteria for the Diagnosis of Alzheimer's Disease from the International Working Group, in addition to the presence of a core clinical phenotypic criterion, recognition of AD *in vivo* requires the presence of biomarker evidence consistent with and supportive of AD.[27] This evidence may be based on topographical techniques, such as PET neuroimaging, or on CSF analysis of Aβ or tau protein.[27]

Along with amyloid PET imaging tests, CSF biomarkers are among the lead candidate biomarkers for use as CDx in AD. CSF markers include Aβ1–42, which inversely reflects the amyloid plaque load; total tau (T-tau), which directly reflects the intensity of neuronal damage; and phosphorylated tau (P-tau), which reflects the formation of neurofibrillary tangles in the brain.[20] CSF levels of Aβ1–42 and tau appear to correlate closely with

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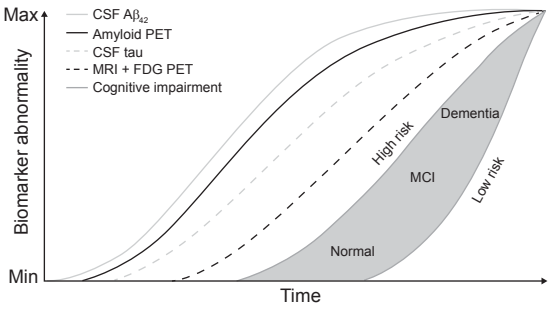

Figure 1. Hypothetical model for biomarkers during the development of Alzheimer's disease.[20,30] Biomarkers for cortical Aβ deposition include CSF Aβ1–42 and amyloid PET imaging. Neurodegeneration is measured by FDG-PET and structural MRI, which are drawn concordantly (black dashed line). Cognitive impairment is illustrated as a zone (filled area) with low-risk and high-risk borders. By definition, all curves converge at the top right-hand corner of the plot, the point of maximum abnormality. **Aβ**, amyloid beta; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography. Reproduced from Ref. 30 with permission from Elsevier.

postmortem AD pathology and provide a robust method for predicting progression from MCI to AD.[28,29] Decreased CSF Aβ1–42 correlates with Aβ aggregation in the brain, reflects plaque pathology, and is altered from a very early stage of AD, before the onset of cognitive symptoms (Fig. 1).[20,27,30] Increased tau in the brain and CSF is also thought to begin during the preclinical asymptomatic phase of AD. However, further studies are warranted to verify the temporal progression of CSF biomarkers.[20] Using combinations of fluid biomarkers, including ratios of biomarker values, may provide greater confidence in the accuracy of differentiating AD versus controls or other forms of dementia and for predicting the rate of progression to AD dementia.[27,28]

Given their high specificity for AD, CSF and/or imaging biomarkers are being evaluated specifically as potential CDx in several ongoing clinical trials. These include a phase III trial of gantenerumab in patients with prodromal AD (NCT01224106), a phase III trial of MK-8931 in patients with prodromal AD (NCT01953601), and a phase III trial of solanezumab in patients with mild AD (EXPEDITION 3; NCT01900665). Biomarker-based CDx will allow identification of the most appropriate patients for specific treatments, and may also allow for monitoring of disease progression/therapeutic response.[20]

Before CSF tests for Aβ and/or tau can be widely accepted as CDx, there is a need to develop reliable protocols for data acquisition and handling of samples.[31] CDx technologies currently available or in development include single-analyte ELISA kits (e.g., INNOTEST®, ADx Neurosciences), multiple-analyte multiplex assays (e.g., INNO-BIA AlzBio3, Mesoscale Diagnostics), and genetic assays (e.g., LiPA). However, these assays suffer from a high level of variability, mainly attributed to interlaboratory and lot-to-lot variation, which makes them unfit for routine clinical use.[32] A number of initiatives have been launched to facilitate the standardization of assay development to allow comparison of CSF biomarker results across AD clinical studies.[31] In addition, Roche is currently developing AD immunoassay tests based on the Elecsys® platform.

