



Patient-Centered Palliative Care Delivery for Adult Patients with Advanced Illnesses and Their Caregivers: Topic Brief

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High-Level Comparative Effectiveness Research Questions

- What is the comparative effectiveness of different communication and decision-making interventions aimed at facilitating care planning over time that is consistent with the goals and preferences of patients with advanced illnesses and their caregivers?
- What is the comparative effectiveness of different models of palliative care delivery for adult patients with advanced illnesses and their caregivers on important patient- and family-centered outcomes?

Assignment for Workgroup Participants

- Based on your perspective (patient, clinician, payer, etc.), please identify two or three of the most relevant comparative effectiveness research questions related to the delivery of palliative care for adult patients with advanced illnesses and their caregivers that warrant further research to address current gaps in knowledge and care?
 - Your questions should address important decisional dilemmas commonly faced by patients, caregivers, clinicians, healthcare systems, or other stakeholders in real-world settings.
 - The workgroup will focus on two broad research areas: 1. Models of care delivery and 2. Communication and decision making. You may focus your questions on one or both areas.
 - Given that different advanced, serious illnesses may have different trajectories from diagnosis to death, when appropriate, please specify the illness context (e.g., advanced cancer, organ failure, dementia, etc.) in your question.
 - When possible, please consider caregiver needs in addition to those of the patient.
- Submitted questions will be used to refine the agenda for the workgroup meeting.

"This document was prepared for informational purposes only and should not be construed as medical advice or used for clinical decision making."



Opportunity Snapshot

As part of PCORI's efforts to fund high-impact and useful research on critical patient-centered health and healthcare issues, the Improving Healthcare Systems (IHS) and Communication and Dissemination Research (CDR) programs are partnering to host a multi-stakeholder workgroup to discuss high-priority topics aimed at facilitating the delivery of patient-centered palliative care for adult patients living with advanced, serious illnesses and their caregivers. *Our overarching goal is to support research that would a. facilitate care planning over time that is consistent with the goals and preferences of patients with advanced illnesses and their caregivers, and b. facilitate the delivery of coordinated palliative care that effectively implements those care plans.*

Workgroup participants will help refine a comparative effectiveness research agenda focused on implementing optimal models of delivering palliative care and improving patient-centered communication and shared decision making within the context of different advanced illnesses. Discussion at the meeting will highlight high-priority decisional dilemmas commonly faced by patients with advanced illnesses, their caregivers, clinicians, healthcare systems, or other stakeholders, and identify opportunities for research to compare different efficacious and/or widely used intervention approaches to address those dilemmas in real-world settings.

PCORI intends to use the feedback from the workgroup to conduct further gap analyses on the list of topics/questions put forth by the workgroup in developing a potential funding announcement in this area. The overall objective of the workgroup is to create a set of comparative research questions with the potential to produce findings that ultimately improve patient- and family-centered outcomes.

I. Introduction

Adult patients with advanced, serious illnesses (e.g., late-stage cancers, advanced heart failure, advanced lung or kidney disease, liver failure, or neurodegenerative diseases such as moderate to severe Parkinson's disease or Alzheimer's disease)¹ experience a high burden of physical and psychosocial symptoms, limitations in functioning, and declining quality of life (QOL) over the course of their illness.² Caring for these patients can take a significant physical and emotional toll on families and loved ones who often perform many medical tasks in addition to providing personal care and conducting household chores.³ The scope of the challenge associated with managing advanced and potentially life-limiting illnesses is only expected to increase due to concurrent trends in which a growing proportion of the US population is aging and is likely to have multiple complex, comorbid health conditions and there is a projected shortage of clinicians to care for them. Addressing the supportive care needs of caregivers and individuals with advanced illnesses throughout their illness trajectory (from diagnosis until death) has been identified as a national priority.³⁻⁵

Definitions of palliative care

The National Consensus Project for Quality Palliative Care, the National Quality Forum, and other organizations have defined palliative care as "patient- and family-centered care that optimizes quality of life by anticipating, preventing, and treating suffering. Palliative care throughout the continuum of illness involves addressing physical, intellectual,



emotional, social, and spiritual needs and facilitating patient autonomy, access to information, and choice.^{1,4}

Similarly, the World Health Organization (WHO) defines palliative care as “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification, impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.”⁶

