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Invited review

Using patient reported outcomes in diabetes research and practice: Recommendations from a national workshop

David G. Marrero [a], *Marisa E. Hilliard* [b], *David M. Maahs* [c], *Alicia H. McAuliffe-Fogarty* [d,*], *Christine M. Hunter* [e]

[a] *University of Arizona Health Sciences, United States*
[b] *Baylor College of Medicine and Texas Children's Hospital, United States*
[c] *Department of Pediatrics and Stanford Diabetes Research Center, Stanford University School of Medicine, United States*
[d] *T1D Exchange, United States*
[e] *Office of Behavioral and Social Sciences Research, National Institutes of Health, United States*

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ABSTRACT

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the American Diabetes Association (ADA) Co-Sponsored the workshop, *Using Patient Reported Outcomes in Diabetes Research and Practice*. The goal of the workshop was to identify PRO research priorities for those living with type 1 or type 2 diabetes, discuss considerations for use of disease specific versus generic measures, as well as outline research priorities to meet key end-user needs for assessing PROs for diabetes researchers, clinicians/hospital systems, patients/caregivers, and regulators. Here, we summarize the conclusions and recommendations from the workshop.

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* Corresponding author at: T1D Exchange, 11 Avenue de Lafayette, 5th Floor, Boston, MA 02111, United States.
E-mail address: amcauliffefogarty@t1dexchange.org (A.H. McAuliffe-Fogarty).

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1. Introduction

Patient Reported Outcomes (PROs) are defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" [1]. Clinicians, researchers, and regulators assert that assessment of PROs in people with diabetes is important and can significantly contribute to clinical treatment decisions, evaluation of intervention efficacy, regulatory approval, and guideline development. PROs complement biomedical outcomes or a clinical diagnosis by helping professionals understand the patient experience of living with a disease including physical, emotional, and social functioning, the demands and tradeoffs related with the treatment regimen, and their overall health-related quality of life (HRQOL). PROs can also help researchers evaluate the impact of new medications, devices, therapies, and behavioral interventions on patient's experiences across these domains. Finally, PROs are also valuable to regulators in overseeing claims related to differentiating the efficacy of a given drug or device.

Despite the increased call for routine use of PROs in care and research, there remains disagreement about what domains to prioritize for evaluation, which measures should be employed, and for what purposes (research, clinical, and other). While some disease areas, such as cancer, are moving toward more consistent use of PROs, diabetes does not currently have a standardized approach to PRO assessments, and there is little agreement about the essential PRO domains to assess [2–4].

The rapid development of new medications and devices for diabetes treatment and an increasing emphasis on adopting a patient-centered approach have further stimulated an increased need to assess PROs. Therapeutic interventions have high potential to impact patient experience and symptoms. For example, lower HRQOL has been found to be associated with sub-optimal self-care and higher HbA1c [5–8] and when diabetes care providers discuss HRQOL with their patients, youth with type 1 diabetes report improvements in HRQOL and possible glycemic benefits [9,10]. Other research suggests that the daily burden associated with treatment may contribute to suboptimal adherence to medications and diabetes self-management recommendations [11,12]. Despite these observations, PROs are not routinely assessed in clinical care or in research of new diabetes treatments or therapies. By not integrating PROs into treatment decision making or efficacy trials, prescribed diabetes regimens may not be adopted effectively by those for whom they are intended and may inadvertently introduce psychosocial challenges and poorer medical outcomes.

To accelerate the consistent use of validated, generalizable, and clinically meaningful PRO measures in diabetes research and practice, there is a need to standardize the assessment of common domains and PRO instruments across studies. To achieve these goals, the National Institute of Digestive Diabetes and Kidney Diseases (NIDDK) of the National Institutes of Health and the American Diabetes Association (ADA) convened a workshop of experts in the development and application of PROs. Experts were invited to present about how PROs can be more effectively used by diabetes researchers, clinicians/hospital systems, patients/-caregivers, and regulators and to identify the highest priority research gaps. Underlying this discussion was the common understanding that PROs are the most direct measure of how patients feel and function, and reflect what each patient is most concerned about in relation to their health. Moreover, PROs are the only way to systematically assess patients' subjective experiences living with diabetes, including pain, fatigue, depressed mood, diabetes-related burden/distress, anxiety (including fear of hypoglycemia), and HRQOL.

This workshop took place over two days (agenda link: https://www.niddk.nih.gov/news/meetings-workshops/2017/using-patient-reported-outcomes-diabetes-research-practice). Participants included researchers, clinicians, representatives from healthcare systems, patients, caregivers, and regulators. The list of speakers is included in Appendix 4. In this report we present the conclusions and recommendations from the workshop. These are organized by themes/issues that were discussed at the conference. Summaries of the framework for PRO measurement and end user needs are available in Appendices 1–2. The purpose of this report is to outline future directions to advance the use of PROs in diabetes research and practice.

