SOFIE
From start to clinic

# Current State of FAP Targeting Radioligands

## SOFIE Educational Webinar Series

May 30th, 2024

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# Learning Objectives

1. Understand the significance of FAP as a target for imaging and therapy
2. Highlight latest progress in FAP targeting for therapeutic use
3. Explain advancements made with FAP targeting radioligands in imaging
4. Describe the clinical development and regulatory approval progress with FAP targeting radioligands

# FAP as a target

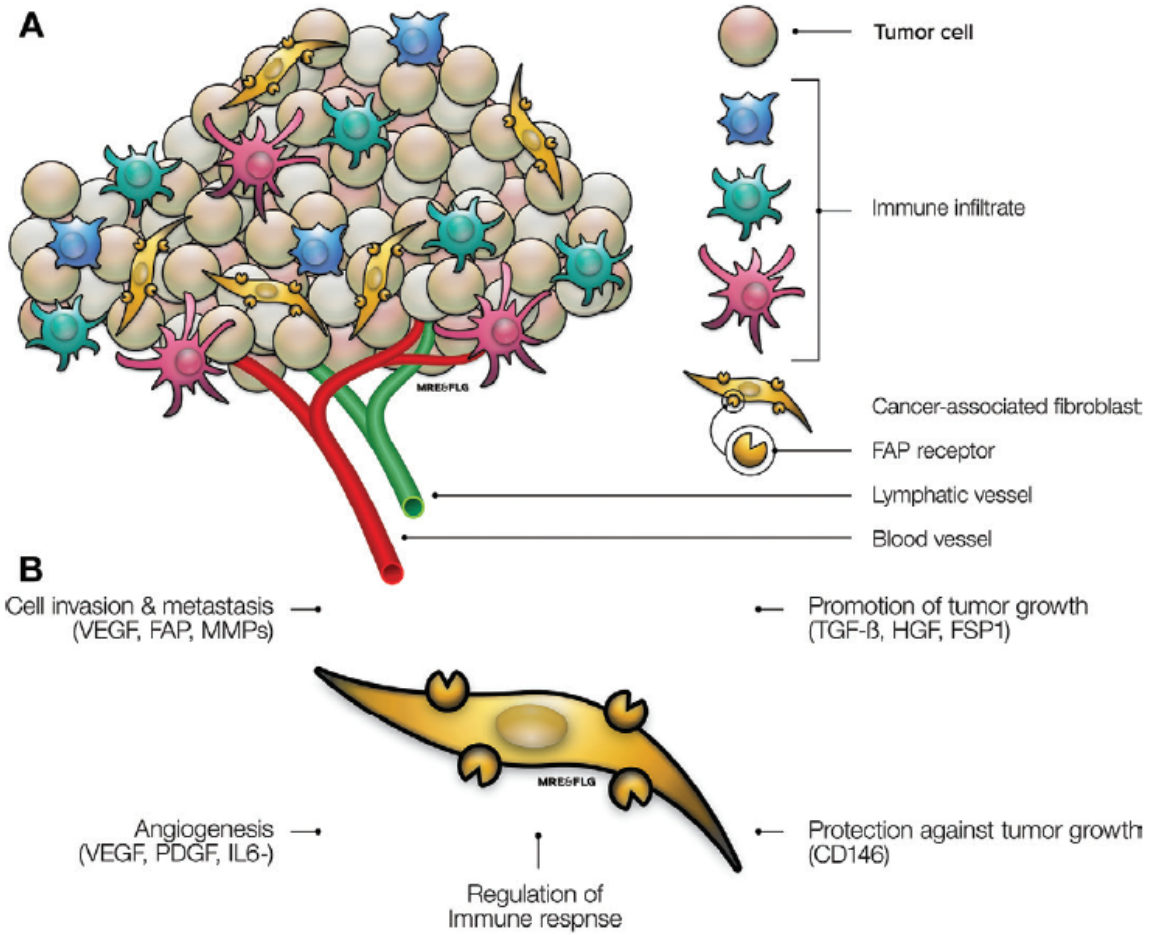
# FAP (Fibroblast Activation Protein)

Activated Fibroblasts express high levels of FAP

Fibroblasts become activated during wound repair and regeneration. Malignant tumors are recognized as “wounds that do not heal”

Among all the stromal cells, **cancer-associated fibroblasts (CAFs)** are dominant populations in the tumor microenvironment

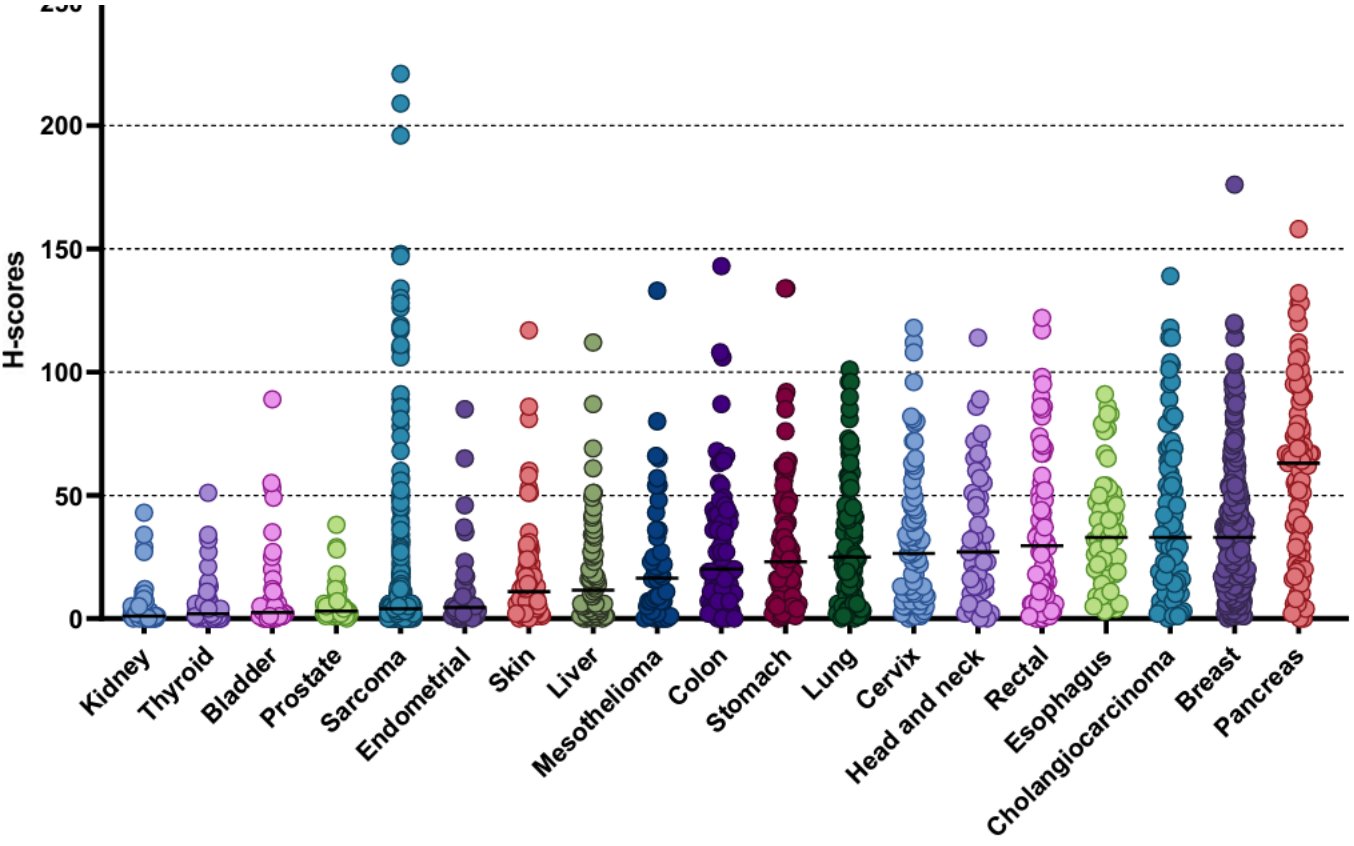
**FAP** is highly expressed on the surface of CAFs

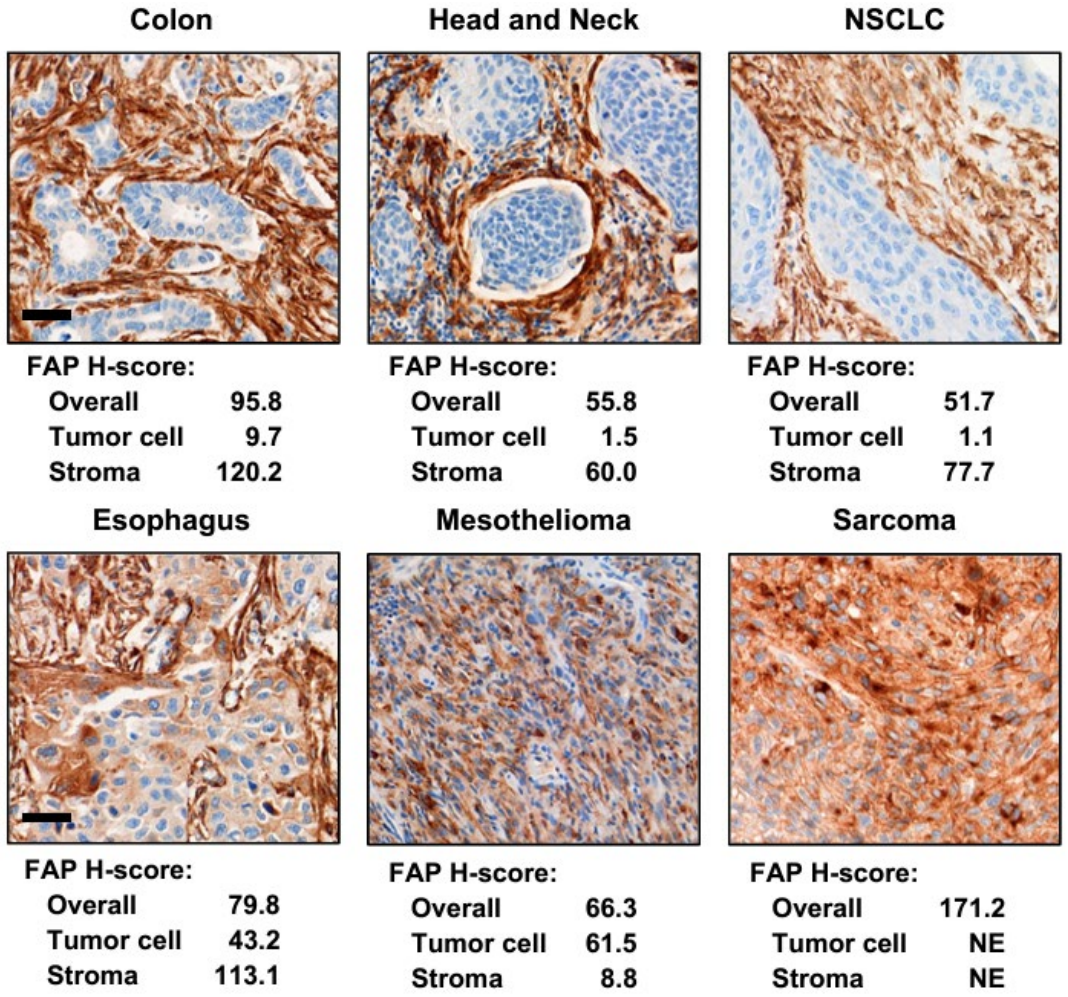



Mori Y, Dendl K, Cardinale J, Kratochwil C, Giesel FL, Haberkorn U. FAPI PET: Fibroblast Activation Protein Inhibitor Use in Oncologic and Nononcologic Disease. Radiology. 2023 Jan 3:220749. doi: 10.1148/radiol.220749. Epub ahead of print. PMID: 36594838.

# FAP expression in human solid cancers

FAP is a great target due to its overexpression in most of the cancer types (90%)




*Zboralski D et.al. Eur J Nucl Med Mol Imaging. 2022 Sep;49(11):3651-3667. doi: 10.1007/s00259-022-05842-5. Epub 2022 May 24. PMID: 35608703.*

