Over the last decade, F-18 fluorodeoxyglucose (FDG) PET/CT has continued to have an ever-increasing role in staging malignancy, evaluating tumor response to treatment, and evaluating indeterminate masses discovered on CT, MRI and US. Many decisions regarding medical and/or surgical interventions are largely based on functional metabolic information gathered from the PET/CT. It is, therefore, critical for the interpreting physician to be aware of potential pitfalls that may lead to an erroneous diagnosis.

As the name implies, FDG is an analog of glucose that is beneficial in detecting a variety of malignancies. The relative increased uptake of FDG by many malignancies compared to background tissues is due to the increased expression of glucose transporters by cancer cells, as well as variations of intracellular enzyme activity with increased activity of hexokinase and decreased activity of glucose-6-phosphatase. Ultimately, this leads to increased accumulation of FDG in many malignant cells as, unlike regular glucose, FDG does not become further metabolized after initial phosphorylation.

Unfortunately for interpreting physicians, a major limitation of FDG is that it is not specific for neoplastic cells. In addition to the variations of normal human metabolism within organs and tissues that universally rely on glucose as a substrate, a variety of nonmalignant inflammatory processes can also demonstrate significant FDG uptake. In fact, FDG is increasingly used clinically for nononcological purposes, including neurodegenerative disorders, cardiac viability, cardiac sarcoid, as well as replacing traditional radiolabeled leukocyte imaging for detecting infection.

There is also an overlap in the amount of FDG uptake between many benign and malignant lesions. This problem is common in evaluating solitary pulmonary nodules and incidental adrenal nodules, for example. Furthermore, certain benign lesions such as Warthin’s tumors may also display a high degree of FDG uptake.

Additionally, whole-body FDG PET/CT is a technically challenging examination compared to many standard radiology studies. Patient preparation, radiotracer injection, uptake period, image acquisition, and processing all have potential for problems that can affect image interpretation.

This article is a pictorial review of a variety of pitfalls in interpreting FDG PET/CT scans. After discussing a variety of general considerations, details of pitfalls related to specific body regions will be presented. With familiarity and understanding of these processes, the reading physician increases the likelihood of diagnostic pitfall recognition, thus avoiding incorrect interpretations.

**General Considerations**

Although patient preparation can vary by institution, practice guidelines from the Society of Nuclear Medicine and Molecular Imaging suggest that patients fast 4 to 6 hours prior to PET imaging to ensure optimal insulin levels. Injection of FDG and subsequent imaging in nonfasting patients can result in a so-called altered biodistribution, in which there is relative increased FDG uptake throughout the body’s skeletal muscles largely due to insulin effect (Figure 1). Similar findings can be seen in patients on insulin and corticosteroids, as well as in those who have recently exercised. Regardless of cause,
FIGURE 1. Altered biodistribution. FDG PET MIP image demonstrates diffuse increased muscular uptake, most consistent with insulin effect in this nonfasting patient.

FIGURE 2. Extravasation at the injection site. FDG PET MIP image demonstrates a large focus of uptake in the right upper extremity (solid arrow) with adjacent lymphatic uptake (dashed arrow) due to extravasation at the injection site. Not only does this create an optical distraction for the interpreter, it also decreases the amount of radiotracer in the blood pool and can lead to inaccurate SUV measurements.

FIGURE 3. Misregistration artifact. Axial FDG PET (A) and fused PET/CT (B) images demonstrate myocardial FDG uptake erroneously localizing to the left lung (arrow, B). The patient changed position between CT and PET acquisition resulting in this artifact.

FIGURE 4. Brown fat uptake. FDG PET MIP image in a pediatric patient demonstrates bilateral uptake in cervical, supraclavicular, and paraspinal fat, as well as additional foci in the upper abdomen (arrows) in a classic pattern of brown fat uptake.

