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## Personalized Medicine and the Role of Health Economics and Outcomes Research: Issues, Applications, Emerging Trends, and Future Research

John C. O'Donnell, PhD, MA\*

Bristol-Myers Squibb Co., Princeton, NJ, USA

### ABSTRACT

The decade since the completion of the sequencing of the human genome has witnessed significant advances in the incorporation of genomic information in diagnostic, treatment, and reimbursement practices. Indeed, as case in point, there are now several dozen commercially available genomic tests routinely applied across a wide range of disease states in predictive or prognostic applications. Moreover, many involved in the advancement of personalized medicine would view emerging approaches to stratify patients in meaningful ways beyond genomic information as a signal of the progress made. Yet despite these advances, there remains a general sense of dissatisfaction about the progress of personalized medicine in terms of its contribution to the drug development process, to the efficiency and effectiveness of health care delivery, and ultimately to the provision of the right treatment to the right patient at the right time. Academicians, payers, and manufacturers alike are struggling not only with how to embed the new insights that personalized medicine promises but also with the fundamental issues of application in early drug development, implications for health technology assessment, new demands on traditional health economic and outcomes research methods, and implications for reimbursement and access. In fact, seemingly prosaic issues such as the definition and composition of the term “personalized medicine” are still unresolved. Regardless of these issues, practitioners are increasingly compelled to find practical

solutions to the challenges and opportunities presented by the evolving face of personalized medicine today. Accordingly, the articles comprising this Special Issue offer applied perspectives geared toward professionals and policymakers in the field grappling with developing, assessing, implementing, and reimbursing personalized medicine approaches. Starting with a framework with which to characterize personalized medicine, this Special Issue proceeds to illuminate issues related to the intersection of personalized medicine and comparative effectiveness; use of personalized medicine approaches in drug development; methodological challenges; and payer approaches to evaluation and reimbursement of pharmacodiagnosics in the United States and Europe. It concludes with a look ahead, underscoring current controversies yet to be resolved along with their implications for further research and policy. It is hoped that these articles will help inform the daily challenges faced by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) community as it collectively addresses what promises to be a new era in drug development and health care delivery.

**Keywords:** health economics and outcomes research, personalized medicine, stratified medicine.

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In the decade since the sequencing of the human genome, personalized medicine has been the focus of a growing body of bench, health services, and health policy research. Indeed, in 2003, the year the Human Genome Project completed its sequencing, there were approximately 250 peer-reviewed articles published under the topic of “personalized medicine.” By 2012, this had grown to nearly 2500 articles annually, 10 times the publication rate of the previous decade [1]. As the implications of truly “personalized” medicine came to be appreciated by policymakers and practitioners, talk ensued of a “brave new world” of personalized care. Typically, the leading advocacy organization refers to a new “age of personalized medicine,” the application of which can “address the most critical challenges of our day” [2].

Despite this real progress, matching the sometimes polemic nature of the discourse around personalized medicine to the

actual changes witnessed in health care delivery can leave the average practitioner confused. Compounding this confusion is the lack of consensus around definitions and nomenclature. Some argue that personalized medicine is defined strictly in the context of a genomic test, with a heavy focus on companion diagnostics. For example, the Personalized Medicine Special Interest Group of the ISPOR defines personalized medicine as the use of genetic or other biomarker information to improve the safety, effectiveness, and health outcomes of patients via more efficiently targeted risk stratification, prevention, and tailored medication and treatment-management approaches [3]. Others underscore aspects of “stratified medicine” that emphasize subpopulations defined in many disparate ways, not simply by genomic information, and whose orientation is somewhat less “personal” but more “population-based” [4].

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\* Address correspondence to: John C. O'Donnell, Bristol-Myers Squibb Co., P.O. Box 4000, Rt. 206 and Province Line Road, Mailstop J23-04, Princeton, NJ 08540, USA.

E-mail: [john.odonnell@bms.com](mailto:john.odonnell@bms.com).

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These doctrinal issues surrounding definition and nomenclature are perhaps typical when a new body of science is in the formative “norming”—indeed storming—stages. Such second-order discourse, however, can serve to obfuscate the current pressing issues at hand and impede the ability of practitioners in outcomes research, reimbursement, and delivery to get on with the tasks at hand, including incorporating early genomic information in the drug development process; evolving health economic and outcomes research methodologies to match the new opportunities and challenges of personalized medicine; grappling with coverage and reimbursement decisions; and addressing the “lag” between current regulatory practices and health systems needs in actual practice.

It is this gap that the current ISPOR Special Issue on Personalized Medicine seeks to fill. In 2011, the Institutional Council of ISPOR, composed of industry, payer, and academic leaders from across the health care continuum, prioritized personalized medicine as a key growth opportunity for ISPOR membership and beyond. The orientation taken was to use the expertise of the Council, in a peer reviewed context, to elicit actual and emerging practices and novel use cases in the area of personal/stratified medicine to help foster greater understanding among practitioners of issues, best practices, barriers, and enablers to help advance a critical area of health care delivery that at times appears mired in doctrinal and operational difficulties.

