PINTAD
The Pharma Imaging Network for Therapeutics and Diagnostics

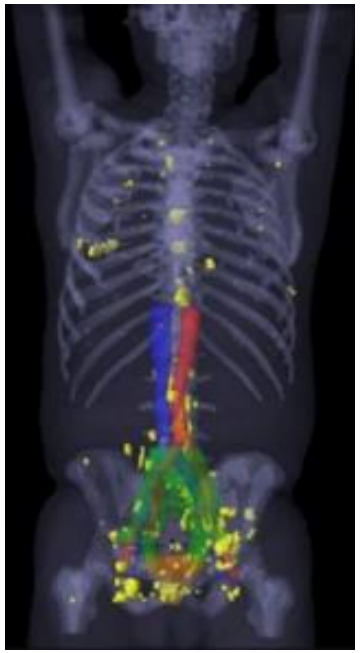
UCLA

THE FDA APPROVAL OF 68GA-PSMA-11 PET: AN ACADEMIC COLLABORATIVE JOURNEY

Jeremie Calais MD MSc
Assistant Professor, Nuclear Medicine and Theranostics
Director, Clinical Research Program

UCLA Health

PINTAD MEETING
01 - 28 - 2021



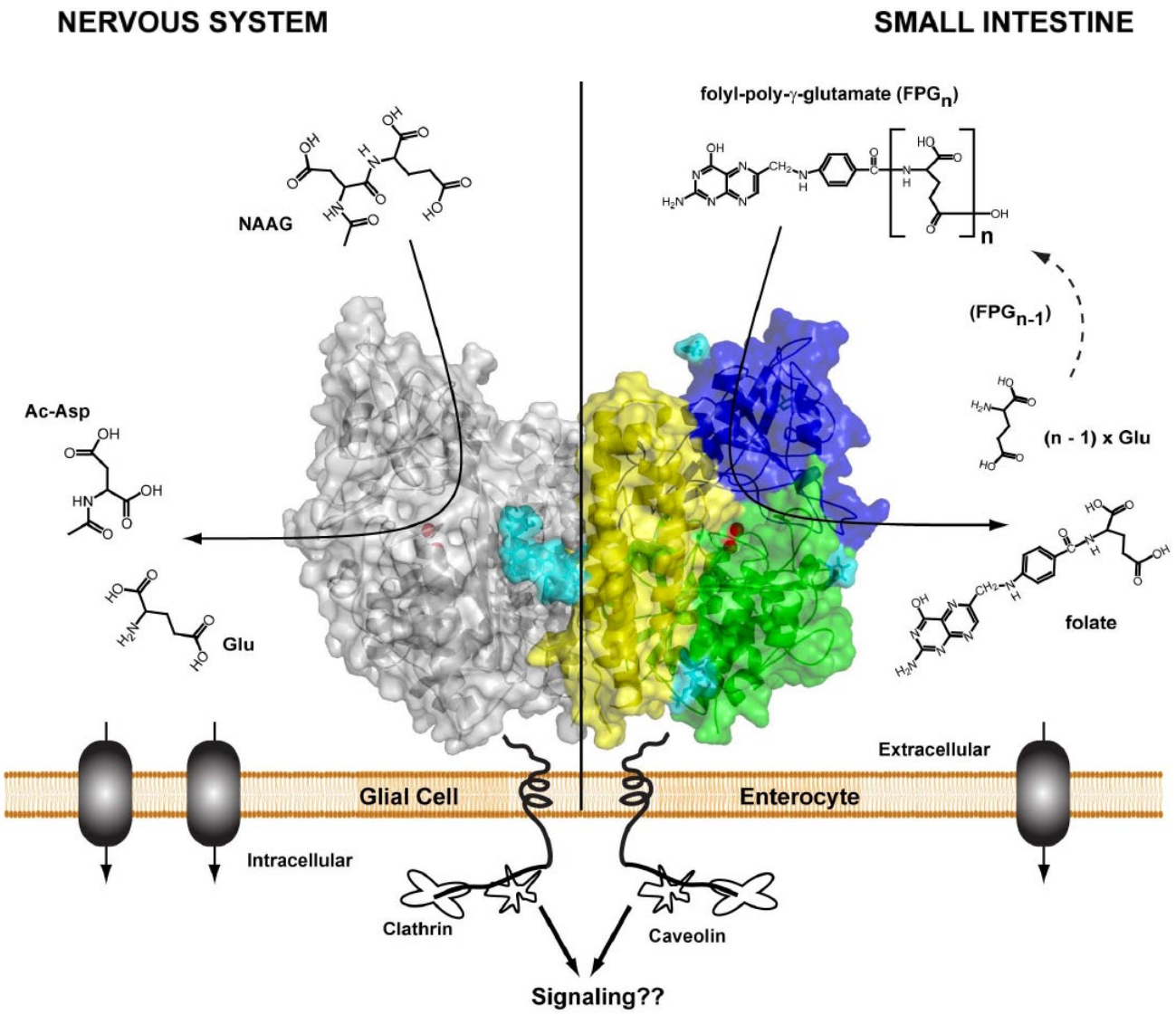
Jeremie Calais

DISCLOSURES

Commercial Interest	Nature of Relevant Financial Relationship	
	What was received	***For what role***
▪ **Advanced Accelerator Applications**	Honoraria	Blinded Independent Central Reader
▪ **Blue Earth Diagnostics**	Honoraria	Consultant
▪ **Curium Pharma**	Honoraria	Consultant
▪ **GE Healthcare**	Honoraria	Consultant
▪ **IBA RadioPharma**	Honoraria	Speaker
▪ **Janssen Pharmaceuticals**	Honoraria	Consultant
▪ **POINT biopharma**	Honoraria	Consultant
▪ **Progenics / Lantheus**	Honoraria	Consultant
	Honoraria	Blinded Independent Central Reader
	Research grant	Principal Investigator
▪ **Radiomedix**	Honoraria	Blinded Independent Central Reader
▪ **Telix Pharmaceuticals**	Honoraria	Speaker

PET imaging Biological Target

PROSTATE SPECIFIC MEMBRANE ANTIGEN



Prostate Specific Membrane Antigen

= glutamate carboxypeptidase II (GCP-II)

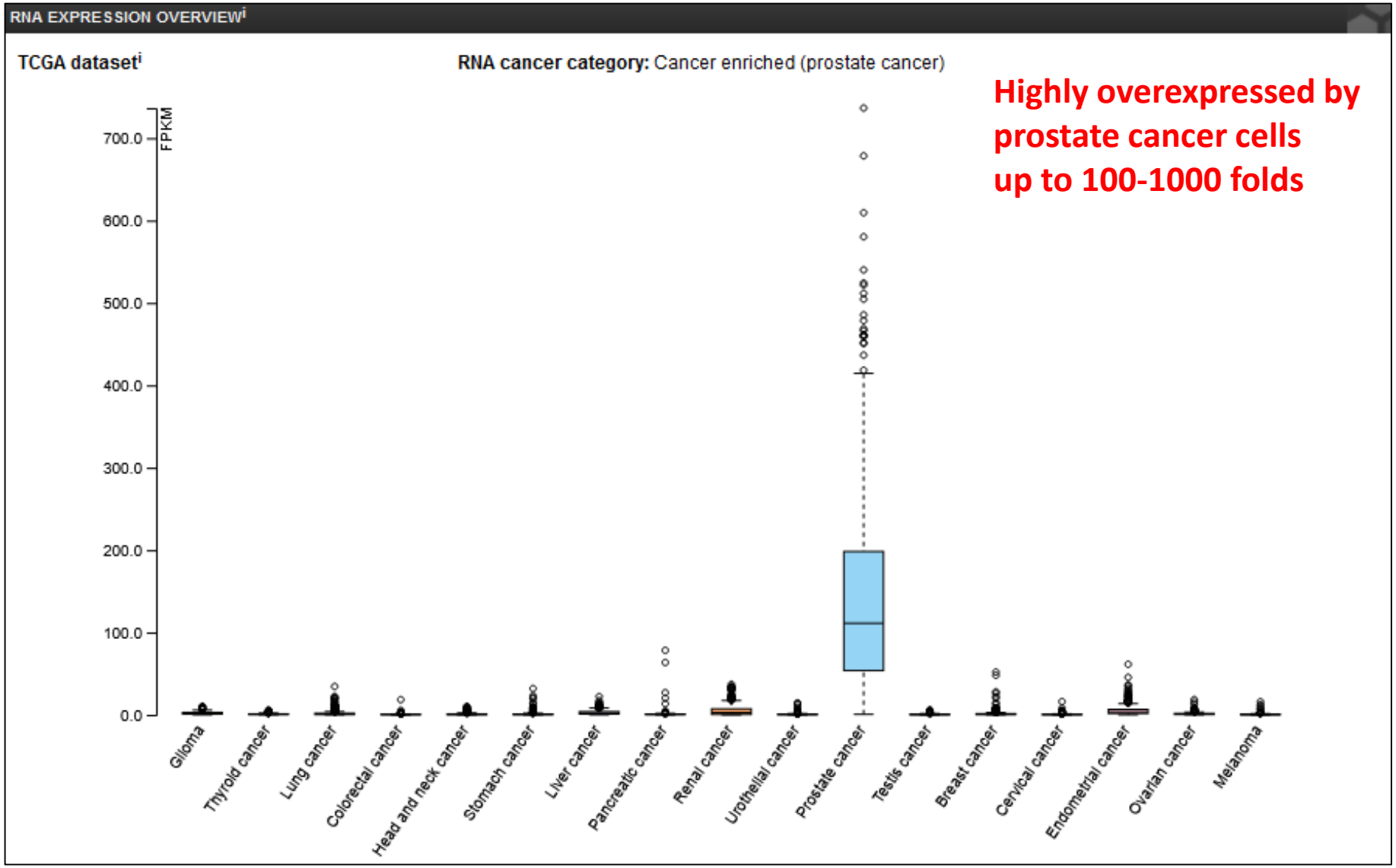
= folate hydrolase 1 (FOLH1)

- cell surface glycoprotein enzyme
- neurotransmission
- glutamate and folate (B9 vitamin) metabolism

Barinka et al. *Current Medicinal Chemistry* 2012

PET imaging Biological Target

PSMA EXPRESSION IN CANCER



Highly overexpressed by prostate cancer cells up to 100-1000 folds

THE HUMAN PROTEIN ATLAS

MENU HELP NEWS

PET imaging Biological Target

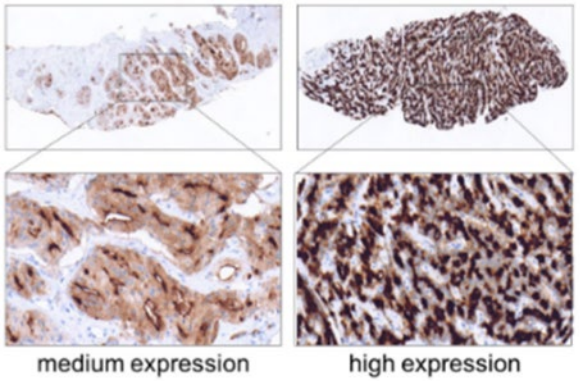
PSMA in PROSTATE CANCER

Reference	Adeno-carcinoma	Lymph node metastaes	Bone metastases	Other or unspecified metastases	Total
Horoszewicz et al., Anticancer Res 1987; 7:927	9/9	2/2			11/11
Lopes et al., Cancer Res 1990; 50:6423	10/10				10/10
Israeli et al., Cancer Res 1994; 54:1807	1/1				1/1
Troyer et al., Int J Cancer 1995; 62:552	3/4				3/4
Wright et al., Urology 1996; 48:326	25/25				25/25
Silver et al., Clin Cancer Res 1997; 3:81	33/35	7/8	8/18		48/61
Liu et al., Cancer Res 1997; 57:3629	21/21				21/21
Kawakami et al., Cancer Res 1997; 57:2321	15/15				15/15
Sweat et al., Urology 1998; 52:637	232/232	227/232			459/464
Bostwick et al., Cancer 1998; 82:2256	129/129	184/184			313/313
Chang et al., Cancer Res 1999; 59:3192	12/12				12/12
Chang et al., Urology 2001; 57:1179		6/6	7/7	9/9	22/22
Ross et al., Clin Cancer Res 2003; 9:6357	138/138				138/138
Birtle et al. BJUI 2005; 96:303	30/33				30/33
Kinoshita et al., World J Surg 2006; 30:628	19/19				19/19
Kusumi et al., Pathology Int 2008; 58:687	42/42				42/42
Hull et al., BJUI 2009; 104:915	85/90				85/90
Mannweiler et al., Pathol Oncol Res 2009; 15:167	49/51	3/3	25/31	15/17	92/102
Ananias et al., Prostate 2009; 69:1101		21/21	17/17		38/38
Ben Jemaa et al., J Exp Clin Cancer Res 2010; 29:171	38/39				38/39
Zhang et al., PLoS ONE 2011; 6:e27970				83/100	83/100
Minner et al., Prostate 2011; 71:281	1606/1700				1606/1700
TOTAL	*2590/2746*	*450/456*	*57/73*	*107/126*	*3204/3401*

22 refs

94%

	76 – 100%
	51 – 75%
	26 – 50%
	0 – 25%
% of tumors stained positive for PSMA	

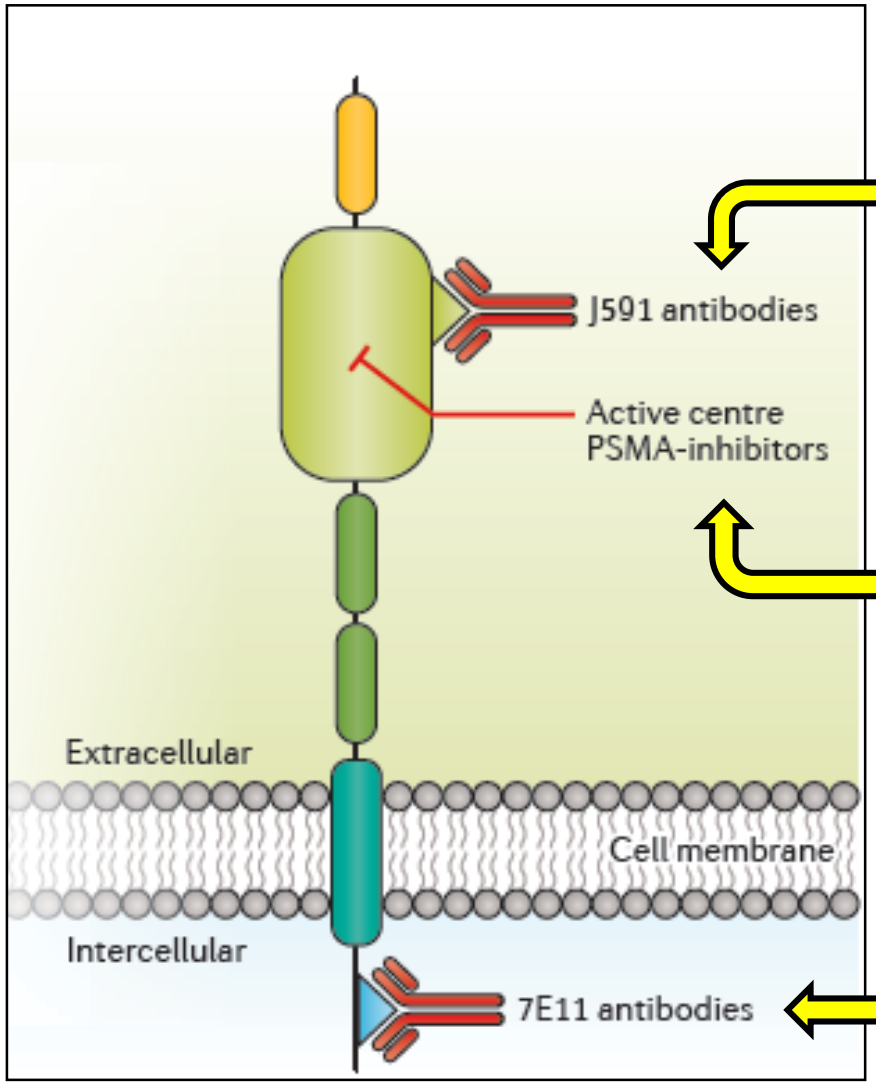


Hupe et al; *Frontiers in Oncology* 2018; 8: 1-7

PSMA overexpression in 94% of prostate cancer cells

PSMA = Nuclear Theranostics Target for Prostate Cancer

PSMA FOR SMALL PEPTIDES INHIBITORS



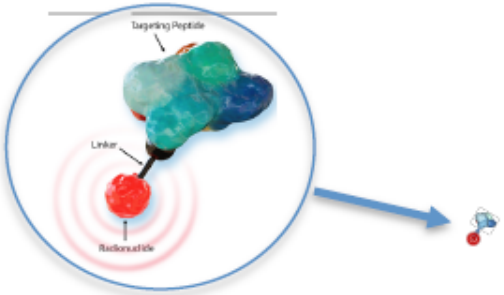
	SPECT	PET	THERAPY
Ab	➢ ^{111}I-J591	➢ ^{89}Zr-J591 ➢ ^{124}I-J591	➢ ^{225}Ac-J591 ➢ ^{177}Lu-J591 ➢ ^{90}Y-J591
Peptides	➢ ^{111}I-PSMA I&T ➢ ^{99m}Tc-MIP-1404 ➢ ^{99m}Tc-MIP-1405 ➢ ^{99m}Tc-PSMA I&S ➢ ^{99m}Tc-HYNIC PSMA ➢ ^{123}I-MIP-1072 ➢ ^{123}I-MIP-1095	➢ ^{68}Ga-PSMA-11 (=HBED-CC) ➢ ^{68}Ga-PSMA-I&T ➢ ^{68}Ga-PSMA-617 ➢ ^{68}Ga-THP-PSMA ➢ ^{18}F-DCFBC ➢ ^{18}F-DCFPyL (PROGENICS) ➢ ^{18}F-PSMA-1007 (ABX) ➢ ^{18}F-rhPSMA (BLUE EARTH) ➢ ^{18}F-JK-PSMA-7 ➢ ^{18}F-PSMA-11	➢ ^{177}Lu-PSMA-I&T ➢ ^{177}Lu-PSMA-R2 (NOVARTIS) ➢ ^{177}Lu-PSMA-617 (ENDOCYTE) ➢ ^{225}Ac-PSMA-617 (ENDOCYTE) ➢ ^{227}Thorium-PSMA-TTC (BAYER) ➢ ^{131}I-MIP-1095 (PROGENICS)
Ab	➢ ^{111}In-capromab (PROSTASCINT)	➢ ^{89}Zr-7E11 PET	

Maurer T et al, *Nat Rev Urol*, 2016

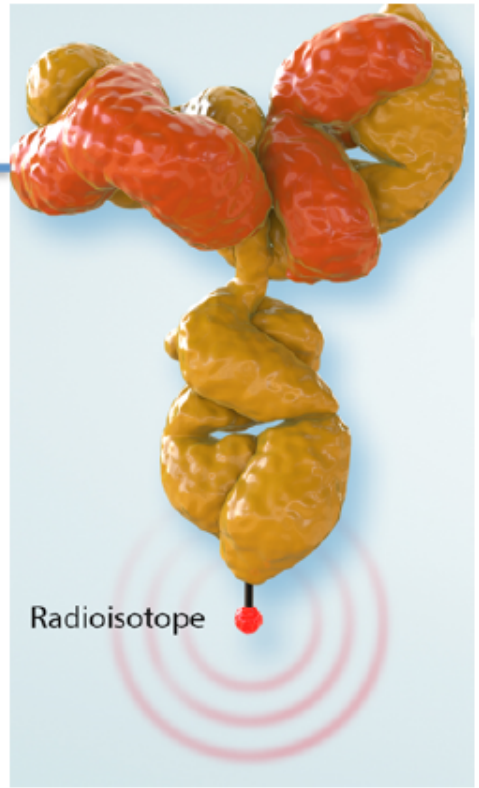
PSMA PEPTIDES vs ANTIBODY

Peptides are attractive targeting molecules due to their small size and ease of manufacture

For PET imaging the rapid systemic clearance, tissue distribution and tumor penetrance favor small peptides vs. other targeting moieties

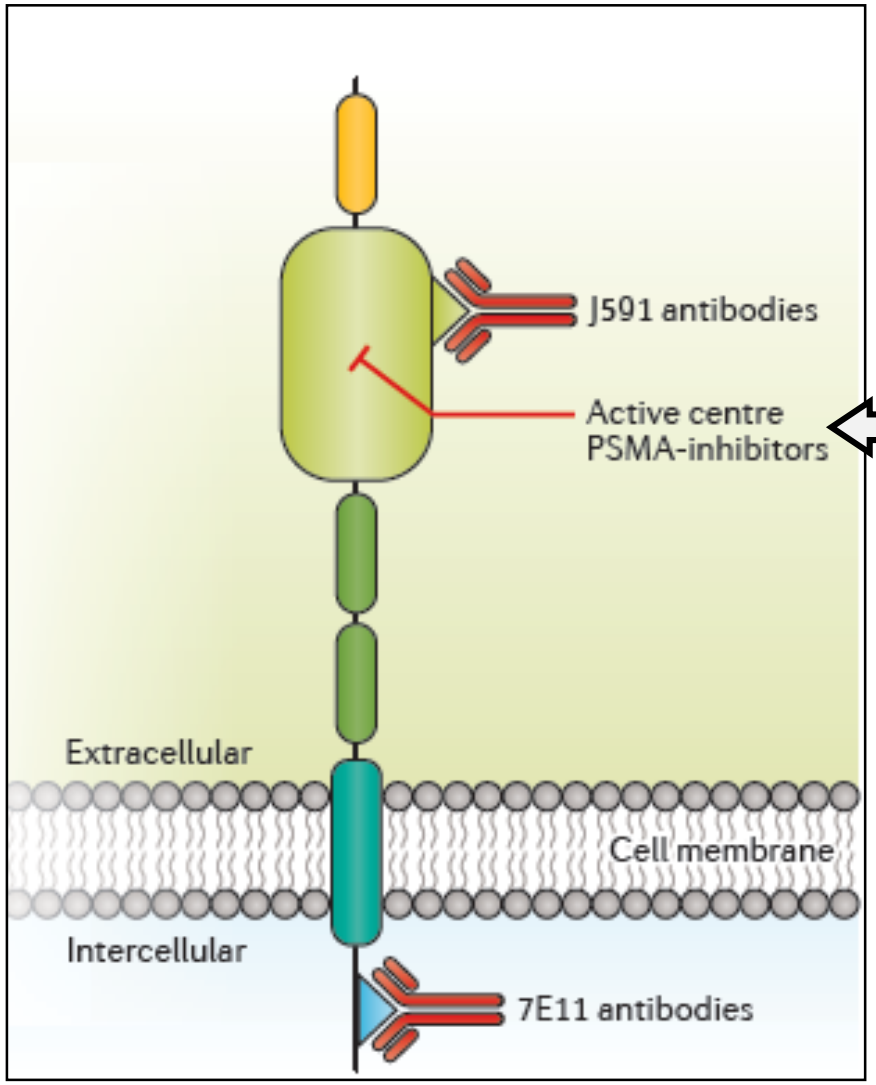


	Peptides	Monoclonal antibodies
Target Affinity	High	High
Selectivity	High	High
Molecular weight (kDa)	1-2	150
Tumor penetration	High	Low
Blood clearance	Fast	Slow
Liver accumulation	Low	High
Dose limiting organ	tbd	Bone marrow



PSMA = Nuclear Theranostics Target for Prostate Cancer

PSMA = TARGET FOR SMALL PEPTIDES PET TRACERS



Maurer T et al, *Nat Rev Urol*, 2016

- ^{68}Ga-PSMA-11
- ^{68}Ga-PSMA-I&T

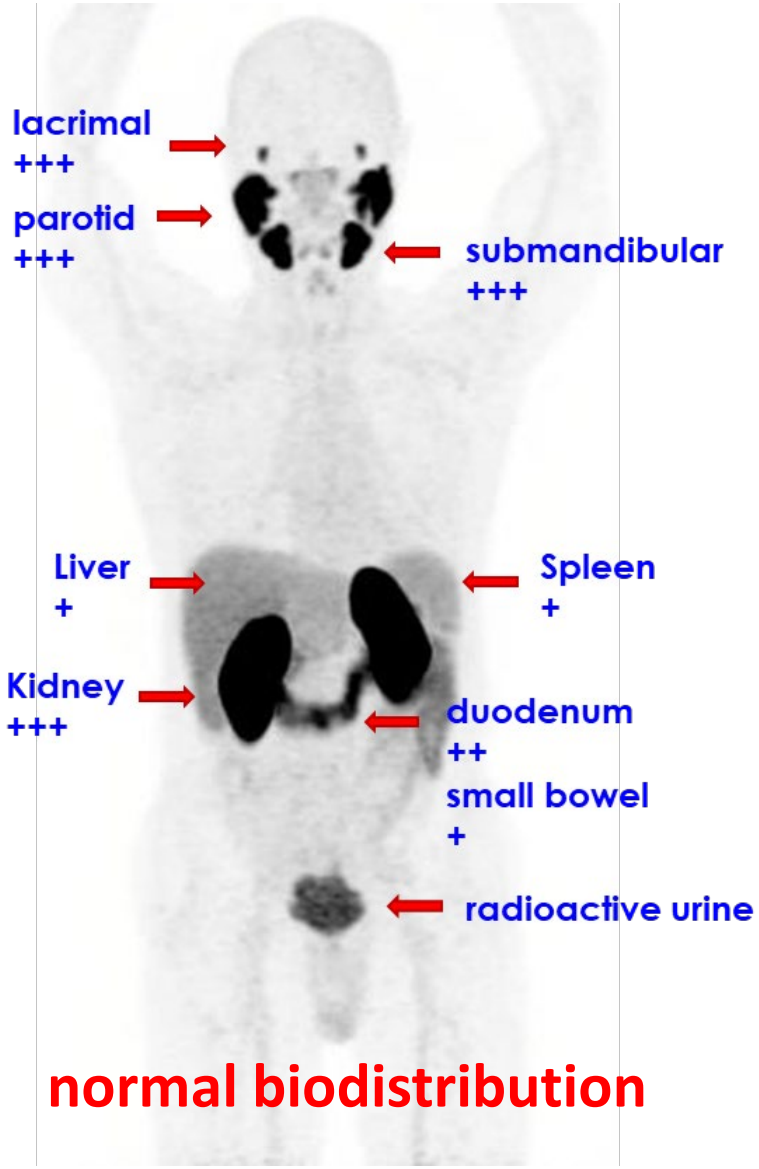
FREE OF USE ACADEMIA

- ^{18}F-DCFPyL (PyL™) — Progenics Pharmaceuticals
- TLX591-CDX (ILLUMET™) — TELIX PHARMACEUTICALS
- ^{18}F-*rh*PSMA — BLUE EARTH DIAGNOSTICS
- ^{18}F-PSMA-1007 — ABX

