

## REVIEW ARTICLE

# Conceptual and Analytical Considerations toward the Use of Patient-Reported Outcomes in Personalized Medicine

Demissie Alemayehu, PhD; Joseph C. Cappelleri, PhD, MPH

**Background:** Patient-reported outcomes (PROs) can play an important role in personalized medicine. PROs can be viewed as an important fundamental tool to measure the extent of disease and the effect of treatment at the individual level, because they reflect the self-reported health state of the patient directly. However, their effective integration in personalized medicine requires addressing certain conceptual and methodological challenges, including instrument development and analytical issues.

**Objectives:** To evaluate methodological issues, such as multiple comparisons, missing data, and modeling approaches, associated with the analysis of data related to PRO and personalized medicine to further our understanding on the role of PRO data in personalized medicine.

**Discussion:** There is a growing recognition of the role of PROs in medical research, but their potential use in customizing healthcare is not widely appreciated. Emerging insights into the genetic basis of PROs could potentially lead to new pathways that may improve patient care. Knowledge of the biologic pathways through which the various genetic predispositions propel people toward negative or away from positive health experiences may ultimately transform healthcare. Understanding and addressing the conceptual and methodological issues in PROs and personalized medicine are expected to enhance the emerging area of personalized medicine and to improve patient care. This article addresses relevant concerns that need to be considered for effective integration of PROs in personalized medicine, with particular reference to conceptual and analytical issues that routinely arise with personalized medicine and PRO data. Some of these issues, including multiplicity problems, handling of missing values and modeling approaches, are common to both areas. It is hoped that this article will help to stimulate further research to advance our understanding of the role of PRO data in personalized medicine.

**Conclusion:** A robust conceptual framework to incorporate PROs into personalized medicine can provide fertile opportunity to bring these two areas even closer and to enhance the way a specific treatment is attuned and delivered to address patient care and patient needs.

---

Stakeholder Perspective,  
page 316

*Am Health Drug Benefits.*  
2012;5(5):310-317  
www.AHDBonline.com

Disclosures are at end of text

---

Personalized medicine aims to assist healthcare providers to individualize a patient treatment based on the patient's attributes, which may include biomarkers, genetics, demographic characteristics, and other covariates. Much progress has been made in recent years in the translational research areas of genomics, proteomics, and metabolomics, and several biomarkers have been identified for a number of important diseases, including atherosclerosis, cancer, and rheumatoid arthritis. Many of these biomarkers are now being studied in clinical trials to identify subgroups of

patients who best benefit from a given therapy. However, despite the growing importance of patient-reported outcomes (PROs) in medical research, their role in customizing healthcare is not widely recognized. Information solicited directly from patients about their health status or health-related quality of life (QOL), disease burden, or other aspects of their disease or treatment should be an essential component of any treatment paradigm that relies on genetic and other patient-specific information to ensure optimal care delivery for the individual patient.

Broadly defined, a PRO is any report on the status of a patient's clinical condition that comes directly from the patient, without interpretation of the patient's response by a clinician or by anyone else. "Patient-

---

*Dr Alemayehu is Vice President, Specialty Care Biostatistics, Pfizer Inc, New York, NY, and Dr Cappelleri is Senior Director, Specialty Care Biostatistics, Pfizer Inc, Groton, CT.*

reported outcomes” is an umbrella term that includes a variety of subjective outcomes, such as pain, fatigue, depression, aspects of well-being (eg, physical, functional, psychological), treatment satisfaction, health-related QOL, and physical symptoms, such as nausea and vomiting. PROs are often relevant for studying different conditions—such as pain, erectile dysfunction, fatigue, migraine, anxiety, and depression—that cannot be assessed adequately without input from the patient on the impact of the disease or the treatment.

To be useful to patients and to other decision makers (eg, physicians, regulatory agencies, reimbursement authorities) who are stakeholders in medical care, a PRO must undergo a validation process to confirm that it is reliably measuring what it is intended to measure. The focus of this article is on the analysis and reporting of PRO data derived from standardized PRO instruments for use mainly in clinical research, such as in clinical trials and in drug development.

In recent years, there has been growing evidence for the impact of genetics on QOL and on PROs.<sup>1,7</sup> Most notably, Raat and colleagues describe the value of a population-based prospective cohort study from fetal life and beyond in Rotterdam, the Netherlands, as a template that enables candidate gene study and genome-wide association study regarding the QOL of mothers and their young children.<sup>3</sup> Although several articles refer to QOL when the focus is on groups of individuals, be they patients or not,<sup>1,3</sup> overall considerations about QOL in the context of personalized medicine are equally applicable to the more general term “PRO” when referring to any health-related report coming directly from the patient. Rijdsdijk and colleagues found that the overall heritability of psychosocial distress ranged from 20% to 44% in their study.<sup>4</sup> In other studies, evidence of genetic influences has been reported for PROs.<sup>5,6</sup> Although much research is still needed to determine the precise proportion of variability in PRO that is explained by genetic factors, considerable progress has been seen in some areas, such as in oncology, to quantify the association between polymorphisms and PROs.<sup>7</sup>

