MONA PATEL ON

Dyspnea in Advanced Cancer
Simple Measures & Strategies

‘Common, distressing, and often difficult to treat’

Review Article
GnRH Antagonists in Prostate Cancer
Adam S. Kittai, MD, Jessica Blank, Julie N. Graff, MD

Ask the PI
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Meagan A. Jacoby, MD, PhD, Matthew Walter, MD

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Dyspnea in Advanced Cancer: Simple Measures and Strategies

Mona S. Patel, DO

PERSPECTIVE: Mehmet Sitki Copur, MD, FACP

A hospice physician and Albert Einstein College of Medicine professor talks about how to manage the dyspnea that often accompanies late-stage cancer, causing anxiety and isolation.

Cognitive Impairment in Survivors of Non-CNS Malignancies

Ni-Chun Chung, MSc, Adam K. Walker, PhD, Haryana M. Dhillon, PhD, and Janette L. Vardy, MD, PhD

PERSPECTIVE: Nicole A. Shonka, MD

Australian researchers from the universities of Queensland and Sydney explore the cognitive impairment that is so common in patients undergoing chemotherapy, and how to address it.

Genomic Testing in Patients With Prostate Cancer: Treatment Guidance

POINT: Brandon Bernard, MD, MPH, and Thomas W. Flaig, MD

COUNTERPOINT: W. Kevin Kelly, DO, and Karen E. Knudsen, PhD

Experts offer differing views on the role of genomic testing to guide prostate cancer treatment.
IN THIS ISSUE

Review Article
599 Gonadotropin-Releasing Hormone Antagonists in Prostate Cancer
Adam S. Kittai, MD, Jessica Blank, and Julie N. Graff, MD
PERSPECTIVE: Oliver Sartor, MD

The authors, from Oregon Health and Science University, review the mechanism of action, as well as the potential risks and benefits, of gonadotropin-releasing hormone agonists vs antagonists.

How An Expert Approaches It
617 Immunotherapy in Head and Neck Cancer
Xinyu Nan, MD, Kathryn A. Gold, MD, and Ezra Cohen, MD
PERSPECTIVE: Conor Steuer, MD

Physician researchers from the University of California, San Diego, discuss the major role immunotherapy will likely play in the treatment of these cancers, based on the KEYNOTE-048 trial.

Ask the PI
627 Identifying Molecular Markers of Relapse in Myelodysplastic Syndrome
Meagan A. Jacoby, MD, PhD, and Matthew Walter, MD

In an exclusive interview with ONCOLOGY, principal study investigators from the Washington University School of Medicine discuss the implications of their recent study, published in the New England Journal of Medicine.

Test Your Image IQ
629 A 58-Year-Old Man With Purpuric Nodules on the Leg and Foot
Cesar A. Moran, MD

Review a pathology image to establish a diagnosis.

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Strategies for the Optimal Management of Dyspnea in Cancer Patients With Advanced Illness

Mona S. Patel, DO

**ABSTRACT:** Dyspnea in cancer patients can lead to significant deleterious effects. There are multiple conditions that can cause dyspnea. It is important to determine which of these causes are potentially reversible and treatable, so that they can be promptly addressed. Both pharmacologic and nonpharmacologic approaches should be used to treat this difficult condition. As patients advance in their illness, palliative treatments can be considered, such as low-dose opioids, oxygen therapy, and treatments directed at anxiety relief. Physicians should also discuss goals of care with their patients.

**Introduction**

Dyspnea is a common condition in patients with advanced cancer, with studies reporting a prevalence of 15% to 55% at initial diagnosis, and 40% to 90% during terminal stages.[1,2] The American Thoracic Society defines dyspnea as a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. It is influenced by psychological, physical, environmental, and social factors.[3,4]

Dyspnea can affect a patient’s quality of life by reducing activity level, functional capacity, and performance status, causing distress to both the patient and his or her family. This can lead to depression, anxiety, social isolation, and fear. Anxiety is a prominent symptom associated with dyspnea, and one tends to perpetuate the other.

Dyspnea has been shown to cause suffering, not only for cancer patients, but for their caregivers as well. Dyspnea in lung cancer patients is the most frequent cause for admission to the hospital. The prevalence of dyspnea also increases as patients near death.[5-7]

Clinicians should be aware that, like pain, dyspnea is often reported by patients who may not have tachypnea or appear to be dyspneic. It is a subjective condition that is reported by the patient. In a study of hospice patients, tachypnea did not correlate with patient-reported dyspnea. Of the patients studied, 77% reported dyspnea, but only 39% were recorded as having symptoms.[8]

**Pathophysiology**

The pathophysiology of dyspnea is complex and multifactorial. It is poorly understood, given the many factors that play a role in the experience. These include mechanical, chemoreceptor, and environmental factors. Often dyspnea occurs when a patient experiences hypoxia, metabolic acidosis, and hypercapnia, or when a patient engages in exercise stimulating the respiratory drive.

One mechanism that can drive dyspnea is when peripheral chemoreceptors in the carotid bodies and aorta respond to hypoxemia. Another mechanism that can occur is when central chemoreceptors in the brain respond to increases in carbon dioxide. A third occurs when mechanoreceptors in the lungs, chest wall, and airways respond to stretch, resulting in dyspnea. An example of this is when patients have airflow obstruction and there is an increase in mechanical resistance. Alternatively, juxtacapillary receptors at the junction of the alveoli and capillaries respond to alveolar fluid or microemboli, resulting in dyspnea.[9,10]

**Etiology and Assessment**

Dyspnea can be caused by a number of reversible and irreversible factors. In cancer patients, it can be caused by factors related to the cancer itself, a patient’s comorbid conditions, or by the treatment given for the cancer.

It is important to determine the underlying cause of the dyspnea to opti-
Dyspnea, the highly threatening experience of breathlessness, can turn simple daily activities for a cancer patient into a major challenge. What is striking and difficult about dyspnea is that by definition it is a subjective feeling. In 25% of the cases, no specific cause can be identified. Yet, it has a very significant impact on quality of life, and not only for patients; family and friends endure great emotional suffering when their loved one is facing loss of independence and increasing physical distress. Dyspnea often leads to severe anxiety, which often causes dyspnea. The psychosocial dimensions and environmental conditions play a major role in this clinical condition.

Dr. Patel nicely reviews the conditions that cause dyspnea in cancer patients and recommends effective treatment strategies. The real challenge, however, is in the management of patients in whom no specific cause of dyspnea can be established. A cancer patient’s self-report of dyspnea may encompass physical, as well as psychological, social, and spiritual, domains. Thus, the term “total dyspnea” has been proposed to be similar to “total pain” to capture the complexity of this condition. The total dyspnea model tries to comprehensively define the suffering of the patient experiencing dyspnea. It describes the patient’s experience in a broader manner to incorporate the wide spectrum of new treatment interventions and approaches, spanning from pharmacological and mechanical strategies, to behavioral strategies, for symptom management and resolution. Utilization of a multidisciplinary approach focusing on the patient’s psychological, social, and spiritual needs, as well as on the physical symptoms, are highlighted in this model.

As pointed out by Dr. Patel, while the body of literature continues to grow in this field, the need persists for further research regarding management strategies for dyspnea. Future research addressing the role of modulating factors and the mechanisms involved in dyspnea processing, particularly on the effects of attention, self-awareness, and distraction, are desperately needed. Integrating behavioral measures and carefully designed neuroimaging protocols to define the neural pathways of the respiratory network in perception and modulation of dyspnea would be invaluable.

Last but not least, Dr. Patel brings awareness to one more very important aspect of cancer care that is currently being underutilized by oncology providers; the integration of palliative care into standard oncology care. Patients with advanced cancer should receive dedicated palliative care services early in their disease course concurrent with active treatment. One of the essential components of palliative care is symptom, distress, and functional status management, which includes the management of dyspnea.

**Management**

The cornerstone of treatment for dyspnea is to determine and treat its underlying cause. Reversible causes should be addressed and managed promptly (Table 2).

Patients with cancer who have comorbidities contributing to their dyspnea...
should undergo treatments directed at the comorbid condition. Many cancer patients may have chronic obstructive pulmonary disease (COPD) or asthma that causes dyspnea and should be managed with bronchodilators, corticosteroids, and oxygen. Antibiotics may be appropriate if there is suspicion of pneumonia or bronchitis. Patients with congestive heart failure as a comorbidity should be treated with oxygen and diuretics.

Patients with cancer may have malignant pleural or pericardial effusions, which can be treated with pleurocentesis or pericardiocentesis, respectively. Another complication of malignancy is superior vena cava syndrome. These patients typically respond well to high-dose steroids and radiation therapy.

Clinicians should also have a high index of suspicion for dyspnea caused by pulmonary toxicity and pneumonitis from treatment with immunotherapy agents, as well as interstitial lung disease (ILD) caused by tyrosine kinase inhibitors (TKIs). While ILD is a rare complication of TKI use, with a variable incidence rate of 0.2% to 10.9%, it can cause significant clinical symptoms and at times can be fatal.[12] Patients who have anemia can benefit from blood transfusions to relieve dyspnea. For patients with obstruction of a bronchus, radiation and bronchial stents may be beneficial, along with laser or cryotherapy as alternative options.

Patients with malignancy are at high risk for developing thrombosis and pulmonary emboli, for which anticoagulation is indicated. Other causes of dyspnea, including ascites or pleural effusions, can be treated with fluid removal.

Dyspnea-associated anxiety can usually be managed with pharmacologic treatments, such as selective serotonin reuptake inhibitors or with benzodiazepines during more advanced stages of illness, as well as nonpharmacologic measures, such as breathing exercises, relaxation techniques, and psychosocial support.

As patients advance in their disease process, palliative therapies may be necessary for symptom relief. Both pharmacologic and nonpharmacologic treatments can be administered to assist patients with symptom management of dyspnea to improve quality of life. When considering what therapies are best, it is important to discuss the goals of care with the patient and family.

Simple measures such as using a fan to blow air on the face or having the patient positioned in front of an open window have been described as helpful for symptom management of dyspnea in cancer patients.[14-17] Other nonpharmacologic strategies include pacing activities, avoiding exertion, and keeping calm to reduce anxiety. The benefits of nonpharmacologic interventions include the fact that they are inexpensive, convenient, have no adverse effects, and are available in many different settings.

Oxygen use for relief of dyspnea has been shown to be beneficial, but only for patients with hypoxemia. It is postulated that ambient air may provide temporary symptomatic relief of dyspnea via a placebo effect caused by the passage of increased airflow along the nasal passageways, which decreases anxiety. According to a multicenter, double-blind, randomized controlled trial, supplemental oxygen was shown to provide no additional benefit for refractory dyspnea in patients with partial pressure of oxygen ≥ 55 mm Hg compared with room air via nasal cannula.[18] Similarly, in a 2012 systematic review and meta-analysis of patients with lung cancer and lung metastasis, researchers found no advantage.

### TABLE 1 Causes of Dyspnea in Cancer Patients

<table>
<thead>
<tr>
<th>Cancer-Related Causes</th>
<th>Indirect Cancer-Related Causes</th>
<th>Comorbidity-Related Causes</th>
<th>Treatment-Related Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Malignant pleural effusions</td>
<td>• Pneumonia</td>
<td>• CHF</td>
<td>• Pulmonary fibrosis due to immunotherapy or TKIs</td>
</tr>
<tr>
<td>• Superior vena cava syndrome</td>
<td>• Pneumonitis</td>
<td>• Cardiac ischemia</td>
<td>• Post-radiation pericarditis</td>
</tr>
<tr>
<td>• Lung metastasis/pleural involvement</td>
<td>• Pneumothorax</td>
<td>• Cardiac arrhythmia</td>
<td>• Pulmonary or cardiac toxicity from chemotherapy</td>
</tr>
<tr>
<td>• Airway or vessel obstruction by tumor</td>
<td>• Pulmonary embolism</td>
<td>• COPD</td>
<td>Surgery (pneumonectomy)</td>
</tr>
<tr>
<td>• Lymphangitic carcinomatosis</td>
<td></td>
<td></td>
<td>• ILD</td>
</tr>
</tbody>
</table>

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; TKIs = tyrosine kinase inhibitors.
Dyspnea in Cancer Patients
Continued from page 585

of supplemental oxygen compared with room air for alleviating dyspnea in cancer patients that were not hypoxemic. [19]

Opioids have been used for symptomatic relief of dyspnea, especially for patients who are advancing in their illness.[20-23] A systematic review and meta-analysis demonstrated a beneficial effect of opioid treatment for dyspnea in patients with lung cancer and lung metastasis.[19] Other studies have also found that low-dose oral morphine may be helpful for symptom management of breathlessness in patients with advanced respiratory and cardiac conditions.[24] In terms of the route of delivery of opioids, the evidence favors the oral and parenteral routes.[24] A Cochrane review in 2001 found no benefit for nebulized opioids over other routes of delivery for relief of dyspnea in advanced cancer patients. However, the evidence and quality of these studies were limited.[25] Of the opioids, morphine has been the most widely studied for the treatment of dyspnea. The other opioids are postulated to have comparable effects on dyspnea given their similar mechanisms of action. However, proof of efficacy of fentanyl in particular is lacking and requires further investigation in randomized controlled trials.[26]

Clinicians often cite concerns for respiratory depression when using opioids, hence their reluctance to use them in the advanced chronically ill patient with dyspnea. However, a meta-analysis showed no evidence of clinically significant respiratory depression in those with chronic breathlessness treated with regular low-dose opioids.[27]

As previously mentioned, anxiety is a common symptom that patients with dyspnea experience. Benzodiazepines may provide relief from anxiety, thereby providing relief from dyspnea as well. However, a Cochrane review did not show evidence for or against the use of benzodiazepines for the symptomatic treatment of dyspnea.[28] There is also concern regarding the drowsiness that benzodiazepines can cause, and they are typically reserved for patients during terminal stages.

Patients with advanced cancer may also experience dyspnea caused by fatigue and respiratory muscle wasting. Typically, breathing exercises and relaxation techniques have been used for symptom relief. Acupuncture has also been considered to assist with dyspnea relief; however, the evidence does not support or refute its effectiveness.[29]

Another modality that is used in patients who have respiratory distress is noninvasive positive pressure ventilation (NPPV). NPPV can be helpful to patients who have respiratory muscle fatigue, either from neuromuscular disorders or COPD. NPPV can be continuous or intermittent and is administered via facial or nasal masks. The majority of patients studied with NPPV are those with COPD. However, patients with cancer can have respiratory muscle weakness causing dyspnea and could potentially also benefit from NPPV.[9]

Clinicians should discuss the goals of care and preferences regarding advance directives with patients who have advanced cancer. These conversations should also include preferences on mechanical ventilation, hospitalization, code status, and palliative measures.

