

# Workshop on Contrast Enhanced Surgical Imaging

Eben Rosenthal, MD  
Ann and John Doerr Medical Director  
Stanford Cancer Center  
Stanford University

Many Thanks to:  
NCI Cancer Imaging Program  
FDA CDER, OCP, CDRH  
ASIGS and WMIS

Lalitha Shankar, Paula Jacobs,  
Bob Nordstrom

Jim Bacion, Mike Tweedle

# Conflicts



Grants or equipment loans:  
Novadaq, LI-COR

Advisory Board: Surgvision,  
Aspyrion, Medrobotics

I love dogs

**DOORBELL**



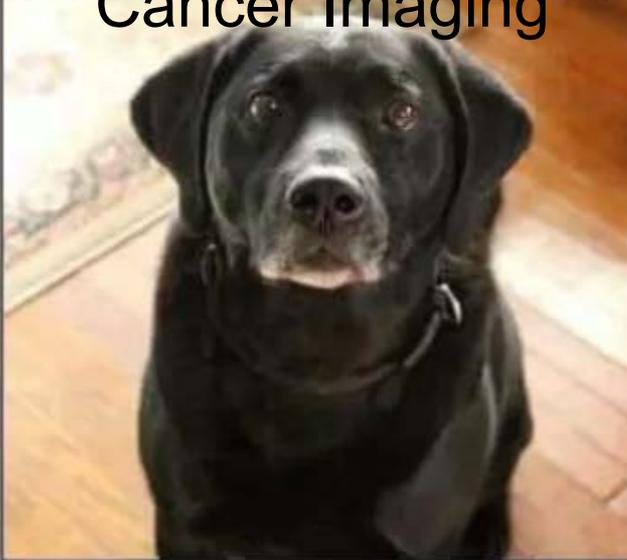
**MAILMAN**



**BURGLARY**



**CHEESE WRAPPER**



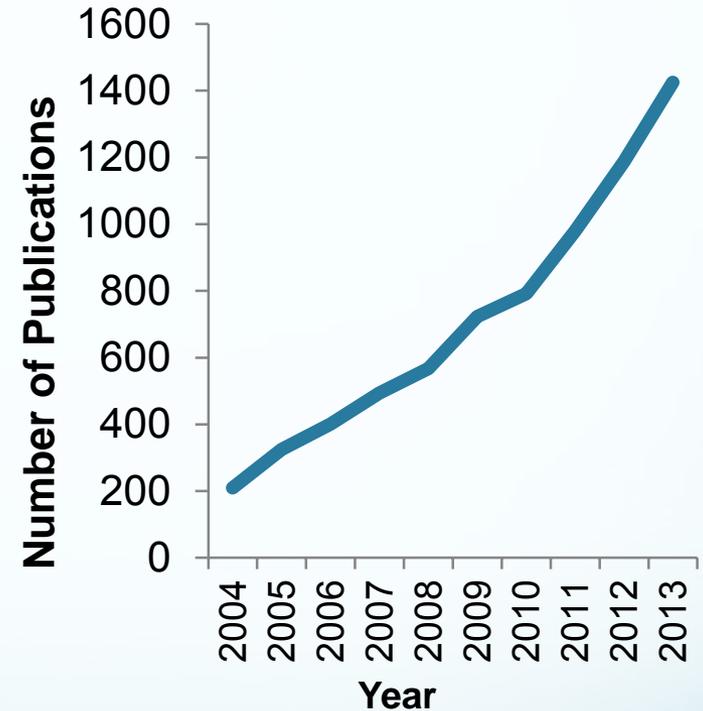
Cancer Imaging



*Why do we need contrast enhanced oncologic surgery?*

# Explosion of Intraoperative Imaging

- Improved technologies
- Publications
- A dozen phase I clinical trials began 2014-15

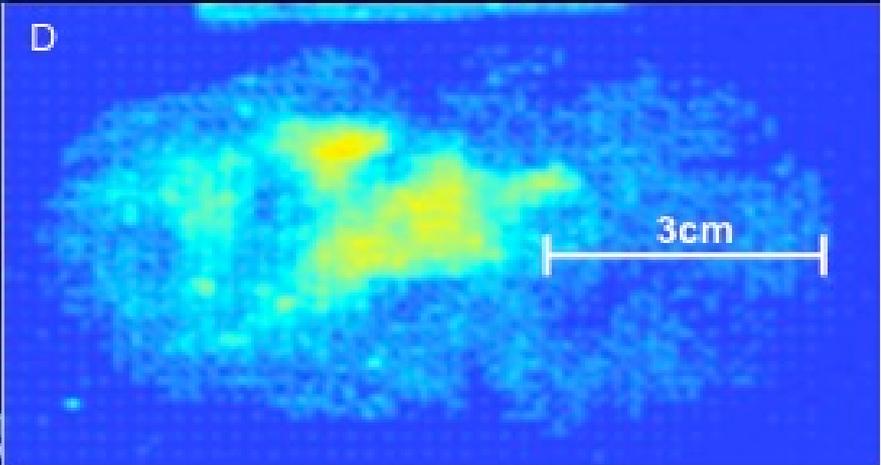
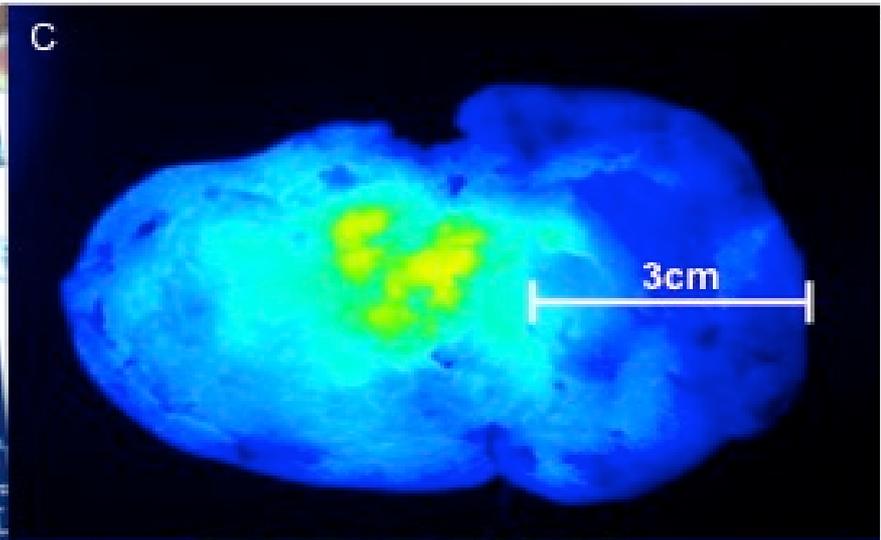


# Case Study

56 year old with recurrent cutaneous squamous cell carcinoma in a previously operated field with skin graft and failed radiation.