Personalized medicine involves the customization of healthcare tailored to the individual patient by use of genetic and other information, including PROs such as symptoms, functional status, treatment satisfaction, and health-related QOL. Yet methodological advancements needed for PROs and genetics are lacking. Insights into the genetics of PROs will ultimately allow early identification of patients susceptible to PRO deficits, as well as to target care in advance. Therefore, by unraveling the genetic understandings of PROs (eg, what specific single-nucleotide polymorphisms, on which specific genes, are associated with pain), researchers will have a greater

## KEY POINTS

- “Patient-reported outcomes” (PROs) refers to any report on the status of a patient’s clinical condition that comes directly from the patient, without interpretation by a clinician or by anyone else.
- Personalized medicine aims to individualize a patient treatment based on the patient’s unique attributes.
- By identifying patients who are susceptible to certain poor aspects of patient-reported health status (eg, pain), healthcare stakeholders will be in a better position to target preventive strategies or provide specific interventions.
- PROs must undergo a validation process to be useful to patients and stakeholders in medical care.
- A major step in the incorporation of PROs in personalized medicine is the establishment and use of standardized instruments that have proven reliability and validity.
- The most important challenge in personalized medicine is to establish a statistical framework for data analysis that links outcomes to concepts of interest, and subsequently links those to specific aspects of patient-reported health status.
- Incorporating PROs into personalized medicine can provide information to enhance patient care.

understanding of diagnosis and treatment management for an individual patient—an understanding that has the potential to lead to improved survival, PRO assessments, and health service delivery.

Effective use of PRO data in the context of personalized medicine entails a careful evaluation of conceptual and methodological issues associated with PRO and with personalized medicine. Guidelines and best practices have been developed to strengthen the value of the data from those two fields.<sup>8-12</sup> The issues surrounding PRO data, which are generally used to quantify PROs in a structured way, have been a particular focus of concerted research.<sup>8</sup> Regulatory guidelines and other guidance documents have also been issued to address several central concerns.<sup>9,10</sup>

Emerging insights into the genetic basis of PROs could potentially lead to new pathways to help to improve patient care. Knowledge of the biologic pathways through which the various genetic predispositions propel people toward negative, or away from positive, health experiences may ultimately transform healthcare. By identifying patients who are susceptible to certain poor aspects of patient-reported health status (eg, pain), healthcare stakeholders will be in a better position to target preventive strategies or provide specific interven-

tions, such as pharmacologic treatment, psychological counseling, lifestyle and behavioral changes, or a combination thereof. The risk of not making PROs an integral component in the genetic profile may have, by not imposing an effective targeted early intervention, a profound and untoward impact wherein individuals experience substantially diminished well-being. Under such a circumstance, healthcare providers would miss the opportunity to effectively screen patients to discover who would likely experience PRO deficits associated with a disease or its treatment or both. Consequently, treatment decision-making and patient care would be compromised.

Furthermore, genetic research shares some of the often-encountered issues that arise in PRO studies, including multiplicity of end points, missing data, reliability, and validity.<sup>11</sup> For genetic research, the need for methodological standards as a resource for researchers has been the focus of a recent study.<sup>12</sup>

The role of QOL in personalized medicine has also garnered increasing attention, in part as a result of the activities of organizations such as the GENEQOL Consortium, which aims to promote research on biologic mechanisms, potential genes, and genetic variants that may be involved in QOL.<sup>13</sup> Advances in that area include summaries on the genetic background of common symptoms and overall well-being.<sup>13</sup>

In this article we consider the role of PRO data in personalized medicine, with a particular reference to analytical issues that routinely arise with personalized medicine and PRO data, including multiplicity problems, missing values, and statistical models. Given the abundance of material relating to personalized medicine, the focus of this article is on the relationship between PRO data analysis and reporting and personalized medicine. Other important aspects of PROs, including data collection and its storage for ease of use in the clinical setting, as well as integration of such data with clinical guidelines of care, are beyond the scope of this article.

## Challenges in Personalized Medicine

### *Clinical Trial Design*

The designs of studies relating to PROs and personalized medicines can affect the analysis of the data and the results of the trials. In both cases, the results may be impacted by biases emanating from flawed designs, particularly designs that do not enable collection of data on pertinent end points or those that do not ensure adequate balance across treatment groups with respect to relevant patient characteristics. In addition, the choice of analytical methods is often determined by the type of study design used to generate data. For example, if PRO or per-

sonalized medicine data are collected over time, the analytical methods to be used would be different from those that collect data only at a specified time point.