FIGURE 5. Normal pediatric red marrow distribution. FDG PET MIP image in a pediatric patient demonstrates heterogenous FDG uptake in the proximal humeri, proximal and distal femurs, and proximal tibias (arrows) reflecting normal FDG uptake in red bone marrow. This uptake is usually minimal or absent in adults due to the conversion of red marrow to yellow marrow, which is typically less metabolically active.
an altered biodistribution can obscure underlying disease and potentially affect tumor-to-background conspicuity.\(^3\)

Similarly, artifacts can be related to suboptimal injection technique of the radiopharmaceutical. A small amount of extravasation at the injection site is common, and correlation with injection site documentation is advised when identifying a small focus of abnormal uptake in the subcutaneous tissues of the upper extremities or in draining lymph nodes. However, occasionally a greater amount of the radiotracer extravasates, causing more significant artifacts (Figure 2). The interpreting physician must use caution when reporting such cases and may need to repeat the study to ensure diagnostic accuracy. Specifically, the calculated standardized uptake values (SUVs) of the lesions of concern may not be accurate as the documented injected dose (one parameter for determining SUV) likely does not reflect the true dosage of FDG in the blood pool due to the extravasation.

In addition to the usual motion artifacts present throughout imaging modalities, PET/CT is susceptible to potentially problematic artifacts when patient position changes between CT and PET acquisition, resulting in misregistration. This is common near the diaphragm, as most PET acquisition is not done with a breath-hold, although respiratory gating can help minimize this misregistration. With more significant motion, FDG uptake can project over the incorrect anatomic structures and may lead to incorrect localization (Figure 3). Some software packages allow the user to adjust registration to align data to correct the error, although these are usually limited to rigid realignments in 3 axes. Patient motion between the PET and CT portion of the studies can also cause an incorrect attenuation map to be applied to the PET region, thus affecting the attenuated corrected data set.

In addition, metal or other high-density implants, as well as oral and intravenous contrast, can create a false area of relative increased uptake due to attenuation correction artifacts. Attenuation correction works well in the range of tissue densities within the human body; however, it is prone to falsely overestimate the degree of attenuation correction in regions of higher density materials. As this activity is usually

![Figure 6. Thymus activity. FDG PET MIP image in a pediatric patient demonstrating normal uptake in the thymus (solid arrow) including a lower cervical component (dashed arrow), a variant of normal.](image)

![Figure 7. Windowing pitfall. FDG PET MIP images (A, B) at two window levels demonstrate a hypermetabolic left cerebellar mass (arrow, B) confirmed in fused PET/CT image (arrow, C). The mass is obscured in the default window (A) due to the relatively high physiologic uptake in the brain.](image)
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not associated with anatomic masses, it is usually discounted by the interpreter by noting the CT findings. However, review of the nonattenuation-corrected data set can confirm the artifact, as this activity should disappear on nonattenuation-corrected images.4

Lymphoma is one of the more common indications for oncological PET/CT. Some of the most common histological subtypes, including Hodgkin disease and diffuse large B-cell lymphoma, are extremely PET-avid, and PET can be used for staging and assessing treatment response. However, other histological subtypes are less likely to be FDG-avid. These include primary cutaneous anaplastic large T-cell lymphoma, extranodal marginal zone lymphoma, and small lymphocytic lymphoma.5 When performing initial staging PET/CT on patients with a known lymphoma, occasionally a non-FDG avid lymphoma will be encountered. It is important to alert the referring physician that the disease being evaluated is not FDG-avid and a follow-up FDG PET/CT for determining treatment response may not be useful. Knowledge of neoplasms that have low FDG avidity is important to prevent inappropriate action regarding false-negative findings, including hepatocellular carcinoma, renal cell carcinoma, neuroendocrine tumors, well-differentiated endocrine malignancy, prostate cancers and some genitourinary cancers.

Pediatric Variants, Pitfalls and Artifacts

PET imaging for childhood cancers is predominately performed for lymphoma, osteosarcoma, Ewing sarcoma, and soft-tissue sarcomas including rhabdomyosarcoma and malignant peripheral nerve sheath tumors. Imaging children requires specific knowledge of changes in the physiological processes of maturation; the more frequent need for sedation; and awareness of the spectrum of childhood cancers, genetic predisposition syndromes, and secondary cancers after treatment.6

Brown Fat

Brown fat contains metabolically active mitochondria that burn energy and release heat. Brown fat uptake has been reported in one-third of children imaged with PET, and is more frequent in children than adults. It is more common in cold climates and can be reduced by
warming techniques. Common locations include the supraclavicular fossa, cervical and axillary soft tissues, mediastinum, thoracic parascapular and paraspinal soft tissues, and the upper abdomen (Figure 4). Marrow