INDUSTRY

PSMA = Nuclear Theranostics Target for Prostate Cancer

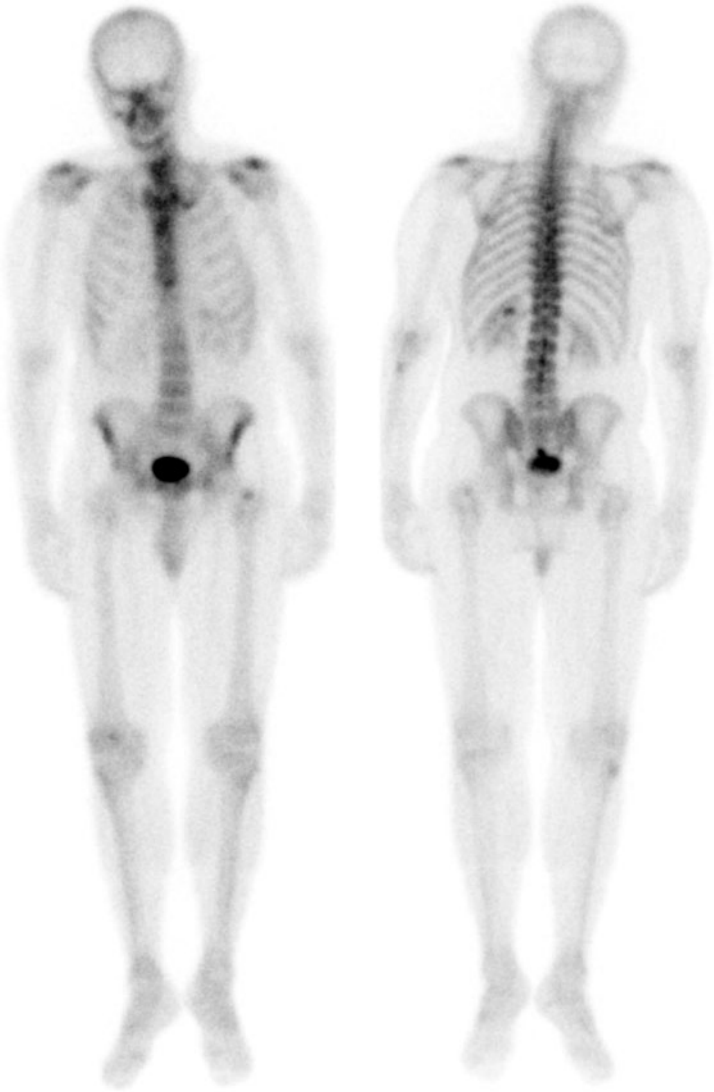
PSMA FOR PET/CT MOLECULAR IMAGING

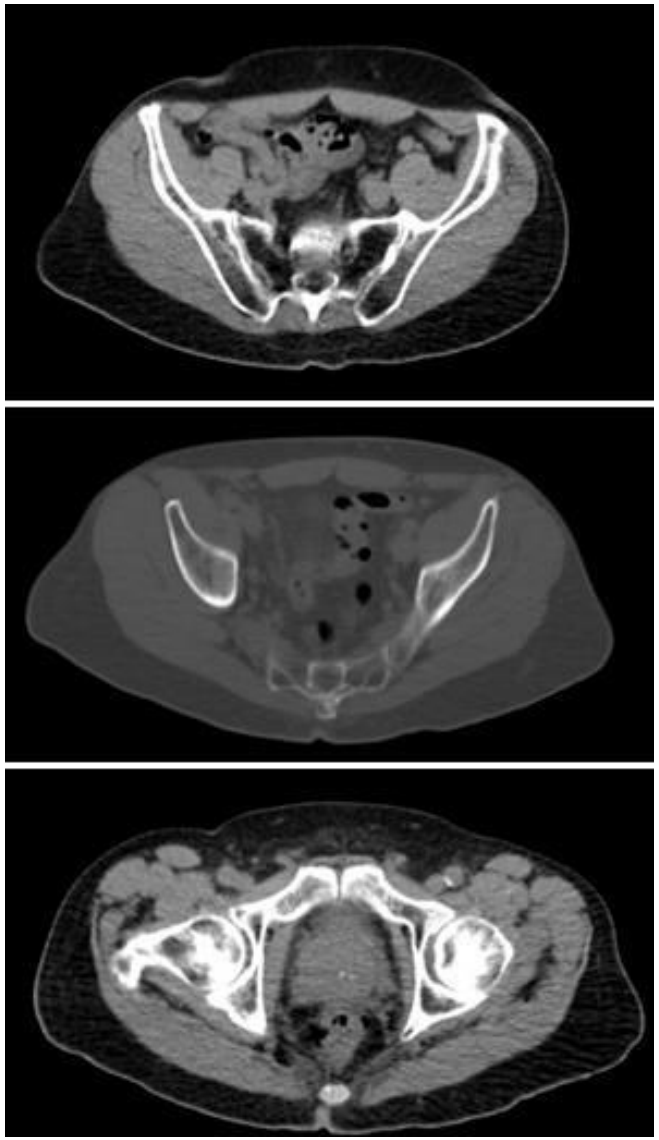


normal biodistribution

PSMA = Nuclear Theranostics Target for Prostate Cancer

PATIENT STORY #1





77 y/o patient

Initial staging of Prostate Cancer

iPSA 7.1

GS 4+5=9

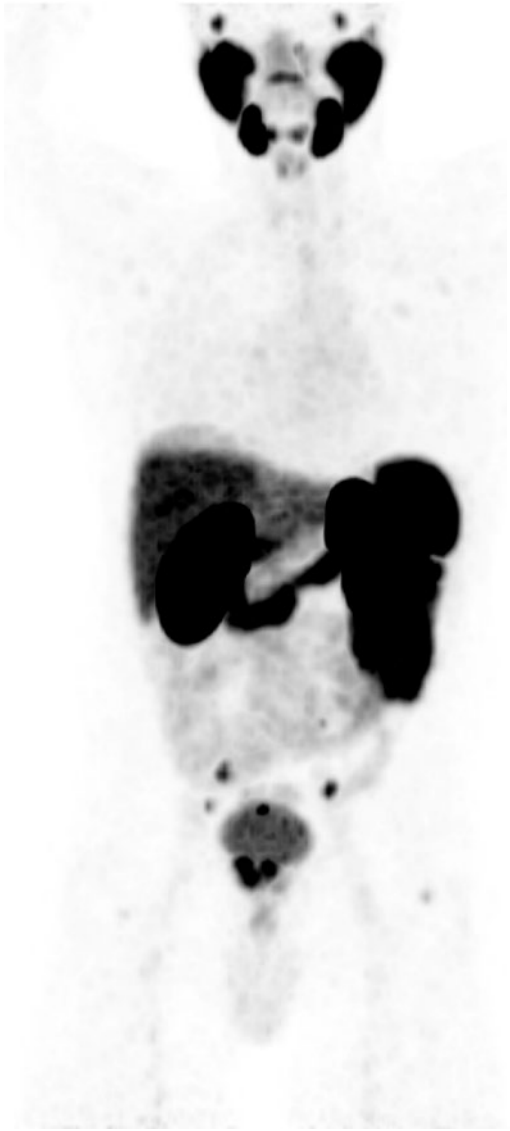
bone scan negative

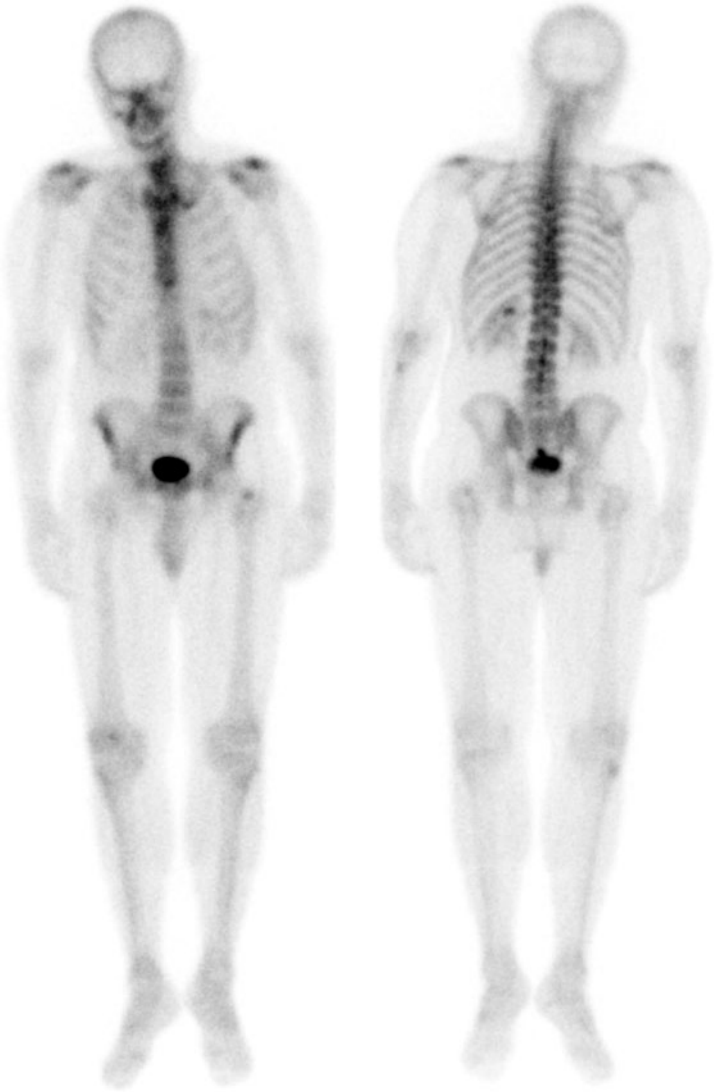
LOCAL TREATMENT:

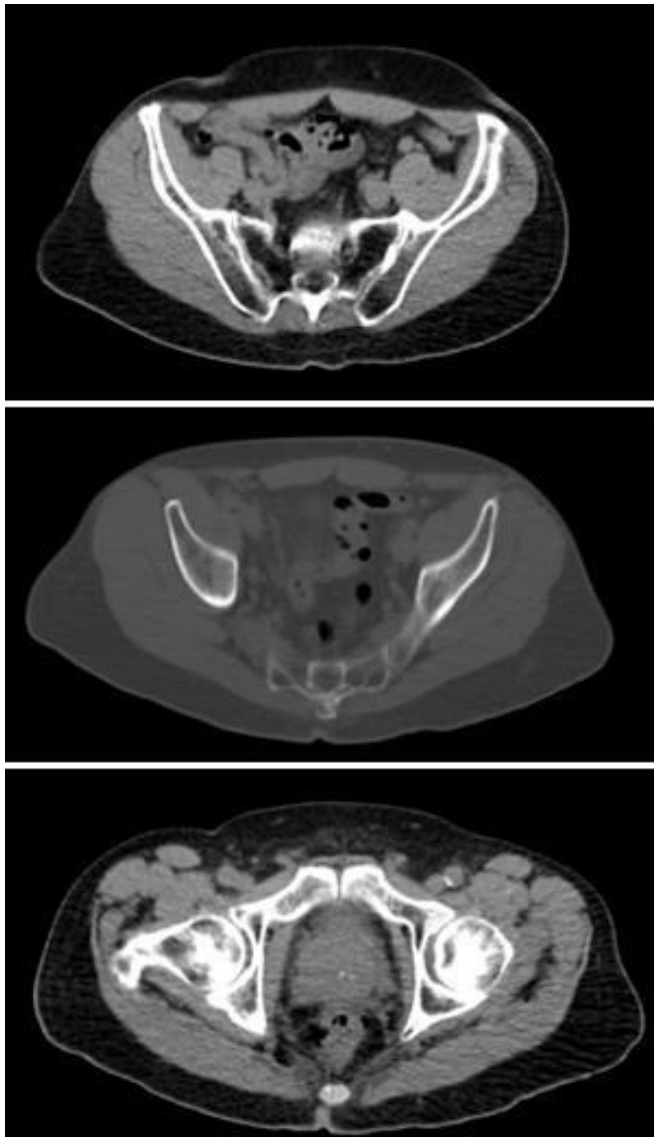
SURGERY
OR
RADIATION THERAPY

PSMA = Nuclear Theranostics Target for Prostate Cancer

PATIENT STORY #1







77 y/o patient

Initial staging of Prostate Cancer

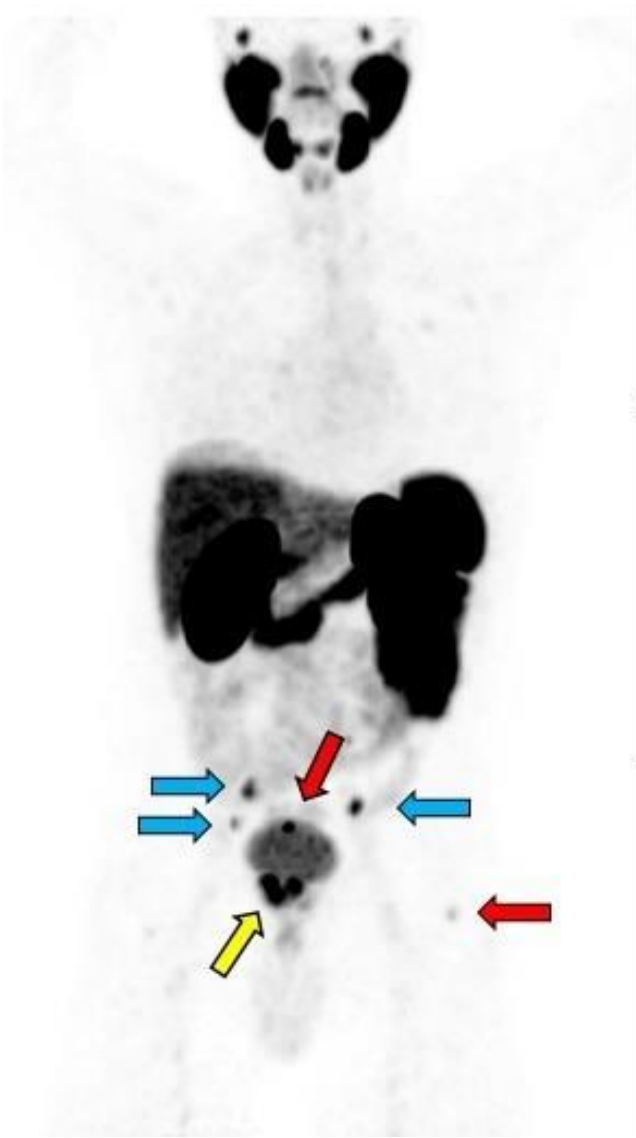
iPSA 7.1

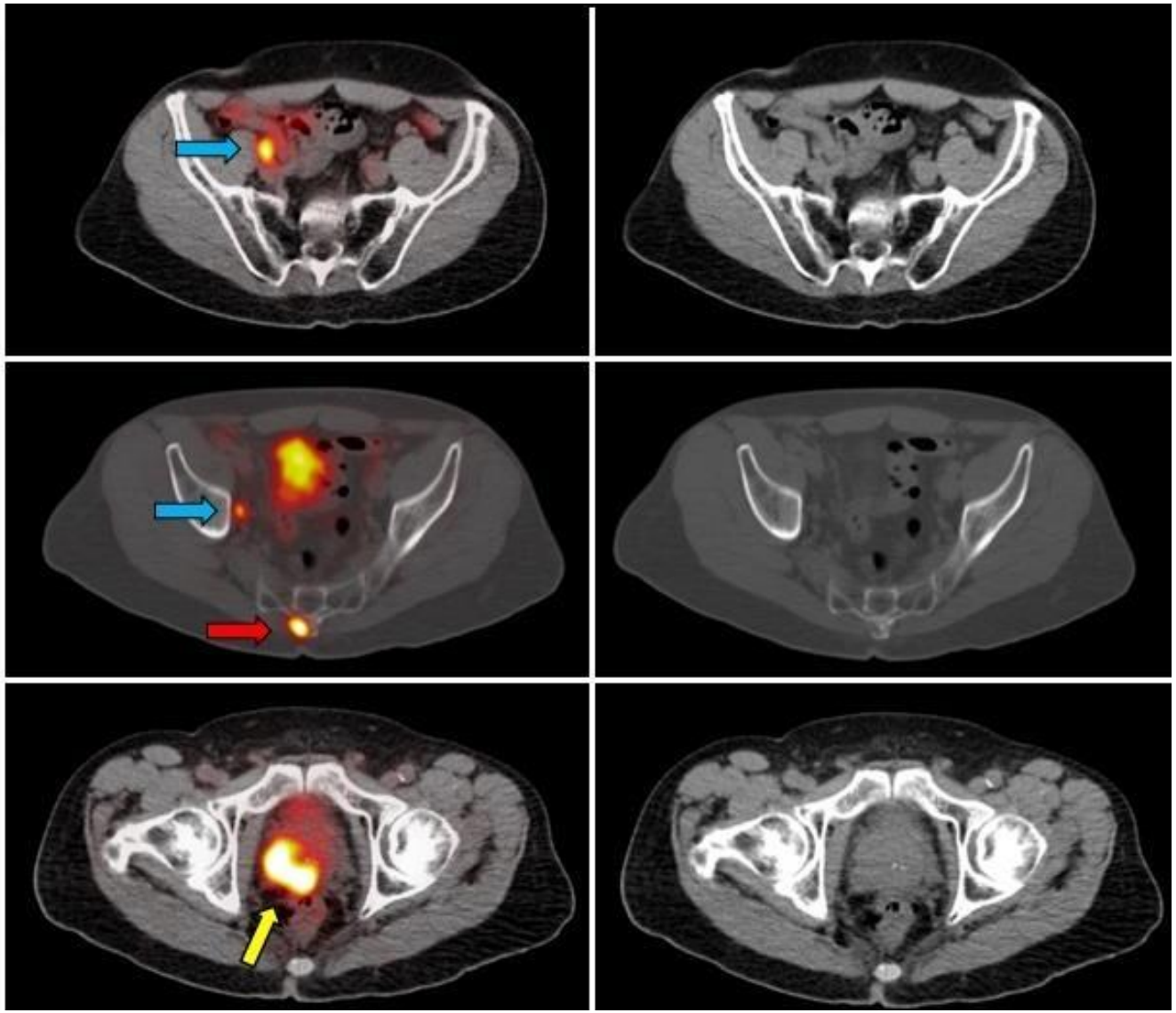
GS 4+5=9

bone scan negative

PSMA = Nuclear Theranostics Target for Prostate Cancer

PATIENT STORY #1





77 y/o patient

Initial staging of Prostate Cancer

iPSA 7.1

GS 4+5=9

bone scan negative

→ primary PCa

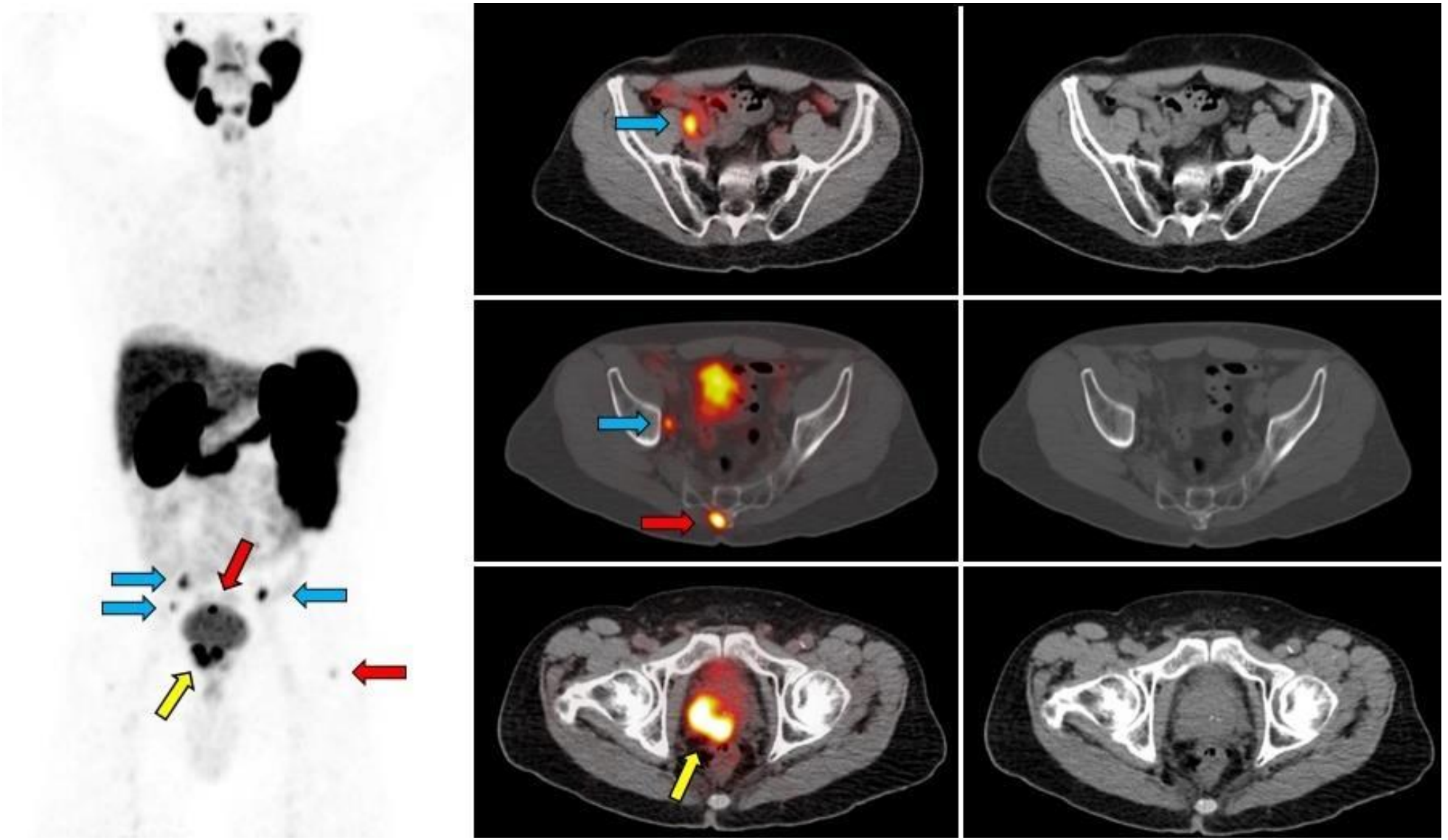
→ nodal metastases

→ bone metastases

Jeremie Calais MD MSc

PSMA = Nuclear Theranostics Target for Prostate Cancer

PATIENT STORY #1



TREATMENT:

SYSTEMIC THERAPY

primary PCa

nodal metastases

bone metastases

PSMA PET guided therapy

PATIENT STORY #02

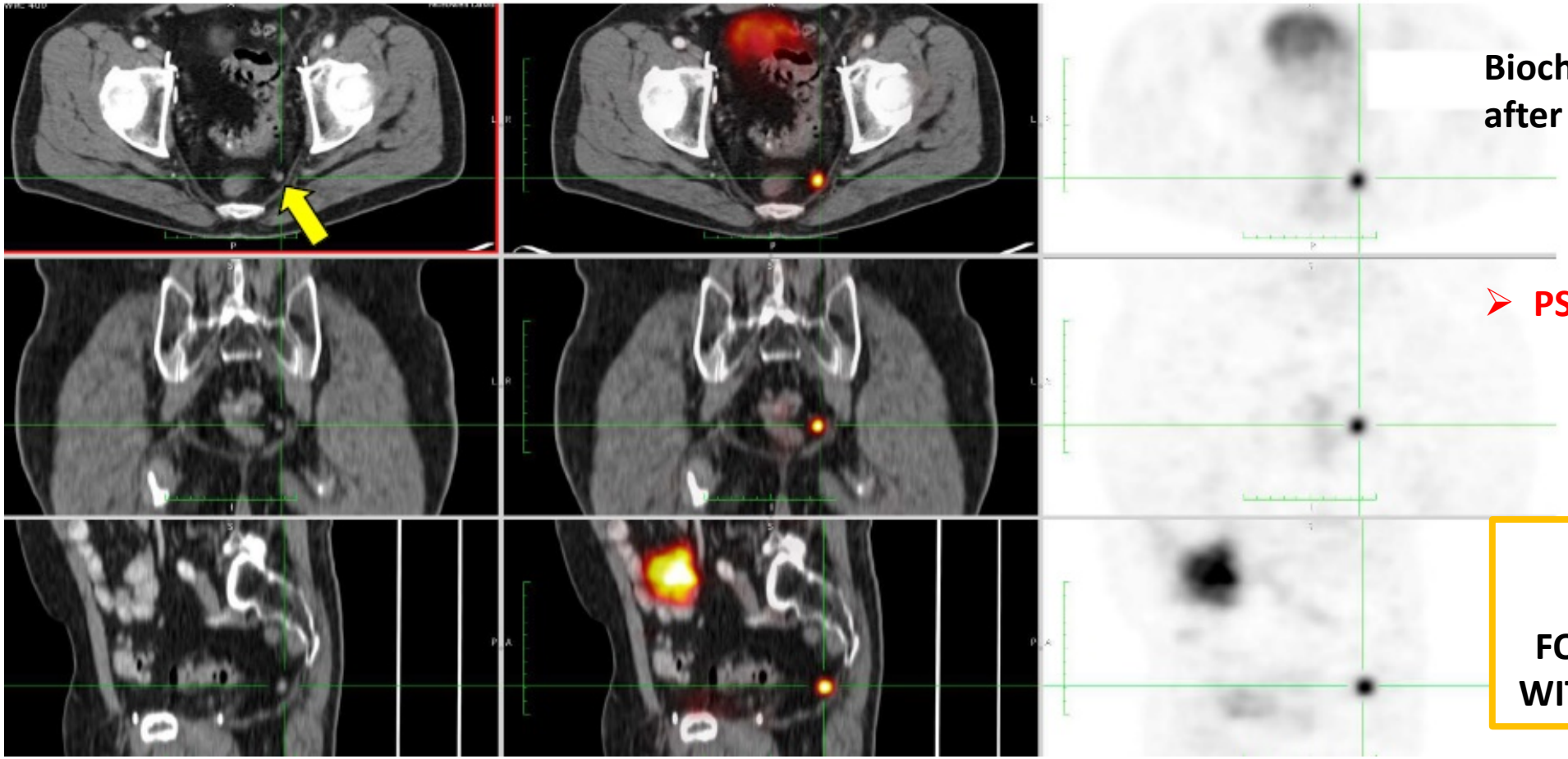
Biochemical recurrence (PSA 1.6) after surgery and salvage RT

TREATMENT:

SYSTEMIC THERAPY (MEDICAL CASTRATION)