Asthma

Asthma, and severe asthma in particular, is a highly heterogeneous, complex disorder in which patients have differing disease characteristics and variable responses to therapy.[33] Historically, asthma has been treated empirically using a stepwise approach according to clinical severity and response to treatment, rather than taking consideration of the underlying biology into account. Inhaled corticosteroids (ICS) are the mainstay of asthma controller medication, as they have proven efficacy in controlling inflammation, improving lung function, decreasing airway hyperresponsiveness, and reducing the frequency of exacerbations.[33,34] However, ICS do not cure asthma and not all patients respond to these treatments; in addition, long-term use of ICS is associated with a range of local and systemic adverse events.[34] Although remission can occur from childhood to young adulthood in a considerable number of patients (reported remission rates range from 16% to 60%), asthma remains a serious health problem affecting all ages.[34,35] Asthma is estimated to affect up to 300 million people worldwide, and joint guidelines from the European Respiratory Society and the American Thoracic Society suggest around 5–10% of the total asthma population has severe asthma, or "asthma which requires treatment with high dose ICS plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy."[34,36]

Rather than being considered as a single disease, asthma may be regarded as a collection of phenotypes that can be classified according to clinical or physiological parameters, responses to environmental triggers, or pathophysiological characteristics.[37] Clinical or physiological phenotypes may be defined by disease severity, response to treatment, age at onset, or susceptibility to exacerbations or to the presence of chronic airflow restriction. Inflammatory phenotypes are characterized by the patterns of inflammation, particularly on the presence or absence of eosinophils or neutrophils.[37] Each phenotype has distinct features and may therefore respond differently to ICS.[33,37]

The heterogeneity of asthma means that not all patients respond in the same way to available treatments.[3,33] Although treatment with ICS is effective in most patients diagnosed with asthma, a proportion of patients (5–10%) are refractory to standard treatment and remain symptomatic when treated with high doses of ICS, even when combined with oral corticosteroids.[33] Therefore, in addition to helping with diagnosis and monitoring of disease progression, differentiating asthma phenotypes may be useful for guiding treatment decisions and predicting treatment responses, thereby increasing the likelihood of developing successful new therapies and ensuring safe and appropriate utilization of existing therapies.[3,33] As a result, minimally invasive diagnostic biomarkers are becoming increasingly important in the management of asthma, and a number of putative biomarkers are being investigated.[33]

Asthma may be classified as atopic (extrinsic), where atopy refers to a predisposition toward developing allergic reactions.[34] Antigen-specific IgE antibodies are central to the etiology of atopic asthma, although measurement of specific IgE is no more reliable than skin-prick tests for diagnosing allergic asthma phenotypes.[34] Despite this limitation, serum IgE measures are used for identifying patients who are eligible for anti-IgE treatment with omalizumab (Xolair) and to determine correct dosing. Therefore, there are already some recommendations in place regarding the use of asthma biomarkers for clinical decision making.[34] However, it should be noted that serum IgE levels do not predict clinical response to omalizumab treatment.[38]

Type 2 inflammation plays a key role in the inflammatory process and contributes to many of the characteristic features of asthma, including mucus secretion, IgE synthesis, pulmonary fibrosis, and airway hyperresponsiveness.[39,40] Type 2 inflammation can be detected using invasive

