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# Imaging Recommendations for Theranostic PET-CT in Oncology

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## Abstract

We in this article have presented a review of the guideline recommendations on theranostic positron emission tomography-computed tomography (PET-CT) imaging which will be helpful to assist practitioners in providing appropriate patient care. Multiple guidelines by different societies and medical associations provide standards for diagnosis, imaging, and treatment of cancer patients. They have generated a number of recommendations related to $^{68}$Ga-DOTATATE and $^{68}$Ga-PSMA-11 PET-CT, which are the classical examples of theranostic PET-CT imaging in current practice.

**Keywords**

- theranostics
- PET-CT
- $^{68}$Ga-DOTATATE PET-CT
- $^{68}$Ga-PSMA-11 PET-CT
- FAPI PET-CT
- neuroendocrine tumors
- prostate cancer
- PRRT

## Introduction

The term "theranostics" is fusion of two words diagnostics and therapeutics in which diagnostic and therapeutic tools related to the same specific molecular targets are coupled. In essence, theranostics integrates diagnostic modality for the detection of a molecular target for which a specific therapy is intended. Although the term theranostics is reportedly new and probably first used by John Funkhouser in 1998 for the development of a test for monitoring the efficacy of a new anticoagulant drug, the concept behind "theranostics" is not and had been applied to imaging and treatment of thyroid diseases for more than 80 years and revisited over the years.[1,2]

In nuclear medicine, the theranostic system includes use of two identical or very closely related radiopharmaceuticals for diagnosis and therapeutic purpose. The tumor-specific substrates, receptor ligands, transporter, or cell surface proteins can serve as target for development of theranostic couples when labeled with specific radionuclides for imaging or therapy purpose as mentioned in ►**Table 1**. Theranostics has been used in nuclear medicine over past eight decades. Radioiodine is a prime example of a classic theranostic agent with use of same radioisotope $^{131}$I for same molecular target of sodium iodide symporter for imaging and therapeutics in patients with differentiated thyroid carcinoma.

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**Table 1** Theranostic pairs commonly used in clinical practice

| Diagnostic agents | Therapeutic agents | Molecular/ Cellular target | Function of target | Oncological conditions |
|---|---|---|---|---|
| $^{68}$Ga-DOTATOC<br>$^{68}$Ga-DOTATATE<br>$^{68}$Ga- DOTANOC | $^{177}$Lu-DOTATATE<br>$^{90}$Y-DOTATATE<br>$^{225}$Ac-DOTATATE | SSTR | Cell-surface receptor | Well-differentiated neuroendocrine tumors |
| $^{68}$Ga-PSMA-11<br>$^{68}$Ga-PSMA-617<br>$^{68}$Ga-PSMA-I&T | $^{177}$Lu-PSMA-617<br>$^{225}$Ac-PSMA-617 | PSMA | Cell-surface protein | Metastatic castration-resistant prostate cancer |
| $^{68}$Ga-FAPI-04 and FAPI-derivatives | $^{90}$Y, $^{177}$Lu or $^{153}$Sm-labeled FAPI-derivatives | FAP | Stroma of cancer-cell surface of activated fibroblasts | Various types of cancers-sarcomas, breast esophageal, lung, pancreatic, prostate cancers, etc. |

Abbreviations: FAPI, fibroblast activation protein inhibitor; PSMA, prostate-specific membrane antigen; SSTR, somatostatin receptor.

Recent advancement in molecular biology and radiochemistry has led to introduction of newer theranostic agents for neuroendocrine tumors (NET) and prostate cancer (PC) in nuclear medicine. These agents used combination of two different radioisotopes (each one emitting different types of radiation: electromagnetic radiation for imaging and particulate irradiations for therapy) lined to the specific molecules that utilized same cellular structure, biologic process and also same target for imaging and therapy intent are called theranostic pairs as shown in ►**Table 1**. The main concept behind theranostics is "We treat what we see and we see what we treated."[3] For this purpose, molecular imaging plays a cornerstone role for determining target lesions, quantification, and prognostication of disease process in individual patients. Over the past two decades, imaging technology evolved tremendously with emergence of hybrid imaging in nuclear medicine such as positron emission tomography-computed tomography (PET-CT) examinations. The hybrid PET-CT imaging is a double-edged sword with improved cutting-edge imaging technology on one side and cost and radiation exposure on another side. Hence, there is requirement for recommendation and appropriate use criteria on clinical use of hybrid PET-CT imaging and these are formulated by multidisciplinary panels and presented in various guidelines. We reviewed the guidelines for clinical use of theranostic PET-CT imaging in oncological conditions and compiled and presented in this article.

