

**Challenges and Priorities for Pediatric Palliative Care Research
in the United States and Similar Practice Settings:
Report from a Pediatric Palliative Care Research Network Workshop**

Authors:

Chris Feudtner, MD, PhD, MPH (1); Abby R. Rosenberg, MD, MS, MA (2); Renee D Boss, MD (3); Lori Wiener, PhD, DCSW, LCSW-C (4); Maureen E. Lyon, PhD (5); Pamela S. Hinds, PhD RN FAAN (6); Myra Bluebond-Langner, PhD (7); Joanne Wolfe, MD MPH (8)

Institutional Affiliations:

- (1) The Ingerman Center for Pediatric Palliative Care, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
- (2) Palliative Care and Resilience Program, Seattle Children's Research Institute; Department of Pediatrics, University of Washington School of Medicine, Seattle, WA, USA
- (3) Department of Pediatrics, Johns Hopkins School of Medicine and Berman Institute of Bioethics, Baltimore, MD, USA
- (4) Lori Wiener, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
- (5) Center for Translational Research, Children's National Health System & Professor of Pediatrics, George Washington University School of Medicine and Health Sciences, Washington, DC, USA
- (6) Children's National Health System, Department of Nursing Science, Professional Practice & Quality, and the George Washington University School of Medicine and Health Sciences, Washington, DC, USA
- (7) Louis Dundas Centre for Children's Palliative Care, Great Ormond Street Institute of Child Health, University College London, London England; Department of Sociology, Anthropology, and Criminal Justice, Rutgers University, Camden, NJ, USA
- (8) Department of Psychosocial Oncology and Palliative Care, Dana-Farber Cancer Institute and Department of Pediatrics, Boston Children's Hospital, Boston, MA, USA

Corresponding Author:

Chris Feudtner, MD PhD MPH
Children's Hospital of Philadelphia
Roberts Center, Room 11123
2716 South Street
Philadelphia, PA 19146-2305

856-287-9700 (cell)
feudtner@email.chop.edu (email)

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ABSTRACT

Context: In order to dramatically advance the evidence base for pediatric palliative care (PPC) interventions, practices, and programs in the United States and similar practice settings, the field needs to better understand the challenges and opportunities for rigorous scholarship.

Objectives: The Pediatric Palliative Care Research Network conducted a workshop to clarify challenges and identify key priorities.

Methods: The workshop focused on PPC research topics and methods, including: outcomes measurement, qualitative inquiry, analyses of “big data,” prospective collection of research data, case series and cohort studies, and intervention trials, with synthesizing summary and follow-up discussions. All attendees reviewed and approved the final report.

Results: Five common challenges were identified: patient diversity and small population size; interdependencies and dynamic interactions between child, family members, and disease processes over time; outcomes and measurement; workforce and infrastructure limitations; and presumed burden of PPC research upon participants. Seven priorities emerged: bolster training and development of PPC investigators; develop core resources; advance symptom measurement (and measurements of other exposures and outcomes); improve symptom management and quality of life interventions; improve communication, elicitation of goals of care, and decision-making; understand family impact and facilitate or improve family adaptation and coping; and analyze and improve systems of care, policy, and education.

Conclusion: These challenges and priorities identify key research areas that can guide individual investigators and research funders to advance the field.

Key words: pediatric, palliative care, research, methodology, training, infrastructure, funding, symptoms, decision-making, family

Running title: Pediatric Palliative Care Research Priorities

BACKGROUND

In the United States, the field of pediatric palliative care (PPC) is a new sub-specialty, still in the first decade of formal recognition, with even the longest-standing clinical programs in their second decade.(1) Research in this area is also in the early phases of development. While the number of published research studies addressing pediatric palliative and hospice care has steadily increased over the past two decades(2), in order to improve the breadth, depth, and quality of PPC research and to dramatically advance the evidence base for PPC interventions, practices, and programs, the field urgently needs to better understand the challenges and opportunities for rigorous scholarship.(3) To this end, the Pediatric Palliative Care Research Network (PPCRN) conducted a one-day workshop to examine the current state of pediatric palliative and hospice care science, seeking to clarify challenges and identify key priorities.