**Conclusion**

Dyspnea is a common and distressing condition in cancer patients, and is often difficult to treat. While the body of literature continues to grow in this field, the need persists for further studies and research regarding management strategies for dyspnea.

**FINANCIAL DISCLOSURE:** Dr. Patel has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

**TABLE 2  Conditions Causing Dyspnea and Their Associated Treatments in Cancer Patients**

<table>
<thead>
<tr>
<th>Conditions Causing Dyspnea</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusions</td>
<td>Pleurocentesis, talc pleurodesis, pleural catheter insertion</td>
</tr>
<tr>
<td>Superior vena cava syndrome</td>
<td>High-dose steroids, radiation therapy</td>
</tr>
<tr>
<td>Pericardial effusions/tamponade</td>
<td>Pericardial drainage</td>
</tr>
<tr>
<td>Bronchial obstruction</td>
<td>External beam radiation or endobronchial radiation, laser treatments, cryotherapy, stents</td>
</tr>
<tr>
<td>Anemia</td>
<td>Blood transfusions</td>
</tr>
<tr>
<td>Lymphangitic carcinomatosis</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>High-dose steroids</td>
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</tbody>
</table>

**Dr. Patel** is the Associate Program Director of the Hospice & Palliative Medicine Fellowship and a Hospice Physician at Metropolitan Jewish Health Systems Hospice & Palliative Care and an Assistant Professor in the Department of Family and Social Medicine at Albert Einstein College of Medicine in New York, New York.
Mechanisms and Treatment for Cancer- and Chemotherapy-Related Cognitive Impairment in Survivors of Non-CNS Malignancies

Ni-Chun Chung, MSc, Adam K. Walker, PhD, Haryana M. Dhillon, PhD, and Janette L. Vardy, MD, PhD

ABSTRACT: Up to 70% of survivors of adult-onset, non–central nervous system (CNS) solid tumors report cognitive symptoms, and approximately 30% have impairment on formal neuropsychological testing. The etiology of the impairment is unknown. There is a lack of robust evidence on how to prevent or treat cancer-related cognitive impairment (CRCI). Here, we review the evidence for the putative mechanisms of CRCI by examining clinical and preclinical models, primarily those associated with chemotherapy. Pharmacologic and nonpharmacologic options for treating CRCI are discussed based on the best evidence available. Practical clinical advice for health professionals managing patients with CRCI is also provided.

Introduction
Most cancer survivors report cognitive symptoms while undergoing chemotherapy, with gradual improvement over time after treatment ends. However, at least one-third of survivors experience sustained cognitive symptoms, which are often associated with fatigue, depression and anxiety, and poor quality of life.[1,2] Commonly reported complaints include increased difficulty with multitasking, word-finding, memory, and concentration. [3] Only a weak association has been found between cognitive symptoms and cognitive performance as assessed by formal neuropsychological testing. The incidence of objective cognitive impairment varies by tumor type, as well as by the treatment received, time from treatment, neuropsychological tests performed, and the definition of impairment used. For instance, the largest longitudinal prospective clinical study to assess cognition in cancer patients found that, soon after diagnosis and prior to any chemotherapy, 43% of colorectal cancer patients had cognitive impairment, compared with 15% of non-cancer controls; in addition, 46% of survivors reported impairment 12 months later, compared with 13% of controls.[4] The cognitive domains most affected included attention/working memory, verbal memory, and processing speed. Interestingly, no difference was seen in neuropsychological performance related to chemotherapy, but the rate of cognitive symptoms at 6 months was significantly higher in those who received chemotherapy, although it improved over time. In studies of women
Chemobrain: Objectively Measuring an Elusive and Troubling Entity

Chemobrain” is the most common phrase patients and clinicians use to describe cognitive deterioration resulting from cancer therapy. Affected survivors report distractibility, as well as impaired short-term memory and executive functioning. While recognition of chemobrain has increased in the last decade, its definition requires improvement, and its mechanisms and pathophysiologic correlates need to be better understood.

As outlined in the thorough review by Chung and colleagues, a number of well-designed studies have prospectively measured changes in cognition before, during, and after chemotherapy—with greatly variable and frequently contradictory findings. The potential confounders affecting cognition in this vulnerable population are almost overwhelming, and several are subjectively assessed: age,[1,2] menopausal status,[2] educational level,[3] number of cycles and type of chemotherapy,[4] time since last treatment,[1] fatigue,[1] and depression and anxiety.[3,4] In regard to the latter two confounders, chemotherapy has been shown to decrease serotonin release in mice; in addition, glial cell line–derived neurotrophic factor produces a neuroprotective environment, which is further supported by a study showing an increase in MRI gray matter signal around the hippocampus in patients given selective serotonin reuptake inhibitors.[5] Only in the last 2 decades has much research been conducted in this area. These studies are assessing the potential roles of hormones, exercise, educational programs, neurocognitive interventions, genetic markers, smoking, anesthesia, and many other factors. The previously discussed confounders, however, make this area of study increasingly complex.

Although researchers have a battery of validated cognitive tests in their arsenal, more is needed to objectively measure this elusive entity. First, studies should remove “healthy controls” and instead compare cognition in groups receiving chemotherapy vs those with cancer not receiving chemotherapy. Second, studies should follow survivors longitudinally to detect within-patient differences to determine acute vs latent effects or recovery. Third, studies should control for concurrent depression or anxiety via exclusion or stratification. Lastly, whenever possible, clinical biomarkers and imaging correlates should be explored and validated. Only through cooperative efforts can psychologists, neuro-psychologists, and medical oncologists learn to predict and protect those at greatest risk.

Mechanisms of Cancer-Related Cognitive Impairment

Inflammation

The role of inflammation is the most extensively studied mechanism in the development of CRCI. It is based on the assumption that malignancy and systemic treatments, such as chemotherapy, induce inflammation in the body, which is then propagated to the brain via well-characterized pathways of immune-to-brain signaling.[8,9] Neuroinflammation then regulates mood, cognitive, and behavioral changes associated with CRCI. Preclinical studies have helped confirm the potential role of inflammation in CRCI. Inflammatory factors, including cytokines and their receptors, NF-κB and STAT3 signaling cascades, and enzymes (eg, IDO, COX, and iNOS), have been identified and tested in rodent models of CRCI.[10-14] Tumor-bearing mice show evidence of depression-like behaviors, with increased expression of proinflammatory cytokines in the tumor microenvironment, plasma or serum, and hippocampus.[15] Hippocampal interleukin (IL)-1β,[16] IL-6, and tumor necrosis factor (TNF)-α[17] have also been associated with cognitive impairment and reduced neurogenesis in tumor-bearing mice. Chemotherapy-treated rodents have elevated proinflammatory cytokines in the circulation, peripheral sensory neurons, and the brain. [18-20] While most studies suggest that proinflammatory cytokines are responsible for CRCI, several have demonstrated that chemotherapy...
also alters anti-inflammatory cytokine profiles.[18,20]

Several clinical studies in breast cancer survivors have shown an association between proinflammatory cytokines and CRCI. Higher circulating IL-1ra and TNF-RII expression levels induced by chemotherapy have been reported to be significantly correlated to memory complaints and lower brain metabolism compared with patients who did not receive chemotherapy[21,22]; in addition, IL-6 and TNF-a levels in the sera of patients post-chemotherapy have been associated with verbal memory performance and hippocampal volume.[23] A number of other clinical studies have described associations between circulating cytokines and aspects of cognitive function in breast cancer patients during and after treatment.

While a number of studies have demonstrated a relationship between inflammation and CRCI, several clinical studies have failed to find any such relationship. Most notably, our large study in colorectal cancer survivors failed to show an association between circulating markers of inflammation and global CRCI.[4] Several explanations are possible: 1) The association between inflammation and CRCI is weak. 2) The relationship between inflammation and CRCI differs by tumor type; most positive studies are in breast cancer. 3) Single cytokine analysis may not be the best approach to detect a relationship between inflammation and CRCI. Instead, downstream receptors, ratios of pro vs anti-inflammatory cytokines, or molecular signaling pathways may be more informative. 4) Circulating cytokines in serum may not reflect the inflammatory milieu of specific organs in which the required cytokine is used (eg, the brain). Given the discrepancy in findings between studies, the jury is still out regarding the role of inflammation in CRCI; if the relationship is positive, the potential exists to use anti-inflammatory agents to treat and prevent CRCI.  

**TABLE 1**Mechanisms Associated With Cancer-Related Cognitive Impairment

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><strong>INFLAMMATION</strong></td>
<td>- Mitochondrial damage</td>
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<tr>
<td></td>
<td>- Glucose metabolism</td>
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<td>- Apoptosis</td>
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<td>- Necrosis</td>
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<td><strong>NEUROTOXICITY</strong></td>
<td>- Hypothalamic-pituitary-adrenal (HPA) Axis</td>
</tr>
<tr>
<td><strong>GENETIC POLYMORPHISMS</strong></td>
<td>- Apolipoprotein E (ApoE)</td>
</tr>
<tr>
<td></td>
<td>- Catechol-O-methyltransferase (COMT)</td>
</tr>
<tr>
<td></td>
<td>- Brain-derived neurotrophic factor (BDNF)</td>
</tr>
</tbody>
</table>

Direct Cytotoxic Damage to the Brain (Neurotoxicity)

Chemotherapy may impair metabolic and cellular function of the brain through direct cytotoxic damage to neurons and other cells. Most studies have used preclinical animal models of CRCI due to the need to access brain tissue. While many agents do not provide predictable responses across the CNS due to variable blood-brain barrier penetration, several studies have demonstrated the capacity of some chemotherapy agents, including fluorouracil, lapatinib, and temozolomide, to cross the blood-brain barrier despite efflux mechanisms, such as the P-glycoprotein transporter.[24]

Several studies have demonstrated increased apoptosis or necrosis[25-27] and reduced neurogenesis in response to chemotherapy.[28-30] While increased apoptosis/necrosis may play a role, chemotherapy agents are typically more effective in killing rapidly dividing cells (ie, tumor cells) compared with more stable neuronal cells.[31] Recent evidence suggests that chemotherapy-induced damage impedes metabolic function and energy utilization of brain cells, as opposed to causing the death of brain cells. This may help explain the relatively subtle effects on cognition that typify CRCI. Several studies support this mechanism. For example, cisplatin was shown to cause mitochondrial DNA damage in clinical studies and to reduce adenosine triphosphate production by 70% in vitro.[32,33] This has been confirmed in preclinical experiments connecting cognitive impairment, mitochondrial damage, and reduced dendritic branching and spine density in the brain after cisplatin.[34-36] Moreover, patients receiving platinum-based treatments have shown decreased glucose metabolism in both gray and white matter structures. [37]

The Hypothalamic-Pituitary-Adrenal (HPA) Axis

Some have suggested that the HPA axis contributes to CRCI, but few studies have directly examined the validity of this statement. Changes in the diurnal rhythmicity of cortisol and blunted cortisol responses to stress, as well as reduced expression of genes that support the possibility of functional glucocorticoid receptor resistance, have been observed in breast cancer survivors.[38-40] However, these studies have focused on fatigue, and a direct examination of the HPA axis in CRCI has yet to be conducted. Regardless, studies in non-cancer populations have demonstrated that the HPA axis plays an integral role in learning and memory.[41,42] McEwen and colleagues postulated that chronic stress caused by cancer and cancer treatment may result in allostatic overload in survivors, which dysregulates stress hormones such as glucocorticoids and homeostasis. This has been reported to contribute to imbalances in metabolism and decreases in neurogenesis, size, or plasticity of the hippocampus.[43,44]

**Genetic Associations**

Several genetic variabilities have been associated with CRCI. Apolipoprotein E (ApoE) plays a role in lipid metabolism and is implicated in Alzheimer’s disease.
### TABLE 2  Summary of Nonpharmacologic Interventions for Cancer-Related Cognitive Impairment

<table>
<thead>
<tr>
<th>Author (Year); Country</th>
<th>Study Design; Number of Patients (N)</th>
<th>Population</th>
<th>Intervention Summary</th>
<th>Outcomes</th>
<th>Gaps/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive Training</strong></td>
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<tr>
<td>Bray (2016), Australia[53]</td>
<td>RCT N = 242</td>
<td>Cancer survivors 6–60 mos post-adjuvant chemotherapy; self-reported cognitive symptoms</td>
<td>• C: 1 telephone consultation to teach compensatory strategies</td>
<td>• Cognitive symptoms significantly improved post-intervention (P &lt; .001) and 6 mos later (P &lt; .001)</td>
<td>• Population largely women with breast cancer</td>
</tr>
<tr>
<td>Kesler (2013), United States[54]</td>
<td>RCT N = 41 C = 20 I = 21</td>
<td>Breast cancer survivors aged at least 40 yrs; ≥ 1.5 yrs post-adjuvant chemotherapy</td>
<td>• C: Waitlist</td>
<td>• Improvement in I vs C: ES 0.58 (P = .008); verbal fluency ES 0.92 (P = .003)</td>
<td>• Very small sample with multiple comparisons</td>
</tr>
<tr>
<td>Von Ah (2012), United States[55]</td>
<td>RCT N = 88 C = 29 Ia = 29 Ib = 30</td>
<td>Breast cancer survivors self-reporting cognitive symptoms; ≥ 40 yrs; postmenopausal; ≥ 1yr post-adjuvant chemotherapy</td>
<td>• C: Waitlist</td>
<td>• Ia showed better immediate (ES 0.59; P = .006) and delayed (ES 0.72; P = .013) memory performance at 2 mos</td>
<td>• Some variability across neuropsychological tests</td>
</tr>
<tr>
<td><strong>Cognitive Rehabilitation</strong></td>
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<tr>
<td>Ercoli (2015), United States[60]</td>
<td>Randomized phase II study N = 48 C = 16 I = 32</td>
<td>Women aged 25–75 yrs with breast cancer stage 0–III; completed primary treatment 18–60 mos prior; cognitive symptoms</td>
<td>• C: Waitlist</td>
<td>• Cognitive symptoms improved in I group (P = .01)</td>
<td>• Randomized phase II study suggests efficacy</td>
</tr>
<tr>
<td>Green (2018), Australia[61]</td>
<td>Feasibility study N = 27</td>
<td>Breast cancer treated with chemotherapy 6–60 mos cognitive symptoms</td>
<td>Single-arm study using RECOG, a 4-wk cognitive rehabilitation program involving skills training, compensatory strategies, group discussion, and homework</td>
<td>• Improved PCI (P = .05); impact on QOL (P = .004); improved information processing efficiency (P = .008) and EF (P = .002); only EF remained significant after correction for multiple comparisons</td>
<td>• Feasibility of clinical implementation study with small numbers and multiple comparisons</td>
</tr>
<tr>
<td>King (2015), Australia[62]</td>
<td>RCT N = 29 C = 13 I = 16 Community control = 16</td>
<td>Adult cancer survivors (non-CNS) completed treatment ≥ 6 mos prior</td>
<td>• C: Waitlist</td>
<td>• I: RECOG (see above)</td>
<td>• Nonrandomized community control</td>
</tr>
<tr>
<td>Mihuta (2018), Australia[63]</td>
<td>RCT N = 59 (51 completed T1 assessment; 44 analyzed) I cancer (Ic): N = 16 (12; 12) I non-cancer (Inc): N = 23 (21; 16) C non-cancer: N = 20 (17; 15)</td>
<td>Cancer: adult-onset cancer (non-CNS); completed primary treatment ≥ 6 mos prior; cognitive symptoms</td>
<td>• C: Waitlist (non-cancer only)</td>
<td>• PCl improved over time in Ic and Inc groups (P = .001); effect maintained at 3 mos (P = .033)</td>
<td>• Nonrandomized cancer group</td>
</tr>
</tbody>
</table>

