Quantitative Response Assessment

1. Standardisation

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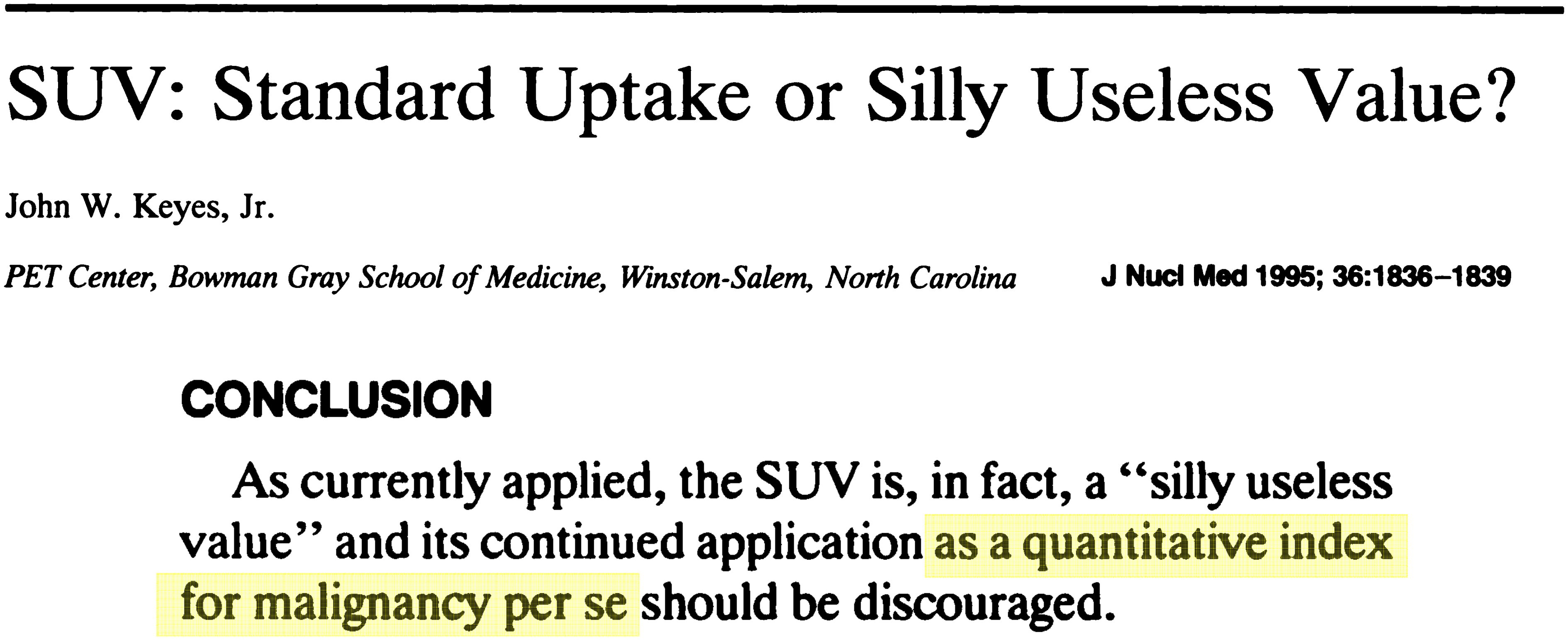
Working Group Recommendations

	RECOMMENDATIONS: RESPONSE ASSESSMENT - QUANTITATIVE
1.	Standardisation of PET methods is mandatory for the use of quantitative approaches (*category 1*)
2.	Data are emerging to suggest that quantitative measures could be used to improve on visual analysis for response assessment in DLBCL but this requires further validation in clinical trials (*category 2*).
3.	The ΔSUV_{max} is the only quantitative measure with published data to indicate its possible utility in response assessment but changes in tumour volumes should also be explored (*category 3*).

