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# Molecular Imaging: Hope or Hype?

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**With help from Marty Pomper JHU, Lisa Baird WMIC, Mike Phelps UCLA**

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# What is hype?

- A fad. promote or publicize (a product or idea) intensively, often exaggerating its importance or benefits.



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# Is there hype in Imaging?

- Drug development
- Patient selection
- Early detection
- Monitoring responses
- Theranostics

# Molecular Imaging in Drug Development

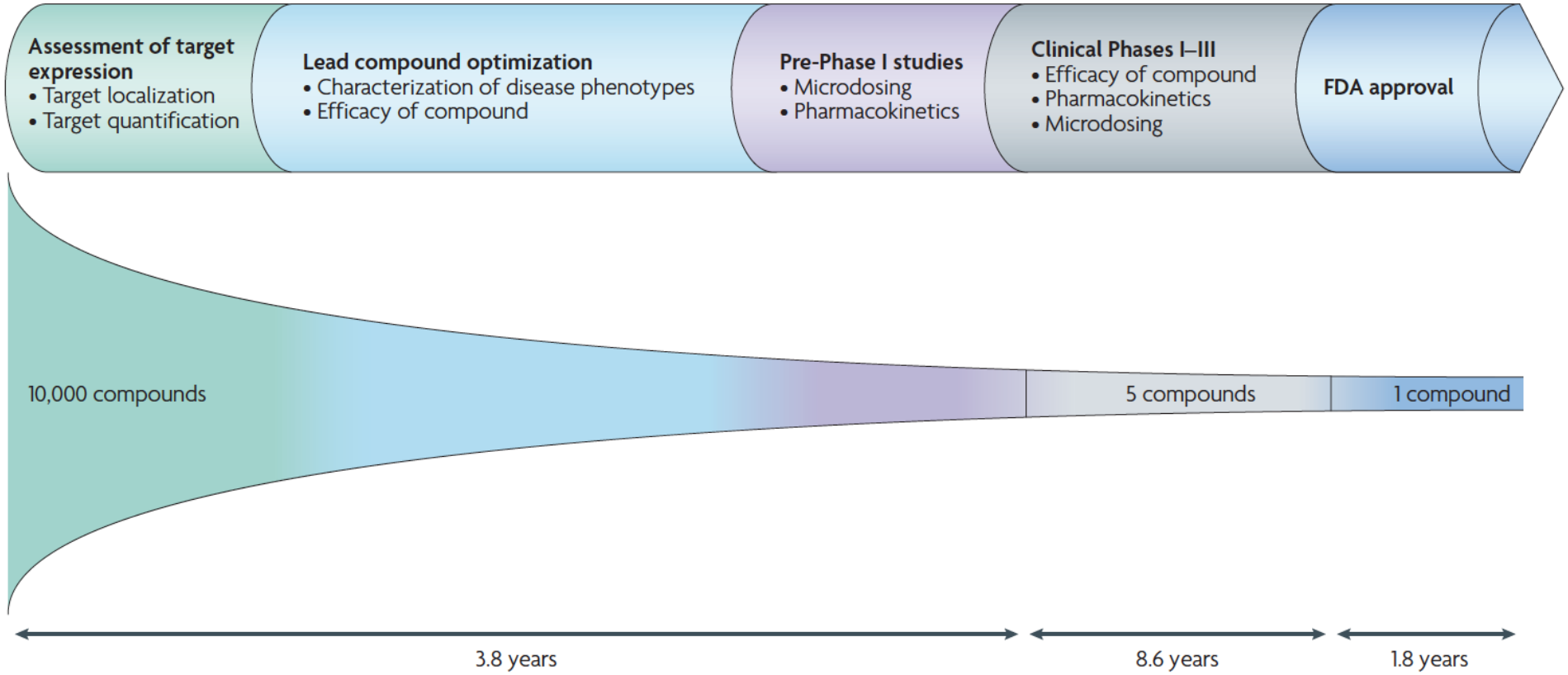


Figure 1 | **Molecular imaging and the drug development process.** On average, for ~10,000 compounds evaluated in preclinical studies, about five compounds enter clinical trials and about one compound finally receives regulatory approval by the US Food and Drug Administration (FDA)[3]. The mean time from synthesis of a new compound to marketing approval in the United States is 14.2 years[137]. Molecular imaging can be used at various stages in the drug development process, as illustrated here, which may help reduce attrition rates and allow the selection of the most promising drug candidates early on in development.

Willmann, J. K.; van Bruggen, N.; Dinkelborg, L. M.; Gambhir, S. S. Molecular imaging in drug development. *Nature Reviews Drug Discovery* **2008,** *7*, 591.