**Cognitive Behavioral Therapy (Compensatory, Mixed)**

| Becker (2017), United States[56] | Pilot study; quasi-experimental N = 20 | Breast cancer; aged 35–65 yrs | Single-arm study using compensatory strategies (6 group sessions building self-efficacy for compensatory strategies and other health behaviors, plus computer-based cognitive training exercises) and brain-training practice | No change in scores for cognitive performance, concerns, or strategies | • Nonrandomized pilot study |
| Ferguson (2007), United States[58] | Pilot study, single arm N = 29 | Breast cancer stage I or II; completed adjuvant chemotherapy ≥ 3 mos prior | Single-arm study using MAAT, including participant workbook, 4 individual monthly visits, and phone support between visits (7 total contacts). Visits 30–50 min duration | • Improved cognitive symptoms from baseline to follow-up (P < .001), and sustained at 2 and 6 mos | • Single-arm pilot study |
| Ferguson (2016), United States[59] | RCT N = 47 (35 analyzed) C = 20 (13) I = 27 (22) | Breast cancer stage I or II; completed adjuvant chemotherapy ≥ 3 mos prior | • C: Supportive therapy (active control) | • MAAT group showed improved PCl at 2 mos (ES, 0.52; P = .02) | • Small study with high attrition rate |

*P values ranged from .01 to < .001*
### Exercise (Aerobic, Resistance, Mixed Exercise, Yoga, Qigong, Tai Chi)

#### Physical Activity (PA)

<table>
<thead>
<tr>
<th>Author (Year); Country</th>
<th>Study Design; Number of Patients (N)</th>
<th>Population</th>
<th>Intervention Summary</th>
<th>Outcomes</th>
<th>Gaps/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park (2017), Korea[57]</td>
<td>Pilot quasi-randomized trial</td>
<td>Breast cancer stage I-II; scheduled for high-dose adjuvant chemotherapy; aged 20–60 yrs at diagnosis</td>
<td>• C: Waitlist&lt;br&gt; • I: Compensatory strategies training – PCHP</td>
<td>• PCHP demonstrated improved objective cognitive function, memory, and executive function compared with control over time&lt;br&gt; • PCI remained stable over time for PCHP compared with C</td>
<td>• Treatment allocation via raffle (odd and even numbers)&lt;br&gt; • Small sample size and high attrition rate</td>
</tr>
<tr>
<td>States[64]</td>
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<td>United States[66]</td>
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<tr>
<td>Vadiraja (2009), India[72]</td>
<td>RCT</td>
<td>Breast cancer stage I-II; planned for radiation therapy; aged 30–70 yrs; high school education; performance status 0–2</td>
<td>• C: Waitlist&lt;br&gt; • I: Yoga 60 mins daily&lt;br&gt; • I: Brief supportive therapy&lt;br&gt; • I: Hatha yoga 2x wk; 90-min sessions for 12 wks</td>
<td>I improved cognitive symptoms post-intervention (P &lt; .03)&lt;br&gt; I improved cognitive symptoms post-intervention (P &lt; .03)</td>
<td>• Multiple endpoints assessed in relatively small sample&lt;br&gt; • Choice of intervention delivery during radiation therapy</td>
</tr>
<tr>
<td>States[66]</td>
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<tr>
<td>Johnston (2011), United States[65]</td>
<td>Pilot RCT</td>
<td>Breast cancer survivors; completed primary therapy; aged 18–65 yrs</td>
<td>• C: Waitlist&lt;br&gt; • I: Self-care training (4x wk); holistic assessment and tailoring of IM advice plus acupuncture sessions 8x wk</td>
<td>No change in cognitive symptoms between groups&lt;br&gt; • Primary endpoint fatigue</td>
<td>• Sample predominantly breast cancer (n = 60)&lt;br&gt; • Small sample size; unblinded assessments&lt;br&gt; • Inclusion criteria based on fatigue rather than cognition</td>
</tr>
<tr>
<td>States[66]</td>
<td></td>
<td></td>
<td>• I: 10-wk Tai chi program; 2x wk sessions</td>
<td>No difference in neuropsychological performance&lt;br&gt; Cognitive symptoms reduced on EORTC-CFS (P = .014) and all FACT-Cog subscales (P = .024–.031)&lt;br&gt; Cognitive symptoms reduced on EORTC-CFS (P = .003) and all FACT-Cog subscales (P = .014)</td>
<td>• No active control group&lt;br&gt; • Mixed cancer stages&lt;br&gt; • Patients receiving active treatment</td>
</tr>
<tr>
<td>States[67]</td>
<td></td>
<td></td>
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<tr>
<td>Narayanan (2019), India[70]</td>
<td>Pilot RCT</td>
<td>Breast cancer survivors; aged 21–85 yrs; diagnosed &lt; 5 yrs prior; &lt; 60 min of moderate-to-vigorous PA in 10-min bouts per wk</td>
<td>• C: Sham Qigong gentle movement control WITHOUT focus on breathing and meditation&lt;br&gt; • I: Easy sessions of Qigong and Tai chi 12x wk</td>
<td>No difference between groups in cognitive symptoms or neuropsychological performance</td>
<td>• Possible effect of control intervention&lt;br&gt; • Relatively small sample size&lt;br&gt; • Short duration of intervention and follow-up</td>
</tr>
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<td>States[69]</td>
<td></td>
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<tr>
<td>O’Connor (2018), Australia[68]</td>
<td>Pilot RCT</td>
<td>Adult cancer patients; had/were receiving chemotherapy with expected survival &gt; 12 mos</td>
<td>• C: Fatigue education and support calls/emails every 3 days&lt;br&gt; • I: Medical Qigong (gentle exercise + meditation) 10x wk</td>
<td>No difference in neuropsychological performance but not maintained on reliable change index&lt;br&gt; Significant improvement in self-report on verbal (P = .01) and visual (P &lt; .05) memory</td>
<td>• No active control group&lt;br&gt; • Mixed cancer stages&lt;br&gt; • Patients receiving active treatment</td>
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<tr>
<td>States[66]</td>
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<tr>
<td>Reid-Arndt (2012), United States[67]</td>
<td>Single-arm pilot</td>
<td>Female cancer survivors; received chemotherapy ≥ 12 mos prior</td>
<td>• C: Waitlist&lt;br&gt; • I: Yoga 60 mins daily&lt;br&gt; • I: Tai chi 12x wk</td>
<td>Significant improvement in neuropsychological performance&lt;br&gt; Cognitive symptoms reduced on EORTC-CFS (P = .004) and all FACT-Cog subscales (P = .024–.031)</td>
<td>• Single-arm pilot study in small sample&lt;br&gt; • Requires evaluation in RCT</td>
</tr>
<tr>
<td>States[67]</td>
<td></td>
<td></td>
<td>• I: 10-wk Tai chi program; 2x wk sessions</td>
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<td>States[70]</td>
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<td>States[72]</td>
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</table>

### Qigong/Tai Chi

<table>
<thead>
<tr>
<th>Author (Year); Country</th>
<th>Study Design; Number of Patients (N)</th>
<th>Population</th>
<th>Intervention Summary</th>
<th>Outcomes</th>
<th>Gaps/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larkey (2016), United States[69]</td>
<td>Pilot RCT</td>
<td>Breast cancer survivors; stage 0-IIIA; 6–60 mos post primary treatment; aged 40–75 yrs; postmenopausal; self-reporting fatigue</td>
<td>• C: Sham Qigong gentle movement control WITHOUT focus on breathing and meditation&lt;br&gt; • I: Easy sessions of Qigong and Tai chi 12x wk</td>
<td>No difference between groups in cognitive symptoms or neuropsychological performance</td>
<td>• Possible effect of control intervention&lt;br&gt; • Relatively small sample size&lt;br&gt; • Short duration of intervention and follow-up</td>
</tr>
<tr>
<td>States[70]</td>
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<td>States[72]</td>
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### Yoga

<table>
<thead>
<tr>
<th>Author (Year); Country</th>
<th>Study Design; Number of Patients (N)</th>
<th>Population</th>
<th>Intervention Summary</th>
<th>Outcomes</th>
<th>Gaps/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derry (2015), United States[70]</td>
<td>RCT (secondary analysis)</td>
<td>Breast cancer survivors; stage 0-IIIA; completed primary breast cancer treatment 2–36 mos prior; engaged in ≥ 5 hrs vigorous PA weekly</td>
<td>• C: Waitlist&lt;br&gt; • I: Hatha yoga 2x wk; 90-min sessions for 12 wks</td>
<td>I reduced cognitive symptoms at 3-mo visit (P = .003)</td>
<td>• No active control group&lt;br&gt; • Participants and assessors not blinded to group allocation</td>
</tr>
<tr>
<td>States[71]</td>
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<td>States[72]</td>
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</table>

### Mind-Body (Mindfulness Meditation, Acupuncture)

<table>
<thead>
<tr>
<th>Author (Year); Country</th>
<th>Study Design; Number of Patients (N)</th>
<th>Population</th>
<th>Intervention Summary</th>
<th>Outcomes</th>
<th>Gaps/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johns (2016), United States[64]</td>
<td>Pilot RCT</td>
<td>Breast or colorectal cancer survivors; stage 0-II, treated with chemotherapy&lt;br&gt; +/- radiation therapy; clinically significant CRF</td>
<td>• C: Fatigue education and support sessions 8x wk, 2 hrs/wk&lt;br&gt; • I: MBSR 8x wk sessions, 2 hrs/wk</td>
<td>• I improved AFI (self-report subjective endpoint) post-intervention (P = .004);&lt;br&gt; Sustained at 6 mos (P &lt; .027)&lt;br&gt; No difference in neuropsychological performance</td>
<td>• Sample predominantly breast cancer (n = 60)&lt;br&gt; • Small sample size; unblinded assessments&lt;br&gt; • Inclusion criteria based on fatigue rather than cognition</td>
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<tr>
<td>States[65]</td>
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<td>States[66]</td>
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</table>

**AFI = Attentional Function Index; BFI = Brief Fatigue Inventory; BRIEF = Global Executive Composite score of the Behavioral Rating Inventory of Executive Function; C = control; CNS = central nervous system; CRF = cancer-related fatigue; EF = executive function; EORTC-CFS = European Organisation for Research and Treatment of Cancer Cognitive Functioning Scale; ES = effect size; FACT-Cog = Functional Assessment of Cancer Therapy-Cognition; IM = integrative medicine; MAIIF = Memory and Attention Adaptation Training; MBSR = mindfulness-based stress reduction; PCHP = Promoting Cognitive Health Program; PCI = Perceived Cognitive Impairment; QOL = quality of life; RCT = randomized controlled trial; REC0G = responding to cognitive concerns.**
Breast cancer survivors who carry the epsilon-4 allele with polymorphisms rs429358 and rs7412 on the ApoE gene may be more vulnerable to CRCI. However, Vardy et al found only a non-significant trend for increased cognitive impairment in colorectal cancer survivors with at least one ApoE4 allele compared with those without the allele.[4] Catechol-O-methyltransferase (COMT) catalyzes the O-methylation of catecholamine neurotransmitters, such as dopamine, adrenaline, and noradrenaline in the prefrontal cortex and limbic system. The polymorphism of COMT represented by a valine (Val or G) and methionine (Met or A) substitution has a high association with cognitive function and dopamine levels in non-cancer patients. The COMT (rs4680) polymorphism has been shown to have decreased enzyme activity,[47] which impacts neural activation patterns.[48] Some research suggests an association between the COMT (rs165599) polymorphism and a higher risk of CRCI in post-chemotherapy breast cancer survivors.[49] Brain-derived neurotrophic factor (BDNF) is a neurotrophin that regulates neuronal function and development. The polymorphism of BDNF (rs6265; Val66Met) has been linked to poor performance in episodic memory and working memory; it is also associated with reduced hippocampal volume and activity in non-cancer populations,[50-52] and may play a role in CRCI. There is limited evidence on the involvement of genetic associations in CRCI, and more research is required. Table 1 summarizes the mechanisms that have been associated with CRCI.

### Interventions for Cancer-Related Cognitive Impairment

**Nonpharmacologic Interventions**

CRCI can be managed with several nonpharmacologic strategies that address brain changes through: 1) neuroplasticity models (cognitive training, rehabilitation); 2) coping (cognitive behavioral therapy [CBT], compensatory strategies); or 3) reducing related symptoms (physical activity, mind-body). The evidence to support each intervention is summarized here and in Table 2, and Table 3 provides a summary of the levels of evidence for each intervention category.

#### Cognitive Training

Cognitive training uses exercises targeting the underlying neural pathways, such as speed of information processing or

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**Table 3: Nonpharmacologic Interventions: Recommendations for Clinical Use and Level of Evidence**

<table>
<thead>
<tr>
<th>Intervention Category</th>
<th>Intervention Summary</th>
<th>Cancer Population</th>
<th>Neuropsychological Performance</th>
<th>Cognitive Symptoms</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive training</td>
<td>Computer or internet-based cognitive training exercises done either at home, group, or individual sessions</td>
<td>Mixed; predominantly breast cancer</td>
<td>✓</td>
<td>✓</td>
<td>II</td>
</tr>
<tr>
<td>Cognitive behavioral therapy and compensatory strategies</td>
<td>Memory attention training, including compensatory strategies</td>
<td>Breast cancer</td>
<td>✓</td>
<td>✓</td>
<td>III</td>
</tr>
<tr>
<td>Cognitive rehabilitation</td>
<td>Manualized program addressing cognitive functions (attention, executive function, memory, etc); delivered in groups or online for 4–5 wk, 1–2 hrs/wk</td>
<td>Mixed solid tumors</td>
<td>✓</td>
<td>✓</td>
<td>III</td>
</tr>
<tr>
<td>Mind-body</td>
<td>MBSR Self-care training and acupuncture</td>
<td>Mixed; predominantly breast cancer</td>
<td>X</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Supported physical activity Qigong/Tai chi Yoga</td>
<td>Mixed; predominantly breast cancer</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Psychoeducation/Support</td>
<td>1-wk residential psychoeducation support program with 4 days’ follow-up</td>
<td>Breast cancer</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

✓ = some evidence of benefit; X = no evidence of benefit; MBSR = mindfulness-based stress reduction.
auditory attention, to increase cognitive capacity through regular training with progressively increasing levels of difficulty. Three randomized controlled trials (RCTs), two of which were pilot/feasibility studies, demonstrated reduced cognitive symptoms in cancer survivors after cognitive training. [53-55] Results for neuropsychological performance were mixed, with the largest trial finding no improvement.[53] At a minimum, cognitive training can be delivered to survivors in a convenient format and at a relatively low cost to reduce cognitive symptoms. Further research is required to determine its effect on neuropsychological performance, as well as whether its effects extend beyond breast cancer populations.