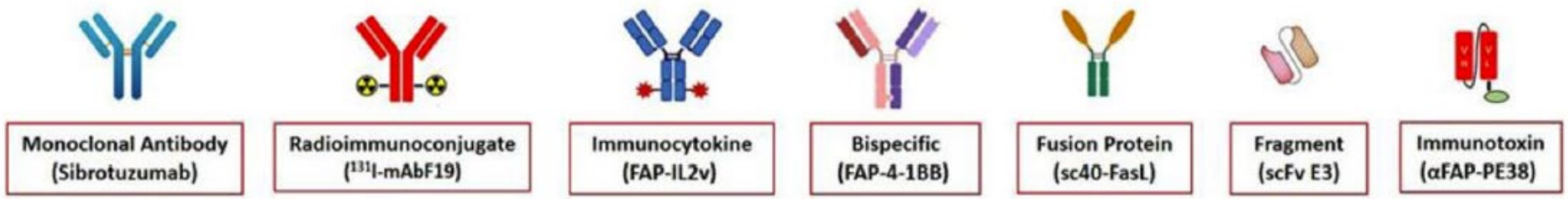
NE, not evaluable

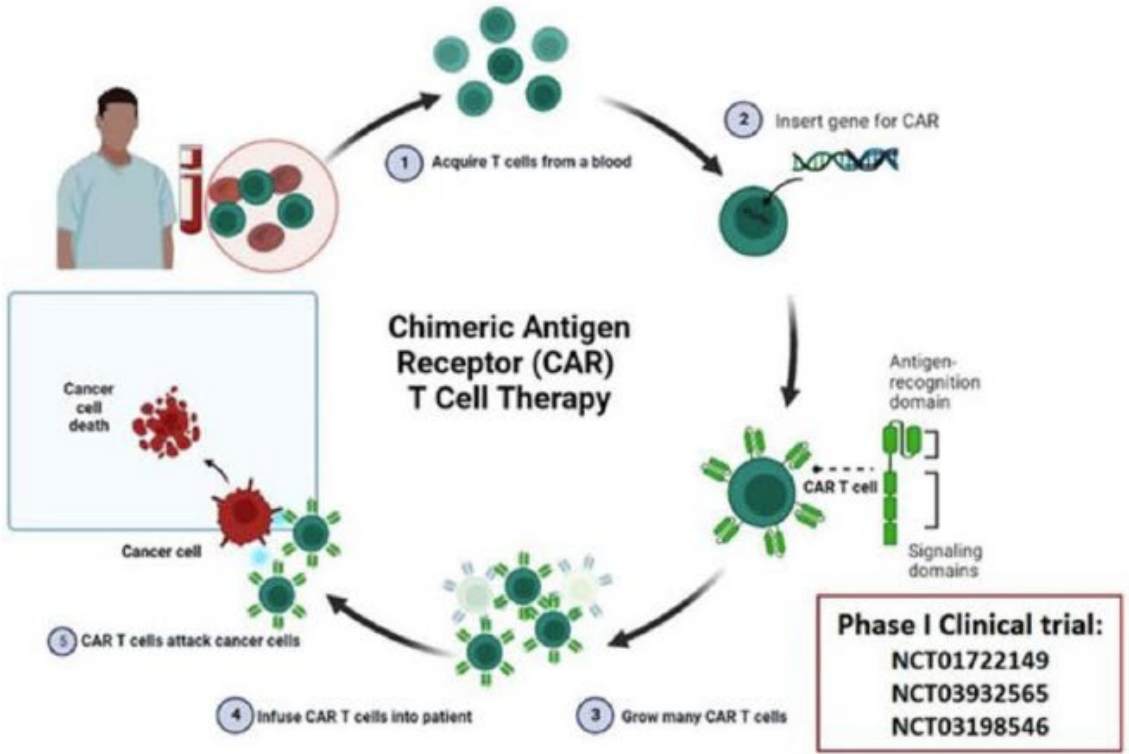
# FAP targeting for therapeutic use

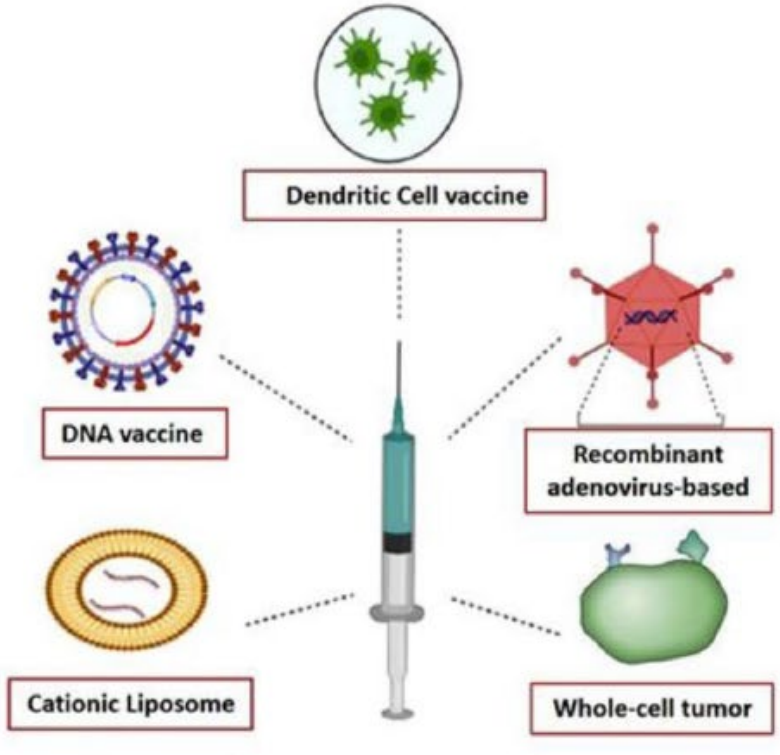
# FAP targeting approaches

- Small Molecule Inhibitors (Talabostat & Linagliptin)
- Pro-Drug (AVA-6000)
- **Immune therapy**

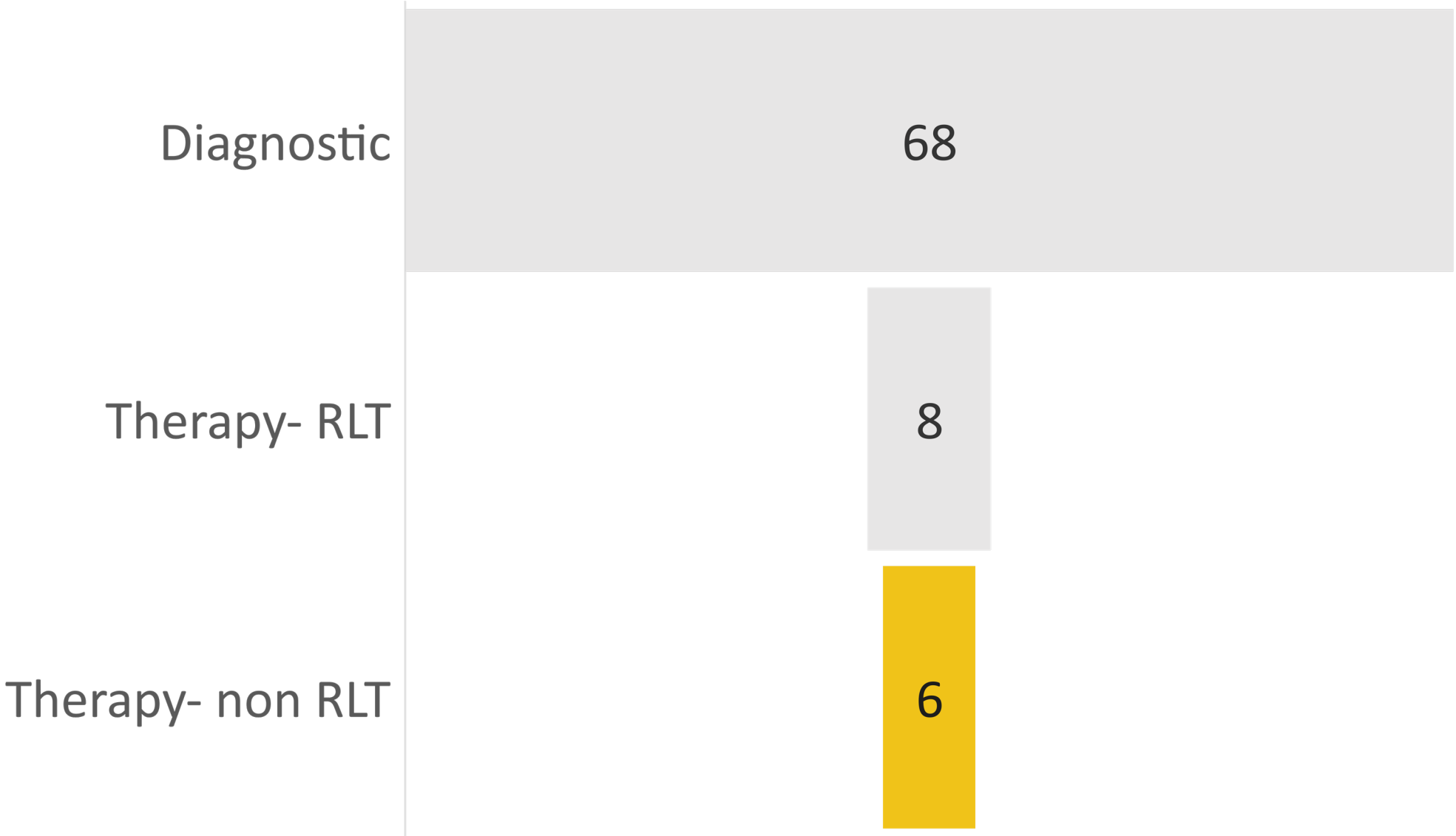
*Shahvali et. al. 2023 https://doi.org/10.1007/s13346-023-01308-9*



# Clinicaltrials.gov studies with FAP targeting



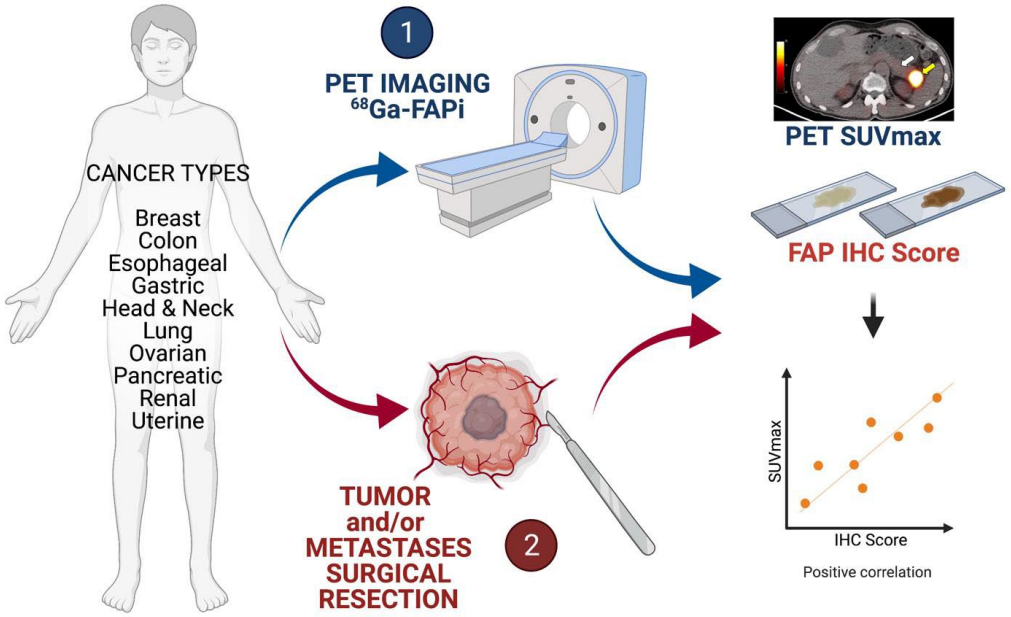

*Data as of May 22nd, 2024*

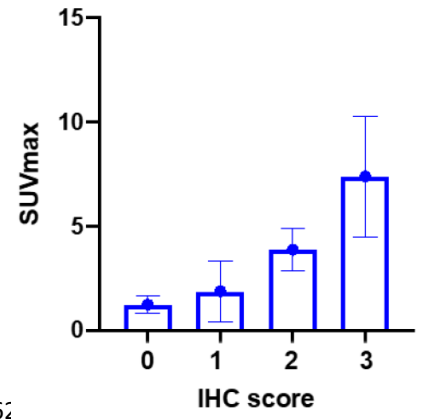
# List of Current Active Clinical Trials with non-RLT targeting FAP

| NCT Number | Sponsor | Interventions | Conditions | Phase | # of subjects |
|---|---|---|---|---|---|
| NCT04053283 | Akamis Bio | BIOLOGICAL: NG-641 | Metastatic Cancer\|Epithelial Tumor | Phase 1 | 186 |
| NCT04830592 | Akamis Bio | BIOLOGICAL: NG-641\|BIOLOGICAL: Pembrolizumab | Squamous Cell Carcinoma of the Head and Neck | Phase 1 | 36 |
| NCT05043714 | Akamis Bio | BIOLOGICAL: NG-641 in combination with Nivolumab | Metastatic Cancer\|Epithelial Tumor | Phase 1 | 30 |
| NCT04826003 | Hoffmann-La Roche | DRUG: RO7122290\|DRUG: Cibisatamab\|DRUG: Obinutuzumab | Metastatic Colorectal Cancer | Phase 1/Phase 2 (active, not recruiting) | 80 |
| NCT04969835 | Avacta Life Sciences Ltd | DRUG: AVA6000 | Pancreatic Cancer\|Colorectal Cancer\|Non-small Cell Lung Cancer\|Head and Neck Cancer\|Cancer of Unknown Primary Site\|Ovarian Cancer\|Breast Cancer\|Soft Tissue Sarcoma\|Bladder Cancer\|Oesophageal Cancer\|Prostate Cancer\|Biliary Tract Cancer | Phase 1 | 80 |
| NCT05547321 | Oncomatryx Biopharma S.L. | DRUG: OMTX705<br>DRUG: Pembrolizumab | Advanced Solid Tumors | Phase 1 | 120 |

# FAP IHC and PET signal validation- 2 independent studies for [$^{68}$Ga]FAPI-46

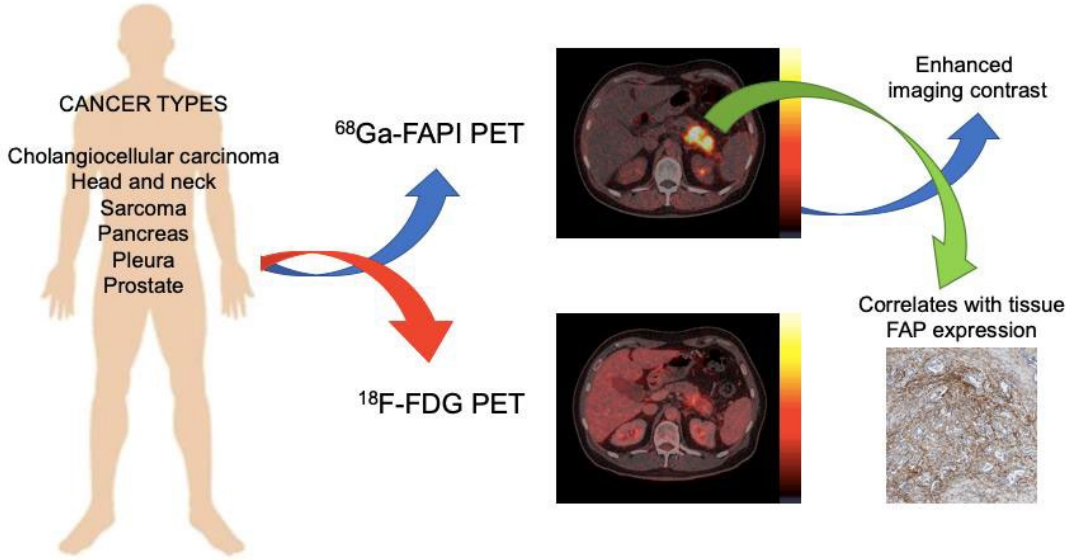
## Correlation between FAP immunohistochemistry score and $^{68}$Ga-FAPI-46 PET SUVs across cancer and non-cancer tissues

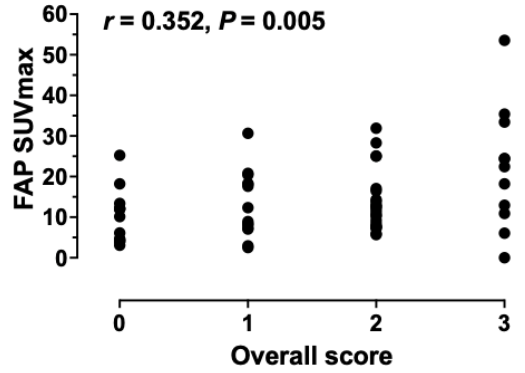



Mona et al. 2021 doi: 10.2967/jnumed.121.262

## Fibroblast activation protein positron emission tomography and histopathology in a single-center database of 324 patients and 21 tumor entities




Hirmas et al.2022 doi: 10.2967/jnumed.122.264689

# Successful Completion of First Cohort and Dosing of Three Patients of the Second Cohort in Arm 2 of Avacta's AVA6000 Phase 1 trial