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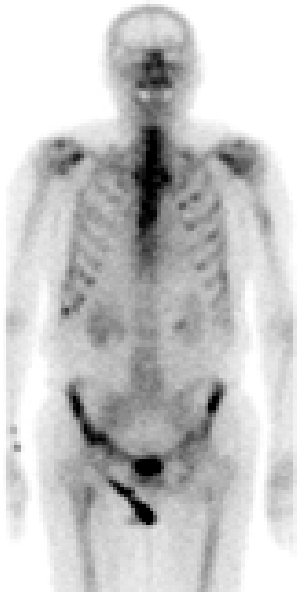
# Targeted Imaging



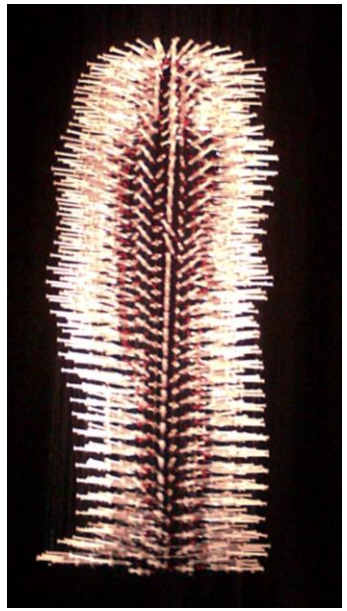
$^{99}$Tc – Bone Scan

$^{18}$F-FDG PET/CT
Glycolysis

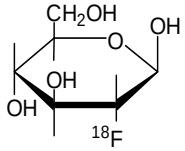
$^{18}$F-FDHT PET/CT
Androgen Receptor

$^{18}$F-FDHT PET/CT
(Baseline)

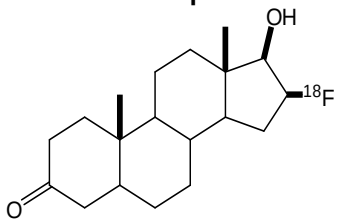
$^{18}$F-FDHT PET/CT
4 wks after Enzalutamide



Grace Cathedral
San Francisco




**$^{18}$F-FDG**
Imaging of Glucose Metabolism




**$^{18}$F-FDHT**
Imaging of Androgen Receptors

Fox et al., JAMA Oncology, 2018.

Hricak, Radiology, 2011

Scher, Sawyer, Larson et al., Lancet 2010

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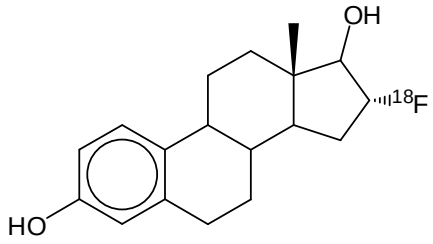
# $^{18}$F-FES PET/CT: GDC-0810 (ARN-810)




**$^{18}$F-FES**
Imaging of Estrogen Receptors

GDC-0810 (ARN-810) – an orally bioavailable selective estrogen receptor degrader

Pre-treatment Post-treatment

## Roche's bought out Seragon for $1.7B

**Confirmed full target occupancy ~20 hours post dose**

Wang et al., Clin Cancer Res., 2017

Courtesy of Drs. Ulaner, Dickler, et al.,

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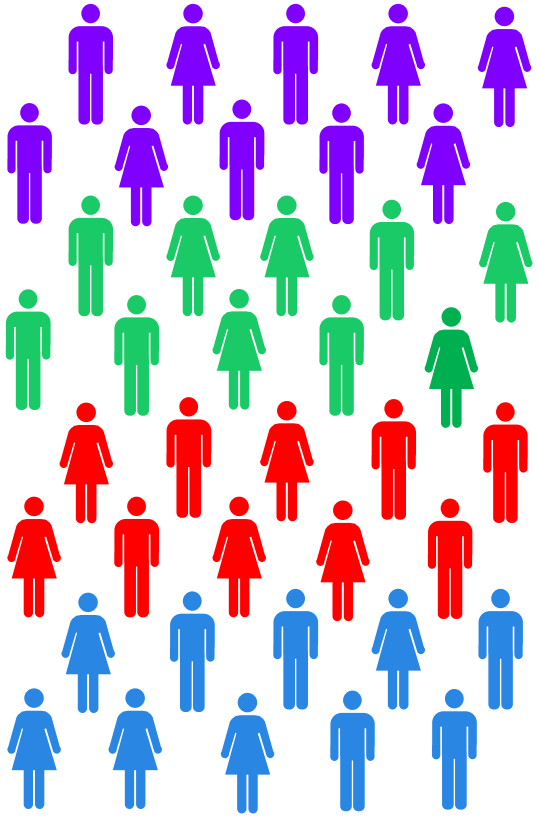
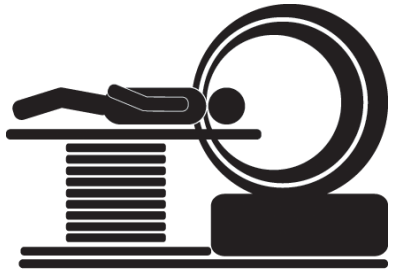
# Molecular Imaging for Target Engagement