WORKSHOP PARTICIPANTS AND FORMAT

The workshop comprised 28 invited attendees from 13 US and 5 international organizations. Participants included 19 physicians, 2 nurses, 2 psychologists, 2 biostatisticians, 1 anthropologist, 1 social worker, and 1 lawyer (see Appendix for details). Participants were selected on the basis of being active pediatric palliative and hospice care investigators, as evidenced by career-development (e.g., NIH “K”-level) or independent (e.g., NIH “R”-level) funding, or extensive history of publishing peer-reviewed PPC research findings. Among the participants, 7 were pediatricians board-certified in hospice and palliative medicine, along with other clinicians in the fields of pediatric critical care medicine, oncology, complex care, and neonatology. Leaders from the National Palliative Care Research Center (NPCRC, which

provided funding support for the workshop) and the Palliative Care Research Collaborative (PCRC), two of the major palliative care research-focused bodies in the U.S., also attended.

The meeting progressed through four main stages. First, participants provided brief synopses of their research programs. Second, the authors addressed key potential PPC research topics, followed by methods to pursue them, including: outcomes measurement, qualitative inquiry, analyses of “big data,” prospective collection of research data, case series and cohort studies, and intervention trials. Third, discussion focused on key stakeholders and funding sources for PPC research. Finally, discussion at the end of the day aimed to specify core challenges to the design, measurement, and conduct of research, and to identify additional key issues that had been raised during the presentations and discussion, without attempting to priority sort these issues.

All discussions were facilitated (by CF, AR, MBL, JW), with facilitators and participants identifying challenges or priorities that emerged in the presentations and discussion. In addition to notes taken by the authors, a scribe took extensive detailed notes throughout the day. At the conclusion of the meeting, several of the authors (CF, AR, JW) organized the challenges into five broad categories and the priority issues into seven main categories. The categories and priorities were subsequently reviewed by all authors and, with editing, consensus was reached. All invited attendees reviewed and approved this report.

FIVE COMMON CHALLENGES

Discussion throughout the day repeatedly touched upon five sets of challenges (Figure).

Patient Diversity and Small Population Size: First, challenges and opportunities arise from patient diversity, not only in terms of race, ethnicity, language, culture, and socio-demographic characteristics, but also in terms of children's developmental age (spanning from infancy or even in utero through young adulthood), the heterogeneous causes of pediatric serious illness, the length of time the child and family live with the threat to the child's life, and the differential severity and dynamism of conditions and their associated impairments. For any given group of patients with a particular disorder, the total number of patients is small, with limited potential for subgroup analysis of diversities of interest. Additionally, many patients receiving palliative or hospice services are either pre-verbal or communication-impaired; variable communication ability translates into variable degrees of patient-report. Patients often have multiple concurrent conditions contributing to their outcomes. Children appropriately receiving palliative care experience survivorship as short as hours or extending for months to years, which creates considerable variance in the timing of physical and psychosocial outcomes, posing both measurement and analytic challenges.(4) Taken together, this relatively small and diverse population limits the power of traditional research methodologies to provide robust conclusions about important patient subgroups.

Interdependencies and Dynamic Interactions: Second are considerations arising from children's typical dependency upon their parents, family members, and other caregivers. The nature and degree of dependency varies across the developmental spectrum and is usually shaped by the degree of illness. For adolescents and young adults who are striving for or exhibiting increasing levels of independence, the study of their care ought to incorporate and potentially emphasize their perspectives and experiences.(5-9) Reciprocally, parents(10, 11)

and other family members, such as siblings(12-14), are affected by the occurrence of serious pediatric illness in the ill child. Thus, the family – parents, siblings, and other family members – is an important research focus and participant. Moreover, the patient and family interact with the patient's underlying condition, formulating opinions and beliefs about the condition, which in turn influence how the patient and family respond to and experience the condition. These interdependencies and dynamic interactions both warrant attention (because of their importance to outcomes for the pediatric patient and other family members) and cannot be ignored (since they greatly influence outcomes). Incorporating these interdependent and dynamically interacting relationships into the analysis of PPC study is conceptually and technically demanding.

