Clinical Policy Title: Fluorescence spectroscopy for prostate cancer diagnosis

Clinical Policy Number: CCP.1277

Effective Date: April 1, 2017
Initial Review Date: November 16, 2016
Most Recent Review Date: November 6, 2018
Next Review Date: November 2019

ABOUT THIS POLICY: AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas’ clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas considers the use of fluorescence spectroscopy for prostate cancer diagnosis to be investigational/experimental, and, therefore, not medically necessary.

Limitations:

None.

Alternative covered services:

- Digital rectal examination
- Fine needle biopsy
- Prostate specific antigen

Background
Prostate cancer is the third most common cancer in the U.S. behind breast and lung. It is the most commonly-detected cancer in men; an estimated 164,690 cases were expected to be diagnosed in 2018. About 13 percent of U.S. males are expected to be diagnosed with the disease during their lifetime (Nooner, 2018).

The most common means of diagnosing the disease is a Prostate Specific Antigen (blood) test, for which levels of 4.0 ng/ml or higher are considered abnormal, followed by a biopsy (or sometimes an ultrasound) to confirm the presence and extent of cancer. Digital rectal exams, and other methods can detect prostate cancer, although the literature supporting efficacy of all non-Prostate Specific Antigen screening approaches are of low to moderate quality, and only relevant in high-risk populations (Carter, 2013).

Prostate biopsy has limited ability to accurately diagnose cancer. After surgery, just 32.2 percent of cancers were found to be detected correctly with a 12-core prostate biopsy using the same mapping, and just 43.3 percent of cancers were assigned the same Gleason score (Serefoglu, 2013). Transrectal ultrasound-guided prostate biopsies cannot differentiate cancer lesions from benign tissue and are only useful for locating boundaries of the gland to guide biopsy. About 90 percent of prostate cancer cores have been reported as benign, and thus targeting prostate cancer lesions and reducing the benign tissue is desirable (Werehara, 2014). Thus, there is a need to improve diagnostic accuracy.

Fluorescence spectroscopy is a type of electromagnetic spectroscopy that analyzes fluorescence from a sample. It uses a beam of light, typically ultraviolet, that causes electrons in molecules to emit light. The technique is also known as fluorometry or spectrofluorometry, and employs two types of instruments (filter fluorometers and spectrofluorometers). It has been used for biochemical, chemical, and medical purposes.

Application of fluorescence spectroscopy in medicine is relatively new. In 1984, the first report of fluorescence spectra measurement in cancerous and normal rat tissue, including prostate cancer, was reported (Alfano, 1984). To date, the technique has been used mostly for diagnosing kidney and prostate disease. One report used fluorescence spectroscopy to detect selenium levels in serum, prostate tissues, and seminal vesicle tissues in prostate cancer patients (Sabaichi, 2006). Another used the technique to measure in vivo fluorescence in photodynamic therapy of the prostate (Finlay, 2006).

In addition to fluorescence spectroscopy, there are several types of spectroscopy that are now being used for diagnostic purposes in medicine. These include elastic scattering spectroscopy, optical coherence tomography, and Raman spectroscopy (A’Amar, 2013). Magnetic resonance spectroscopy has been found to have high sensitivity and specificity in diagnosing prostate cancer (Mowatt, 2013), especially in low-risk patients (Umbehr, 2009).

Searches

AmeriHealth Caritas searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.

The Centers for Medicare & Medicaid Services.

We conducted searches on September 6, 2018. Search term was: “fluorescence spectroscopy prostate.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

- **Guidelines based on systematic reviews**.

- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

While there are some promising findings assessing the ability of fluorescence spectroscopy to differentiate benign from malignant tissue, use of this technique has been restricted. Current equipment is limited, and there is a dearth of *in vivo* studies (Olweny, 2014). The American Urological Society’s guideline on early detection for prostate cancer did not rate the efficacy of diagnostic tools other than Prostate Specific Antigen, based on lack of evidence (Carter, 2013). The American College of Radiology’s most recent guideline on prostate cancer detection and staging does not list fluorescence spectroscopy as a means of staging prostate cancer (Coakley, 2017).

No systematic reviews or meta-analyses on the topic exist. Small *in vitro* studies (n=12 and 20) of fluorescence spectroscopy used to differentiate malignant prostate tissues documented sensitivity and specificity above 85 percent (Masilamani, 2011) and above 90 percent (AlSalhi, 2012). Another showed fluorescence spectroscopy identified levels of tryptophan in spectra in advanced metastatic prostate cancers that exceeded moderately metastatic cancers and normal cells (Pu, 2013). Fluorescence spectrography has also showed varying concentrations of fluorophores (a chemical that can re-emit light on light excitation) in prostate tissue according to disease state (Werahara, 2015).