PSMA PET guided therapy

PATIENT STORY #02



Biochemical recurrence (PSA 1.6) after surgery and salvage RT

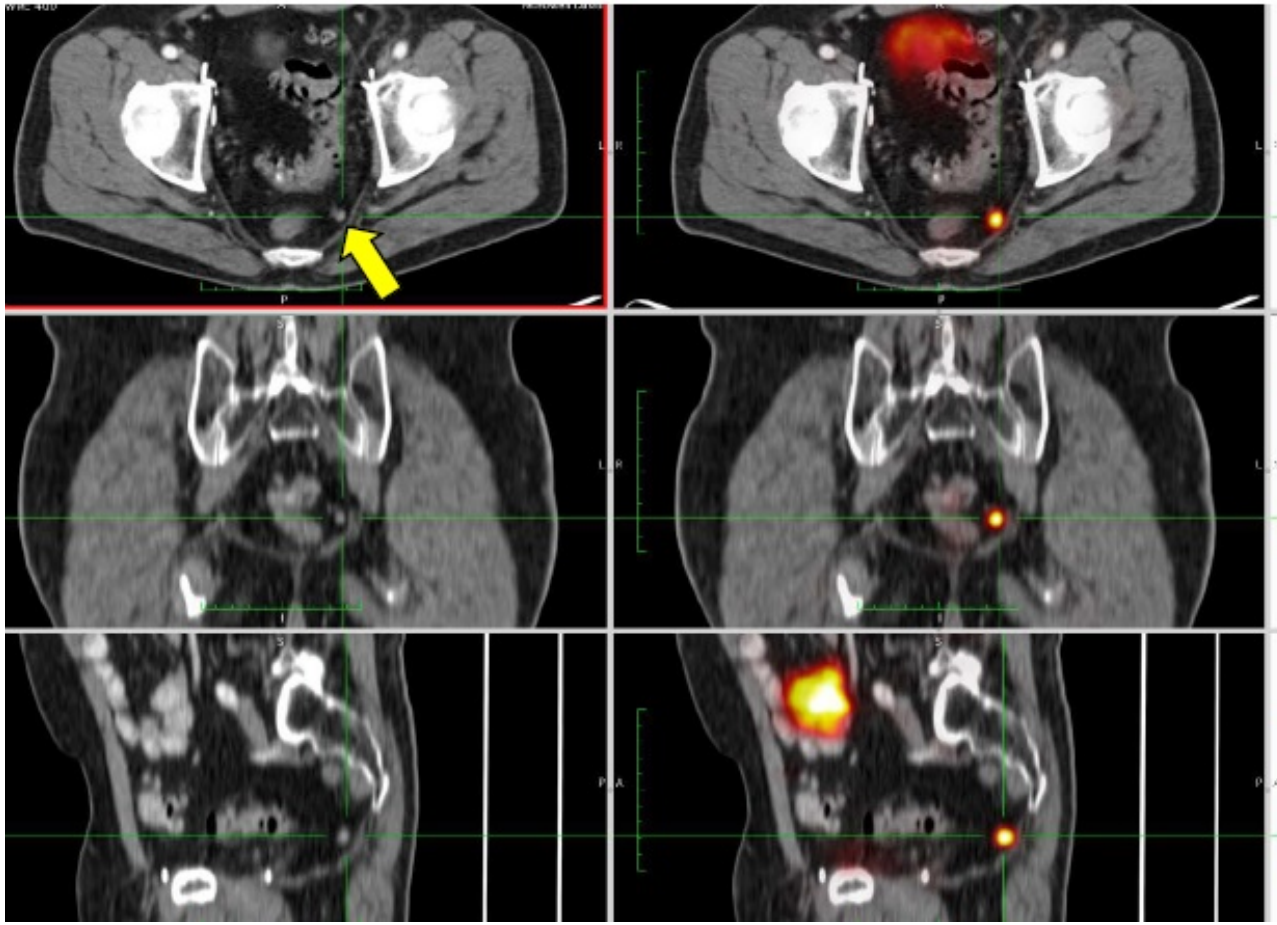
- **PSMA single perirectal LN 4 mm**

TREATMENT:

FOCAL RADIATION THERAPY WITHOUT SYSTEMIC THERAPY

PSMA PET guided therapy

PATIENT STORY #02



Biochemical recurrence (PSA 1.6) after surgery and salvage RT

- **PSMA single perirectal LN 4 mm**
  SBRT 40Gy (x5)
  No ADT

- Follow-up
  + 3 mo **PSA 0.05 ng/ml**
  + 3 years PSA < 0.01 ng/ml

^{68}Ga-PSMA-11 PET is FDA APPROVED at UCLA and UCSF

U.S. FOOD & DRUG ADMINISTRATION

← Home / News & Events / FDA Newsroom / Press Announcements / FDA Approves First PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer

FDA NEWS RELEASE

FDA Approves First PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer

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For Immediate Release: December 01, 2020

Español

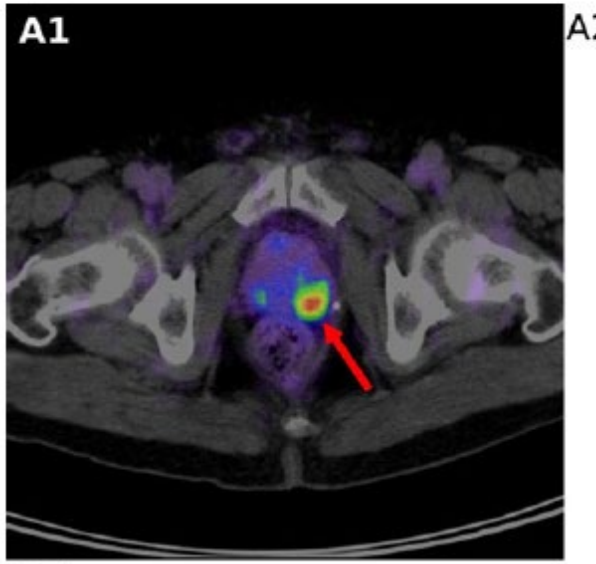
Today, the U.S. Food and Drug Administration approved Gallium 68 PSMA-11 (Ga 68 PSMA-11) – the first drug for positron emission tomography (PET) imaging of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer.

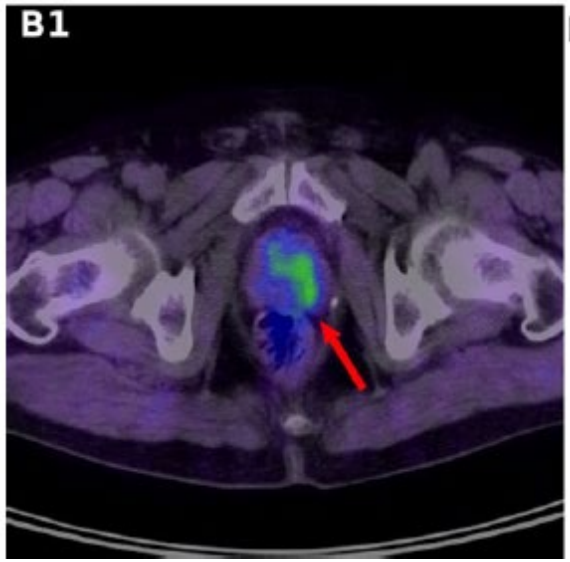
UCSF

UCLA
University of California, Los Angeles

History

Eur J Nucl Med Mol Imaging (2012) 39:1085–1086





Eur J Nucl Med Mol Imaging (2012) 39:1085–1086
DOI 10.1007/s00259-012-2069-0

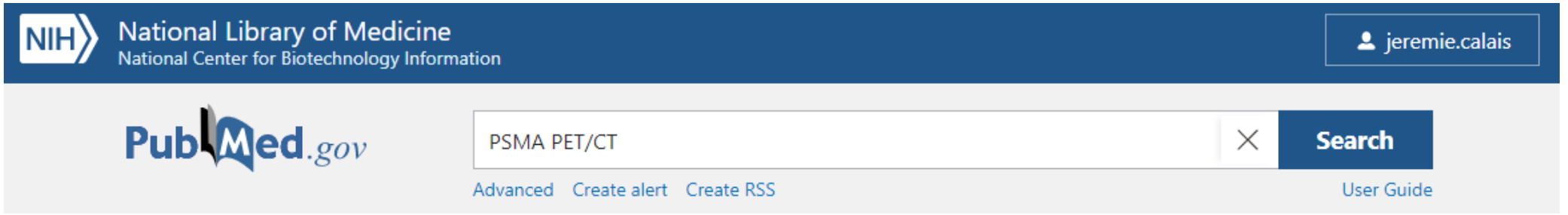
IMAGE OF THE MONTH

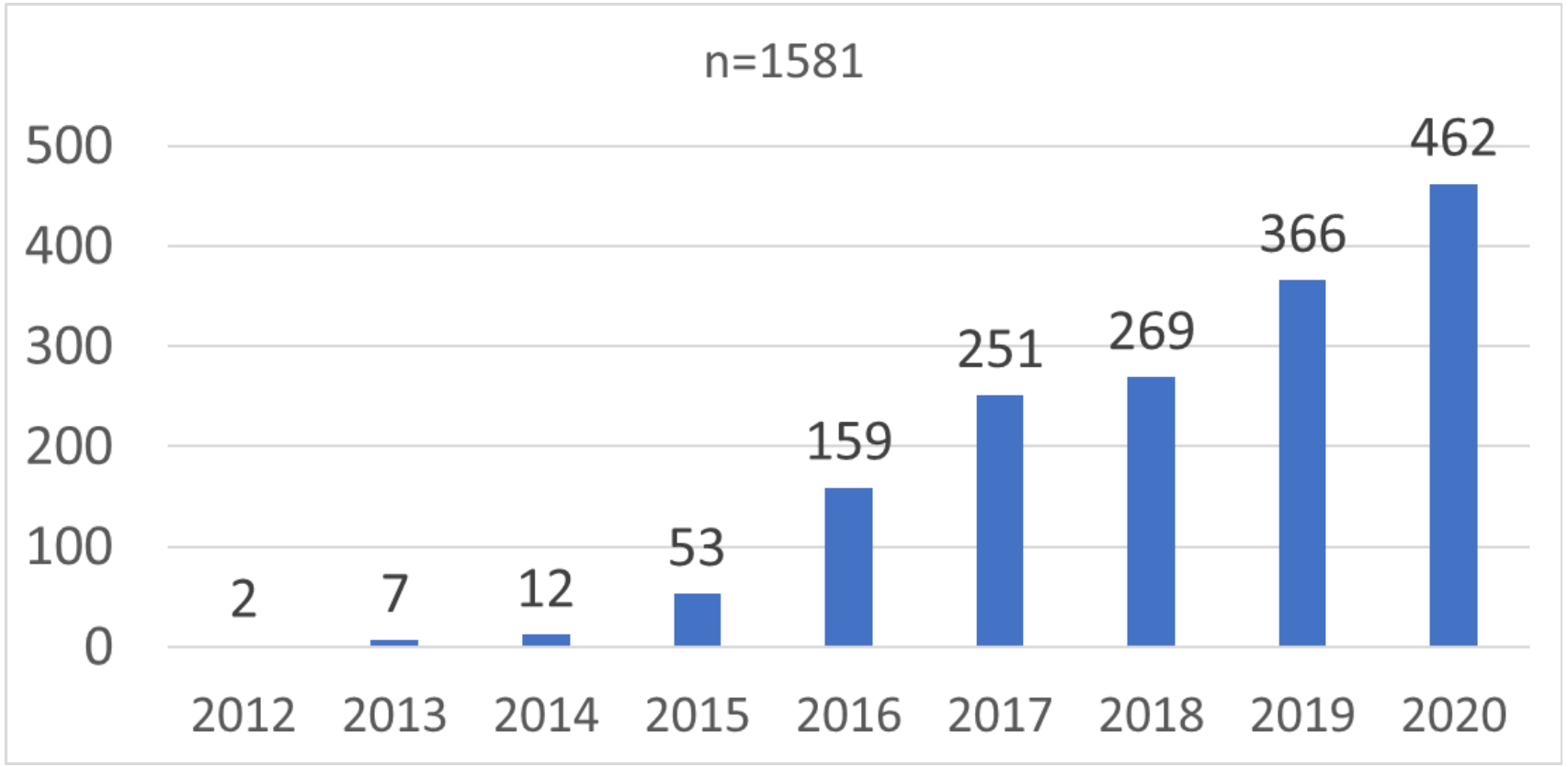
[^{68}Ga]Gallium-labelled PSMA ligand as superior PET tracer for the diagnosis of prostate cancer: comparison with ^{18}F-FECH

A. Afshar-Oromieh · U. Haberkorn · M. Eder · M. Eisenhut · CM. Zechmann

HEIDELBERG UNIVERSITY HOSPITAL

History


National Library of Medicine
National Center for Biotechnology Information
jeremie.calais
PubMed.gov
PSMA PET/CT
Search
Advanced
Create alert
Create RSS
User Guide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500
400
300
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100
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2
7
12
53
159
251
269
366
462
2012
2013
2014
2015
2016
2017
2018
2019
2020

UCLA AHMANSON TRANSLATIONAL THERANOSTICS DIVISION

68GA-PSMA-11 PET CLINICAL RESEARCH PROGRAM

ACADEMIC INVESTIGATOR INITIATED AND SPONSORED

IND #130649

UCLA
University of California, Los Angeles

Since Oct. 2016

IRB #	NCT #	Protocol	enrollment
16-001095	NCT02940262	Biochemical Recurrence	1200 / 1200 - **Closed**
16-001684	NCT03368547	Primary Staging before Surgery	400 / 400 - **Closed**
17-001885	NCT03515577	PSMA vs AXUMIN comparison	50 / 50 - **Closed**
18-001776	NCT04282824	MSG impact on PSMA PET signal	16 / 16 - **Closed**
18-000484	NCT03582774	Phase 3 randomized Trial of PSMA PET based SRT	193 / 193 - **Closed**
17-001336	NCT04050215	Metastatic Staging / Other indications / “Basket”	936 / 1200 - **Closed**
19-001868	NCT04348682	Expanded Access protocol	400 / 2500 - **Closed**
19-002024	**NCT04279561**	**PSMA ADT ARSI**	**04 / 30 - Open**
20-000378	**NCT04457245**	**Randomized Trial of PSMA for dRT**	**13 / 316 - Open**

UCLA AHMANSON TRANSLATIONAL THERANOSTICS DIVISION

68GA-PSMA-11 PET CLINICAL RESEARCH PROGRAM

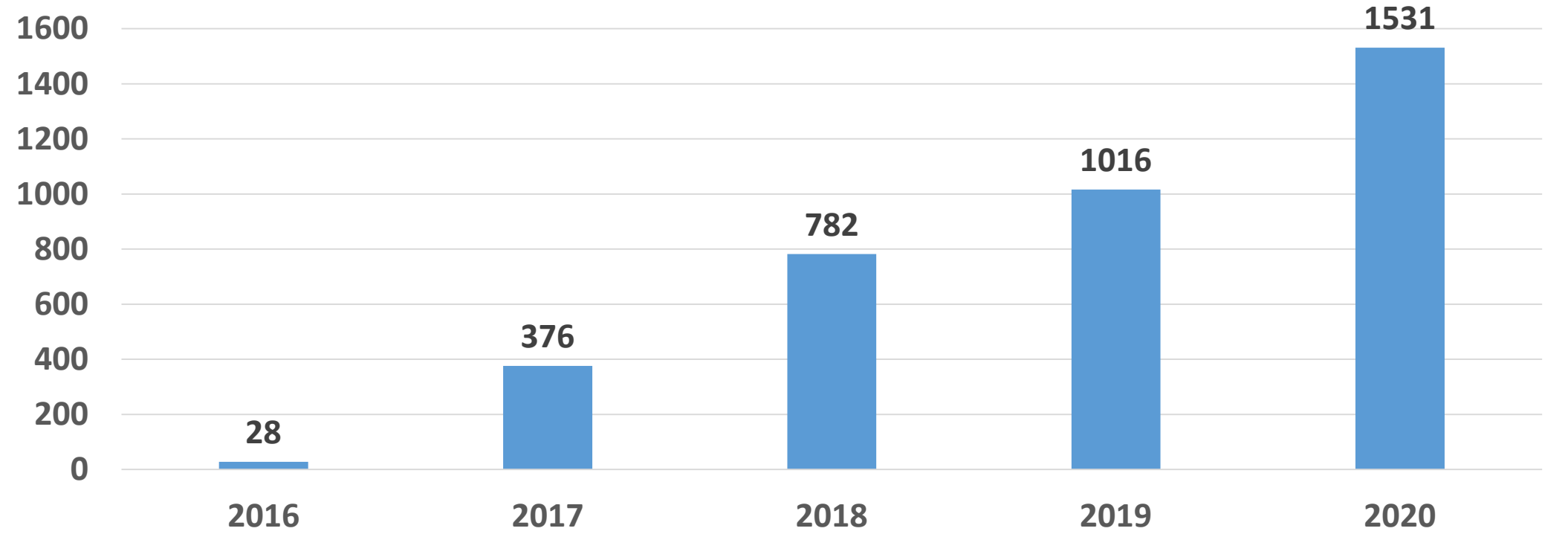
ACADEMIC INVESTIGATOR INITIATED AND SPONSORED

IND #130649

UCLA University of California, Los Angeles

Since Oct. 2016

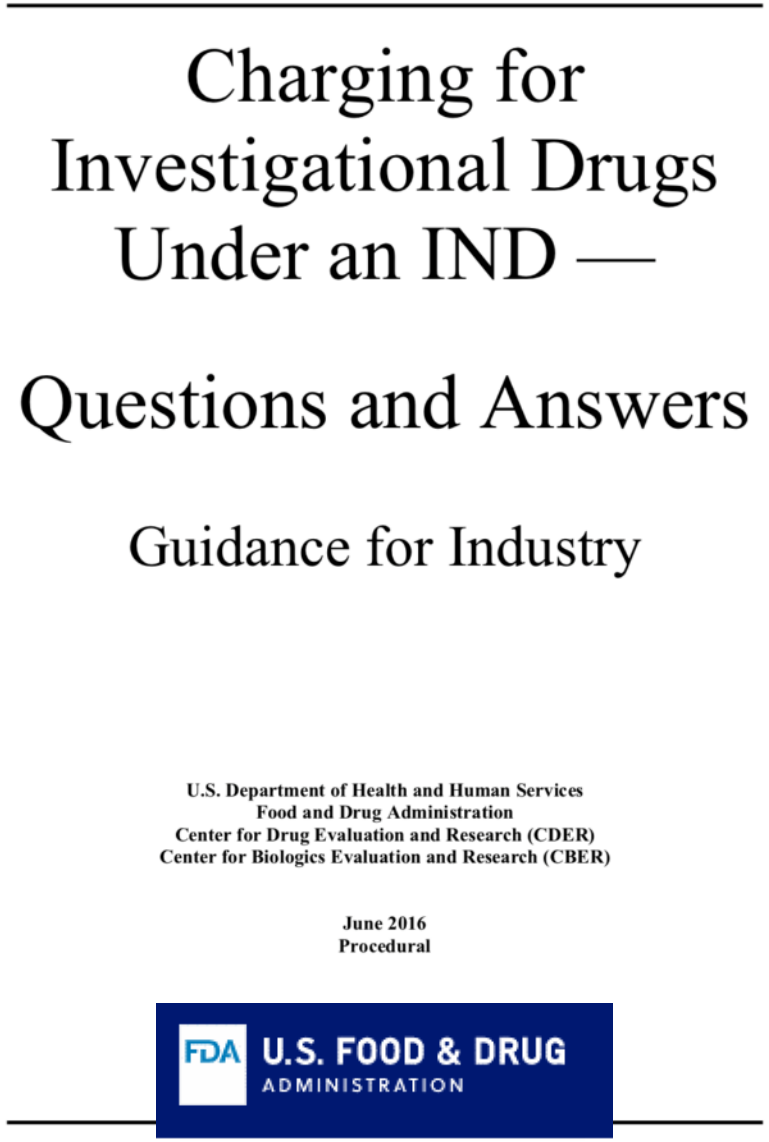
Total PSMA scans = 3733



01.28.2021

COST-RECOVERY

- Provide evidence that the drug has a potential clinical **benefit**
- Demonstrate that the data to be obtained from the clinical trial would be **essential** to establishing that the drug is effective or safe for the purpose of obtaining initial approval
- **Demonstrate that the clinical trial could not be conducted without charging because the cost of the drug is extraordinary to the sponsor**



Charging for Investigational Drugs Under an IND —

Questions and Answers

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2016
Procedural

FDA U.S. FOOD & DRUG ADMINISTRATION

SELF-FUNDING

Johannes Czernin, MD
Chief, Ahmanson Translational Theranostics Division
Associate Director, JCCC Cancer Molecular Imaging
Professor and Vice Chair, Molecular & Medical Pharmacology

^{68}Ga-PSMA-11 PET/CT

NDA timeline

Non-clinical Pharm
PD/PK
Pharm/Tox
Dosimetry

Pivotal Phase 3 protocols for IND
Uniform UCLA & UCSF protocols

UCSF/UCLA Data review

2011

Spring 2016

Fall 2017

European Compassionate Use Studies

Thomas Hope MD

UCSF

UCLA
University of California, Los Angeles

Prior academic sponsored NDAs

- C-11 choline (2012): Mayo Clinic
- Ga-68 DOTATOC (2019): University of Iowa
- F-18 fluorodopa (2019): Feinstein Institutes for Medical Research

NDA timeline

Non-clinical Pharm
PD/PK
Pharm/Tox
Dosimetry

Pivotal Phase 3 protocols for IND ***Uniform UCLA & UCSF protocols***

UCSF/UCLA Data review

Pre-NDA meeting request

Pre-NDA meeting

2011

Spring 2016

Fall 2017

Spring 2018

August 2018

European Compassionate Use Studies

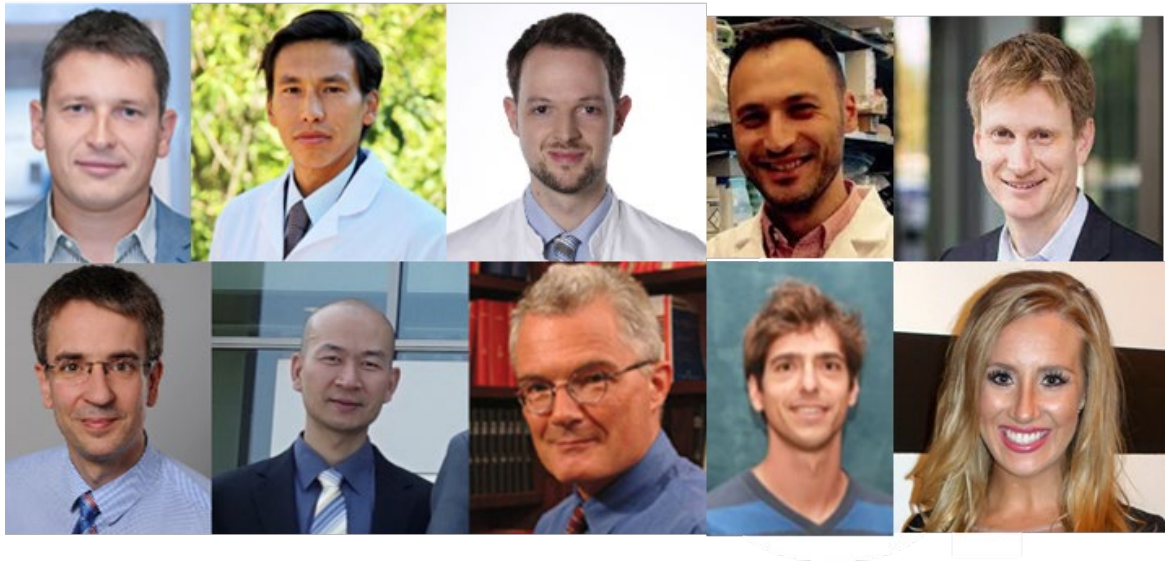
UCLA University of California, Los Angeles

UCSF

ACADEMIC COLLABORATION

UCLA

UCLA
University of California, Los Angeles



UCSF

Ken Herrmann
Wolfgang Fendler
Matthias Eiber
Johannes Czernin
Shaojun Zhu
Roger Slavik
Giuseppe Carlucci

Enabled by the FDA's willingness to allow two paired NDAs

Thomas Hope
Joseph Blecha,
Robin Ippish
Ashley Mishoe
Sara St. James

NDA timeline

2011	Spring 2016	Fall 2017	Spring 2018	August 2018	September 2019	Spring 2020	Summer 2020
Non-clinical Pharm *PD/PK* *Pharm/Tox* *Dosimetry*	Pivotal Phase 3 protocols for IND *Uniform UCLA & UCSF protocols*	UCSF/UCLA Data review	Pre-NDA meeting request	Pre-NDA meeting	**NDA Submission** *Regulatory* *Non-clinical* *Statistical* *CMC*	**FDA AUDIT** *CLINIC*	**FDA AUDIT** *CYCLOTRON*

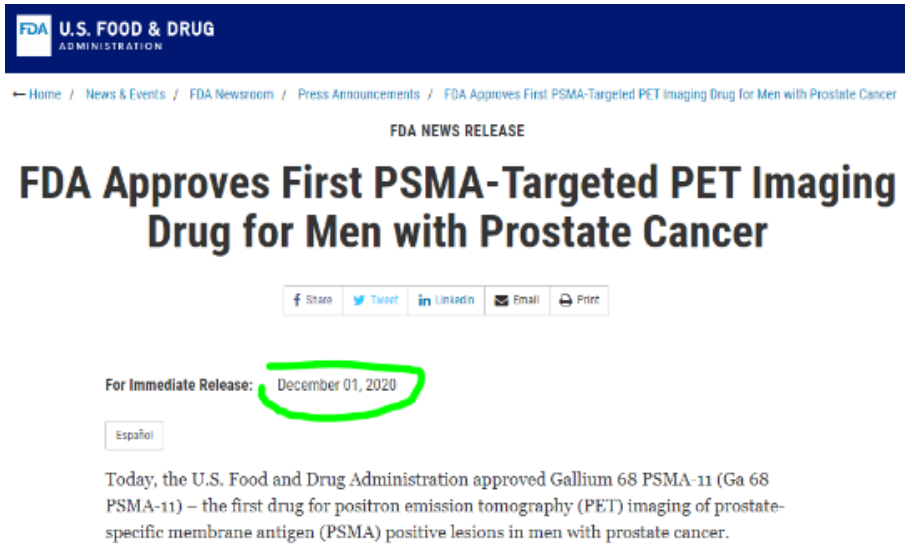
European Compassionate Use Studies

UCLA University of California, Los Angeles UCSF

NDA timeline

2011	Spring 2016	Fall 2017	Spring 2018	August 2018	September 2019	Spring 2020	Summer 2020
Non-clinical Pharm *PD/PK* *Pharm/Tox* *Dosimetry*	Pivotal Phase 3 protocols for IND *Uniform UCLA & UCSF protocols*	UCSF/UCLA Data review	Pre-NDA meeting request	Pre-NDA meeting	**NDA Submission** *Regulatory* *Non-clinical* *Statistical* *CMC*	**FDA AUDIT** *CLINIC*	**FDA AUDIT** *CYCLOTRON*

European Compassionate Use Studies



December 1st, 2020

UCLA University of California, Los Angeles

UCSF

UNIQUE REGULATORY APPROACH - KEY POINTS

UCLA

- **Two separate** NDAs : UCSF NDA 212643 and UCLA NDA 212642
- **Same clinical and non-clinical information**
- **Site-specific CMC** modules (Chemistry Manufacturing and Controls)
- **Similar package insert**; different vial label
- **Waiving market exclusivity**
- 505(b)(2) NDA pathway
  - Data from literature, not conducted by the applicant
  - Nonclinical pharmacology and clinical dosimetry

^{68}Ga-PSMA-11 PET is FDA APPROVED at UCLA and UCSF

WHAT DOES IT MEAN NOW? - KEY POINTS

- UCSF and UCLA **only** distribute 68Ga-PSMA-11 within their institutions
- UCSF and UCLA are filing new HCPCS code request with **Medicare (currently not covered)**
- Open to 68Ga-PSMA-11 ANDA applications immediately (Abbreviated)
  - **No patent protection**
  - **Market exclusivity waived**
  - **Not required**: nonclinical and clinical studies
  - **Required**: site and product/process specific CMC information
    - Final product composition, formulation, specification and controls;
    - manufacturing process and controls etc.