Outcomes and Measurement: The third set of challenges stem from the specification of outcomes and the measurement or assessment of these outcomes, as well as measurement of different important exposure variables. Although pediatric palliative and hospice care do not have one overall prime goal, modes of care often aim to minimize suffering of patients and family members while enhancing their quality of life. Because such a large proportion of pediatric patients receiving palliative care survive for months to years, objective measures of mortality and lifespan are not typically suitable primary outcome measures (although sometimes they are suitable as complementary outcome measures, especially if weighted by participants' quality of life over time). Rigorous subjective measures of suffering and quality of life depend upon robust patient- (or parent-) reported outcome instruments. These are rare in pediatrics for patients who are severely affected by illness, do not exist in suitable versions across the pediatric age spectrum, have critical limitations regarding ceiling or floor effects, do

not adequately assess family or social life, or are not sufficiently sensitive to detect change over time.(15, 16) Furthermore, concordance between child and parent report is highly variable and dependent on child-age, duration of symptoms, and frequency of assessment,(17-19) indicating that the PPC experience is not the same for the ill child as it is for the caregiving parent. Both experiences need to be solicited in PPC research and interpreted to foster family and clinician understanding of the unique and shared perspectives that could influence care outcomes. PPC studies thus far also have not consistently used the same measurement instruments or same data points, even when studying the same outcome, making comparison across studies difficult if not impossible.(20) Finally, there are very few longitudinal studies and no best practice standards for when reassessments should occur in longitudinal studies, again limiting comparison across studies.

Workforce and Infrastructure: Fourth are challenges for research workforce and infrastructure. As the clinical practice of PPC is rapidly expanding in terms of the number of clinical programs and the volume of patients receiving PPC care, the pipeline to train and support PPC investigators is woefully inadequate. Of note, the current sub-specialty palliative care fellowship program for physicians requires 1 year of structured clinical training, with no research expectation. A substantial number of PPC fellows are trained in adult-focused fellowships, with limited exposure to the pediatric clinical challenges that generate research questions. PPC fellowship or post-doctoral training opportunities for nurses, social workers, psychologists, and others are rare and only a few are research-focused; few of these are interprofessional. Given the burgeoning clinical workload being experienced by most academic pediatric palliative care programs, these programs are understaffed, limiting time for research

training or conduct. PPC research has limited funding resources, not unlike the resource constraints experienced by the adult realm of palliative and hospice research, yet exacerbated by the comparatively small number and size of academic palliative care programs.

Presumed Burden of PPC Research Upon Participants: Finally, many PPC investigators encounter a presumption held by certain clinicians, institutional review board members, and funding agencies that participating in PPC research is unduly burdensome for the ill child and family members, and therefore pediatric patients with serious illness and their parents or caregivers warrant special protections.(21) This in turn can result in clinical gatekeeping that limits patients' and parents' opportunities to participate in research (and that can also create sample bias(22, 23)); in protracted IRB reviews that sometimes result in impractical recruitment, enrollment, or data collection procedures; and in restricted funding opportunities. Importantly, this presumption of undue burden is strongly refuted by empirical data from patients and parents about the valued benefits and limited burdens of participating in PPC research.(24-28)

SEVEN KEY PRIORITIES

Seven key priorities emerged from the group's discussion of PPC research topics (Figure), which were refined and clarified by further discussion among the authors and then affirmed by the convened group.

The first two priorities relate to research infrastructure.

1. Bolster Training and Development of PPC Investigators

Critically, we must enhance the pipeline for developing PPC investigators in all relevant disciplines. This pipeline begins with initial recruitment of research-talented individuals into the field during medical, nursing, or other professional schooling and ensuing general clinical training. The pipeline must include provision of early career development support (such as opportunities to pursue dedicated 2-year research training as provided via the NIH T32, F31, and F32 mechanisms), and protected time for mentored scholarship during the initial stage of early career faculty development (as is provided by career development awards from the NIH, AHRQ, and private foundations). These opportunities should be available both for individuals who are exclusively pursuing PPC clinical and research training, and for individuals in other areas of pediatric practice pursuing PPC research. Ideally, this training and development should occur in interprofessional educational settings. These steps are necessary to enable rigorous scientific training and significant research projects as the foundations of durable scientific careers.

We should support, interconnect, and leverage national and local PPC research support groups, which have spontaneously developed in several settings. Given the rarity and dispersion of PPC research expertise, the most must be made of national meetings for face-to-face engagement, as well as continued (and potentially more sophisticated) internet-based research educational webinars and works-in-progress sessions, as are already facilitated by PPCRN for national and international participation, with ready access to all members of the PPC research community.