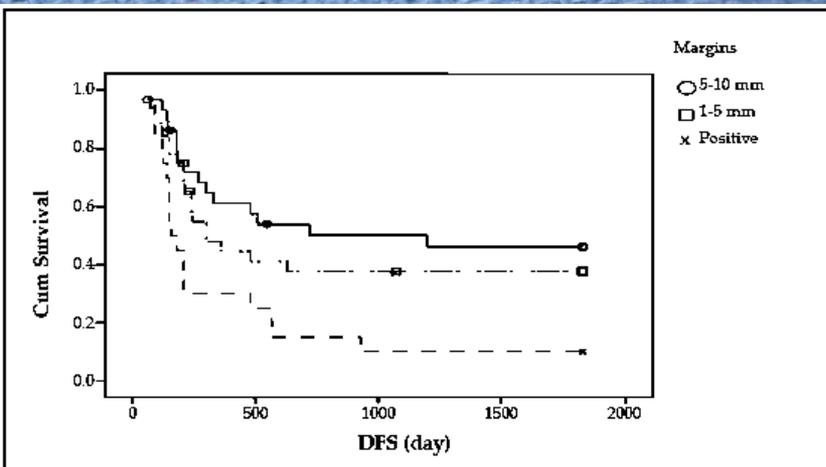
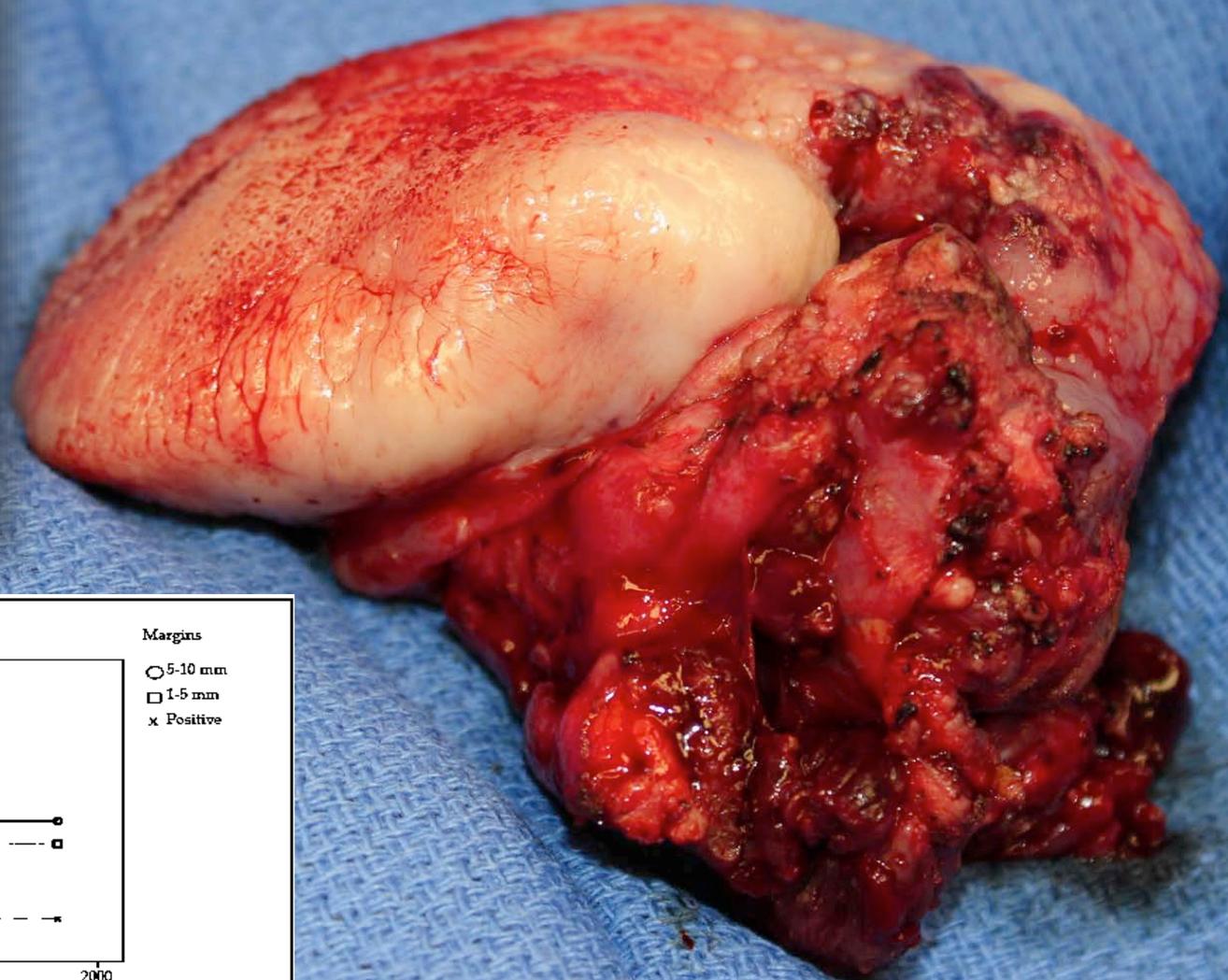


*Where do you make the cuts?  
How deep to you go?*



*Where do you make the cuts?  
How deep to you go?*

# Measuring margins in head and neck is challenging ... but it matters





**Bang Head**

**HERE**

## Sampling Error



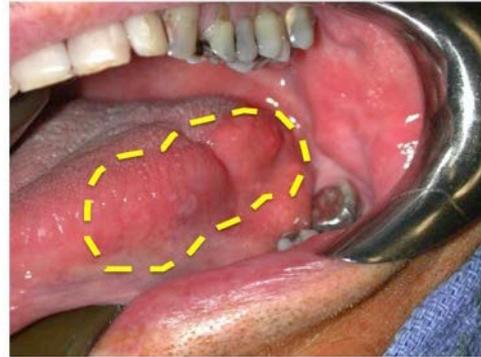
X1



X2



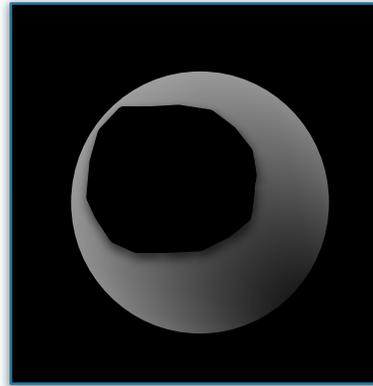
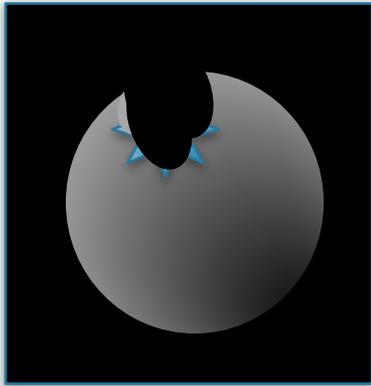
X3



## Limitations of Frozen Section

- Time consuming
- Reversal on permanent
- Not applicable to all tissues
- Sampling error
- It must be resected to assess (eye lid)

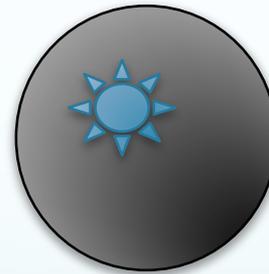
# Which Surgical Procedure?



Infiltrative  
Fixed to key structures  
Brain, pancreas



Wide local resection  
Skin, breast



Wide local resection  
Lung, colon, larynx

Debulking  
Ovarian, metastatic

Pathological  
Assessment





# Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial

Walter Stummer, Uwe Pichlmeier, Thomas Meinel, Otmar Dieter Wiestler, Friedhelm Zanella, Hans-Jürgen Reulen, for the ALA-Glioma Study Group\*

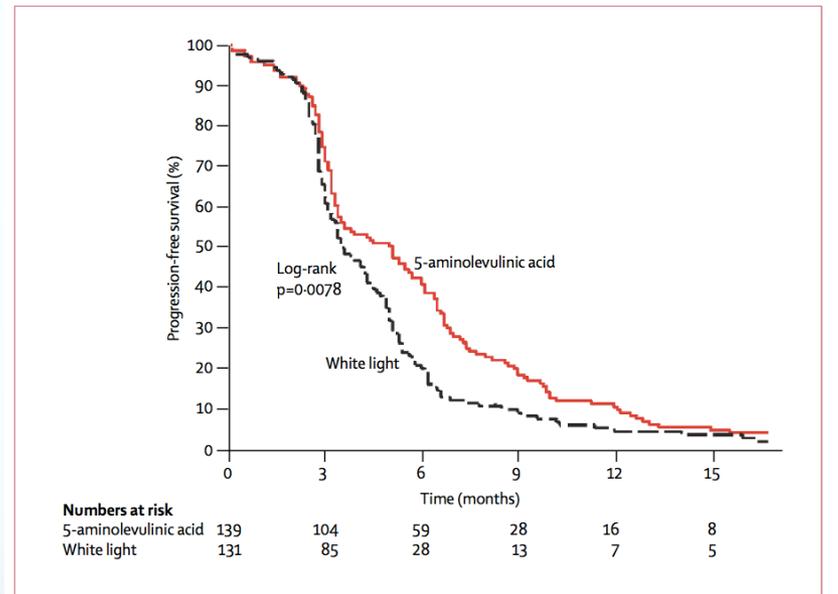
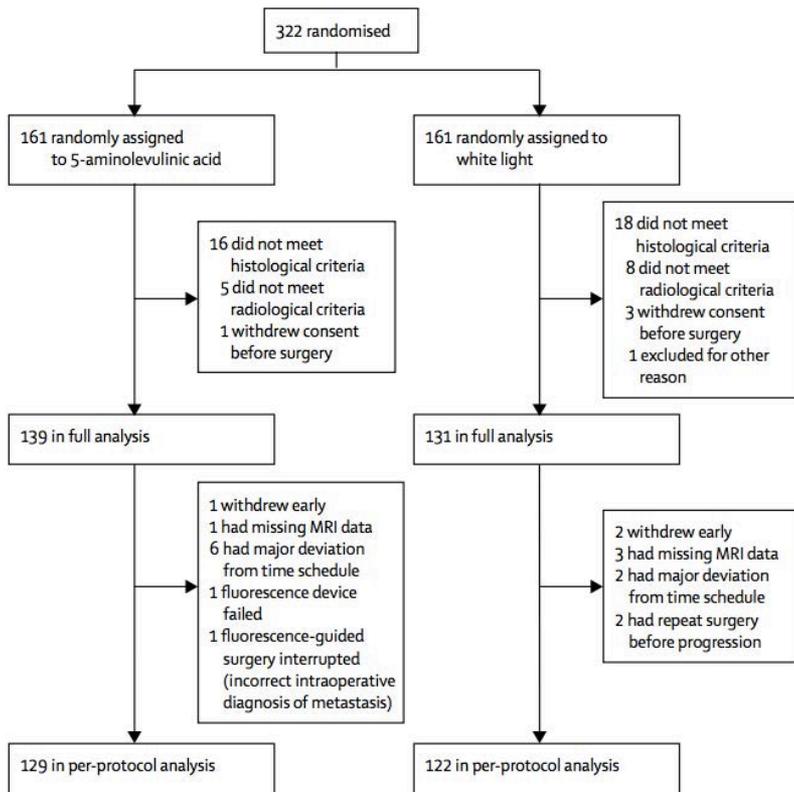