Characteristics of palliative care

Core characteristics of palliative include the following:^{1,3,4,6,7}

- Care is provided and services are coordinated by an interdisciplinary team
- Patients, families, palliative, and non-palliative healthcare providers collaborate and communicate about care needs
- Palliative care is NOT the same as hospice care
 - Hospice is a specialized setting for delivering palliative care to individuals nearing death
- Palliative care is not limited to the end-of-life phase alone and can be provided to patients and their families *at any point* in the illness trajectory
- Palliative care may be provided independently or in conjunction with medical treatments targeting the disease

Palliative care can encompass both primary and specialty care and may be delivered by a range of clinicians. Basic services may be provided by primary care clinicians and specialists who care for people with advanced, serious illnesses (e.g., oncologists, pulmonologists, cardiologists), while specialty palliative care is often delivered by specialists in hospice, palliative medicine, nursing, social work, chaplaincy, and other palliative care fields. The setting for palliative care can include hospitals, nursing homes, long-term acute care facilities, the patient’s home, hospice, or outpatient clinics.³ Given the involvement of multiple clinicians providing differing levels of palliative care across multiple healthcare settings, ***communication and coordination among various clinicians as well as communication and decision making between various clinicians, patients, and their caregivers*** becomes critical to ensuring palliative care’s primary goal: addressing supportive care needs and improving the quality of life of patients and their caregivers.

The efficacy of numerous palliative care interventions has been established with respect to reducing the illness burden for patients with advanced illnesses and their caregivers.^{2,8,9} However, several recent reports highlight the need to conduct rigorous comparative effectiveness studies in order to identify the optimal mix of providers, settings, content, and timing of palliative care at different stages of the illness trajectory from diagnosis until death.^{2,5} ***Studies conducting head-to-head comparisons of communication and decision-making interventions aimed at facilitating care planning over time that is consistent with the goals and preferences of patients with advanced illnesses and their caregivers as well as head-to-head comparisons of models of coordinated palliative care delivery that are needed to effectively implement those care plans are notably absent from the current literature.***

Based on significant stakeholder input, the National Institute of Nursing Research (NINR) at the National Institutes of Health (NIH) has also identified research on models of care and patient and caregiver engagement in decision making within the context of palliative care for advanced illnesses as leading results-oriented, innovative questions in symptom science and palliative and end-of-life care.¹⁰ A sub-domain of this topic, care coordination at the end of life, was also identified by the Institute of Medicine (IOM) as a national priority topic for comparative effectiveness research.¹¹



II. Patient-Centeredness

Palliative care, by definition, is patient-centered. Palliative care aims to deliver patient-centered care by tailoring and implementing care plans consistent with patient and caregiver goals and preferences. Moreover, the primary focus of palliative care is on reducing the burden of illness on patients and their caregivers, relieving suffering (to the extent possible), and improving patient and caregiver quality of life as they confront advanced illness situations.¹ Thus, CER studies that compare different approaches to delivering palliative care to patients with advanced illnesses and their caregivers are highly relevant to patients, their caregivers, and their clinicians.

III. Impact/Burden of the Condition

As the US population ages, a greater proportion of individuals are likely to be diagnosed with advanced illnesses, resulting in tremendous burden associated with debilitating symptoms, compromised functioning, and reduced quality of life. In addition to patients themselves, family members also suffer profound physical and emotional consequences due to caregiver burden and associated decrements in their quality of life. Additionally, patients with advanced illnesses are likely to suffer from multiple chronic conditions, compounding their illness burden. A recent report from the Centers for Medicare and Medicaid Services (CMS) shows that more than 80 percent of Medicare beneficiaries diagnosed with heart failure and more than 60 percent of those diagnosed with cancer had three or more other chronic health conditions.¹² Overall, almost 1-in-4 (23 percent) Medicare beneficiaries suffered from four or five chronic health conditions.¹² Almost a third of Medicare's expenditures arise in patients' last year of life,¹³ yet patients and their caregivers continue to report significant unmet supportive care needs during this time.³