We should attend to the support of senior scientific mentors, so that they are able to devote the required time and effort to provide guidance to early investigators, especially when the

lines of mentorship cross divisional or departmental boundaries within institutions, or cross over different institutions (since “distance mentorship” is often necessary due to the small size of the PPC research field).

2. Develop Core Resources

High impact research requires resources. The community of PPC researchers, dispersed across the United States and beyond, would greatly benefit from having crucial core resources available, specifically to enable the conduct of higher quality research.

We need to curate and make analyzable large administrative databases, such as Medicaid or commercial insurance claims data, and suitably de-identified data from PPC studies that secured permission from participants for re-use, so that preliminary studies or “big data” studies can be performed. These resources might then provide robust descriptions of patient populations or clinical practice, or enable the study of temporal trends or policy effects. We need to cultivate expertise in the measurement of patient symptoms and other patient exposures and outcomes, and also in the measurement of outcomes for parents, siblings, and other family members or caregivers. This expertise will need to produce valid and reliable measures, and work to facilitate the reporting of comparable metrics across studies. We need scientific expertise in epidemiology, biostatistics, computer programming, and information technology so that studies are soundly designed, sufficiently powered, and rigorously analyzed, as well as to ensure that data are collected and managed at the highest standard. We need expertise in implementation science so that interventions that have evidence of efficacy are incorporated into clinical practice effectively.

All of these resources and expertise need to be pediatric-pertinent, and as described both above and below, they need to surmount specific challenges confronting PPC research. Avenues forward include increasing the capacity of the PCRC to provide pediatric-pertinent core resources and expertise (in areas such as study design, measurement of patient experience, and assessment of parent and other caregiver experiences), as well as other efforts to develop and share core resources, such as large datasets and advanced analytic methods, across PPC research sites.

In particular, support is required for multi-center study collaborative efforts, as no one site has a sufficient number of patients to address many of the important PPC topics. This support will need to maintain a viable research network with ongoing core and site-specific resources (so as to limit the time and cost of starting studies, as well as to collect pilot data and demonstrate evidence of multi-center study feasibility), and to provide adequate funding for multi-center research study projects, which often require large budgets to cover all associated costs.

The remaining five priorities each highlight crucial topics for the advancement of pediatric palliative care research.

3. Advance Symptom Measurement (and Measurement of Other Exposures and Outcomes)

Pediatric palliative care has several major goals, of which the reduction of suffering for seriously ill children is paramount. While suffering is a complex phenomenon, one tractable way to assess the degree of suffering is to measure patient disease symptoms and treatment toxicities. Research to date has demonstrated that children receiving PPC or at the end of life experience

many symptoms(4, 29, 30), and the aim of many PPC interventions is to reduce specific symptoms and improve overall quality of life.

Our emphasis on symptoms and symptom assessment measures is in part a critique of the status of pediatric quality of life measures, which currently do not exist for neonates, may not be suitable for pediatric patients with serious illness without further validation, and generally are incommensurable for patients who have had life-long serious illness or conditions.

Various pediatric-specific patient reported outcome (PRO) measures exist. The science of pediatric symptom assessment and analysis, though, needs to advance to address a variety of challenges to determine symptom burden and response to interventions, including:

- how to best select pediatric-patient reported measures for symptoms other than pain;
- best practices for symptom assessment in communication-impaired patients;
- how to adjudicate or interpret differences between patient reports and assessments by either parents/caregivers or clinicians;
- how to parse or combine different manifestations of symptoms, such as frequency, intensity or severity, and bother or distress;
- how to best quantify a patient's total symptom burden consisting of several symptoms;
- best practices for analyzing response to intervention for not only the target symptoms, but also other potential symptoms due to the patient's medical condition or due to medication side effects; and
- how to communicate information about symptoms back to clinicians effectively, resulting in better symptom management and abatement.

We need clearer delineation of the key concepts and best practices for symptom assessment, and more consistent (and thus comparable) uses of these practices in research studies.

