Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: Keystone First	**Submission Date**: 1/2/2025
Policy Number: ccp.1504	**Effective Date:** 1/2022 **Revision Date:** December 1, 2024
Policy Name: Volatile organic compounds for urinary tract infection	

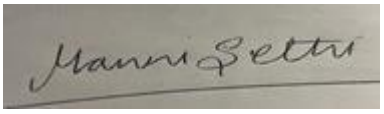
Type of Submission – Check all that apply:

- ☐ **New Policy**
- ☒ **Revised Policy***
- ☐ **Annual Review – No Revisions**
- ☐ **Statewide PDL**

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

See tracked changes below.

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Volatile organic compounds for urinary tract infection

Clinical Policy ID: CCP.1504

Recent review date: 12/2024

Next review date: 4/2026

Policy contains: Electronic noses, mass spectroscopy, urinary tract infection, volatile organic compounds.

Keystone First- CHIP has developed clinical policies to assist with making coverage determinations. Keystone First- CHIP's 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 Keystone First- CHIP, on a case by case basis, 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. Keystone First- CHIP's 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. Keystone First- CHIP's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First- CHIP will update its clinical policies as necessary. Keystone First- CHIP's clinical policies are not guarantees of payment.

Coverage policy

Volatile organic compounds for diagnosing urinary tract infection are investigational/not clinically proven and, therefore, not medically necessary.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

- Laboratory analyzed Urine culture and sensitivity.
- Urine dipstick test.

Background

There are multiple challenges associated with the diagnosis of urinary tract infections. Current methods such as gas chromatography mass spectroscopy are expensive, require trained personnel, and are time consuming. In addition, hematuria or chronic urinary catheter use for a neurogenic or anatomically impaired bladder can complicate diagnosis (Dospinescu, 2020).

Bacteria are present in the tissues around the urethral opening and often colonize the urine. Because bacteria are more likely to ascend to the female bladder, which has a shorter urethral length, rates of urinary tract infection are higher among women. Various gram-positive and gram-negative bacteria, most commonly *Escherichia coli*,

cause most urinary tract infections. Common infection diagnostic terms include cystitis, hemorrhagic cystitis, pyelonephritis, and catheter-associated urinary tract infection (Flores-Mireles, 2015; Foxman, 2014).

Risk factors for urinary tract infection include female sex; shorter urethra; prior infection; advanced age; recent sexual intercourse; use of a condom, diaphragm, or spermicide; vaginal infection; trauma/manipulation; diabetes; obesity; genetic susceptibility; or anatomic abnormalities. The estimated lifetime risk of urinary tract infection for women, based on self-reported history of diagnosis by a physician, is 60.4%. Recurrence is common. Most complicated infections are attributed to indwelling catheters (Flores-Mireles, 2015; Foxman, 2014).

Antibiotics are the standard treatment for urinary tract infections. The ever increasing rising rates of antibiotic resistance, combined with high recurrent infection rates are of great concern to health care providers, and underline the need for alternative therapies less susceptible to resistance (Flores-Mireles, 2015). An estimated 10% of urinary tract infections are resistant to antibiotics (Smart, 2019).

Improved diagnosis may enhance appropriate selection of antibiotics. Current diagnosis of urinary tract infection relies on two options. One is a dipstick test, which is rapid but often not accurate; one study places sensitivity and specificity, compared to lab culture, at 75.7% and 68.9% (Najeeb, 2015). The alternative is culturing to identify a pathogen, which takes 24 – 72 hours; during this delay, broad-spectrum antibiotics may be prescribed, leading to resistance (Dospinescu, 2020).

Volatile organic compounds are carbon-based compounds that can originate from microbial pathogens or a host response to infection and inflammation; many are associated with common urinary tract pathogens. These compounds can improve diagnosis of urinary tract infections. In addition, volatile organic compounds have been proposed as a diagnostic or screening tool for other conditions; one of the most commonly cited is cancer, although these uses are not established (Brusselmans, 2018; Catino, 2019; Farraia, 2022; Oakley-Girvan, 2017; Zhou, 2020). Several technologies have been developed, including gas chromatography, proton transfer reaction mass spectrometry, ion mobility spectrometry, selected ion flow tube mass spectrometry, field asymmetric ion mobility spectrometry, gas chromatography flame ionization detection, and odor sensors (Dospinescu, 2020).

In 2001, the U.S. Food and Drug Administration granted premarket approval for use of the Osmetech Microbial Analyser for diagnosis of urinary tract infection. The product uses “electronic nose” (odor sensor) technology to measure the presence of bacteria by semiquantitative analysis of volatile compounds (U.S. Food and Drug Administration, 2001).