Randomized controlled trials (RCTs) are the gold standard for evaluating the comparative risks and benefits of alternative treatment options. However, RCTs are typically designed to address a relatively narrow set of hypotheses and often lack generalizability to real-world settings as a result of strict study protocol criteria about patient selection and follow-up. Accordingly, in the study of personalized medicine and PROs, RCTs may not provide reliable data to characterize the profile of a drug on those excluded subjects. An alternative approach that incorporates both randomization and generalizability is the so-called pragmatic RCTs. Such trials typically aim at reflecting the heterogeneity of patients in the real world, thereby facilitating the collection of pertinent data germane to personalized medicine, as well as to PRO research.

Developments in personalized therapies have been affected by many experimental, modeling, and analytical challenges, including handling multiple end points and missing values. A key step in operationalizing personalized medicine is “stratified medicine,” wherein the goal is to use clinical biomarkers to identify subgroups of patients who are likely to benefit from a given therapy.<sup>14</sup> In conventional clinical trial designs, stratified medicine is routinely executed using alternative covariate-adjusted designs to ensure balance of treatment assignment across various strata defined by patient-level attributes. However, existing approaches fall short of handling the complex covariate structure that typically arises in clinical trials related to personalized medicine.<sup>15</sup>

A related issue is the inability of common trial designs to efficiently detect the interaction between treatment and biomarkers. Because of ethical and cost considerations, the number of subjects recruited for such studies is seldom adequate to incorporate the desired amount of covariate information into the design, thereby lowering the efficiency, or the precision, of the estimated effects of treatments.

The widely publicized methods of adaptive trial designs<sup>16</sup> to reduce cost and enhance designs based on accumulating information are not yet fully developed for use in personalized medicine, which generally involves covariate information.

From an analytical standpoint, among the major issues related to personalized medicine are multiplicity, that is, conducting multiple statistical inferences on potentially several outcomes, and missing data. Perhaps the single most important challenge in personalized medicine is the establishment of a robust statistical framework for multi-dimensional patient-level data analysis. The traditional

approaches are no longer viable to address the cases where the number of study variables is substantially larger than the number of patients or the units of analysis.<sup>17</sup> Furthermore, approaches developed for dealing with missing data in conventional trials need substantial modification to handle the situations that arise in personalized medicine, because the latter involve larger data points than those generated by typical PRO trials.<sup>18</sup>

The usual assumption of linearity that is basic to data analytical approaches for the conventional clinical trials may not be valid to model the complex relationships between genetic and nongenetic patient characteristics. In this regard, advances in the application of network graphs and other machine learning, and data-mining techniques in the analysis of high-dimensional data seem to be promising strategies.<sup>16</sup> These advanced analytical techniques are particularly useful for mitigating the issues associated with subgroup and heterogeneity analyses.<sup>19</sup> Despite the known pitfalls of such analyses, even in conventional randomized clinical trials,<sup>20</sup> there is still a methodological gap in researching a reliable approach, especially for personalized medicine.

## Issues Concerning PRO Data Analysis

### *Instrument Development and Validation*

A major step in the incorporation of PROs into personalized medicine is the establishment and use of standardized instruments with proven reliability and validity. Although there are numerous validated instruments that measure different domains of health from the perspective of the patient, the choice of a PRO instrument is a function of the research question, the disease, and the population under study. A partial list of common PRO instruments can be found, for example, in a book by Fayers and Machin.<sup>21</sup>

The development of a new PRO instrument for a given disease requires the establishment of a robust and theory-based conceptual framework, linking the desired outcome to the concept of interest, and subsequently linking that concept to the specific symptoms or other aspects (such as physical functioning) being measured. The use of focus groups and cognitive interviews with patients can provide the considerable input needed to establish validity and to ensure that the PRO questionnaire covers what patients consider important.

Related to but distinct from conceptual issues, analytical measurement using standard psychometric methods should be applied to test the reliability, validity, and responsiveness of the PRO measure. Among them, exploratory factor analysis and confirmatory factor analysis (as discussed below) should be considered to examine the factor structure regarding which items go with what domains; in addition, item response theory

(also discussed below) should also be considered to further evaluate the performance of individual items and their response categories.

Some of the analytical issues that arise in the context of personalized medicine data also arise in the context of PRO data analysis. These issues include longitudinal analysis, item response theory, and missing data. In addition, PRO data may require specialized approaches that facilitate interpretation of results. Although the analytical topics are not necessarily particular to personalized medicine, they do share common ground with it.

### *Longitudinal Analysis*

From a modeling perspective, longitudinal analysis appears to be well suited for PRO data. For outcomes measured over time, the data may be analyzed using several approaches, with the two most common or useful being random coefficient models (ie, time taken as continuous) and repeated measures models (ie, time taken as categorical). Other approaches, which may also be used for discrete outcomes, include generalized estimating equations and generalized linear mixed-effects models. Details on longitudinal analysis can be found elsewhere.<sup>22</sup>

An analytical framework for individual response using mixed-effects analyses has the ability to distinguish systematic or explained effects, which are true for all persons sharing a common set of covariate values (ie, fixed effects), not only from random error (ie, residual effects) but also from reliable individual differences, which are inferred and unexplained within the statistical model (ie, random effects).