A recent IOM report on the quality of palliative and end-of-life care³ highlighted healthcare system strain associated with the provision of optimal palliative care. The report attributed this strain to the relatively small number of individuals specializing in palliative care in the United States and a lack of confidence and proficiency among primary and specialty care clinicians in planning for and delivering basic palliative care services. In addition, palliative care services are at risk for fragmentation and lack of coordination due to the variety of care settings through which patients with advanced illnesses are likely to transition in the course of their illness. An urgent need exists to identify, evaluate, and implement coordinated and efficient models of palliative care that leverage the expertise of diverse clinicians caring for patients with advanced illnesses in a way that care is planned and delivered consistent with patient and caregiver goals and preferences and minimizes the burden of illness for patients and their caregivers.³

IV. Evidence Gaps

Systematic Reviews

- Lorenz et al. (2008)⁸ conducted a meta-review of 33 systematic reviews and 89 reports of interventions focused on improving palliative care at the end of life. Topics included care of pain, dyspnea and depression; advance care planning; continuity of care; and caregiver burden. They concluded that a majority of palliative and end-of-life care research directed at patients was dominated by studies on cancer whereas studies about caregiving focused primarily on dementia, and to a lesser extent, cancer. The review found strong evidence to support the use of multidisciplinary approaches to improve continuity and coordination of palliative care for patients. Multicomponent interventions were more consistent in showing improvement in caregiver burden and completion of advance directives. Several studies focused on healthcare utilization as the primary outcome with less attention given to patient- and family-centered outcomes. Finally, the authors observed that while several individual interventions had been tested to facilitate care planning and delivery of palliative care, including skilled facilitators to improve communication, peer mentoring, nurse care managers, multidisciplinary teams, and telephone support, ***palliative care trials that improved communication and coordination of palliative care services did not include head-to-head comparisons of different approaches.***
- In 2012, the Agency for Healthcare Research and Quality (AHRQ) published an evidence-based practice report on the topic of palliative care for advanced and serious illnesses that systematically reviewed 90 different intervention studies on a range of topics including pain management; communication and decision making; continuity, coordination, and transitions in care; and patient and family distress.⁹ Twenty-three studies focused on continuity, coordination, and care transitions; only 12 of these 23 studies were randomized controlled trials (RCTs). The report noted that while the strength of evidence was moderate for systems-focused interventions to improve patient and family satisfaction, the strength of evidence was low for interventions targeting improvement in patient quality of life, symptoms, and healthcare utilization. Interventions that included multiple components such as care coordinators, patient and family health education, and systematic patient assessment were more likely to affect patient outcomes. ***The authors of the report observed that no study compared integrated versus consultative approaches to palliative care delivery.***
Twenty intervention studies focused on communication and decision making in advanced and serious illness; only nine were RCTs and a majority (n=13) were conducted in the intensive care unit setting. The strength of evidence for interventions on communication and decision making was found to be moderate for improvements in healthcare utilization but low for improvements in patient satisfaction. The report cautioned that many studies in the review were of moderate to low quality due to methodological shortcomings: small sample sizes, insufficient recruitment, high rates of attrition, outcomes not specifically targeted to the intervention, and measurement tools that lacked specificity and relevance for populations with advanced or serious illness. The report called for future studies that included populations other than cancer, focused on multiple settings and providers of care, and followed patient populations over longer periods of time.
- A third systematic review titled “Building the momentum: The science of end-of-life and palliative care” was published in 2013 by the National Institute of Nursing Research (NINR).¹⁴ This report included a review of 3,155 research manuscripts published between 1997 and 2010, identifying several evidence gaps and areas for future



research. The report noted that scientific publications had tripled since 1997 with the primary emphasis on topics related to advance care planning, care settings and standards, and pain and other symptom management. In terms of medical conditions, approximately 63 percent of end-of-life research focused on specific conditions, with cancer accounting for more than half of these studies (53.5 percent/1,059 studies); while neurologic conditions (13.7 percent/271 studies), cardiac conditions (10.6 percent/210 studies), and respiratory conditions 8.8 percent (176 studies) followed far behind. Research on advanced HIV/AIDS, musculoskeletal, renal, and liver failure has remained limited—a combined 11.7 percent (232 studies).

The report noted a need for more rigorous research as only a small portion (13.3 percent of 3,155 studies) used experimental designs. Studies of care delivery models only accounted for 10.3 percent of published research, with relatively few of these being conducted in settings other than hospice. The report called for systematic evaluation of models of early, integrated palliative care for patients with advanced illnesses across a broad spectrum of services, including acute critical care and nursing home facilities. The report also called for innovative measures for evaluating and monitoring health risks among caregivers and evaluation of interventions that improve the caregiver experience.