4. Improve Symptom Management and Quality of Life Interventions

Improving the effectiveness of symptom management for patients receiving pediatric palliative care is the clearest and most urgent priority. To do this, we simply must increase the number and quality of controlled trials of symptom management interventions to determine efficacy, and subsequent implementation studies to effectively translate beneficial interventions into clinical practice. The target symptoms will undoubtedly include pain, but studies are needed across the variety of symptoms that cause distress to children and their families. The interventions may include medication regimens, psychological or behavioral treatments, complementary therapies, or combination therapy. Given the levels of polypharmacy and use of medical technology that many PPC patients experience(4, 31, 32), and the potential for side effects and other inadvertent iatrogenic causes of suffering(33), some interventions may entail controlled deprescribing or cessation of ongoing interventions.

Methodologically, the challenges mentioned above regarding patient diversity (as well as interdependency and measurement) will require both rigor and some combination of adaptability, flexibility, and innovation. The study designs will need to account for the heterogeneity in the pediatric PPC population in terms of patient developmental and physiologic age, disease stage, current severity of the condition, co-morbid conditions, and other ongoing treatments, along with small numbers of patients with a given condition or symptom at any particular clinical site, and even across the United States. Standard randomized

control trials, adaptive trial designs, aggregated n=1 trials, and other study designs may, for different conditions and clinical circumstances, be needed to gauge the efficacy of symptom management interventions.

In order to conduct rigorous studies, we also urgently need a better taxonomy of the components of various palliative and non-palliative interventions; better measures of “exposure” to these components, including measures of the dose, frequency, and quality; and then to use the best study designs to identify key components.(34) Similar to the ways in which we can specify these parameters of medications, we need to be able to do the equivalent for technologies (including not only “yes/no” technologies such as gastrostomy tubes, but also the timing of exposures to tube feeding, or the dosage of titratable technologies such as non-invasive ventilatory support) and for complementary therapies.

The underlying goal justifying the prioritization of symptom assessment and symptom management improvement, as mentioned above, is to alleviate pain, discomfort, and suffering, and to improve the quality of life for patients and their families. Given the complexity of the phenomenon of suffering, those pursuing this work will need to be vigilant for unanticipated effects and side effects, which strongly suggests a role for mixed method approaches that combine qualitative evaluations with quantitative measurement strategies.

5. Improve Communication, Elicitation of Goals of Care, and Decision-Making

Communication is central to the provision of PPC.(35, 36) Within the broad and deep category of communication, we particularly prioritize communication (and other techniques) to provide

parents or patients with decision-making capacity with help regarding clarifying goals of care and with support making specific decisions.(37-40)

The ongoing empirical work regarding communication, elicitation of goals of care, and decision-making, along with parallel work regarding clarifying key concepts and identifying optimal study design and methods for these topics, needs to continue, but at a more rapid pace.(41-44)

Conceptually, parents often hold several goals (or hopes), which may or may not be harmoniously aligned for any specific decision, and which evolve over time.(45-48) Similarly, there are diverse types of decisions, which occur not once but iteratively, and there is no consensus regarding what criteria constitute a “good” or “better” decision (and perhaps there can be no single universal set of criteria). There is no consensus regarding how to think about changes in goals or the evaluation of complex decisions over time.

Clarification is also warranted regarding the methods to best conduct, document, and enact advance care planning; the degree to which the preferences and choices of patients who are still minors should be integrated; the stability of preferences over time (especially as patients become more life-threateningly ill); and what advance care planning for parents *means* when the most likely scenario is that the parents will still have decision-making capacity whenever the child needs a medical decision to be made. Methodologically, the solicitation and measurement of preferences from parents, as well as younger children and adolescents, and self-reported outcome measures for the decision-making process, need work. Lastly, while the study of decision-making support via RCTs is conceivable, here, too, a range of study designs likely will be necessary.