Red marrow is more metabolically active than yellow marrow and, therefore, demonstrates relatively increased FDG uptake. In neonates, the distribution of red marrow involves the distal long extremities. As infants grow, the red marrow shifts from the skull and extremities to the axial skeleton (spine, pelvic bones, ribs and sternum) with yellow fatty marrow replacement occurring earlier at the epiphyses and diaphysis (Figure 5). By around 15 years of age, this process is largely complete. In adults, only a little hemopoietic red marrow remains in the proximal metaphysis of the femur and humerus. Additionally, the skeleton in children is rapidly growing at the physes and synchondroses, which can appear relatively “hot” on PET imaging. Thymus

Children, adolescents, and young adults have a greater incidence of thymus visualization on PET imaging, with hyperplasia occurring in the setting of severe stress or chronic disease,
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termed thymic rebound when found after chemotherapy. With maturity, the thymus varies considerably in shape, and often can be difficult to distinguish from an anterior mediastinal mass. Neonates have a large thymus, which increases up to 2 years of age. It can cover both the left and right aspects of the heart, and has been described as quadrangular. Gradually, the thymus assumes the more classic sail or spin-naker sign. On PET imaging, the thymus should have uniform FDG uptake and smooth convex margins. Cervical thymic extension is an important variant to recognize, wherein thymic tissue extends into the superior mediastinum and lower neck (Figure 6). This represents an embryologic remnant along the track of descent. It may occasionally appear as a lower cervical mass, discontinuous with the thymus, and can be mistaken for a tumor or enlarged lymph node.

**Lymphoid Tissue**

Children have prominent lymphoid tissue compared to adults, including the above-described thymus and in bone marrow. They also have prominent secondary lymphoid tissue, including the adenoid, palatine, and lingual tonsils. Furthermore, they are more prone to symmetric low-grade FDG uptake in reactive lymph nodes due to inflammation or infection in common sites, including cervical, axillary, mesenteric, andinguinal lymph nodes.

**Head and Neck**

Evaluation for brain masses is potentially problematic, largely due to the high physiologic FDG uptake in the gray matter structures. It is critical for the interpreting physician to adjust the window to detect potential hypermetabolic brain masses, such as those resulting from lymphoma, metastatic melanoma, or lung cancer (Figure 7). On the other hand, brain lesions with significant cystic and/or necrotic components may appear relatively photopenic (Figure 8). When encountering subtle foci, it is best to correlate with contrast-enhanced, diagnostic quality CT or MR. Other causes of photopenic defects in the brain include postoperative changes and prior infarcts (Figure 9).

In patients with no history of head and neck cancer, incidental asymmetric uptake in the pharynx poses a diagnostic dilemma, as both malignancy and infection/inflammation can result in focal asymmetric uptake (Figure 10). Focal uptake at the midline of the nasopharynx has also been described in inflamed Thornwaldt’s cysts. Despite a variety of attempts to find a reliable prospective means to differentiate benign from malignant uptake, there is no clinical consensus for a reliable absolute or relative SUV to differentiate inflammation...
from malignancy. Ultimately, clinical and/or endoscopic evaluation will likely be needed to exclude malignancy.

Recent phonation will increase FDG uptake in the vocal cords. When this is symmetric, no diagnostic challenge is present. Focal asymmetric uptake in the vocal cords, however, likely requires further investigation. A common cause of asymmetric uptake is unilateral vocal cord paralysis. Vocal cord paralysis will result in decreased FDG uptake in the affected cord and a search for an underlying cause, such as a thoracic mass impinging the recurrent laryngeal nerve, cervical mass involving the course of the vagus nerve, or history of neck surgery (Figure 11). In the absence of an underlying cause, laryngoscopy will likely be necessary.

As with pediatric patients, brown fat FDG uptake is a common cause of focal uptake in adult necks, and is potentially problematic when evaluating patients with head and neck cancers as well as lymphoma. The key for identifying this pitfall is localization of the uptake to fat density on CT and lack of corresponding soft-tissue mass. At times, however, it can be difficult to separate this activity from closely adjacent lymph nodes. This entity occurs more in colder climates. Because brown fat is sympathetically innervated, patient anxiety at the time of the PET scan may contribute to its visualization. A variety of means can help minimize this brown fat uptake, the simplest of which is to ensure adequate warming prior to injection and uptake. Several drugs, including propranolol, diazepam, and fentanyl, have also shown to decrease brown fat uptake; however, the routine clinical implementation of these medications is challenging in the outpatient setting. Although uncommon, hibernomas, which are benign neoplasms composed of brown fat, can demonstrate increased FDG uptake.

