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Value-Based Assessment of Pharmacodiagnostic Testing from Early Stage Development to Real-World Use

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ABSTRACT

Disease etiology may be regarded as a consequence of both genotypic and biochemical phenomena, which impact individual patients in different ways. Disease prognosis, beneficial treatment response, and susceptibility to adverse drug effects are often intimately tied to individual biology. Clinical and genetic biomarkers applied individually or in concert are increasingly used to stratify patient populations in terms of prognosis, therapeutic benefit, or safety. As a result, clinical trialists are challenged to design studies that reflect these determinants of outcome, to optimize the patient's eventual clinical course both in the trial and in actual practice. These designs are informed both by preclinical studies and by real-world research that can establish proof of concept for a novel biomarker and provide a basic understanding of the relationship between biomarker and clinical outcome. As clinical and real-world studies unfold, a deeper understanding of the nature of the biomarker and its potential uses in

drug development is gained. Specifically, one can eventually define the biomarker as prognostic (i.e., predicts disease progression), predictive (predicts treatment response or adverse outcome(s)), or exhibiting both prognostic and predictive properties. One must further validate the performance of these emerging biomarkers, again in both the trial and real-world environments. The eventual adoption of the biomarker as a useful pharmacodiagnostic test is premised upon this early translational research. In this article, the development and validation of predictive and prognostic biomarkers is discussed by using selected examples that highlight factors contributing to the valuation of biomarkers and their application to personalized medicine in the real world.

Keywords: biomarkers, drug industry, economics, personalized medicine, pharmacodiagnosics.

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Introduction

The core belief that underscores the concept of personalized medicine (PM) (i.e., the right therapy in the right patient at the right time) is that PM will both expedite drug development and lead to greater efficiencies in health care. Furthermore, as economic pressures emerge to constrain the health care system, the dual promise that PM might favorably address these challenges becomes even more important.

The processes inherent to the conduct of PM research are complex, and require considerable investigation. Experience has shown, for example, that genetic markers are neither perfect predictors of prognosis (e.g. APOe4 in Alzheimer's disease [AD]) nor response (e.g. CYP2 with clopidogrel) [1,2]. Furthermore, biomarker qualification requires the concerted effort of the diagnostic developer, regulatory bodies, and the therapeutic sponsor. These parties inherently have different priorities. For example, the diagnostic test developer may simply wish to produce a saleable product (i.e., a test kit), and may do so in the absence of regulatory endorsement. The regulator, while concerned about reliability and reproducibility, may offer no clear guidance as to the acceptable coefficient of variability of the diagnostic assay, nor its prognostic accuracy, other than setting a

goal of "trial enrichment" [3,4]. The drug developer while looking for ways to optimize benefit/risk may be reluctant to wed its therapy to a particular diagnostic, given that the life cycle of the former is likely to be much greater than that of the latter. Appropriate end-point definition has proven to be an even greater challenge.

In spite of all these challenges, the feasibility of a PM paradigm has been demonstrated for a variety of therapies in a number of disease states. Genomic research, coupled with advancements in large-scale database informatics technology, does permit the development and validation of biomarker algorithms that can reliably predict disease progression and/or treatment response. Biomarkers can also be developed for products that have long been marketed to optimize the risk/benefit profile of the therapeutic.

In this article, three examples of prognostic and/or predictive biomarker validation either derived in concert with drug development or long after market authorization are highlighted. These examples are drawn from three disease areas: neuroscience (AD), virology (hepatitis C), and cardiovascular disease (stroke prevention). How these research endeavors support a PM strategy that highlights the value of both the diagnostic and the therapy, thus contributing to the PM vision of optimal patient care at an optimal cost, is also described.

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article. The authors are employees of Bristol Myers Squibb.

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Prognostic Biomarker Development: AD Example

Perhaps no area of clinical research has benefited more from the development of prognostic algorithms than AD. Despite recent discouraging results from several clinical trials in both mild/moderate and predementia AD [5–7], the ability to diagnose the disease in its early stages and reliably predict progression has been greatly enhanced by such research. Defining the window of opportunity for early intervention can catalyze lifestyle changes or intervention with investigational disease-modifying therapies (DMTs) in the hopes of changing the course of this devastating disease, bringing the science closer to true patient benefit [8].