REGULATORY LANDSCAPE
(DIAGNOSTIC PET DRUGS INDICATED FOR PROSTATE CANCER)

- FDA Approved
  - 2012 Choline C 11 Injection
    - For positron emission tomography (PET) imaging of patients with suspected prostate cancer recurrence and non-informative bone scintigraphy, computerized tomography (CT) or magnetic resonance imaging.
  - 2016 AXUMIN (fluciclovine F 18) injection
    - Indicated for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment.
  - 2020 Gallium Ga 68 PSMA-11 Injection
    - Indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:
      - with suspected metastasis who are candidates for initial definitive therapy.
      - with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.
- Submitted to FDA (information disclosed in public domain)
  - Lantheus NDA for PyL™ (^{18}F-DCFPyL): Submitted September 2020; PDUFA date May 28, 2021
  - Telix NDA for TLX591-CDx (Kit for the preparation of ^{68}Ga-PSMA-11): Submitted September 2020; Accepted for filing in November 2020.

^{68}Ga-PSMA-11 PET is FDA APPROVED at UCLA and UCSF

U.S. FOOD & DRUG ADMINISTRATION

Home / News & Events / FDA Newsroom / Press Announcements / FDA Approves First PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer

FDA NEWS RELEASE

FDA Approves First PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer

Share Tweet Linkedin Email Print

For Immediate Release: December 01, 2020

Español

Today, the U.S. Food and Drug Administration approved Gallium 68 PSMA-11 (Ga 68 PSMA-11) – the first drug for positron emission tomography (PET) imaging of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer.

Gallium Ga 68 PSMA-11 Injection, for intravenous use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------

Ga 68 PSMA-11 Injection is a radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:

- with suspected metastasis who are candidates for initial definitive therapy.
- with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level. (1)

UCSF UCLA University of California, Los Angeles

2 PIVOTAL STUDIES

2 pivotal studies

Biochemical Recurrence	n=635
UCLA NCT02940262	n=250
UCSF NCT03353740	n=385

Initial Staging before surgery	n=277
UCLA NCT03368547	n=130
UCSF NCT02611882, NCT02919111	n=147

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UCSF NCT02611882, NCT02919111	n=147

STUDY DESIGN

Primary Endpoint

positive predictive value (PPV) on a per-patient and per-region basis of 68Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology

STATS

- **Estimated sample size needed: ≥107 patients with biopsy and/or surgery follow-up**
- **Hypothesis: PPV of 70%**

Fendler WP et al. *JAMA oncol*. 2019

STUDY DESIGN

Primary Endpoint

positive predictive value (PPV) on a per-patient and per-region basis of 68Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology or "composite" reference standard (PSA, imaging).

STATS

- **Estimated sample size needed: ≥107 patients with biopsy and/or surgery follow-up**
- **Hypothesis: PPV of 70%**

Fendler WP et al. *JAMA oncol*. 2019

STUDY DESIGN

COMPOSITE ENDPOINT

- Histopathology
- PSA decrease after focal therapy without ADT
- Correlation with Other imaging modality

STUDY DESIGN – COMPOSITE ENDPOINT

All patients will be followed up 3-12 months with conventional imaging (dedicated CT, MRI and/or bone scan). Interpretation of follow-up imaging will be performed by local read. For lesions that are reported in the blinded reads but not reported in the local evaluation of follow-up imaging, the local readers will be informed of the location of the lesions and follow-up will be performed for these additional lesions. Preferably, the follow-up conventional imaging should be the same modality/modalities as the initial staging work-up to allow for reproducible and accurate comparisons.

^{68}Ga-PSMA-11 PET validation based on follow-up imaging:

i) Lymph nodes will be assessed by change in size. ^{68}Ga-PSMA-11 positive lymph nodes will be considered:

(1) True positive:

- For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI decrease by more than 30% in short axis diameter and PSA declines by more than 50%.

  - If PSA increases by more than 50% on systemic therapy, then a increase in the size of lesion by more than 20% will be considered a true positive lesion.

- In subjects with localized suspected lymph node(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet true positive disease:

  - If the subject shows a decrease of PSA by greater than 50% after targeted treatment and the lymph node does not enlarge (change in size less than 20% or less than 3 mm increase in short axis diameter) [*OR*]

  - If on post-treatment follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI decrease by more than 30% in short axis diameter (with a minimum of 3 mm in change in size)

- For untreated patients: If on follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI increase by more than 20% in short axis diameter (with a minimum of 3 mm in change in size).

(2) False positive:

- For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI increase by more than 20% in short axis diameter and PSA decreases by more than 50%.

- In subjects with localized suspected lymph node(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet false positive disease:

  - If the subject does not demonstrate a decrease of PSA by greater than 50% after targeted treatment [*OR*]

  - If on post-treatment follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI increase by more than 20% in short axis diameter (with a minimum of 3 mm in change in size)

- For untreated patients: If on follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI decrease by more than 30% in short axis diameter (with a minimum of 3 mm in change in size).

(3) If all regions in a patient/region do not meet criteria for either True positive or False positive disease, then the patient/region will be considered inevaluable for primary endpoint.

ii) Visceral lesions (non-lymph node soft tissue or organ) will be assessed by change in size. ^{68}Ga-PSMA-11 positive visceral lesions will be considered:

(1) True positive:

- For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter and PSA declines by more than 50%.

  - If PSA increases by more than 50% on systemic therapy, then a increase in the size of lesion by more than 20% will be considered a true positive lesion.

- In subjects with localized suspected lesions(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet true positive disease:

  - If the subject demonstrates a decrease of PSA by greater than 50% after targeted treatment [*OR*]

  - If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter (with a minimum of 3 mm in change in size)

- For untreated patients: If on follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter (with a minimum of 3 mm in change in size).

(2) False positive:

- For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter and PSA decreases by more than 50%.

- In subjects with localized suspected lesions(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet false positive disease:

  - If the subject does not demonstrate a decrease of PSA by greater than 50% after targeted treatment [*OR*]

  - If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter (with a minimum of 3 mm in change in size)

- For untreated patients: If on follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter (with a minimum of 3 mm in change in size).

(3) If all regions in a patient/region do not meet criteria for either True positive or False positive disease, then the patient/region will be considered inevaluable for primary endpoint.

iii) ^{68}Ga-PSMA-11 positive bone lesions will be considered:

(1) True positive:

- If there was a corresponding positive sclerotic lesion on the CT portion of the ^{68}Ga-PSMA-11 PET or on a separate CT obtained ≤ 30 days before or after the PET/CT in the same location as the PSMA uptake.

- If there is focal uptake seen in the same location as the PSMA uptake on the baseline bone scan performed within one month of ^{68}Ga-PSMA-11 PET.

- If there is a lesion noted in the same location as the PSMA uptake on the initial MRI performed within one month of ^{68}Ga-PSMA-11 PET.

- If within 12 months follow-up CT demonstrates development of sclerosis in the same location as the PSMA uptake.

- If within 12 months follow-up MRI demonstrates a new bone lesion in the same location as the PSMA uptake.

- If within 12 months follow-up bone scan demonstrates new focal uptake in the same location as the PSMA uptake.

- In subjects with localized suspected bone lesion(s) receiving targeted treatment without concomitant systemic treatment:

  - If the subject demonstrates a decrease of PSA by greater than 50% after targeted treatment.

(2) False positive:

- In subjects with localized suspected bone lesion(s) receiving targeted treatment without concomitant systemic treatment:

  - If the subject does not demonstrate a decrease of PSA by greater than 50% after targeted treatment with curative intent (ie non-palliative radiation).

- If ^{68}Ga-PSMA-11 positive bone lesions do not meet the criteria for true positive findings, and appropriate correlative and follow-up imaging was acquired.

STUDY DESIGN – COMPOSITE ENDPOINT

(3) If bone lesions do not meet criteria for either true positive or false positive disease listed above, then the patient/region will be considered inevaluable for primary endpoint.

iv) ^{68}Ga-PSMA-11 positive prostate bed and prostate lesions will be considered:

(1) True positive:

- For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter

- In subjects with localized suspected lesions(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet true positive disease:

  - If the subject demonstrates a decrease of PSA by greater than 50% after targeted treatment [*OR*]
  - If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter (with a minimum of 3 mm in change in size)

- For untreated patients: If on follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter (with a minimum of 3 mm in change in size).

(2) False positive:

- For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter and PSA decreases by more than 50%.

- In subjects with localized suspected lesions(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet false positive disease:

  - If the subject does not demonstrate a decrease of PSA by greater than 50% after targeted treatment [*OR*]
  - If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter (with a minimum of 3 mm in change in size)

- For untreated patients: If on follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter (with a minimum of 3 mm in change in size).

(3) If the lesion does not meet criteria for either True positive or False positive disease, then the lesion will be considered inevaluable for primary endpoint.

c) Histopathology/Biopsy:

i) ^{68}Ga-PSMA-11 positive findings are aimed to be confirmed by histopathology/biopsy if clinically feasible. Pathology performed 60 days before the PSMA PET will be available for correlation.

ii) Histopathological procedures and biopsies will be performed as clinically indicated and as per institutional protocol.

(1) Positive Histopathology/Biopsy: Confirmed sites of metastatic or tumor involvement by histopathology/biopsy will be discussed with the responsible physician/surgeon.

(a) True Positive: lesion is positive on targeted biopsy/surgical sampling and is read as positive on PSMA PET.

(b) False Negative: lesion is positive on targeted biopsy/surgical sampling and is read as negative on PSMA PET.

(2) Negative Biopsy: Patients with suspected tumor recurrence on ^{68}Ga-PSMA-11 PET with negative histopathology/biopsy will be handled as outlined below:

(a) Lymph nodes:

- For patients undergoing nodal dissection: Patients will be rescanned with dedicated CT, MRI or a repeat ^{68}Ga-PSMA-11 PET to determine if the suspicious ^{68}Ga-PSMA-11 positive node was removed.

  1. If ^{68}Ga-PSMA-11 positive lymph node is still present, a repeat biopsy can be pursued if clinically feasible and applicable, or follow-up using imaging as described above will be performed.
  2. If the corresponding node was removed, then this will be considered a False Positive.

- For patients undergoing needle biopsy: Images of the procedure will be reviewed to determine if the correct node was biopsied.

  1. If the correct node was biopsied, then a negative biopsy will be considered a False Positive.
  2. If the incorrect node was biopsied, then follow-up imaging as described above will be performed.

(b) Bone lesions: Given the high rate of false negative biopsies for osseous metastases in patients with prostate cancer, patients with negative bone biopsies of PSMA PET positive lesions will be further evaluated:

- If pathology demonstrates an alternative diagnoses that is known to be PSMA positive (eg Renal Cell Carcinoma metastases, Paget's disease), then this will be considered a False Positive.
- If pathology is indeterminate, then follow-up imaging as described above will be performed.

(3) Although not routinely performed during standard practice, immunohistochemical staining for PSMA of tumor specimens (primary and lymph node metastases) may be performed, although not required.

d) Definitions of True Positive, False Positive, True Negative, and False Negative patients and regions: Pathology will be considered superior to imaging and clinical follow-up when available as described below. Patient and region level classification will be performed for each blinded reader, and be reported separately. The following criteria serve as a guide for interpretation. However not all findings on a lesions, region and patient level can be detailed here and investigators may deviate from these criteria in individual patients. These will be recorded for each interpretation that is not described in this protocol for the definition of a region or patient.

i) Patient level evaluation:

(1) True positive patient: A single region in a patient contains a true positive node either by pathology or imaging/clinical follow-up.

(a) For a patient to be considered a True Positive, only one region is required to have a true positive lesion as described above, unless one region is categorized as a false positive based on pathology. This means that a single pathology false positive region outweighs regions with imaging/clinical follow-up true positive disease.

(b) A patient will be considered a True Positive if one region contains a lesion that is True Positive, even if other regions are categorized as inevaluable or false positive based on imaging or clinical follow-up.

(2) True negative patient: in the absence of True Positive or False Positive lesions, a patient will be considered a True Negative if there is pathology that is negative for disease and corresponding lesion is negative by PSMA PET.

(3) False positive patient:

(a) Pathology confirms a false positive lesion that is read as positive on PSMA PET.

(b) In the absence of pathology: there are no true positive regions, and there is a region that is categorized as false positive based on imaging or clinical follow-up.

(4) False negative patient: in the absence of True Positive or False Positive lesions, a patient will be considered a False Negative if there is pathology that is positive for disease and corresponding lesion is negative by PSMA PET.

ii) Region level evaluation: Each patient will have four evaluable regions (Table 1: prostate bed, pelvis, extrapelvic soft tissue, and bone metastases). Each region will be categorized as true positive or false positive as described above. Regions without evidence of PSMA positive disease or deemed inevaluable will not be included in the analysis.

(1) True positive region:

(a) Pathology confirms a PSMA avid lesion as a true positive in the region.

STUDY DESIGN

Primary Endpoint

positive predictive value (PPV) on a per-patient and per-region basis of 68Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology or "composite" reference standard (PSA, imaging).

STATS

- **Estimated sample size needed: ≥107 patients with biopsy and/or surgery follow-up**
- **Hypothesis: PPV of 70%**

3 blinded independent central readers (BICR) with no clinical data available (**Majority Score 2:1**)

Fendler WP et al. *JAMA oncol*. 2019

^{68}Ga-PSMA-11 PET/CT for **biochemical recurrence localization**

UCLA + UCSF Phase 3 trial - 635 patients

Research

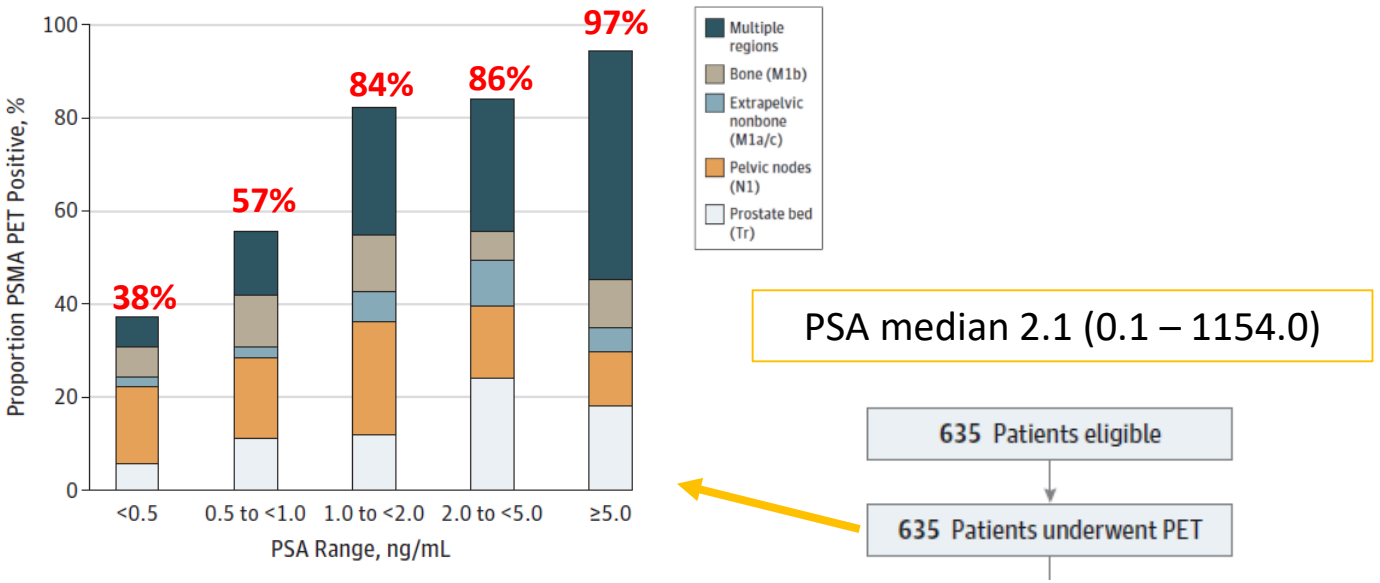
JAMA Oncology

JAMA Oncology | Original Investigation

Assessment of ^{68}Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer

A Prospective Single-Arm Clinical Trial

Wolfgang P. Fendler, MD; Jeremie Calais, MD; Matthias Eiber, MD; Robert R. Flavell, MD, PhD; Ashley Mishoe, PharmD; Felix Y. Feng, MD; Hao G. Nguyen, MD, PhD; Robert E. Reiter, MD; Matthew B. Rettig, MD; Shozo Okamoto, MD; Louise Emmett, MD; Helle D. Zacho, MD; Harun Ilhan, MD; Axel Wetter, MD; Christoph Rischpler, MD; Heiko Schoder, MD; Irene A. Burger, MD; Jeannine Gartmann; Raven Smith; Eric J. Small, MD; Roger Slavik, PhD; Peter R. Carroll, MD, MPH; Ken Herrmann, MD; Johannes Czernin, MD; Thomas A. Hope, MD



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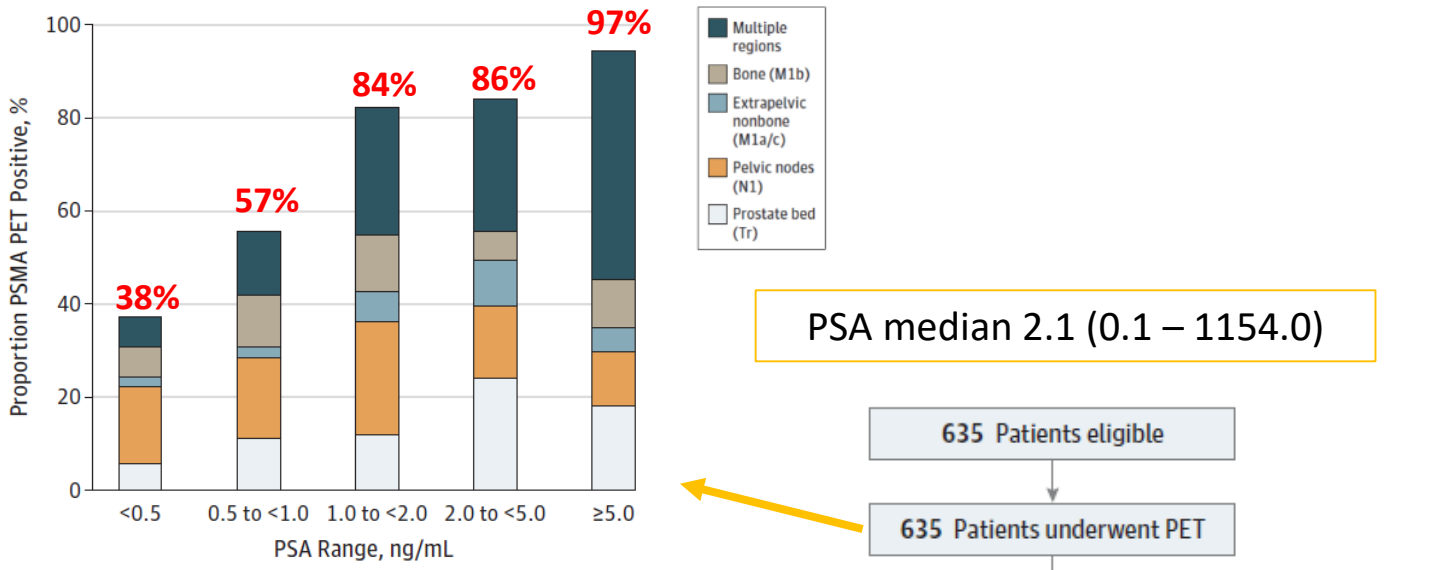


PSA median 2.1 (0.1 – 1154.0)

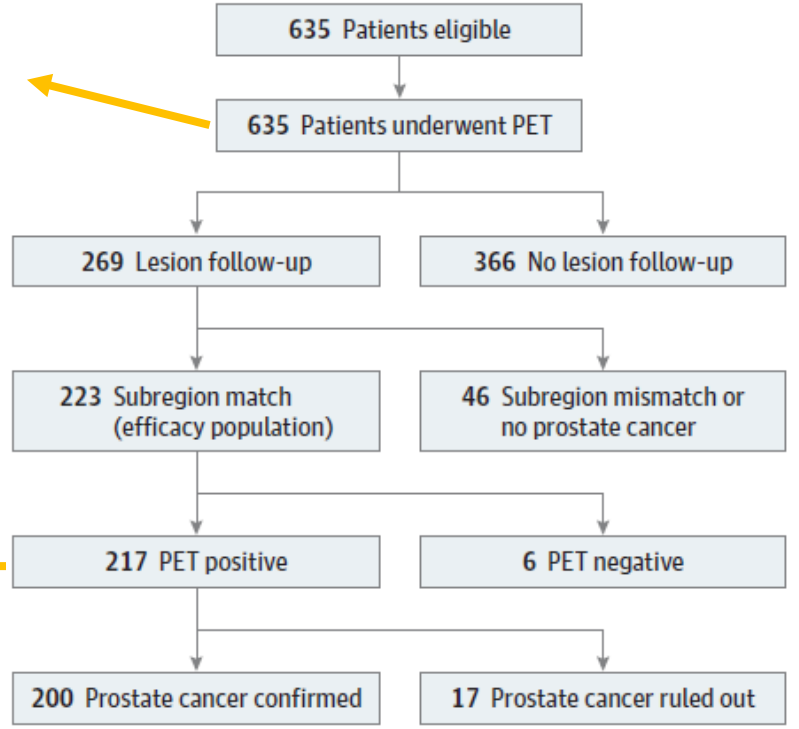


Table 3. ^{68}Ga-PSMA-11 PET Accuracy

Validation Group	Total Regions/Patients, No.	No. (%) Confirmed	No. (%) Ruled Out	PPV or SE (95%CI)
Positive Predictive Value				
Composite validation				
PET positive (per-patient)	217	200 (92)	17 (8)	0.92 (0.88-0.95)
PET positive (per-region)	249	229 (92)	20 (8)	0.92 (0.88-0.95)
Histopathologic validation				
PET positive (per-patient)	87	73 (84)	14 (16)	0.84 (0.75-0.90)
PET positive (per-region)	90	76 (84)	14 (16)	0.84 (0.76-0.91)
Sensitivity				
Histopathologic findings				
Confirmed (per-patient)	79	73 (92)[a]	6 (8)[b]	0.92 (0.84-0.96)
Confirmed (per-region)	84	76 (90)[a]	8 (10)[b]	0.90 (0.82-0.95)

Fendler WP et al. *JAMA oncol*. 2019

2 PIVOTAL STUDIES

2 pivotal studies

Biochemical Recurrence	n=635
UCLA NCT02940262	n=250
UCSF NCT03353740	n=385

Initial Staging before surgery	n=277
UCLA NCT03368547	n=130
UCSF NCT02611882, NCT02919111	n=147

STUDY DESIGN

UCLA

Primary Endpoint

Se, Spe, PPV, NPV, of 68Ga-PSMA-11 PET for the detection of regional nodal metastases compared to histopathology at radical prostatectomy on a per patient basis and using nodal regional correlation (left/right/other) in patients with intermediate to high-risk prostate cancer

STATS

- **Estimated sample size needed: 61 pN1 patients (= with nodal metastases per pathology)**
- **Hypothesis: Sensitivity of 65%**

3 blinded independent central readers (BICR) with no clinical data available (**Majority Score 2:1**)

Hope T … Calais J et al *under review* 2021

RESULTS: SENSITIVITY AND SPECIFICITY

123 / 325 (38%) patients underwent surgery = efficacy cohort

Table 5: Patient-Level Performance of Ga 68 PSMA-11 PET for Detection of Pelvic Lymph Node Metastasis* in the PSMA-PreRP Study (n=123)

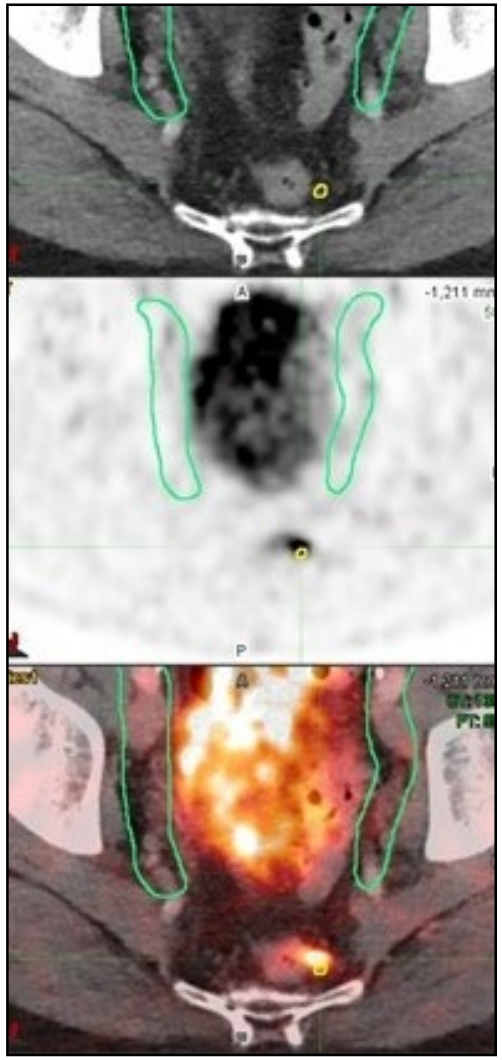
		Histopathology		Predictive value** (95% CI)
		Positive	Negative	
PET scan	Positive	14	9	PPV 61% (41%, 81%)
	Negative	16	84	NPV 84% (79%, 91%)
Total		30	93	
Diagnostic performance (95% CI)		Sensitivity 47% (29%, 65%)	Specificity 90% (84%, 96%)	

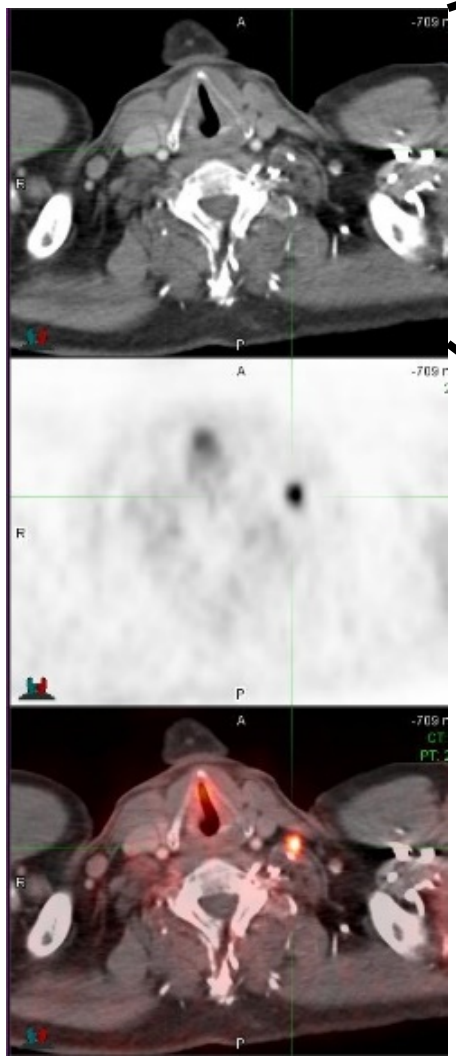
*with region matching where at least one true positive region defines a true positive patient
**PPV: positive predictive value, NPV: negative predictive value

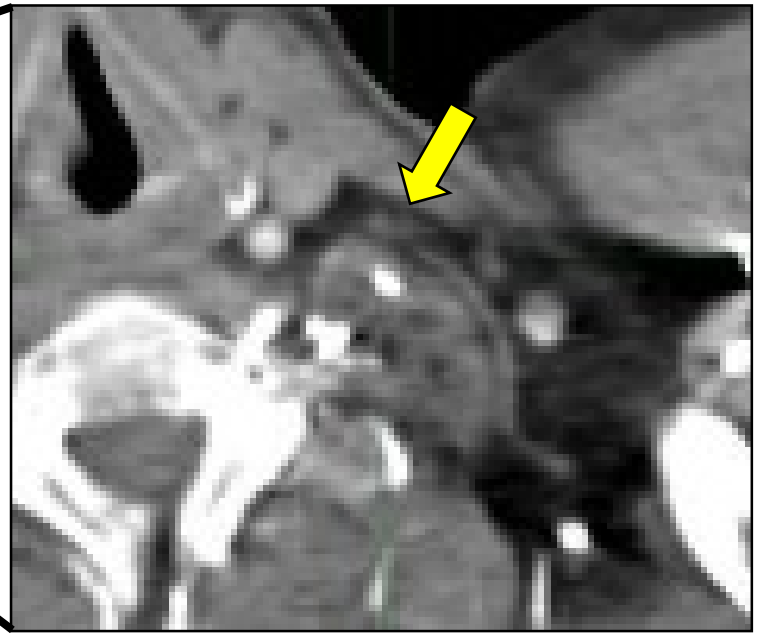
Among the pool of six readers, sensitivity ranged from 36% to 60%, specificity from 83% to 96%, positive predictive value from 38% to 80%, and negative predictive value from 80% to 88%.