Finally, NINR recognized the need for patient and family engagement in palliative care delivery research and called for greater partnerships between patients, families, clinicians, and scientists that would allow the community to help define priorities and improve research at all levels on this topic. This sentiment for greater patient and family engagement was echoed in a 2011 NINR summit on compassionate care, which concluded there was a “need to involve patients and family members in palliative care research: ideas to consider in collaborating in research design include equal partnerships in all phases of research, enhanced relevance of research for patients and their families, recruitment of research subjects, and informed consent processes.”⁵

- A 2014 systematic review and meta-analysis examining the efficacy of 56 advance care planning (ACP) interventions¹⁵ concluded that ACP interventions increase the completion of advance directives, the occurrence of discussions about end-of-life care preferences, and the concordance between patient’s preferences and end-of-life care received in different adult populations. However, the authors noted ***a lack of RCTs that conduct head-to-head comparison of the effectiveness of interventions that are limited to completion of advance directives versus communication interventions that focus on the broader ACP process.*** The authors also identified a need for systematic evaluations to identify the effective elements of ACP as well as effective ways to implement structured ACP in standard care. The IOM made similar observations in its “Dying in America” report³ where it identified the need for research on the effectiveness of thorough advanced care planning over time versus care planning tailored to immediate decisions as well as research investigating the effectiveness of strategies for advance care planning versus advance directives alone and their effects on achieving concordance with patients’ informed preferences and quality of care delivered to them.
- A recent evidence-based review commissioned by AHRQ of decision aids for advance care planning¹⁶ found numerous decision aids widely available to the public, but unrepresented in the empirical literature. Widely available tools vary in the degree to which they meet quality criteria established by the International Patient Decision Aids Standards Collaboration (IPDAS), and information about the effectiveness of these tools is generally lacking. ***The authors cite as a future direction that the comparative effectiveness of widely used***

- While not a systematic review, Bauman and Tremel (2014)² recently published an important review of the state of palliative care delivery in cancer. The authors discussed three different models of delivering outpatient palliative care services in the oncology setting: standalone, co-located, and fully embedded clinics that allow for co-management of patients between oncology and palliative care specialists. They observed that while integrating palliative care within oncology care had the potential to both reduce the burden on oncology professionals and efficiently address patients' supportive care needs, many cancer centers, despite having specialty palliative care teams, often engaged them only in the hospital setting and late in the patient's disease course.

The authors reviewed in detail three seminal randomized controlled trials that demonstrated significant benefits of integrating palliative care early with outpatient oncology care for patients diagnosed with advanced, incurable cancers.¹⁷⁻¹⁹ While one of the studies examined the impact of a specific psychoeducational intervention delivered by palliative care trained advanced nurse practitioners,¹⁷ the other two studies evaluated the effectiveness of more comprehensive, fully embedded co-management, outpatient palliative care models.^{18,19} **However, none of these important clinical trials conducted head-to-head comparison of alternative delivery models.** Overall, the three studies showed that compared to usual oncology care, patients assigned to integrated palliative care experienced greater improvements in depression and quality of life.

Given that disease trajectories, prognosis, and symptom burden can vary significantly across different types of advanced cancers, the authors identified a need to better understand which cancer patients were more likely to benefit from early integrated palliative care. In addition, given the shortage of clinicians trained in palliative care, the authors noted a need to determine whether and to what extent oncology professionals not trained in palliative care could integrate some beneficial aspects of palliative care in their practices.

Clinical Practice Guidelines

The National Consensus Project for Quality Palliative Care (NCP), a consortium of leading hospice and palliative care organizations, has developed clinical practice guidelines for palliative care.¹ The goal of the NCP guidelines is to "promote quality palliative care, foster consistent and high standards in palliative care, and encourage continuity of care across settings." These guidelines focus on multiple domains of palliative care including structure and processes of care; physical, psychological, and social aspects of care; spiritual, religious, and existential aspects of care; cultural aspects of care; care of the patient at the end of life; and ethical and legal aspects of care. The guidelines are intended to serve as a blueprint to create new programs or guide developing programs and have been adopted by the National Quality Forum, the nation's leading public-private partnership devoted to improving quality of care in the United States. Given that these guidelines are largely consensus-based, informed by the existing scientific evidence as well as the personal experiences of the developers, future systematic comparative effectiveness studies can serve to refine and validate these guidelines.