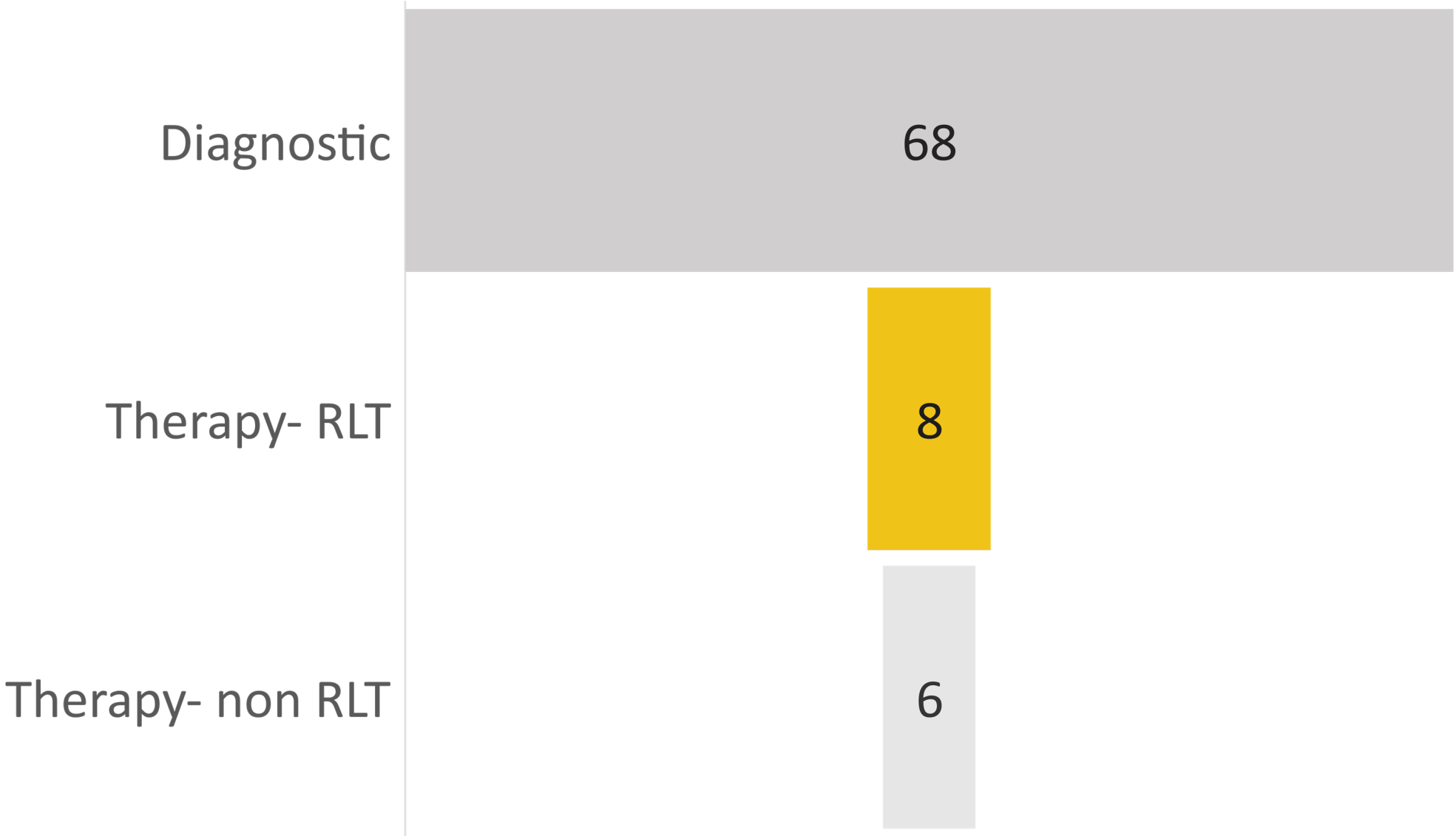
*"We're delighted to be progressing the two weekly dosing schedule arm of the Phase 1 trial of AVA6000. This is an important milestone which supports our continued confidence in AVA6000 and in the wider pre|CISION™ platform. The introduction of a new diagnostic approach of [$^{18}$F]FAPI-74 -PET scanning into the program will help to better characterize the FAP expression among patients, potentially assisting in indication selection.*

*"We're excited to be working with our investigators to integrate these tools to accelerate our efforts to optimise indications, dosing and schedule, as we bring this promising program through clinical studies."*

**Christina Coughlin MD, PhD**
**Chief Executive Officer of Avacta**

Non RLT FAP targeting therapies can significantly benefit from FAP targeting diagnostics

# Clinicaltrials.gov studies with FAP targeting




*Data as of May 22nd, 2024*

# List of Current Clinical Trials with RLT targeting FAP

| Affiliation | Therapy | Condition | Clinical.Trials.gov | Notes |
|---|---|---|---|---|
| Novartis | FAP-2286 | Solid Tumors | NCT04939610 Phase 1-2 | Active- Not recruiting |
| Point Biopharma/Lilly | PNT6555 | Pancreatic Ductal Adenocarcinoma\|Colorectal Cancer\|Esophageal Cancer\|Melanoma (Skin)\|Soft Tissue Sarcoma\|Head and Neck Squamous Cell Carcinoma\|Cholangiocarcinoma | NCT05432193 Phase 1 | Active- Not recruiting |
| Yantai LNC Biotech | LNC1004 | Solid Tumor, Unspecified, Adult | NCT05723640 Phase 1 | Recruiting |
| Academic | EB-FAPI and [177Lu]-XT117 | Solid Tumor | NCT05410821<br>NCT05963386<br>NCT06081322<br>NCT06197139<br>NCT06211647 | Active and Recruiting |
| Philogen | OncoFAP | Solid Tumors | Not on clinicaltrials.gov | |
| 3BP | 3BP-3940<br>FO-004 | Solid Tumors | Not on clinicaltrials.gov | |
| Ratio Therapeutics | RTX-12358 | Solid Tumors | Not on clinicaltrials.gov | |
| Precirix | CAM-FAP | Solid Tumors | Not on clinicaltrials.gov | |
| Dr. Frank Rosch | DOTAGA(SA.FAPI) Compounds | Solid Tumors | Not on clinicaltrials.gov | Dimer version showing promise |

*Note: This represents industry FAP assets in clinical development (clinicaltrials.gov or other published data).*
*Not a comprehensive list of all FAP assets in pipeline*

Journal of Nuclear Medicine, published on November 9, 2023 as doi:10.2967/jnumed.123.266930



# The Hierarchy of SUVs: From Diagnostics to Therapeutics and the Pathway to Effective Theranostics

Michael S. Hofman

*Cancer Imaging, Molecular Imaging and Therapeutic Nuclear Medicine; Prostate Cancer Theranostics and Imaging Centre of Excellence, Peter MacCallum Cancer Centre; and Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia*

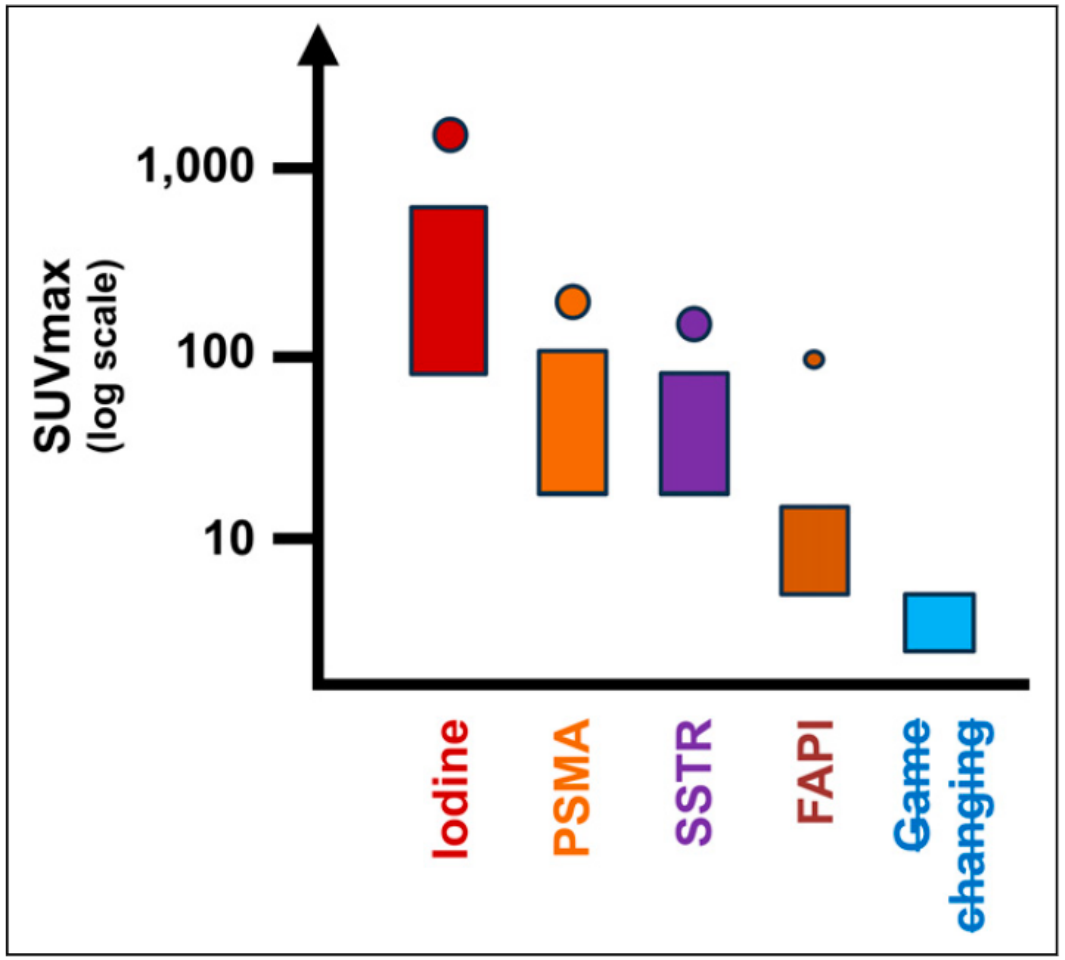



**FIGURE 2.** Hierarchy of SUVs: from left to right, $^{131}$I, PSMA, somatostatin receptor (DOTATATE), fibroblast activation protein inhibitor, and purported next-generation theranostic. $^{131}$I has uptake that is unmatched by any other radiopharmaceutical.

# Therapeutics takeaways

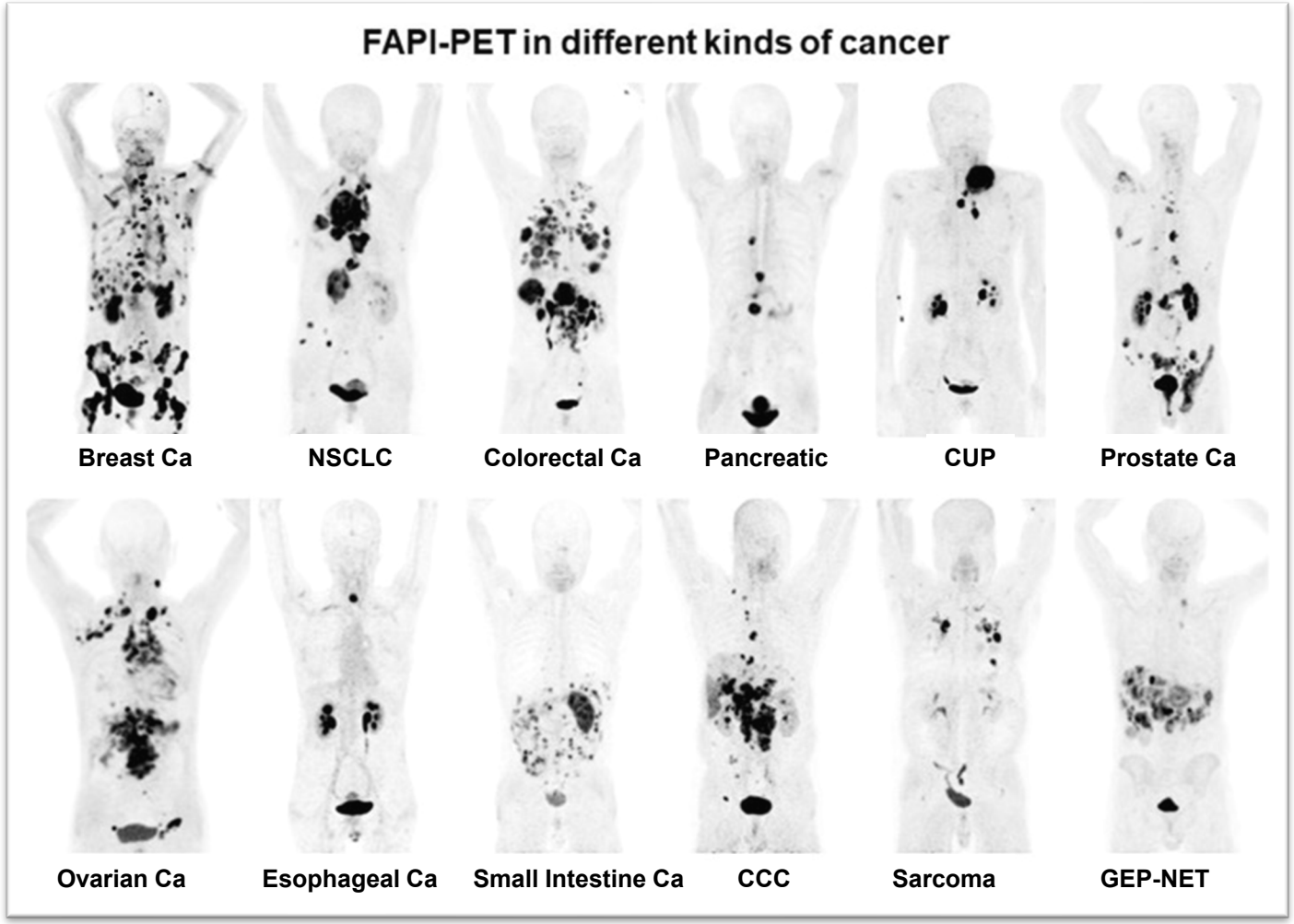
- Majority of pharmaceutical companies along with theranostic start-ups have a FAP targeted RLT, either in Phase 1 or preclinical stage
- Existing trials are all in early stage- Phase 1
- Initial first-in-human results, especially in compassionate use have been mixed- no slam dunk impact yet
- Current and future focus
  - Dimer approach: Examples- SA.FAPI and OncoFAP
  - Albumin binders to increase circulation: Example: EB-FAPI
  - Isotope selection: Use of Alphas
  - Combination therapy early on