### $^{68}$Ga-labeled Somatostatin Analogs for PET-CT Imaging

Somatostatin is a naturally occurring hormone that acts by binding to somatostatin receptors (SSTR) and these receptors are over-expressed in most of NETs. SSTR is a target for therapy in NET over last three decades. In initial years of peptide receptor radionuclide therapy (PRRT) procedures, $^{111}$In-pentetreotide (imaging by using gamma camera based scintigraphy and therapy with help of Auger electrons) was used as theranostic agent in metastatic NET cases.[4–6] The emergence of hybrid PET-CT imaging and development of newer radiopharmaceuticals based on $^{68}$Ga-labeled somatostatin analog ($^{68}$Ga-DOTATOC, $^{68}$Ga-DOTATATE, and $^{68}$Ga- DOTANOC) was a game changer and led to upgradation of imaging in NET,[7] as PET-CT imaging with $^{68}$Ga-labeled somatostatin analog has several advantages, including improved radiation dosimetry, measurement of lesional activity by using semiquantitative PET-based analysis, higher spatial resolution with better sensitivity and specificity compared to scintigraphy, and conventional imaging.[8,9]

On June 1, 2016, U.S. Food and Drug Administration approved $^{68}$Ga-DOTATATE PET-CT imaging as a diagnostic tool for the detection of location and extent of tumor in NET patients.[10] This led to inclusion of $^{68}$Ga-labeled somatostatin analog PET-CT scans in many guidelines.[11–13]

## European Association of Nuclear Medicine (EANM) Recommendations

Recently, the procedure guideline given by EANM on PET-CT study with $^{68}$Ga-labeled somatostatin analogs has been revised and updated.[14] They provided the clinical indication of $^{68}$Ga-labeled somatostatin analogue PET-CT imaging in NET as follows:

i. To detect and localize primary site (diagnosis of NET).
ii. To determine extent of local and metastatic disease (staging of NET).
iii. To detect residual, recurrent, or progressive disease (restaging of NET).
iv. To determine SSTR status and select patients with metastatic disease for PRRT based upon SSTR status (management and prognosis of NET).
v. To determine therapy response (surgery, radiotherapy, chemotherapy or PRRT).

They recommended discontinuation of somatostatin analogue therapy prior to $^{68}$Ga-labeled somatostatin analog PET-CT scan for 1 day for short-lived molecules and 3 to 4 weeks for long-acting somatostatin analogue therapy to avoid possible SSTR blockade. They also recommended use of $^{68}$Ga-labeled somatostatin analog PET-CT scan for determining primary site in metastatic NET case of an unknown primary with no evidence of a primary disease on conventional imaging and cited use of $^{68}$Ga-labeled somatostatin analogue PET-CT scan for characterization of a bronchial

mass suspicious of bronchial NET, when other diagnostic modalities are inconclusive.[15–29]

## ESMO Recommendations

The ESMO provided guidelines for diagnosis, treatment, and follow-up of patients with gastroenteropancreatic NET. They recommended use of $^{68}$Ga-labeled somatostatin analog PET-CT scan for tumor staging, preoperative imaging, and restaging in NET patients. They also mentioned if PET not available, somatostatin receptor scintigraphy (SRS) may be used as less sensitive imaging modality as compared to PET-CT examination. They recommended the use of PRRT as second-line therapy in patients with midgut and pancreatic NET who fulfil general requirements for PRRT. One important prerequisite for PRRT is high-grade SSTR expression (Krenning 3/4) in lesions, which is assessed by using $^{68}$Ga-labeled somatostatin analogue PET-CT scan before PRRT in these NET patients. They cited lifelong follow-up in treated NET patients, which included clinical symptom evaluation, biochemical parameters analysis, conventional, and SSTR imaging. Hence, they recommended use of $^{68}$Ga-labeled somatostatin analog PET-CT scan in follow-up of SSTR expressing NET patients at the interval of 12 to 36 months.[30]