A study of the contrast agents Cybesin and Cytate, measured with fluorescence spectroscopy, found differences in rotation time and fluorescence anisotropies differed between cancerous and normal prostate tissue. A preferential uptake exists for Cytate/Cybesin in cancerous tissues suggesting a new optical approach to detect cancerous from non-cancerous tissue areas in the prostate (Pu, 2011).

A study of 20 surgically excised prostate glands addressed the issue of most prostate cores reported as benign. After measuring fluorescence in 187 cores, optical biopsy needles with light-sensitive probes took
samples, and found 78 of them to be malignant. Sensitivity and specificity were 86 and 87 percent, and negative and positive predictive values were 90 and 83 percent (Werahara, 2014).

A review of 724 samples of capsular and parenchymal tissue samples from 37 patients with intermediate-to-high grade prostate cancer used auto-fluorescence lifetime spectroscopy and light reflectance spectroscopy to test accuracy of the Gleason scale score. The study resulted in agreement of 87.9, 90.1, and 85.1 percent for parenchymal tissues, and 91.1, 91.9, and 94.3 percent when capsular tissues were included, for Gleason scores 7, 8, and 9, or high risk of the cancer spreading (Sharma, 2014).

One review used 50 prostate specimens from radical prostatectomy patients to obtain six punch biopsies from each, and four measurement points for each biopsy, making a total of 1200 measurement points. Time-resolved fluorescence spectra resulted in a 93.4 percent correct classification (malignant versus non-malignant) of the 1200 samples, suggesting a helpful diagnostic tool for both pathologists and surgeons (Gerich, 2011).

A study of concentrations of endogenous fluorophores in prostate tissue using an optical biopsy needle guided by fluorescence spectroscopy in 208 males undergoing prostatectomy surgery found 72 percent sensitivity and 66 percent specificity. The study also found a 93 percent negative predictive value to indicate benign tissue, leading authors to conclude that this technique can increase the diagnostic accuracy of prostate biopsies (Werahara, 2015).

A newly-constructed immunoassay system with surface plasmon field-enhanced fluorescence spectrometry that detected Prostate Specific Antigen levels was able to make distinctions between cases of prostate cancer and benign prostatic hypertrophy (Kaya, 2015).

Potential new uses of fluorescence spectroscopy in the diagnosis of cancer continue to emerge. A recent study of 966 cases each of colorectal cancer and matched controls revealed a copper-to-zinc ratio of 1.70, significant at $P < .0005$, that was positively associated with colorectal cancer risk. Copper and zinc are micronutrients essential for antioxidant functions, and may indicate oxidative stress (Stepien, 2017).

Policy updates:

A total of two guidelines/other were added to, and two guidelines/other removed from this policy in September, 2018.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Werahara (2015)</td>
<td>Key points:</td>
</tr>
<tr>
<td>Feasibility study of fluorescence spectroscopy to diagnose prostate cancer</td>
<td>- Used guided optical biopsy needle to obtain biopsy core.</td>
</tr>
<tr>
<td></td>
<td>- 208 in vivo cores, 224 ex vivo cores analyzed.</td>
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<tr>
<td></td>
<td>- Sensitivity 72 percent (%), specificity 66%, neg. predictive value for in vivo.</td>
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<tr>
<td>Citation</td>
<td>Content, Methods, Recommendations</td>
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<tr>
<td></td>
<td><strong>Key points:</strong></td>
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<tr>
<td></td>
<td>• Equipment currently in use is limited.</td>
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<tr>
<td></td>
<td>• Dearth of in vivo studies on ability of fluorescence spectroscopy to diagnose prostate cancer.</td>
</tr>
<tr>
<td>Sharma (2014)</td>
<td>Both methods used to assess 185 prostate capsular tissues, 539 parenchymal tissues.</td>
</tr>
<tr>
<td></td>
<td>• Tissues taken from prostate cancer patients with Gleason Score = 7, 8, or 9.</td>
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<td></td>
<td>• Accuracies for parenchymal tissues at Gleason Score 7, 8, 9 were 87.9%, 90.1%, and 85.1%.</td>
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<td>• Accuracy for capsular tissues at Gleason Score 7, 8, and 9 were 91.1%, 91.9%, and 94.3%.</td>
</tr>
<tr>
<td>Gerich (2011)</td>
<td>• 50 prostate specimens were obtained after radical prostatectomy.</td>
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<tr>
<td></td>
<td>• Six punch biopsies from each specimen, and four measurement points for each biopsy, using time-resolved fluorescence spectra.</td>
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<td></td>
<td>• Of 1200 points, 93.4% were correctly classified.</td>
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**References**

**Professional society guidelines/ other:**


Peer-reviewed references:


**Centers for Medicare & Medicaid National Coverage Determinations:**

No National Coverage Determinations identified as of the writing of this policy.

**Local Coverage Determinations:**

No Local Coverage Determinations identified as of the writing of this policy.
**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<td>0443T</td>
<td>Real time spectral analysis of prostate tissue by fluorescence spectroscopy</td>
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