Incidental uptake in the thyroid gland is often encountered on PET imaging. Diffuse increased FDG uptake throughout the thyroid gland is usually benign; correlation can be made for diffuse thyroid diseases, including Graves’ disease or chronic lymphocytic (Hashimoto’s) thyroiditis (Figure 12). Although rare, diffuse FDG uptake has been associated with malignancy, including cases of thyroid lymphoma and metastatic non-small cell lung carcinoma. Focal thyroid FDG uptake, on the other hand, requires additional evaluation with ultrasound and possible tissue sampling, as there is a significant association with malignancy. In one study, Choi et al demonstrated malignancy in 18 of 49 focal thyroid lesions detected on FDG PET/CT and it is generally accepted that one-third of FDG-avid thyroid nodules are malignant, with the remainder being benign thyroid adenomas (Figure 13).

Muscle uptake in the neck is variable and mostly related to recent use, pain,
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anxiety or inflammation. As with brown fat uptake, this muscular uptake can be readily localized to muscle with CT correlation and the lack of a correlating mass lesion. Regardless, this should be minimized, particularly when evaluating patients with head and neck cancer, as this uptake may obscure small disease foci. Most patient protocols request witholding eating and chewing gum prior to the exam, as this can result in intense FDG uptake throughout the muscle of mastication (Figure 14).

Additional hypermetabolic lesions may be encountered incidentally in the head and neck. Most commonly, these include incidental foci in the salivary glands (Figure 15) and sinuses (Figure 16). When encountering such lesions, it is appropriate to suggest additional work-up with imaging and/or tissue sampling. Seo et al documented focal FDG uptake in the parotid gland in 2.1% of patients with head and neck malignancy, of which 33.3% were metastatic foci disease and 66.7% demonstrated a variety of benign pathologies. 24

Thorax

Evaluation of the solitary pulmonary nodule is one the most common indications for FDG PET/CT, which aids characterization of indeterminate pulmonary nodules. In a study evaluating 89 patients with solitary pulmonary nodules, FDG PET/CT demonstrated a sensitivity of 92% and specificity of 90% for detecting

FIGURE 22. Cardiac melanoma metastases. Axial CT (A) and fused FDG PET/CT (B) images demonstrate multiple hypermetabolic cardiac masses (arrows) in a patient with widely metastatic melanoma.

FIGURE 23. Adrenal nodular hyperplasia. Axial FDG PET (A) and fused PET/CT (B) images demonstrate low-level FDG uptake, equal to slightly less than liver background, and nodular thickening of the adrenals (arrows) in a patient with lung carcinoma. These findings correspond to benign nodular adrenal hyperplasia.

FIGURE 24. Fibroid uptake. Sagittal CT (A) and fused FDG PET/CT (B) images show intense FDG uptake in a large fundal fibroid (arrow, B). FDG PET cannot readily distinguish leiomyomas from leiomyosarcomas.

FIGURE 25. Physiologic ovarian uptake. Fused FDG PET/CT image in a young woman with lymphoma demonstrates focal uptake in the right ovary (arrow), a normal finding representing functional changes in a premenopausal female.
malignancy. However, smaller nodules pose potential problems given the spatial resolution of PET (7 to 8 mm). Both the 2013 American College of Chest Physicians practice guidelines for pulmonary nodules and the 2017 Fleischner Society guidelines for incidental pulmonary nodules have indications for FDG PET/CT for nodules > 8 mm. In routine clinical practice, any non-FDG avid nodule < 8 mm should be considered too small to accurately characterize by PET, and continued CT followup should be considered to ensure stability.

