April 7, 2020

Suchitra Iyer, Ph.D.
Task Order Officer
Agency for Healthcare Research and Quality
5600 Fishers Lane
Rockville, MD 20857

RE: AHRQ Draft Comparative Effectiveness Review: Interventions for Dyspnea in Patients with Advanced Cancer

Dear Dr. Iyer:

The National Comprehensive Cancer Network® (NCCN®) is pleased to comment on the draft Comparative Effectiveness Review: Interventions for Dyspnea in Patients with Advanced Cancer as it relates to recommendations within the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®).

**NCCN Background**

As an alliance of 30 leading academic cancer centers in the United States that treat hundreds of thousands of patients with cancer annually, NCCN’s mission is to improve and facilitate quality, effective, efficient, and accessible cancer care so patients can live better lives. NCCN develops and maintains guidelines covering cancer prevention, screening, diagnosis, treatment, and supportive care that is widely used by clinical professionals throughout the spectrum of oncologic management, and apply to 97 percent of cancers affecting patients in the United States.

NCCN Guidelines and Library of Compendia products help ensure access to appropriate care, clinical decision-making, and assessment of quality improvement initiatives. Since 2008, CMS has recognized the NCCN Drugs & Biologics Compendium (NCCN Compendium®) as a mandated reference for establishment of coverage policy and coverage decisions regarding the use of drugs and biologics in cancer care. Commercial payers that represent more than 85 percent of covered lives in the United States also utilize the NCCN Guidelines and Library of Compendia products. The NCCN Guidelines are transparent, continuously updated, available free of charge online for non-commercial use, and are available through a multitude of HIT vendors. NCCN works with HIT vendors through permissions and licensing arrangements to allow for use of the NCCN Guidelines and the NCCN Compendium when supporting decision making that impacts patient access to appropriate therapy. NCCN appreciates the opportunity to respond to this Supplemental Evidence and Data Request and will focus comments on data supporting pharmacological and non-pharmacological interventions.
NCCN Categories of Evidence and Consensus

NCCN applauds AHRQ for acknowledging the importance of evidence in determining appropriate care and treatment of cancer patients, and appreciates the thoughtful and thorough draft review. The proposed review, however, contains an inaccurate statement regarding the emphasis placed on specific NCCN Guideline recommendations. As such, NCCN would like to provide clarifying information on our guidelines development process and the evidence-base for our guideline recommendations.

The NCCN Guidelines are composed of recommendations based on the best evidence available at the time they are derived. Recommendations within the NCCN Guidelines are derived from critical evaluation of evidence, integrated with the clinical expertise and consensus of a multidisciplinary panel of cancer specialists, clinical experts, and researchers in those situations where high-level evidence does not exist. Panels are charged with evaluating the efficacy of treatment, utility of tests or evaluations, and toxicity of the various interventions. Recommendations or changes to existing recommendations are agreed upon by Panel Members following review and discussion of the evidence during the Panel meetings. The Panel Members deliberate on the interpretation of the clinical evidence, and vote on how the evidence should be incorporated into the existing Guidelines.

NCCN Categories of Evidence and Consensus for recommendations are based on both the level of clinical evidence available and the degree of consensus within the NCCN Guidelines Panel. The Panel considers evidence of both efficacy and safety of interventions. Because most cancer therapies are associated with adverse effects, the Panel weighs the overall balance of therapeutic benefit, efficacy, safety and toxicity before making their recommendations for the NCCN Guidelines.

The specific definitions of the NCCN categories for recommendations are:

- **Category 1**: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate;
- **Category 2A**: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate;
- **Category 2B**: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate;
- **Category 3**: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Citing NCCN Guidelines within Proposed Report

Evidence for appropriate treatment of cancer patients with dyspnea is outlined in the NCCN Palliative Care Guidelines Version 1.2020.¹ This guideline contains

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recommendations for nonpharmacologic therapies including fans, cooler temperatures, stress management, relaxation therapy, and physical comfort measures. It also includes pharmacologic recommendations, including opioids and benzodiazepines, and noninvasive positive-pressure ventilation. All recommendations listed, highlighted in the attached Appendix, share a 2A Category of Evidence and Consensus, meaning no stronger emphasis is placed on pharmacologic over nonpharmacologic recommendations. In addition, when opioids and benzodiazepines are recommended, the panel includes caveats in the footnotes. For instance, benzodiazepines are proposed to be “considered if coexisting with anxiety”, and the side effects are well documented as well.