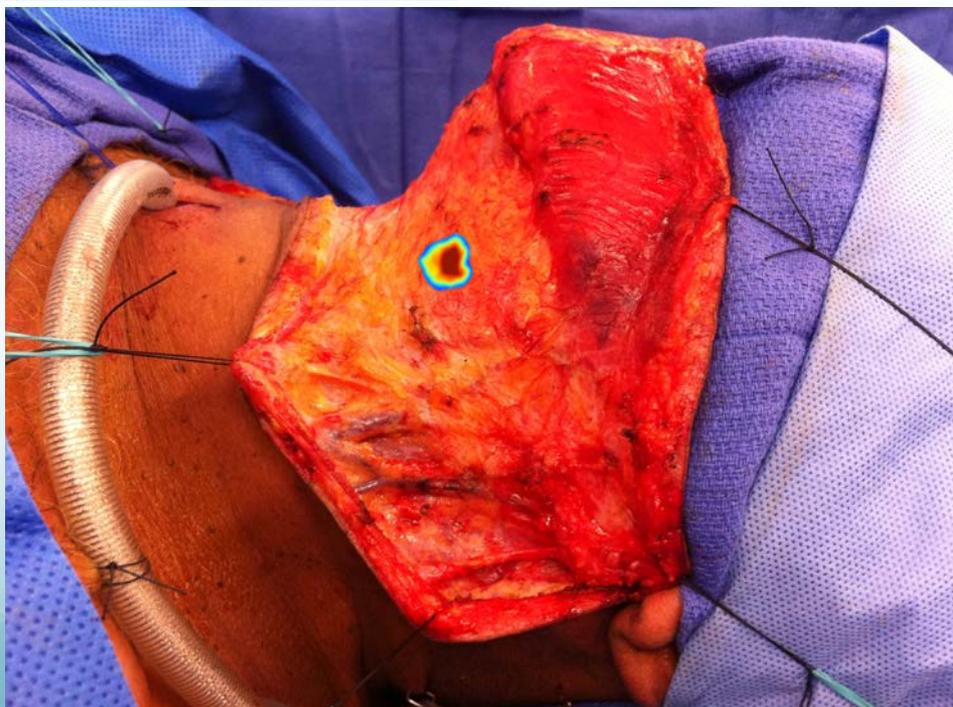
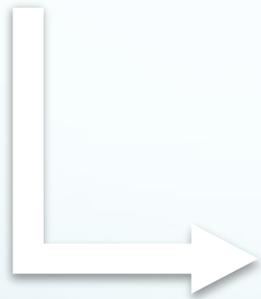
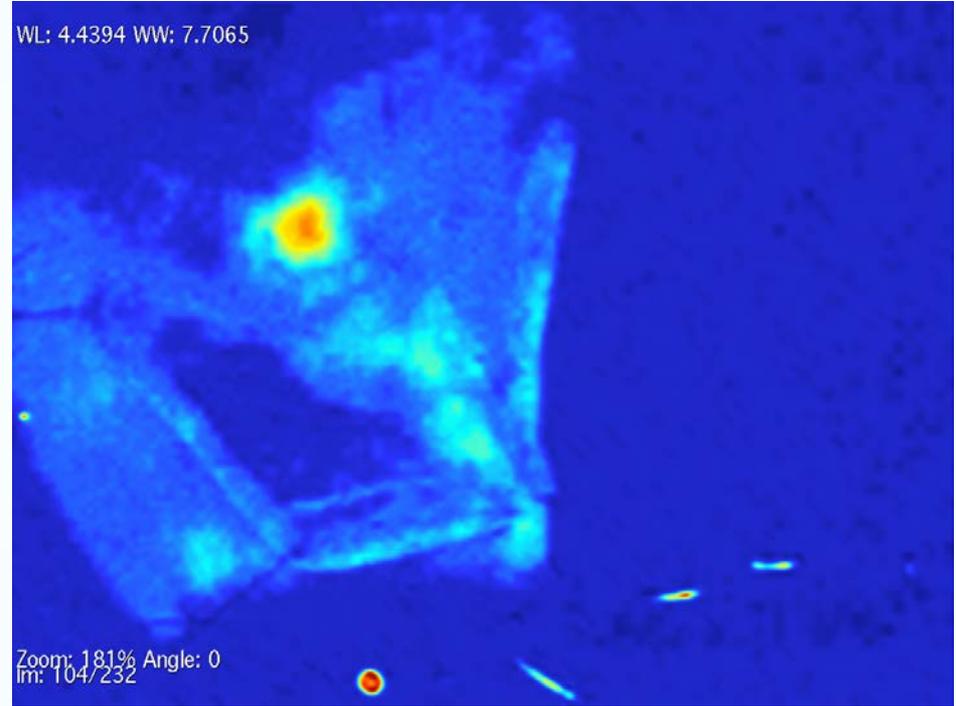
Figure 2: Progression-free survival by surgical group

# Lymph Node Identification

- Sentinel node identification
- Tumor containing node

Limit extent of nodal dissection

- Improve survival
- Reduce operative time
- Reduction in morbidity
  - lymphedema, nerve injuries