John Keyes' Editorial on SUV "…as a measure to characterize the malignancy vs. benignancy of lesions"

$$\text{SUV} = \frac{\text{FDG concentration in Lymphoma (measured by PET)}}{\text{Average body concentration (injected act./bodyweight)}}$$



SUV: Standard Uptake or Silly Useless Value?

John W. Keyes, Jr.

PET Center, Bowman Gray School of Medicine, Winston-Salem, North Carolina

J Nucl Med 1995; 36:1836–1839

CONCLUSION

As currently applied, the SUV is, in fact, a "silly useless value" and its continued application as a quantitative index for malignancy per se should be discouraged.

17 years ago

Quantitation Errors – Inevitable?

Error Reduction

- (Cross-) calibrate PET scanner and dose calibrator
- Eliminate common error sources
- Standardize
  - PET physics corrections
  - data reconstruction and processing
  - quantitation algorithms
  - patient preparation
  - PET scanning protocol
  - same PET scanner
  - PET scanning protocol

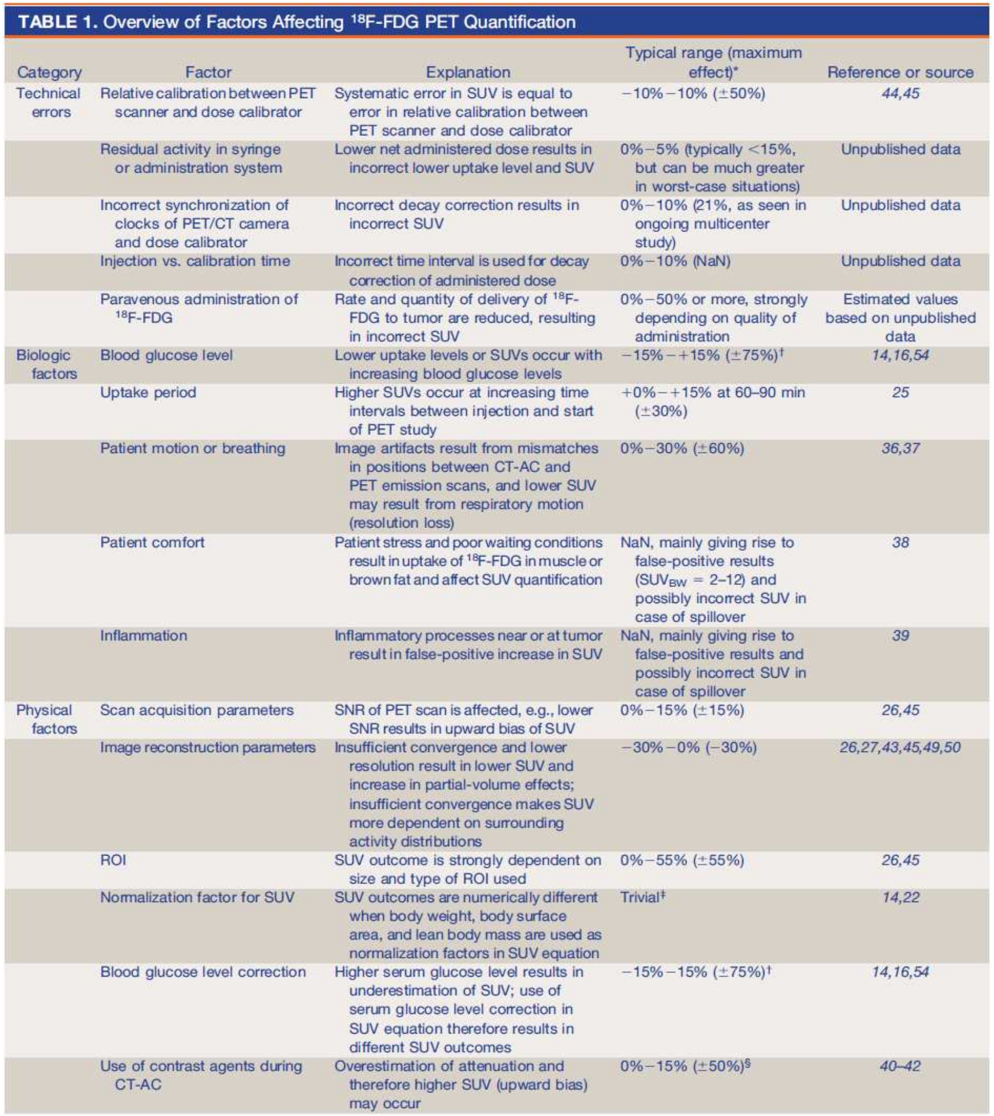


TABLE 1. Overview of Factors Affecting ^{18}F-FDG PET Quantification

Category	Factor	Explanation	Typical range (maximum effect)*	Reference or source
Technical errors	Relative calibration between PET scanner and dose calibrator	Systematic error in SUV is equal to error in relative calibration between PET scanner and dose calibrator	−10%−10% (±50%)	*44,45*
	Residual activity in syringe or administration system	Lower net administered dose results in incorrect lower uptake level and SUV	0%−5% (typically <15%, but can be much greater in worst-case situations)	Unpublished data
	Incorrect synchronization of clocks of PET/CT camera and dose calibrator	Incorrect decay correction results in incorrect SUV	0%−10% (21%, as seen in ongoing multicenter study)	Unpublished data
	Injection vs. calibration time	Incorrect time interval is used for decay correction of administered dose	0%−10% (NaN)	Unpublished data
	Paravenous administration of ^{18}F-FDG	Rate and quantity of delivery of ^{18}F-FDG to tumor are reduced, resulting in incorrect SUV	0%−50% or more, strongly depending on quality of administration	Estimated values based on unpublished data