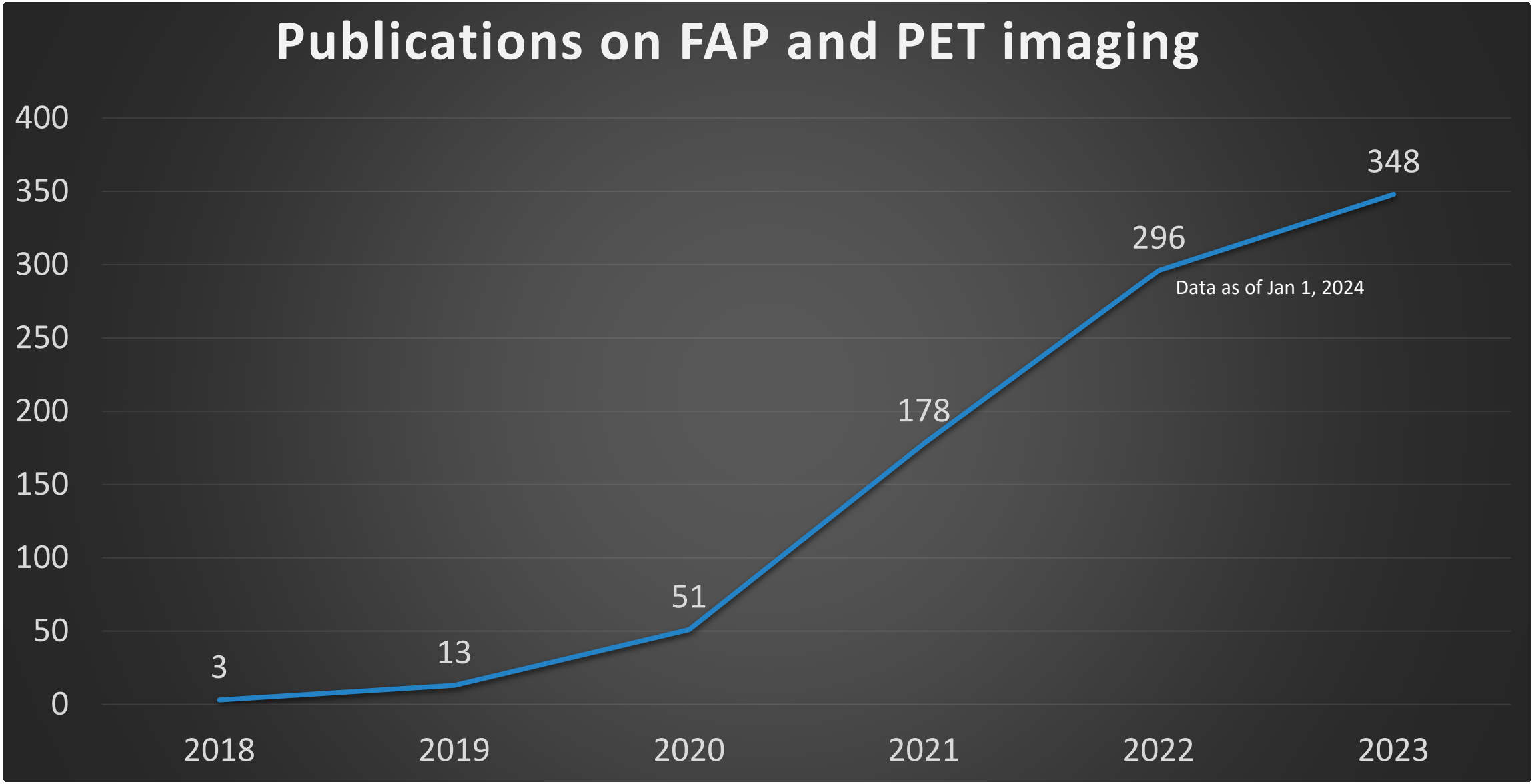
# FAP targeting for diagnostic use

# (Fibroblast Activation Protein Inhibitor)-FAPI family of compounds

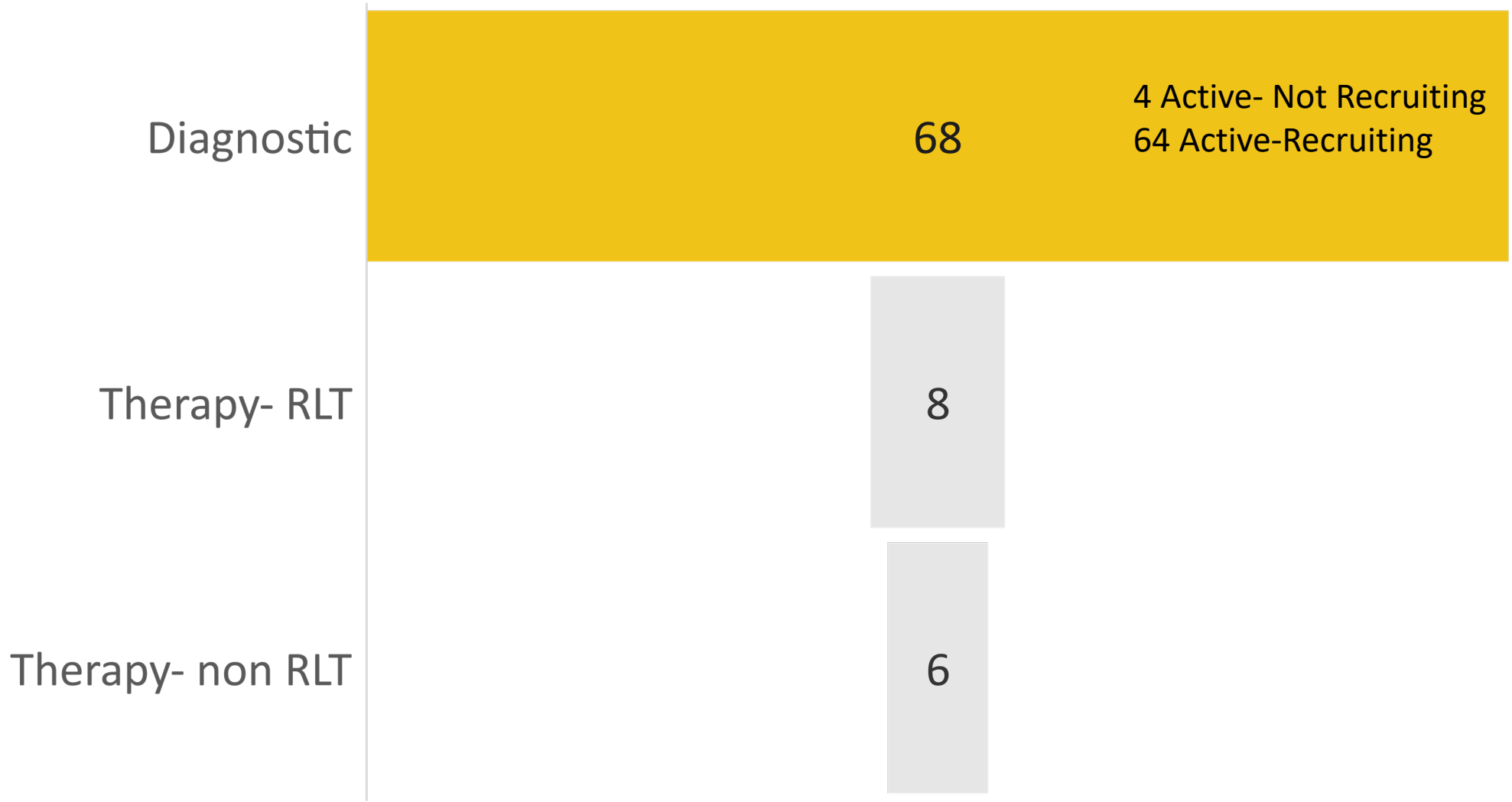
"A single radiotracer can identify nearly 30 types of cancer, allowing for new applications in noninvasive diagnosis, staging and treatment, according to research presented at the 2019 Annual Meeting of the Society of Nuclear Medicine and Molecular Imaging (SNMMI). This honor goes to a team of researchers at University Hospital Heidelberg, Germany, showcasing the efficacy of the FAPI radiotracer."

## SNMMI Image of the Year 2019



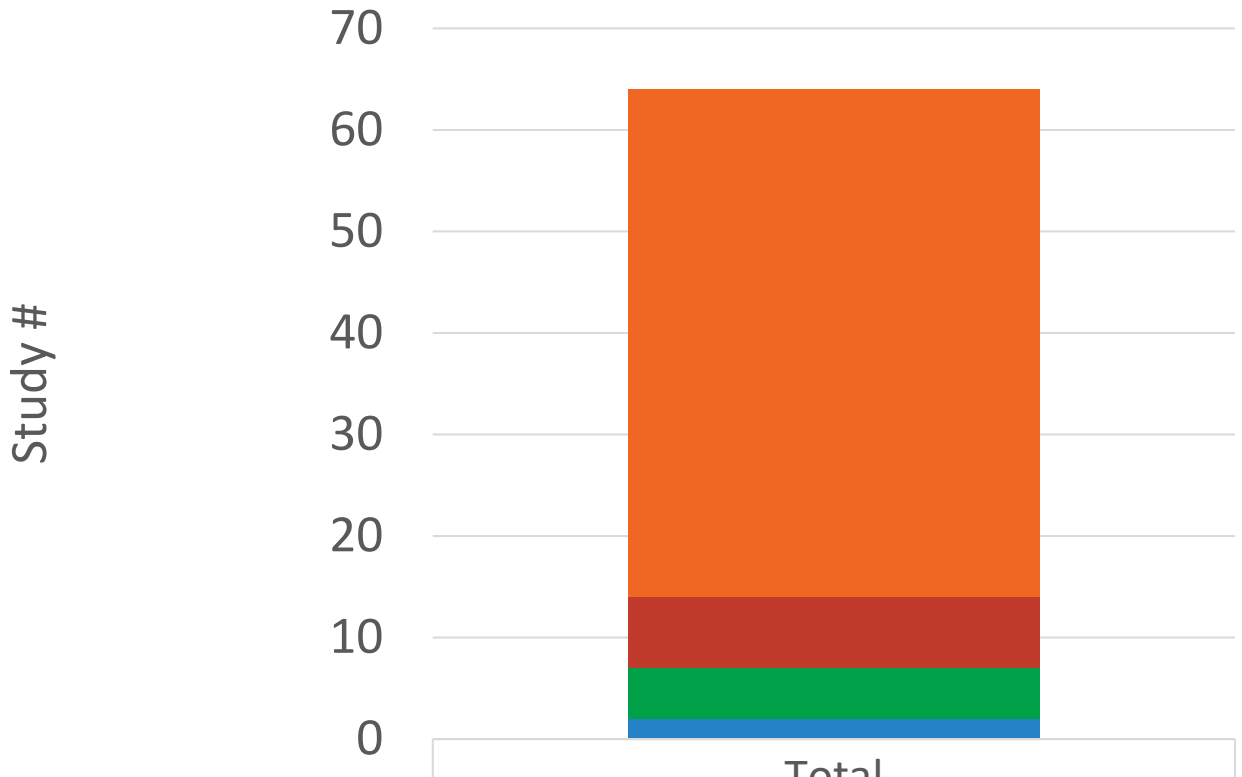

Publications on FAP and PET imaging
400
350
300
250
200
150
100
50
0
3
13
51
178
296
348
Data as of Jan 1, 2024
2018
2019
2020
2021
2022
2023

## Clinicaltrials.gov studies with FAP targeting



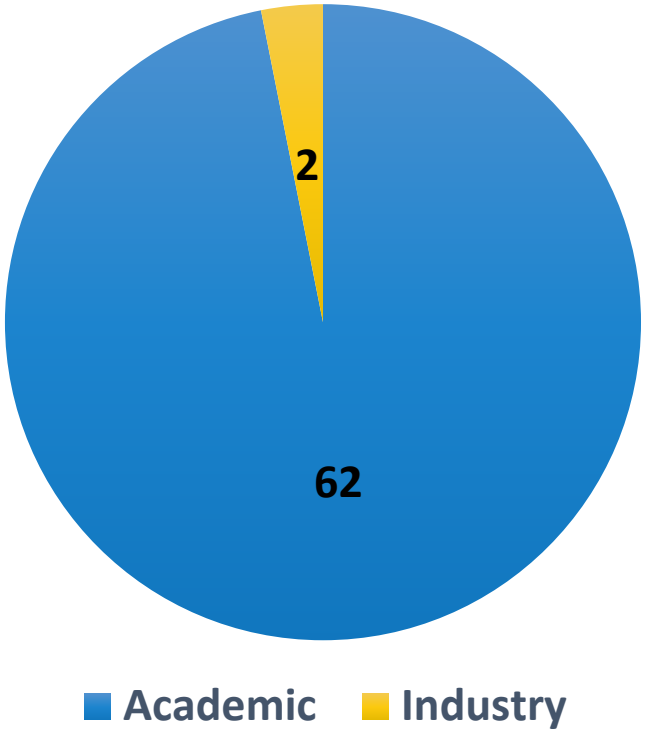

*Data as of May 22nd, 2024*

## Studies by disease type



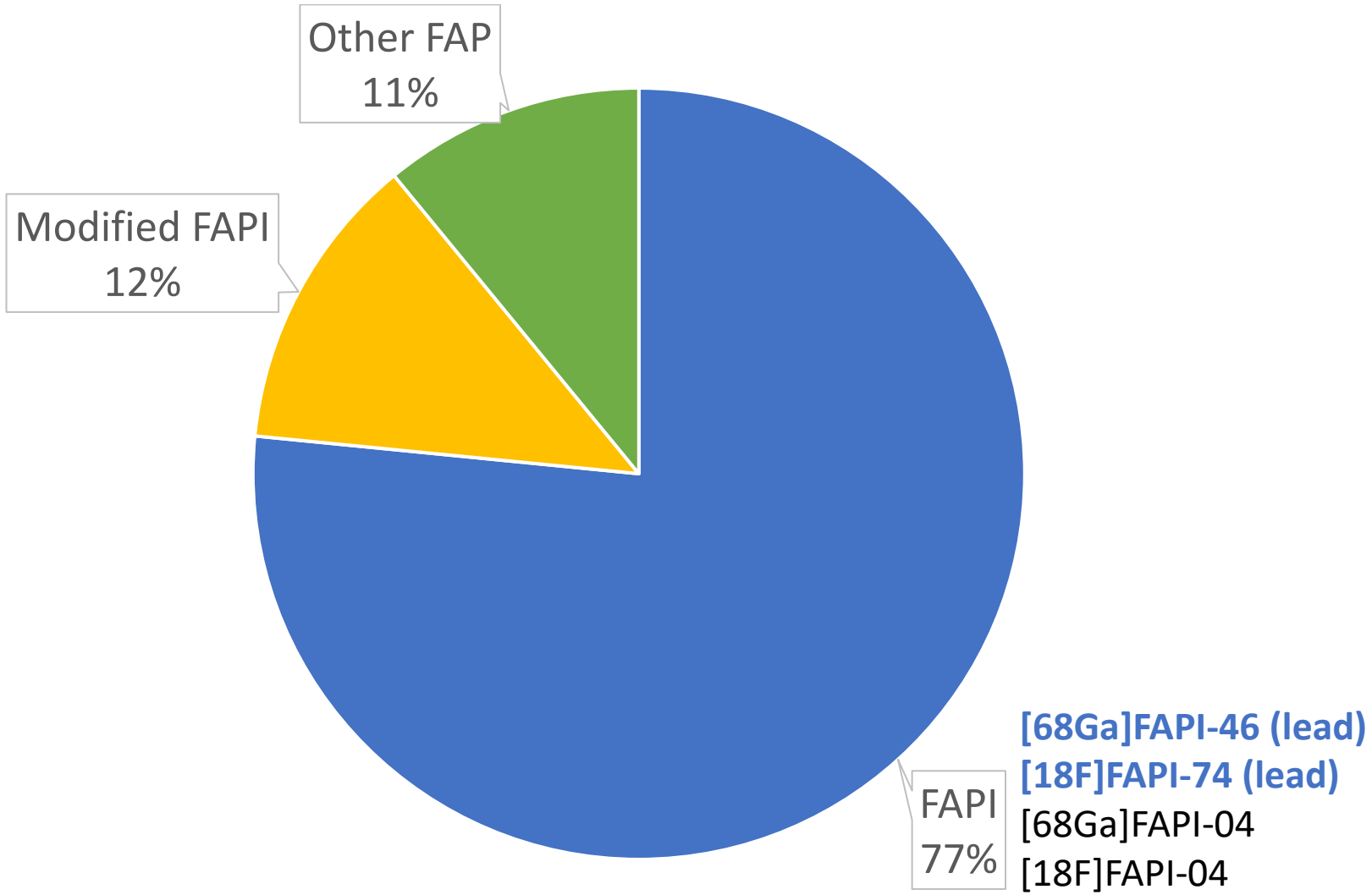

| | Total |
|---|---|
| Oncology | 50 |
| Fibrotic Disease | 7 |
| Fibroinflammatory Disease | 5 |
| Cardiovascular Disease | 2 |