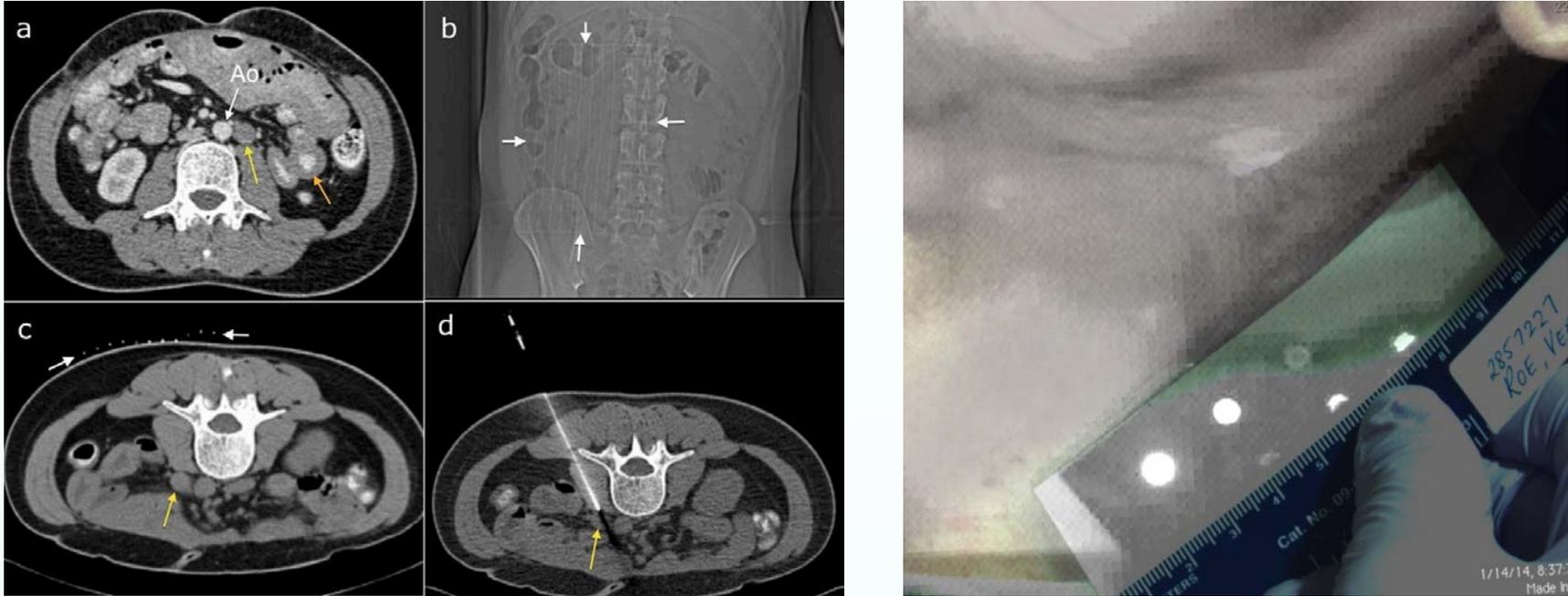


# Contrast Enhanced Surgery

*How are tumor enhancing agents used to  
improve outcomes today?*

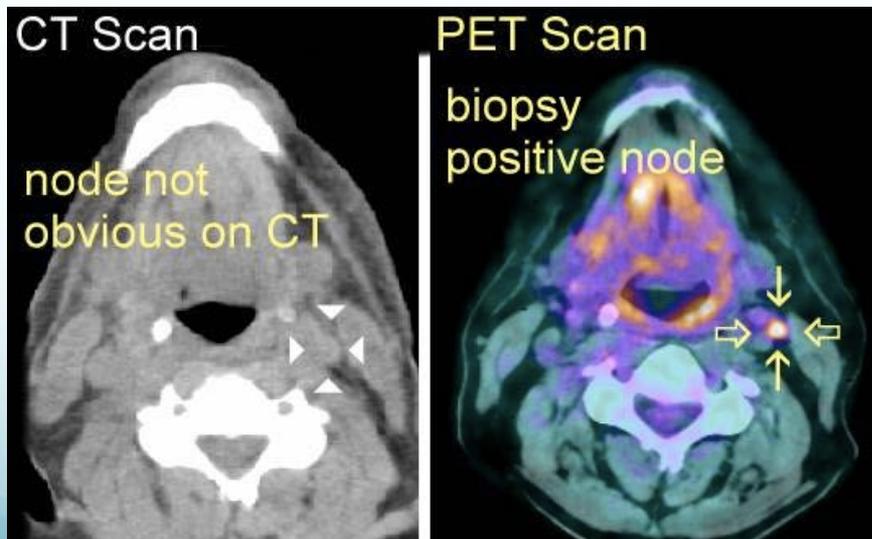
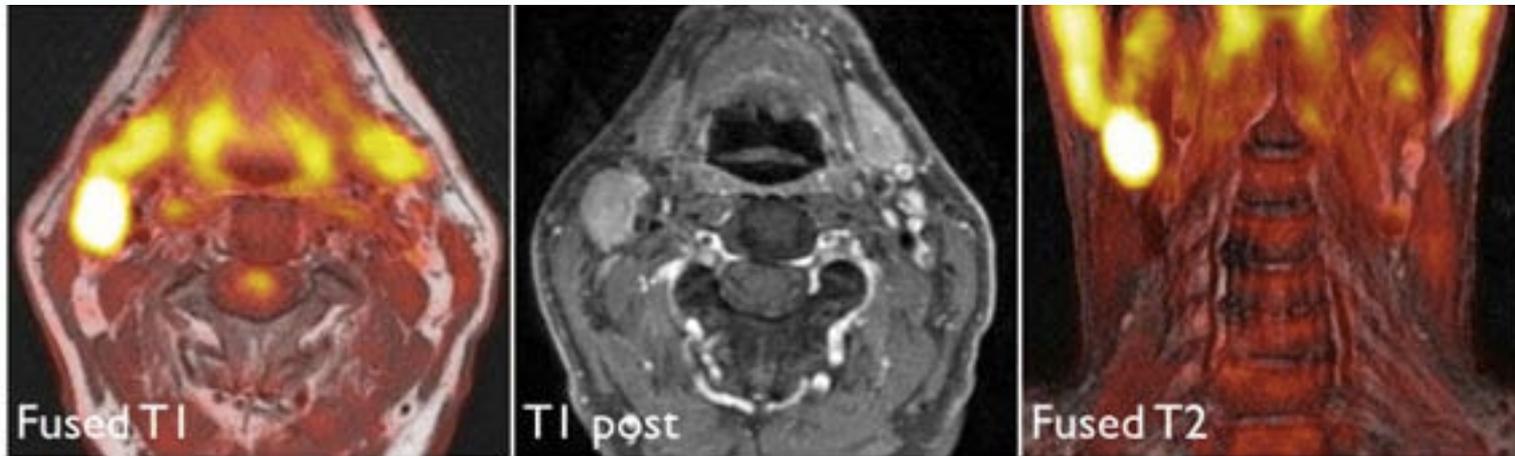
# CT-Guided Biopsy:

Non-specific contrast used to guide invasive procedure



Exogenous contrast for vasculature injected to identify areas of interest for further assessment

# Molecular Imaging Provides Additional Information



*Non-specific imaging common...but successfully provides actionable information*

## *What about real time surgery?*

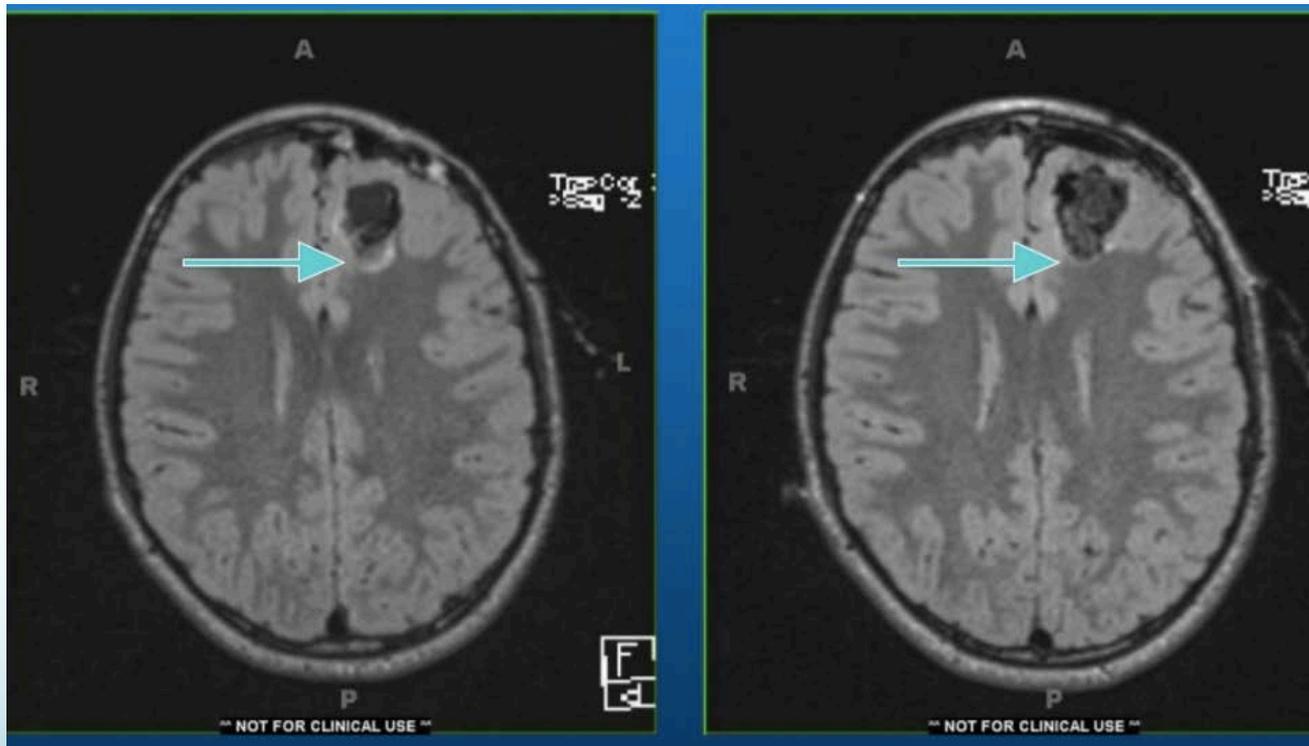
### MRI Guided Surgical Resection

MRI uses gadolinium as contrast enhancement of vasculature



- Approximately 90 hospitals world wide
- 4-7 million dollars per OR to purchase device
- Requires 2 operating rooms

# MRI with vascular enhancement as an indicator for additional resection



# MRI-guided brain surgery

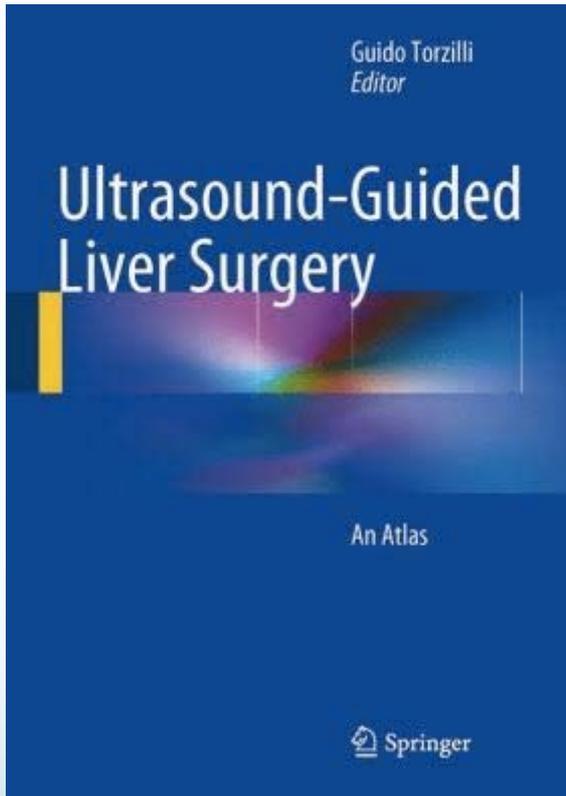
## Supra-complete surgery via dual intraoperative visualization approach (DiVA) prolongs patient survival in glioblastoma