Biologic factors	Blood glucose level	Lower uptake levels or SUVs occur with increasing blood glucose levels	−15%−+15% (±75%)†	*14,16,54*
	Uptake period	Higher SUVs occur at increasing time intervals between injection and start of PET study	+0%−+15% at 60–90 min (±30%)	*25*
	Patient motion or breathing	Image artifacts result from mismatches in positions between CT-AC and PET emission scans, and lower SUV may result from respiratory motion (resolution loss)	0%−30% (±60%)	*36,37*
	Patient comfort	Patient stress and poor waiting conditions result in uptake of ^{18}F-FDG in muscle or brown fat and affect SUV quantification	NaN, mainly giving rise to false-positive results (SUV_{BW} = 2–12) and possibly incorrect SUV in case of spillover	*38*
	Inflammation	Inflammatory processes near or at tumor result in false-positive increase in SUV	NaN, mainly giving rise to false-positive results and possibly incorrect SUV in case of spillover	*39*
Physical factors	Scan acquisition parameters	SNR of PET scan is affected, e.g., lower SNR results in upward bias of SUV	0%−15% (±15%)	*26,45*
	Image reconstruction parameters	Insufficient convergence and lower resolution result in lower SUV and increase in partial-volume effects; insufficient convergence makes SUV more dependent on surrounding activity distributions	−30%−0% (−30%)	*26,27,43,45,49,50*
	ROI	SUV outcome is strongly dependent on size and type of ROI used	0%−55% (±55%)	*26,45*
	Normalization factor for SUV	SUV outcomes are numerically different when body weight, body surface area, and lean body mass are used as normalization factors in SUV equation	Trivial‡	*14,22*
	Blood glucose level correction	Higher serum glucose level results in underestimation of SUV; use of serum glucose level correction in SUV equation therefore results in different SUV outcomes	−15%−15% (±75%)†	*14,16,54*
	Use of contrast agents during CT-AC	Overestimation of attenuation and therefore higher SUV (upward bias) may occur	0%−15% (±50%)§	*40–42*