NCCN values the work of the draft report committee, and appreciates the committee’s conclusions regarding strength of evidence to support the use of nonpharmacological as opposed to pharmacological interventions. However, NCCN suggests amending the following statement found on page 61 of the draft report:

“In contrast to existing guidelines, which emphasize the use of pharmacologic interventions, particularly opioids and benzodiazepines, however we found stronger evidence to support use of nonpharmacological as opposed to pharmacological interventions”

This language could easily be amended to more accurately reflect the level of preference or emphasis placed on recommendations within the NCCN Guidelines, without negating the findings of the report. NCCN respectfully recommends using a similar statement as below:

“Existing guidelines recommend the use of both pharmacologic and nonpharmacologic interventions, however we found stronger evidence to support use of nonpharmacological as opposed to pharmacological interventions.”

NCCN again appreciates the opportunity to comment on AHRQ’s draft Comparative Effectiveness Review: Interventions for Dyspnea in Patients with Advanced Cancer as it relates to recommendations within the NCCN Guidelines. We would welcome the opportunity to discuss our comments further and look forward to working together to ensure access to high quality, high value care for patients with cancer. Thank you for your time and consideration of our comments.

Sincerely,

Robert W. Carlson, MD
Chief Executive Officer
National Comprehensive Cancer Network
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### Palliative Care

**NCCN Guidelines Version 1.2020**

#### Palliative Care

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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<th>ESTIMATED LIFE EXPECTANCY</th>
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1. **Assess symptoms comprehensively**
2. **Educate patient/family/caregiver on patient’s condition and risk/benefit of treatment options**
3. **Treat potentially reversible underlying causes/comorbid conditions:**
   - Radiation/chemotherapy
   - Therapeutic procedure for cardiac, pleural, or abdominal fluid
   - Bronchoscopic therapy
   - Bronchodilators, diuretics, steroids, antibiotics, or transfusions
   - Anticoagulants for pulmonary emboli
4. **Relieve symptoms**
   - Oxygen therapy for symptomatic hypoxia
   - Educational, psychosocial, and emotional support for the patient/family/caregiver
   - Nonpharmacologic therapies, including fans, cooler temperatures, stress management, relaxation therapy, and physical comfort measures
   - Pharmacologic therapy
     - Opioids
     - Consider benzodiazepines if coexisting anxiety
   - Noninvasive positive-pressure ventilation (e.g., CPAP, BiPAP) support if clinically indicated for severe reversible condition
   - Consider palliative RT for SVC syndrome or respiratory obstruction by tumor mass

**Acceptable outcomes:**
- Adequate dyspnea and symptom management
- Reduction of patient/family/caregiver distress

**If unacceptable:**
- Re-evaluate palliative care interventions and intensify as possible
- Consult or refer to specialized palliative care services or hospice

**Continue to treat and monitor symptoms and quality of life**

**Ongoing reassessment**

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**See Interventions (PAL-12)**

1. **See Drug Appendix (PAL-A)** for specific recommendations for medical management of symptoms.

kFor acute progressive dyspnea or for patients who are not opioid naive, more aggressive titration may be required.

lThe addition of benzodiazepines to opioids can increase the risk of respiratory depression.
### Dysepsnea

#### Interventions

- **Assess symptoms comprehensively**
  - Use labored breathing or other physical signs of dyspnea in noncommunicative patients
  - Address patient/family/caregiver preferences, prognosis, reversibility of respiratory failure, and treatment options
  - Consider time-limited trial of mechanical ventilation if indicated
  - Consider therapy with high-flow nasal cannula
  - Provide anticipatory guidance for patient/family/caregiver regarding dying of respiratory failure
  - Provide emotional and spiritual support
  - Focus on comfort
  - Continue to treat underlying condition as appropriate
  - Relieve symptoms
    - **Nonpharmacologic therapies**
      - Educational, psychosocial, and emotional support (See PAL-11)
      - Fans, cooler temperatures
    - **Pharmacologic therapies**
      - Oxygen if hypoxic and/or subjective relief is reported
      - If opioid naive, morphine<sup>m</sup>
        - If on chronic opioids, consider increasing dose by 25% for unrelieved dyspnea; See NCCN Guidelines for Adult Cancer Pain for additional information on opioid titration
      - Benzodiazepines
      - If fluid overload is a contributing factor:
        - Decrease/discontinue enteral or parenteral fluid
        - Consider low-dose diuretics
      - Reduce excessive secretions<sup>n</sup> with anti-secretory agents

#### Reassessment

Acceptable outcomes:
- Adequate dyspnea and symptom management
- Reduction of patient/family/caregiver distress

Continue to treat and monitor symptoms and quality of life

If unacceptable:
- Re-evaluate palliative care interventions and intensify as possible
- Consider a consultation with a palliative care specialist
- Consider sedation for intractable symptoms (See PAL-33)

Ongoing reassessment

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<sup>i</sup>See Drug Appendix (PAL-A) for specific recommendations for medical management of symptoms.

<sup>m</sup>For acute progressive dyspnea or for patients who are not opioid naive, more aggressive titration may be required.


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