**Ilker Y. Eyüpoglu<sup>1</sup>, Nirjhar Hore<sup>1</sup>, Andreas Merkel<sup>1</sup>, Rolf Buslei<sup>2</sup>, Michael Buchfelder<sup>1</sup>, Nicolai Savaskan<sup>1</sup>**

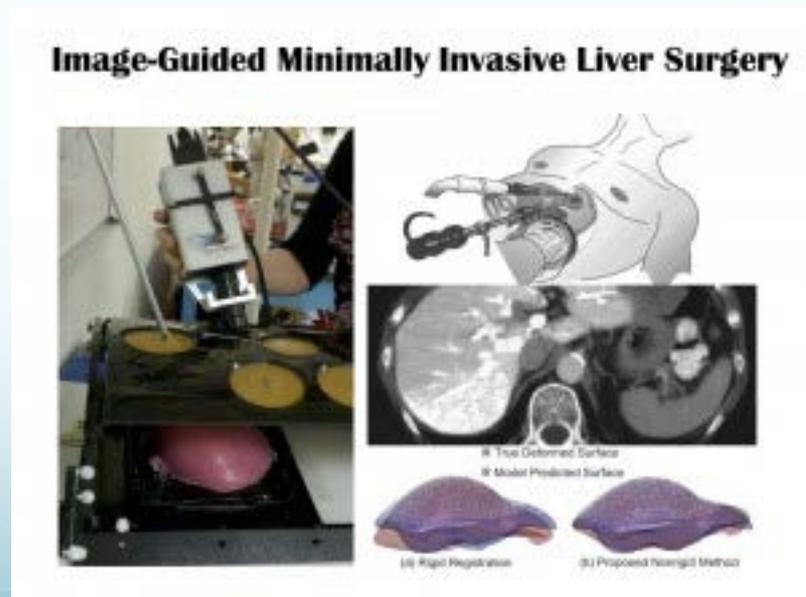
<sup>1</sup>Department of Neurosurgery, Translational Neurooncology Division, Medical Faculty of the Friedrich Alexander University of Erlangen-Nürnberg (FAU), Erlangen, Germany

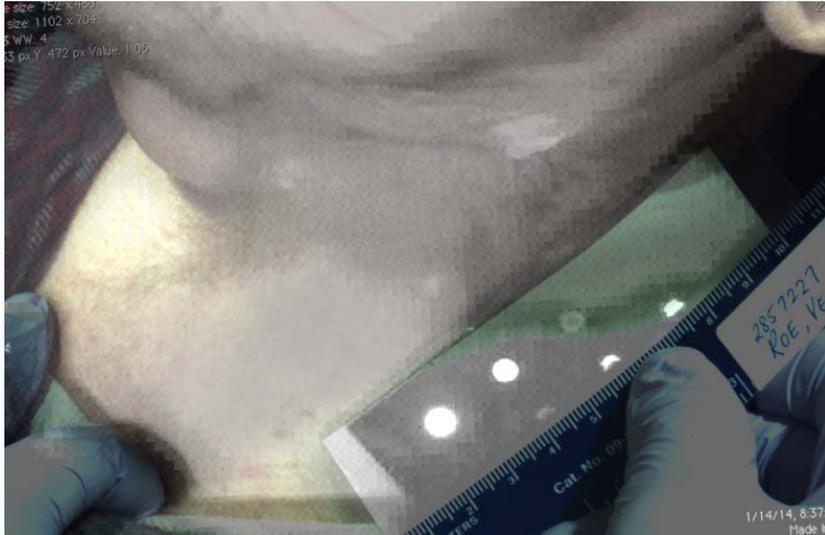
- The median survival time in the **control group** operated according to the current gold standard in surgical neuro-oncology was **14 months**, whereas surgery according to the **DiVA protocol** (= intraoperative-MRI and 5-ALA) resulted in a significantly longer median survival time of **18.5 months** in the corresponding group.

# Ultrasound-Guided Resections: Prostate and Liver



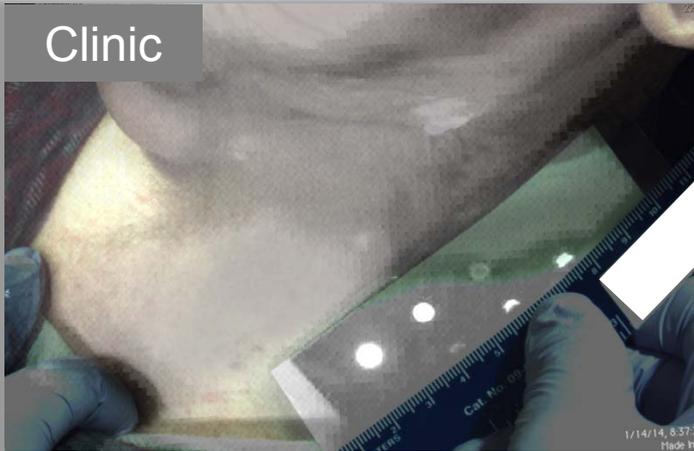
'Ultrasound guidance of liver surgery is a very sophisticated approach that permits the performance of otherwise unfeasible operations, discloses the true extent of tumors, increases the indications for hepatectomy, and renders surgery safer'



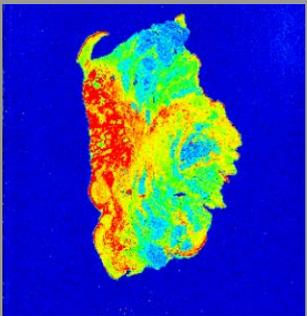
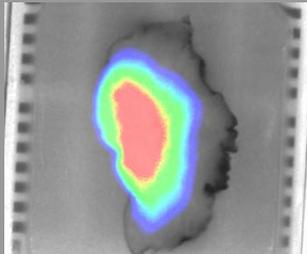


# Case Study: Contrast Enhanced Surgery

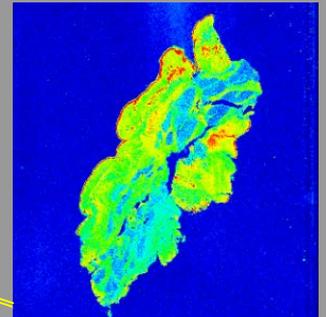
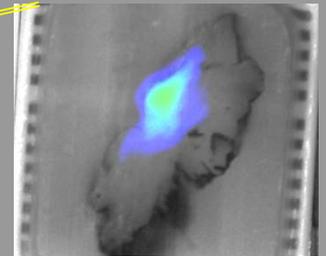
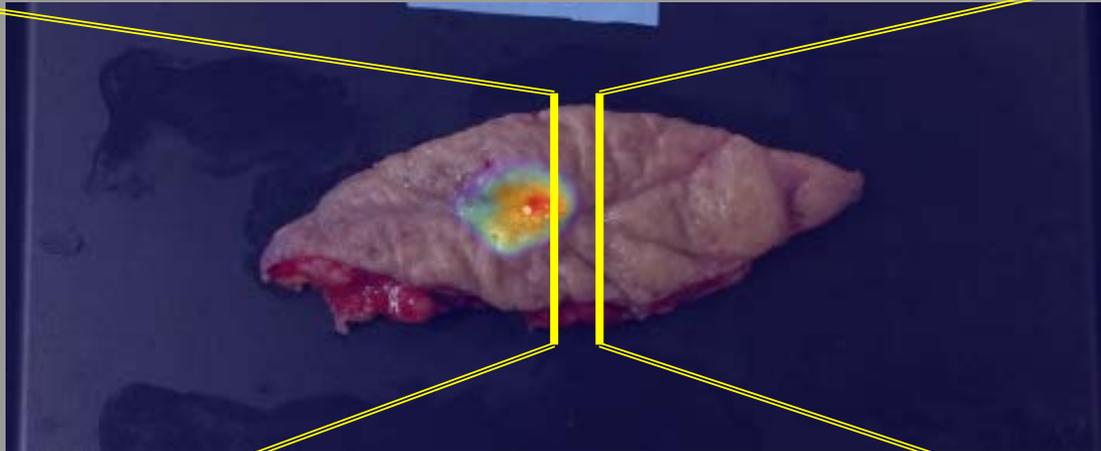
# Contrast enhanced surgical imaging with EGFR targeting antibody as guide for assessment



64 yo with history of previous neck node biopsy with suspicious 5 mm lesion in scar.



**Positive**



Negative

# Devices Reflect the Changing Field

[HOME](#)[COMPANY](#)[TECHNOLOGY](#)[APPLICATIONS](#)[CLINICAL PRODUCTS](#)[PRECLINICAL PRODUCTS](#)[NEWS](#)[CONTACT](#)

## CLINICAL

FLUOBEAM®  
INTEGRATED  
SOLUTION

FLUOBEAM®

FLUOBEAM® REFILL  
KIT

PUBLICATIONS

## Imaging devices

Fluobeam® is hand held CE medical Class IIa certified medical devices performing real time fluorescence imaging during open surgery. These device is indicated to visualize on a screen the flow, the distribution and/or the accumulation of Indocyanine Green (ICG) during and after surgery for the visualization of the blood flow.