Boellaard J.Nucl.Med 50, S11, 2009

Absolute vs. ΔSUV

$$\Delta\text{SUV} = 1 - \frac{\cancel{k_{calib}}\,\cancel{k_{RC}}\,\cancel{k_{recon}}\,\cancel{k_{quant}}\,SUV_{\text{interim}}}{\cancel{k_{calib}}\,\cancel{k_{RC}}\,\cancel{k_{recon}}\,\cancel{k_{quant}}\,SUV_{\text{baseline}}}$$

- **PET quantitation depends on calibration and correction factors**
- **factors cancel out in a ratio if they are constant**
- **Standardize to keep these factors as constant as possible**
- **Error of ratio potentially smaller than that of absolute value**

Repeatability of ^{18}F-FDG Uptake Measurements in Tumors: A Metaanalysis

Adrianus J. de Langen[1], Andrew Vincent[2], Linda M. Velasquez[3], Harm van Tinteren[2], Ronald Boellaard[4],
Lalitha K. Shankar[5], Maarten Boers[6], Egbert F. Smit[1], Sigrid Stroobants[7], Wolfgang A. Weber[8], and Otto S. Hoekstra[4]

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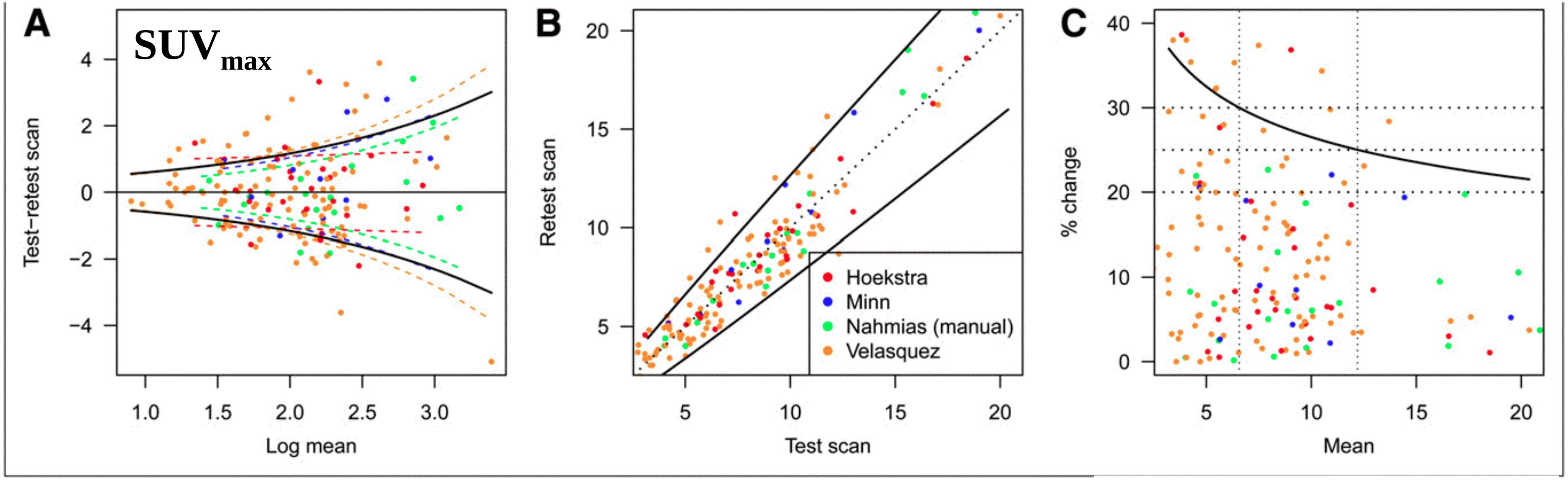
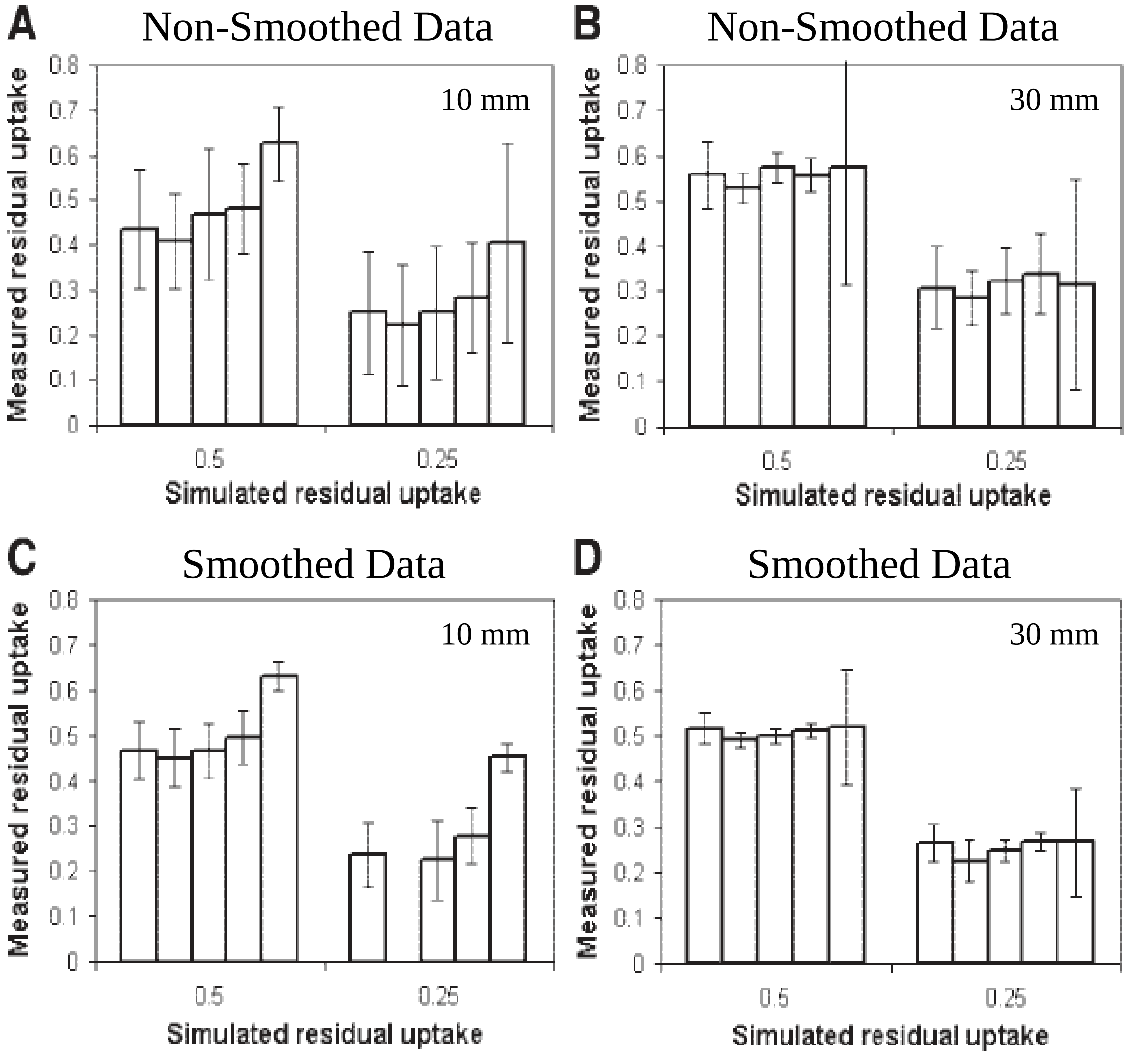


J Nucl Med 2012; 53:701–708
DOI: 10.2967/jnumed.111.095299

SUV Change



- ROIs (left to right)
  - Maximum
  - 50% Isocontur
  - 70% Isocontur
  - Isocontur 0.5 (BG + Max)
  - ROI 15x15 mm