V. Likelihood of Implementation of Research Results in Practice

Methodologically rigorous CER studies that address important decisional dilemmas commonly faced by patients, caregivers, clinicians, and healthcare systems when dealing with advanced, serious illnesses are sorely needed. Identifying the most effective ways to facilitate communication and decision making within the context of advanced,



serious illnesses and deliver coordinated, patient-centered palliative care is likely to make a significant impact on meeting the supportive care needs of patients and their caregivers as well as improving their quality of life. Current practice guidelines are largely consensus-based statements that reflect an ideal blueprint for delivering palliative care, with several components requiring rigorous evaluation and validation in well-designed CER studies. Studies that systematically evaluate the effectiveness of different palliative care interventions would help healthcare systems to understand how to best deliver quality palliative care for patients and families dealing with advanced, serious illnesses.

VI. Durability of Information

CER on effective ways of planning for and delivering palliative care to patients with advanced, serious illnesses and their caregivers is likely to have a significant and enduring impact on healthcare practices and patient and family outcomes, given the significant attention the topic area has garnered in high-level reports and the dearth of CER in this area. The potential benefit of effective communication and decision-making interventions as well as new models of coordinated and efficient palliative care delivery to patients, caregivers, clinicians, and healthcare systems is clear. The need for CER on such topics is an urgent priority that is unlikely to diminish given the combined trends of population aging, increased longevity, greater comorbidity, along with projected shortage over time of clinicians needed to care for patients with advanced illnesses.

VII. Potential Research Questions

While specific CER questions addressing real-world decisional dilemmas faced by patients with advanced illnesses, caregivers, clinicians, healthcare systems, and other stakeholders will be developed based on the discussions at the workgroup meeting, we present example CER questions to facilitate discussion at the meeting.

- Timing of palliative care delivery: What is the comparative effectiveness of models involving palliative care specialists early in the disease course versus at key points based on changes in symptom burden on improving patient functioning and quality of life, reducing caregiving burden, and avoiding hospital and emergency department visits?²
- Coordination of palliative care: What is the comparative effectiveness of fully integrated palliative care models versus different modalities of consultative approaches (in person vs. virtual) on patient- and family-centered outcomes across different advanced illnesses?^{8,9}
 - Does the relative impact of different palliative care approaches vary with the trajectory of symptom burden and life expectancy associated with different advanced illnesses?
- Communication, shared decision making, and advance care planning: What is the comparative effectiveness of efficacious and widely used interventions designed to facilitate advance care planning conversations (e.g., patient decision aids, clinical decision support, etc.) between patients, caregivers, clinicians, and healthcare agents on patient- and family-centered outcomes including understanding of prognosis, congruence between patient preferences and care choices made, healthcare utilization, production of advance directives, patient and caregiver activation, and decision satisfaction?^{3,8,9}

- What is the comparative effectiveness of thorough advance care planning over time versus care planning tailored to immediate tasks and decisions such as production of advance directives on patient- and family-centered outcomes?^{3,15}
- Clinician communication training: What is the comparative effectiveness of clinician-directed education/training interventions designed to improve communication in the context of palliative care (e.g., facilitating advance care planning discussions, discussing prognosis with patients, handling emotional encounters, etc.) on patient-clinician communication, clinicians' ability to recognize patient psychosocial needs, patient understanding of prognosis, patient and caregiver distress, and patient satisfaction with care?³
- Caregiver burden: What is the comparative effectiveness of different approaches for facilitating caregiver preparedness and self-care ability across the trajectory of advanced illnesses on caregiver functioning and quality of life?¹⁰
- Caregiver burden: What is the comparative effectiveness of multicomponent interventions that include systematic assessment of caregiver burden and education tools tailored to caregivers' risk profile versus untailored caregiver education interventions versus usual care on caregiver functioning and quality of life?^{8,14}
- Symptom assessment and monitoring: What is the comparative effectiveness of real-time, in-home assessment/monitoring of patients' symptom burden using technology-supported interventions such as patient portals and mhealth applications versus clinic-based assessment of patient symptoms on patients' functioning and quality of life during the course of an advanced, serious illness?¹
- Dissemination and implementation: What is the comparative effectiveness of different approaches for disseminating and integrating effective palliative care interventions into routine clinical practice in various care delivery settings?