2. Measuring PROs in diabetes research and practice

The workshop attendees and speakers agreed that to achieve the goal of optimally matching treatment to patient needs and improving lives of people living with diabetes, measuring PROs was just as important as objective indicators of medical status, such as HbA1c or blood pressure. However, it was recognized that without a common set of measures or co-calibrated assessments (to harmonize data from studies that use different measures, a co-calibration equation is needed to make comparisons between validated instruments) of PRO

domains, the short and long-term effects of treatments on non-biological outcomes cannot be accurately compared. This gap limits the ability to guide the tailoring of treatments based on patient needs.

From the outset of the meeting it became clear that, for the promise of PROs to be fully realized in development of therapeutics and in routine care, there is a need for further validation and co-calibration of measures. To permit comparisons of findings across samples, there is also a need for more consistent use of common constructs and measures across trials and in practice. Several limitations to existing PRO instruments and their use in both research and clinical applications were identified. Disagreement on PRO definitions and the key domains to assess exists. This leads to the use of multiple instruments purporting to measure the same construct but not necessarily having the same operational definitions, which makes it impossible to compare results across studies. This is particularly evident in measures of HRQOL, which have included a wide variety of constructs including general subjective well-being, problems with physical or emotional functioning, diabetes-related burden, social and family relationship dynamics, and functioning in other areas of daily life [3]. The workshop attendees highlighted the need for research to focus on evaluating the psychometric properties and factor structure of commonly used instruments [13], developing and validating new measures as needed to better assess important constructs, and using more advanced measurement approaches and methods such as Item Response Theory and computer adaptive testing to maximize the efficiency and utility of new measures [14,15]. There was also a call for more research on the predictive validity of PRO instruments for later disease outcomes and greater attention to using developmentally appropriate measurement strategies for respondents at different stages across the life span.

3. Understanding different populations

The workshop focused on identifying the important PRO domains to understand the unique experiences and responses to treatment by individuals with different types of diabetes and at different ages.

3.1. *Type 2 diabetes*

Although the diagnosis of type 2 diabetes is rising in youth and young adults, it primarily affects adults [16,17], many with one or more comorbid chronic conditions [18]. The compounded demands of type 2 diabetes and comorbidities can increase treatment burden and psychosocial outcomes. In individuals with type 2 diabetes, the focus on HbA1c as a primary outcome does not capture the patient's experience of living with and managing diabetes. For example, people with type 2 diabetes who have complications or comorbidities report lower quality of life than those without [19], can experience substantial stigma [20], and are at elevated risk for depression [21]. In addition, often treatments for type 2 diabetes can have physical and emotional consequences (e.g., hypoglycemia, side-effects, inconvenience, stigma, and perceived burden) [22]. It is possible that the benefits of intensive management to delay complications are outweighed by emotional costs for some patients and that the emotional and functional side of diabetes management should be an equal priority. Measurement of PROs in type 2 diabetes can help guide care decisions.

3.2. *Type 1 diabetes*

While 84% of the people living with type 1 diabetes are adults, it is most often diagnosed in children and adolescents [17,23]. The daily demands of type 1 diabetes are substantial, requiring nearly continuous attention to fluctuating blood glucose levels to guide decisions about administering glucose or insulin to prevent dangerous hyper- or hypoglycemic events. In youth, these demands often exceed children's self-management capabilities, and therefore parents must conduct and oversee diabetes care tasks throughout the day and night [24]. As children age, the transition of self-management responsibility can introduce multiple stressors for the child and family that can impact psychosocial well-being and glycemic outcomes. While there have been significant advances in treatment and care of type 1 diabetes, there is considerable room for further advances to increase life expectancy and the lived experience of managing the disease [25,26]. Newer technologies, such as continuous glucose monitoring and closed loop insulin delivery systems, involve human factors that will influence the usefulness of these tools, such as comfort wearing devices visible on the body and trusting technology to safely dose insulin and manage glucose [27]. With new advances in treatment, it is important to understand their impact on PROs including burden of care, access to treatment, and concerns about current and future health.

3.3. *Youth with diabetes*

Many PROs in children and adolescents with diabetes are reported by parents/caregivers about the experience of the youth (e.g. proxy measures); however, there was strong argument against solely relying on proxy assessments except when self-report is unable to be collected. When a parent reports on their perception of their child's subjective experience, it may not accurately reflect the experiences of the youth and may be confounded by the parent's own experiences and psychosocial wellbeing [28]. For example, parents' assessment of children's HRQOL is often discordant with children's own assessments [29,30]. Moreover, although family members are often significantly impacted by their child's diabetes, parents' self-report of their own experiences are rarely assessed, largely due to a lack of validated PRO measures about parents. Therefore, it was recommended that PROs should be measured for both parents and children whenever possible, with the goal of obtaining accurate and comprehensive assessments of youth and family functioning.