Mixed-effects modeling subsumes average treatment differences and individual differences in a unified statistical analysis. Adding a set of substantive predictors that can explain the attributes of individual initial status on a PRO and therapeutic changes on that PRO could be potent determinants of individual response. Results from mixed-effects models can be portrayed in graphic displays that summarize the spectrum of individual responses and associated prediction intervals, which can convey clinically meaningful information regarding the impact of a treatment on an individual's PRO score.<sup>23</sup>

Subgroups are often undertaken to examine heterogeneity or differences in treatment effect among patients. Perhaps the treatment works better for one subgroup over another. Limitations of subgroup analyses—the conventional means for exploring differences in treatment effect based on patient characteristics—are well documented.<sup>19</sup> Undisciplined searches for patient subgroups can result in “fishing expeditions,” leading to incorrect inferences and conclusions. Too many characteristics exist that can potentially influence treatment effect; myriad subgroup analyses can lead to underpow-



ered results or be vulnerable to false-positive results related to multiple comparisons.<sup>20</sup>

### **Item Response Theory**

Item response theory is a statistical theory consisting of nonlinear logistic models to express the probability of a particular response to a scale item as a function of the quantitative attribute of interest (latent “unobservable” trait or concept, such as depression).<sup>24</sup> The mathematical description for the item response is known as an “item characteristic curve,” which gives the probability of responding to a particular category of an item for an individual with an estimated amount on the attribute. Each item typically has its own level of difficulty (items that are more difficult are harder to endorse) and can have its own level of discrimination (items with more discrimination are more likely to distinguish among persons with varying levels on the attribute).

The applications and relevance of item response theory for PROs has increased considerably over the past several years. For example, item response theory has been the cornerstone of the Patient-Reported Outcomes Measurement Information System (PROMIS), a large initiative of the National Institutes of Health (NIH), which aims to revolutionize the way PROs are selected and used in clinical research and practice.<sup>25</sup>

The broad objectives of the NIH PROMIS network are to develop and test a large bank of items measuring PROs; create a computerized adaptive testing system that allows for efficient, psychometrically robust assessment of PROs in clinical research involving a wide range of chronic diseases; and create a publicly available system that can be added to and modified periodically, and that allows clinical researchers to access a common repository of items and computerized adaptive tests at the individual patient level.

### **Missing Data**

Methods to address missing data for clinical outcomes in clinical trials, including the PRO questionnaire with all items missing, have been published.<sup>26</sup> In the context of PRO analysis, missing data may arise in a variety of ways. For example, data may be missing on a patient for certain visits because of poor compliance. Such data may be missing for an entire domain or for specific items within domains. Although the former is generally true for other clinical end points, the latter is more specifically associated with PRO measures. In all cases, the handling of the missing values is a function of the “missingness” mechanism. When it can be justified that the missing data are random, well-established approaches, such as mixed-effects modeling, can we successfully address the problem. By contrast, if the missingness is nonrandom, then the

data analysis requires caution. Although there are techniques to determine if the missing data are random or nonrandom, no definitive way is available to rule out the latter. Therefore, in case of doubt, sensitivity analysis should be performed to ensure the robustness of the findings under alternate scenarios.<sup>18,22,26</sup>

### **Interpretation**

An inherent and fundamental issue for a PRO is its meaning. Interpretation of PRO scores, although distinct from validity and reliability, is central for a PRO to gain currency and usefulness. Approaches to interpretation of PRO scores are available.<sup>21,27,28</sup> Methods generally fall under two broad strategies—anchored-based approaches and distribution-based approaches—and the variations within them are aimed at enhancing the understanding and meaning of PRO scores.

An anchor is a measure or criterion related to the targeted PRO under examination, and it can be different from, or even part of, the PRO measure under consideration. The chosen anchor should be clearly understood in context and be easier to interpret than the PRO measure of interest, and it should be appreciably correlated with the targeted PRO. An anchor-based approach links the targeted concept of the PRO to the meaningful concept (or criterion) emanating from the anchor, such as patient assessment on the severity of the condition. Four avenues to apply an anchor-based methodology include percentages based on thresholds, criterion group interpretation, content-based interpretation, and clinically important difference.<sup>21,27,28</sup>

Distribution-based approaches exist for individual difference and group difference, and they can give valuable insights into the magnitude of an effect. It is well known that changes for an individual need to be much larger than changes for a group to be statistically significant. Several similar approaches to determine the statistical significance of individual change have been described, including standard error of measurement, standard error of prediction, and reliable change index.<sup>29</sup>

Three useful distribution-based methods for determining the importance of group differences include effect size, responder analysis, and cumulative proportions.<sup>21,28</sup> Distribution methods for group differences allow for a standardization of different scales with various ranges and ways of scoring. A limitation of distribution-based methods in general is that they do not provide information about clinical meaningfulness, because they are strictly statistically based approaches.