Boellaard J.Nucl.Med 45, 1519, 2004

Visual vs. Quantitative Analysis

- **Quantitation reduces inter- and intra-observer variability**
  - **Important for multicentric trials**
  - **No reference reading necessary**
- **Many determinants of SUV also affect visual analysis**
- **Standardization required for both, visual and quantitative**
- **Defined Protocols for**
  - **Time of PET after last cycle**
  - **Patient preparation**
  - **Scanner calibration**
  - **Data acquisition**
  - **Data analysis**
- **Similar to clinical routine PET protocols**

Quantitative PET is an established Research Tool

thank you for your constructive critique, John Keyes!

ber	Title
3083	Fludeoxyglucose F18 Positron Emission Tomography Imaging In Assessing Patients Before and After Treatment for Locally Advanced Non-Small Cell Lung Cancer
7539	Positron Emission Tomography in Predicting Response in Patients Who Are Undergoing Treatment With Pemetrexed Disodium and Cisplatin With or Without Surgery for Stage I, Stage II, or Stage III Non-Small
6832	Early On-therapy PET at First-line Treatment in Diffuse Large B-cell Lymphoma Stage IIB-IV
7093	Elaboration of a Model for Predicting Efficacy of Monoclonal Antibodies (Cetuximab and Bevacizumab) in Patients With Colorectal Cancer and Liver Metastases
6125	PET Scan Combined With CT Scan in Predicting Response in Patients Undergoing Chemotherapy and Surgery for Soft Tissue Sarcoma
2973	PET Scans in Assessing Response To Treatment in Patients Receiving Hormone Therapy or Trastuzumab for Breast Cancer
5203	The Biological Activity of Cediranib (AZD2171) in Gastro-Intestinal Stromal Tumours(GIST).
4138	Fludeoxyglucose F 18 PET/CT Scans in Patients With Stage IIIB or Stage IV Non-Small Cell Lung Cancer Undergoing Chemotherapy
4994	Sunitinib in Treating Patients With Metastatic, Locally Advanced, or Locally Recurrent Sarcomas
7614	Positron Emission Tomography in Rheumatoid Arthritis With Adalimumab (PETRA)
3150	Everolimus, Temozolomide, and Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma
4733	FDG-Labeled PET Scan in Planning Chemotherapy in Treating Patients With Stage IIIB or IV Non-Small Cell Lung Cancer
0243	Pilot Study to Evaluate 18F-fluorodeoxyglucose (FDG) Positron Emission Tomography /Computed Tomography (PET/CT) in Prediction of Early Response to Chemotherapy in Ovarian Cancer.
9022	Neo-adjuvant Therapy and the Effect on Synchronous Metastatic Growth
1437	Determine Tumor Response Using Fluorodeoxyglucose (FDG)- Positron Emission Tomography (PET)/Computed Tomography (CT) Before and After Cetuximab in Patients With Head and Neck Cancer
1481	PET Evaluation of Response After 1 Course of Chemotherapy as Predictor of Treatment Outcome.
5268	18F- Fluorothymidine to Evaluate Treatment Response in Lymphoma
8489	A Prospective Study to Evaluate FDG-PET, Breast MRI, and Breast Ultrasonography in Monitoring Tumour Responses in Patients With Locally Advanced Breast Cancer (LABC) Undergoing Neoadjuvant Chemothe
2880	Dacarbazine for Metastatic Soft Tissue and Bone Sarcoma
4410	Early Assessment of the Response to Neo-adjuvant Chemotherapy in Breast Cancer Patients With FDG-PET
2048	Effect of Atorvastatin on Vascular Inflammation in Type 2 Diabetes
9582	Positron Emission Tomography/Computed Tomography (PET/CT) in Relapsed Ovarian Cancer (MK-0000-143)