PSMA PET/CT reading

SMALLEST LYMPH NODE PSMA PET CAN DETECT

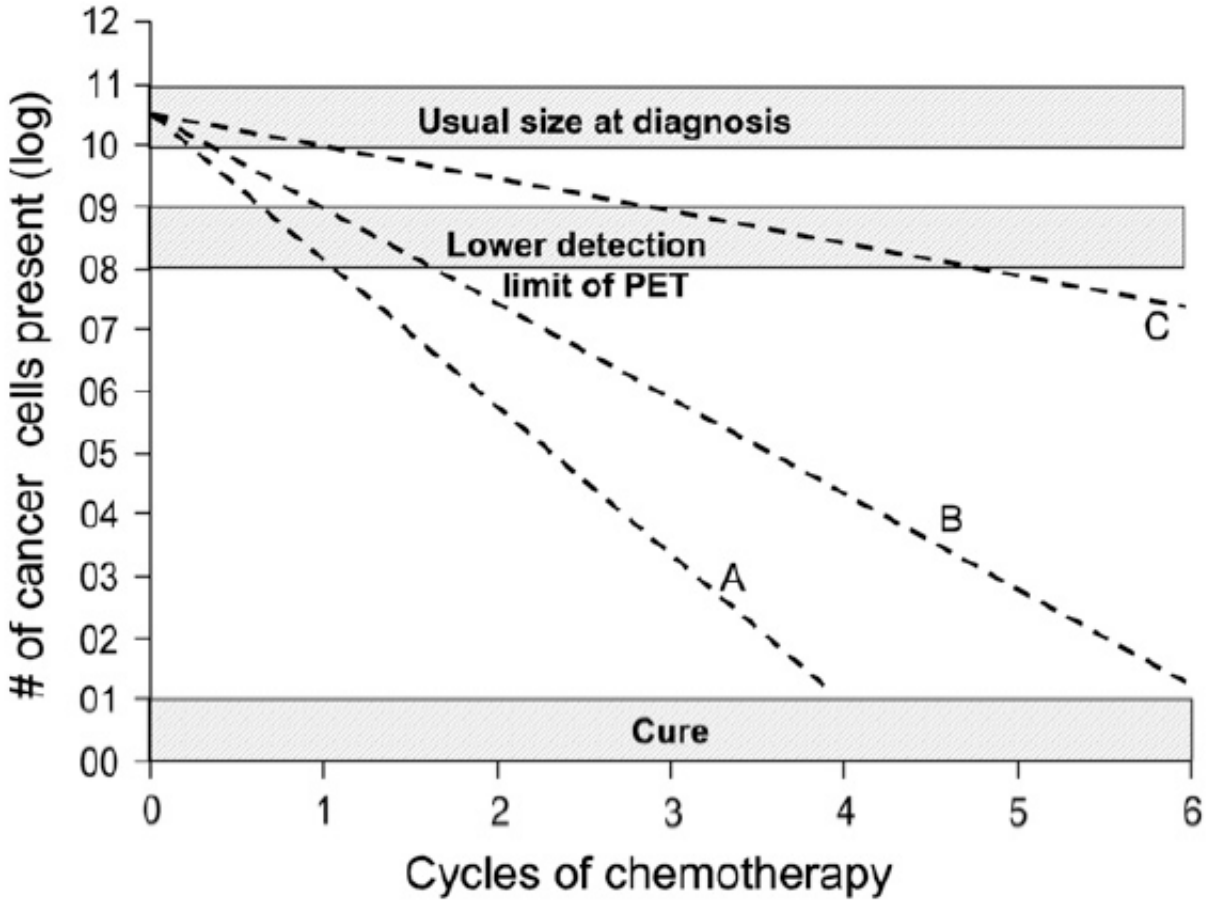






SMALLEST LESION PET CAN DETECT

FDG PET/CT



RL Wahl, *J Nucl Med* 2009

0.4 - 1.0 cm = 0.1 - 1.0 grams = 10^8 – 10^9 cells

Negative PET scan

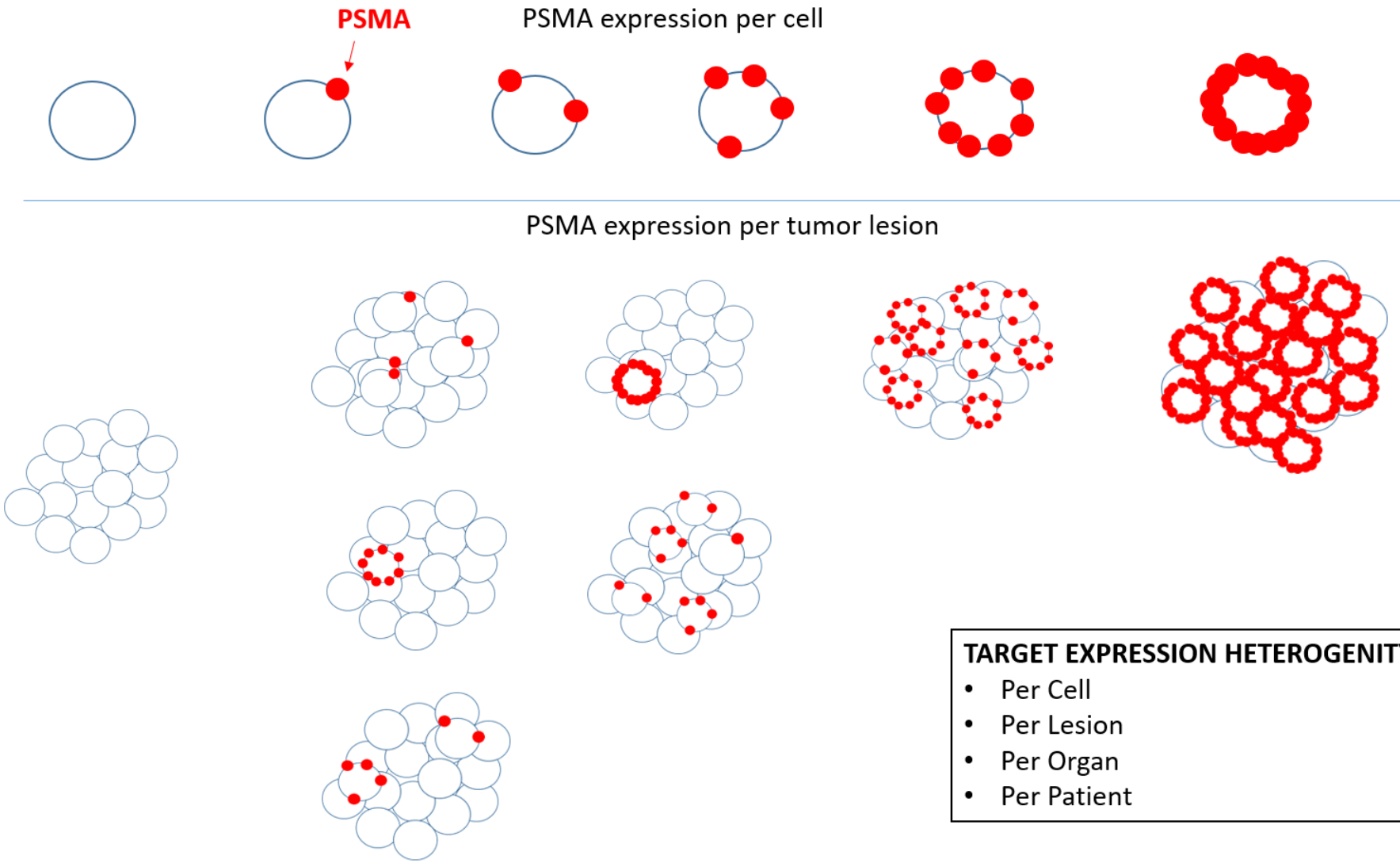
➢ no cancer cells present

OR

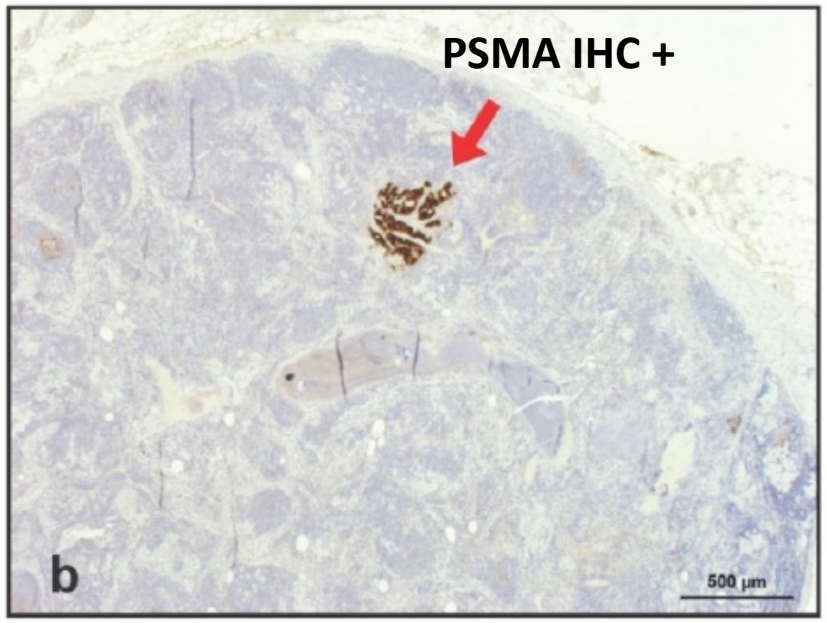
➢ ≤ 10^7 cells ~microscopic

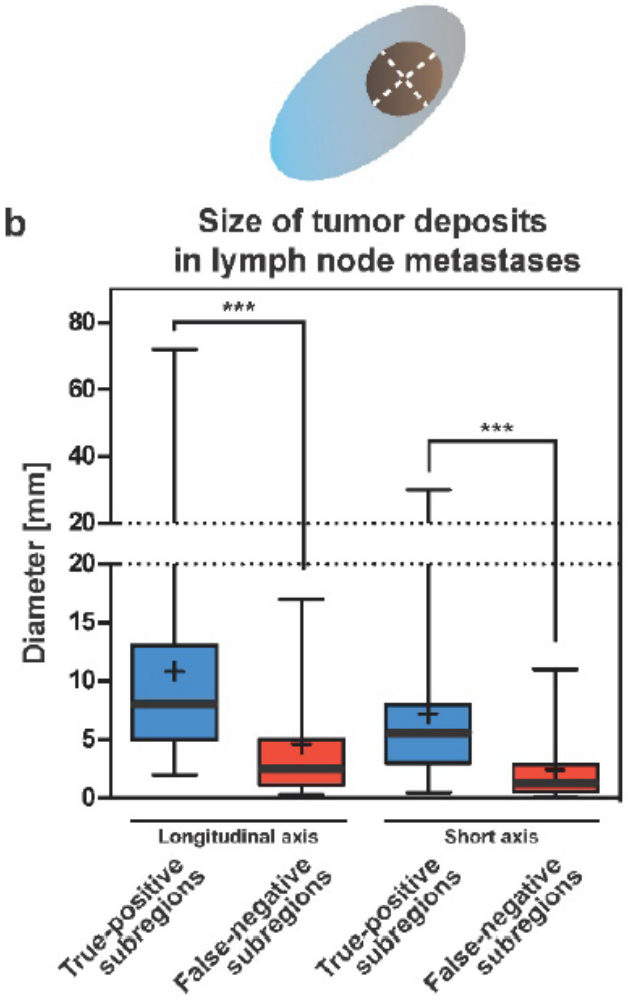
PET imaging Biological Target

SMALLEST LESION PET CAN DETECT

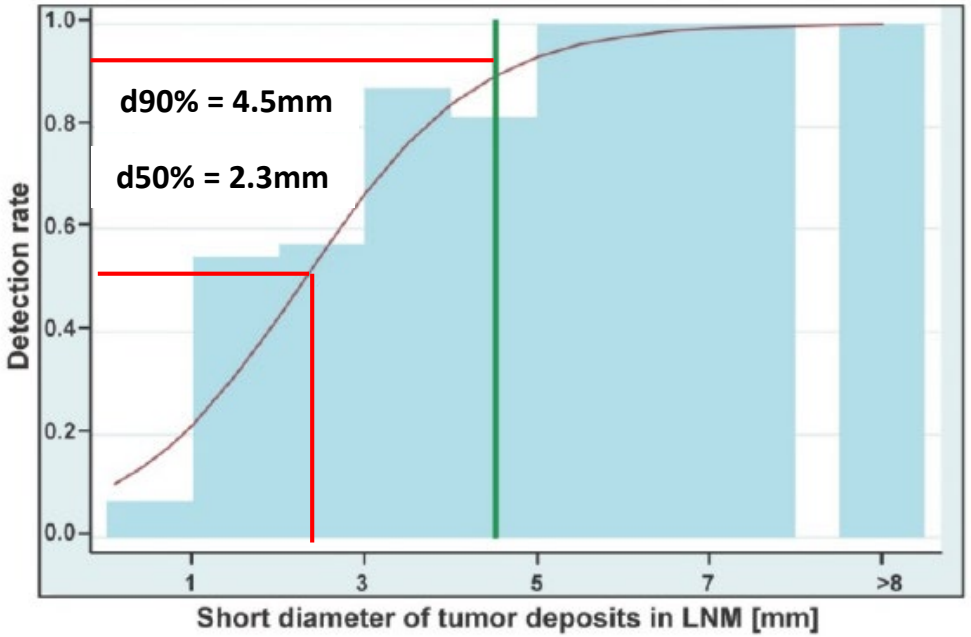


SMALLEST LESION PSMA PET CAN DETECT





MICROMETASTASIS



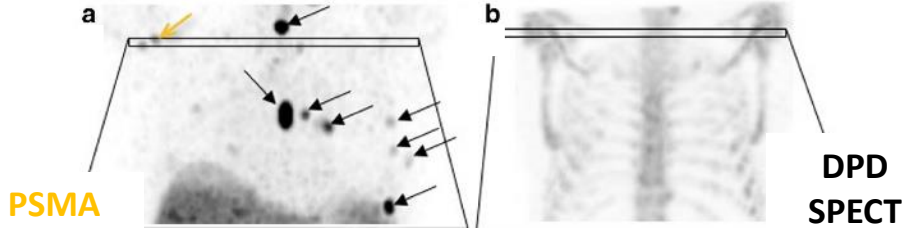
Jilg CA et al. *Theranostics*. 2017

Prostate Cancer **ADVANCED** PET imaging Biological Target

PSMA PET = CURRENT MOST SENSITIVE IMAGING

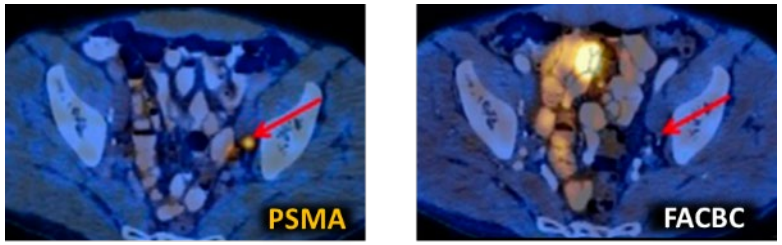
UCLA

➢ PSMA PET superior to Conventional Imaging



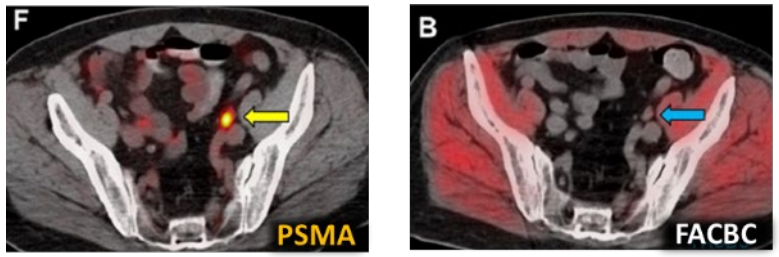
Pyka et al. Eur *J Nucl Med Mol Imaging* 2016
Janssen JC et al *Eur Radiol* 2018
Lengana et al. *Clin Genitourin Cancer* 2018
Esen T, et al.. *Eur Urol Focus* 2019
Zacho et al. *EJNMMI Research* 2020
Hofman M et al *Lancet* 2020
Lenis A et al. *Eur Urol Oncol* 2020

➢ PSMA PET superior to Choline PET



Afshar-Oromieh A, et al. *Eur J Nucl Med Mol Imaging* 2014
Morigi JJ et al. *J Nucl Med*. 2015
Schwenck J, et al. *Eur J Nucl Med Mol Imaging* 2017
Cantiello F, et al. *Clin Genitourin Cancer* 2018
Alonso O, et al. *Eur J Hybrid Imaging* 2018
Treglia G, et al. *Am J Nucl Med Mol Imaging* 2019
Witkowska-Patena E, et al. *Clin Nucl Med*, 2019

➢ PSMA PET superior to Fluciclovine PET



Calais J, et al. *J Nucl Med* 2018
Calais J, et al. *Lancet Oncol* 2019
Tan N et al *Radiology* 2020

PSMA Overexpression >> Upregulated Metabolism

PSMA vs AXUMIN

AXUMIN = Standard-of-Care

FDA approved in **2016**

U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA Approves ^{18}F-Fluciclovine and ^{68}Ga-DOTATATE Products

J Nucl Med. 2016;57:9N.

AXUMIN®
Fluciclovine F 18 Injection

Fluciclovine = FACBC = Standard of Care PET/CT imaging for patients with prostate cancer recurrence

NCCN National Comprehensive Cancer Network®

Category 2A:

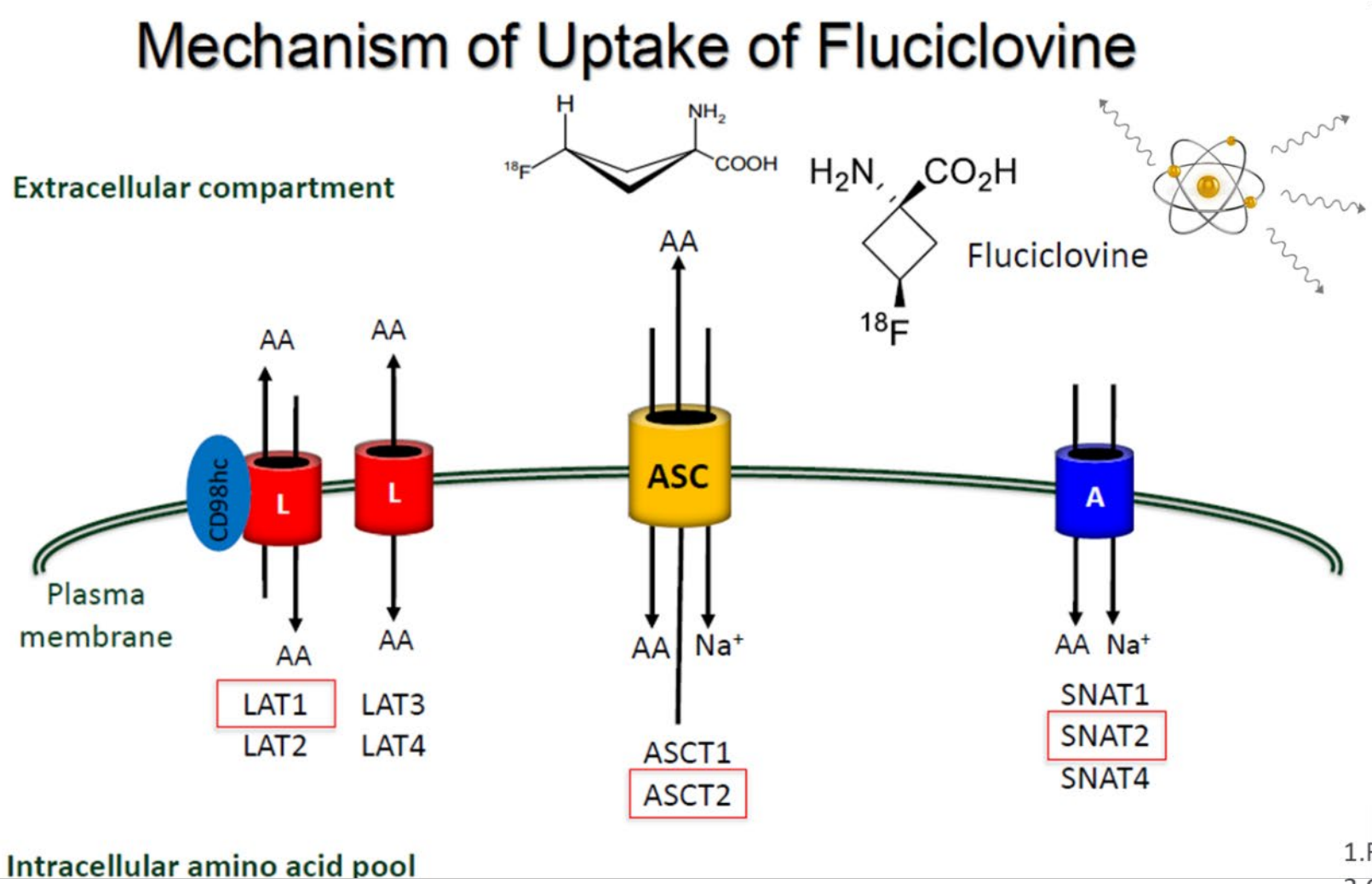
Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

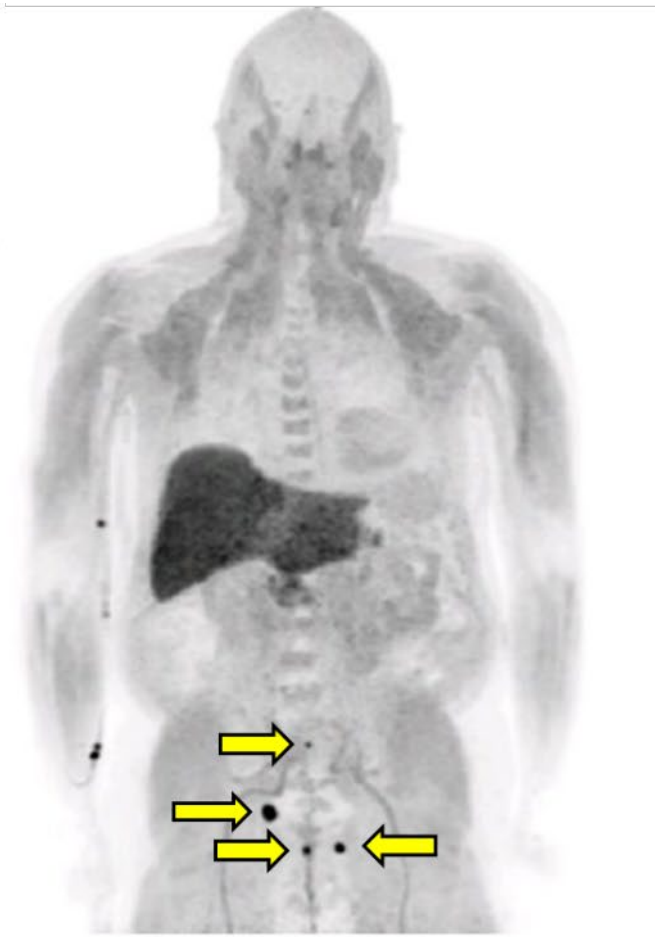
ACR® AMERICAN COLLEGE OF RADIOLOGY

Procedure	Appropriateness Category	Relative Radiation Level
C-11 choline PET/CT skull base to mid-thigh	Usually Appropriate	☢☢☢
MRI pelvis without and with IV contrast	Usually Appropriate	O
F-18 fluciclovine PET/CT skull base to mid-thigh	Usually Appropriate	☢☢☢☢
CT abdomen and pelvis with IV contrast	May Be Appropriate	☢☢☢
MRI-targeted biopsy prostate	May Be Appropriate	O
Tc-99m bone scan whole body	May Be Appropriate	☢☢☢

PSMA vs AXUMIN

AXUMIN = Standard-of-Care





1.Fuchs BC et al. *Sem Cancer Biol.* 2005
2.Okudaira H et al. *Mol Imaging Biol.* 2014

PET imaging Biological Target

PSMA vs AXUMIN - Head-to-head comparison

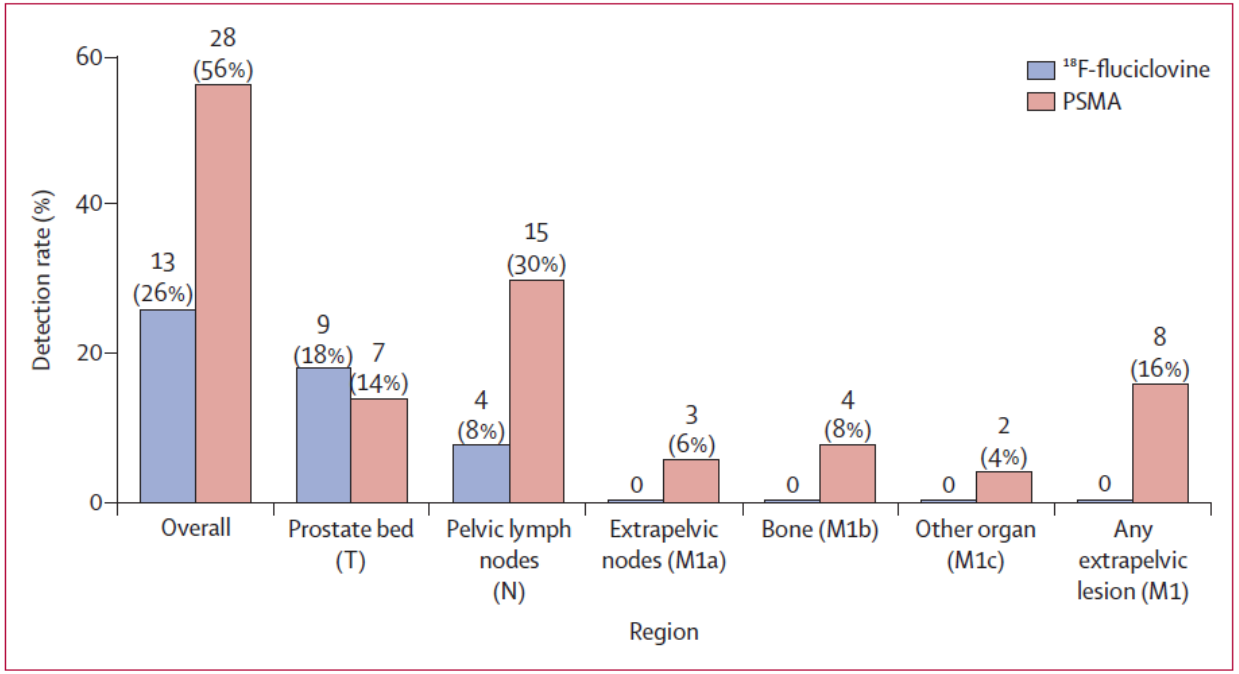


Figure 2: Detection rates per region and per patient (majority consensus reads)
PSMA=prostate-specific membrane antigen.