Molecular Imaging Technologies

Target Engagement

No Target Engagement

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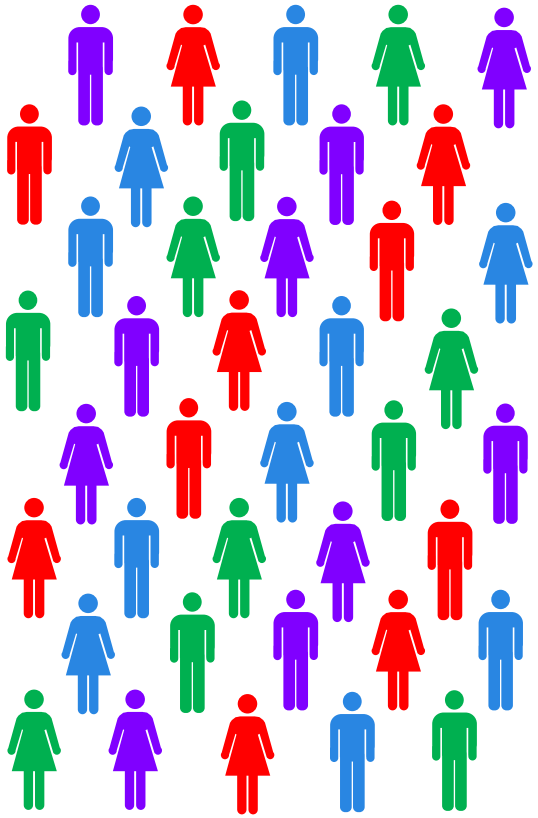
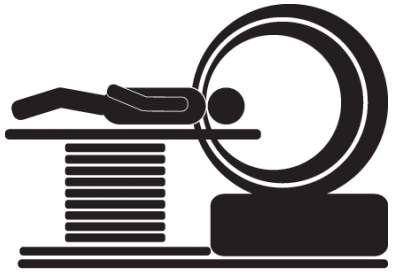
# Molecular Imaging for Patient Selection





Molecular Imaging Technologies

Oncogene 1

Oncogene 2

Oncogene 3

Oncogene 4

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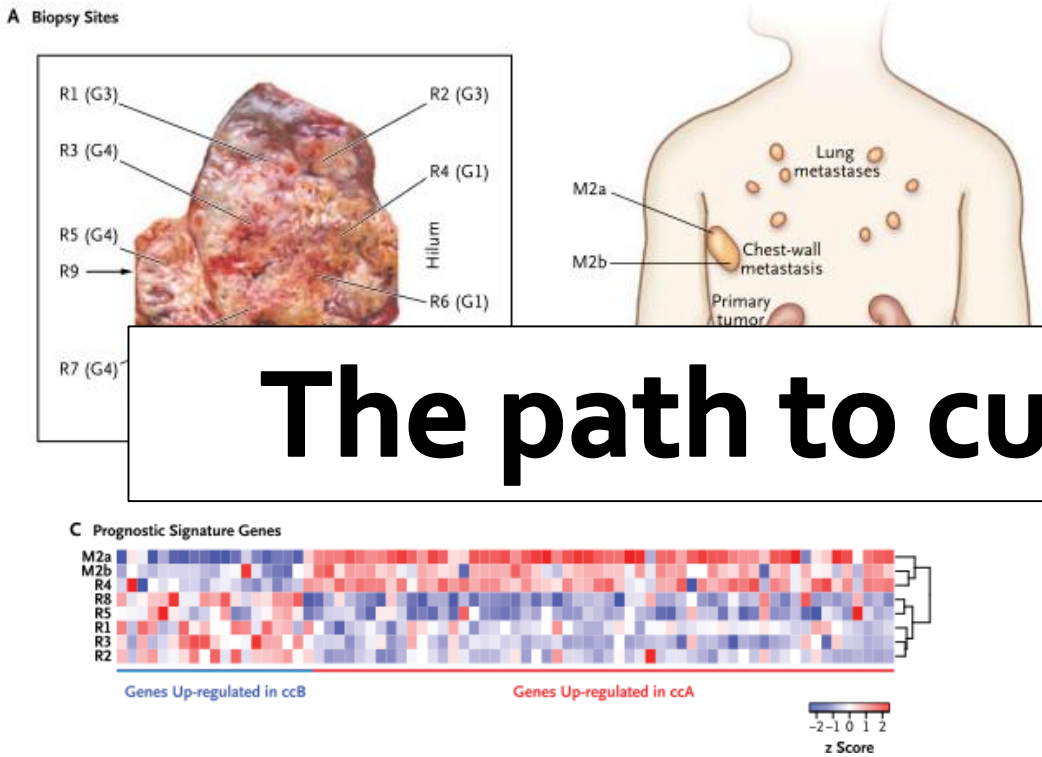
# Cancer is Heterogeneous