CBT and Compensatory Strategies

CBT is a psychotherapeutic approach involving short-term, goal-oriented problem-solving strategies to change patterns of thinking. Four trials have assessed the efficacy of CBT or compensatory strategies training in women with breast cancer. Two were quasi-randomized,[56,57] one was a pilot study,[58] and the other was a small RCT.[59] Results across all trials were equivocal, with the RCT indicating an improvement in cognitive symptoms compared with active controls.[59]

Cognitive Rehabilitation

Cognitive rehabilitation aims to restore normal functioning through specific skills training and meta-cognitive strategies in individuals experiencing cognitive impairment. Four studies have reported on the efficacy of cognitive rehabilitation interventions: one in breast cancer survivors[60] and three in adult cancer survivors of non-CNS tumors.[61-63] Interventions included individual and group delivery, either in person or online. All trials demonstrated improved cognitive symptoms, but mixed results for neuropsychological performance; the same results also occurred in non-cancer control participants. Small sample sizes and multiple comparisons were utilized in all studies.

Four randomized controlled trials have found that cognitive behavioral therapy improves cognitive symptoms compared with active controls.

Mind-Body Interventions

Few studies have assessed the efficacy of mind-body interventions, such as mindfulness-based stress reduction (MBSR). Two pilot trials investigated MBSR in cancer survivors, but cancer-related fatigue was an inclusion criterion. [64,65] The largest (N = 71) demonstrated an improvement in cognitive symptoms, but not neuropsychological performance. [64]

Physical Activity Interventions

One RCT in breast cancer survivors, which assessed a 12-week program of goal setting, activity monitoring, and remote support, demonstrated improved cognitive symptoms but not neuropsychological performance.[66] Despite a number of cross-sectional and cohort studies suggesting improved cognitive performance and symptoms, research in this area has been limited; however, at least four RCTs are underway.

Qigong/tai chi has been assessed in two RCTs and one single-arm pilot study.[67] In one RCT, medical qigong demonstrated improved cognitive symptoms compared with usual care, but neuropsychological performance was not assessed.[68] A second RCT, which used a sham qigong control with both groups, found improved cognitive symptoms and neuropsychological performance, but no difference between the groups.[69]

Yoga interventions have been assessed in three RCTs, which reported positive effects on cognitive symptoms.[70-72] Cognitive symptoms were secondary outcomes, and none of the trials assessed neuropsychological performance.

Pharmacologic Interventions

Outside of clinical trials, there is a lack of evidence for the use of pharmacologic agents in treating CRCDL. The following agents have been investigated, but are either not effective or have been evaluated in only pilot studies.

Erythropoietin

Two RCTs evaluated erythropoietin delivered during adjuvant chemotherapy in breast cancer survivors. Both were underpowered and did not use comprehensive neuropsychological assessments. One study in 94 women reported an improvement in cognitive function in the erythropoietin group at cycle four, but not at 6 months.[73] The second, which randomized 87 women with a hemoglobin level of less than 12 g/L to receive erythropoietin or a placebo with adjuvant chemotherapy, showed no difference in cognitive function when assessed 12 to 30 months later.[74]

Stimulants

Methylphenidate is commonly used to treat attention-deficit/hyperactivity disorder. Two placebo-controlled studies of this agent showed no improvement in CRCDL.[75] Both were underpowered to show a difference, with one study closing early due to poor accrual; in addition, the cognitive assessment used was unlikely to detect subtle differences. Another study of 154 patients with fatigue at least 2 months after completion of chemotherapy randomized participants to 8 weeks of dexamethasone or a placebo. An improvement in fatigue (primary
to manage CRCI is currently in preclinical trials. Most research on the use of antidepressants for depression, participants on paroxetine hydrochloride in 781 breast cancer survivors. After adjusting for depression, participants on paroxetine reported a greater improvement in attention and memory symptoms compared with placebo. [81] Neuropsychological performance was not evaluated.

Complementary and Alternative Medicines
An RCT of a standardized extract of the Chinese herb Ginkgo biloba (Egb761) compared 10 weeks of Egb761 60 mg twice daily vs placebo during adjuvant chemotherapy in 166 women with breast cancer. [82] No improvement in neuropsychological performance or cognitive symptoms was seen, but the cognitive test selected was a poor measure of performance.

Modafinil, a central nervous system stimulant used to treat narcolepsy, has been shown to reduce severe fatigue and improve speed and episodic memory in cancer patients.

Modafinil is a CNS stimulant generally used to treat narcolepsy. It has been shown to reduce severe fatigue in cancer patients. [77] A secondary analysis evaluating cognitive function in 82 breast cancer survivors with fatigue suggested some improvement in speed and episodic memory on a computerized test in the modafinil group. [78] Another study of 28 patients with advanced cancer found some improvement in psychomotor speed and visual information processing 4.5 hours after modafinil compared with placebo. [79]

Alzheimer Drugs
To date, most research has been conducted in animal models or in cancer patients with CNS involvement. A phase II RCT was conducted among 62 female breast cancer survivors with cognitive symptoms 1 to 5 years after adjuvant chemotherapy. Participants were randomized to receive a placebo or 5 mg of the acetylcholinesterase inhibitor donepezil daily for 6 weeks, then 10 mg/day if tolerated for 18 weeks. [80] Patients taking donepezil performed better on two verbal memory tasks at 24 weeks. More anxiety was reported in the donepezil group at 12 weeks, but this difference was not significant at 24 weeks. The authors are planning a larger study to evaluate donepezil further.

Antidepressants
Most research on the use of antidepressants to manage CRCI is currently in preclinical trials. However, one unpublished RCT evaluated paroxetine hydrochloride in 781 breast cancer survivors. After adjusting for depression, participants on paroxetine reported a greater improvement in attention and memory symptoms compared with placebo. [81] Neuropsychological performance was not evaluated.

Miscellaneous
Other potential interventions based on putative mechanisms of CRCI are being evaluated in preclinical trials, and no data are yet available. These agents include aspirin, nonsteroidal anti-inflammatory drugs, cytokine inhibitors for inflammatory processes, and metformin for mitochondrial protection of the microglia. A study is currently underway assessing metformin in breast cancer survivors.

Conclusion
Survivors reporting CRCI should be referred for an evaluation of fatigue, sleep disturbance, anxiety, or depression, and/or to a neuropsychologist for a formal assessment. The best evidence for treatment of cognitive symptoms associated with cancer and cancer treatment is for cognitive training; however, it is not clear if these approaches translate to improvement in formal neuropsychological tests or “real-world” tasks. The evidence for physical activity, MBSR, cognitive rehabilitation, and CBT is weaker, but physical activity and mindfulness are associated with other benefits and worth considering. Pharmacologic agents for CRCI should not be prescribed outside of clinical trials.

FINANCIAL DISCLOSURE: The authors have no financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

For references visit cancernetwork.com/cog-impairment
Introduction
Prostate cancer is the third leading cause of cancer death in the United States and accounts for one-fifth of new cancer diagnoses.[1] Androgen deprivation therapy (ADT) is the backbone of treatment for patients with advanced prostate cancer, and it is indicated for use in multiple clinical settings of prostate cancer. Chemical castration consists of gonadotropin-releasing hormone (GnRH) agonist or GnRH antagonist therapy. ADT is a critical treatment for high-risk and metastatic prostate cancer. There are important differences between GnRH agonists and antagonists. Here we review the mechanism of action between GnRH agonists and antagonists and the studies that led to the approval of degarelix. We also comment on the potential risks and benefits of degarelix, particularly when it comes to cardiovascular health. Finally, we describe an oral GnRH antagonist, which is not currently used in prostate cancer, but is included for completeness.

Mechanism of Action
Degarelix and abarelix are both injectable GnRH antagonists and relugolix is taken orally. They all bind to the GnRH receptor on the anterior pituitary. They are analogs of GnRH, and act as a competitive inhibitor of GnRH.[4] GnRH mediates stimulation of gonadotropin (ie, follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) secretion. Unlike GnRH agonists, the GnRH antagonists do not cause an initial surge of
Gonadotropin-releasing hormone (GnRH) antagonists in prostate cancer treatment were initially considered to be a substantial advance because there is no initial surge of gonadotropin; testosterone falls rapidly to castrate levels, and no testosterone "flare" is detected. At the time that GnRH antagonists were conceived, most patients had marked metastasis, and advanced disease was rampant. Today, most patients treated with GnRH analogs have much lower-volume disease and may not have metastases at all. Consequently, the implications of testosterone flare are much less significant in today's patient.

Pooled analyses have suggested a lower risk of cardiovascular disease for patients treated with GnRH antagonists; however, prospective randomized trials have yet to be concluded. GnRH antagonists are more expensive and must be given more frequently than GnRH agonists. As such, in my mind, there should be clear evidence supporting their use. Currently, that clear evidence is lacking.

Prospective randomized trials should demonstrate unequivocal improvement in outcomes in order to justify their expense and inconvenience. Assuming that cost will be higher than conventional alternatives, oral GnRH antagonists should be held to the same standard; higher cost and greater effectiveness should go hand in hand.

Ultimately, men will prefer to avoid castration. The side effects of castration are similar for GnRH antagonists and agonists. Researchers need to continue the search for non-castrating alternatives in order for real advances to occur. Can prostate-specific membrane antigen–targeted radiopharmaceuticals serve that purpose?

**FINANCIAL DISCLOSURE:** Dr. Sartor has served an advisory role for Advanced Accelerator Applications, Astellas, Bavarian-Nordic, Bellicum, Blue Earth Diagnostics, Inc, Celgene, EMD Serono, Myovant, Pfizer, and Teva. He has been both consultant for, and a grant/research support recipient of, AstraZeneca, Bayer, BMS, Constellation, Dendreon, Endocyte Innocrin, Invitae, Johnson & Johnson, Merck, Progenics, Sanofi, and SOTIO. He has provided expert testimony for Sanofi.

**Dr. Sartor** is C.E. & Bernadine Laborde Professor of Cancer Research and Medical Director of Tulane Cancer Center, and Assistant Dean for Oncology at Tulane Medical School in New Orleans, Louisiana.

gonadotropins. They rapidly decrease the secretion of LH and FSH from the pituitary, thereby leading to an immediate decrease in testosterone secretion from the Leydig cells of the testicles.[5-7]

The FDA has approved degarelix given subcutaneously as a 240-mg initial dose, followed by 80 mg injected every 28 days. It has a half-life of 43 days for the starting dose, and 28 days for the maintenance dose.

**Degarelix: Efficacy**

The pivotal trial that ultimately led to the approval of degarelix was published by Klotz et al in 2008. This trial, herein referred to as “CS21,” was a phase III randomized non-inferiority trial comparing standard-of-care leuprolide acetate vs degarelix. Patients with all stages of prostate cancer were randomized in a 1:1:1 fashion to receive degarelix 240 mg, followed by monthly maintenance dosing of 80 mg or 160 mg, or to receive leuprolide acetate 7.5 mg per month. The primary endpoint was defined as suppression of testosterone level to < 50 ng/dL between 28 and 364 days, which was achieved in > 96% of patients in all groups. As a secondary endpoint, the clinical trial also showed that degarelix was superior to leuprolide at decreasing testosterone levels to < 50 ng/dL within 3 days of initial treatment in > 90% of patients. Injection site reactions were more common in the group that received degarelix, but urinary tract infections were decreased in the degarelix arm; rates of all other adverse events were not significantly different. Interestingly, 22 of 202 patients (11%) receiving leuprolide acetate also received bicalutamide during the initial administration for tumor flare protection. In a subgroup analysis, the patients who had concomitant bicalutamide with leuprolide had rapid reductions in their prostate-specific antigen (PSA) level, similar to those patients receiving degarelix.[8] As the primary endpoint of non-inferiority was met, this clinical trial ultimately led to the approval of degarelix, at a dose of 240 mg/80 mg, for the treatment of patients with prostate cancer as an alternative to leuprolide acetate.

CS21 led to further subset analyses, each attempting to evaluate the efficacy of degarelix when compared with leuprolide acetate. Based on these analyses, it appears that degarelix is superior to leuprolide in PSA recurrence or death at 1 year, is faster at decreasing testosterone to castrate levels, and is more effective at decreasing alkaline phosphatase in those patients with metastatic disease to the bone.[9-11] Only PSA progression–free survival was a preplanned analysis. One such subset analysis attempted to study the concept of a “testosterone microsurge,” a testosterone surge occurring after prolonged GnRH agonist therapy. They examined testosterone levels on day 252, day 255, and day 259, attempting to see if there was a rise in testosterone after having been on treatment for 252 days. They found that after receiving the ninth dose of leuprolide acetate or degarelix on day 252 that there was an
increase in testosterone for patients receiving leuprolide acetate ($P < .001$). An increase in mean change in testosterone of 0.018, 0.040, and 0.054 ng/mL was seen for baseline testosterone levels of < 3.5, 3.5–5.0, and > 5.0 ng/mL, respectively, in those patients receiving leuprolide, whereas for degarelix the mean change was negative.[10] This suggests that even after the first month of therapy, a testosterone surge occurs upon subsequent dosing of leuprolide acetate. However, it is not known if this increase is clinically significant.