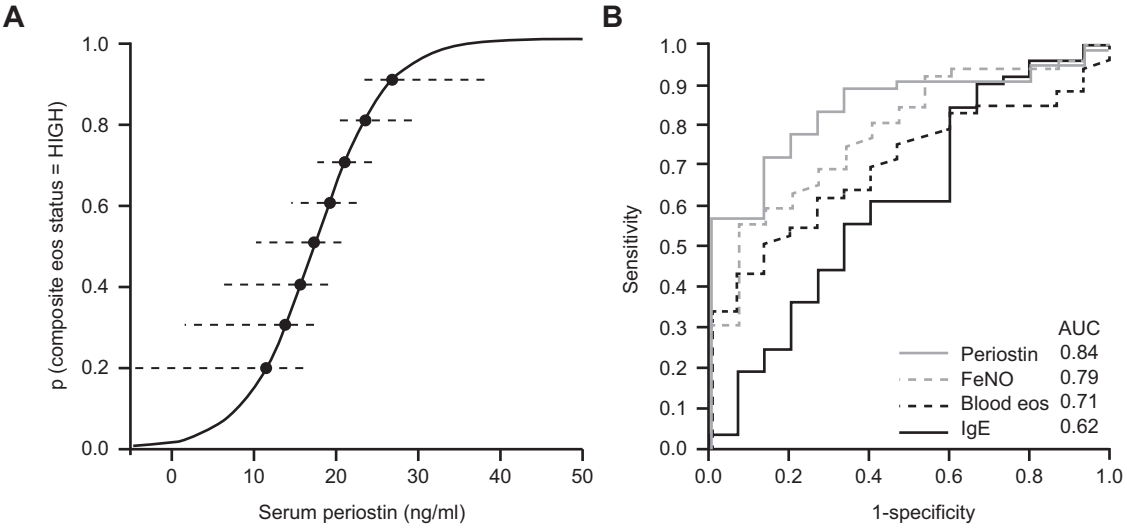

Figure 2. **Periostin sensitivity and specificity versus other biomarkers.[43] (A) Probability of composite eosinophil status = "high" as a function of serum periostin. Dashed lines indicate 95% confidence intervals. (B) Receiver-operating characteristic curve analysis of the sensitivity and specificity of serum periostin, FeNO, and serum IgE levels and blood eosinophil numbers. Periostin performed favorably compared with each of the other biomarkers. AUC, area under the curve; eos, eosinophils; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E. Reproduced from Ref. 43 with permission from Elsevier.**

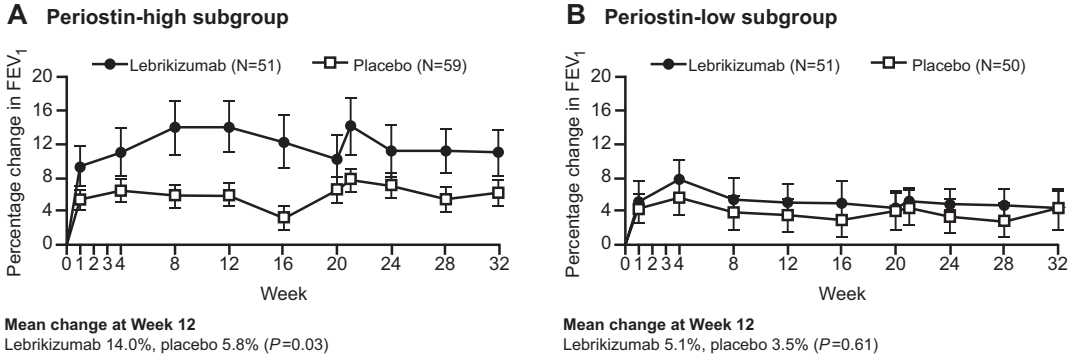

Figure 3. Efficacy of lebrikizumab in periostin-high and periostin-low patients with asthma.[44] (A) Lebrikizumab significantly improved FEV_1 in the periostin-high group versus placebo ($P = 0.03$). (B) There was no significant improvement in FEV_1 in the periostin-low subgroup versus placebo ($P = 0.61$). FEV_1, forced expiratory volume in 1 s. Reproduced from Ref. 44 with permission from Massachusetts Medical Society.

methods, such as tissue biopsy, or noninvasive methods, such as induced sputum analysis and fractional exhaled nitric oxide (FeNO).[41] Sputum eosinophil–guided treatment is associated with a reduced rate of exacerbations; however, inducing sputum is somewhat uncomfortable for the patient and not suitable for children aged under 8 years, and the benefits of sputum-guided treatment have mainly been observed in patients managed in secondary care.[3,34] FeNO provides another measure of eosinophilic airway inflammation and is closely correlated with sputum eosinophilia. However, FeNO levels are not necessarily specific for asthma and can be affected by other factors, such as diet or concurrent viral infections.[33] Furthermore, there is discordance among studies regarding the potential benefit of using FeNO-guided treatment versus treatment guided by standard evaluations.[34,41] Currently, neither sputum- nor FeNO-guided treatment is recommended in guidelines from either the National Heart Lung and Blood Institute or the Global Initiative for Asthma for use in the general asthma population.[34,42]

Multiple mediators contribute to Type 2 inflammation, including inflammatory cytokines such as interleukin (IL)-4, IL-5, and IL-13.[16] Of these, IL-13 plays a central role in the Type 2 immune response and is therefore an attractive therapeutic target for new asthma treatments.[39,40] Although some groups have successfully measured serum or sputum levels of IL-13 and detected an association with asthma severity, rapid disappearance from the site of inflammation impedes consistent detection of IL-13 in serum.[39] There is, therefore, a need for a surrogate systemic marker of IL-13 levels to identify which patients are most likely to benefit from IL-13–targeted therapy.[16]