6. Understand Family Impact and Facilitate or Improve Family Adaptation and Coping

While the central focus of PPC is on the pediatric patient, serious childhood illness has substantial impact on all members of the child's family and beyond. There is burgeoning interest in, and research on, parental, sibling, and other family members' physical and emotional wellbeing throughout the illness trajectory, including feelings of anticipatory grief and subsequent bereavement.(49-53) Unfortunately, the research to date is woefully insufficient to guide the design of best clinical practices, let alone determine which emotionally supportive practices are most effective. Experientially interwoven with emotional responses to the child's serious illness are other key aspects of parent and family member outcomes, including the degree of satisfaction with different forms of healthcare (including but not limited to PPC), decisional contentment, conflict, or regret with the overall medical decision making process or with specific decisions(54, 55), not to mention the degree to which parents meet their internal expectations of what they feel that they should be doing or should have done on behalf of their child.(56-58)

Other domains of impact on family members also need attention, including potential adverse and positive effects on the physical and mental health of parents and siblings and the financial impact on individuals and whole families.(59) The latter, for example, may be mediated via mechanisms such as having to pay medical bills, lost wages, or withdrawal of a household member from the workforce. Interventions need to be designed and tested to promote family adaptation, problem solving, coping, and resilience when confronting serious pediatric illness,

and to mitigate specific mechanisms that create financial or other strain on families with seriously ill children.(60, 61)

Given the importance of religion, spirituality, and life philosophies in the lives of many families, these are also important domains that may be impacted by and also affect how families respond to serious childhood illness.(62-65) We need to identify suitable measures and to recognize and account for the potential heterogeneity of beliefs and views within a given family.

All of this work will need to be undertaken with full appreciation of the diversity of family sociodemographic characteristics, structures, and cultures.(66) Dedicated effort will be required to include under-represented populations.

7. Analyze and Improve Systems of Care, Policy, and Education

The final priority aims to improve our understanding of healthcare systems, policy, and education that effect outcomes for children with serious illness and their families, and to enhance our ability to constructively and effectively intervene in a timely manner. Topics include, but are not limited to:

- the availability and quality of home-based PPC services, hospice services, home duty nursing services and telehealth;
- differences in the receipt of services based on types of insurance coverage;
- the impact of policies such as concurrent care provision in the Affordable Care Act;
- the ways that family medical leave is implemented across the U.S.; and

- educational techniques and programs for specialty and primary PPC.

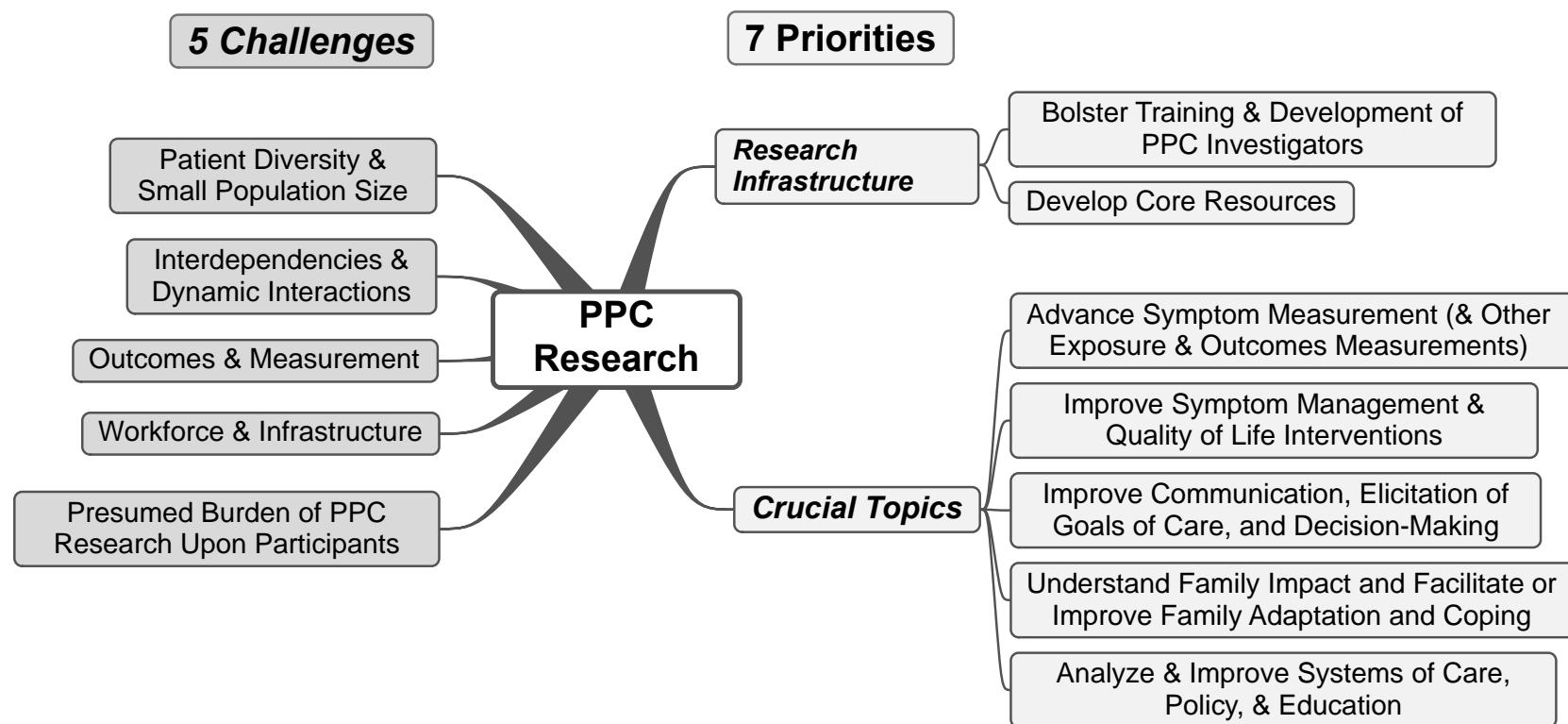
This priority is especially sensitive to requirements of infrastructure, including the development of PPC investigators who can design and conduct large data and policy studies, educational program interventions, and core data and data analytic resources.

