Following Patients With Inborn Errors of Metabolism: What Do We Value and How Do We Know?

Jeffrey P. Brosco, MD, PhD,[a] Cynthia F. Hinton, PhD, MS, MPH[b]

In the current drive to improve health care systems in the United States, "value" has been defined as the ratio of quality to cost. Measuring quality, in turn, relies on the common-sense definition of the word value: what do we find important in life? Agreeing on what we value, and how to measure it, has become a critical research task with implications for health policy and clinical practice. Within the research world, there is a movement to define "core outcome sets" (COSs) or variables that should be included in the results of any clinical trial.[1] Reporting such common measures facilitates comparison of and synthesis across studies. COSs can also ensure that researchers focus on what matters to patients and families, as well as to health policy leaders.

Pugliese et al[2] propose COSs for medium chain acyl-coA-dehydrogenase (MCAD) deficiency and phenylketonuria (PKU), two relatively common inborn errors of metabolism, to address the lack of uniform outcome variables in clinical research studies. They employed a Delphi survey and consensus workshop approach to determine 8 core outcomes for MCAD deficiency and 9 for PKU; they also provide measurement recommendations. One significant strength of their approach is to include on their research team 2 patient partners with rare disease experience. What holds value may differ among stakeholders, and the authors show exemplary support of family and caregivers' voice: whether making public policy or establishing relevant outcomes for research studies, the population of people affected by a condition should have a prominent role in deciding what outcomes matter.

The selected core outcomes hold some surprises. Caregiver burden makes the list for MCAD deficiency but not for PKU, although the latter requires daily attention to diet and lifestyle changes.[3] Death but not disability is included for MCAD deficiency. For PKU, 3 psychometric outcomes (IQ, child development, and executive functioning) score high, whereas everyday consequences related to these cognitive attributes (school achievement, behavior concerns) do not.

COSs reflect the values of the specific participants, and therein lie the limitations of any attempt to define a COS. Pugliese et al recognize 1 limitation of their study, which includes only Canadian participants, when they ask for international reaction to their proposal. Family members and/or caregivers and researchers and clinicians were well represented throughout the process, but only 1 health policy advisor completed all stages, and neither children nor young adults with the condition were included. The

[a]*University of Miami, Miami, Florida; and* [b]*National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia*

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Address correspondence to Jeffrey P. Brosco MD, PhD, Institute for Bioethics and Health Policy, Department of Pediatrics, Miller School of Medicine, Miami FL 33101. E-mail: jbrosco@miami.edu

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caregivers in the study were mostly married women with college or graduate degrees, and the authors do not report race, ethnicity, or national origin of participants.

The absence of health policy participants has consequences. For example, both PKU and MCAD deficiency are primary targets for state newborn screening (NBS) programs, and public health leaders may have ranked "age at initiation of treatment" much higher, given the consequences of delayed treatment of these conditions. All is not lost, however, because COSs are primarily designed for randomized controlled trials and represent the minimum outcomes to be reported. A study with implications for the state public health NBS system could easily add a time-of-first-treatment variable to the core set. And given increasing interest in measuring long-term outcomes of NSB programs,[4,5] the COSs developed by Pugliese et al fit neatly into the systems evaluation framework developed by the Advisory Committee on Heritable Disorders in Newborns and Children for the long-term follow-up of children identified by state NBS programs.[6] After all, it is hard to define success without understanding the appropriate targets. Moreover, Pugliese et al demonstrate that achieving some consensus on outcomes can be valuable to the process of deciding what conditions should be added to the Recommended Uniform Screening Panel for NBS.[7] Prospective conditions undergo a rigorous evidence review and structured decision-making process. A condition-specific COS is critical for evaluating the evidence and for helping policy leaders know what outcomes matter to clinicians and caregivers and family members.

The history of medicine in the United States over the last century is characterized by the emergence of the voices of patients, caregivers, and family members. In the mid-20th century, the prestige and power of physicians and scientists seemed to justify a distinctly doctor-centered approach to clinical practice and medical research. Starting in the 1960s and 1970s, the patient perspective became more central, whether in medical ethics (the rise of autonomy), research (patient-centered outcomes research), or clinical practice (value-based medicine). COSs are one manifestation of this larger, and welcome, trend, and defining COSs will require many more studies that balance professional and personal views of what we value. Pugliese et al demonstrate that it is possible to develop COSs that are condition-specific, but it requires substantial effort. Their methods, particularly including the voice of the caregiver, deserve to be emulated.

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ABBREVIATIONS

COS: core outcome set
MCAD: medium chain acyl-coA dehydrogenase
NBS: newborn screening
PKU: phenylketonuria

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