### **Toward a Conceptual Framework for PROs in Personalized Medicine**

As discussed by Sprangers and colleagues, the study of

the genetic disposition of PROs requires a conceptual model to establish the relationships among QOL domains, biologic mechanisms, and genetic variants.<sup>1</sup> A model that appears to be appropriate in this setting is the one introduced by Wilson and Cleary, which links biologic factors and patient-reported QOL.<sup>30</sup>

This model has been further enhanced by Spranger and colleagues to include the genetic underpinnings of biologic variables, as well as other individual characteristics.<sup>1</sup> Notably, the model is general enough to allow the study of interactions among patient characteristics and environment and genetic factors. Sprangers and colleagues focus on QOL, because the research and the paradigm center mainly on the individual in general, whether or not that person's response is patient-reported.<sup>1</sup> These researchers reserve the more general term "PRO" in their article for situations applied to any self-report of health coming directly from the patient.<sup>1</sup>

A framework has been proposed to assess risk-based heterogeneity of treatment effects, and this framework is especially promising in personalized medicine and PRO assessment.<sup>31,32</sup> This framework, which acknowledges that "one size does not fit all" in addressing individual differences, has been originally applied to a binary outcome, be it a PRO or not. The framework, however, can be adapted to continuous PRO (and non-PRO) outcomes and consists of the five following recommendations<sup>31,32</sup>:

- Evaluate and report on the distribution of baseline risk in the overall study population and in the separate treatment arms using a risk prediction tool
- Report how relative and absolute changes vary by baseline, using a multivariate prediction tool, in the primary subgroup analyses
- Prespecify additional primary subgroup analyses for single variables and limit these to patient attributes with strong pathophysiologic or empirical justification
- Distinguish secondary (exploratory) subgroup analyses from primary subgroup comparisons
- Report all conducted analyses with statistical testing of heterogeneity of treatment effects using appropriate methods (eg, interaction terms) and avoid over-interpretation.

Multiplicity issues, which have been noted earlier in the context of genomic and subgroup analysis, are also important in the analysis of PRO data. First, multiple end points are an integral component of PRO analysis. In addition, there may be a desire to evaluate treatment effects at different time points and for various subgroups. Therefore, when used in the context of personalized medicine, the problem of missingness is compounded and poses further analytical challenges.

Approaches that adjust for multiplicity exist, depend-

ing on research objectives, end points, decision rules, and other factors.<sup>33</sup> These approaches may include the use of familiar standard statistical techniques (eg, false discovery rates and step down, step up, and other gatekeeping procedures), as well as definitions of composite end points to reduce the number of potential end points to be evaluated. Composite end points, however, require caution and subject matter expertise to ensure that their interpretation, validity, and original intent are preserved.

Of special interest in personalized medicine are the individual differences in treatment responses in longitudinal data.<sup>23,34</sup> These differences describe how patients respond in various ways to the same treatment and qualify the generality of an overall treatment effect. Differences in treatment response are generally the result of personal dispositions (encoded in genes, bodies, or brains) that, along with clinical and demographic characteristics, enable patients to respond in certain ways to particular therapies. In this regard, the approaches discussed earlier in the context of PRO longitudinal data analysis may serve as a framework to incorporate genetic and other patient-level characteristics.

## Conclusions

With the growing interest in personalized medicine, there are compelling reasons to incorporate PROs as an integral part of the research endeavor in personalized medicine. Specifically, insights into the genetics of PROs will ultimately allow early identification of patients susceptible to PRO deficits, as well as the targeting of care in advance. Therefore, by unraveling the genetic understandings of PROs (eg, what specific single-nucleotide polymorphisms, on which specific genes, are associated with pain), researchers will have a greater understanding of diagnosis and treatment management for an individual patient, an understanding that has the potential to lead to improved survival, PRO assessments, and health service delivery. However, to ensure that PROs play an effective complementary role to traditional clinical end points in personalized medicine, it is essential to understand the issues that are inherent in PRO data and to put in place processes to guide researchers and other stakeholders.

We highlighted the need for a conceptual frame to incorporate PRO data in personalized medicine and reviewed methodological and analytical approaches that are relevant for the analysis and interpretation of PROs. Of note, some of the issues—including multiplicity problems, handling of missing values, and modeling approaches—that arise in genetic data analysis are also shared by PROs.<sup>35</sup> This provides challenges and opportunities from the standpoint of application, as well as methodological research. Recent developments in the

specialized areas of PROs and personalized medicine provide fertile opportunity to bring the two areas even closer, and to advance the way treatment is attuned and delivered to address patient care and needs.