3.4. *Older adults with diabetes*

The goal of care in the older adult population is the "compression of morbidity," or reducing factors that speed the onset and progression of morbidity and mortality [31]. Diabetes

increases the likelihood of developing common risk factors that contribute to poor outcomes, including falls, dementia, depression, polypharmacy, and functional decline [32]. As such, routine assessment of outcomes beyond HbA1c were highlighted as particularly important, including treatment burden and indicators of physical and cognitive functioning. Because older adults often have multiple comorbidities, it was argued that PROs focusing on general issues (e.g., pain, fatigue, depression, anxiety, basic task difficulty) rather than diabetes-specific issues (e.g., diabetes distress, diabetes-related physical symptoms) are most appropriate. In addition, assessing regimen adherence and treatment burden may be valuable. The importance of assessment of caregivers' psychosocial outcomes including stress and burden was also highlighted because significant others often take on diabetes management responsibility and their wellbeing can have a substantial impact on treatment outcomes [33].

3.5. *Populations at elevated risk*

For PROs to meaningfully add to treatment decision-making they must be valid in the context of individual differences and contextual variables such as the natural environment, macrosocial environment, resource inequity, health literacy, social support, diabetes knowledge, health behavior attitudes, and beliefs related to care outside of healthcare system. In this context, demographic characteristics associated with elevated risk for poorer outcomes should be considered as they relate to meaningful psychosocial and quality of life differences. These include but are not limited to older age, low income, unemployment, low education status, minority racial and ethnic group membership, immigration status, language barriers, transportation access, and geographic barriers [34]. These factors can influence patients' perception of their health status and health care, especially among high risk groups, yet are rarely considered in relation to PROs.

4. Research gaps and priorities

Workshop participants broke out into groups to discuss PRO research priorities in type 1 diabetes and type 2 diabetes separately. Each group deliberated on the same topics but with the unique needs associated with the specific diabetes type in mind. The focused discussion topics were related to identification of: (1) key PRO domains to assess; (2) circumstances for appropriate use of diabetes-specific versus general symptom PRO measures; (3) research priorities for PROs in clinical use; and (4) priorities for future PRO-related research and regulatory purposes. Using nominal group process technique, the breakout groups brainstormed topics and then rank ordered ideas for each topic area [35]. Results are shared below and summarized in Appendix 3.

4.1. *Type 2 diabetes*

In the type 2 diabetes breakout group, stakeholders agreed that the key global PRO domains to assess for research and support of clinical care are emotional distress of those living with the disease and their supporters/caregivers followed by assessment of the burdens associated with the treatment of diabetes. The group agreed that understanding how symptoms affect functional goals (e.g. work, school, family, leisure activities) should follow in priority.

When the group deliberated on using diabetes-specific versus general symptom measures for clinical care and research, there was agreement that both types of measures are needed. Measures that are not disease specific are valuable for screening in a primary (not specialist) healthcare setting and because they are relevant regardless of disease and comparable across diseases [36]. However, diabetes-specific measures are also needed to capture unique experiences and burden in living with and managing type 2 diabetes. Further, in diabetes research, the use of diabetes-specific measures across trials can permit comparisons of nuanced differences in treatment outcomes unique to the experience of living with diabetes. The recommendation was that healthcare practices conduct universal screening with a general PRO measure and do follow-up assessment with disease-specific measures as appropriate based on patient needs and the care plan. There was also a call for more rigorous qualitative research to assess new PROs important to those living with type 2 diabetes.

The discussion regarding the most important knowledge gaps to advance PRO measurement to address patient, caregiver, and healthcare provider/system needs identified the importance of demonstrating how PROs predict or influence clinical outcomes and disease trajectory. It was emphasized that for real-world application of PROs to be viable for both patients and providers they must be efficient and actionable in clinical management and be related to both regimen adherence and health outcomes. For example, if a treatment increases anxiety or fatigue, adherence to the treatment regimen may be diminished. Addressing these research gaps would facilitate the standard adoption and routine implementation of PROs within the clinical setting.

During the discussion about the use of PRO measurement in research to improve comparisons across trials and provide meaningful data for device and drug regulation, the group advocated for including PROs as a primary endpoint in trials rather than as a secondary outcome. For example, PROs offer important information about treatment benefits and tolerability. There was also robust discussion regarding the lack of longitudinal PRO research in type 2 diabetes. Tracking PROs over the course of the disease from those at-risk, with prediabetes, and at diagnosis and beyond, can inform our understanding of disease process from the patient perspective and of population differences over time. Understanding common issues as well as the stability or fluctuation in patient experience over the disease course can point to opportunities for more tailored and timely intervention approaches.