Fluobeam® can also be used in the frame of clinical trials with markers different from ICG such as molecular imaging probes to detect tumors or to visualize tumor margin.

The Fluobeam® Integrated Solution has been designed to facilitate the fluorescence imaging visualization and set up management.

- Enhancement techniques
  - Vascular (ICG, gadolinium)
  - Metabolic (FDG-Glucose, 5-ALA, hexvix)
  - Enzymatic (optical)
  - Antibody targeting (PET or optical)

Enhancement strategy	Tumor Type	Target
Gadolinium/iodine contrast	Glioma, lung	Vasculature
Ultrasound	Liver, prostate	Tissue density
PET	Multiple	Metabolic activity
5-ALA/Hexivx	Brain, bladder	Metabolic activity



american society of  
image guided surgery



# OSN Workshop

May 4<sup>th</sup>

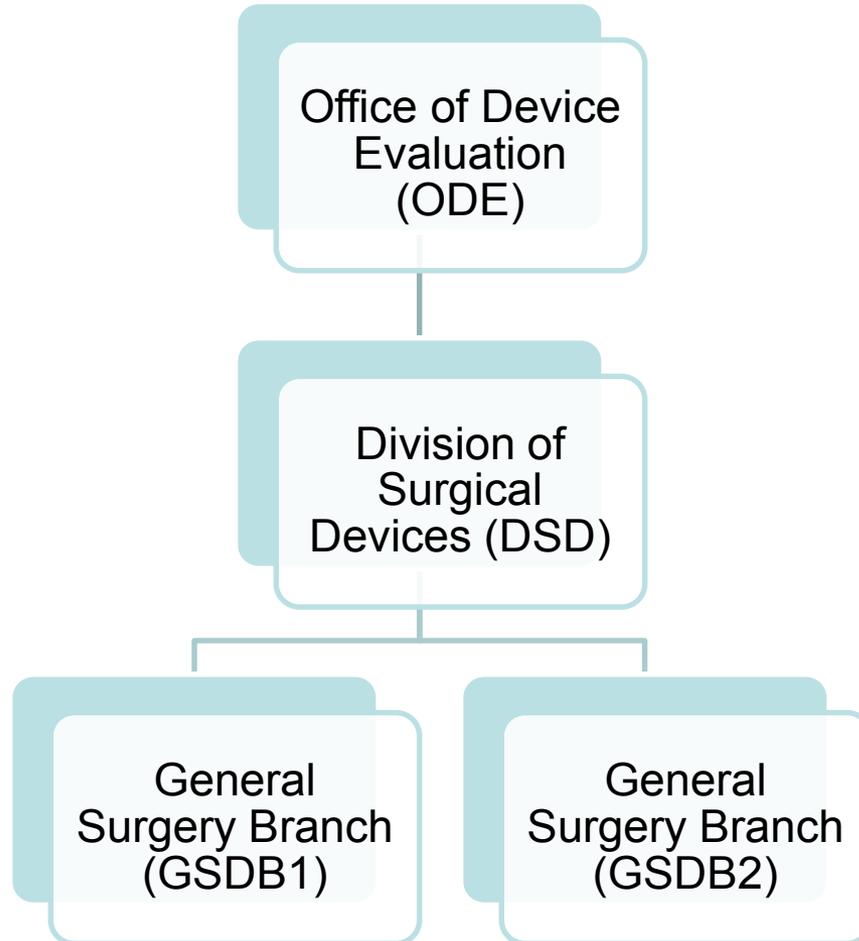
Betsy Ballard, MD FACS



# Who do I contact for advice on imaging drug development



# Contacting CDRH for Optical Imaging Devices



# Multi-disciplinary review teams

- **OND/ODEIV/DMIP**
  - Medical Officer
  - Pharmacologist/Toxicologist
  - Health Physicist
- **Other CDER Offices**
  - Chemist
  - Biologist
  - Statistician
  - Clinical Pharmacologist
  - Epidemiologist
  - Risk Management Specialist
  - Safety Evaluator
- **Collaborative Reviews with other Centers**

# CDER submissions/milestone meetings

- Investigational new drug application (IND)
  - Pre-submission, exploratory, original
  - End of phase 1, 2
  - Pre-phase 3
  
- Drug/Biologic Application (NDA/BLA)
  - Pre-submission
  - 21 Century review process

# CDRH Submissions

## Types of submissions

- Q submission
- 510(k)
- IDE
  - Early feasibility study (EFS)
  - Traditional feasibility
  - Pivotal trial
- PMA

# Review Process

- Received by division
- Assigned to a project manager and medical officer
- Determine what additional disciplines will be needed
- Determine if consults will be needed from other centers

# Optical Imaging

- Combination products
- Light based devices usually in the infra-red range
- Imaging agent tagged with a fluorophore that fluoresces at a particular wavelength

# Devices

- Uses a cleared device
- Makes modifications to an existing device
- New device altogether

# Fluorophores

- Approved/Investigational Dyes combined with
  - Investigational New Molecular Entity
  - Approved small molecule/ Biologics
  - Biologics in advanced stage of development
- Enzyme activated Products
- Supra paramagnetic iron oxide (SPIO) molecule
- Gold nanoparticles

## Scope

- Number of submissions have doubled each year over the last 3-4 years
- Consults from CDRH have increased
- Able to identify 26 submission currently under IND/IDE

# Contact Information

- For inquiries:

## CDRH

Neil Ogden

Neil.Ogden@fda.hhs.gov

## CDER

Kaye Kang

Kyong.Kang@fda.hhs.gov

# Pertinent Guidances

- The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]  
<http://www.fda.gov/downloads/MedicalDevices/.../UCM284443.pdf>
- Guidance on IDE Policies and Procedures  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf>
- Guidance for Industry and Food and Drug Administration Staff - FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089733.htm>

# Overview of Approval Paths Optical Surgical Navigation

*Paula M. Jacobs, Ph.D.  
Associate Director, Division of Cancer Treatment and Diagnosis, NCI  
Cancer Imaging Program*

# Complexity

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- Imaging used during surgery to identify specific tissue
- Intrinsically affects the patient treatment
- Generally involves one or more devices
- Often involves a drug – non-specific, specific, activatable

# Regulatory

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- Class II devices equivalent to an marketed device are cleared by the 501(k) process. A 510(K) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device
- Class III devices are cleared by a pre-market process (PMA). Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.
- Drugs are approved by the New Drug Application process NDA

# Variations on a theme, for science or for commerce

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- Drug with no device
- Device with no drug
- Drug with approved device
- Device with approved drug
- Device with required drug
- Drug with required device

# Drug with no device – approved as drug

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- Isosulfan blue for sentinel node (FDA approved)
- Methylene blue for sentinel node (not approved for this use but widely used)
- Injected subcutaneously (labeled method), peritumoral, intradermal
- Evaluated visually
- These are very old drugs even if specific NDAs are recent

# Device with no specific drug – cleared as device

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- Can rely on intrinsic properties of biological tissue
  - Autofluorescence
  - Raman spectroscopy
  - NIR spectroscopy
- Large number of optical coherence tomography (OCT) devices, especially in ophthalmology
- Also general imaging devices like PET (requires drug), MR, CT, US

# Drug with cleared general device

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- Can use any cleared device that qualifies
- Tc-99 sulfur colloid – “handheld gamma counter”, “planar imaging techniques”
- Tc-99 tilmanocept (Lymphoseek)– “handheld gamma counter”- intradermal, subcutaneous, subareolar, or peritumoral
- Indocyanine Green– hepatic function “recording densitometer”; ophthalmic angiography “imaging equipment”

# Device with approved drug

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- Camera systems for use with ICG, not sold with or brand of ICG specified
  - Photodynamic Eye (Hamamatsu) – 510(k) approved use with ICG (called combo by FDA)  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K110480>
  - Fluobeam (Fluoptics) – 510(k) approved use with ICG (called combo by FDA)  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K132475>
  - Predicate device Novadaq SPY, not called combo but still requires ICG
- Not cleared for use of other drugs with same spectral characteristics

# Drug with required device

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- Combination product for bladder cancer
  - Hexaminolevulinate (Cysview) NDA 022555
  - Karl Storz D Light C PDD system PMA P050027

# Device with required drug

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- Novadaq Spy Fluorescent Imaging System
  - Camera 510(k)
  - Sold with specific brand of ICG that is called out in the 510(k)
- DaVinci Firefly
  - Device for visible and NIR fluorescence 510(k)
  - Requires specific ICG kit that is called out in the 510(k)

# Drug with General Device – example Lymphoseek

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- Approval 2013
- Toxicology
  - Single dose in rats, rabbits and dogs
  - Repeat dose in rats and dogs
  - Genotoxicology – three studies
- Pharmacology -- In vitro and in vivo
  - Safety in dogs
  - PK in dogs, rabbits, and rats
  - Biodistribution