Finally, personalized medicine and PROs have attracted considerable attention from regulatory agencies. For example, the recent US Food and Drug Administration guidance on PROs for a label claim in clinical trials provides a roadmap for inclusion of PROs in a label claim.<sup>36</sup> Similar efforts are also under way to establish the regulatory science for evaluating the strategies and outcomes for personalized medicine.<sup>37</sup> ■

#### Author Disclosure Statement

Dr Alemayehu and Dr Cappelleri are employees and stockholders of Pfizer Inc.

#### References

- Sprangers MA, Sloan JA, Barsevick A, et al. Scientific imperatives, clinical implications, and theoretical underpinnings for the investigation of the relationship between genetic variables and patient-reported quality-of-life outcomes. *Qual Life Res*. 2010;19:1395-1403.
- Shi Q, Cleeland CS, Klepstad P, et al. Biological pathways and genetic variables involved in pain. *Qual Life Res*. 2010;19:1407-1417.
- Raat H, van Rossem L, Jaddoe VW, et al. The Generation R study: a candidate gene study and genome-wide association study (GWAS) on health-related quality of life (HRQOL) of mothers and young children. *Qual Life Res*. 2010;19:1439-1446.
- Rijsdijk FV, Snieder H, Ormel J, et al. Genetic and environmental influences on psychological distress in the population: General Health Questionnaire analysis in UK twins. *Psychol Med*. 2003;33:793-801.
- Leinonen R, Kaprio J, Jylhä M, et al. Genetic influences underlying self-rated health in older female twins. *J Am Geriatr Soc*. 2005;53:1002-1007.
- Romeis JC, Scherrer JF, Xian H, et al. Heritability of self-reported health. *Health Serv Res*. 2000;35:995-1010.
- Yang P, Mandrekar SJ, Hillman SH, et al. Evaluation of glutathione metabolic genes on outcomes in advanced non-small cell lung cancer patients after initial treatment with platinum-based chemotherapy: an NCCTG-97-24-51 based study. *J Thorac Oncol*. 2009;4:479-485.
- Sloan JA, Dueck AC, Erickson PA, et al. Analysis and interpretation of results based on patient-reported outcomes. *Value Health*. 2007;10 (suppl 2):S106-S115.
- Bottomley A, Jones D, Claessens L. Patient-reported outcomes: assessment and current perspectives of the guidelines of the Food and Drug Administration and the reflection paper of the European Medicines Agency. *Eur J Cancer*. 2009;45:347-353.
- Acquadro C, Berzon R, Dubois D, et al. Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the Patient-Reported Outcomes (PRO) Harmonization Group meeting at the Food and Drug Administration, February 16, 2001. *Value Health*. 2003;6:522-531.
- Hübner C, Petermann I, Browning BL, et al. Triallelic single nucleotide polymorphisms and genotyping error in genetic epidemiology studies: MDR1 (ABCB1) G2677T/A as an example. *Cancer Epidemiol Biomarkers Prev*. 2007;16:1185-1192.
- Bogardus ST Jr, Concato J, Feinstein AR. Clinical epidemiological quality in molecular genetic research: the need for methodological standards. *JAMA*. 1999;281:1919-1926.
- Sprangers MAG, Sloan JA, Veenhoven R, et al. The establishment of the GENEQOL Consortium to investigate the genetic disposition of patient-reported quality-of-life outcomes. *Twin Res Hum Genet*. 2009;12:301-311.
- Trusheim MR, Berndt ER, Douglas FL. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. *Nat Rev Drug Discov*. 2007;6:287-293.
- Rosenberger WF, Sverdlov O. Handling covariates in the design of clinical trials. *Stat Sci*. 2008;23:404-419.
- Mahajan R, Gupta K. Adaptive design clinical trials: methodology, challenges and prospect. *Indian J Pharmacol*. 2010;42:201-207.
- Marko NF, Weil RJ. Mathematical modeling of molecular data in translational medicine: theoretical considerations. *Sci Transl Med*. 2010 Nov 3;2(56):56rv4.
- Little RJA, Rubin DB. *Statistical Analysis with Missing Data*. 2nd ed. Hoboken, NJ: John Wiley and Sons; 2002.
- Pujol A, Mosca R, Farrés J, Aloy P. Unveiling the role of network and systems biology in drug discovery. *Trends Pharmacol Sci*. 2010;31:115-123.
- Wang R, Lagakos SW, Ware JH, et al. Statistics in medicine—reporting of subgroup analyses in clinical trials. *N Engl J Med*. 2007;357:2189-2194.
- Fayers PM, Machin D. *Quality of Life: The Assessment, Analysis and Interpretation of Patient-reported Outcomes*. 2nd ed. Chichester, England: John Wiley & Sons; 2007.
- Fairclough DL. *Design and Analysis of Quality of Life Studies in Clinical Trials*. 2nd ed. Boca Raton, FL: Chapman & Hall/CRC; 2010.
- Donaldson GW, Moynihan CM. Individual differences in quality-of-life treatment response. *Med Care*. 2002;40(6 suppl):III-39-III-53.
- Hambleton RK, Swaminathan H, Rogers HJ. *Fundamentals of Item Response Theory*. Newbury Park, CA: Sage Publications; 1991.
- Cella D, Gershon RC, Lai JS, Choi S. The future of outcomes measurement: item banking, tailored short-forms, and computerized adaptive assessment. *Qual Life Res*. 2007;16(suppl 1):133-141.
- Panel on Handling Missing Data in Clinical Trials, National Research Council. *The Prevention and Treatment of Missing Data in Clinical Trials*. Washington, DC: National Academies Press; 2010.
- Marquis P, Chassany O, Abetz L. A comprehensive strategy for the interpretation of quality-of-life data based on existing methods. *Value Health*. 2004;7:93-104.
- McLeod LD, Coon CD, Martin SA, et al. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. *Expert Rev Pharmacoecon Outcomes Res*. 2011;11:163-169.
- Hays RD, Brodsky M, Francis M, et al. Evaluating the statistical significance of health-related quality-of-life change in individual patients. *Eval Health Prof*. 2005;28:160-171.
- Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA*. 1995;273:59-65.
- Kent DM, Rothwell PM, Ioannidis JP, et al. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. *Trials*. 2010;11:85.
- Kent DM, Hayward RA. Limitations of applying summary results of clinical trials to individual patients: the need for risk stratification. *JAMA*. 2007;298:1209-1212.
- Dmitrienko A, Tamhane A, Bretz F, eds. *Multiple Testing Problems in Pharmaceutical Statistics*. Boca Raton, FL: Chapman & Hall/CRC; 2009.
- Donaldson G. Patient-reported outcomes and the mandate of measurement. *Qual Life Res*. 2008;7:1303-1313.
- Mayo MS, Gajewski BJ, Morris JS. Some statistical issues in microarray gene expression data. *Radiat Res*. 2006;165:745-748.
- US Food and Drug Administration. Guidance for industry on patient-reported outcome measures: use in medical product development to support labeling claims. *Federal Register*. 2009;74:65132-65133.
- US Food and Drug Administration. Building the infrastructure to drive and support personalized medicine. [www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm274440.htm](http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm274440.htm). Accessed July 25, 2012.