## European Neuroendocrine Tumor Society (ENETS) Recommendations

The European Neuroendocrine Tumor Society (ENETS) provided consensus guidelines on radiological, nuclear medicine, and hybrid imaging with standards of care in NET patients. Similar to ESMO guidelines, they also recommended use of $^{68}$Ga-labeled somatostatin analog PET-CT scan for tumor staging, preoperative imaging, and restaging in NET patients. They also mentioned high sensitivity of $^{68}$Ga-labeled somatostatin analog PET-CT imaging for the detection of lymph node metastases, bone metastases, liver metastases, small peritoneal lesions, and primary site of small-intestinal NET as compared with conventional imaging modalities.[31]

## National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) version 4.2021 to January 2022 mentioned appropriateness of SSTR imaging by using $^{68}$Ga-labeled somatostatin analogue PET-CT or PET- magnetic resonance imaging (MRI) for assessment of distant disease and SSTR status in NET patients. They mentioned that SSTR imaging is particularly important for evaluation of benefit from SSTR-directed therapies. They also mentioned that whenever possible PET-CT or PET-MRI should be performed in combination of contrast-enhanced CT or MRI imaging in order to minimize total numbers of imaging studies.[32]

## North American Neuroendocrine Tumor Society and Other Societies

Representatives from various societies assembled under auspices of an autonomous workgroup to develop appropriate use criteria for SSTR-PET imaging ($^{68}$Ga-DOTATOC and $^{68}$Ga-DOTATATE) in patients with well-differentiated NET (grade 1 and grade 2). They evaluated 12 clinical scenarios. Out of these, nine were recommended as appropriate use criteria:

i. Initial staging of NET after the histological confirmation
ii. Detection of primary site in known metastatic NET
iii. Selection NET patients for PRRT
iv. Staging of NET prior to plan surgery
v. Evaluation of a mass suggestive of NET not amenable to endoscopic or percutaneous biopsy
vi. Monitoring of NET
vii. Evaluation of patients with biochemical evidence and symptoms of a NET without evidence of it on conventional imaging and or prior histological diagnosis
viii. Restaging of NET patients with symptomatic or biochemical progressive disease but without progressive disease on conventional imaging
ix. Conventional imaging showing new indeterminate lesion but having unclear progressive disease in NETs

They mentioned that SSTR-based PET demonstrated better sensitivity and specificity than conventional imaging and $^{111}$In-pentetreotide. They also cited that, SSTR-based PET is clearly preferred in initial diagnosis, selecting patients for PRRT, and localizing of unknown primaries in known metastatic NETs.[13]

## Prostate-Specific Membrane Antigen PET-CT Imaging

The PC over-expresses the prostate-specific membrane antigen (PSMA), a transmembrane glycoprotein, present on cell membrane. Over-expression of PSMA is associated with higher grade tumor, metastatic castration-resistant tumor, and tumor aggressiveness in PC. The PSMA is an excellent target for theranostics in PC, as it is internalized after binding to the ligand, leading to high detection rate and better lesion to background uptake ratio for imaging purpose and inducing direct DNA damage with less risk of nonspecific radiation for therapeutic purpose. The $^{68}$Ga-PSMA-11, $^{68}$Ga-PSMA-617, and $^{68}$Ga-PSMA-I&T are developed as PET tracer in PC imaging. There is no data available for direct comparison of these different ligands. Most of published clinical work and clinical practices in nuclear medicine used $^{68}$Ga-PSMA-11 PET-CT imaging in PC and translated into $^{177}$Lu-PSMA-617 and $^{225}$Ac-PSMA-617 agents for therapeutic purposes.[33–42] Various clinical guidelines given by the medical societies (namely urological, oncological, nuclear medicine, and radiation oncology societies) have recommended use of $^{68}$Ga-PSMA PET-CT imaging in PC.