## # of Diagnostic Studies

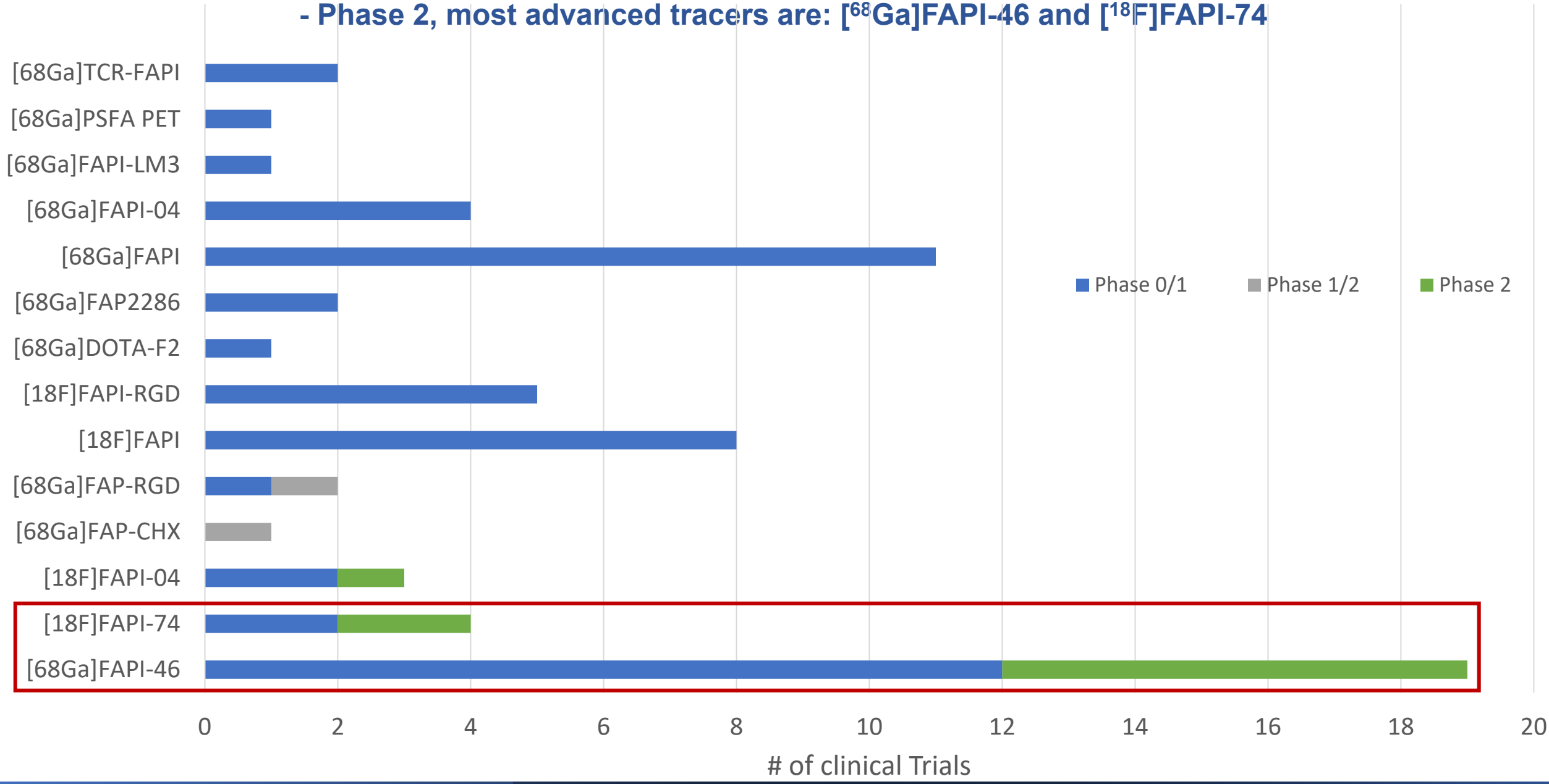



| Study | Sponsor |
|---|---|
| [$^{68}$Ga]FAPI-46 in PDAC in US | SOFIE and GEHC |
| [$^{18}$F]FAPI-74 in GI cancers in US | SOFIE |

# FAPI tracers comprise the largest number of clinical studies



- Majority of the studies are in Phase 0/1 as IITs
- Phase 2, most advanced tracers are: [$^{68}$Ga]FAPI-46 and [$^{18}$F]FAPI-74



# What disease areas are showing the most promise with FAP targeting diagnostics?

# Publication analysis

| | Total Publications/Patients with ALL FAP targeted radiopharmaceuticals | Publications/Patients with FAPI family of compounds | |
|---|---|---|---|
|  # of patients reported | 9,848 | 9,048 | 92% |
| | | 7,000- Oncology<br>2,048- Non-Oncology | |
|  # of publications | 748 | 650 | 87% |

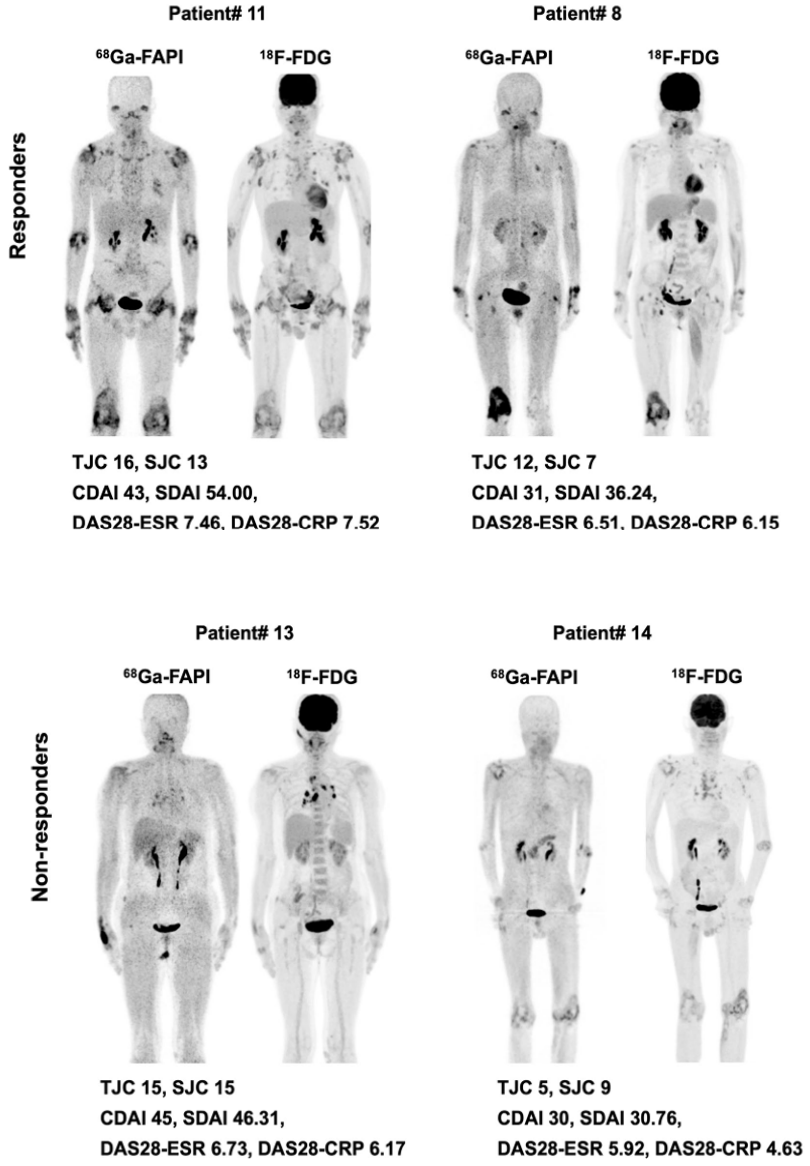
Takeaway: FAPI family of compounds comprise the majority of publications and patient reported data to date (March 2024). *(Review articles are excluded)*

# Non oncologic disease studies- some examples

| | Patient # |
|---|---|
| Cardiovascular | 789 |
| Bone Disease | 131 |
| Lung Fibrosis | 130 |
| Shoulder joint | 77 |
| IgG4 | 61 |
| Crohn's Disease | 42 |
| Rheumatoid Arthritis | 39 |
| Liver Fibrosis | 29 |

# [$^{68}$ Ga]Ga-FAPI-04 PET/CT may be a predictor for early treatment response in rheumatoid arthritis

- **19 subjects**
- **Conclusion:** [$^{68}$ Ga]Ga-FAPI-04 uptake at baseline were significantly higher in early responders than those in non-responders.

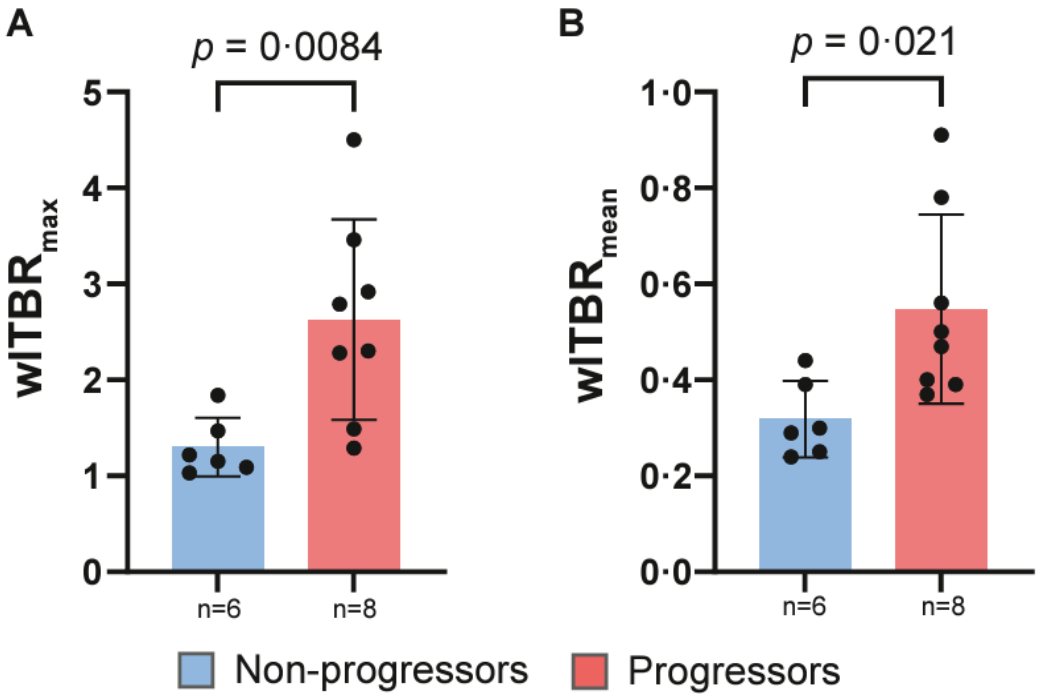



https://pubmed.ncbi.nlm.nih.gov/38175339/

# FAPi PET/CT for assessment and visualisation of active myositis-related interstitial lung disease: a prospective observational pilot study

- **Subjects: 32**
- Conclusion: The study demonstrates higher fibroblast activation in patients with IIM-ILD compared to non-ILD patients and controls. **Intensity of pulmonary FAPi accumulation was associated with progression of ILD**. Considering that this study was carried out on a small population, FAPi PET/CT may serve as a useful non-invasive tool for risk stratification of lung disease in IIM.

idiopathic inflammatory myopathies (IIM)



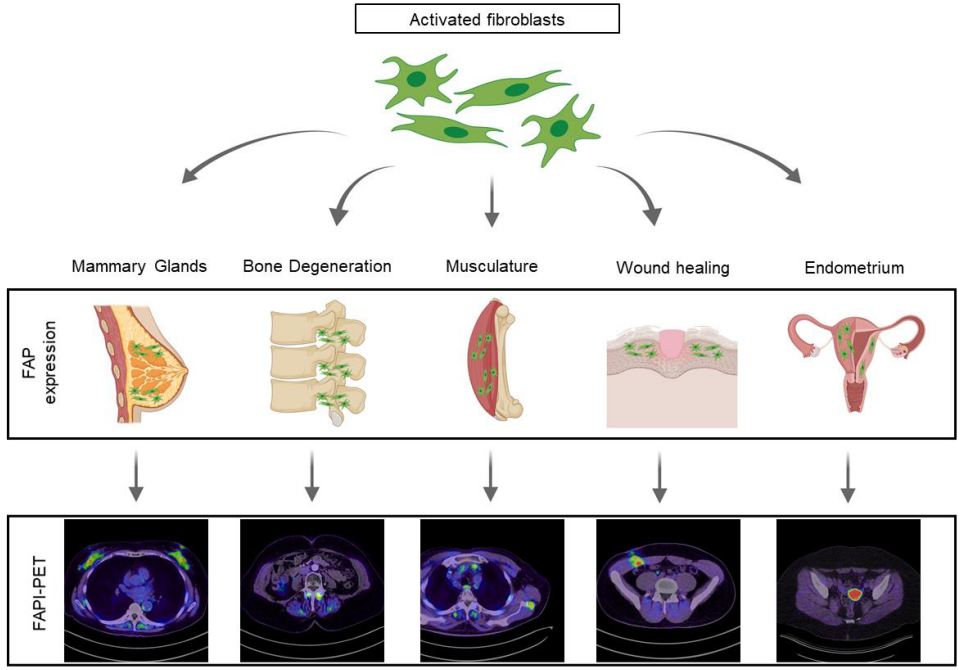

https://pubmed.ncbi.nlm.nih.gov/38633577/

# Pitfalls and common findings in $^{68}$Ga-FAPI-PET - A pictorial analysis

Lukas Kessler [1], Justin Ferdinandus [1], Nader Hirmas [1], Fadi Zarrad [1], Michael Nader [1], David Kersting [1], Manuel Weber [1], Sandra Kazek [1], Miriam Sraieb [1], Rainer Hamacher [2], Katharina Lueckerath [1], Lale Umutlu [3], Wolfgang P Fendler [1], Christoph Rischpler [1]

**University Hospital Essen**

Common pitfall findings were **degenerative lesions** mostly associated to joints and vertebral bones