CANCER ETIOLOGY

**Variation in cancer risk among tissues can be explained by the number of stem cell divisions**

Cristian Tomasetti[1]* and Bert Vogelstein[2]*

her
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f the variation
ed

predispositions. The majority is due to "bad luck," that is, random mutations arising during DNA replication in normal, noncancerous stem cells. This is important not only for

DNA replication in normal, noncancerous stem cells. This is important not only for understanding the disease but also for designing strategies to limit the mortality it causes.

## The path to cure: early detection

Gerlinger et al. N Engl J Med (2012) 366:883-892, Figures 2 and 3

Vogelstein et al, *Science* 2015

**Benjamin Mazer**: "When you go about testing everyone for everything, you don't create a world of healthy people….you create a nightmare where everyone is sick"
— https://blogs.bmj.com/bmj/2018/06/19/benjamin-mazer-theranos-dystopian-vision-lives-on/ …

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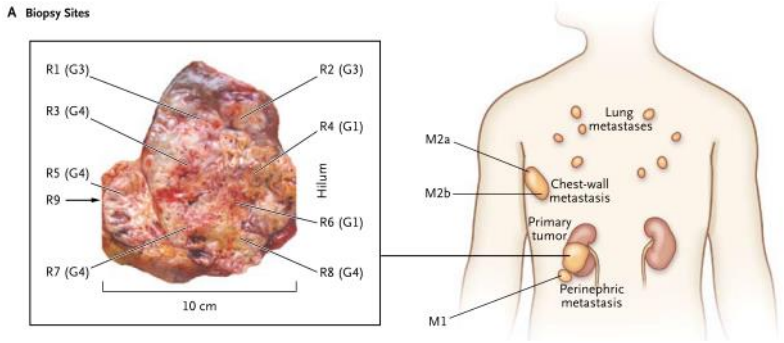
# Biopsy *vs*. Serum Biomarker *vs*. Imaging

## Serum (or other) biomarker

- Does not define *source* of biomarker
- Minimally invasive
- Not lesion specific
- Neglects tumor heterogeneity, extent of disease and location(s)




Gerlinger et al. N Engl J Med (2012) 366:883-892

## Tissue Biopsy

- Sampling of very heterogeneous tissue – sampling error
- Invasive and often technically challenging

## Imaging

- Minimally invasive
- Wholes body quantitative measurements are possible
- Delineates intra- and interlesional heterogeneity

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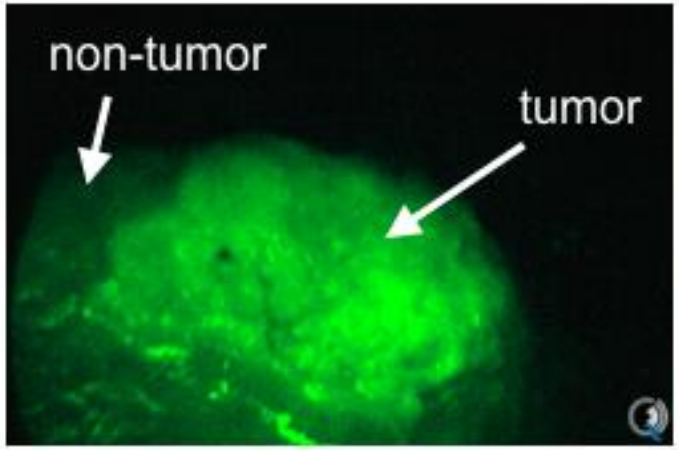
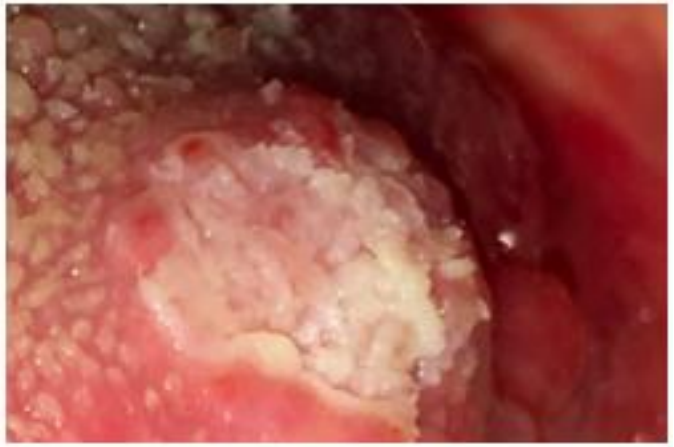
# PARP Imaging (Tom Reiner, MSK)