## Society of Nuclear Medicine and Molecular Imaging and European Association of Nuclear Medicine

The Society of Nuclear Medicine and Molecular Imaging and EANM jointly provided procedure guidelines[43] for the

recommendation, performance, interpretation, and reporting of PSMA PET-CT imaging in PC as follows:

i. To detect tumor lesions in the presence of biochemical recurrence of PC (especially low serum prostate-specific antigen [PSA] values between 0.2 and 10 ng/mL).
ii. For primary staging of PC with high-risk disease before surgical or external beam radiation planning.
iii. For staging prior and during PSMA-based radionuclide therapy.
iv. To do molecular targeted biopsy in high suspicion case of PC with prior negative biopsy.
v. To monitor response of systemic therapy in metastatic PC.

## American Society of Clinical Oncology (ASCO) Recommendations:

The ASCO provided evidence and expert recommendations for optimal use of imaging in advanced PC. They mentioned use of either conventional imaging (defined as CT, bone scan, and prostate MRI) and/or next generation imaging (PET, PET-CT, PET-MRI, whole-body MRI) in advanced PC according to the clinical scenario. They recommended use of PET-CT for added clinical benefits and clarification in high-risk/very high-risk localized PC with negative or equivocal finding on conventional imaging. Another clinical scenario in which PSMA-based PET-CT imaging is recommended by ASCO is rising serum PSA level after prostatectomy or radiotherapy with negative conventional imaging in men for whom salvage local or regional therapy is contemplated. ASCO also recommended use of PET-CT imaging in hormone-sensitive metastatic PC at initial diagnosis or after initial treatment. For metastatic castration-resistant prostate cancer (CRPC) with serum PSA progression, they mentioned that use of next-generation imaging (PET, PET-CT, PET-MRI, whole-body MRI) for this cohort is unclear in view of a paucity of prospective data. However, they mentioned that use of next-generation imaging (PET, PET-CT, PET-MRI, whole-body MRI) could be contemplated, especially in the setting of a clinical trial.[44]

**European Association of Urology, European Society of Urogenital Radiology, and Other Societies (The EAU-EANM-ESTRO-ESUR-ISUP-SIOG),** in their guidelines on PC, recommended use of PSMA-based PET-CT imaging for staging in PC with high-risk localized disease/locally advanced disease and for the management of PC with persistent/recurrence serum PSA level after radical prostatectomy (serum PSA level $>$ 0.2 ng/mL) or radiotherapy in which the result of PSMA PET-CT imaging will influence subsequent treatment decisions. This guideline also recommended use of $^{177}$Lu-PSMA-617 therapy in metastatic CRPC patients, which are showing high expression of PSMA (exceeding uptake in lesion over liver) on PSMA PET-CT scan.[45,46]

## NCCN Recommendations

The NCCN version 3.2022-January 2022 mentioned that $^{68}$Ga-PSMA-11 PET-CT imaging can be considered as an alternate to standard imaging of bone and soft tissue for initial staging, detection of lesions in biochemically recurrent disease, and as workup for progressive disease in bone and soft tissue. They cited that $^{68}$Ga-PSMA-11 PET-CT imaging has increased sensitivity and specificity for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at initial staging and biochemical recurrence. Therefore, the panel of NCCN does not feel that conventional imaging is a necessary prerequisite to PSMA PET-CT. To reduce false-positive rate of PSMA PET-CT in PC, use of radiographic or histological confirmation is recommended by NCCN.[47]

## $^{68}$Ga-Fibroblast Activation Protein Inhibitors PET-CT Imaging

The fibroblast activation protein (FAP) is a serine proteinase and highly expressed on cell surface of activated fibroblasts but absent in resting fibroblasts. Over-expression of FAP is related in wound healing, fibrotic processes, and stroma of many malignancies. The FAP-associated fibroblasts are found in more than 90% of epithelial tumors on histopathological studies. The cancer-associated fibroblasts with extracellular fibrosis contributed up to 90% of gross tumor mass, leaving original tumor cells in minority. Hence, FAP is a potential target for theranostic in a large variety of cancers.[48]