	PSMA	^{18}F-fluciclovine	p value
Detection at the patient level			
Overall	0·67 (0·51 to 0·83)	0·20 (0·04 to 0·36)	0·0020
Detection at the regional level			
Prostate bed (T)	0·65 (0·49 to 0·81)	0·43 (0·27 to 0·59)	0·046
Pelvic lymph nodes (N)	0·76 (0·60 to 0·92)	0·05 (−0·11 to 0·21)	<0·0001
Extrapelvic nodes (M1a)	0·60 (0·44 to 0·76)	−0·02 (−0·18 to 0·14)	0·0025
Bone (M1b)	0·46 (0·30 to 0·62)	−0·03 (−0·19 to 0·13)	0·0051
Other organ (M1c)	0·65 (0·49 to 0·81)	−0·01 (−0·17 to 0·15)	0·016
Any extrapelvic lesion (M1)	0·60 (0·44 to 0·76)	−0·07 (−0·23 to 0·09)	<0·0001

Data are the multi-rater κ statistic (95% CI). Negative κ statistics signify less observed agreement than that expected by chance. 95% CIs overlapping with zero indicate that the observed agreement was statistically indistinguishable from chance agreement. PSMA=prostate-specific membrane antigen.

Table 2: **Inter-reader measures of agreement**

- **50 early BCR patients**
- **PSA < 2.0 median 0.5**
- **3 expert BICR per scan**

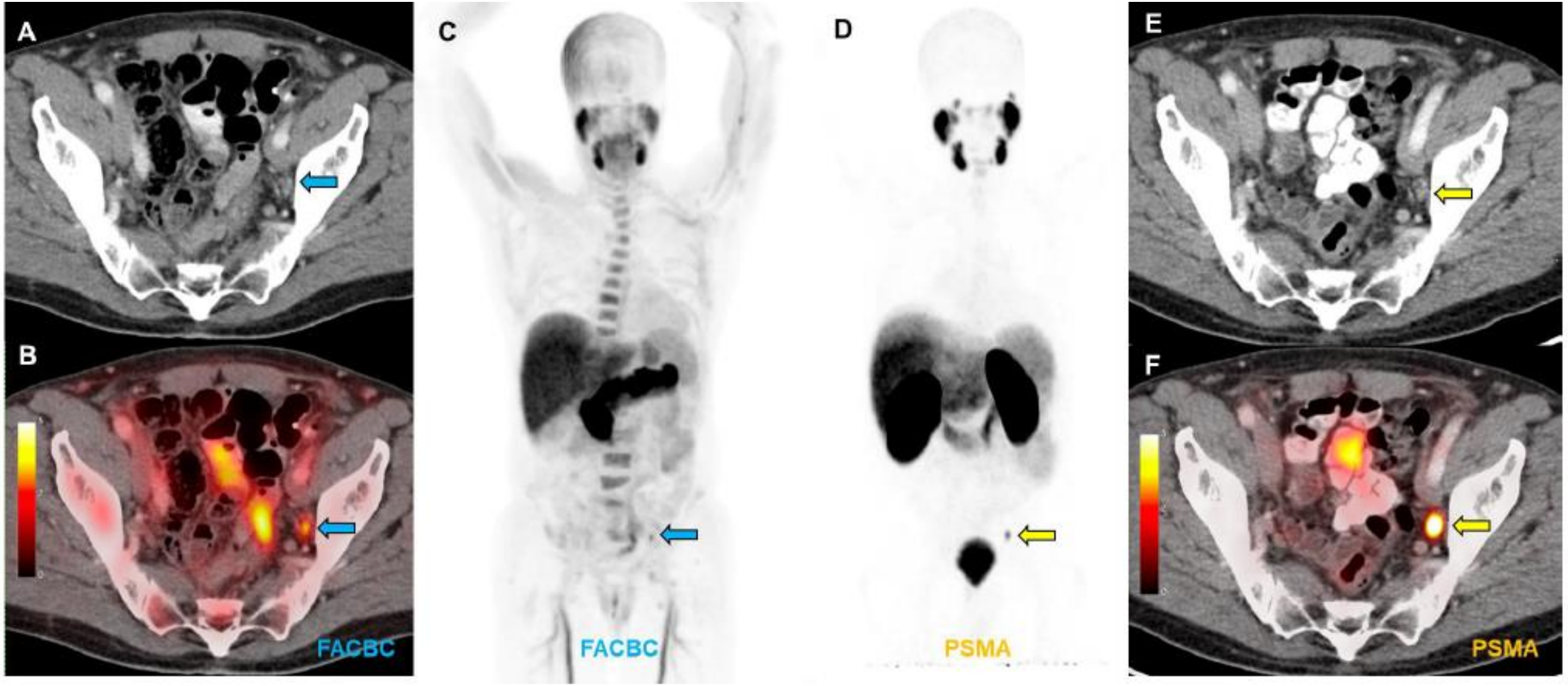
Detection rate = PSMA 56% vs AXUMIN 26%

THE LANCET Oncology

Calais J, et al. Lancet Oncol 2019

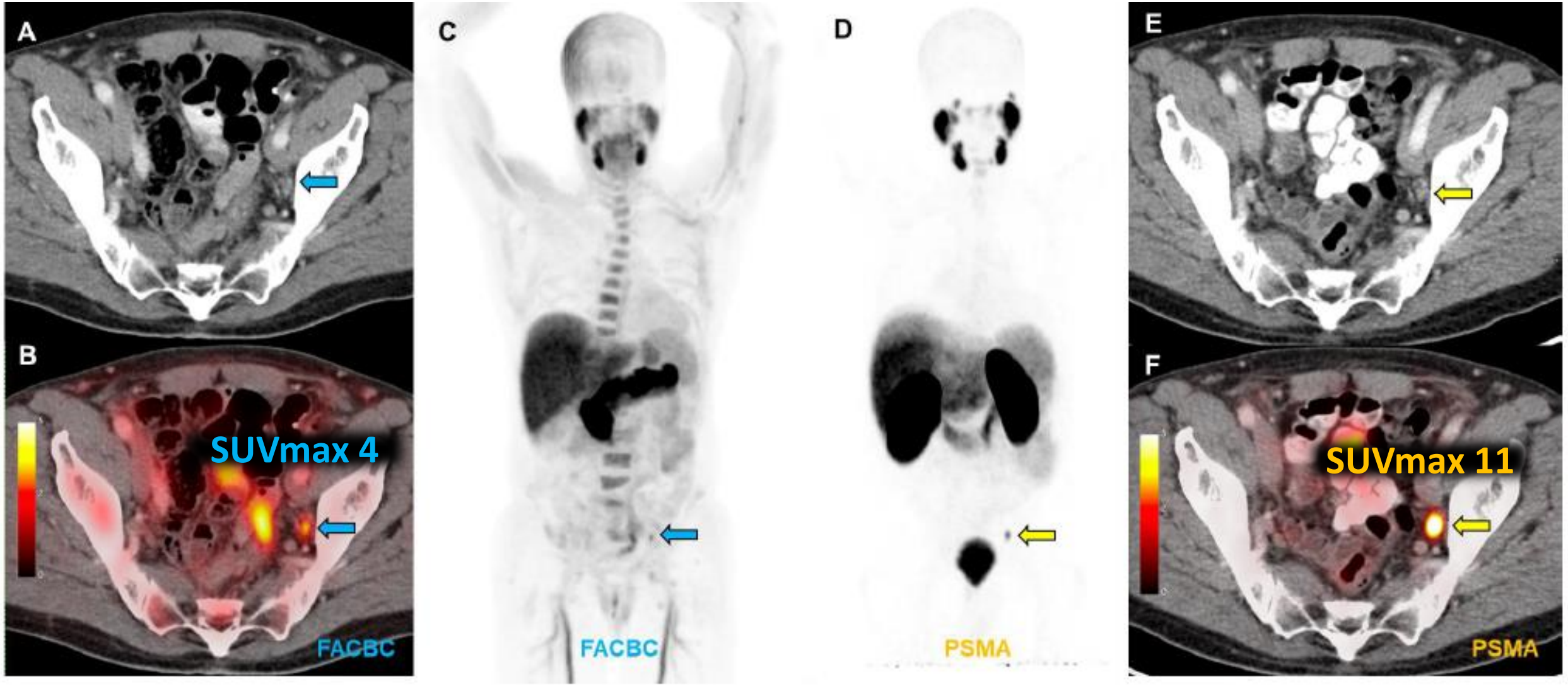
PET imaging Biological Target

PSMA vs AXUMIN – Example 01



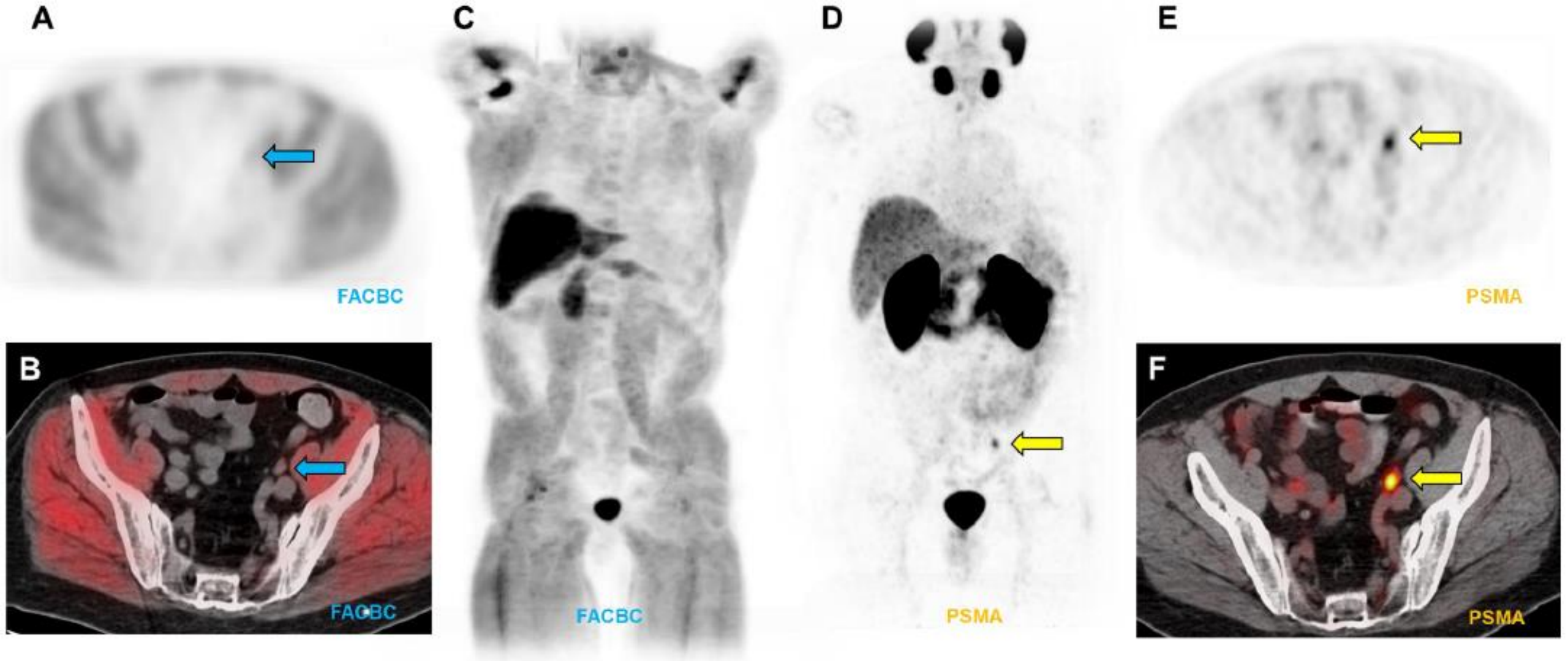
PET imaging Biological Target

PSMA vs AXUMIN – Example 01



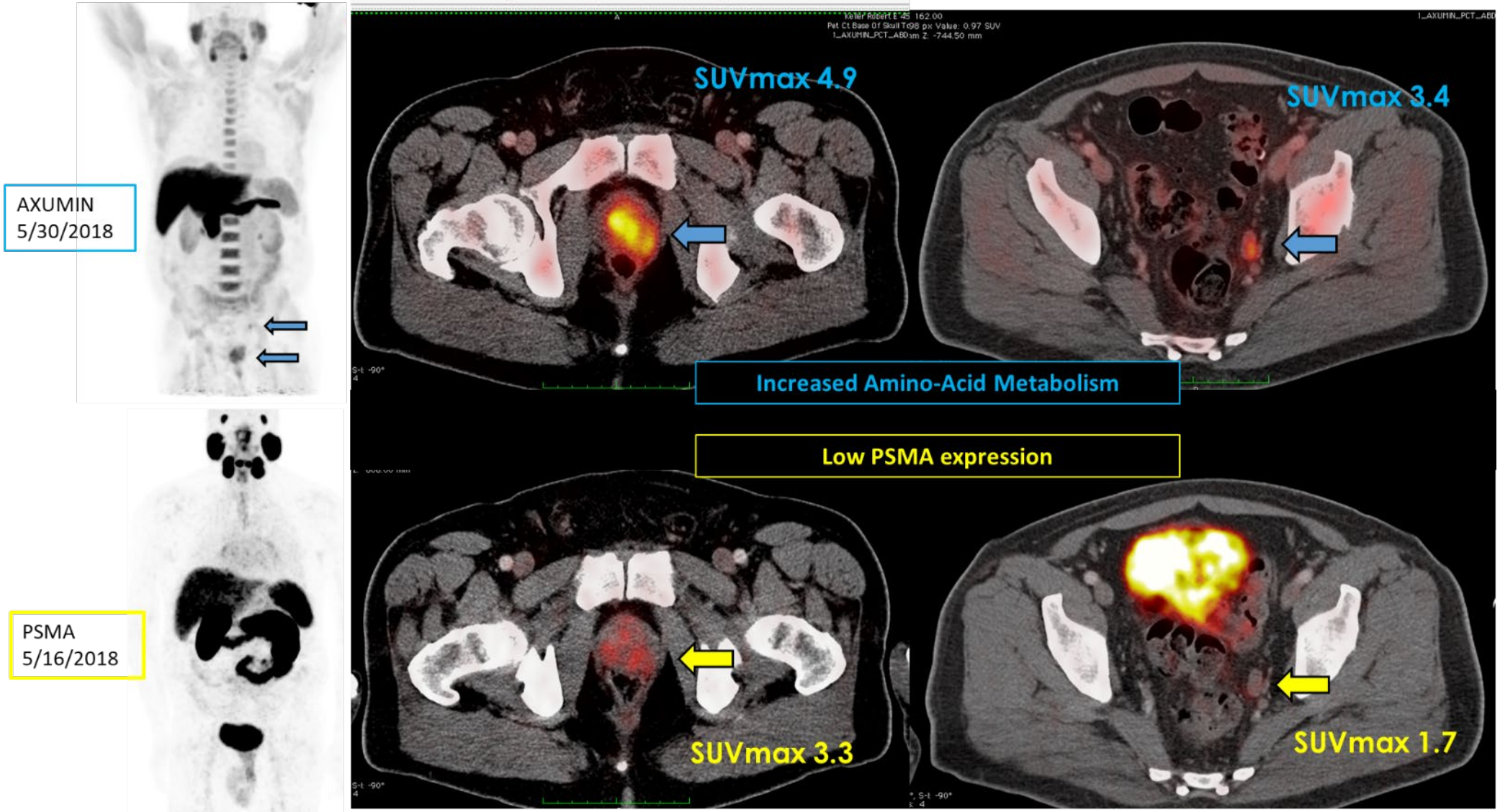
PET imaging Biological Target

PSMA vs AXUMIN – Example 02

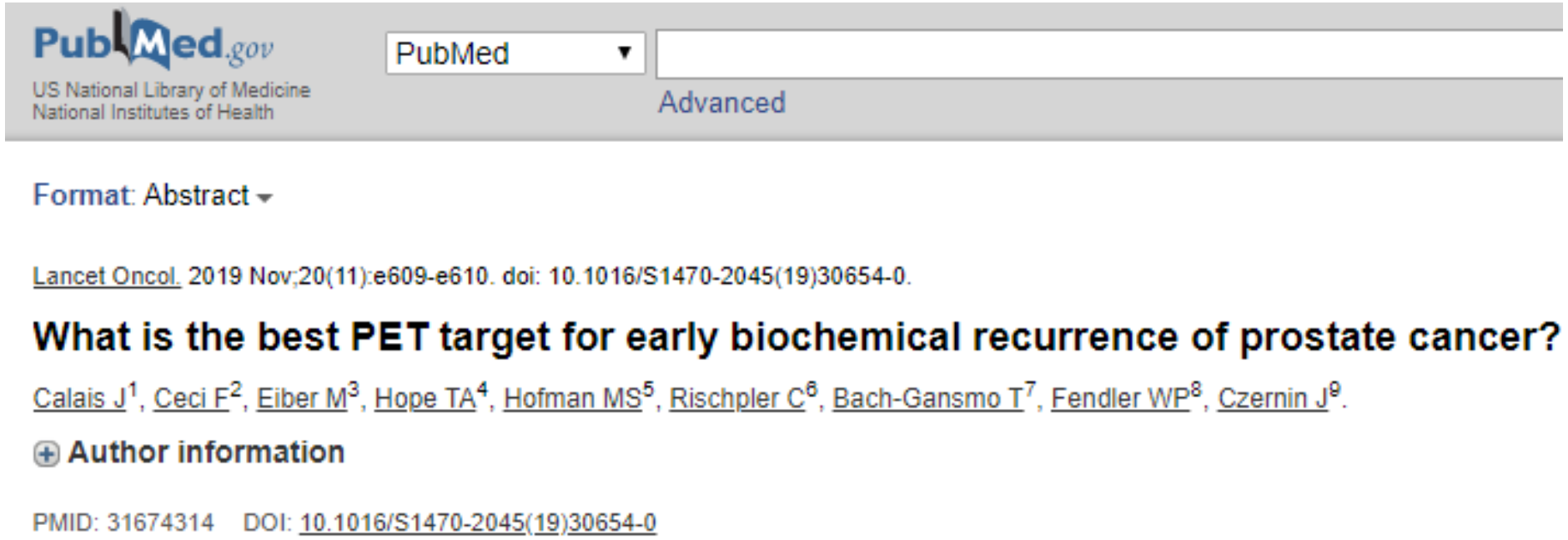


PSMA vs AXUMIN

One Case



PROSTATE CANCER PET IMAGING BIOLOGICAL TARGET



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National Institutes of Health

PubMed ▾ Advanced

Format: Abstract

Lancet Oncol. 2019 Nov;20(11):e609-e610. doi: 10.1016/S1470-2045(19)30654-0.

What is the best PET target for early biochemical recurrence of prostate cancer?

Calais J[1], Ceci F[2], Eiber M[3], Hope TA[4], Hofman MS[5], Rischpler C[6], Bach-Gansmo T[7], Fendler WP[8], Czernin J[9].

⊕ Author information

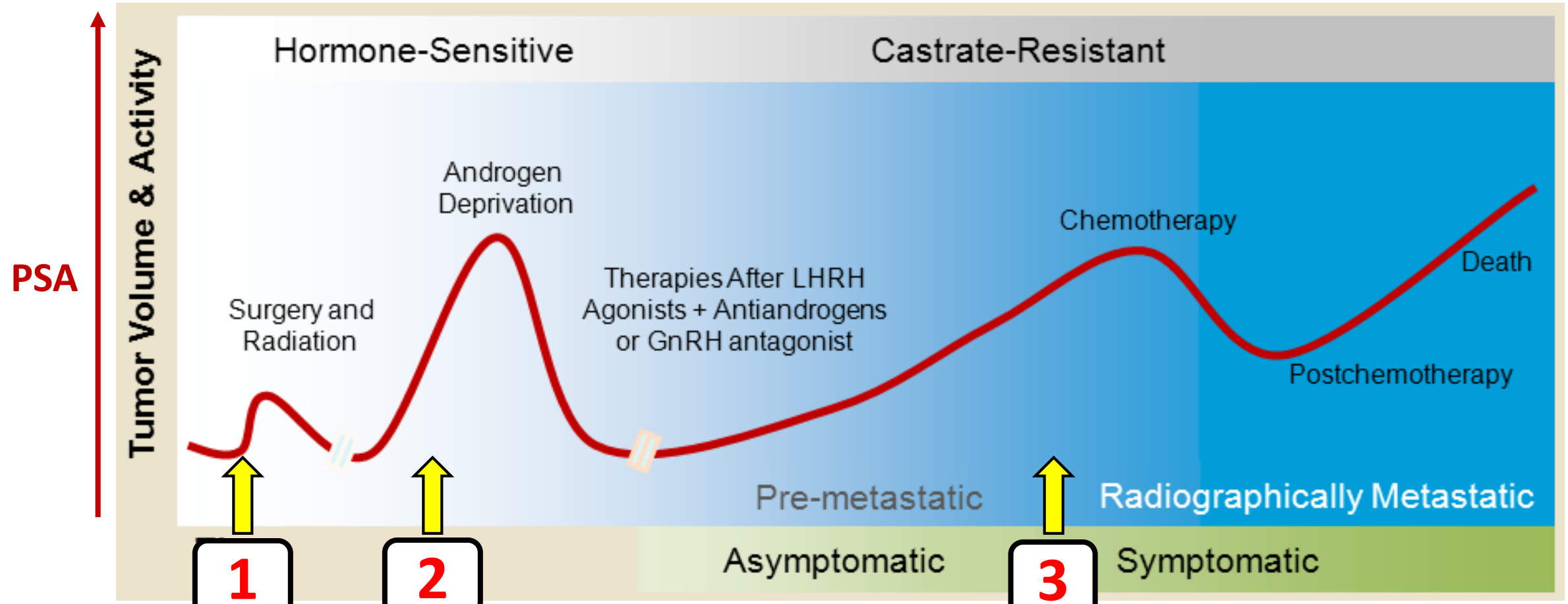
PMID: 31674314 DOI: 10.1016/S1470-2045(19)30654-0

Upregulated Metabolism (GLUT, CK, LAT1, ASCT2)

vs

PSMA Overexpression

Indications



- **Initial Staging (Intact Prostate)**

- **Localization of biochemical recurrence (PSA disease Only – Unknown location)**

- **Re-staging M1 disease**
- **Therapy response Evaluation**
- **RadioNuclide therapy selection**

PSMA PET based new practices

- Disease Stage Redefinition – Migration
- Patient selection – PSMA PET = biomarker

PSMA PET based new practices

- **Disease Stage Redefinition – Migration**
- Patient selection – PSMA PET = biomarker