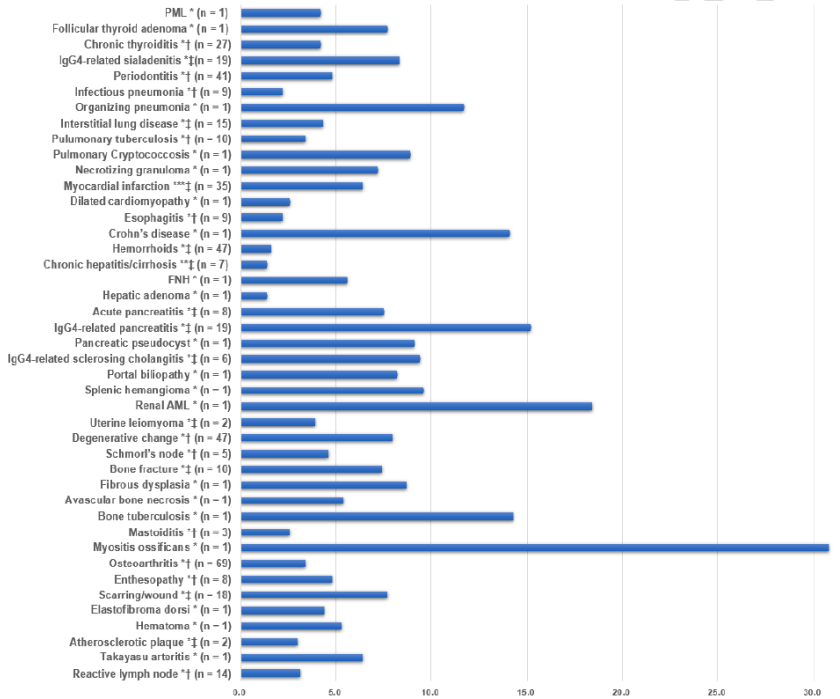

# Non-oncologic incidental uptake on FAPI PET/CT imaging

Masatoshi Hotta, Angela C Rieger, Mahbod G Jafarvand, Nandakumar Menon, Andrea Farolfi, Matthias R Benz, Jeremie Calais

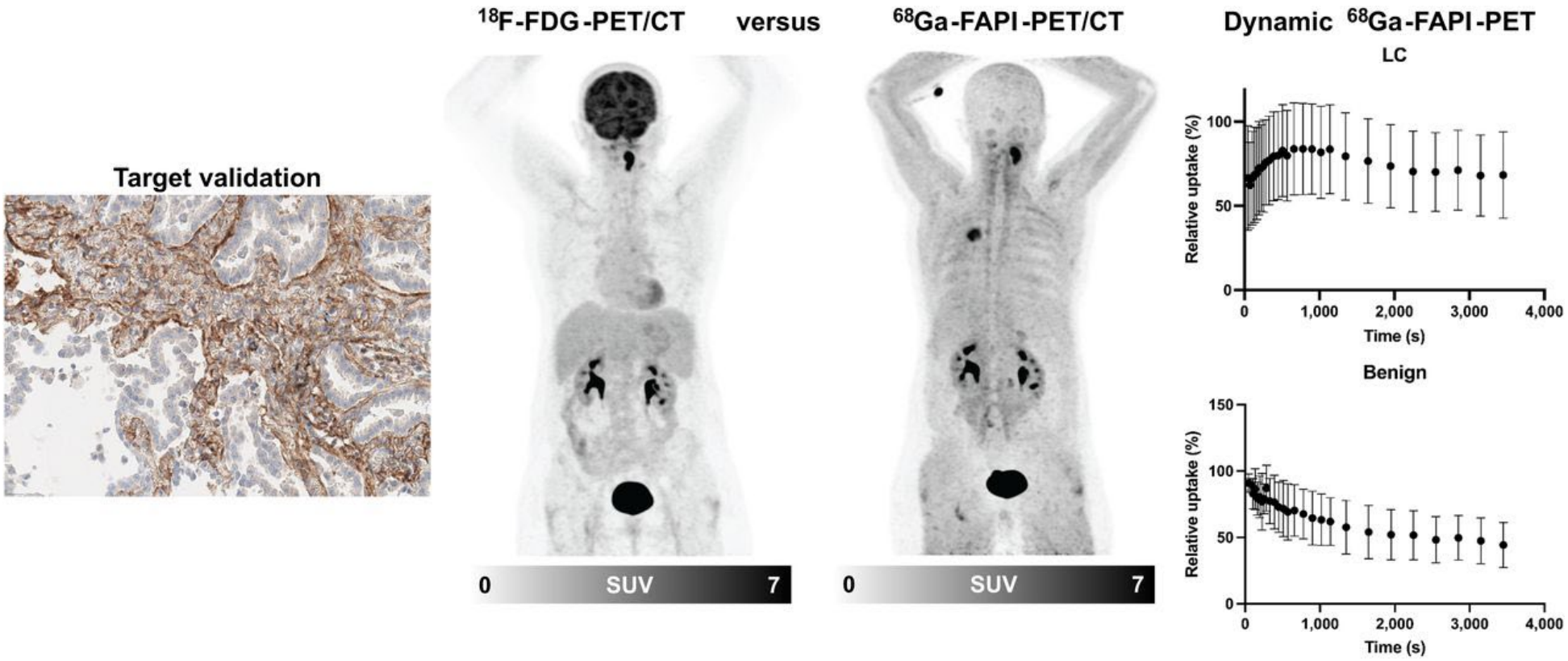
Published Online: 13 Jul 2022 · Doi: https://doi.org/10.1259/bjr.20220463

**UCLA**

In this review article, they describe for each organ system the patterns of physiological FAPI uptake and the main causes of non-oncological uptake reported from the literature



# Diagnostic Potential of Supplemental Static and Dynamic 68Ga-FAPI-46 PET for Primary 18F-FDG–Negative Pulmonary Lesions




*Diagnostic Potential of Supplemental Static and Dynamic 68Ga-FAPI-46 PET for Primary 18F-FDG–Negative Pulmonary Lesions. Rohrich et al. JNM. Apr 2024 ; DOI: 10.2967/jnumed.123.267103*

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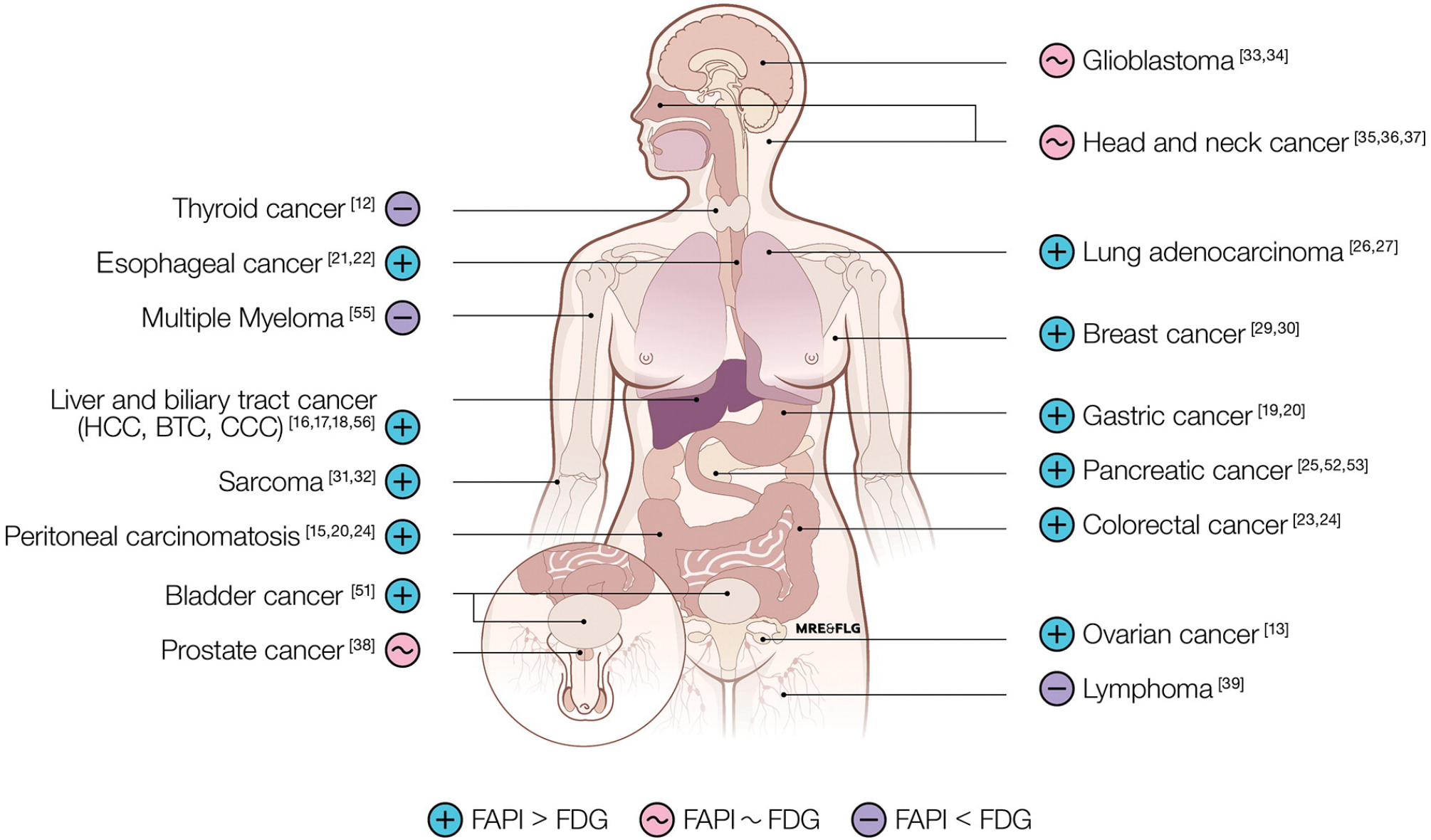
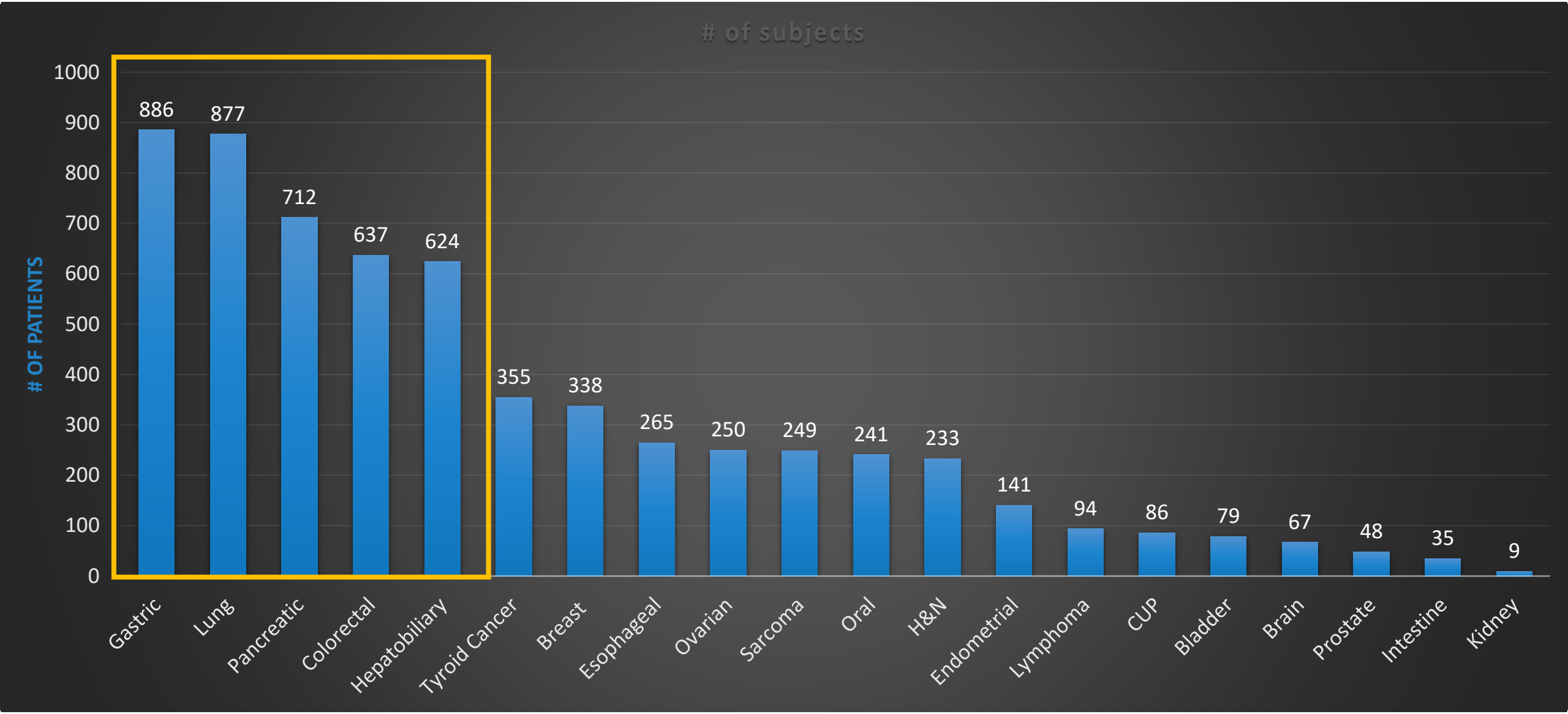
Takeaway: FAPI family of compounds comprise the majority of publications and patient reported data to date (March 2024). *(Review articles are excluded)*

# Comparison of FAPI vs. FDG in oncological PET-imaging



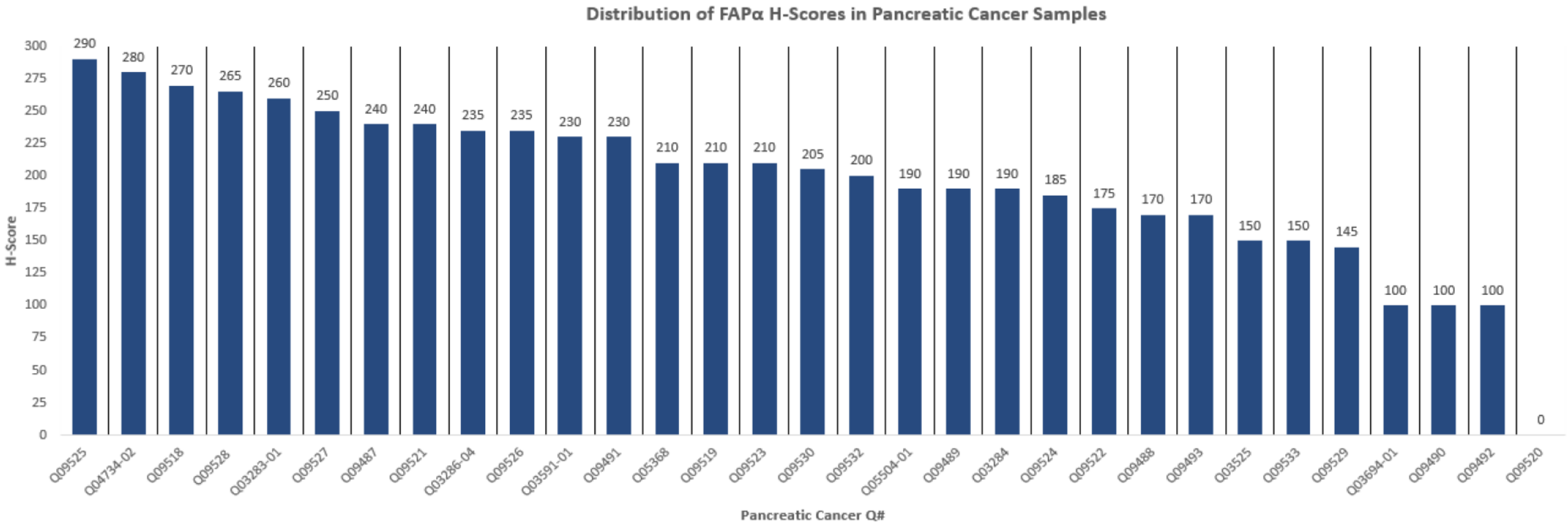

Mori Y, Dendl K, Cardinale J, Kratochwil C, Giesel FL, Haberkorn U. FAPI PET: Fibroblast Activation Protein Inhibitor Use in Oncologic and Nononcologic Disease. Radiology. 2023 Jan 3:220749. doi: 10.1148/radiol.220749. Epub ahead of print. PMID: 36594838.