The University Hospital Heidelberg group recently developed a series of quinoline-based FAP inhibitors (FAPI) based on clinical and preclinical research.[49] They labeled these FAPI compounds with diagnostic and therapeutic radioisotopes via chelator DOTA. For diagnostic purposes, they labeled FAPI-01, FAPI-02, FAPI-04, FAPI-21, and FAPI-46 with $^{68}$Ga. Kratochwil et al demonstrated that $^{68}$Ga-FAPI-04 PET-CT imaging is capable to visualize tumor lesions in 28 different types of cancer with high sensitivity and image quality. They cited that $^{68}$Ga-FAPI-04 PET-CT imaging showed overall intense tracer uptake with high-contrast images in various types of cancers, such as sarcomas, cholangio-carcinoma, esophageal, breast, lung, hepatocellular, colorectal, head-neck, ovarian, pancreatic, and PCs, etc., and use of $^{68}$Ga-FAPI-04 PET-CT imaging led to non-invasive tumor characterization, tumor staging, and radio-ligand therapy pre-evaluation for theranostic purpose.[50]

The $^{90}$Y, $^{177}$Lu, or $^{153}$Sm-labeled FAPI-derivatives (FAPI-46, DOTA.SA.FAPI, and FAPI-04) were used as therapeutic agents on compassionate ground in treating breast cancer, sarcoma, and pancreatic cancer patients in various case reports and a few studies. Case report and studies cited that FAPI-derivatives therapies were well tolerated and showed signs of clinical responses, such as stable disease or tumor lesion shrinkage as well as reduction in clinical symptoms.[51–53]

## Guideline for FAPI PET-CT Imaging

There is paucity of FAPI PET-CT imaging data in literature. Hence, role of FAPI PET-CT scan in cancer imaging and management required further exploration in larger prospective trials before coming to any conclusion on clinical use of

these imaging agents. Radiolabeled FAPI as theranostic agents is under development and still in its infancy but showed promising results in preliminary reports and expected to enter clinical trials in near future. Therefore, at present no guidelines on FAPI PET-CT imaging exist in the literature.

## Advantages of Theranostic PET over Conventional Imaging in PC and NET

►**Supplementary Table S1** (in supplement) shows the comparison of CECT, FDG-PET-CT, MRI, and PSMA PET-CT for PC.[54–60] As shown in ►**Table 1**, PSMA PET-CT is superior to the conventional imaging modalities for the localization of primary lesion, staging, and detection of relapse. Besides, PSMA PET-CT also gives lower radiation exposure when compared to CECT and FDG-PET-CT. ►**Supplementary Table S2** (in supplement) shows the comparison of CECT, FDG-PET-CT, MRI, and $^{68}$Ga- DOTATOC PET-CT for NET.[61–65] Similarly, $^{68}$Ga-DOTATOC PET-CT appears to be better for the localization of primary lesion, staging, and response evaluation. Also, radiation exposure with $^{68}$Ga-DOTATOC PET-CT is lower than CECT and FDG-PET-CT.

### Indian Experience on $^{68}$Ga-DOTA-NOC/TATE and $^{68}$Ga-PSMA PET-CT

There has been substantial use of both $^{68}$Ga-labeled somatostatin analogs and $^{68}$Ga-PSMA PET-CT imaging for varied applications in a wide variety of tumors, though no Indian guideline exists on the clinical use of these diagnostic modalities. Naswa et al conducted a prospective study on comparison of $^{68}$Ga-DOTANOC PET-CT and conventional imaging in NETs. They found superior sensitivity and specificity of $^{68}$Ga-DOTANOC PET-CT imaging over conventional imaging in detecting primary site and metastatic disease, with significant change in the management of NETs after use of $^{68}$Ga-DOTANOC PET-CT imaging.[66] In our experience, $^{68}$Ga-labeled somatostatin analogs PET-CT have outperformed over conventional imaging both for staging and restaging of NETs.[67–77] Sampathirao and Basu studied 51 patients with CUP-NETs with $^{68}$Ga-DOTATATE PET-CT: unknown primary was detected in 31 of 51 patients (resulting in sensitivity of 60.78%), while overall lesion detection sensitivity was 96.87%. Tumor heterogeneity exists in NET, hence $^{68}$Ga-labeled somatostatin analogs PET-CT in combination of $^{18}$F-FDG-PET-CT (dual tracer PET-CT) have evolved as an important functional imaging approach over Ki-67 labelling index for deciding treatment strategies in metastatic and inoperable NETs (PRRT vs. chemo-PRRT). In neoadjuvant setting, cross-sectional imaging modality, such as triphasic CECT, is superior for identifying involvement of major abdominal blood vessels by tumor over noncontrast PET-CT imaging. The whole body $^{68}$Ga-labeled somatostatin receptor-based PET-CT is more valuable imaging modality over conventional imaging for response evaluation and surveillance in NETs. Theranostic $^{68}$Ga-labeled somatostatin analogs PET-CT is an excellent imaging modality for deciding PRRT in clinical conditions beyond NETs such as metastatic/inoperable medullary thyroid carcinoma, metastatic/inoperable paraganglioma/pheochromocytoma, noniodine concentrating metastatic differentiated thyroid carcinoma, Merkel cell carcinoma, meningioma, and recurrent/inoperable phosphaturic mesenchymal tumor.[67–77] Jain et al prospectively evaluated diagnostic accuracy of $^{68}$Ga-PSMA PET-CT imaging in PC. They found that $^{68}$Ga-PSMA PET-CT imaging significantly improved detection rate of PC by using a SUVmax cutoff value in patients with raised PSA between 4 and 20 ng/mL or abnormal digital rectal examination findings.[78] Kallur et al evaluated the clinical utility of $^{68}$Ga-PSMA PET-CT imaging in 262 patients of PC.[79] In our experience, $^{68}$Ga-PSMA PET-CT imaging is better imaging modality in detection of primary, staging, restaging, response evaluation, and prognostication of PC patients.[79,80]