## STAKEHOLDER PERSPECTIVE

### No Physician Treats an Average Patient: Bridging the Gap between Group-Based Data and Patient-Specific Treatment Outcomes

It has been suggested that researchers live at the mean, whereas clinicians live in the standard deviation. This often-cited nostrum reflects a general sentiment that data that are derived on a group level frequently map poorly to treatment outcomes for individual patients who have unique genetic and phenotypic signatures that modify and mediate treatment response. The review article by Alemayehu and Cappelleri is an attempt to bridge this gap by providing a methodological substrate for the use of patient-reported outcomes (PROs) in the evaluation of novel therapy. The recom-

mended approaches ensure that the evidence for efficacy, safety, and utility that are usually filtered through the perception of a clinician can be expressed on a patient-specific basis. Implications for researchers, payers, and patients are derived from this approach.

**RESEARCHERS:** A pathway toward personalized medicine represents a sequence of research opportunities ranging from target validation, investigation of pharmacokinetic/pharmacodynamic relationships, description of modifiers of safety and efficacy, stratification of populations based on anticipated response, and

## STAKEHOLDER PERSPECTIVE *(Continued)*

finally, the ability to characterize treatment effects in easily interpretable constructs, given known patient-specific variables. Within this mosaic, the inclusion of PROs in prospective, interventional research can be considered an end point for a number of antecedent activities, which capture a patient's perceptions of a broad spectrum of disease and treatment outcomes. As in other reviews,<sup>1</sup> the emphasis by Alemayehu and Cappelleri on longitudinal data analyses, adjustments for missing data, and the need for clearly articulated concepts and actionable information is noteworthy. Indeed, the ability to incorporate PRO results into product labeling reflects attention to "fit-for-purpose" issues (ie, content validity, recall, cross-cultural validation) and experimental design (ie, potential bias, clinical meaningfulness, missing data),<sup>2</sup> which are addressed within this review.

Among the design elements that must be considered in a research program are the lack of generalizability of trial participants, the variety of PRO measures encountered (eg, 14 in chronic heart failure<sup>3</sup>), and potential discrepancies in physician- versus patient-reported assessments, which are based on the source of the data and the nature of the outcomes.<sup>4,5</sup> Differences in maturation rates for physician-reported outcomes versus PROs can also be noted, even if they are ultimately concordant.<sup>6</sup> Mixtures of positive and negative PRO results can occur when contrasting treatment versus control as a reflection of the pharmacologic properties of the intervention. Therefore, the position of PROs in a hierarchy of measures and outcomes must be approached within a clear conceptual framework, as suggested in this review, to adjudicate possible qualitative or quantitative treatment interactions across measures.