CONCLUSIONS AND NEXT STEPS

The challenges and priorities for PPC research described in this article reflect the discussion that occurred at a workshop dedicated to this topic, with subsequent consideration and clarification by the authors, and thus reflects the experience and opinions of some – but certainly not all – experts and rising investigators in the field. With this caveat in mind, we offer this report to the broad and varied field of PPC clinical practice, education and training, and research.

This report provides a strategic surveillance of the current state of pediatric PPC research and identifies key research areas that can guide next steps. For individual investigators, we hope that the list of topics for methodological development and empirical study are helpful when considering personal research agendas. For clinical, training, and educational programs, as well as the few dedicated PPC research programs that exist, we hope that both the topics and the infrastructure needs are given consideration when planning future activities. Finally, for potential funders, we hope that the paper provides actionable guidance regarding which funding investments are likely to yield the largest gains in terms of improving the provision of PPC and outcomes for children with serious illness and their families.

Figure: Pediatric Palliative Care Research Challenges and Priorities



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Addendum: Workshop Invited Attendees

Conveners

Joanne Wolfe, MD MPH
Professor of Pediatrics, Harvard Medical School
Director, Pediatric Palliative Care
Department of Pediatrics, Boston Children's Hospital
Division Chief, Pediatric Palliative Care Service
Department of Psychosocial Oncology and Palliative Care, Dana-Farber Cancer Institute

Chris Feudtner, MD, PhD, MPH
Professor of Pediatrics, Medical Ethics and Health Policy
The Perelman School of Medicine, University of Pennsylvania
Director, Department of Medical Ethics
Director of Research for the Pediatric Advance Care Team
Children's Hospital of Philadelphia

Invited Participants

Justin N. Baker, MD
Chief, Division of Quality of Life and Palliative Care
Attending Physician, Quality of Life Service
Director, Hematology/Oncology Fellowship Program
Associate Member, Department of Oncology
St Jude Children's Research Hospital

Myra Bluebond-Langner, MA, PhD
Professor and True Colours Chair in Palliative Care for Children and Young People
University College London-Institute of Child Health
Board of Governors' Professor of Anthropology Emeritas, Rutgers University, Camden, NJ
Honorary Contract, Palliative Care Service, Great Ormond Street Hospital for Children, London

Kira Bona, MD, MPH
Instructor, Harvard Medical School
Dana-Farber/Boston Children's Cancer and Blood Disorders Center

Renee Boss, MD, MHS
Associate Professor, Division of Neonatology
Johns Hopkins School of Medicine
Berman Institute of Bioethics

Veronica Dussel, MD, MPH
Associate Research Scientist, Pediatric Palliative Care, Boston Children's Hospital