Safety, tolerability, and long-term efficacy were explored in an extension trial that continued with the same patient population as CS21. Patients who completed 1 year of therapy on CS21 were either continued on degarelix at the same maintenance dose they were randomized to, or if they were on leuprolide acetate, they were randomized to receive degarelix at a dose of 240 mg followed by either 160- or 80-mg maintenance for a total of 5 years. After a median follow-up of 27.5 months, the patients who had switched from leuprolide acetate to degarelix had a statistically significant decrease in the rate of PSA progression–free survival at year 1 compared with every year thereafter. Incidence of treatment-related adverse events were similar in the 3 groups. [12] At the 5-year analysis of the trial, the most common adverse event was once again injection site reactions at the initial injection vs subsequent injections (31% and 2.5%, respectively). Forty-two percent of patients completed the 5-year study; discontinuations were not thought to be related to study treatment, but the authors did not elaborate.[13]

**Degarelix: Lower Urinary Tract Symptoms and the International Prostate Symptom Score**

The clinically meaningful outcome of lower urinary tract symptoms (LUTS) was first evaluated in a randomized trial comparing degarelix vs goserelin plus bicalutamide in patients receiving ADT, with an endpoint of total prostate volume (TPV) reduction. They randomized 182 patients in a 1:1 fashion to degarelix vs goserelin for 12 weeks. Patients who received goserelin also received bicalutamide for the first 28 days to prevent a testosterone flare. They found that degarelix was non-inferior to goserelin plus bicalutamide for decreasing TPV (−37.2% vs −39.0%). They also found that patients receiving degarelix had more relief of their LUTS, as defined by the International Prostate Symptom Score (IPSS). There was also a trend towards improved quality of life for those patients receiving degarelix, but this trend was not significant.[14]

TPV was studied in the neoadjuvant setting as well, and degarelix was found to be non-inferior to goserelin plus bicalutamide in decreasing TPV prior to radical radiotherapy for localized disease. It is important to note that neoadjuvant ADT is not standard of care. In this study, degarelix was again found to be more efficacious at decreasing IPSS scores. Furthermore, this is one of the only clinical trials to prospectively evaluate the efficacy of a GnRH antagonist vs a GnRH agonist plus an anti-androgen in terms of lowering testosterone levels. Although this wasn’t a prespecified endpoint, the researchers noted there was no difference in median levels of testosterone at weeks 4, 8, and 12 in both groups.[15] Combining three phase III randomized trials,[14-16] a pooled analysis published in 2015 showed that degarelix was significantly better at decreasing IPSS scores when compared with goserelin at 12 weeks. Once again, no difference was seen in TPV reduction or urinary tract infection–related adverse events.[17]

**Degarelix: Pooled and Meta-Analyses**

Two large hypothesis-generating meta- and pooled analyses have since been performed. One pooled analysis looked at five phase III clinical trials comparing degarelix vs leuprolide acetate or goserelin after 3 or 12 months of treatment. From the 1,925 patients analyzed, the researchers reported that patients treated with degarelix had a statistically significant improvement in PSA progression–free survival at 1 year, overall survival (OS), joint-related symptoms, urinary tract infection events at 12 months, and musculoskeletal events at 12 months. It is thought that the difference in OS may have been driven by cardiovascular disease (CVD), since 51% of the 37 deaths occurred in the 29% of patients with baseline CVD. Patients with baseline CVD had a trend towards a decrease in death when treated with degarelix. One interesting correlation that was observed was that death at 1 year was predicted by testosterone level > 2 ng/mL and age > 70, and not disease stage or PSA level.[18]

Hosseini et al performed a systematic review and meta-analysis comparing six randomized controlled trials evaluating degarelix vs GnRH agonists. A total of 2,296 patients were evaluated. They discovered that there was a statistically significant difference between the groups, with the patients treated with degarelix...
had injection site reactions, but no one discontinued treatment because of this. Thus, the 480-mg dose was chosen as the dose to continue on to phase III trials.[20]  

**Degarelix and Cardiovascular Risk**  
There is controversy surrounding whether ADT in and of itself is an independent risk factor for CVD. The leading hypothesis is that ADT causes a distinct metabolic syndrome, caused by low testosterone levels and heightened by increased insulin resistance, body weight, and dyslipidemia, leading to an increase in cardiovascular deaths.[22,23] There are large studies that both support and weaken this theory. However, it must be noted that CVD is the most common cause of death in men with early-stage prostate cancer, and thus this theory needs to be clarified more extensively.[24,25] Furthermore, there is a retrospective analysis that suggests that this risk may be confined to patients with pre-existing CVD.[26] This controversy ultimately led the FDA, along with the American Heart Association, the American Cancer Society, and the American Society for Radiation Oncology, to issue warnings about the potential risk of increased cardiovascular events for patients receiving ADT.[22]  

As the efficacy of GnRH antagonists was being elucidated, interest rose around the idea that GnRH antagonists could lead to fewer cardiovascular events than GnRH agonists. In 2010 and 2011, two articles were published addressing this hypothesis. They first analyzed the CS21 trial, focusing on the effect of degarelix vs leuprolide acetate on QT intervals and serious adverse events suggesting arrhythmia. They found no significant increase in QT interval for either treatment arm, nor did they find a significant difference in the change of QT measurements between the two groups. Furthermore, they found no significant difference in rates of new ischemic heart disease or arrhythmia between the two groups. They concluded that the cardiovascular safety profile was similar for both degarelix and leuprolide acetate. Interestingly, ischemic heart disease was lower in patients receiving the FDA-approved dose of degarelix compared with those patients receiving leuprolide acetate (8% vs 21%).[27]  

A larger analysis of nine clinical trials was then performed, examining changes in cardiovascular events before and after patients received degarelix, with a focus on delineating effect of pre-existing CVD. For all patients, they found that CVD events were no different before and after degarelix treatment. However, they did note two interesting findings. For men with no CVD history, cardiovascular events decreased when started on degarelix, though these results were not statistically significant. In comparison, for men with pre-existing CVD at baseline, cardiovascular events increased after degarelix was given, from 5.3 to 10.5 events per 100 person-years, respectively (P = .0013).[28] Although both of these articles are retrospective analyses, they suggest that, like GnRH agonists, GnRH antagonists might cause an increase in cardiovascular events in patients with CVD history, and that GnRH antagonists may be safer than GnRH agonists when it comes to cardiovascular events in those without a cardiac history.  

It is unclear why GnRH antagonists may lead to a decrease in cardiovascular events as opposed to agonists. One theory is that GnRH receptors are located on T cells and may increase T-cell activation and differentiation into the T helper 1 phenotype, destabilizing atherosclerotic plaques.[29-31] Also, FSH may play a role in endothelial cell function, and the GnRH antagonists’ ability to decrease
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### TABLE: Current Clinical Trials Using Degarelix in the Setting of Prostate Cancer

<table>
<thead>
<tr>
<th>Official Trial Name (NCT Identifier)</th>
<th>Phase</th>
<th>Arms/Intervention</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>An Open-label, Single-Arm, Multicenter, Phase IV Trial to Evaluate the Safety of Firmagon® in Androgen Deprivation Therapy in Indian Patients Diagnosed With Advanced Hormone-dependent Prostate Cancer (NCT02726009)</td>
<td>IV</td>
<td>Degarelix</td>
<td>Frequency and severity of AEs at 1 year, clinically significant changes in lab values and vital signs</td>
</tr>
<tr>
<td>Phase II Trial Assessing the Feasibility and Toxicity of Degarelix in Achieving Prostate Downsizing Prior to Treatment With Permanent Seed Prostate Brachytherapy (NCT01448991)</td>
<td>II</td>
<td>Arm 1 - degarelix in favorable prostate cancer&lt;br&gt;Arm 2 - degarelix in intermediate-risk prostate cancer</td>
<td>Prostate volume reduction at 3 months</td>
</tr>
<tr>
<td>A Pilot Phase IV Study to Evaluate Variation in Bone Mineral Density, Lean and Fat Body Mass Index Measured by Dual-energy X-ray Absorptiometry in Patients With Prostate Cancer Without Bone Metastasis Treated With Degarelix (NCT0322381)</td>
<td>IV</td>
<td>Degarelix</td>
<td>Changes in fat body mass</td>
</tr>
<tr>
<td>A Phase 2, Randomized, 3-arm Study of Abiraterone Acetate Alone, Abiraterone Acetate Plus Degarelix, a GnRH Antagonist, and Degarelix Alone for Patients With Prostate Cancer With a Rising PSA or a Rising PSA and Nodal Disease Following Definitive Radical Prostatectomy (NCT01751451)</td>
<td>II</td>
<td>Arm 1 - abiraterone acetate&lt;br&gt;Arm 2 - abiraterone acetate + degarelix&lt;br&gt;Arm 3 - degarelix</td>
<td>PFS at 18 months, soft tissue CR at 1 year</td>
</tr>
<tr>
<td>A Pilot Study on Endothelial Function and Cardiovascular Biomarkers in Prostate Cancer (PCa) Patients, With Pre-existing Cardiovascular Disease, Treated With Degarelix vs. Luteinizing-Hormone-Releasing Hormone (LHRH) Agonists (NCT02475057)</td>
<td>IV</td>
<td>Arm 1 - degarelix&lt;br&gt;Arm 2 - LHRH agonist</td>
<td>Change in Reactive Hyperemia Index from baseline to 12 months</td>
</tr>
<tr>
<td>A Phase 2 Study Combining Ipilimumab, Degarelix, and Radical Prostatectomy in Men With Newly Diagnosed Metastatic Castration Sensitive Prostate Cancer or Ipilimumab and Degarelix in Men With Biochemically Recurrent Castration Sensitive Prostate Cancer After Radical Prostatectomy (NCT02020070)</td>
<td>II</td>
<td>Arm 1 - degarelix + ipilimumab + RP&lt;br&gt;Arm 2 - degarelix + ipilimumab with prior RP</td>
<td>Undetectable PSA at 12 and 20 months</td>
</tr>
<tr>
<td>A Phase II Study of Docetaxel Before Medical Castration With Degarelix in Patients With Newly Diagnosed Metastatic Prostatic Adenocarcinoma (NCT03069937)</td>
<td>II</td>
<td>Docetaxel + degarelix</td>
<td>PSA response at 10 months</td>
</tr>
<tr>
<td>A Study Into the Pharmacodynamic Biomarker Effects of Olaparib (a PARP Inhibitor) ± Degarelix (a GnRH Antagonist) Given Prior to Radical Prostatectomy (NCT02324998)</td>
<td>I</td>
<td>Arm 1 - olaparib&lt;br&gt;Arm 2 - olaparib + degarelix</td>
<td>Determination of PARP inhibition</td>
</tr>
<tr>
<td>Phase III Randomized Trial Comparing Short Course Androgen Deprivation Therapy and Ultra-Hypofractionated SBRT Versus SBRT Alone For Intermediate Prostate Cancer (NCT03056638)</td>
<td>III</td>
<td>Arm 1 - degarelix + SBRT&lt;br&gt;Arm 2 - SBRT</td>
<td>Number of patients with positive biopsy at 2 years</td>
</tr>
<tr>
<td>A Phase 3 Study of Androgen Annihilation in High-Risk Biochemically Relapsed Prostate Cancer (NCT03009981)</td>
<td>III</td>
<td>Arm 1 - degarelix&lt;br&gt;Arm 2 - apalutamide + degarelix&lt;br&gt;Arm 3 - apalutamide + abiraterone acetate + degarelix + prednisone</td>
<td>PFS</td>
</tr>
<tr>
<td>A Multi-Center, Randomized, Assessor-Blind, Controlled Trial Comparing the Occurrence of Major Adverse Cardiovascular Events (MACES) in Patients With Prostate Cancer and Cardiovascular Disease Receiving Degarelix (Gonadotropin-Releasing Hormone (GnRH) Receptor Antagonist) or Leuprolide (GnRH Receptor Agonist) (NCT02663908)</td>
<td>III</td>
<td>Arm 1 - degarelix&lt;br&gt;Arm 2 - leuprolide</td>
<td>Time from randomization to the first confirmed (adjudicated) occurrence of the composite MACE endpoint</td>
</tr>
<tr>
<td>Establishing a Neo-Adjuvant Platform for Developing Targeted Agents: Androgen Deprivation Therapy Prior to Prostatectomy for Patients With Intermediate and High Risk Prostate Cancer (NCT01542021)</td>
<td>I</td>
<td>Arm 1 - degarelix 4 days before RP&lt;br&gt;Arm 2 - degarelix 7 days before RP&lt;br&gt;Arm 3 - degarelix 14 days before RP&lt;br&gt;Arm 4 - continuation of previous ADT</td>
<td>To assess between the time to determine the maximal change in prostate cancer cell proliferation (Ki-67) and apoptosis rates (cleaved caspase-3)</td>
</tr>
<tr>
<td>A Phase II Neoadjuvant Study of Apalutamide, Abiraterone Acetate, Prednisone, Degarelix and Indomethacin in Men With Localized Prostate Cancer Pre-prostatectomy (NCT02849990)</td>
<td>II</td>
<td>Abiraterone acetate + apalutamide + degarelix + indomethacin</td>
<td>Pathologic complete response rate as assessed from prostatectomy specimens following neoadjuvant treatment</td>
</tr>
<tr>
<td>A Neoadjuvant Immunologic Study of Androgen Deprivation Therapy Combined With a GM-CSF-secreting Allogeneic Prostate Cancer Vaccine and Low-dose Cyclophosphamide in Men With High-risk Localized Prostate Cancer Undergoing Radical Prostatectomy (NCT01696877)</td>
<td>I/II</td>
<td>Arm 1 - degarelix&lt;br&gt;Arm 2 - degarelix + cyclophosphamide + GVAX (GM-CSF–secreting allogeneic cell-based vaccine)</td>
<td>Intraprostatic CD8+ T-cell infiltration and number of participants with adverse events</td>
</tr>
</tbody>
</table>
### Degarelix and Cardiovascular Risk

Continued from page 602...

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Both LH and FSH may be favorable in the setting of CVD.[32,33] Regardless of the reason, it is not entirely clear if GnRH antagonists should be used in lieu of GnRH agonists in the setting of CVD, and more research is needed to help clarify these hypotheses.

### Degarelix: Criticisms, and Cost

While degarelix is currently approved for the treatment of advanced prostate cancer, its niche is still not well defined, even after an abundance of clinical evidence of efficacy. Furthermore, clinicians have an alternative to degarelix in leuprolide, which is superior in its ease of injections (ie, there is a 6-month formulation of leuprolide), as well as fewer injection site reactions. Aside from an improvement in LUTS, a clinically meaningful outcome that proves the greater efficacy of degarelix compared with GnRH agonists is yet to be proven. There have been some hints at benefit in terms of improved OS at 1 year and improved PSA progression-free survival, but these outcomes have not been shown in a randomized phase III clinical trial. Furthermore, it has been argued that the clinical trials that have been done with degarelix are fraught with bias. The pivotal trial CS21 that led to the approval of degarelix did not have a great comparator arm. Only 11% of patients received an anti-androgen along with leuprolide acetate. Moreover, there was large patient heterogeneity in CS21. Clinical stage ranged from localized disease with PSA recurrence to metastatic disease. These biases extend through every subsequent subset, pooled, and meta-analysis on the efficacy of degarelix.[34]

There have been some endpoints that have shown clear benefit from the use of degarelix. The clinical trials that evaluated TPV clearly show a benefit in favor of degarelix at improving IPSS scores at 4, 6, and 12 weeks, as opposed to GnRH agonists. This clinically makes sense, in that degarelix has been shown to decrease testosterone levels with greater rapidity, and efficacy in the first 28 days, than GnRH agonists. This clinical effect could be translated to use in the setting of vertebral metastatic disease. The avoidance of a testosterone flare could be translated to use in the setting of vertebral metastatic disease.