**NCT03085147**

1 min PARPi-FL swish and spit
1 min clearing solution swish and spit

phase I: imaging pre-surgery
phase II: imaging in the OR, followed by biopsy confirmation



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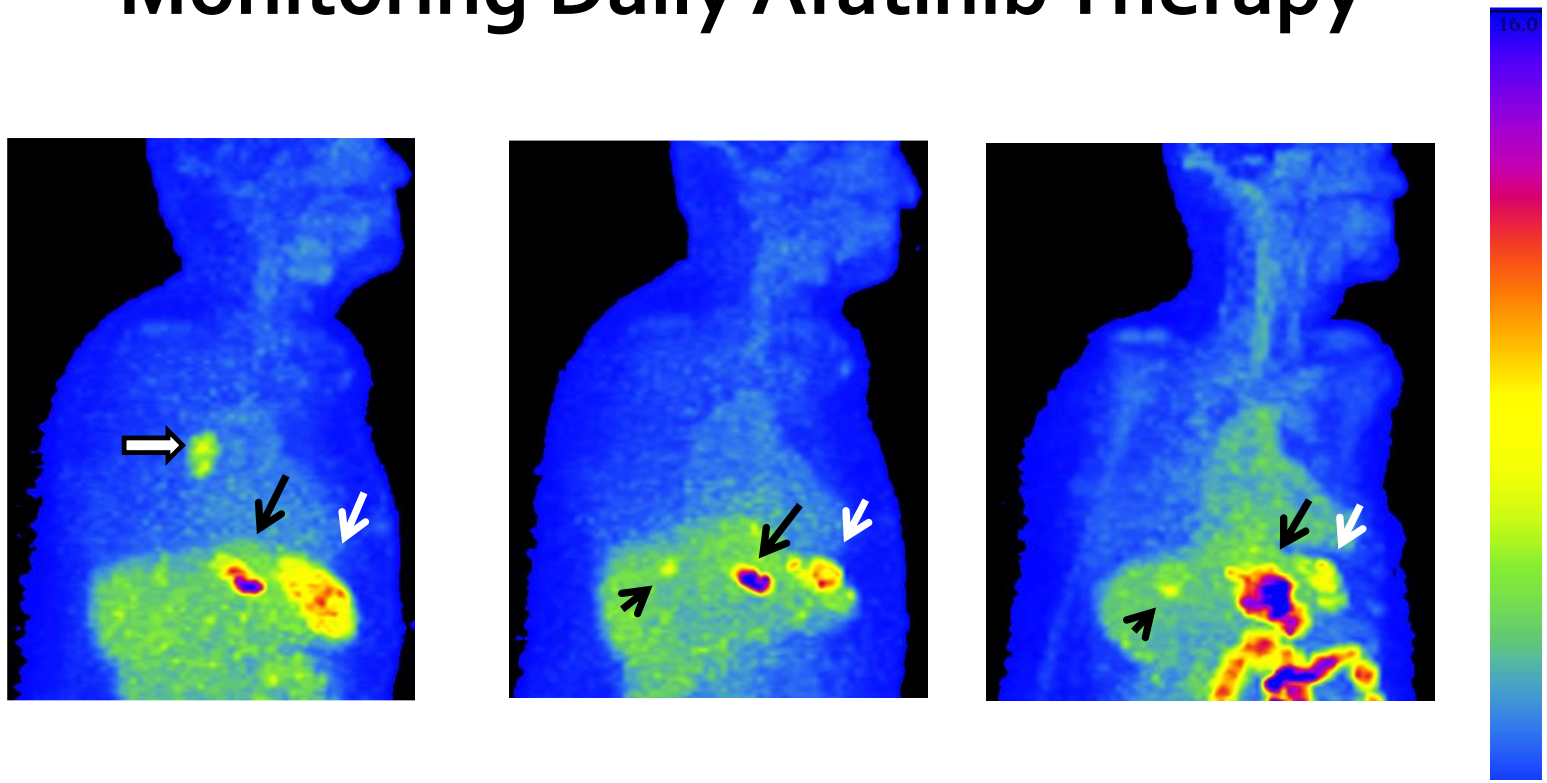
# Detection of HER2+ Gastric Cancer Monitoring Daily Afatinib Therapy