In addition to issues with small pulmonary nodules, PET/CT has been shown to be less sensitive for several types of pulmonary malignancy. Adeno-carcinoma in situ (formerly called bronchoalveolar carcinoma) and carcinoid are classically associated with being falsely PET negative, although other low-grade or early broncogenic malignancies have also been shown to be falsely PET negative. Given the relatively low metabolic rate of these malignancies, it is necessary to continue CT surveillance of pulmonary nodules that demonstrate low (less than mediastinal vascular blood pool) FDG uptake (Figure 17). Continued follow-up is recommended, as the referring physician may not be aware of these potentially significant false negatives. The 2017 Fleischner Society guidelines provide generally accepted follow-up intervals.

**FIGURE 26.** Occult bladder mass. Fused FDG PET/CT (A) and unfused CT (B) images demonstrate a subtle polypoid bladder mass (arrows) that is largely obscured on fused imaging due to the physiologic FDG uptake in the urine.

**FIGURE 27.** Renal cell carcinoma. Contrast-enhanced coronal CT image (A) demonstrates a small enhancing exophytic right lower pole renal mass consistent with renal cell carcinoma (arrow). However, on FDG PET/CT (B), the lesion is metabolically indistinguishable from high physiologic background uptake of the kidney.

**FIGURE 28.** Crohn’s disease. Axial CT (A) and fused PET/CT (B) images show focal FDG uptake localizing to a short segment of small bowel in the right lower quadrant with wall thickening (arrows).
for indeterminate pulmonary nodules. If a non-FDG avid nodule demonstrates enlargement at follow-up, tissue sampling should be considered.

A variety of infectious or inflammatory processes can be incidentally detected on PET/CT. Unfortunately, there is no reliable SUV threshold that can routinely differentiate infection/inflammation from malignancy with certain infectious/inflammatory processes being hypermetabolic and certain malignancies being non-FDG avid, including cystic or necrotic neoplasms. Additionally, measured SUVs depend on numerous factors independent of the target lesion of concern, including body fat composition, uptake time, and patient blood glucose levels. In the chest, pneumonia, tuberculosis, mycobacteria avium complex, aspergillosis, sarcoidosis, rheumatoid nodules, postsurgical inflammatory changes, tace pleurodesis, esophagitis, and postradiation inflammation are common (Figures 18-20). The sequelae of chronic granulomatous infections often include FDG-avid lung nodules and mediastinal lymph nodes that are often calcified.

Cardiac uptake is highly variable in fasting FDG PET/CT, ranging from essentially background to diffuse, intense FDG uptake. This is largely due to the heart’s ability to metabolize carbohydrates or fatty acids with a switch to glucose in the presence of insulin or glucose loading. Unfortunately, this makes interpreting PET findings challenging. Occasionally, an infarct may be encountered as a focal area of photopenia (Figure 21). Although uncommon, malignancies can occasionally involve the heart with regions of hypermetabolic activity, most often due to metastases with primary cardiac neoplasms being rare (Figure 22).

Abdomen and Pelvis

The adrenal glands are common locations for metastases and, therefore, should be closely evaluated on oncological PET/CT. Studies have shown PET/CT to be reasonably sensitive and specific for differentiating benign from malignant lesions. However, one must be careful not to misdiagnose a variety of common benign adrenal processes.
as metastases (eg, adrenal adenomas, hyperplasia, myelolipomas, benign pheochromocytomas, oncocytomas, hemorrhage, and cysts), as some of these benign entities can demonstrate mild FDG uptake (Figure 23).\(^{35}\) Although no absolute SUV threshold exists for differentiating benign from malignant uptake, Boland et al suggest a combination of CT characteristics (< 10 HU indicating a benign adenoma) and ratio of adrenal lesion to liver background PET activity (with a ratio of > 1 suspicious for malignancy) to be a reasonable means to characterize adrenal lesions as malignant with a sensitivity of 100% and specificity of 99%.\(^{36}\)

Expected uptake in the uterus and ovaries depends on a patient’s menopausal status. Uptake in the endometrium can vary during the menstrual cycle, with greatest levels during menstrual flow and ovulatory phases.\(^{37}\) This can pose particular diagnostic problems when evaluating women with cervical carcinoma. Consideration may be given to coordinating PET/CT with menstrual cycle phase to perform the PET/CT in the late secretory or early proliferative phases (just before or after menstruation).\(^{38}\) Increased FDG uptake can also be seen in uterine fibroids; however, PET cannot reliably distinguish leiomyomas from leiomyosarcomas (Figure 24).\(^{39,40}\)

**FIGURE 31.** Focal FDG uptake in a benign rib fracture. Axial-fused FDG PET/CT image demonstrates focal FDG uptake in a non-pathological traumatic left rib fracture (arrow).