PSMA PET IN NMCRPC

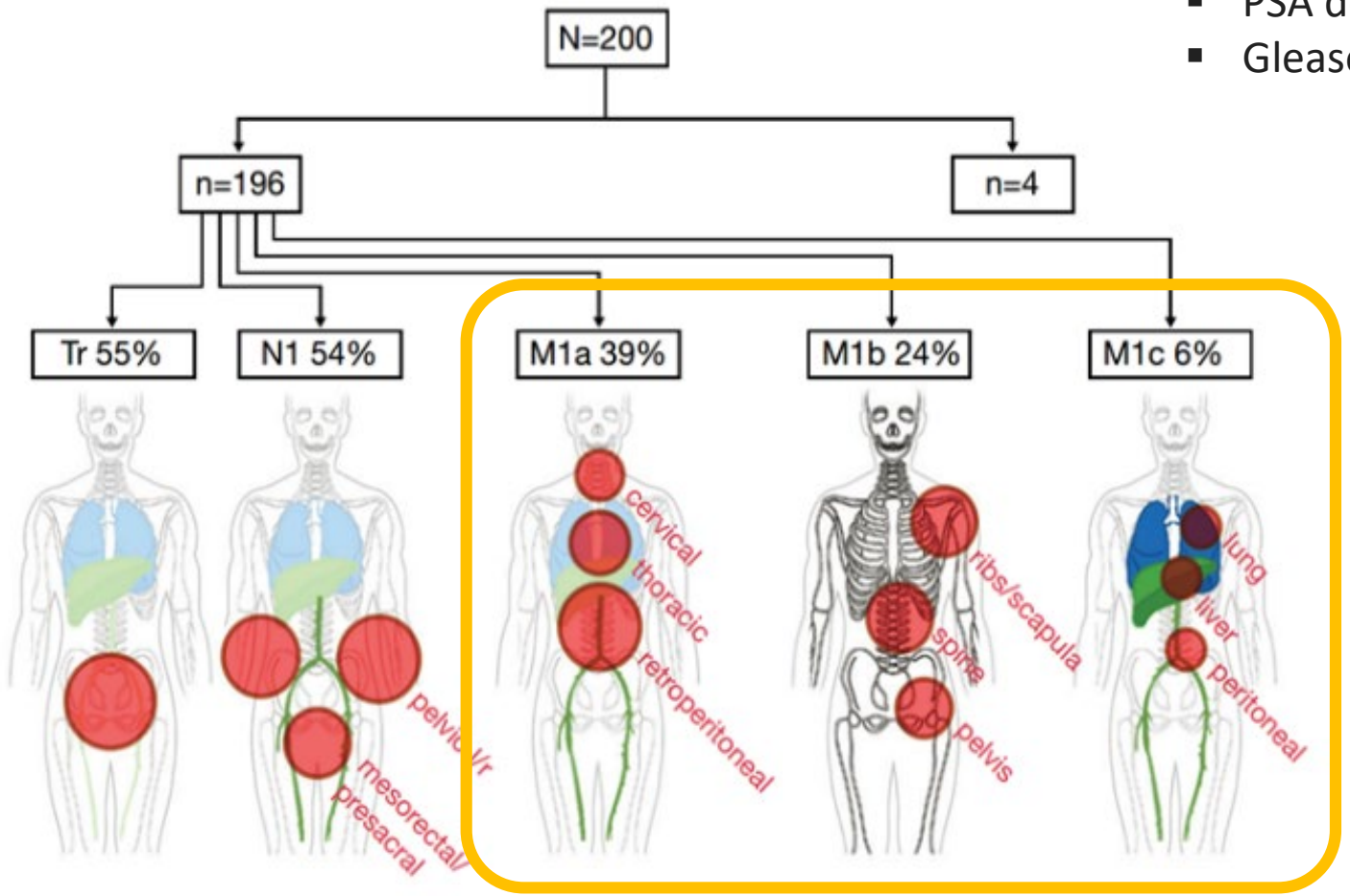
"SPARTAN-like" - "ARAMIS-like" - "PROSPER-like"
High-risk nmCRPC

- PSA >2 ng/mL
- high risk for M1 disease
  - PSA doubling time ≤10 months
  - Gleason score ≥8

PSMA PET STAGE MIGRATION

PSMA PET IN NMCRPC

"SPARTAN-like" - "ARAMIS-like" - "PROSPER-like"
High-risk nmCRPC



- PSA >2 ng/mL
- high risk for M1 disease
  - PSA doubling time ≤10 months
  - Gleason score ≥8

55% M1

- University of Essen
- Peter MacCallum Cancer Centre, Melbourne
- University of California Los Angeles
- Ludwig-Maximilian-University, Munich
- Université de Montréal
- University of California San Francisco
- Harvard Medical School, Boston
- Technical University of Munich
- Janssen Research & Development

AACR American Association for Cancer Research

Fendler et al. *Clin Cancer Res 2019*

PSMA PET STAGE MIGRATION

PSMA PET IN EARLY CRPC

UCLA

Before guidelines definition thresholds

- **PCWG3 (PSA≥ 1.0 ng/mL)**
- **EAU (PSA≥ 2.0 ng/mL)**

- n= 55 patients with
  - rising PSA during continuous ADT
  - PSA <3 ng/mL

- PSMA-PET/CT positive in **41/55 (75%)**
- CT positive in 18/55 (33%)

- Stage migration to PET-M1 disease in **25/55 (45%)**

PSMA-PET/CT findings	Total (n=55)	Pre-PCWG3 PSA: <1.0 ng/mL (n=21)	Early PCWG3 PSA: 1.0-<2.0 ng/mL (n=11)	Early EAU PSA: 2.0-≤3.0 ng/mL (n=23)
Negative	**14 (25)**	**10 (48)**	**0 (0)**	**4 (17)**
Tr/N1 only	**16 (29)**	**6 (29)**	**3 (27)**	**7 (30)**
Local recurrence (Tr)	9 (16)	3 (14)	1 (9)	5 (22)
Pelvic lymph nodes (N1)	9 (16)	3 (14)	2 (18)	4 (17)
Any M1	**25 (45)**	**5 (24)**	**8 (73)**	**12 (52)**
Extrapelvic lymph nodes (M1a)	15 (27)	3 (14)	3 (27)	9 (39)
Bone (M1b)	13 (24)	3 (14)	4 (36)	6 (26)
Soft tissue/ visceral (M1c)	2 (4)	0 (0)	2 (18)	0 (0)
N/M disease extent	**n=34**	**n=8**	**n=10**	**n=16**
Unifocal (1)	6 (18)	2 (25)	1 (10)	3 (19)
Oligometastatic (2-5)	17 (50)	4 (50)	9 (90)	4 (25)
Multiple/ disseminated (≥6)	11 (32)	2 (25)	0 (0)	9 (56)

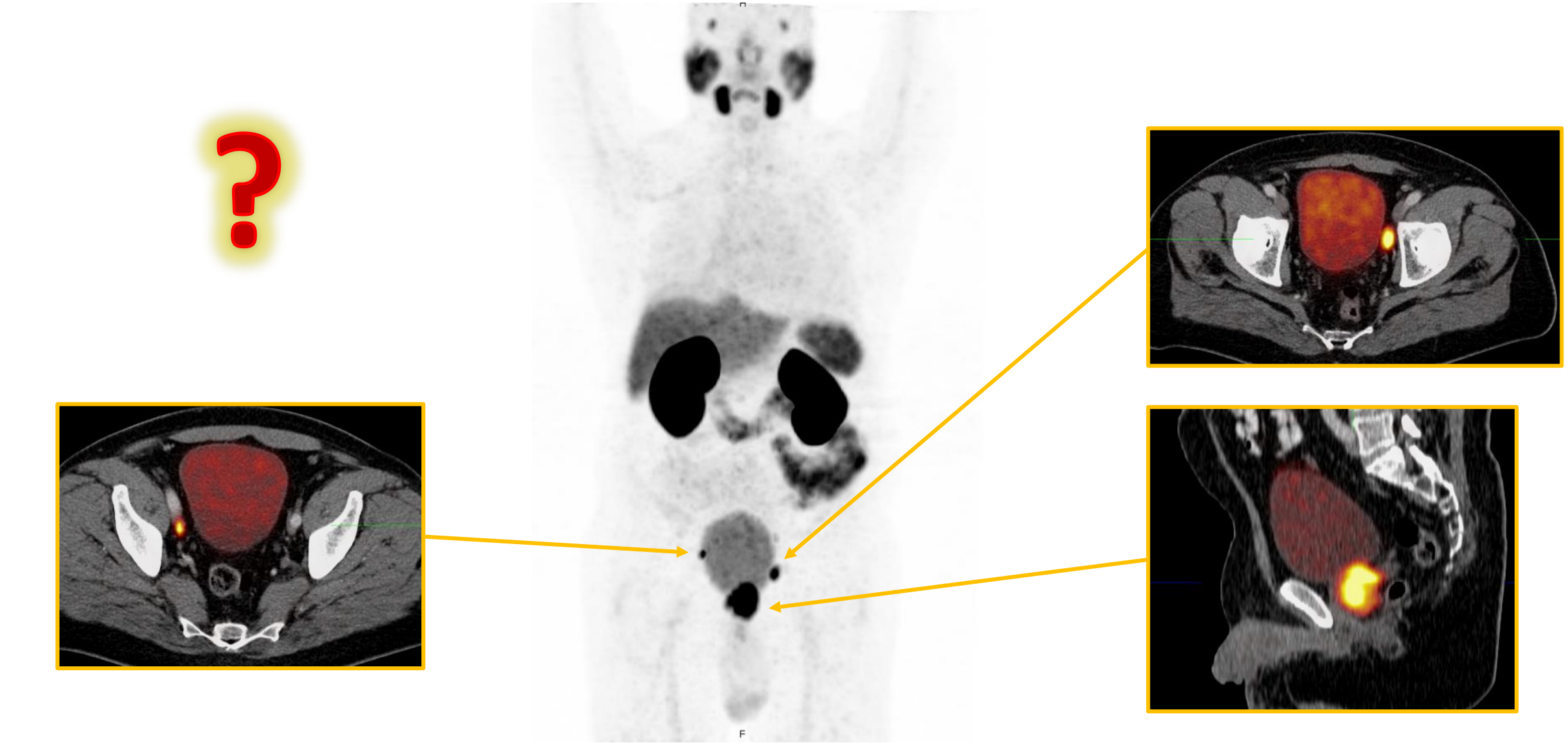
JNM | THE JOURNAL OF NUCLEAR MEDICINE

Weber et al. *J Nucl Med* 2020

PSMA PET based new practices

- Disease Stage Redefinition – Migration
- **Patient selection – PSMA PET staging = biomarker**

WHAT TO DO WITH PSMA PET N1 DISEASE ?



PSMA = Nuclear Theranostics Target for Prostate Cancer

How to integrate PSMA PET to the practice for better outcome ?

UCLA

- PSMA PET diagnostic performances well established:

  ➡ **THE BEST BUT STILL NOT PERFECT (Micrometastasis +++)**

- New redefinition of disease stage
  - ex: M0 conventional = PSMA M1 ?
  - ex: M0 conventional ≠ PSMA M0 ?

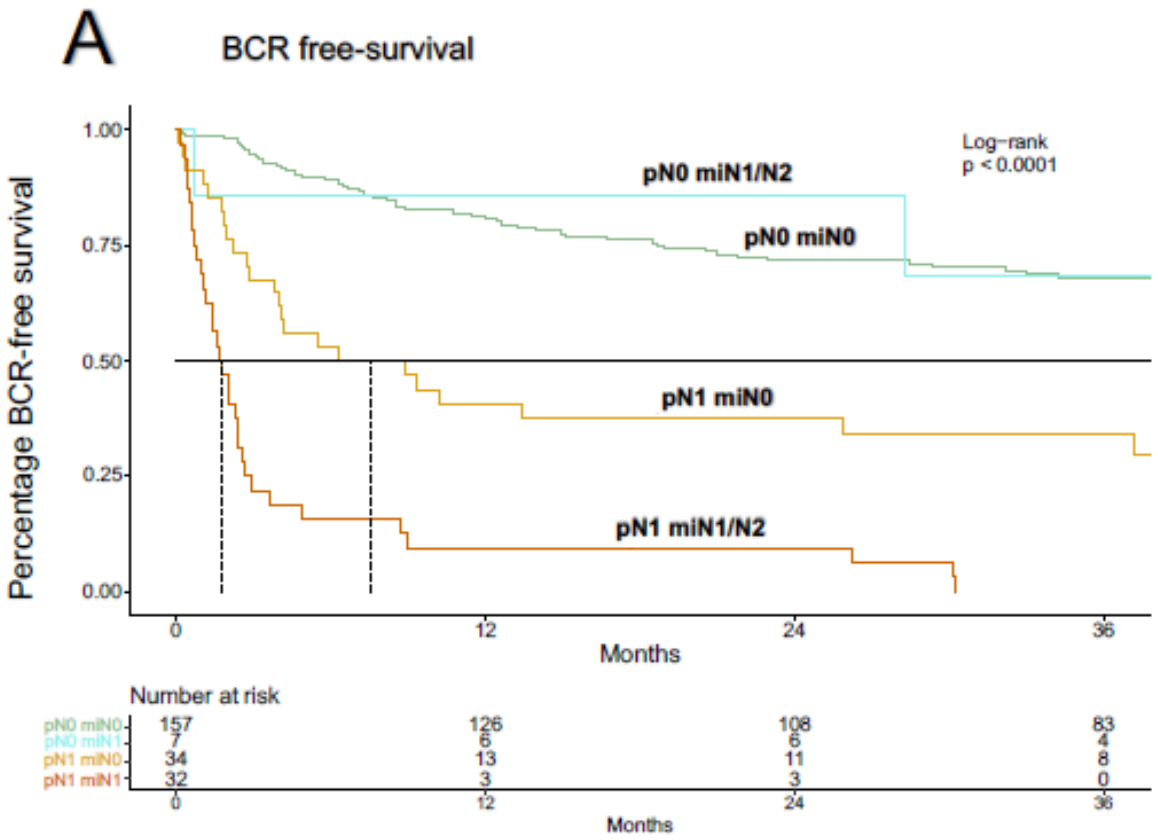
  - ex: **PSMA N0** = **Micro N0** vs **Micro N1** ?
  - ex: **PSMA N1** = **Micro N1 M0** vs **Micro N1 M1** ?

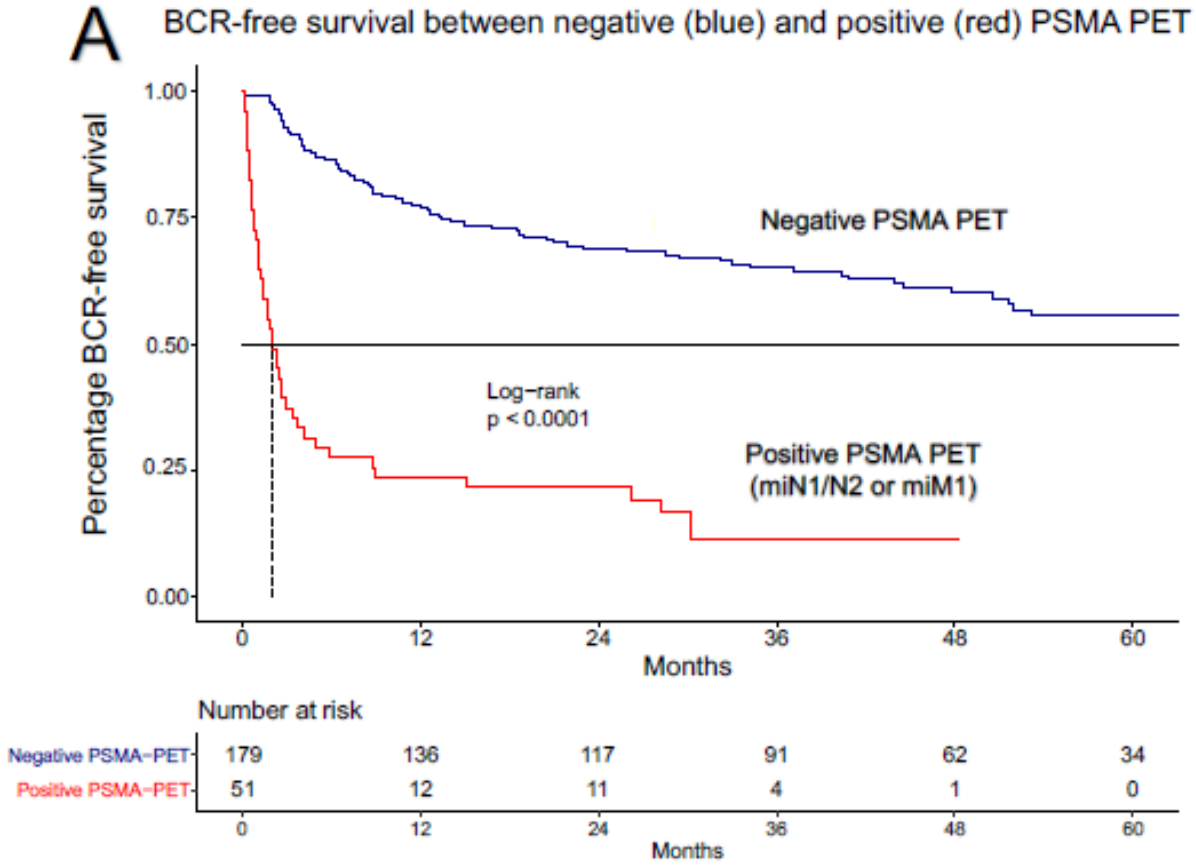
Fendler WP, et al. Clin Cancer Res. 2019
W Weber J Nucl Med 2020

- Significance on appropriate management
  - **PSMA N0** = surveillance vs. pelvic LN treatment (surgery or RT) ?
  - **PSMA N1** = not surgical candidate ? (too late)
  - **PSMA N1** = RT boost ? extend RT field coverage ?
  - **PSMA N1** = systemic therapy ?

PSMA PET imaging for **Primary Staging**

PSMA PET N0 PREDICTIVE OF RP OUTCOME

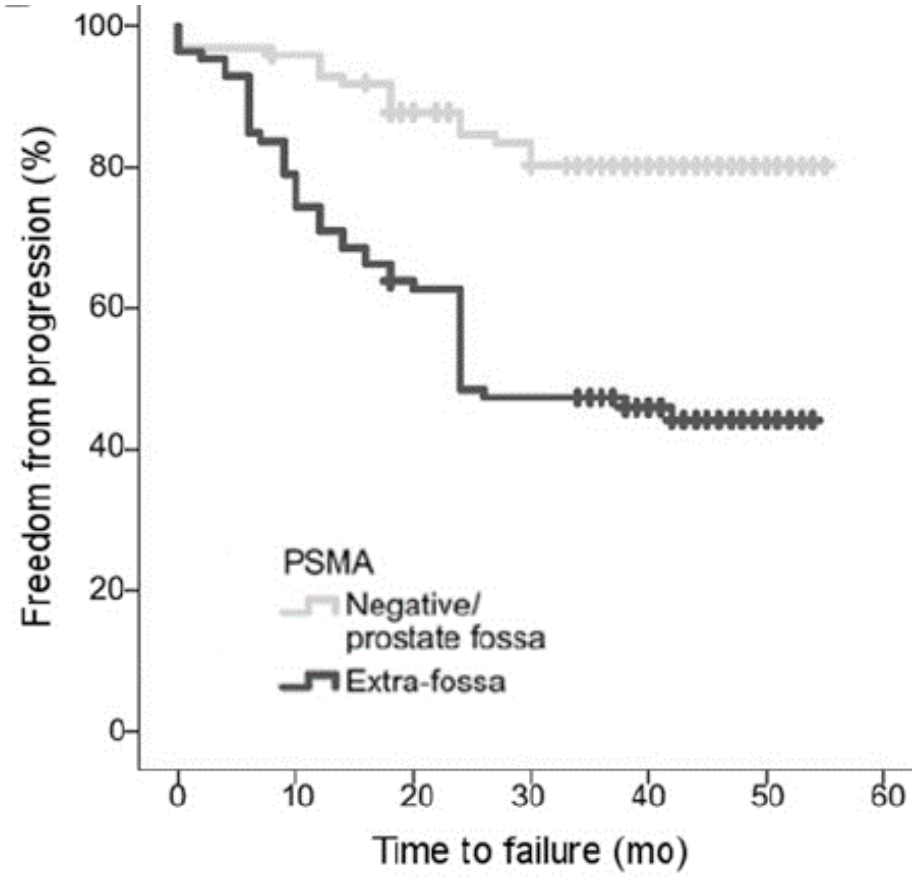




n= 230

T Amiel et al. J Urol 2021

PSMA PET N0 PREDICTIVE OF SRT OUTCOME



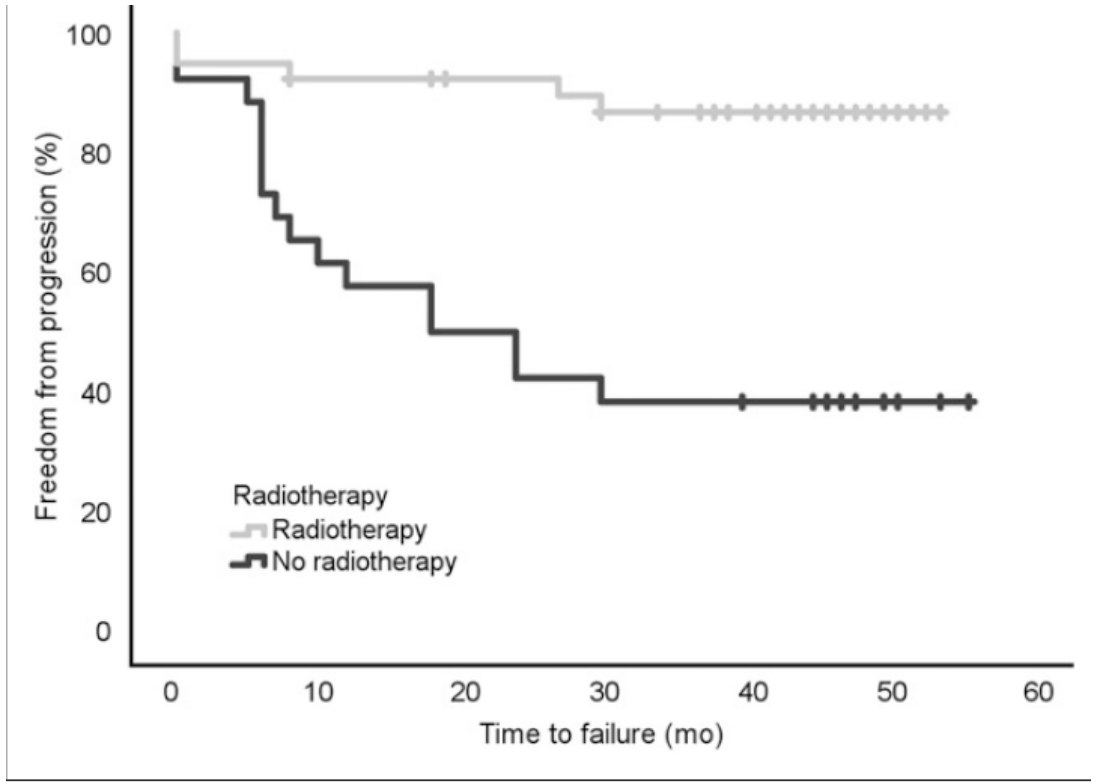


FIGURE 3. FFP in men with negative scan results who underwent sRT vs. men who were observed over 3 y ($P < 0.0001$).

n= 260

Emmett et al. *J Nucl Med* 2020

IMPACT on RT Planning – PSMA PET biomarker for patient selection

UCLA

PSMA PET/CT can show

Disease outside of the standard radiation fields

- *Salvage RT:*

Major impact in **19%** of patients with Early Recurrence after surgery (PSA <1.0)

- *Definitive RT:*

Major impact in **17%** of patients with intermediate to high-risk disease

J.Calais et al. *J Nucl Med* 2018

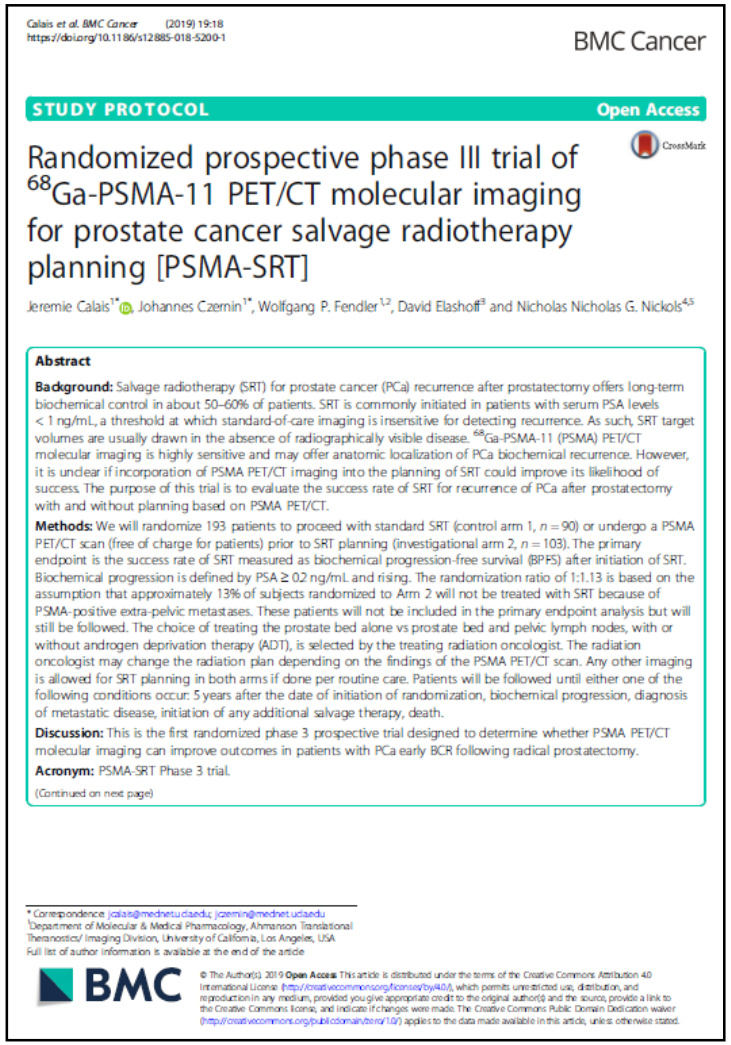
Best Paper of the Year 2018

Salvage RT

Definitive RT

PSMA-SRT Phase 3 Trial - NCT03582774

STUDY DESIGN



Calais et al. BMC Cancer (2019) 19:18
https://doi.org/10.1186/s12885-018-5200-1

BMC Cancer

STUDY PROTOCOL Open Access

Randomized prospective phase III trial of ^{68}Ga-PSMA-11 PET/CT molecular imaging for prostate cancer salvage radiotherapy planning [PSMA-SRT]

Jeremie Calais[1*], Johannes Czernin[1*], Wolfgang P. Fendler[1,2], David Elashoff[3] and Nicholas Nicholas G. Nickols[4,5]

Abstract

Background: Salvage radiotherapy (SRT) for prostate cancer (PCa) recurrence after prostatectomy offers long-term biochemical control in about 50–60% of patients. SRT is commonly initiated in patients with serum PSA levels < 1 ng/mL, a threshold at which standard-of-care imaging is insensitive for detecting recurrence. As such, SRT target volumes are usually drawn in the absence of radiographically visible disease. ^{68}Ga-PSMA-11 (PSMA) PET/CT molecular imaging is highly sensitive and may offer anatomic localization of PCa biochemical recurrence. However, it is unclear if incorporation of PSMA PET/CT imaging into the planning of SRT could improve its likelihood of success. The purpose of this trial is to evaluate the success rate of SRT for recurrence of PCa after prostatectomy with and without planning based on PSMA PET/CT.