Start Afat and Tras d1

Stop Afat and Tras d111

Baseline d0
$^{89}$Zr-trastuzumab PET

On-treatment d21
$^{89}$Zr-trastuzumab PET

Progression 116d
$^{89}$Zr-trastuzumab PET

Janjigain et al., Cancer Discovery, 2018

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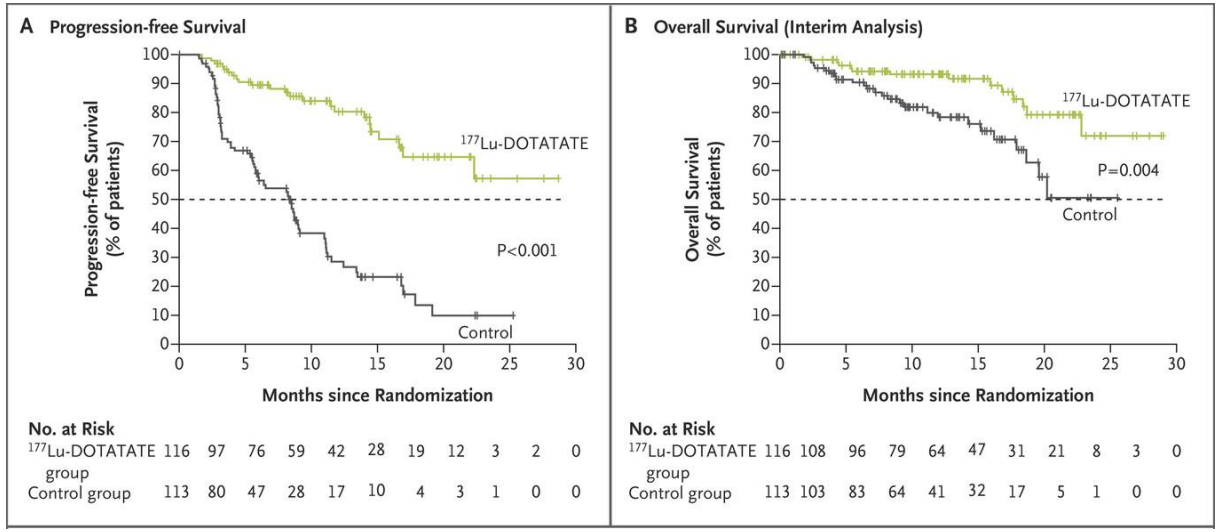
# Examples of Radiotheranostic Agents Currently Used or Under Clinical Development

| Cancer Type and Molecuar Target | Theranostic Pair |
|---|---|
| Thyroid | |
| NIS | $^{123}$I, $^{124}$I, or $^{131}$I for imaging, $^{131}$I for therapy (FDA approved) |
| Neuroendocrine tumors | |
| SSTR | $^{68}$Ga DOTATATE (FDA approved), $^{68}$Ga DOTATOC, or $^{68}$Ga DOTANOC for imaging, $^{177}$Lu or $^{90}$Y version for therapy, with alpha-emitting metals ($^{213}$Bi) in early human evaluation |
| Prostate cancer | |
| PSMA | $^{68}$Ga -PSMA-617 for imaging, $^{177}$Lu-PSMA-617 for therapy, with alpha-emitting metals ($^{225}$Ac PSMA-617, $^{213}$Bi PSMA-617) in early human evaluation |
| GRPR | $^{68}$Ga-NeoBOMB1 for GRPR imaging, $^{177}$Lu version for therapy |
| Lymphomas, myeloma | $^{68}$Ga-pentixafor for imaging, $^{177}$Lu-pentixafor for CXCR4 therapy; |
| CXCR4 | $^{111}$In-ibritumomab tiuxetan for imaging and $^{90}$Y version for CD20-targeted therapy (FDA approved) |
| CD20 | $^{131}$I-tositumomab for imaging and CD20-targeted therapy (FDA approved) |
| Neuroblastoma | |
| Norepinephrine receptor | $^{123}$I-MIBG for imaging, $^{131}$I-MIBG for therapy |
| Ovarian, breast | |
| Human epidermal growth factor receptor 2 | $^{212}$Pb-TCMC-trastuzumab for imaging and therapy; other radiometals such as $^{89}$Zr, $^{64}$Cu have also been used |

Jadvar, Chen, Cai, Mahmood, Radiology, 2018;286(2):388-400.