Findings

The American Academy of Family Physicians practice guidelines on urinary tract infection for children/infants and adults only mentions urine microscopy and dipstick testing as diagnostic methods (Michels, 2015; Veauthier, 2020). For diagnosing recurrent urinary tract infections and asymptomatic bacteriuria, the American Urological Association and the Infectious Diseases Society of America recommend urine culture but do not mention volatile organic compound testing (Anger, 2022; Nicolle, 2019).

A systematic review of 25 studies and meta-analysis of ten studies examined the efficacy of portable electronic noses for diagnosis or monitoring various pathologies through analysis of urine samples, including four studies (n = 211) using different electronic nose systems for diagnosis of urinary tract infections. The authors stated the heterogeneity of the diagnostic measurements and findings did not permit conclusions about their use for diagnosing urinary tract infections and called for additional research and standardization of analytical methods (Afonso, 2022).

One review concludes that of the existing models, electronic noses and ion mobility spectrometry systems are still the most suitable candidates in the diagnosis of urinary tract infection, since they are easy to use, portable, relatively low-cost, and have methods which can be automated (Dospinescu, 2020).

A study of 84 urine samples that tested for 85 volatile organic compounds identified five isolates positively associated with *Escherichia coli*-resistant strains, and two with sensitive strains of urinary tract infections. The accuracy of identifying resistant and sensitive strains was 91.1% and 79.5%, respectively (Hewett, 2020).

A study used thermal desorption-gas chromatography-mass spectrometry to 'smell' antibiotic-resistant bacteria in 18 bacterial isolates (*Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*). The isolates were grown with and without the presence of antibiotic. Nine and 22 compounds differed significantly between cephalexin and ciprofloxacin sensitive/resistant isolates, respectively ($P < .05$) (Smart, 2019).

In 2023, we added two guidelines (Anger, 2022; Nicolle, 2019) and one new systematic review (Afonso, 2022) and deleted two older individual studies and two studies that were assessed in the systematic review. No policy changes are warranted.

In 2024, no new relevant literature was found. No policy changes warranted.

References

On November 2, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "volatile organic compounds" (MeSH), "urinary tract infections" ([MeSH), "electronic noses," "Mass spectroscopy," "urinary tract infection," and "volatile organic compounds." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

Afonso HAS, Farraia MV, Vieira MA, Cavaleiro Rufo J. Diagnosis of pathological conditions through electronic nose analysis of urine samples: A systematic review and meta-analysis. *Porto Biomed J*. 2022;7(6):e188. Doi: 10.1097/j.pbj.0000000000000188.

Anger JT, Bixler BR, Holmes RS, Lee UJ, Santiago-Lastra Y, Selph SS. Updates to recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline. *J Urol*. 2022;208(3):536-541. Doi: 10.1097/JU.0000000000002860.

Brusselmans L, Arnouts L, Millevert C, Vandersnickt J, van Meerbeeck JP, Lamote K. Breath analysis as a diagnostic and screening tool for malignant pleural mesothelioma: A systematic review. *Transl Lung Cancer Res*. 2018;7(5):520-536. Doi: 10.21037/tlcr.2018.04.09.

Catino A, de Gennaro G, Gilio AD, et al. Breath analysis: A systematic review of volatile organic compounds (VOCs) in diagnostic and therapeutic management of pleural mesothelioma. *Cancers (Basel)*. 2019;11(6):831. Doi: 10.3390/cancers11060831.

Dospinescu V-M, Tiele A, Covington JA, et al. Sniffing out urinary tract infection-diagnosis based on volatile organic compounds and smell profile. *Biosensors (Basel)*. 2020;10(8):83. Doi: 10.3390/bios10080083.

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Michels TC, Sands JE. Dysuria: Evaluation and differential diagnosis in adults. *Am Fam Physician*. 2015;92(9):778-788. https://www.aafp.org/pubs/afp/issues/2015/1101/p778.html.

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Oakley-Girvan I, Davis SW. Breath based volatile organic compounds in the detection of breast, lung, and colorectal cancers: A systematic review. *Cancer Biomark*. 2017;21(1):29-39. Doi: 10.3233/CBM-170177.

Smart A, Costello BL, White P, et al. Sniffing out resistance – rapid identification of urinary tract infection-causing bacteria and their antibiotic susceptibility using volatile metabolite profiles. *J Pharm Biomed Anal*. 2019;167:59-65. Doi: 10.1016/j.jpba.2019.01.044.

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Policy updates

12/2021: initial review date and clinical policy effective date: 1/2022

12/2022: Policy references updated.

12/2023: Policy references updated.

12/2024: Policy references updated.