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### Table: Official Trial Name (NCT Identifier) | Phase | Arms/Intervention | Primary Outcome

<table>
<thead>
<tr>
<th>Official Trial Name (NCT Identifier)</th>
<th>Phase</th>
<th>Arms/Intervention</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Multicenter Randomized Phase II Study Comparing the Efficiency of a HT Concomitant With RT vs RT Alone in the Salvage of Patients With a Detectable PSA After Prostatectomy (NCT01949239)</td>
<td>II</td>
<td>Arm 1 - pelvic radiotherapy</td>
<td>Event-free survival</td>
</tr>
<tr>
<td>Arm 2 - degarelix + pelvic radiotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized, Open-label, Neoadjuvant Phase 2 Study Comparing the Effects of AR Inhibition With and Without SRC or MEK Inhibition on the Development of EMT in Prostate Cancer (NCT01990196)</td>
<td>II</td>
<td>Arm 1 - degarelix + enzalutamide</td>
<td>N-cadherin and vimentin expression on prostatectomy</td>
</tr>
<tr>
<td>Arm 2 - degarelix + enzalutamide + trametinib</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Arm 3 - degarelix + enzalutamide + dasatinib</td>
<td></td>
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<tr>
<td>Neoadjuvant Degarelix +/- Apalutamide (ARN-509) Followed by Radical Prostatectomy for Intermediate and High-risk Prostate Cancer: a Randomized, Placebo-controlled Trial (NCT03080116)</td>
<td>II</td>
<td>Arm 1 - apalutamide + degarelix</td>
<td>Minimal residual disease</td>
</tr>
<tr>
<td>Arm 2 - degarelix</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Pilot Study of MK-3475 With Cryotherapy for Men With Newly Diagnosed Oligo-metastatic Prostate Cancer (NCT02489357)</td>
<td>I</td>
<td>Cryosurgery + degarelix + pembrolizumab</td>
<td>Proportion of men with PSA &lt; 0.6 ng/mL at 1 year</td>
</tr>
<tr>
<td>Neoadjuvant Androgen Deprivation Therapy and Chemotherapy Followed by Radical Prostatectomy in Patients With Prostate Cancer (NCT02494713)</td>
<td>II</td>
<td>Degarelix + doxuribin + ketoconazole + docetaxel + estramustine</td>
<td>Pathologic response</td>
</tr>
<tr>
<td>Arm 2 - degarelix with radiation therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2 Study of Androgen Deprivation Therapy (ADT) Plus Chemotherapy as Initial Treatment for Local Failures or Advanced Prostate Cancer (NCT02560051)</td>
<td>II</td>
<td>Arm 1 - doxuribin + ketoconazole + docetaxel + estramustine + degarelix for 12 months</td>
<td>Time to disease progression</td>
</tr>
<tr>
<td>Arm 2 - doxuribin + ketoconazole + docetaxel + estramustine + degarelix for 18 months</td>
<td></td>
<td></td>
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<tr>
<td>Arm 3 - doxuribin + ketoconazole + docetaxel + estramustine + degarelix for 24 months</td>
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</table>

**ADT** = androgen deprivation therapy; **AE** = adverse event; **AR** = androgen receptor; **CR** = complete response rate; **EMT** = epithelial-mesenchymal transition; **GM-CSF** = granulocyte-macrophage colony-stimulating factor; **GnRH** = gonadotropin-releasing hormone; **HT** = hormonal therapy; **PARP** = poly (ADP-ribose) polymerase; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **RP** = radical prostatectomy; **SBRT** = stereotactic body radiation therapy.
testosterone microsurgs, has frequently been evaluated. Some authors have suggested that increases in testosterone from a nadir to > 50 ng/dL might be clinically relevant.[35] The clinical implications of testosterone breakthroughs with GnRH agonists were investigated in a study of patients with nonmetastatic prostate cancer that looked at androgen-independent progression. Patients with testosterone increases > 0.32 ng/mL had significantly shorter survival free of androgen-independent progression compared with those without these events.[36] However, when anti-androgens were used to abrogate testosterone flare, correlations to a clinical outcome (ie, spinal cord compression, fractures, bladder outlet obstruction) were not significant.[37]

One factor to consider is the cost of GnRH agonists. Per Lexicomp, the 3-month formulation of leuprolide acetate 22.5 mg is $5,252.86, calculating to a yearly cost of $21,011.44. Degarelix 120 mg costs $914.51, and $586.14 for the 80-mg dose, calculating to a yearly cost of $8,276.54. In 2016, a summary of the ERG report determined that the incremental cost-effectiveness for degarelix compared with triptorelin (every 3 months), goserelin (every 3 months), and leuprolrelin (monthly) was at least 35,600, 28,000, and 26,200 pounds, respectively, per quality-adjusted life-year gained. Ultimately, the National Institute for Health and Care Excellence recommended the use of degarelix as an option for treating advanced hormone-dependent prostate cancer in patients with spinal metastases.[38]

**Relugolix: An Orally Available GnRH Antagonist**

The oral GnRH antagonist relugolix, also known as TAK-385, is currently being evaluated as a potential treatment for prostate cancer. The benefits of an oral GnRH antagonist include avoiding injection site reactions and the ability to stop the medication at any time, since it is not formulated for sustained release. In a phase II trial, relugolix was compared with degarelix in patients with localized prostate cancer. The primary outcome measure was the percentage of participants with an effective castration rate over 25 weeks. Ninety-five percent of patients receiving relugolix, and 89% of patients receiving degarelix remained castrate over 25 weeks.[39] Additionally, relugolix was directly compared with leuprolrelin in another phase II trial. Thirty-nine patients received relugolix 80 mg once daily, 36 patients received relugolix 120 mg once daily, and 20 patients received 22.5-mg leuprolrelin subcutaneously every 12 weeks. Ninety-two percent of patients on relugolix and 95% of patients on leuprolrelin achieved the primary outcome of sustained testosterone < 50 ng/dL from weeks 5–24. Adverse events were comparable.[40] Currently, there is an active phase III clinical trial (NCT03085095) comparing relugolix 120 mg daily vs leuprolide acetate 22.5 mg every 3 months for 48 weeks in patients with castration-sensitive advanced prostate cancer. The primary outcome measure for the study is a sustained castration rate.

Although relugolix has yet to be approved by the FDA, one concern regarding an oral GnRH antagonist is compliance. Patient compliance on an oral medication has been estimated to be 79%.[41] The half-life of relugolix is 36–65 hours, allowing for patients to miss a dose; however, the ease of use of a depot formulation of degarelix may be a better option.[42] If relugolix is approved, cost, compliance, and side effect profile will have to be evaluated to determine its utility in the clinical setting.

**GnRH Antagonists: Treatment Recommendations and Conclusions**

Based on the data we have discussed, we cannot say that degarelix is superior or inferior to GnRH agonists when it comes to prostate cancer outcomes, such as PSA response and OS. However, we would favor using degarelix over leuprolide in patients with spinal metastases to avoid the risk of cord compression. The cost differential is significant in favor of degarelix, but this may be outweighed by the injection site reactions associated with degarelix, which would occur on a monthly basis. Finally, whether degarelix is safer for patients with cardiovascular disease is unclear, but there is potential that this may be the case.

In summary, degarelix appears to be a reasonable alternative to GnRH agonists in the treatment of advanced prostate cancer. Whether degarelix will eventually be approved for an alternative indication or if it is found to be superior in efficacy to GnRH agonists remains to be seen. Having an orally available option in relugolix may serve an important role in the treatment of prostate cancer in the future. More research is needed to determine what the exact role of the GnRH antagonists are in the treatment of prostate cancer.

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For references visit cancernetwork.com/gnRH-ant-prostate

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Prostate Cancer Genomic Analysis: Routine or Research Only?

Genomic Testing Should Be Routine in the Management of Prostate Cancer Patients

Brandon Bernard, MD, MPH, and Thomas W. Flaig, MD

Advances in next-generation sequencing (NGS) are revolutionizing cancer research and care. Specifically, the accuracy, processing time, and cost of such tests have improved, and access to this technology has rapidly expanded. Its application to clinical care, however, is not new. Indeed, genomic analysis in melanoma, lung, and colorectal cancers is standard of care and predictive of response to numerous targeted drugs. Furthermore, genetic testing for hereditary cancer syndromes, including carriers of DNA damage repair (DDR) genes such as BRCA1/2, has been widely utilized for years, with breast cancer being an archetype for this approach. Until recently, the clinical value of NGS in prostate cancer was unclear, with DDR alteration frequency underappreciated. Notably, prostate cancer was shown to be highly heritable, with twin studies demonstrating a heritability estimate of 57% (95% CI, 51%–63%).[1] Of those, germline BRCA carriers display a more aggressive phenotype, with poorer outcomes.[2-5] Compellingly, the National Comprehensive Cancer Network (NCCN) guidelines now recommend consideration of germline testing.

Limitations Exist for Guiding Therapeutic Treatment

W. Kevin Kelly, DO, and Karen E. Knudsen, PhD

The era of genomic medicine has dawned and is rapidly accelerating as a result of expanded knowledge and technical advances. Next-generation sequencing (NGS) unmasked new, unanticipated understanding of genetic alterations that drive tumor development and progression. Currently, the US Food and Drug Administration (FDA) recognizes more than 160 pharmacogenomic biomarkers and biomarker signatures (of which approximately one in three are for oncology), which can be used to stratify patients to treatments or to define a patient’s prognosis (https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm). An unprecedented level of genomic data sharing was made possible through major efforts, such as the The Cancer Genome Atlas Project (TCGA), the Catalog of Somatic Mutations in Cancer (COSMIC), and the International Cancer Genomics Consortium (ICGC), which hastened the pace of discovery. For prostate cancer, wherein molecular understanding of metastatic castration-resistant prostate cancer (mCRPC) has been a major barrier to prog-

Continued on page 608
for all patients with high-risk localized or metastatic prostate cancer.[6] Moreover, studies have demonstrated that DDR status may be a predictive biomarker in prostate cancer.[7,8] In light of these data, it has been argued that genomic testing should be offered to all patients with advanced disease.

NGS methods offer advantages over MSI-PCR, including no requirement for matched non-tumor tissue and an automated analysis pipeline with quantitative interpretation of MSI-status.


The rationale for routine clinical use stems from emerging literature, including two large studies that sequenced primary tumors and metastases and found pathogenic DDR variants in approximately 20% of cases.[9,10] Surprisingly, 8% of mutations were identified in the germline. A subsequent study found that over 10% of metastatic prostate cancer patients had deleterious germline mutations in DDR genes.[11] Specifically, up to 12% of tumors may display microsatellite instability (MSI) as a consequence of deficient mismatch repair (dMMR) genes.[12] As mentioned, the prognostic implications of such findings are noteworthy. Additionally, a role for DDR as a predictive biomarker is rapidly emerging. Indeed, one phase II trial demonstrated a response rate of 88% in patients with somatic alterations in DDR treated with the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib.[7] Furthermore, there are data suggesting that germline carriers may derive benefit from platinum-based chemotherapy.[8]

Other relevant genes in prostate cancer include HSD3B1, with studies demonstrating germline status as predictive of worse response to androgen deprivation therapy, yet improved response to abiraterone acetate,[13,14] and CDK12, where loss was shown to be associated with increased neoantigen burden and tumor T-cell infiltration, thus potentially identifying a tumor subset that may benefit from immuno-therapy.[15] Ultimately, further work is needed to clarify the value of DDR status as both a prognostic and predictive biomarker in prostate cancer, and if that value differs when alterations are germline vs somatic.

Genomics aside, RNA expression for prostate cancer prognostication is being utilized clinically in some settings. Tests such as Prolaris and Oncotype DX Prostate may aid in risk stratifying men with low-risk or favorable intermediate-risk disease when deciding between active surveillance and treatment.[16-20] Similarly, the Decipher test may predict for risk of metastasis or death following local therapy.[21-24] Moreover, Decipher data have been used to develop predictive signatures for the potential benefit of adjuvant or salvage radiation following radical prostatectomy.[25] While not validated in large prospective clinical trials, these tools showcase the potential value of molecular analysis in localized prostate cancer.

Beyond the individual patient, assessment of germline status may have risk and prognostic implications for immediate and extended family members. Thus, from a public health perspective, the impact of cascade genetic testing is large and, if appropriate interventions are pursued, has the potential to dramatically affect those with familial syndromes, including those with BRCA findings. For example, female carriers of BRCA mutations may undergo earlier screening and potential prophylactic treatment to decrease the risk of breast and ovarian cancers; likewise, patients with dMMR may have Lynch syndrome and thus undergo specific colorectal and endometrial cancer screening. While not presently part of guidelines, knowledge of germline DDR status in prostate cancer patients may impact prostate-specific antigen and other screening modalities in the patient and in family members. Currently, the NCCN recommends consideration of germline testing for all men with metastatic and high-/very-high-risk clinically localized prostate cancer.[6] With an estimated 28,000 men diagnosed with metastatic disease at time of presentation in 2018,[26] this represents a large population in which screening may be of benefit. Such an approach has been adopted by breast cancer practitioners and has shown success with hereditary cancer clinics.

With widespread genomic profiling of prostate cancer patients, there are a number of practical considerations worth mentioning. First, there is the option of tumor genomic profiling vs germline genetic testing, individually, sequentially, or in parallel. Clinicians have the option of tumor genomic vs germline genetic testing, individually, sequentially, or in parallel.

Beyond the individual patient, assessment of germline status may have risk and prognostic implications for immediate and extended family members. Thus, from a public health perspective, the impact of cascade genetic testing is large and, if appropriate interventions are pursued, has the potential to dramatically affect those with familial syndromes, including those with BRCA findings. For example, female carriers of BRCA mutations may undergo earlier screening and potential prophylactic treatment to decrease the risk of breast and ovarian cancers; likewise, patients with dMMR may have Lynch syndrome and thus undergo specific colorectal and endometrial cancer screening. While not presently part of guidelines, knowledge of germline DDR status in prostate cancer patients may impact prostate-specific antigen and other screening modalities in the patient and in family members. Currently, the NCCN recommends consideration of germline testing for all men with metastatic and high-/very-high-risk clinically localized prostate cancer.[6] With an estimated 28,000 men diagnosed with metastatic disease at time of presentation in 2018,[26] this represents a large population in which screening may be of benefit. Such an approach has been adopted by breast cancer practitioners and has shown success with hereditary cancer clinics.