# Phase 3 Trial of $^{177}$Lu-Dotatate for Midgut Neuroendocrine Tumors (NETTER-1 Trial)

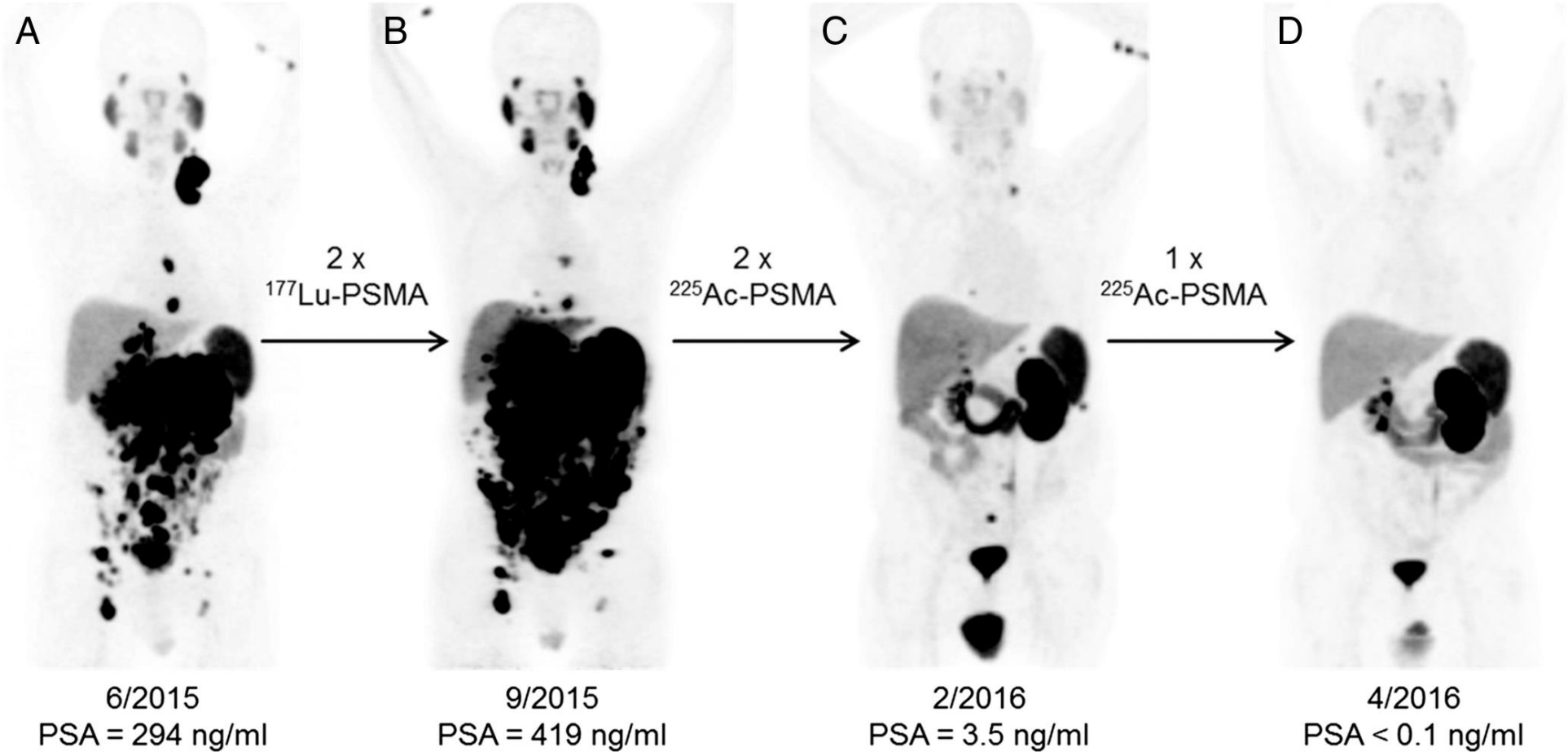



- January 26th, 2018: FDA Lutathera ($^{177}$Lu-dotatate) – this is the **first** time a radiopharmaceutical, has been approved for the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

- Life expectancy in **years** not months.

Strosberg et al., N Engl J Med 2017; 376:125-135

# $^{225}$Ac-PSMA-617 for PSMA-Targeted Radiation Therapy of CRPC




Kratochwil et al., JNM, 2016, 57, 1941-1944

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# What is the MI/Theranostics Market?

- **LUTHATHERA** - Novartis acquired AAA for $3.9 billion – Oct 2017
- **Endocyte** ($^{177}$Lu-PSMA-617) - Novartis acquired Endocyte for $2.1 billion on "on candidate with blockbuster potential" – Oct 2018
- Other companies activity exploring imaging, therapy and theranostic agents

- --10% improvement in lowering death rates – billions of $$s saved.