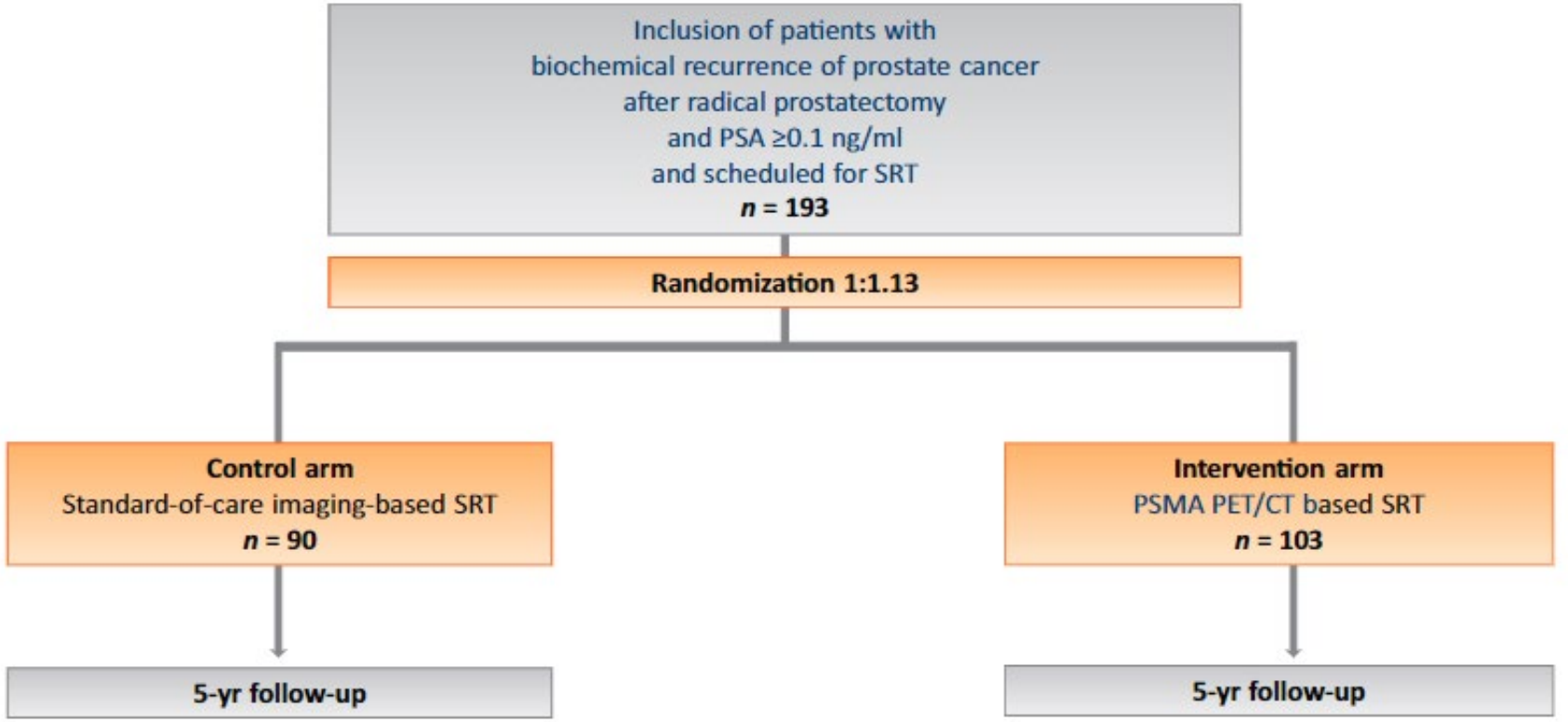
Methods: We will randomize 193 patients to proceed with standard SRT (control arm 1, $n = 90$) or undergo a PSMA PET/CT scan (free of charge for patients) prior to SRT planning (investigational arm 2, $n = 103$). The primary endpoint is the success rate of SRT measured as biochemical progression-free survival (BPFS) after initiation of SRT. Biochemical progression is defined by PSA ≥ 0.2 ng/mL and rising. The randomization ratio of 1:1.13 is based on the assumption that approximately 13% of subjects randomized to Arm 2 will not be treated with SRT because of PSMA-positive extra-pelvic metastases. These patients will not be included in the primary endpoint analysis but will still be followed. The choice of treating the prostate bed alone vs prostate bed and pelvic lymph nodes, with or without androgen deprivation therapy (ADT), is selected by the treating radiation oncologist. The radiation oncologist may change the radiation plan depending on the findings of the PSMA PET/CT scan. Any other imaging is allowed for SRT planning in both arms if done per routine care. Patients will be followed until either one of the following conditions occur: 5 years after the date of initiation of randomization, biochemical progression, diagnosis of metastatic disease, initiation of any additional salvage therapy, death.

Discussion: This is the first randomized phase 3 prospective trial designed to determine whether PSMA PET/CT molecular imaging can improve outcomes in patients with PCa early BCR following radical prostatectomy.

Acronym: PSMA-SRT Phase 3 trial.

(Continued on next page)

* Correspondence: jcalais@mednet.ucla.edu; jczernin@mednet.ucla.edu
[1]Department of Molecular & Medical Pharmacology, Ahmanson Translational Theranostics/ Imaging Division, University of California, Los Angeles, USA
Full list of author information is available at the end of the article



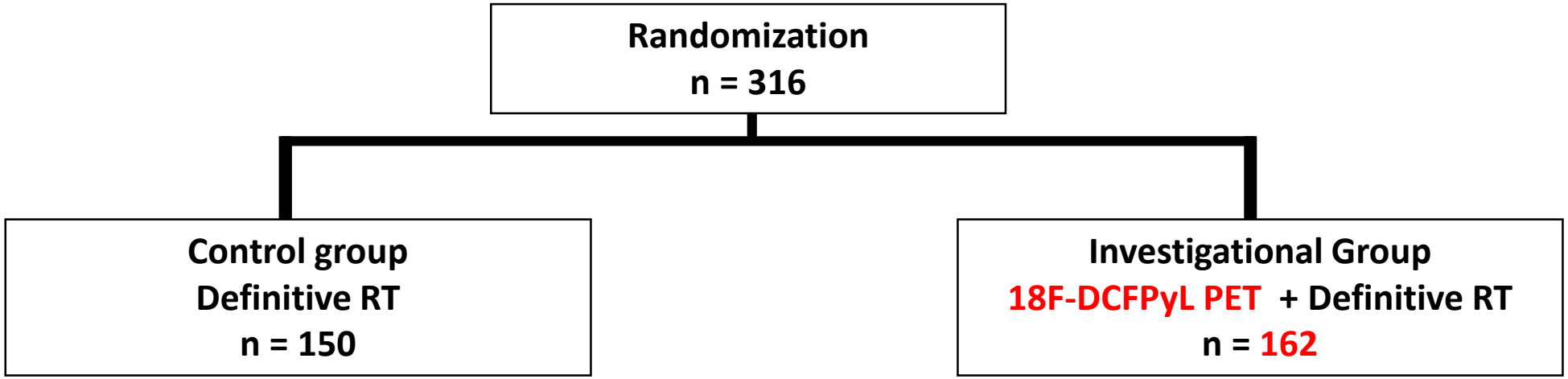
Enrollment Complete

Calais J et al. *BMC cancer* 2019
Calais J et al *Eur Urol Focus* 2020

18F-DCFPyL PET guided definitive radiotherapy

Phase 3 randomized trial of PSMA PyL PET definitive RT [PSMA DRT]

Patient candidate for primary definitive RT



Progenics Pharmaceuticals

Lantheus Medical Imaging

STUDY OPEN

IRB#20-000378
NCT04457245
Investigator Initiated IND #147,591
Cross-reference Industry IND 129,952

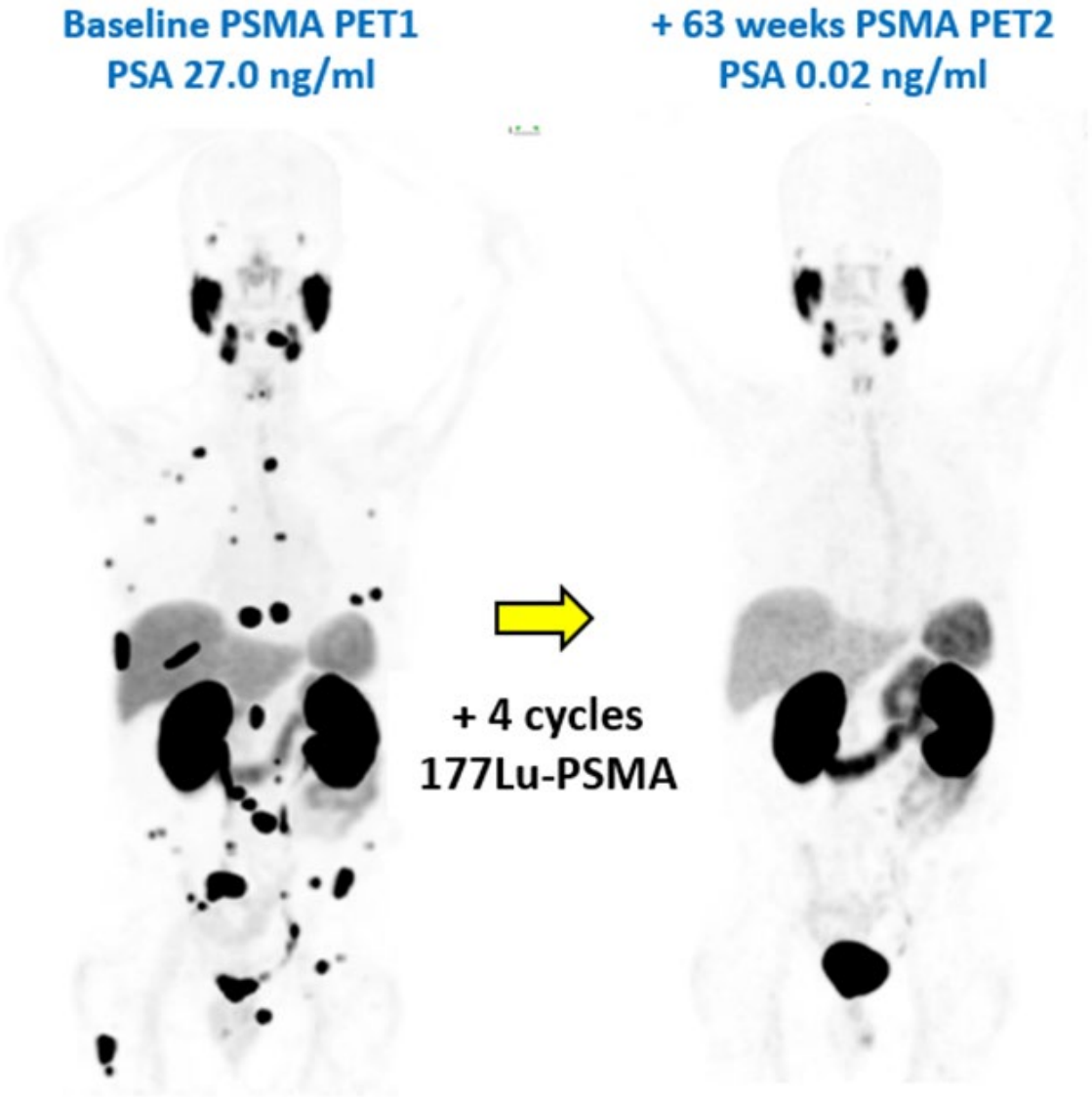
Calais J et al. *BMC cancer* 2021

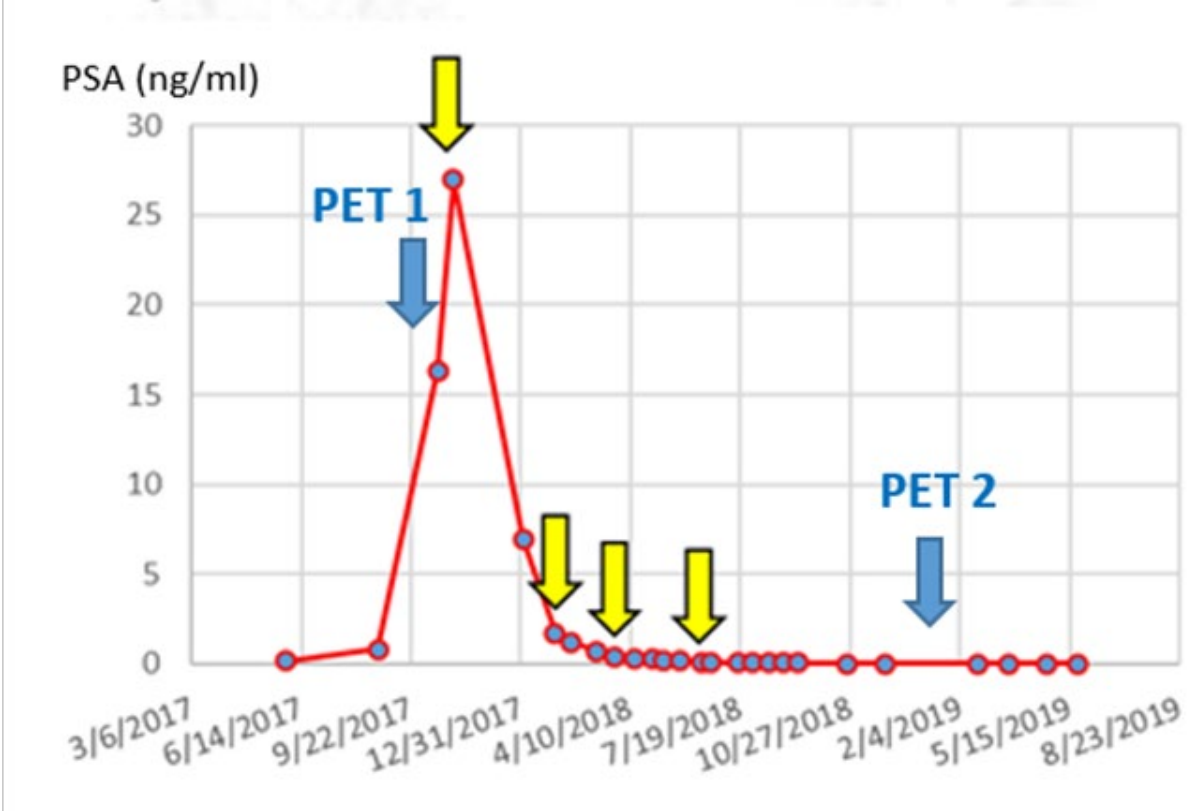
PSMA PET based new practices

- Disease Stage Redefinition – Migration
- **Patient selection – PSMA expression by PET = biomarker**

PSMA THERANOSTICS

^{177}Lu-PSMA-617 Radionuclide Therapy



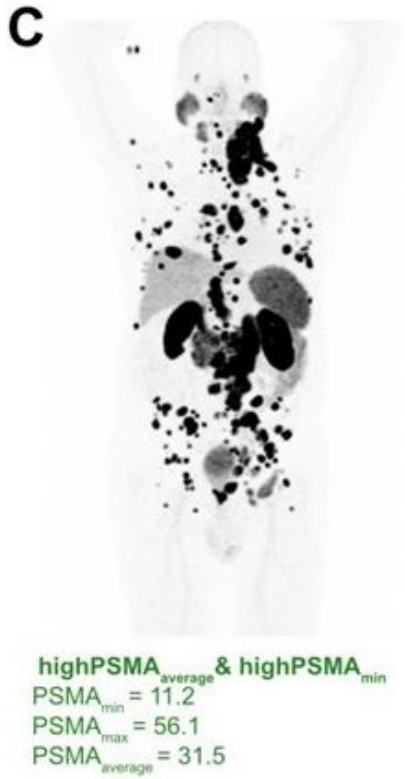


PSMA THERANOSTICS

RESPONSE TO ^{177}Lu-PSMA-617 Radionuclide Therapy

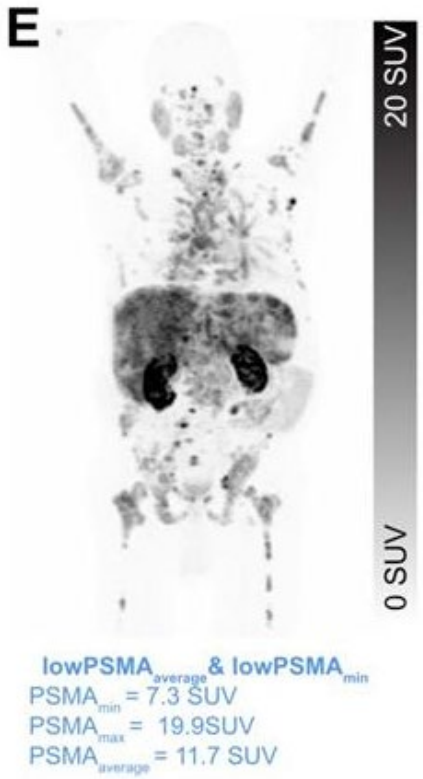
Retrospective
N= 85 pts

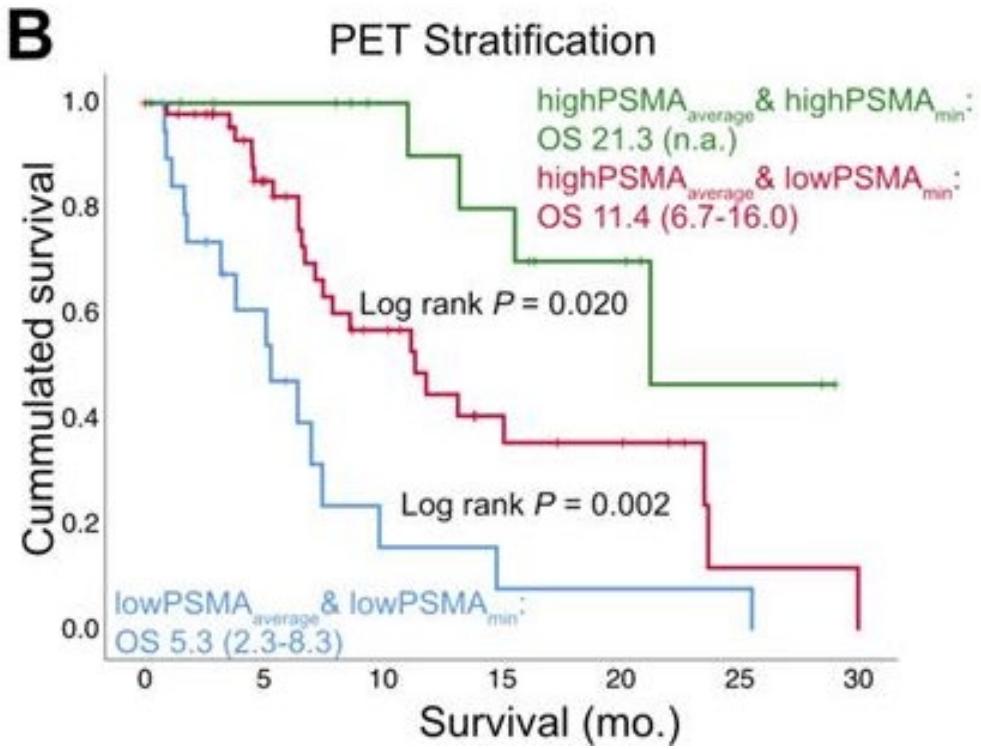
High and homogeneous



High and Heterogeneous

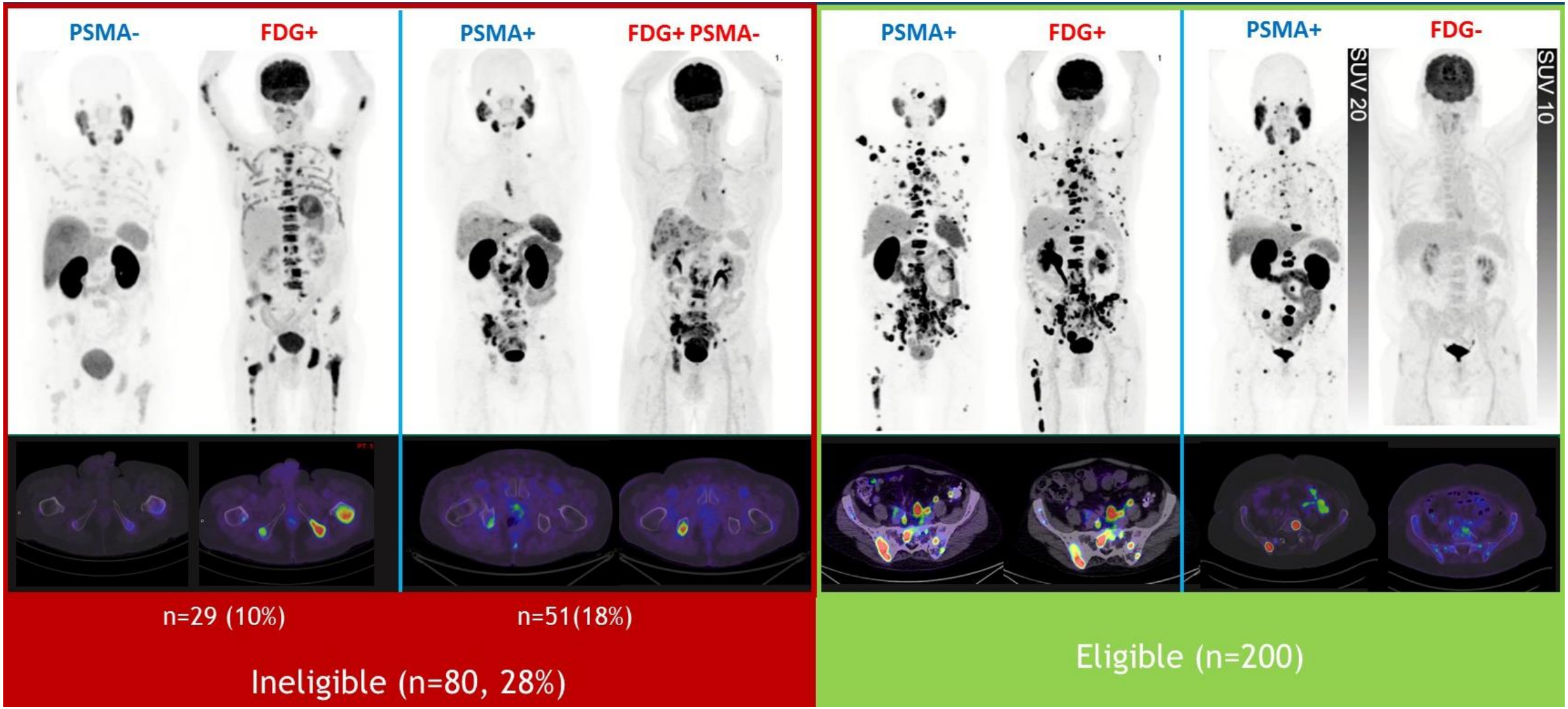
Low and homogeneous





Seifert et al; Theranostics 2020

Combined PSMA and FDG PET for patient selection



Hofman M et al. *ASCO* 2020

PERSPECTIVES

- Reimbursement
- Availability - multiple players
- Integration into clinical guidelines
- Integration into clinical trials
  - Biomarker
  - Patient selection/stratification
  - Therapy response assessment
- Artificial intelligence – automatic software

USEFUL LINKS

- **FDA Label**

UCSF NDA https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212643Orig1s000TOC.cfm

UCLA NDA https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212642Orig1s000TOC.cfm

- **^{68}Ga-PSMA-11 NDA Approval: A Novel and Successful Academic Partnership"**
  Part I: ^{68}Ga-PSMA-11 development and regulatory approval process https://doi.org/10.2967/jnumed.120.260455
  Part II: Key CMC Information for 68Ga-PSMA-11 https://doi.org/10.2967/jnumed.120.260455

- **Oliver Sartor Talks with Thomas A. Hope, Jeremie Calais, and Wolfgang P. Fendler About FDA Approval of PSMA**
  https://jnm.snmjournals.org/content/62/2/146
- https://www.snmmi.org/Research/Content.aspx?ItemNumber=35274
- "Guidance for Industry: ANDA Submissions-Content and format" (June 2019, https://www.fda.gov/media/128127/download)
- "PET Drug Applications – Content and Format for NDAs and ANDAs" (August 2011, https://www.fda.gov/media/72271/download)
- "Referencing Approved Drug Products in ANDA Submissions" (October 2020, https://www.fda.gov/media/102360/download)

UCLA Ahmanson Translational Theranostics Division Research Program

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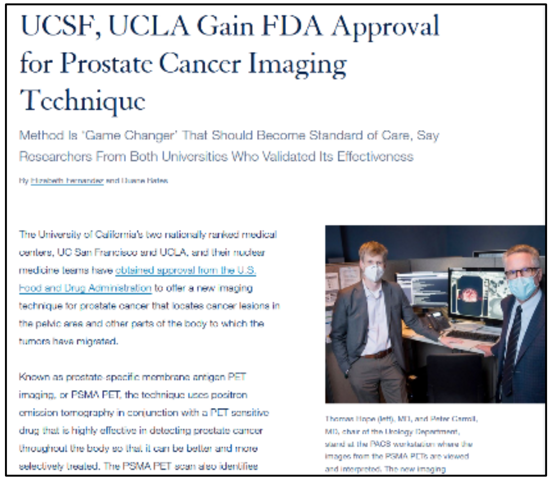
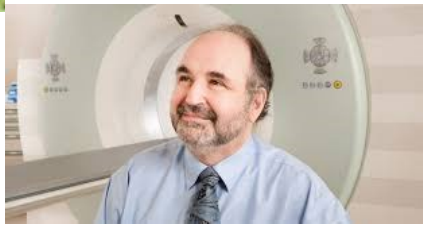
TRANSLATIONAL PROSTATE CANCER RESEARCH PROGRAM





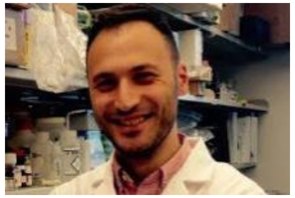



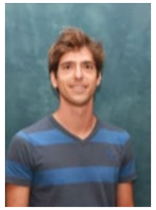






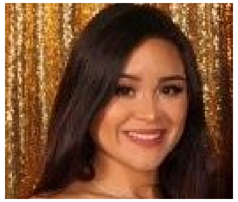
















PINTAD
The Pharma Imaging Network for Therapeutics and Diagnostics

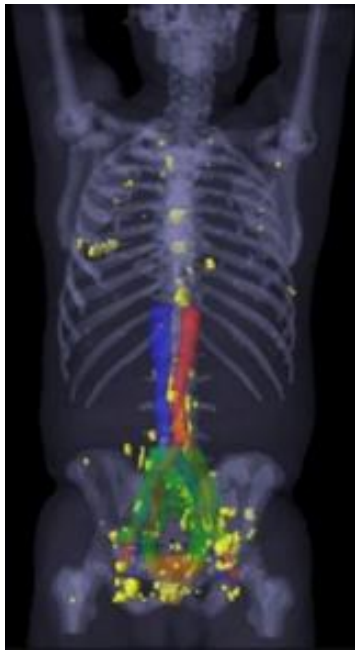
UCLA

THE FDA APPROVAL OF 68GA-PSMA-11 PET: AN ACADEMIC COLLABORATIVE JOURNEY

Jeremie Calais MD MSc
Assistant Professor, Nuclear Medicine and Theranostics
Director, Clinical Research Program

UCLA Health

PINTAD MEETING
01 - 28 - 2021



BACK-UP