Brief Backgrounder—

PSMA-Targeted PET for the Imaging of Advanced Prostate Cancer

Prostate cancer is one of the most frequently diagnosed cancers in men and a leading cause of cancer-related mortality in the United States. [Kovar 2014; Siegel 2016; ACS 2020] Of the new prostate cancer cases diagnosed, 77% are localized, 13% have spread to regional lymph nodes, and 6% are distantly metastasized. [Cancer Stat Facts 2019] Discerning the extent and spread of tumors in prostate cancer is key in determining treatment plans. However, the highly heterogeneous nature of the disease makes accurate staging a challenge. [Zimmerman 2019; Derks 2019, Paller 2013; Darwish 2012; Agarwal 2018; Hershman 2016]. Moreover, the conventional imaging modalities used to assess prostate cancer are limited in sensitivity and specificity, leading to under-staging of disease, incomplete assessment of advanced prostate cancer, and improper treatment selection. [Zimmerman 2019; Calais 2008] A common cancer, inadequately evaluated, does not bode well for clinical outcomes across the healthcare system.

> ***"There are a variety of prostate-specific imaging modalities on the horizon, predominantly incorporating PET. By giving the most accurate and specific information regarding the burden of their prostate cancer, men with advanced disease can make good judgments on the specific treatments available, and accelerate the treatment intensity when needed or minimize treatment when not needed.***
>
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Next-generation imaging addresses this problem. Novel molecular radiotracers have been developed for NGI, which can more accurately visualize advanced prostate cancer. [Kulshrestha 2016; Yen 2010; Chakraborty 2013; Iagaru 2012; Rieves 2012; Guo 2018; Contractor 2011; Oka 2012] Among NGI modalities, PET targeted to PSMA is an especially attractive candidate. PSMA is ubiquitously expressed by prostate cancer cells, and PSMA expression correlates with increasing tumor grade and severity. [Zimmerman 2019, Ceci 2019]. PSMA-targeted radiotracers capitalize on these features; they bind to PSMA-expressing cells, then are internalized via endocytosis and detected by PET (Figure 1). [Zimmerman 2019; Ceci 2019] These tracers, commonly labeled with 68Ga, 18F, or 177Lu radionuclides, are being developed rapidly, [Werner 2020] and there are 25 different PSMA radiotracers currently under clinical investigation in prostate cancer. [Zippel 2020] Many studies have reported on 68Ga-PSMA-11, which has shown good diagnostic accuracy and benefits in treatment selection. [Zippel 2020; Han 2018; Perera 2016; von Eyben, Picchio 2018; Cimadamore 2018; Afshar-Oromieh 2017; Meredith 2016; Hofman 2019] There has been a recent shift, however, toward 18F-labeled PSMA radiotracers; these tracers yield high image quality, provide very reliable lesion detection, and offer relatively long half-lives, making them amenable to off-site production and distribution (rather than requiring an onsite 68Ge/68Ga generator). [Werner 2020; Wondergem 2017; Rousseau 2019; Giesel 2018; Rowe, Gorin 2016; Rowe,

Macura 2016; Rowe, Mana-ay 2016; Maurer 2016; Harmon 2018; Li 2017; Hofman 2019] For example, in the phase 2/3 OSPREY trial, 18F-DCFPyl PET/CT imaging demonstrated high sensitivity for metastatic prostate cancer, with excellent specificity in pelvic-node metastases. [Rowe 2019; NCT02981368] In the phase 3 CONDOR trial in recurrent prostate cancer, 18F-DCFPyl PET/CT imaging met its primary endpoint for correct localization rate. [Werner 2020; NCT03739684; Bloomberg News 2019] Another tracer, 18F-PSMA-1007 for PET/CT has demonstrated high labelling yields, good tumor uptake, fast non-urinary background clearance, and high biochemical recurrence detection rates. [Werner 2020; Giesel 2017; Szabo 2015, Hofman 2019; Giesel 2019] Clinicians' ability to optimize selection of PSMA-targeted PET and other NGI technologies—based on patient need and key criteria in dosimetry, visualization, and tolerability—will be facilitated by ASCO's 2020 imaging guideline update. [Trabulsi 2020] The ASCO update focuses on advanced prostate cancer and covers NGI extensively, building on previous EANM/SNMMI and NCCN recommendations. [Trabulsi 2020; Fendler 2017; NCCN 2019]

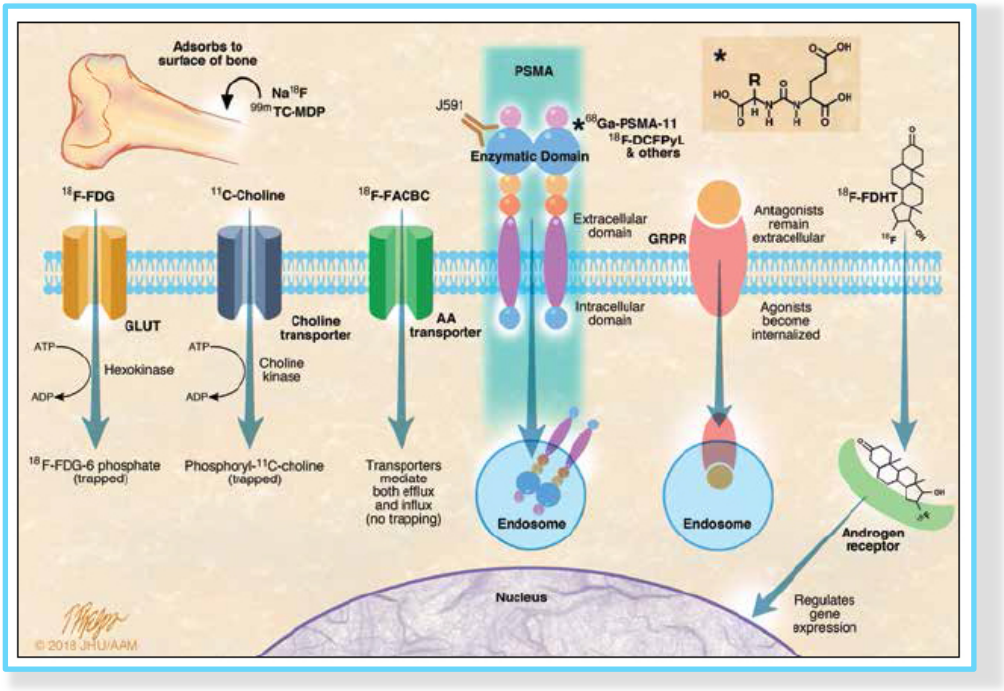

Figure 1. Comparison of mechanisms of uptake for PSMA-targeted PET imaging radiotracers with other radiotracers used in PET (eg, 18F-FDG). Blue arrows indicate the uptake of each radiotracer. Uptake (internalization) of PSMA-targeted radiotracers (eg, 18F-DCFPyl, 68Ga-PSMA-11) occurs via endocytosis. PSMA targeting takes advantage of 1) the high degree of PSMA expression in prostate cancer sites (100 to 1000 times greater than in benign prostate tissue and other tissues); 2) the positive correlation of PSMA expression with increasing tumor grade and stage.[Zimmerman 2019] Abbreviations: AA, amino acid transporter; 18F-FDG, 18F-fluorodeoxyglucose; 18F-FDHT, 16-beta-18F-fluoro-5-alpha-dihydrotestosterone; GLUT, glucose transporter; GRPR, gastrin-releasing peptide receptor; PSMA, prostate-specific membrane antigen; 99mTc-MDP, 99mTc-methylene diphosphonate. Adapted from: Zimmerman et al (2019).

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