Chair, Center for Research and Implementation in Palliative Care
Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina

Elana E. Evan, PhD
Director, Pediatric Palliative Care Program Development
Associate Professor of Pediatrics
Pediatric Pain and Palliative Care Program, David Geffen School of Medicine at UCLA

Jennifer A. Faerber, PhD
Biostatistician
The Children's Hospital of Philadelphia

James Feinstein, MD, MPH, MSPH
Assistant Professor, Pediatrics-General Pediatrics
Attending Physician, Special Care Clinic and Child Health Clinic
Pediatric Director, Epidermolysis Bullosa Regional Program
Principal Investigator, Adult and Child Consortium for Health Outcomes Research and Delivery Science (ACCORDS)

Angela M. Feraco, MD MMSc
Instructor, Harvard Medical School
Pediatric Hematology/Oncology, Dana-Farber Cancer Institute and Boston Children's Hospital

Pamela Hinds, RN, PhD
Director, Nursing Research and Quality Outcomes, Children's National Health System
Professor of Pediatrics, George Washington University
Adjunct Professor of College of Nursing, University of Maryland

Maureen E. Lyon, PhD
Clinical Health Psychologist
Professor, Department of Pediatrics
George Washington University School of Medicine and Health Sciences
Center for Translational Science/Children's Research Institute
Children's National Health System

Kelly Michelson, MD, MPH
Professor of Pediatrics, Julia and David Uihlein Professor in Medical Humanities and Bioethics
Northwestern University Feinberg School of Medicine
Director, Center for Bioethics and Medical Humanities
Northwestern University Feinberg School of Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago

Jennifer Needle, MD, MPH
Assistant Professor of Pediatrics and Bioethics

University of Minnesota

Tessie October, MD, MPH
Critical Care Specialist
Children's National Health System

Liliana Orellana, PhD
Associate Professor of Biostatistics
Director Biostatistics Unit
Deakin University, Geelong, Australia

Abby R. Rosenberg, MD, MS
Associate Professor, Pediatrics, University of Washington
Director, Palliative Care and Resilience Program, Seattle Children's Research Institute
Medical Director, Adolescent and Young Adult Oncology, Seattle Children's Hospital Cancer and Blood Disorders Center
Research Faculty, Treuman Katz Center for Pediatric Bioethics.

Hal Siden, MD, MHSc
Medical Director, Canuck Place Children's Hospice
Medical Director Palliative Care and Research Institute Investigator, BC Children's Hospital
Clinical Professor, Pediatrics, University of British Columbia

Jennifer Snaman, MD, MS
Physician Scientist Training Fellow
Chief Fellow in Pediatric Hematology-Oncology
St. Jude Children's Research Hospital, Memphis, TN

Christina Ullrich, MD, MPH
Assistant Professor in Pediatrics, Harvard Medical School
Senior Physician, Pediatric Hematology / Oncology, Dana-Farber Cancer Institute / Boston Children's Hospital

Jen Walter, MD, PhD, MS
Assistant Professor of Pediatrics, Perelman School of Medicine at the University of Pennsylvania
Attending Physician, Children's Hospital of Philadelphia

Kimberley Widger, RN, PhD, CHPCN(C)
Assistant Professor, Lawrence S. Bloomberg Faculty of Nursing, University of Toronto
Nursing Research Associate, Hospital for Sick Children

Lori Wiener, Ph.D., DCSW, LCSW-C
Co-Director, Behavioral Health Core

Director, Psychosocial Support and Research Program
Pediatric Oncology Branch
Center for Cancer Research, National Cancer Institute
National Institutes of Health

Invited Guests

James A. Block, MD
President, J.A. Block Health Associates

Jean Kutner, MD, MPH, MSPH
Professor, Medicine-Internal Medicine
Professor of Medicine
Associate Dean for Clinical Affairs
Chief Medical Officer, University of Colorado Hospital
Co-Director, Palliative Care Research Consortium

Rebecca A. Kirch, JD
Executive Vice President, Healthcare Quality and Value
National Patient Advocate Foundation

Sean Morrison, MD
Ellen and Howard E. Katz Professor and Chair
Brookdale Department of Geriatrics and Palliative Medicine
Mount Sinai School of Medicine
Director, National Palliative Care Research Center