Accordingly, the first article in the Special Issue seeks to bring together various threads in definition and nomenclature to advance a basic framework with which to support the subsequent discussion, and which thereby may also be of service to the broader practitioner community seeking some level of consensus upon which to engage in increment health systems adaptation. Redekop and Mladsi proffer a framework starting from a series of applied clinical questions that researchers, practitioners, and policymakers confront on a daily basis relating to susceptibility, diagnosis, prognosis, treatment, and surveillance. From there, the authors show the linkages between these classic clinical questions and how various personalized medicine technologies influence decision making and ultimately patient care and outcome.

The Special Issue also addresses emerging methodological issues focused in three broad (sometimes overlapping) areas: applications in comparative effectiveness research (CER), drug development, and economic evaluation. With respect to CER, it becomes clear to even the casual observer that variation in patient populations impact outcome and thus can have profound implications for evidence generation, its utilization, and the overlay of economic considerations. In the end, Willke and colleagues see personalized medicine as somewhat synonymous with the heterogeneity of treatment effect CER seeks to understand, if only to control for while pursuing key health services research questions.

Personalized medicine has presented a brand new set of challenges and opportunities in the drug development process, and manufacturers have faced a classic “institutional lag” in which standard operating procedures and organizational boundaries are having to give way to new processes and procedures through which to identify, understand, and embed personalized medicine insights. New entities such as centers of excellence in personalized medicine have evolved to help companies come to grips with the emerging imperatives, while advancing even broader but interrelated initiatives such as translational medicine. In the midst of this change, health economics and outcomes research professionals find themselves in the sometimes unenviable position of assuming new accountabilities, for example, in the use of observational research methods to understand the associations between stratification of patient populations, risk, prognosis, and outcome. As Burns and colleagues highlight, in this context exciting new perspectives are being advanced, or tried and true methods are being redeployed, to assist in understanding the predictive and prognostic properties of biomarkers, their accurate measurement, their sensitivity and

specificity, and ultimately their ability to change patient and physician behavior in actual practice.

In a similar fashion, personalized medicine offers the promise, as evinced in emerging economic evaluation studies, to point the way to greater efficiency and effectiveness in health care. A number of leading thinkers in this area, at both the “macro” and “micro” economic policy levels (some of whom have joined this Special Issue), have showcased how personalized medicine can help target appropriate patients, but more important, how this can yield positive net benefit to manufacturers, payers, and governments as a whole. As Annemans, Redekop, and Payne note herein, these new methods, or rather, redeployed methods of economic evaluation, will help the ecosystem move beyond stale arguments related to the dangers of “niching” products and restricting patient choice and access, to explore win-win approaches that appropriately value new technologies, both at the time of launch and possibly over time.

In the US payer environment, arguably the most active current reimbursement space for personalized medicine, emerging issues and use cases abound and in this Special Issue Frueh felt it important to illuminate and contrast the way in which US payers have opportunistically at times embraced personalized medicine approaches, against current regulatory barriers and practice inertia. The case of warfarin “metabolizers” in the context of the next-generation antiplatelets is particularly illuminating because it juxtaposes the limits of basic science, compelling payer interest in controlling costs, and ultimately the challenging dynamic of influencing practice patterns on the basis of an imperfect, and at best, emerging evidence base. Similarly, in Europe, the continuing austerity has brought to the fore serious challenges, and indeed dissent, about who should bear the costs of personalized medicine and in what manner. The advanced health technology assessment (HTA) “regimes” in Europe have been highly active in assessing the merits of personalized medicine technologies and approaches, and have perhaps inadvertently brought to the fore controversy that unresolved could serve to stifle further evolution in the area and impede creative approaches that could yield positive value to the broader ecosystem. Here Payne and Annemans underscore the need to assess societal, patient, and providers perspectives when evaluating companion diagnostics, along with the limits to HTA decision making imposed by weak clinical and economic evidence bases. Perspectives vary as well, they observe, when considering national HTA decisions versus subnational, sometimes mediated by “supplier” versus “consumer” utility (e.g., academic community vs. patients). They conclude with several key recommendations for Europe to foster a more receptive climate for personalized medicine, recognizing that its positive benefits are conferred to patient, provider, and payer alike.

With these key issues helping to characterize the current “state of the state,” we conclude this Special Issue with a look ahead at emerging trends and the need for future research. A broad set of opportunities is addressed, with emphasis on evidentiary needs ex ante and ex post stratification, regulatory gaps, and evidence of clinical utility in actual practice. Notably, Towse and Garrison argue that raising the threshold for evidence will mean less pharmacodiagnostic research and development unless reimbursement and intellectual property demands are kept realistic.

Thomas Kuhn in his classic work *The Structure of Scientific Revolutions* [5] cites not dramatic advances, like the sequencing of the human genome, as the key drivers of scientific progress, but rather the incremental learnings that illuminate inadequacies of current scientific dogma, which, in turn, prepare the ground for revolutionary change. As this Special Issue in some measure conveys, we believe that we find ourselves within that incremental process that has the potential to usher in a scientific revolution, and with appropriate foresight and integration, health

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