With widespread genomic profiling of prostate cancer patients, there are a number of practical considerations worth mentioning. First, there is the option of tumor genomic profiling vs germline genetic testing, individually, sequentially, or in parallel. Clinicians have the option of tumor genomic vs germline genetic testing, individually, sequentially, or in parallel.
Advanced prostate cancer patients found to have MSI may be eligible for pembrolizumab, a humanized antibody used as immunotherapy.

made if the criteria are met. Somatic testing, however, is less clear, given the uncertainty regarding prognostication and actionability should a deleterious DDR alteration be identified. However, if a somatic DDR mutation is identified that suggests a hereditary syndrome, a referral to a genetic counselor and germline testing should be considered.

Secondly, there are the technical aspects of testing to consider. For example, the Centers for Medicare and Medicaid Services have recently finalized a National Coverage Determination approving NGS tests as a companion diagnostic for patients with advanced cancer for which a US Food and Drug Administration (FDA)-approved drug exists. This announcement coincided with the FDA approval of a commercial NGS-based in vitro diagnostic.

Despite the described benefit of routine genomic sequencing for men with prostate cancer, certain pitfalls remain. As mentioned, the identification of germline changes may have far-reaching and unintended negative consequences for family members, including heightened anxiety, uncertainty regarding how and when to screen positive individuals, and adverse impact on certain insurance coverage. In terms of management, there is no clear guidance on how to incorporate genomic data into therapeutic recommendations when clinical trial data may be lacking and when proven standard therapies exist. Notably, there is at best level IIB evidence for therapy based on somatic alterations in prostate cancer[27]; as such, obtaining insurance reimbursement presents a challenge. The exception, of course, is identifying patients who may be eligible for biomarker-based clinical trials.

Next, there is the question of which assay is used and the interpretability of the results; currently, physicians may opt to sequence archival tissue, obtain a fresh biopsy, or utilize a liquid biopsy to analyze circulating tumor DNA. Each of these carries its own limitations, including nucleic acid breakdown, temporal changes from the time of biopsy, and tumor heterogeneity. Moreover, without clear instruction, it can be difficult to determine if an alteration is a pathogenic driver, a passenger, or a variant of unknown significance. Also, with rapidly changing technology, being aware of the validity of specific assays is critical. For example, studies leading to the approval of the checkpoint inhibitor pembrolizumab for solid tumors with MSI/dMMR used investigator-developed polymerase chain reaction (PCR) to determine MSI status and immunohistochemistry for MMR. Commercial NGS assays routinely used targeted exome sequencing; thus, interpreting and applying MSI/MMR results from such tests presents a challenge. That said, recent studies have demonstrated that NGS performs well and has high sensitivity and concordance with PCR at identifying tumors with MSI, including prostate cancer.[28,29] Such studies do well to allay concerns among oncologists regarding use of these assays.

Lastly, one must be cognizant of cost and the uncertainty of insurance coverage for the growing number of available tests. Given the FDA approval of pembrolizumab for MSI-high/dMMR solid tumors, it is reasonable to assume that men with prostate cancer would be included and thus covered for diagnostic testing. For those with commercial insurance, reimbursement is likely variable; therefore, an open discussion with patients about potential direct costs is necessary.

In conclusion, the benefits of genomic testing for patients with advanced prostate cancer are clear. Patients may derive meaningful benefit if their tumor or germline contains a predictive alteration for a targeted treatment, platinum-based chemotherapy, or clinical trial enrollment. Moreover, those found to have MSI may be eligible for immunotherapy with pembrolizumab. Overall, comprehensive genomic sequencing carries both clinical and research implications, as the lines between these are blurred. In terms of cost, it may be argued that overall healthcare expenditures are less if the right drug is chosen for the right patient based on a genomic profile and the application of precision medicine. Patients with other cancer types have a long history of access to novel technology and treatments; the time is now for men with prostate cancer to attain what’s right, what’s necessary, and what the evidence shows with routine genomic testing to improve their lives and those of their families.

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Counterpoint continued on page 630
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Immunotherapeutic Approaches to the Management of Head and Neck Cancer

Xinyu Nan, MD, Kathryn A. Gold, MD, and Ezra Cohen, MD

ABSTRACT: The two programmed death 1 checkpoint inhibitors nivolumab and pembrolizumab are approved by the US Food and Drug Administration as second-line treatment for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). Based on the existing data, the effectiveness of these two drugs is similar in this setting. When choosing between them, the decision should be individualized and can be determined by patient and provider preferences, as well as scheduling. Testing for tumor programmed death ligand 1 (PD-L1) and human papillomavirus status is not required for use of these checkpoint inhibitors in the second-line setting, but the level of tumor PD-L1 expression can be useful for decision making in special situations. There are many ongoing trials that are studying immunotherapy as frontline treatment for recurrent or metastatic HNSCC, as well as trials combining immunotherapy with definitive chemoradiation in locally advanced disease. Based on the updated results of the KEYNOTE-048 trial, checkpoint inhibitors will likely be a part of first-line therapy in the near future.

The standard frontline treatment for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) is platinum-based chemotherapy with fluorouracil (5-FU) and cetuximab. This regimen was tested in the phase III EXTREME trial, which demonstrated significantly longer median overall survival (from 7.4 months to 10.1 months) and progression-free survival (from 3.3 months to 5.6 months).[1] Immunotherapy with checkpoint inhibitors has activity in head and neck cancer, and the programmed death 1 (PD-1) inhibitors nivolumab and pembrolizumab have both been approved by the US Food and Drug Administration (FDA) for patients with platinum-refractory disease. In general, tumors are considered platinum refractory if disease progression occurs within 6 months of the last dose of platinum-based therapy administered as part of definitive therapy, or if disease progression occurs following a platinum-containing regimen for recurrent or metastatic disease.

Both nivolumab and pembrolizumab have demonstrated superior activity over standard single-agent systemic chemotherapy in phase III randomized controlled trials. In the CheckMate 141 study, the median overall survival was significantly longer (7.5 months vs 5.1 months) in the nivolumab group compared with the group that received investigator’s choice of therapy (methotrexate, docetaxel, or cetuximab).[2] Treatment with pembrolizumab showed a clinically
Why Immunotherapy Will Become the New Standard of Care in HNSCC

The treatment of head and neck squamous cell carcinoma (HNSCC) is a rapidly evolving landscape. The article by Nan et al describes the impressive advances in immuno-oncology in HNSCC, specifically with checkpoint inhibitors in the recurrent/metastatic setting. The recent US Food and Drug Administration approval of nivolumab and pembrolizumab in platinum-exposed patients, based on improved survival compared with chemotherapy, has opened the door for the use of these agents in a variety of clinical settings.

Importantly, data reported at the European Society for Medical Oncology (ESMO) 2018 Congress on the results of KEYNOTE-048 confirmed the significant activity of programmed death 1 (PD-1) inhibitors in the first-line recurrent or metastatic HNSCC setting. This phase III randomized trial compared the standard-of-care EXTREME study regimen (platinum-containing chemotherapy with fluorouracil [5-FU] plus cetuximab) vs pembrolizumab monotherapy and the combination of chemotherapy plus pembrolizumab. The primary endpoints were progression-free survival (PFS) and overall survival (OS) in patients with a programmed death ligand 1 (PD-L1) combined positive score (CPS) ≥ 1 and a CPS ≥ 20. Most importantly, for patients with PD-L1 CPS ≥ 1, pembrolizumab monotherapy had significantly improved OS over standard chemotherapy. The improved OS was most pronounced in the patients with PD-L1 CPS ≥ 20 (hazard ratio [HR], 0.61; 95% CI, 0.45–0.83; \( P = .0007 \)). The pembrolizumab/chemotherapy arm also demonstrated improved survival over the EXTREME regimen in all patients (HR, 0.77; 95% CI, 0.63–0.93; \( P = .0034 \)). There was no significant difference in overall response rate or PFS seen and, as expected, pembrolizumab monotherapy was better tolerated than the EXTREME regimen.

This study has led the way for pembrolizumab to be the new standard of care for the upfront treatment of recurrent/metastatic HNSCC. Given the improvement in OS noted in KEYNOTE-048 and the toxicity and logistical challenges of the EXTREME regimen, this represents a significant step forward in the first-line recurrent/metastatic space. However, as important as these findings are, clinicians and researchers need to continue to strive to better understand the biology of the disease and develop treatments that target the vast majority of patients who still succumb to this disease. Fortunately, there are multiple ongoing studies incorporating immunotherapy in earlier-stage disease, examining the activity of drugs focused on various immune pathways, novel combinations, and targeted therapies. Overall, these recent findings are translating into a significant benefit for HNSCC patients.

**FINANCIAL DISCLOSURE:** Dr. Steuer is a speaker for Merck and serves on the advisory boards for AbbVie, ARMO Biosciences, and BerGenBio.

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**Dr. Steuer** is an Assistant Professor in the Department of Hematology and Medical Oncology at Winship Cancer Institute of Emory University in Atlanta, Georgia.
nivolumab is beneficial in this setting, given that it is less toxic and provides a longer duration of response compared with single-agent chemotherapy. In addition, these data tell us that positive tumor PD-L1 expression predicts for greater magnitude of benefit with nivolumab.

Similar results were demonstrated in the phase II KEYNOTE-055[5] and phase III KEYNOTE-040[3] trials, in which both PD-L1–positive and PD-L1–negative groups showed benefit with pembrolizumab. Both studies showed that a higher PD-L1 combined positive score (CPS) predicts for a higher response rate with pembrolizumab.[3,5] Therefore, currently, we believe that tumor PD-L1 status is not required to be tested for use of checkpoint inhibitors in the second-line setting, but it can be helpful with decision making for patients in special situations. One example of such a situation is in patients with higher than average risk for toxicity with checkpoint inhibition. It can also be useful when making decisions for patients who are qualified for first-line platinum-containing chemotherapy regimens, such as the EXTREME regimen, but who may not be able to tolerate the therapy (eg, those with poor performance status, old age, and/or comorbidities, etc). In these settings, high tumor PD-L1 expression may more strongly indicate for the use of checkpoint inhibitors as an alternative option. However, it should be noted that regardless of PD-L1 status, neither pembrolizumab nor nivolumab is FDA approved for the first-line treatment of recurrent or metastatic HNSCC, and are considered off-label.

Human papillomavirus (HPV) status is an important prognostic marker for oropharyngeal squamous cell carcinoma. In the majority of recurrent or metastatic HNSCC immunotherapy trials, p16 immunohistochemical testing is used to assess HPV status in patients with oropharyngeal cancer. In the CheckMate 141 study, approximately 50% of the patients had p16 status reported, and suggested that both p16-positive and p16-negative patients benefited from nivolumab. For p16-positive patients, the median overall survival was significantly longer in the nivolumab group (9.1 months) vs single-agent chemotherapy (4.4 months). For p16-negative patients, the overall survival was also longer in the nivolumab group compared with the single-agent chemotherapy group (7.5 months vs 5.8 months), but was not statistically significant.[2] The magnitude of benefit appears to be larger among p16-positive patients in this study. However, there are inconsistent results among other studies and when directly comparing the response rates between p16-positive and p16-negative groups. In a subgroup analysis of the KEYNOTE-040 trial, the HR for overall survival was lower in the p16-negative group compared with the p16-positive group.[3] In the phase II KEYNOTE-055 study, the response rate to pembrolizumab between p16-positive and p16-negative patients was similar (16% vs 15%).[5] However, in the phase Ib KEYNOTE-012 trial, the response rate was significantly different, at 32% vs 14% among those with HPV-associated and non–HPV-associated disease.[6] Overall, we believe there are no clear differences between response in p16-positive and p16-negative patients, and it should not be a factor in selecting therapy.

There are three ongoing trials studying the use of checkpoint inhibitors for recurrent or metastatic HNSCC in the frontline setting (Table 1). KEYNOTE-048 is a phase III study comparing pembrolizumab monotherapy vs the current standard of care, the EXTREME study regimen, and vs pembrolizumab in combination with platinum and 5-FU chemotherapy as first-line therapy.[7] The results of this study were presented at the European Society for Medical Oncology (ESMO) 2018 Congress and showed that pembrolizumab monotherapy had met the primary endpoint of overall survival in patients whose tumor PD-L1 CPS was ≥ 1 and ≥ 20. Based on these updated data, the pembrolizumab monotherapy group had significantly longer overall survival compared with the EXTREME study regimen group (12.3 months vs 10.3 months for the PD-
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L1 CPS ≥ 1 population and 14.9 months vs 10.7 months for the PD-L1 CPS ≥ 20 population). Although response rate was lower in the pembrolizumab monotherapy group, the duration of response was substantially longer compared with the EXTREME study regimen (20.9 months vs 4.5 months in the PD-L1 CPS ≥ 1 population and 20.9 months vs 4.2 months in the PD-L1 CPS ≥ 20 population).[7] In addition, there was a significantly lower incidence of adverse effects (all grade adverse events, 58.3% vs 96.9%; grade 3–5 adverse events, 16.7% vs 69%) with pembrolizumab monotherapy compared with the EXTREME regimen.[7]

The updated data also suggest that overall survival in the group that received pembrolizumab with chemotherapy was significantly longer than the group that received the EXTREME study regimen, regardless of PD-L1 status (13.0 months vs 10.7 months). The safety profile was similar between these two regimens.[7] Based on these data, we believe that pembrolizumab monotherapy will become the new standard first-line treatment for recurrent and metastatic HNSCC, regardless of PD-L1 status, or for patients who require urgent response.

The CheckMate 651 trial is another phase III trial that is studying nivolumab in combination with ipilimumab compared with the standard of care (EXTREME study regimen) as first-line treatment for patients with recurrent or metastatic HNSCC.[8] They are in the process of accruing patients, and no preliminary results are available at this point. There is also an ongoing phase III trial (the EAGLE trial) testing durvalumab alone and in combination with tremelimumab vs the standard of care (ClinicalTrials.gov identifier: NCT02369874). Durvalumab is a PD-L1 inhibitor that has shown clinical activity in a phase II study.[9] Tremelimumab is a human monoclonal antibody against cytotoxic T-lymphotoxin–associated antigen 4 (CTLA-4). The results of this study are still pending.

