Approval status: On May 27, 2016, the FDA approved Axumin® (fluciclovine F 18) for PET imaging in men with suspected prostate cancer recurrence based on elevated blood PSA levels following prior treatment.[1] Since that time, its use in the US has grown significantly and is expected to expand further based on the recent inclusion of the product into several sections [PROS 11-17] of the 2018 NCCN® prostate cancer guidelines.[2] F-18 fluciclovine was also recently included in the American College of Radiology’s Appropriateness Criteria® as “usually appropriate” for the post-treatment follow-up of prostate cancer.[3]

While Blue Earth Diagnostics is delighted that F-18 fluciclovine is now included in the NCCN guidelines, we are very concerned about the language in the Principles of Imaging PROS-B section (p. 3 of 3). It states that “Performance is generally poor at low PSA where pre-test probability of disease is low (PSA <2.0 ng/mL) and where salvage treatment is most likely to be beneficial.” As positioned in PROS-B, this statement appears to apply to both C-11 choline and F-18 fluciclovine.

However, while there is a statement in the C-11 choline US Prescribing Information [4], under Warning and Precautions, that “blood PSA levels < 2ng/mL have been associated with poor imaging performance”, there is no such statement or restriction in the Axumin US Prescribing Information. [1] Furthermore, C-11 choline’s indicated use is restricted to patients “with suspected prostate cancer recurrence and non-informative bone scintigraphy, computerized tomography (CT) or magnetic resonance imaging”. There is no such restriction on the use of F-18 fluciclovine.

The performance of F-18 fluciclovine in men with suspected recurrent prostate cancer and a PSA < 2.0 ng/mL is, in fact, addressed in the US Prescribing Information. While noting that the “detection rate of Axumin seems to be affected by PSA levels”, the US Prescribing Information notes a detection rate for F-18 fluciclovine of 60% (15/25) in men with a PSA ≤ 1.78 ng/mL (lowest quartile), with 11/15 (73%) of those scans confirmed as histologically positive. In terms of the performance of F-18 fluciclovine in men with suspected recurrent prostate cancer and even lower PSA levels, Bach-Gansmo, et al [11] reported a detection rate of 41.4% (53/128) in men with a PSA level ≤ 0.79 ng/mL. Of those 53 men, 13 (25%) had involvement in the prostate/prostate bed only, 16 (30%) had pelvic lymph node involvement (without more distant metastases) and 24 (45%) had distant metastases.

These result clearly demonstrate that, not only can F-18 fluciclovine PET/CT imaging be used successfully in men with PSA values lower than 2.0 ng/mL and, indeed, even in men with PSA values < 1.0 ng/mL, this PET/CT imaging provides clinically meaningful information. Based on the available data, including data carefully reviewed by the US FDA, we do not believe that the statement noted above is appropriate, when applied to F-18 fluciclovine, nor in the best interests of patient care. Suggesting that men with recurrent prostate cancer delay F-18 fluciclovine imaging until their PSA level reaches 2.0 ng/mL prevents them from receiving potentially curative treatment at lower PSA values, when the literature suggests such treatment might be more beneficial in men that have adverse pathological features. [5,6]

Comparison to CT: Odewole et al [7] compared the diagnostic performance of 18F-fluciclovine and CT in a retrospective study of postprostatectomy and non-prostatectomy men. Of 53 fluciclovine PET/CT and 53 CT examinations, 41 (77%) and 10 (19%), respectively, had positive findings for recurrent disease. All subjects were bone-scan negative. In this study, F-18 fluciclovine detection rates of 38% at a PSA level of < 1 ng/mL, 78% at 1–2 ng/mL, 92% at > 2 ng/mL, and 83% at > 5 ng/mL were observed. In the prostate bed, of the 43 index lesions used to prove positivity, 42 (98%) had histological proof of disease. Of 33 patients with histological proof of disease, fluciclovine PET/CT accurately detected disease in 31 (94%), but CT detected disease in only 4 (12%).

Low disease detection rates in men with biochemical recurrence using conventional standard of care imaging, such as CT or bone scan, are not unexpected. Choueiri et al [8] analyzed imaging data for all men in the CaPSURE
national disease registry who had detectable PSA after definitive therapy with radical prostatectomy or radiation therapy. He found that only 11% of subjects that had been imaged had a positive imaging finding on bone scan, CT or magnetic resonance imaging (MRI) of abdomen and pelvis. Positive imaging results were far more likely to be obtained in the majority of men that had PSA values greater than 5 ng/mL. Despite this fact, NCCN guidelines still recommend considering the use of CT, bone scan and/or MRI for restaging of prostate cancer, as the impact of positive findings can be significant. We feel that the same should hold true for the use of F-18 fluorocholine, which has been found to have higher detection rates at substantially lower PSA values.

Post-prostatectomy BCR: For example, Akin-Akintayo [9] studied the influence of fluorocholine PET/CT on the decision to offer radiotherapy and on radiotherapy treatment field recommendations in postprostatectomy patients with recurrent prostate cancer. On a per-patient basis, the sensitivity of F18-fluorocholine PET for detecting recurrent disease was found to vary with PSA level, with reported detection rates in the post-prostatectomy biochemical failure setting of 72%, 83%, and 100% at PSA levels of <1 ng/mL, 1–2 ng/mL, and ≥ 2 ng/mL, respectively.

Additional studies have reported F-18 fluorocholine detection rates ranging from 21% to 39% at a PSA level of < 1 ng/mL [10,11,12]. It is believed that some variation in detection rate at low PSA levels is related to PSA kinetics. For example, higher original Gleason scores and a shorter PSA doubling time are correlated with positive findings on F-18 fluorocholine PET/CT; in one study, the average PSA doubling time was 3.25 ± 2.1 mos. in patients with positive findings, versus 31 ± 22 mos. in patients with negative findings [13].

Blue Earth Diagnostics respectfully requests NCCN clarify the statement in PROS-B and the implication that F-18 fluorocholine has generally poor diagnostic performance at PSA values < 2.0 ng/mL, as this statement is inconsistent with the FDA-approved product label, the reported clinical findings and increasing clinical experience.

References

3 American College of Radiology, ACR Appropriateness Criteria®: Post-treatment Follow-up of Prostate Cancer [https://acsearch.acr.org/docs/69369/Narrative/](https://acsearch.acr.org/docs/69369/Narrative/)