# # of patients published in various oncologic disease



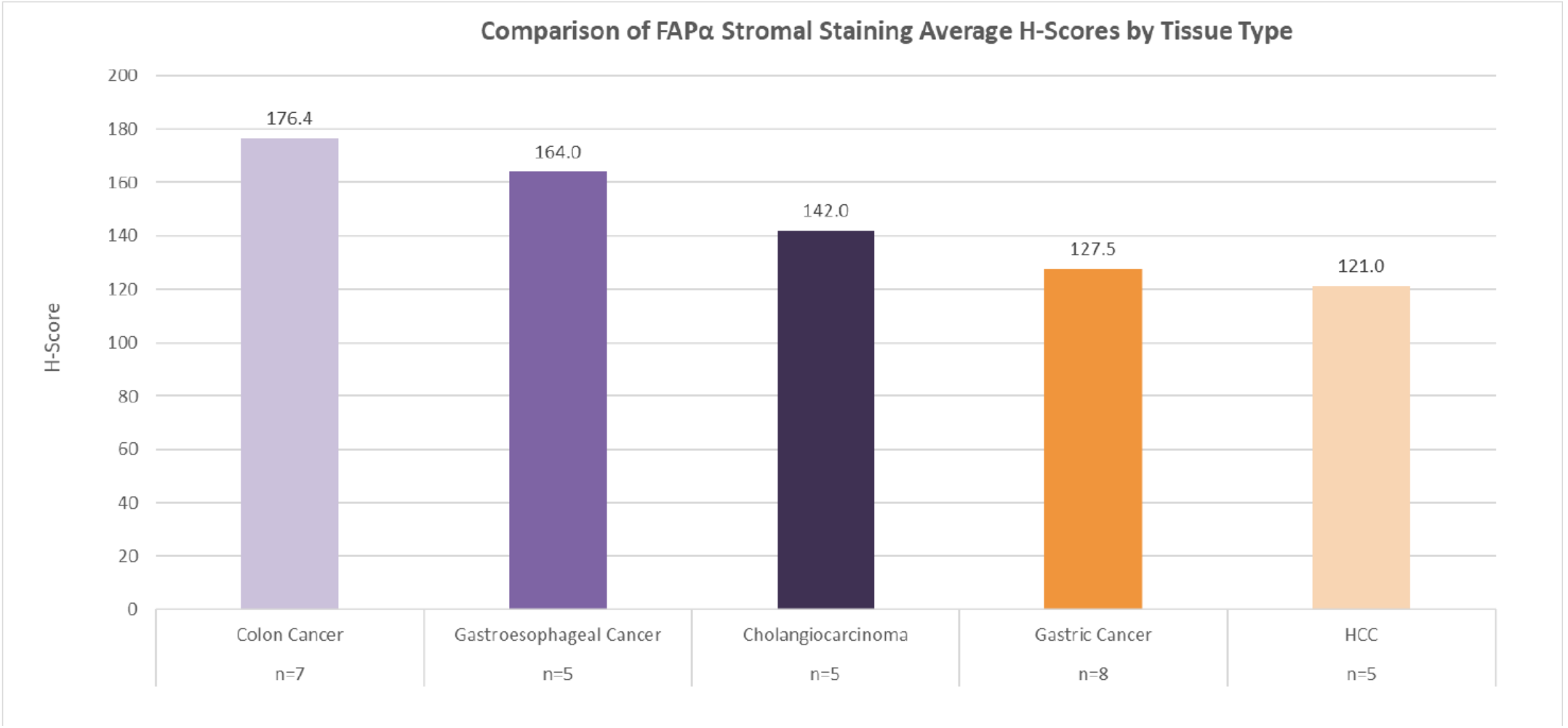

GI cancers encompass majority of the patient numbers reported with FAPI

# Proof of concept FAP IHC on pancreatic cancer tissue




SOFIE conducted study with DLS

# Proof of concept FAP IHC on GI cancer tissues




SOFIE conducted study with DLS

# Meta Data Analysis of FAP radioligands in imaging

## Takeaway: strong prelim data of performance in various cancers, especially GI/hepatobiliary

diagnostics

MDPI

*Systematic Review*

**FAPI PET versus FDG PET, CT or MRI for Staging Pancreatic-, Gastric- and Cholangiocarcinoma: Systematic Review and Head-to-Head Comparisons of Diagnostic Performances**

Sophie E. M. Veldhuijzen van Zanten [1,*,†], Kay J. Pieterman [1,†], Bas P. L. Wijnhoven [2], Ilanah J. Pruis [1], Bas Groot Koerkamp [2], Lydi M. J. W. van Driel [3], Frederik A. Verburg [1] and Maarten G. J. Thomeer [1]

1 Department of Radiology and Nuclear Medicine, Erasmus Medical Center, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands
2 Department of Surgery, Erasmus Medical Center, 3015 GD Rotterdam, The Netherlands
3 Department of Gastroenterology and Hepatology, Erasmus Medical Center, 3015 GD Rotterdam, The Netherlands
* Correspondence: s.veldhuijzenvanzanten@erasmusmc.nl
† These authors contributed equally to this work.

Meta-Analysis > Hell J Nucl Med. 2023 May-Aug;26(2):123-131. doi: 10.1967/s002449912575. Epub 2023 Aug 4.

**Diagnostic value of $^{18}$F-FDG PET/CT and $^{68}$Ga-FAPI PET/CT in primary liver cancer: A systematic review and meta-analysis**

Ma Jiao [1], Tang Mingsong, Jiang Hao, Zhang Chunyin

Affiliations + expand

PMID: 37527048 DOI: 10.1967/s002449912575

Free article

Wang *et al.*
*European Journal of Medical Research* (2023) 28:34
https://doi.org/10.1186/s40001-023-00997-9

European Journal of Medical Research

REVIEW Open Access

**[$^{68}$Ga]Ga-FAPI-04 PET MRI/CT in the evaluation of gastric carcinomas compared with [$^{18}$F]-FDG PET MRI/CT: a meta-analysis**

Yawen Wang[1†], Wenhao Luo[2†] and Ye Li[3*]

frontiers in Oncology

Front Oncol. 2023; 13: 1202505. PMCID: PMC10332156
Published online 2023 Jun 26. doi: 10.3389/fonc.2023.1202505 PMID: 37434980

**Head-to-head comparison of $^{68}$Ga-FAPI-04 PET/CT and $^{18}$F-FDG PET/CT in the evaluation of primary digestive system cancer: a systematic review and meta-analysis**

Jiqi Ouyang, [1,2] Peiwen Ding, [3,4] Runshun Zhang, [✉1,*] and Yuexia Lu [1,2]



> Front Oncol. 2023 Feb 17;13:1093861. doi: 10.3389/fonc.2023.1093861. eCollection 2023.

**Comparison of $^{68}$Ga-FAPI and $^{18}$F-FDG PET/CT for the diagnosis of primary and metastatic lesions in abdominal and pelvic malignancies: A systematic review and meta-analysis**

Xue Liu [1], Huiting Liu [1], Cailiang Gao [1], Wenbing Zeng [2]

Affiliations + expand

PMID: 36874127 PMCID: PMC9982086 DOI: 10.3389/fonc.2023.1093861

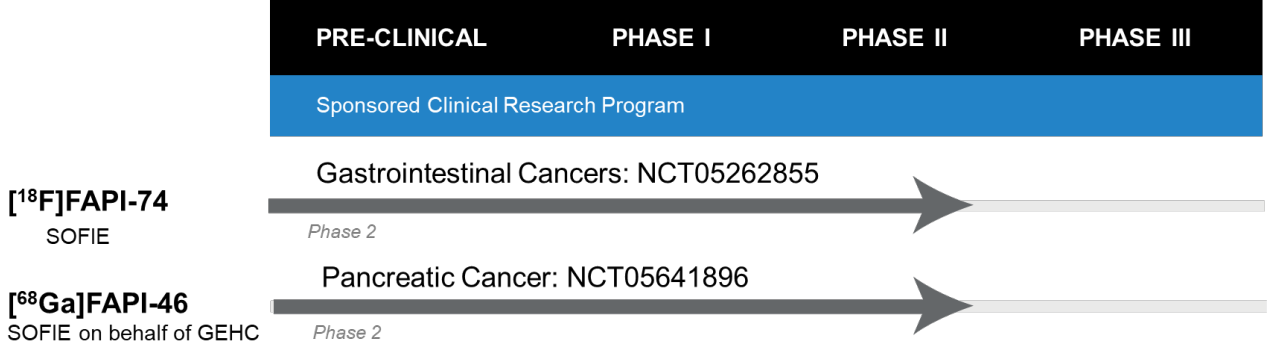
International Journal of Molecular Sciences

MDPI

nt J Mol Sci. 2023 Jun; 24(12): 10136. PMCID: PMC10299436
ublished online 2023 Jun 14. doi: 10.3390/ijms241210136 PMID: 37373285

**Diagnostic Performance of Positron Emission Tomography with Fibroblast-Activating Protein Inhibitors in Gastric Cancer: A Systematic Review and Meta-Analysis**

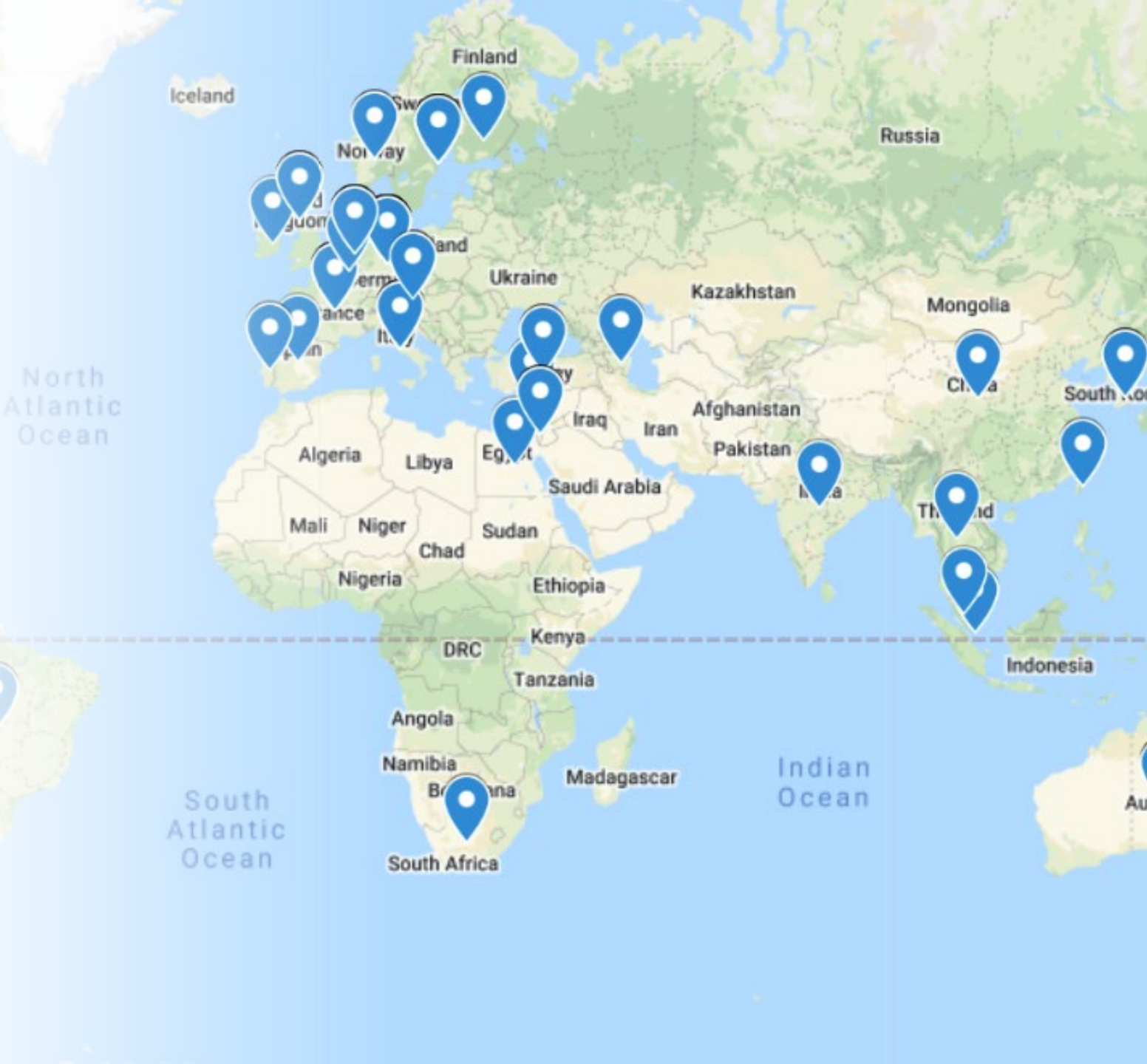
Jessio Rizzo,[1] Manuela Racca,[1] Federico Garrou,[2] Elisabetta Fenocchio,[3] Luca Pellegrino,[4] Domenico Albano,[5] rancesco Dondi,[5] Francesco Bertagna,[5] Salvatore Annunziata,[6] and Giorgio Treglia[7,8,9,*]




| [68Ga]FAPI-46 | | [18F]FAPI-74 |
|---|---|---|
| • Phase 2 in patients with Pancreatic Ductal Adenocarcinoma (PDAC) |  | • Phase 2 in patients with GI Cancers: hepatocellular carcinoma, gastric cancer, colorectal, cholangiocarcinoma and pancreatic cancer |
| 4 sites activated: (Study activated May 2022)<br>• **NYU Langone**<br>• **Mayo Clinic**<br>• **UCLA**<br>• **BAMF Health** |  | 5 sites selected: (Study activated May 2023)<br>• **MGH**<br>• **MSKCC**<br>• **BAMF Health**<br>• **Northwell**<br>• **UCLA** |
| 68 Minutes |  | 110 Minutes |
| 60 subjects planned<br>• 54 patients imaged (at least one FAPI image) |  | 75 subjects planned<br>• 55 patients imaged |

# FAPI Global Outreach Program: Current State

- 39 Countries
- 265 research studies (80 single study sites, 62 multi study sites)
- Studies include: Chemistry, pre-clinical, clinical, oncology and non-oncology
- 151 unique institutions
- Compounds: [$^{18}$F]-FAPI-74 and [$^{68}$Ga]-FAPI-46



# Why FAPI Global Outreach Program?

**Primary Objective:**

1. **Access:** Provide academic institutions access to FAPI for investigator-initiated studies to advance their and SOFIE/GEHC research interests.
2. **Learn**: SOFIE/GEHC to learn through this program the utility of FAPI in various indications.
3. **Data:** Identify key partners/data in support of approvals in key indications.