We believe that these three trials have a high likelihood of changing the standard of care for the frontline management of recurrent or metastatic HNSCC. Checkpoint inhibitors will likely be a part of the new first-line therapy in the near future.
There are also ongoing trials to incorporate checkpoint inhibitors into definitive treatment for locoregionally advanced HNSCC (Table 2). The first study to test the safety of this approach was a phase Ib trial that combined pembrolizumab with weekly cisplatin and concurrent radiation therapy for stage III to IVB HNSCC. Preliminary results of this trial showed that the combination is tolerable and does not appear to affect radiation or chemotherapy dosing.\[10\] The Radiation Therapy Oncology Group (RTOG) 3504 trial is a phase I trial that is studying the safety and toxicity of nivolumab combined with weekly cisplatin, high-dose cisplatin, or cetuximab during concurrent radiation therapy.\[11\] NRG-HN003 is another phase I trial that will determine the optimal dosing of pembrolizumab when combined with cisplatin and radiation therapy for high-risk stage III to IV HNSCC (ClinicalTrials.gov identifier: NCT02775812). JAVELIN is a phase III trial that is testing avelumab (a human IgG1 monoclonal antibody against PD-L1) together with standard chemoradiation therapy (CRT) compared with CRT alone in high-risk locally advanced HNSCC.\[12\] Final results from these trials are not yet available.

In addition, there are several ongoing phase II and III trials studying nivolumab, pembrolizumab, and durvalumab combined with radiation or chemoradiation as definitive treatment for locoregionally advanced HNSCC (Table 2). Most of the trials are early stage and have no preliminary results, so we cannot draw any conclusions on the effectiveness of immunotherapy in this setting. However, several preclinical studies have already shown the synergistic effects of combining immunotherapy with radiotherapy for both local and distant tumor control.\[13\] Therefore, using this approach could potentially improve the current standard of care for locally advanced HNSCC.

In summary, immunotherapy has an important role in the treatment of head and neck cancer. Nivolumab and pembrolizumab are now the standard of care for locally advanced HNSCC. Testing for tumor PD-L1 and HPV status is not required when initiating treatment with nivolumab or pembrolizumab, but higher tumor PD-L1 expression levels predict for greater magnitude of benefit. There are also many ongoing trials studying immunotherapy in the frontline setting for recurrent or metastatic HNSCC and combined with definitive chemoradiation in locally advanced disease. Based on some preliminary results, immunotherapy has the potential to be part of the first-line treatment for recurrent or metastatic HNSCC in the near future.

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A study published in the *New England Journal of Medicine* this past September analyzed molecular strategies to monitor patients with myelodysplastic syndrome (MDS) at risk of relapse. The research also identified markers associated with a risk of progression following a potentially curative stem cell transplant. In this month’s installment of *Ask the PI*, ONCOLOGY spoke with two authors of the study, Meagan A. Jacoby, MD, PhD, and Matthew Walter, MD, about their findings and what they might mean for practicing oncologists.

**Q:** For patients with MDS who have opted to undergo an allogeneic hematopoietic stem cell transplantation, are there currently ways to clinically or molecularly assess the risk of relapse before the transplant? Additionally, can tests monitor for relapse following transplantation?

**DR. JACOBY:** Yes, there are ways to look for predictors of relapse prior to a transplant. This is usually done via a scoring system, such as the International Prognostic Scoring System (IPSS) or the Revised International Prognostic Scoring System (IPSS-R). Both look at things like cytogenetics of the MDS cells, the number of blasts in the bone marrow, and the number of peripheral cytopenias. By looking at these factors, we can predict patients’ overall survival and risk of developing a secondary acute myeloid leukemia based on which factors have been shown to be predictive for risk.

The other molecular factor that can often predict a poor outcome after transplant is the p53 gene. Patients with p53 mutations don’t do as well after transplant as those without the mutation. In terms of monitoring for risk post-transplant, a bone marrow biopsy is conducted at milestones, including at day 30 and day 100. We then look at the morphology under the microscope, as well as the cytogenetics and the percentage of engraftment. If engraftment decreases or is not attained—that we call a mixed chimera—then the patient’s risk of relapse is higher.

**Q:** In that context, can you tell us the setup of the mutation detection study that you and your colleagues conducted in these types of MDS?
patients and the question you were addressing?

DR. WALTER: Based on post-transplant monitoring, which Dr. Jacoby just mentioned, there are some limitations for morphology. In particular, when we look at a bone marrow biopsy and the morphology of the aspirate, we are often looking for the blast percentages in those samples. For MDS, we know that blast count can underrepresent the tumor burden that is present in patients. So, we wanted to come up with a technique that would be applicable to everyone. Another limitation of using cytogenetics, or fluorescence in situ hybridization (FISH), to look at molecular abnormalities is that those changes will be present in only a fraction of patients going into transplant.

Our goal was to use an assay that could be applicable to every patient with MDS and to utilize molecular markers to monitor tumor burden. We wanted to address the question of whether persistent molecular disease, detectable early after transplant—at day 30 or at day 100 after transplant—could provide prognostic information that was associated with outcome. Several DNA sequencing approaches could have been used: a gene panel approach or whole genome sequencing. However, each has limitations. In the end, we chose a middle ground, exome sequencing, to discover mutations prior to transplant. This method allowed us to detect mutations in almost every patient. Then, we simply genotyped those mutations 30 or 100 days after transplantation. Since we wanted a sequencing technique that was very sensitive after transplant, we incorporated the use of unique molecular indexes, which were ligated to DNA molecules, us to identify an average of 29 mutations per patient before transplantation. We then used a cutoff of detecting one mutant cell in 100 cells, and we classified a patient as having detectable tumor cells if we found at least one mutation above this threshold at day 30 or day 100.

We found that mutant-positive patients had an increased risk of progression. At 1 year after transplant, those who had a mutation detectable at that level at 30 days after transplant had a fourfold higher risk of progression compared with those who were mutation-negative at that threshold. About 53% of patients with a mutation detectable at that level had progressed compared with 13% who didn’t have a mutation detectable at that level. This also translated into worse progression-free survival in patients with mutations detectable at day 30. The largest effect, for the group of patients who were at highest risk of progression, was seen in individuals who received a reduced-intensity conditioning regimen compared with those who received myeloablative conditioning. Nearly all patients who received reduced-intensity conditioning and had a mutation detected at 30 days after transplant ended up progressing at some time point.

Q: It sounds like more studies are needed before this type of mutational analysis could be used in the clinic. Are there any direct clinical applications for patients now, and would you like to add anything else on the future studies on how this mutational analysis could be used in the clinic?

DR. JACOBY: We are looking [at the risk of relapse] prior to transplant now with gene panels, although this is not quite as sensitive as the exome sequencing that we utilized in this study. Certainly, post-transplant, it is not routine to look for persistent mutations that have not been cleared. I think more studies are needed before this could become clinically routine and, as I said before, a prospective clinical trial evaluating tests at day 30 and day 100 to detect low-level persistent disease is needed.

DR. WALTER: The other thing to highlight is that we designed the study to try to detect mutations in every patient. We used...
a broader sequencing approach encompassing the exome, and this is currently not feasible to do clinically. I think that we need to go back and study whether we can use gene panel sequencing to achieve a similar result as we did here. We did address this in the publication by down-sampling the data to look at only 40 of the most recurrently mutated genes in MDS. When we did that, we found the same result. So, detection of mutations at day 30 after transplant remained prognostic for progression and progression-free survival. However, only 79% of the patients that we originally analyzed were able to be evaluated using the gene panel sequencing because those additional patients didn’t have a mutation in one of those genes that we could follow after transplant. Because we used a paired-normal DNA sample from each patient to identify somatic mutations, we need to know whether the 40-gene panel using tumor-only sequencing is still feasible. Plus, we need to incorporate insertions and deletions, as well as structural variants present in each patient. Finally, we need to think about how we are going to incorporate these molecular studies into the current standard of care, as well as into multiparameter flow cytometry, which is also being tested for its ability to detect residual tumor cells after transplant. Ultimately, as Dr. Jacoby mentioned, all of these things will need to be tested prospectively in a clinical trial to move to the next stage.

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ABOUT THE STUDY

To access the complete study, please reference:

TEST YOUR IMAGE IQ

A 58-year-old man presents with a history of several purpuric nodules on the right leg and foot.

Based on the image shown, what is your diagnosis?

A. Hemangioma
B. Leiomyoma
C. Kaposi sarcoma
D. Schannoma

To find the answer to the above quiz, scan the QR code or go to cancernetwork.com/purpuric-nodules-leg-foot. You’ll find additional “TestYour Image IQ” quizzes under the “Image IQ” tab, too!
Counterpoint. Limitations Exist in Guiding Treatment
Continued from page 607

progress for developing novel therapeutic...assembly of genomic information from...

Complementing these advances, it is likely to significantly contribute to the next phase of therapeutic advances. Open access to these databases has nominated new candidate therapeutic targets, and the impact of this wealth of genomic information will further increase as clinical annotation is added. On balance, delineation of cancer genomes has and will continue to support translational studies designed to uncover or refine clinical treatment strategies.

Indeed, emergent promise of integrating genomics and transcriptomics into clinical practice has been realized. For example, molecular subtyping of breast cancer has allowed for delivery of more precise modes of therapy, wherein gene expression panel testing can be used to inform the need for chemotherapy and risk of recurrence in a subset of patients; these panels have been prospectively validated and are routinely used in clinical practice.[1,2] For solid tumors with established mismatch repair dysfunction or microsatellite instability, immune checkpoint inhibitors were recently approved by the FDA. This was a landmark, as the approval represented the first biomarker agnostic to site or histology of the tumor. [3] Complementing these advances, it has been proposed that non-specific genetic alterations, such as total mutational burden (TMB), were associated with improved response to checkpoint immunotherapy based on early clinical studies, thus expanding the repertoire of means by which genomic information can be translated into clinical practice. [4,5] Programmed death 1 (PD-1) was shown to be effective in 12 different tumor types, each with measurable alterations in the mismatch repair pathway.[6] Despite these advances, significant barriers exist for implementation into the clinical setting outside of clinical trials, especially in the case of prostate cancer.

In the localized setting, some advances have been made in using gene expression profiling for evaluation of post-operative patients (eg, Decipher). In addition, the Prolaris gene expression test has been shown to have potential for predicting disease-specific mortality with needle biopsy, and may estimate the risk of biochemical recurrence after prostatectomy. The Oncotype DX Genomic Prostate Score also tests gene expression and is designed to inform treatment decisions at diagnosis and for men with low-risk or favorable intermediate-risk disease. These tests are included in the National Comprehensive Cancer Network (NCCN) guidelines as testing options for consideration. However, the multifocal nature of localized disease and current inability to distinguish indolent from aggressive disease using either genomics or transcriptomics remain a barrier for developing precision oncology-guided treatment plans. Genetic analyses of primary disease showed that there is a high degree of heterogeneity amongst lesions; in a recent study of multiple clones from 41 patients, 76% of pairwise assessed tumor foci from the same surgical resection had no shared point mutations.[7] Genomic analyses examining primary and metastatic disease revealed that multiple clonal expansions occur, followed by extensive branching and mixing of clones.[8] Moreover, there are no genomic analyses that have been prospectively validated to help guide use of a targeted drug therapy.

For metastatic disease (both hormone-sensitive and metastatic CRPC), there is an increase in somatic mutations compared with localized disease, including alterations in candidate actionable pathways, such as those related to androgen receptor (AR) signaling, cell cycle control, and DNA repair. However, it is not yet clear how to readily identify passenger from driver mutations without laboratory modeling and functional interrogation.[9,10] For example, whereas alterations in AR regulatory pathways are frequent in mCRPC (including loss of the AR corepressor NCoR or gain of AR coactivators such as SRC-2 [NCOA2]), there is limited to no clinical evidence that these alterations cause altered responsiveness to AR-directed therapeutics. Similarly,
whereas BRAF alterations have now been observed in advanced prostate cancer (including BRAF V600E), clinical evidence that shows that prostate cancers harboring such alterations may respond to BRAF inhibitors is lacking. As the list of potential driver alterations grows, it will be of increasing importance for the translational prostate cancer field to define what constitutes actionable genomic alterations. Amongst other organizations, the European Society for Medical Oncology (ESMO) has developed a six-level scale for assigning clinical actionability to molecular targets, which is a major advance towards this goal.[11]

Once a definition of “actionable” for prostate cancer is determined, it will be of equal importance for the field to delineate priority for the instances in which two or more targetable alterations are identified. Mathematical modeling studies have predicted that the majority of cancer types are associated with at least 5 to 8 potential driver mutations.[12] Additionally, weaker driver alterations typically arise as a result of tumor evolution, thus further complicating the capacity to determine which therapeutic strategy might be most effective.[13,14] Identifying driver mutations is challenged by both intratumoral and intertumoral heterogeneity; as such, driver mutations may be distinct across metastatic sites, thus reducing the potential efficacy of a single targeted agent. Deep sequencing has further exacerbated the capacity to narrow selection of genomically matched therapies, since tumors contain a broad spectrum of genetic alterations that include complex mutations and large-scale chromosomal rearrangements. The latter is particularly relevant for advanced prostate cancer, in which chromothripsis and structural variations are highly prevalent.[15,16] How these collective, dynamic genetic changes can be assessed, curated, and translated into improved clinical intervention remains an area of intensive research focus.

Perhaps one of the most promising targeted therapies to date are those designed to suppress DNA repair in tumors demonstrating defects in homologous recombination, as achieved through genetic disruption of BRCA1/2 function or related pathways (ie, acquisition of BRCA-ness phenotypes).[17,18] Laboratory evidence strongly supports the concept that tumor models demonstrating BRCA-ness show an enhanced response to PARP1/2 inhibitors, as a result of excessive accumulation of DNA breaks.[19] In clinical practice, identification of genomic markers to predict response to PARP1/2 inhibitors remains a work in progress, and understanding of the factors that contribute to purported synthetic lethality remains incomplete. Clinical experience in breast and ovarian cancers has shown that only a minority of patients with detectable pathogenic alterations in BRCA1/2 experience an objective response to PARP1/2 inhibitors. Furthermore, a large phase III trial in ovarian cancer (the NOVA trial) showed that BRCA1/2 alterations (and/or evidence of genomically detectable defects in homologous recombination) proved neither necessary nor sufficient for tumor response to PARP1/2 inhibitors.[20] In the case of advanced prostate cancer, the TOPARP study revealed that response to PARP1/2 inhibitors is enriched in patients with detectable tumor mutations in DNA repair pathways; however, responses were also seen in the absence of DNA repair mu-
Barriers Limiting the Feasibility and Deployment of Genomically Informed Prostate Cancer Management

DISPARITIES
Although research has found that oncogenic mutations are differentially mutated in different ancestral groups, most large genome-wide studies were performed on only Caucasian patients.

FEASIBILITY
A significant number of providers in community settings, where most patients are treated, are not confident in interpreting sequencing reports and/or modifying therapy based on genomic data.

LIMITED ACCESS
In the United States, in most cases, patients must enroll in a clinical trial to receive access to targeted therapies.

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How to More Effectively Leverage Cancer Genomics Databases as Clinical Decision-Making Tools
Jason Roszik, PhD, MBA
Dr. Roszik explores existing sources and how oncologists can best utilize them in clinical practice.