VIII. Conclusions

Evidence gaps identified in this topic brief include the need for more methodologically sound studies that utilize randomized controlled designs, conduct head-to-head comparisons of efficacious interventions, and are statistically powered to detect significant and clinically meaningful effects of effective approaches to planning for and delivering palliative care in multiple patient populations and illness trajectories. Recognizing the inherently patient-centered nature of palliative care, recent reports have called for engaging patients and family members as integral members of research teams focused on improving palliative care delivery. It is thus no surprise that a recent IOM report³ calls on organizations such as PCORI to fund the next generation of comparative effectiveness studies in palliative care that would have the potential to significantly improve the quality of life and care experience of patients and family members dealing with advanced, serious illnesses.



References

1. National Consensus Project for Quality Palliative Care (NCP). Clinical Practice Guidelines for Quality Palliative Care, 3rd ed.; 2013. http://nationalconsensusproject.org/Guidelines_Download2.aspx
2. Bauman JR, Temel JS. The integration of early palliative care with oncology care: the time has come for a new tradition. *J Natl Compr Can Netw.* 2014;12:1763-1771.
3. Institute of Medicine (IOM). Dying in America: Improving Quality and Honoring Individual Preferences Near the End of Life. 2014. Washington, DC: The National Academies Press.
4. National Quality Forum (NQF). A National Framework and Preferred Practices for Palliative and Hospice Care Quality: A Consensus Report. 2006. Washington, DC: NQF.
5. The Science of Compassion: Future Directions in End-of-Life and Palliative: A Summit Sponsored by the National Institute of Nursing Research and Partners. 2011. <https://www.ninr.nih.gov/sites/www.ninr.nih.gov/files/science-of-compassion-executive-summary.pdf>
6. WHO Definition of Palliative Care. <http://www.who.int/cancer/palliative/definition/en/>.
7. Fadul N, Elsayem A, Palmer JL, et al. Supportive versus palliative care: what's in a name? A survey of medical oncologists and midlevel providers at a comprehensive cancer center. *Cancer.* 2009;115:2013-2021.
8. Lorenz KA, Lynn J, Dy S, et al. Evidence for improving palliative care at the end of life: a systematic review. *Ann Intern Med.* 2008;148:147-159.
9. Dy SM, Aslakson R, Wilson RF, et al. Improving Health Care and Palliative Care for Advanced and Serious Illness. Closing the Quality Gap: Revisiting the State of the Science. Evidence Report No. 208. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2007-10061-I.) AHRQ Publication No. 12(13)-E014- EF. Rockville, MD: Agency for Healthcare Research and Quality. October 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
10. The NINR Innovative Questions (IQ) Initiative. <http://www.ninr.nih.gov/newsandinformation/iq#.VUFbuVlVko>
11. Institute of Medicine (IOM). Initial National Priorities for Comparative Effectiveness Research. 2009. Washington, D.C: The National Academies Press.
12. Centers for Medicare and Medicaid Services. Chronic Conditions among Medicare Beneficiaries, Chartbook, 2012 Edition. Baltimore, MD. 2012.
13. Hogan C, Lunney J, Gabel J, Lynn J. Medicare beneficiaries' costs of care in the last year of life. *Health Aff (Millwood).* 2001;20:188-95.



14. Building Momentum: The Science of End-of-Life and Palliative Care. A Review of Research Trends and Funding, 1997-2010. 2013. The National Institutes of Health, the National Institute of Nursing Research
15. Houben CHM, Spruit MA, Groenen MTJ, Wouters EFM, Janssen DJA. Efficacy of advance care planning: a systematic review and meta-analysis. *JAMDA* 2014;15: 477-489.
16. Butler M, Ratner E, McCready E, Shippee N, Kane RL. Decision aids for advance care planning: an overview of the state of the science. *Ann Intern Med*. 2014;161:408-418.
17. Bakitas M, Lyons KD, Hegel MT, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. *JAMA* 2009;302:741–749.
18. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010;363:733–742.
19. Zimmermann C, Swami N, Krzyzanowska M, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 2014; 383:1721–1730.