### Theranostic $^{68}$Ga-Labeled SSTR-Based PET-CT imaging in Pediatric Population

At present no guideline exists for $^{68}$Ga-labeled somatostatin analogs PET-CT imaging in pediatric group. As such, available literature for clinical use of theranostic $^{68}$Ga-labeled somatostatin analogs PET-CT imaging in pediatric group is limited in view of low prevalence and rare incidence of NETs in this group. Most studies suggest $^{68}$Ga-labeled somatostatin analogs PET-CT imaging should be considered as first-line imaging modality in pediatric NETs. Goel et al evaluated role of $^{68}$Ga-DOTATATE PET-CT in 30 pediatric NET patients and they found that $^{68}$Ga-DOTATATE PET-CT was superior imaging technique over conventional imaging for detecting bone metastases.[81] Jha et al found that better lesion detection rate of $^{68}$Ga-DOTATATE PET-CT in pediatric group of pheochromocytomas.[82] Well-differentiated neuroblastoma has high expression of SSTR2, resulting in better sensitivity of $^{68}$Ga-labeled somatostatin analogs for lesion detection as compared to $^{123}$I-MIBG imaging. But still there are no current guidelines on $^{68}$Ga-labeled somatostatin-based PET-CT imaging in view of scarcity of data in pediatric population. Overall, $^{68}$Ga-labeled somatostatin analogue PET-CT imaging in pediatric group showed number of advantages over conventional imaging such as low radiation exposure, fast clearance time, simple preparation, few pharmacological interactions, higher prognostic value, and identifying individuals for PRRT.[83]

## Conclusion

Theranostic approach in oncological condition requires integration of therapeutic and diagnostic modality for targeting specific molecule, which can be labeled with radiopharmaceuticals for imaging or therapeutic purpose. Theranostic PET-CT imaging is helpful for diagnosis, finding status of target molecule in the tumor cells, and determining extension of disease that helps in clinical decision-making and design of effective treatment plan. Other advantages of theranostic PET-CT imaging include assessment of biologic behavior and tumoral heterogeneity, prognostification of disease, and predicting response and toxicities of therapies.

This guideline review on theranostic PET-CT imaging thus summarizes the perspectives expressed in multiple guidelines on various receptor-based PET-CT imaging by different societies, discussing upon their clinical use, in order to achieve the goal of best management of cancer patients with reduced expenditure and avoiding potentially unnecessary treatments and interventions.

Authors' Contributions

Rahul V. Parghane was involved in conceptualization, designing, definition of intellectual content, literature search, manuscript preparation, manuscript editing, and manuscript review. Abhishek Mahajan contributed to conceptualization, designing, manuscript editing, and manuscript review. Nivedita Chakrabarty edited and reviewed the manuscript. Sandip Basu contributed to conceptualization, designing, definition of intellectual content, manuscript editing, and manuscript review.

Ethical Committee Clearance

Not required as patient data not revealed.

Conflict of Interest

None declared.

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