0999	Radiation Therapy in Treating Patients With Stage I Non-Small Cell Lung Cancer
3807	Trial Comparing the Use of FLT PET to Standard CT to Assess Treatment Response of Neoadjuvant Docetaxel and Cisplatin in Stage IB-IIIA Resectable NSCLC
9098	Response Evaluation in Malignant Pleural Mesothelioma
4864	Preoperative Chemosensitivity Testing to Predict Treatment Benefit in Adjuvant Stage II Colon Cancer
8251	Positron Emission Tomography in Monitoring Treatment Response in Women With Newly Diagnosed Breast Cancer
0283	A Study to Evaluate [18F]-FDG PET (Fluorodeoxyglucose-positron) in Patients With Pancreatic Cancer (MK-0000-144)
2766	Breathing Synchronized PET/CT Scans for the Detection of Malignant Lung & Liver Lesions and Assessment of Tumor Glycolysis
8026	Response-Based Therapy Assessed By PET Scan in Treating Patients With Bulky Stage I and Stage II Classical Hodgkin Lymphoma
9360	Combined FDG PET/CT Imaging in Response Evaluation After Radiochemotherapy in Patients With Locally Advanced Head and Neck Squamous Cell Carcinoma (HNSCC)
0566	PET-MR for Prediction and Monitoring of Response to Neoadjuvant Chemotherapy in Breast Cancer
2416	Positron Emission Tomography (PET)-Computed Tomography (CT) PET/CT Evaluation of Treatment Response in Breast Cancer
2183	Radio-chemotherapy With or Without Panitumumab (VectibixÂ®) in Unresectable Squamous Cell Carcinoma or Adenocarcinoma of the Oesophagus
1322	Sequential FDG-PET (Positron Emission Tomography) and Induction Chemotherapy in Locally Advanced Adenocarcinoma of the Esophagogastric Junction (AEG)
5765	Study Evaluating the Non-inferiority of a Treatment Adapted to the Early Response Evaluated With 18F-FDG PET Compared to a Standard Treatment, for Patients Aged From 18 to 80 Years With Low Risk (aa I
6272	Ofatumumab and Bendamustine Hydrochloride With or Without Bortezomib in Treating Patients With Untreated Follicular Non-Hodgkin Lymphoma
3936	High-Dose 131I-MIBG Therapy Combined With Vincristine and Five Days of Irinotecan for Resistant/Relapsed Neuroblastoma
2477	Contribution of F-18 Fluoro-Deoxy-Glucose PET/CT (Positron Emission Tomography) to the Assessment of HCC (Hepato-cellular Carcinoma) Treatment Efficiency
7733	Interim FDG PET/CT in Diffuse Large B Cell Lymphoma (DLBCL) Patients
2030	Neoadjuvant and Adjuvant Chemotherapy in High-risk Soft Tissue Sarcoma
3377	Neoadjuvant Radiochemotherapy Combined With Panitumumab in Locally Advanced KRAS Wild-type Rectal Cancer
6809	Pazopanib Hydrochloride Followed By Chemotherapy and Surgery in Treating Patients With Soft Tissue Sarcoma
4[illegible]8	The Use of PET/CT to Evaluate Synovitis in the Temporomandibular Joint (TMJ)
0[illegible]9[illegible]	First Line Ceritinib By FDG-PET Metabolic Response
3948	Axitinib in Treating Patients With Melanoma That is Metastatic or Cannot Be Removed By Surgery
7881	Positron Emission Tomography/Magnetic Resonance Imaging in Patients
4203	Contribution of F18-FDG PET/CT to the Early Assessment of Pazopanib Therapy Efficacy in Advanced Soft Tissue Sarcoma
[illegible]558	Assessing Response to Treatment in Non-Hodgkin's Lymphoma Patients Using 64Cu-DOTA-Rituximab PET/CT
[illegible]19[illegible]	18F-FDG PET/CT for IgG4-Related Disease
6[illegible]53	PET Quantitative Assessments of Solid Tumor Response to Immune Checkpoint Blockade Therapy

linicalTrials.gov 9/2012:

51 Clinical Trials with PET Response Assessment