# Clinical Studies

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- Three studies
- 411 patients, melanoma, breast, SCC
- Comparison of planar scintigraphy with hand held device
- Comparison with blue dye
- Safety: 531 patients exposed

# Cysview as a modern example of a combination product

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- Cysview is indicated for use in the cystoscopic detection of non-muscle invasive papillary cancer of the bladder among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy. Cysview is used with the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system to perform cystoscopy with the blue light setting (Mode 2) as an adjunct to the white light setting (Mode 1).
- Priority Review 2009
- Approved 5/28/2010 as combination product, one primary study

# Karl Storz D-Light C PDD

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- Original PMA clearance was not designated as combination product in the database but was in the clearance letter
- Summary of Bench Testing and Sterilization processes
- Component camera system 510(k)cleared

# General Advice

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- Approval status of really old drugs does not provide any precedence
- Be wary of consultants who give you firm and absolute advice on how to approach a combo as drug or device
- Consider if you want to completely tie device and drug together or generalize both or either
- Consider which of the components presents the largest safety risk
- When in doubt, meet with FDA division you think most relevant, tell them what you intend to do, and listen to their input

# Where to get regulatory information about approved drugs and cleared devices

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- Devices (both have check box for combination products)
  - 510(k) cleared devices:  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>
  - PMA cleared devices:  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>
  - Summary statements available, supplements
- Drugs
  - Drugs at FDA <https://www.accessdata.fda.gov/scripts/cder/drugsatfda/>
  - Links to approval pages, with SBOA, labeling
  - Old drugs may not have either, get labeling at Daily Med:  
<https://dailymed.nlm.nih.gov/dailymed/>



**NATIONAL  
CANCER  
INSTITUTE**

[www.cancer.gov](http://www.cancer.gov)

[www.cancer.gov/espanol](http://www.cancer.gov/espanol)

# Precedence:

## What parallels can be drawn with other procedures or agents?

### Panel:

Neil Ogden, MS (Center for Devices and Radiologic Health)

Louis Marzella, MD, PhD (Center for Drug Evaluation and Research)

Bambi Reynolds, BS (LI-COR)

John Fengler, MA Sci (Novadaq)

Paula Jacobs, PhD (NCI Cancer Imaging Program)

### Moderator:

Michael Bouvet, MD (UCSD)

# Topics to discuss

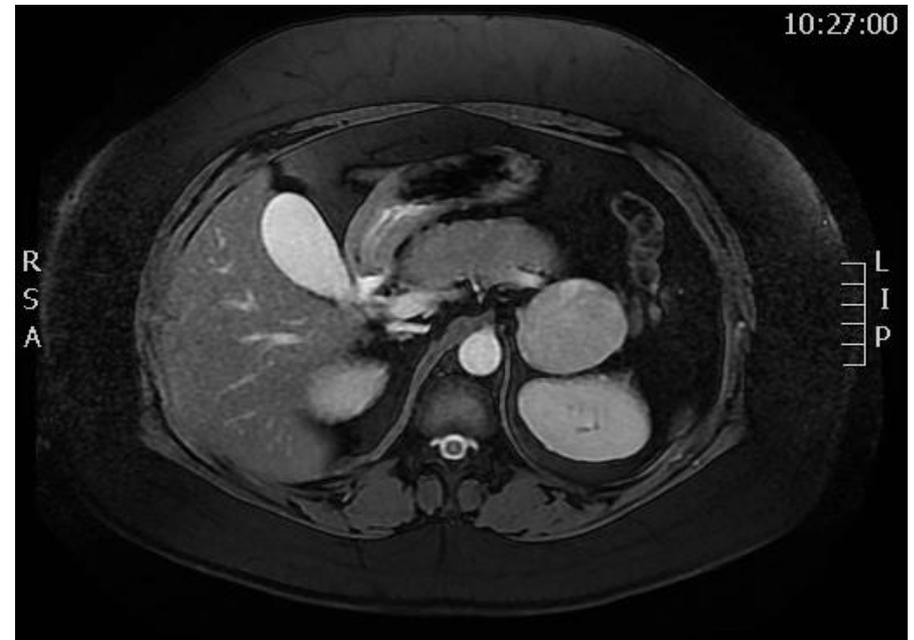
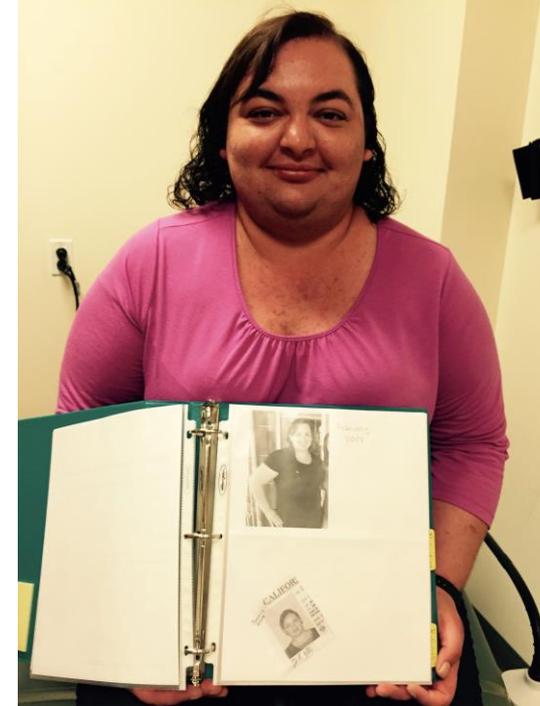
- Historical regulatory aspects of each imaging technology
- How are these imaging techniques similar to targeted molecular imaging technology
- How has the FDA's thinking evolved since the approval of these imaging technologies

# Case 1

## Adrenal tumor

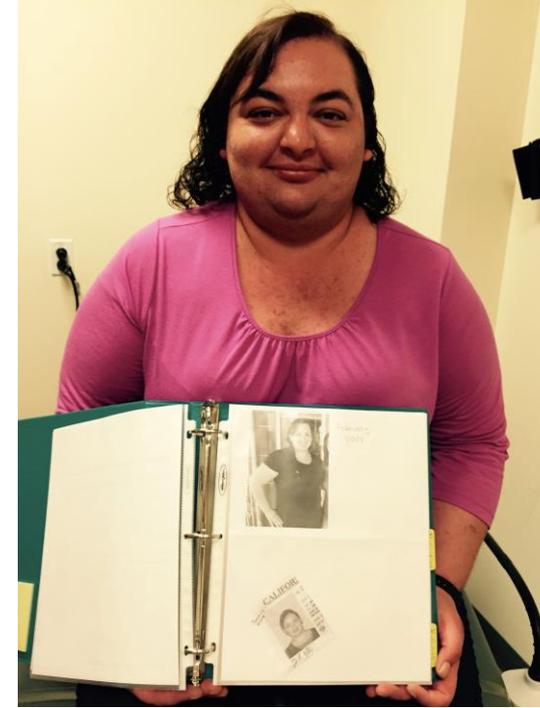
# Laparoscopic Adrenalectomy with ICG

- 27 year old female with Cushing's syndrome
- MRI shows 5 cm mass in left adrenal gland