Improved diagnostic testing is a consequence of concerted research in a variety of areas that include discovery (assay development and validation), external database research (e.g., AD Neuroimaging Initiative), and the clinical trial experience with several candidate therapies. For example, assays that quantify the levels of certain proteins that are regarded as precursors to amyloid deposition in the brain have been incorporated into observational longitudinal databases [9]. These data are then used to refine the assays themselves and to develop algorithms incorporating assay test results and other clinical information to define patients according to progression risk [10]. Several studies have shown that certain cerebrospinal fluid markers, associated with the pathology of and eventual development of AD dementia, can be used to help assess the risk of progression among patients accompanied by early changes in cognition. Of these, the established cerebrospinal fluid biomarkers of AD (amyloid beta [$A\beta_{40-42}$], tau, and tau phosphorylated at threonine 181 [p-tau]) [11–13] have demonstrated good sensitivity and specificity for predicting the progression to AD dementia in patients with mild cognitive impairment [14–16]. Total-Tau protein has also demonstrated properties of a prognostic biomarker. The current state of the sciences permits the prediction that patients who present with mild cognitive impairment and who exhibit abnormal amyloid pathology based on validated cut points for the cerebrospinal fluid markers are approximately 40% more likely to progress to AD within 2 or 3 years. Additional markers of Alzheimer's pathology, for example, positron emission tomography scans and volumetric magnetic resonance imaging, have also demonstrated acceptable prognostic accuracy in both clinical trials and observational longitudinal studies [17]. A recent important study by Derby et al. [18] demonstrated the superior prognostic accuracy of the Free and Cued Selective Reminding Test over the Wechsler Memory Scale for prediction of incident AD dementia among individuals from a community-based cohort. The Free and Cued Selective Reminding Test is thus better positioned to discern imminent risk for AD among patients experiencing memory complaints, leading not only to enriched clinical trial enrollment but also highlighting those patients who might benefit from future approved therapies.

The implications of such research are profound for two key reasons: First, within the specialty setting, it is now feasible to identify patients with predementia who are highly likely to progress to AD within a few years. Patients so identified could

be given the opportunity to enroll in well-designed clinical trials for therapies that may delay disease progression. Second, in clinical practice, patients with mild cognitive impairment must be guided to make informed decisions regarding further testing and possibly to apply nonpharmacologic lifestyle changes. Until effective DMTs are approved, the need to confirm a prognosis is complex and indeed controversial, beyond a willingness to enroll in a clinical trial or adapt one's lifestyle. There are also significant cost implications to testing and no clear guidance as to which entities must bear the burden of payment.

With regard to costs, pharmacoeconomics models can aid in understanding whether or not a treatment and the accompanying tests are cost-effective under different scenarios. For example, the use of prognostic markers may prove cost-effective if they lead to an enriched patient population in terms of risk and when effective treatments prevent or reduce the rate of cost-intensive events in the long term. A hypothetical model developed by Budd et al. assessed the economic implications of early AD screening with prognostic biomarkers and use of potential DMTs. The authors concluded that earlier treatment yielded modest gains in total life-years; the distribution, however, was skewed favorably toward milder disease as shown in Table 1 and Figure 1. Specifically, if a therapy were to deliver a 25% reduction in the annual risk of progression, treatment was projected to increase life-years in predementia to mild AD on average from 3.2 to 4.2, while life-years spent in moderate to severe AD decreased from 2.6 to 2.2. Accurate screening and earlier treatment with DMTs were projected to have important patient benefits in terms of prolonging time in milder disease, reducing time spent with more severe disease, increasing time in the community, and reducing time in long-term care [19].

Demonstrating Value of Predictive/Prognostic Biomarkers: Hepatitis C Example

AD provides an important example of the contribution of database research to prognostic biomarker development and validation. However, the establishment of these markers as predictors of therapeutic response must await the development of effective DMTs. A more relevant illustration of biomarker application to both predict prognosis and treatment response is seen in hepatitis C. Viral genotype information, applied in concert with additional risk factors such as high hepatitis C virus RNA load, advanced liver fibrosis stage, and African American ancestry, are shown to be associated with poor prognosis, leading to cirrhosis or hepatocellular carcinoma. These same viral genotype and subtype markers are also predictive of response to standard antiviral therapies, expressed as sustained virologic response (SVR). Further extensive viral genotype subtyping has led to a refinement in the application of therapeutic regimens for patients so characterized. Newer, emergent treatments for hepatitis C virus are anticipated to further tailor both the therapeutic intervention and treatment duration when applied jointly with more elaborate viral genotyping.

Table 1 – Average life-years in disease states by DMT efficacies (all data in years).

DMT relative advantage	DMT during predementia		DMT during moderate AD		SOC during moderate AD	
	Mild	Severe	Mild	Severe	Mild	Severe
10%	3.46	2.54	3.35	2.60	3.19	2.56
20%	3.78	2.40	3.54	2.53	3.19	2.56
25%	3.96	2.32	3.65	2.49	3.19	2.56

AD, Alzheimer's disease; DMT, disease-modifying therapy; SOC, standard of care.

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