Periostin is a matricellular protein that is upregulated by IL-4 and IL-13 stimulation in patients with Type 2–driven asthma and has been reported to be the single best predictor of eosinophilic airway inflammation in patients with severe asthma (Fig. 2).[39,41,43] Serum periostin is currently being evaluated for its utility as a CDx to identify patients with Type 2–driven asthma who are most likely to benefit from treatment with the anti-IL-13 therapy lebrikizumab (currently in clinical development).[44] Encouragingly, the results of two completed phase II clinical studies support the theory that steroid-refractory patients with high levels of serum periostin derive greater benefits from lebrikizumab than periostin-low patients. In a proof-of-concept phase II study (MILLY), for example, lebrikizumab treatment significantly improved the forced expiratory volume in 1 s (FEV_1; a measure of lung function) in the periostin-high subgroup versus placebo (Fig. 3; $P = 0.03$).[44] In a subsequent study with exacerbations as the primary end point, lebrikizumab treatment decreased the rate of exacerbations by 60% in periostin-high patients.[45]

Periostin meets the criteria for an ideal biomarker in several respects: (1) it plays a key role in asthma pathology, mediating subepithelial fibrosis, mucus production, and eosinophil recruitment, rather than being secondary to the disease;[40,46,47] and (2) serum levels of periostin are measurably higher in patients with Type 2–high asthma versus Type 2–low asthma.[48] In addition, the Elecsys

Periostin immunoassay currently in development as a CDx test for lebrikizumab is an automated electrochemiluminescence immunoassay that takes 18 min to perform. This assay has shown promising results, demonstrating a high level of precision, repeatability, and reproducibility in clinical studies.[49] Numerous other commercial ELISA kits are available for detecting periostin, marketed by several companies under various names; however, these tests are, so far, "For Research Use Only" and not approved for clinical diagnosis. To date, the Elecsys Periostin immunoassay is the only assay being developed for clinical use in asthma.[49,50]

Finally, in addition to its role as a predictive biomarker, a number of studies have investigated the prognostic value of periostin in asthma. For example, in the EXTRA omalizumab study, the exacerbation rate over 48 weeks in the placebo arm was 0.93 in patients with high serum periostin levels compared to 0.72 in the periostin-low subgroup,[50] although this finding was not replicated over 24 weeks in the placebo group of the intention-to-treat population in the MILLY lebrikizumab study.[44] In a separate study of 224 asthmatic patients receiving ICS, serum periostin was associated with an accelerated decline in lung function, assessed as by FEV_1; in addition, polymorphisms in *POSTN* were related to a decline in FEV_1 of $\geq$ 30 mL per year.[51] There is therefore some evidence to suggest that periostin can be used as a prognostic biomarker to predict the risk of exacerbations and/or functional decline in asthma.

Conclusions

The advent of PHC requires reliable and robust biomarker-based CDx tests that are fit for routine use in laboratories serving the clinical community. These tests will allow physicians to (1) confirm disease diagnosis; (2) understand different disease phenotypes and their clinical relevance, including their effects on the rate of disease progression; (3) predict the likely response of a patient to a specific treatment in terms of safety, thereby minimizing the risk of ADRs; (4) select and predict clinical responses to treatments based on underlying disease pathophysiology, and therefore potentially reduce the number of patients who receive ineffective treatments; and (5) quickly and definitively monitor responses to treatments at a biological level.[2,3]

Although oncology has been the main focus of CDx research to date, many other therapeutic areas with complex disease pathophysiology are likely to benefit significantly from the application of PHC. Central nervous system and infectious and inflammatory diseases are likely future targets, for example, with clinical biochemistry laboratories having an increasingly important role in supporting treatment decisions.[3,18,20] Each disease area may require a tailored diagnostic approach. For example, novel immunoassay diagnostic tests have the potential to allow for an earlier diagnosis of AD at a time when therapies have a better chance of a making a significant impact on the course of the disease, whereas, in asthma, CDx will provide benefit in stratifying patients and selecting treatment according to the phenotypic profile.[3,20]

Finally, the utility of biomarker-based CDx in indications outside of oncology will rely on the development of assays that provide accurate measurements, with low levels of variability across studies and laboratories.[3,31,32]

Acknowledgments

All authors contributed equally to this manuscript. Support for third-party writing assistance for this manuscript, furnished by Fiona Scott of MediTech Media, U.K., was provided by Roche Diagnostics International Ltd.

Conflicts of interest

Richard Batrla and Bruce Jordan are employees of Roche Diagnostics International Ltd.

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