**FIGURE 32.** Bone metastases and bone marrow stimulation. FDG PET MIP image (A) demonstrates innumerable hypermetabolic osseous metastases. After treatment (B), there is evidence of marrow stimulation with diffuse increased uptake throughout the red marrow as well as the spleen, hampering treatment assessment.

**FIGURE 33.** Chronic radiation changes. FDG sagittal PET (A) and fused PET/CT (B) images demonstrate relative decreased uptake in the thoracic spine (arrows) due to chronic radiation changes.
Similarly, ovarian activity in premenopausal women can be physiologic and related to ovulation (Figure 25). In postmenopausal women, focal increased FDG uptake in either the endometrium or the ovary should be further evaluated to exclude malignancy. Other portions of the genitourinary system may pose difficulty for the interpreting physician, largely due to the high physiologic FDG uptake in the urine, which can obscure small disease foci. It is advisable to adjust PET window and fusion level to avoid missing subtle lesions (Figure 26). Similarly, the relatively high background uptake in the kidneys, FDG PET/CT has questionable utility in characterizing renal masses (Figure 27), although higher-grade, clear-cell and papillary subtypes have been shown to have greater activity than renal background. Additional, pooling of radioactive urine in the ureters can often be difficult to distinguish from retroperitoneal or pelvic lymph nodes, often at the pelvic brim where the ureters cross the psoas muscles.

FDG uptake in the bowel continues to present a diagnostic challenge, as the uptake is highly variable. When focal FDG uptake is identified, further investigation (usually with endoscopy) is recommended, as there is an association with malignant and premalignant conditions. Additionally, correlation with CT findings is warranted, as this may reveal an underlying infectious or inflammatory process such as appendicitis, diverticulitis, or inflammatory bowel disease (Figure 28). Metformin, an oral diabetic medication, results in diffuse intense uptake in the colon as well as the small bowel (Figure 29). This can unfortunately obscure metabolic activity from foci of malignancy, warranting consideration of holding the medication prior to FDG PET/CT imaging. Postsurgical changes from certain urinary diversion procedures also can result in intense bowel activity as FDG-avid urine enters the bowel (Figure 30).

**Muskuloskeletal**

Focal FDG uptake can be identified in both pathological and nonpathological fractures (Figure 31). Some studies indicate that relatively high SUVs suggest malignant pathological fractures, although no absolute SUV can be used in routine clinical practice to reliably differentiate benign from malignant fractures. Correlation with the co-acquired CT for features suggesting a benign or malignant process is suggested. If the focus of uptake remains indeterminate, consideration can be given to MR if it would change clinical management. Alternatively, attention should be given on follow-up PET/CT, as the activity from benign post-traumatic or postsurgical fractures should normalize over several months.

Diffuse red marrow uptake on FDG PET/CT is another common pattern of normal variant uptake. This is most often related to bone marrow stimulation with drugs such as filgrastim and pegfilgrastim. Given the marrow stimulation, this may also result in increased uptake in the spleen. Given the history of marrow stimulation, the interpreting physician can readily identify this marrow uptake as benign. However, occasionally the diffuse uptake can obscure previously present hypermetabolic osseous foci, making it difficult to evaluate response to treatment (Figure 32). Waiting several weeks after discontinuation of such drugs will help decrease this uptake, but must be balanced with the need for timely clinical results.

Patients who have undergone prior radiation therapy may have relative decreased marrow uptake in affected areas (Figure 33). Knowledge of treatment history and location is beneficial in PET interpretation to identify this unusual pattern of uptake. The interpreting physician must be mindful to not misinterpret the normal, nonirradiated marrow as pathologic.

**Conclusion**

Oncologic FDG PET/CT is prone to many pitfalls and incidental findings, largely related to whole-body imaging and the nonspecific mechanism of FDG. This article reviewed a variety of processes that can lead to potential false-positive and false-negative findings. Interpreting radiologists must maintain constant vigilance for these common pitfalls.

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