**PAYERS:** Large-scale population trials may ignore genetic and environmental exposure differences across individuals that influence response, yet financial and regulatory models exist in a framework of these data. The emphasis on PROs (including functional status, psychological well-being, treatment hearings, and satisfaction) brings with it an implied stratification of treatment based on prognostically important variables which places new demands for innovative payer interface with providers. For example, the PRO construct may imply a risk-assessment decision-support algorithm in which static metrics (eg, current disease characteristics, genotype, medical history) are integrated with basic lifestyle planning, advanced dynamic metrics (eg, targeted proteomic and gene expression labo-

ratory profiles), and personalized health interventions, including tailored pharmaceutical interventions.<sup>7</sup>

Predictive modeling capabilities move payers beyond mediators in a transaction to key participants in clinical decisions regarding risk stratification and treatment planning. Similarly, reimbursement and authorization decisions can be based on information derived from group data expressed as the proportion of patients who achieved a clinically important response on a PRO (eg, the number needed to treat). Precedence for requiring specific improvements in discrete outcomes for individual patients after treatment initiation already exists.<sup>8</sup> Finally, the links between PROs and economic outcomes (both examples of healthcare outcomes) are often tenuous, even for well-established, high-visibility chronic illnesses, such as type 2 diabetes,<sup>9</sup> which offers impetus for future payer-sponsored research.

**PATIENTS:** PROs exemplify the emergence of predictive, preventive, personalized, and participatory medicine (together known as "P4 medicine").<sup>10</sup> Rather than being passive recipients of care, patient data that are generated in the context of a clinical trial, and then later in a commercial environment, can help adapt treatment decisions to particular patient circumstances. As an example, the prevalence of PROs in a patient-centered online platform suggests that web-based data entry can be a useful source for hypothesis generation.<sup>11</sup>

Michael F. Murphy, MD, PhD

Chief Medical Officer and Scientific Officer  
Worldwide Clinical Trials

1. Revicki DA, Erickson PA, Sloan JA, et al. Interpreting and reporting results based on patient-reported outcomes. *Value Health*. 2007;10 (suppl 2):S116-S124.

2. DeMuro C, Clark M, Mordin M, et al. Reasons for rejection of patient-reported outcome label claims: a compilation based on a review of patient-reported outcome use among new molecular entities and biologics license applications, 2006-2010. *Value Health*. 2012;15:443-448.

3. Chang S, Gholizadeh L, Salamonson Y, et al. Health span or life span: the role of patient-reported outcomes in informing health policy. *Health Policy*. 2011;100:96-104.

4. Cobden DS, Niessen LW, Barr CB, et al. Relationships among self-management, patient perceptions of care, and health economic outcomes for decision-making and clinical practice in type 2 diabetes. *Value Health*. 2010;13:138-147.

5. Neben-Wittich MA, Atherton PJ, Schwartz DJ, et al. Comparison of provider-assessed and patient-reported outcome measures of acute skin toxicity during a phase III trial of mometasone cream versus placebo during breast radiotherapy: the North Central Cancer Treatment Group (N06C4). *Int J Radiat Oncol Biol Phys*. 2011;81:397-402.

6. Poole CD, Connolly MP, Nielsen SK, et al. A comparison of physician-rated disease severity and patient reported outcomes in mild to moderately active ulcerative colitis. *J Crohns Colitis*. 2010;4:275-282.

7. Langheier JM, Snyderman R. Prospective medicine: the role for genomics in personalized health planning. *Pharmacogenomics*. 2004;5:1-8.

8. Blue Cross of California. Medicare part D coverage criteria. AMPYRA (dalfampridine). January 2012. [www.blueshieldca.com/sites/medicare/documents/PA\\_CY2012\\_AMPYRA\\_dalfampridine\\_MCweb.pdf](http://www.blueshieldca.com/sites/medicare/documents/PA_CY2012_AMPYRA_dalfampridine_MCweb.pdf). Accessed August 13, 2012.

9. Vieta A, Badia X, Sacristán JA. A systematic review of patient-reported and economic outcomes: value to stakeholders in the decision-making process in patients with type 2 diabetes mellitus. *Clin Ther*. 2011;33:1225-1245.

10. Hood L, Balling R, Auffray C. Revolutionizing medicine in the 21(st) century through systems approaches. *Biotechnol J*. 2012;7:992-1001.

11. Frost J, Okun S, Vaughan T, et al. Patient-reported outcomes as a source of evidence in off-label prescribing: analysis of data from PatientsLikeMe. *J Med Internet Res*. 2011;13:e6.