# What we do:

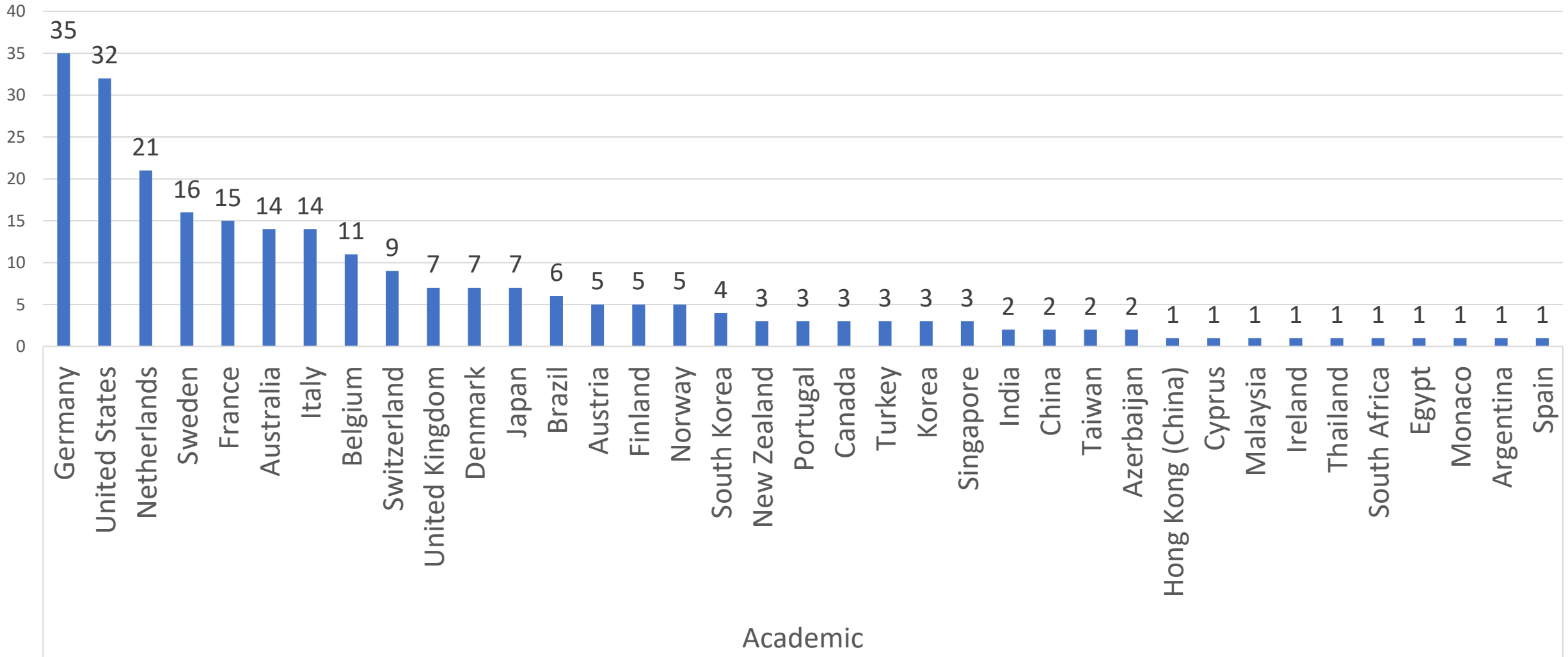
**Gain access to GMP grade precursor and reference standard in support of investigator-initiated trial**

**Technical manufacturing assistance to get the sites started**

**Cross Reference to SOFIE/GEHC IND(s) or IND content to pursue investigator-initiated trial**

**Allows sites to expand their research program and grant opportunities**

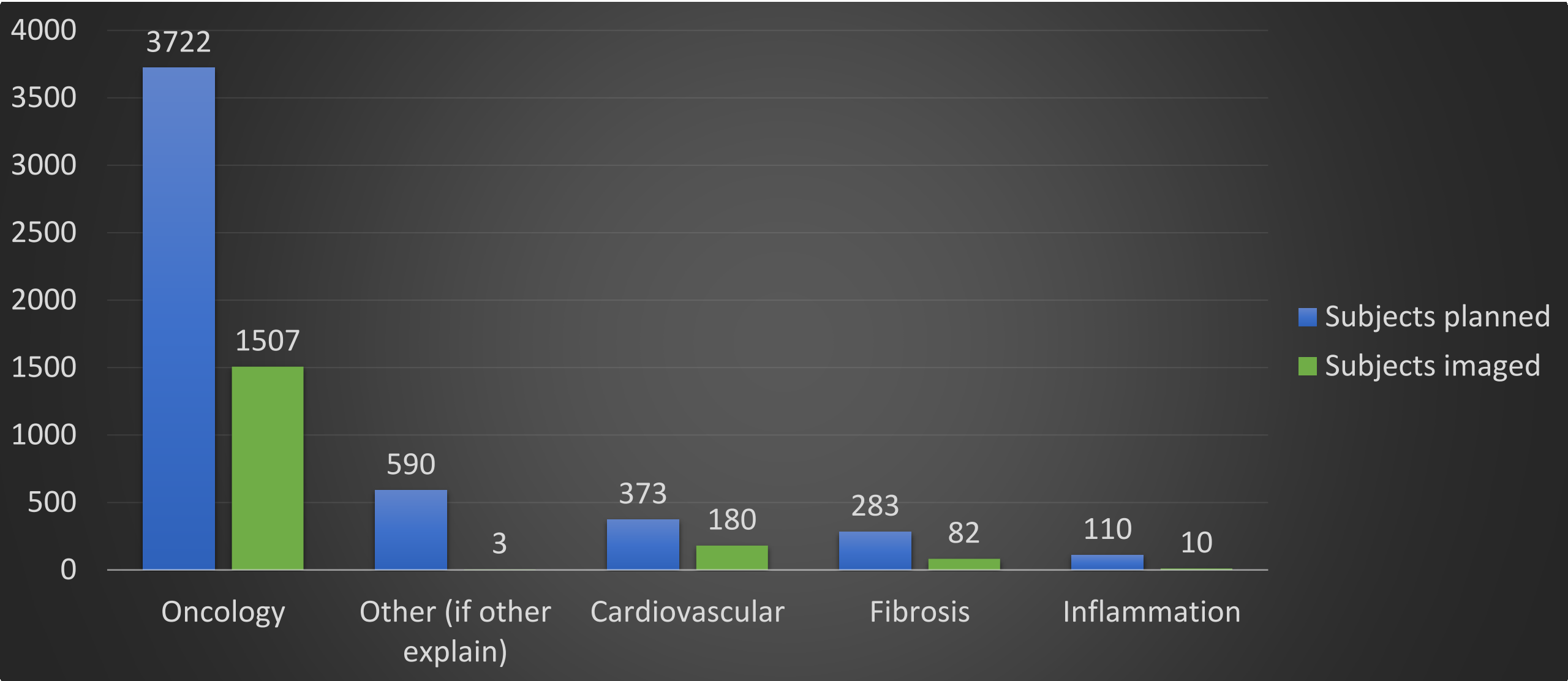
# Country breakdown of academic studies



Data as of progress report Oct 2023

**5,078** subjects planned

**1,782** subjects imaged



# Challenges and Considerations

Challenges:

- Use of various FAP targeting compounds and diluting the data (FAPI-04 for example is an older generation instead of FAPI-46 or FAPI-74)
- Many case studies. Shortage of larger prospective cohort studies

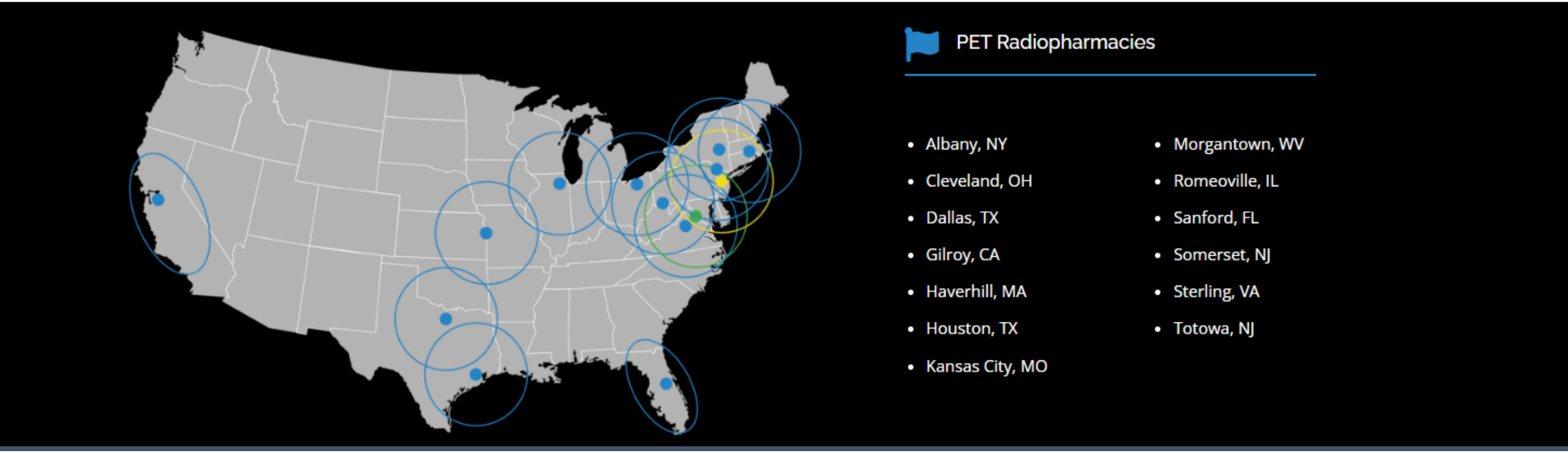
Need

- Identifying and pursuing strong indications that address an area of unmet need
- Confirming identity of lesions seen by FAP PET not simply # of lesions
- Pursuing value of FAP ligands for imaging as companion diagnostics for RLT and non-RLT in oncology and non oncology
- Ensuring strong supply chain availability to support standalone and companion diagnostic use

# FAP Diagnostic

- Stand-alone diagnostic
  - Oncology
  - Non-oncology
- Companion diagnostic
  - RLT
    - Oncology
  - Non-RLT
    - Oncology
    - Non-oncology

# 18F-FAPI-74 manufacturing network




Activated sites:

- Totowa, New Jersey (complete)
- Gilroy, CA (complete)
- Romeoville, IL (due July 2024)

Upcoming sites: due by summer 2025

- Cleveland, OH
- Texas
- Sanford, FL

# SOFIE and the FAPI team will be at SNMMI 2024 in Toronto

# Driving Molecular Imaging innovation with “FAPI”

Symposium co-sponsored by SOFIE and GE HealthCare

TIME: Sunday, June 9, 2024, 6:30-8:30pm
ROOM: South Building, 700 Level, Room 718A

VENUE: Metro Toronto Convention Center
SNMMI’24 annual meeting, Toronto (CAN)
Refreshments will be provided

| TIME | SCIENTIFIC AGENDA | SPEAKERS |
|---|---|---|
| 6:30 – 6:35pm | Introduction & speakers presentation | Chair/Host:<br>**Paul Evans** (Head of Global R&D, GE HealthCare)<br>**Sherly Mosessian** (Chief Scientific Officer, SOFIE) |
| 6:35 – 6:50pm | Current state of FAP imaging:<br>technology vs research applications | **Andrew Scott**<br>(Olivia Newton-John Cancer Research Institute, Melbourne, AUS) |
| 6:50 – 7:30pm | Perspectives on FAPI* Phase II progress | **Shadi Esfahani** (Massachusetts General Hospital, Boston, USA) |
| 7:30 – 7:45pm | The pivotal role of Fibroblasts in Inflammation and Fibrosis | **Olivier Gheysens** (Cliniques Universitaires Saint-Luc UCLouvain, Bruxelles, BE) |
| 7:45 – 8:15pm | Panel discussion:<br>Fibroblast-targeting therapeutic strategies in Cancer, Inflammation and Fibrotic diseases | Panel’s Chair/Moderator: **Andrew Scott**<br>• **Josie Gayton** (Chief Development Officer, Precirix)<br>• **Philippe Legenne** (Chief Medical Officer, Molecular Partners)<br>• **Stephen Moran** (Global Program Head & Platform Lead, Radiopharmaceuticals, Novartis) |
| 8:15 – 8:25pm | Q&A | All |
| 8:25 - 8:30pm | Wrap up and greetings | Chair/Host:<br>**Paul Evans** (Head of Global R&D, GE HealthCare)<br>**Sherly Mosessian** (Chief Scientific Officer, SOFIE) |

SOFIE
From start to clinic

GE HealthCare

*Represent concepts in development that are not yet products and may never become products. None of these concepts are being offered for sale today or have been cleared or approved by any regulatory authority for commercial availability.


Development
Leading the clinical development of [68Ga]FAPI-46 and [18F]FAPI-74. SOFIE's studies are in prospective Phase 2 trials in the United States.
SOFIE Sponsored Trials
PRE-CLINICAL
PHASE I
PHASE II
PHASE III
Gastrointestinal Cancers
Pancreatic Cancer
Scan the code to learn more: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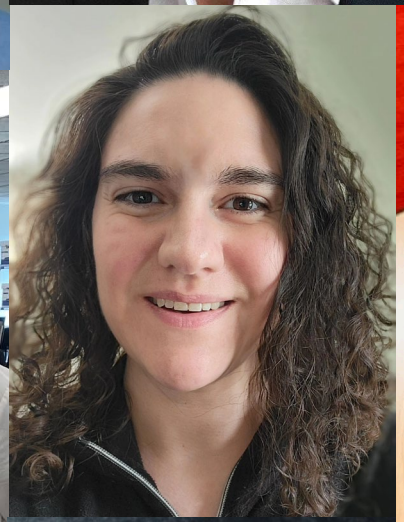


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NUCLEAR MEDICINE RECEIVING ROOM

# Thank you

For FAPI-related inquiries, e-mail us: FAPIprogram@sofie.com