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# US Market 6.8 billion (2023)
# Neuroendocrine tumors & prostate cancer

## $819 mil

Diagnostic Market

### $^{68}$Ga-DOTATATE (Neuroendocrine)

$60 mil

20,000 patients /yr

$ 3,000.00 per patient

### $^{18}$F-PSMA[1] (Prostate Ca)

$759 mil

196,000 patients /yr

$ 3,875.00 per patient

## $6.2 bil

Therapeutic Market

### $^{177}$Lu-DOTATATE (Neuroendocrine)

$1.4 bil

7,500 patients /yr

30,000.00 cycles

$47,000 per cycle

### $^{177}$Lu-PSMA (Prostate Ca)

$4.8 bil

40,000 patients /yr

160,000 cycles

$30,000 per cycle

[1] national average for CMS reimbursement for the product PSMA will replace (Axumin)

Courtesy of Johannes Czernin, UCLA

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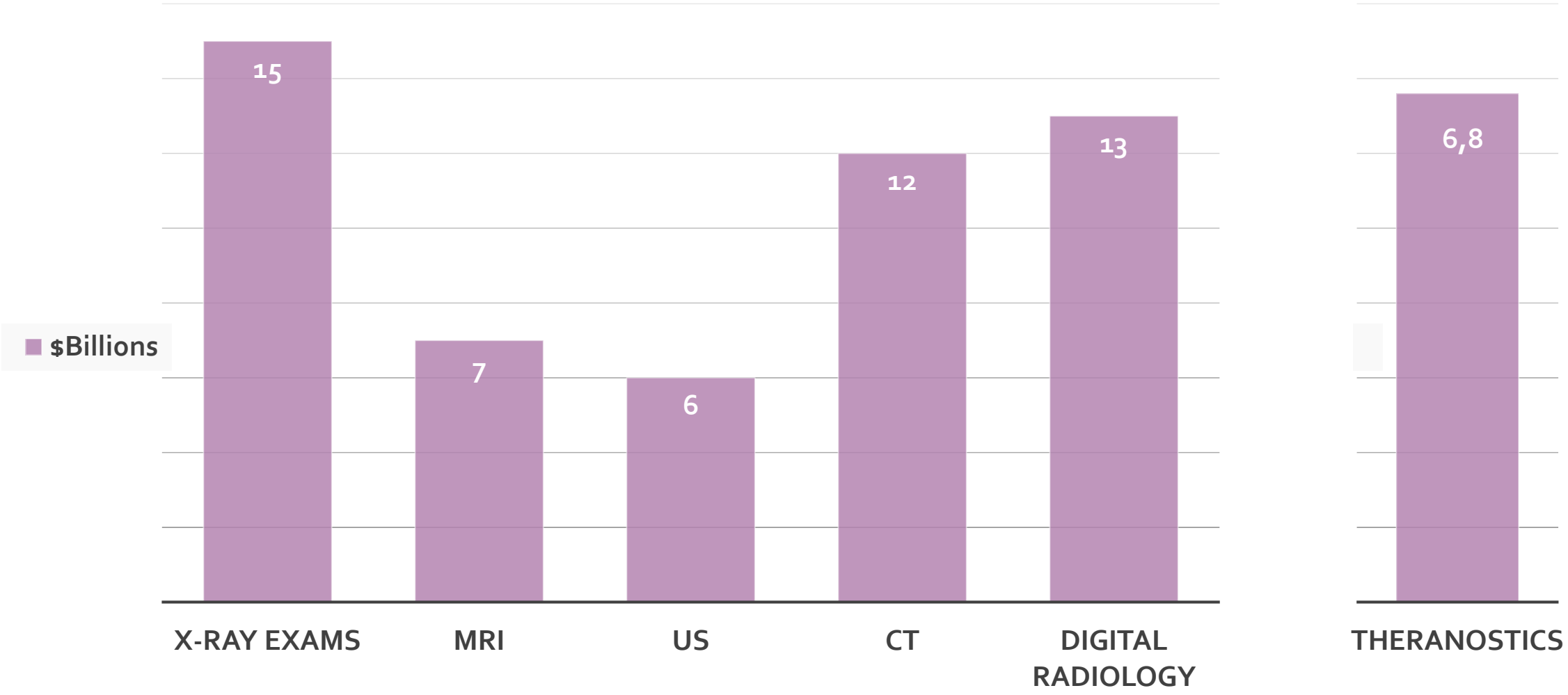
# Radiology Market

(The global medical imaging devices market is expected to generate revenue of $46.65 billion by 2023)



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# What are the threats to MI?

- Losing Radiology's value/ownership
  - the probe-building experts are generally in Radiology
  - intraoperative probes going to surgery
  - theranostics going to radiation oncology
- Major hurdle of imaging tracers is the FDA approval process

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# What about hype in Molecular Imaging?

- The concept of an "actionable image" – for "precision medicine" you need "precision imaging".
- MI can do a better job than AI/ML – because its about the underlying biology!
- Major benefits of MI
  - streamlining the drug development process (narrowing pipeline and lower cost)
  - stratifying patients for therapy
  - precursor to patient selection

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# Molecular Imaging: Hope or Hype?
# Lots of hope and not enough hype!

**"Imaging provides essential roadmaps for treatment planning"**

Oncologic Imaging: A Guiding Hand of Personalized Cancer Care

– H. Hricak, Radiology, 2011