4.2. *Type 1 diabetes*

In the type 1 diabetes breakout group, the PRO domain identified as most valuable for clinical care and research was diabetes distress/burnout, which has been shown to compromise self-management and glycemic outcomes [37,38]. The group identified the need for research on social support, which has been related to self-management behaviors, psychosocial and medical outcomes [39]. There was also

an emphasis on measuring diabetes-related strengths that can buffer the impact of risk factors, including self-efficacy and mastery related to living with type 1 diabetes [40], and not solely focusing on PROs related to the challenges and burdens of diabetes treatment strategies.

As the group discussed considerations for diabetes-specific versus general measures in research and clinical care, the agreement was that diabetes-specific measures were better to assess more nuanced domains related to living with type 1 diabetes such as distress/burden and diabetes-related worries/fears (e.g., fear of hypoglycemia). For global psychosocial outcomes (e.g., depression, anxiety), non-disease specific measures are appropriate. Additionally, benefits of using either diabetes-specific or general measures were identified in relation to evaluating treatment satisfaction, strengths-based aspects of self-care, and HRQOL in patients and caregivers/supporters, depending on the purpose of the assessment. For example, disease specific measures might be most appropriate for regulatory or efficacy determinations while general measures might be more useful for informing healthcare practice and policy.

4.3. *Key gaps in both type 1 and type 2 diabetes*

The key gaps for PRO use in healthcare included studying the cost-effectiveness of providers using PROs and the efficacy of strengths-based PRO assessment and intervention. The workshop participants agreed that additional research is needed regarding the use of PROs to optimize treatment regimens and to assess patients' perceived benefits of care and trust in healthcare providers/systems. In addition, the group recommended evaluation of the optimal mode, method, and frequency for PRO implementation in clinical practice to assist with dissemination and implementation of PROs in practice.

Finally, with regard to gaps for the use of PROs in research and regulatory approval processes, stakeholders agreed with the need to use PROs for comparison across trials and to understand individual differences in response. There was a robust discussion on measuring the meaning and application of PRO domains for different populations as well as understanding trade-offs for more demanding treatments and their impact on PRO and medical outcomes. The group recommended prioritizing and evaluating how well PRO instruments perform in terms of sensitivity and specificity, or whether new measurements need to be created for implementation of PROs in research and clinical trials.

5. Conclusion

This report summarizes the central themes and lessons derived from the discussion among the workshop participants. Some PROs, such as HRQOL, are complex constructs without a standard definition, leading to inconsistent assessment using scales that measure different aspects of the subjective experience of disease and treatment. A central theme that emerged is that it is impossible to select a single, one size fits all approach to the development or selection of PROs for use in all contexts and purposes. PRO assessment is reliant on contextual factors: what one is interested in measuring and what changes one expects an intervention to produce. This makes it more challenging to harmonize PROs across studies and stakeholders, so the field must balance harmonization with the need to consider specific end user goals.

Over the course of the meeting it was clear that the patient perspective needs greater attention when considering PROs in clinical care and research as they are the end users for all diabetes treatments. However, patient perspectives may not always align with clinical goals such as achieving target HbA1c levels. For example, the burden of self-care and treatment may be more important to someone with diabetes than reducing physical symptoms or lowering HbA1c. Using strength-based approaches to PRO assessment and measuring the subjective experiences of parents, spouses, and other support people will also be important in optimizing treatment from the patient perspective.

There was agreement among the experts and stakeholders that identifying and standardizing definitions of core constructs and concepts (e.g., HRQOL, patient-centered) that are meaningful to patients was a high priority. The experts agreed that the development of these definitions and any new measures should be based on a conceptual model that takes into account the socioecological context. It will also be important to norm scales on diverse populations to ensure the resulting measures retain sensitivity and specificity and account for population differences across groups. Multi-stakeholder involvement (especially of patients underrepresented in research) was recommended throughout the process of measure development and selection. As treatment options expand and their complexity increases, it will be essential to understand how they impact PROs and to illustrate whether there is improvement or worsening as a result of treatment.

Overall, commonalities in research priorities were evident across type 1 and 2 diabetes, underscoring the importance of assessing diabetes-related distress, burnout, and burden, as well as the need for both diabetes-specific and general PRO measures. Additionally, there was consensus that PROs should be used to illustrate outcome impacts and to assess treatment benefits and tolerability to help guide clinical decision making and regulatory approval.

D.G.M. was chair of the conference and wrote the manuscript. M.E.H. was chair of the conference and reviewed/edited the manuscript. D.M.M. was chair of the conference and reviewed/edited the manuscript. A.H.M.F. was chair of the conference and wrote the manuscript. C.M.H. was chair of the conference and wrote the manuscript.

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Declaration of Competing Interest

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Disclaimer

The opinions expressed herein and the interpretation and reporting of these data are the responsibility of the author and in no way should be seen as an official recommendation, interpretation, or policy of the National Institutes of Health or the U. S. Government.

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