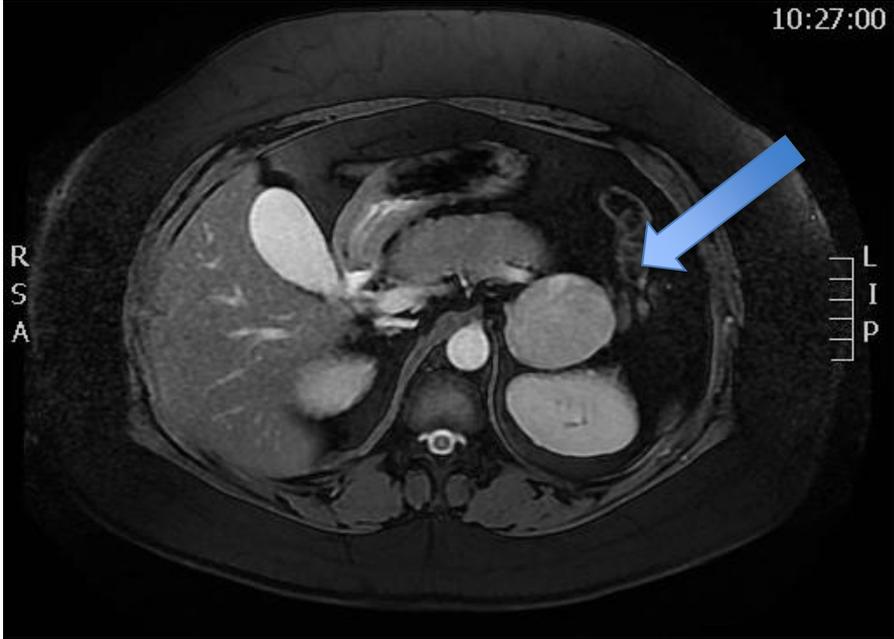
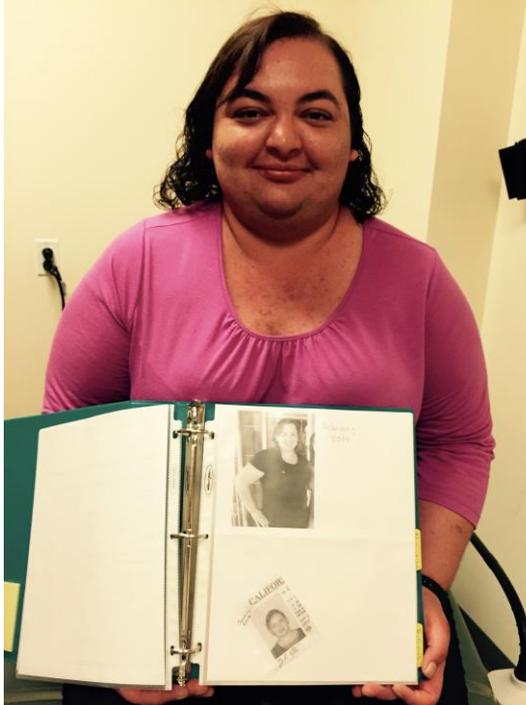
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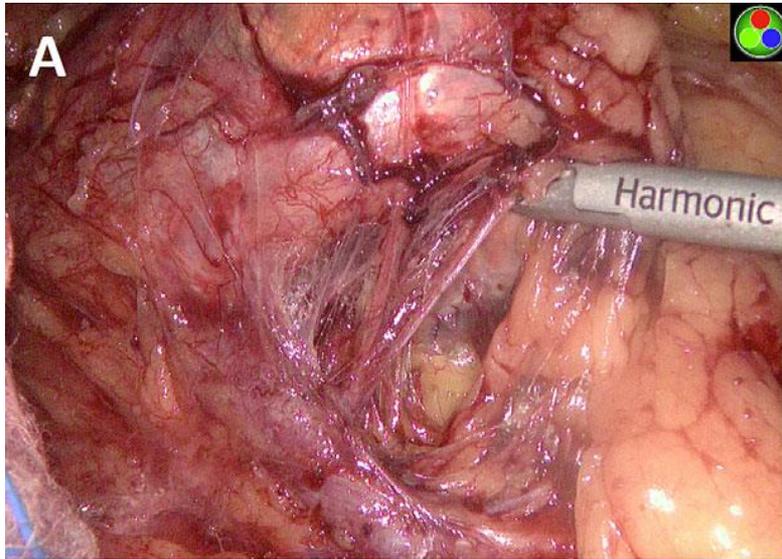




# ICG Regulatory History

- Developed by Kodak Research labs 1955
- FDA approval 1959 for hepatic function tests and cardiology
- 1969 Used for retinal studies in ophthalmology
- Novadaq SPY Fluorescent Imaging system obtained FDA 510(k) clearance in Jan 2005 for plastic, micro, and reconstructive surgery
- Novadaq PINPOINT imaging system for combined full-color reflectance and NIR imaging patent filed 2008 and awarded Nov 2015

# Intraoperative ICG



# Laparoscopic Left Adrenalectomy with ICG

# Questions

- Is ICG sufficient or are there better fluorescent probes that could help with intraoperative surgical navigation?

# Questions

- Is ICG sufficient or are there better fluorescent probes that could help with intraoperative surgical navigation?
- What about fluorophore-conjugated antibodies?

# Questions

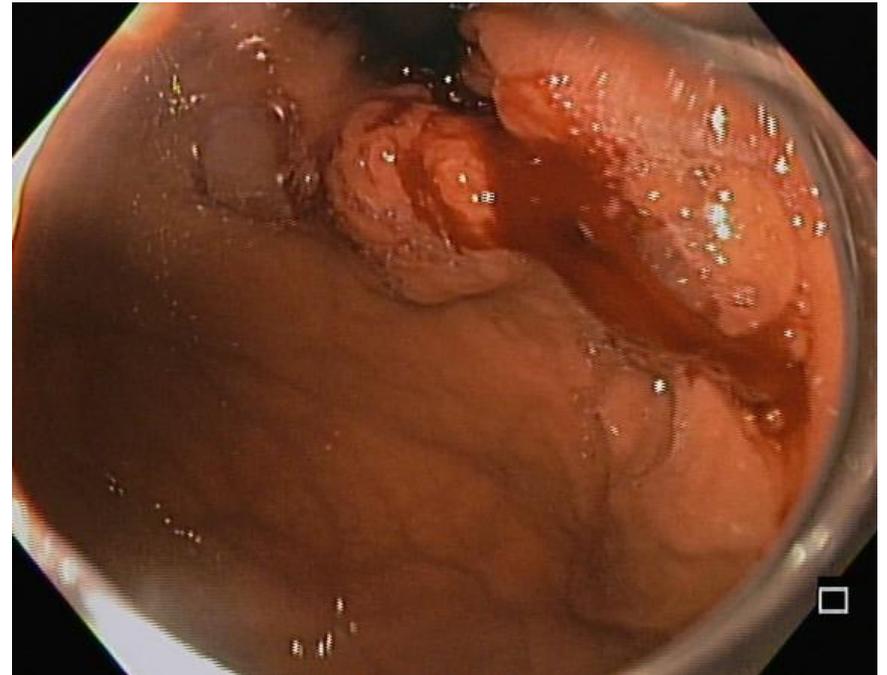
- Is ICG sufficient or are there better fluorescent probes that could help with intraoperative surgical navigation?
- What about fluorophore-conjugated antibodies?
- What is the ideal fluorophore for intraoperative imaging?

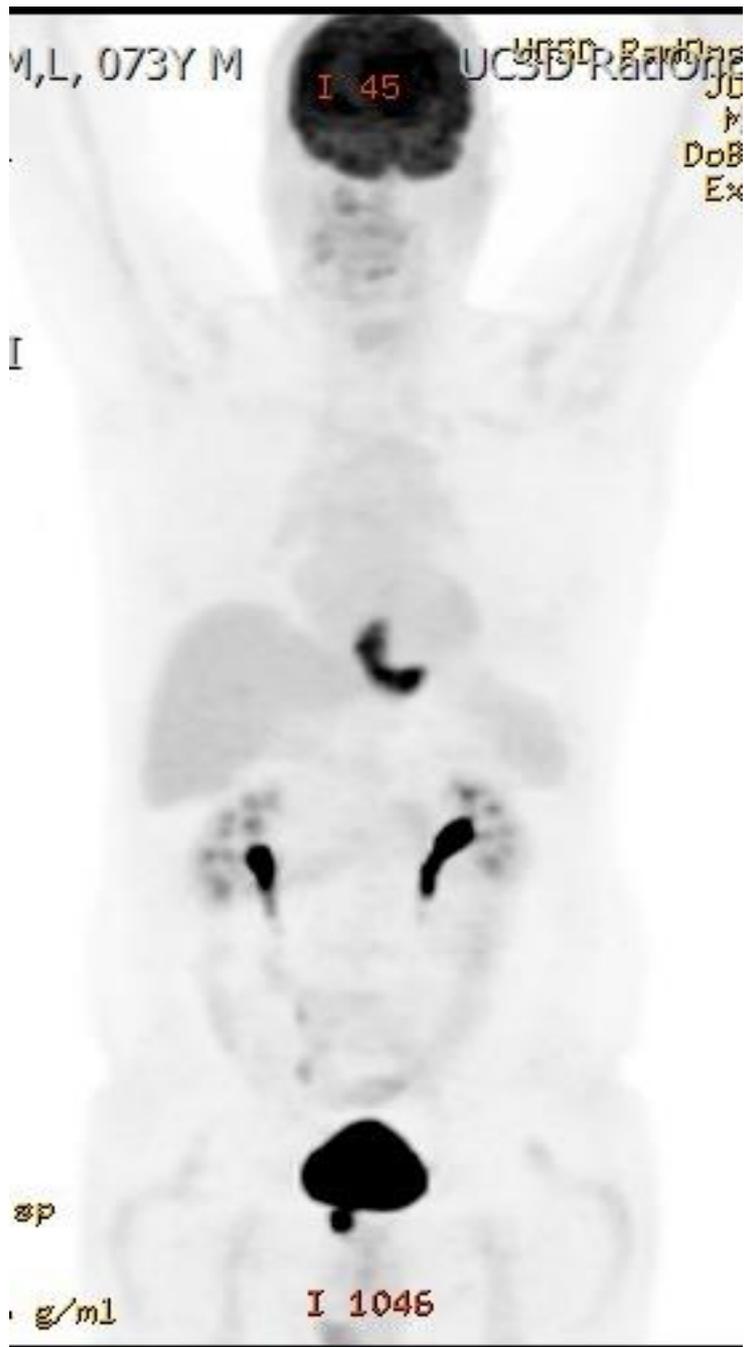
# Case 2

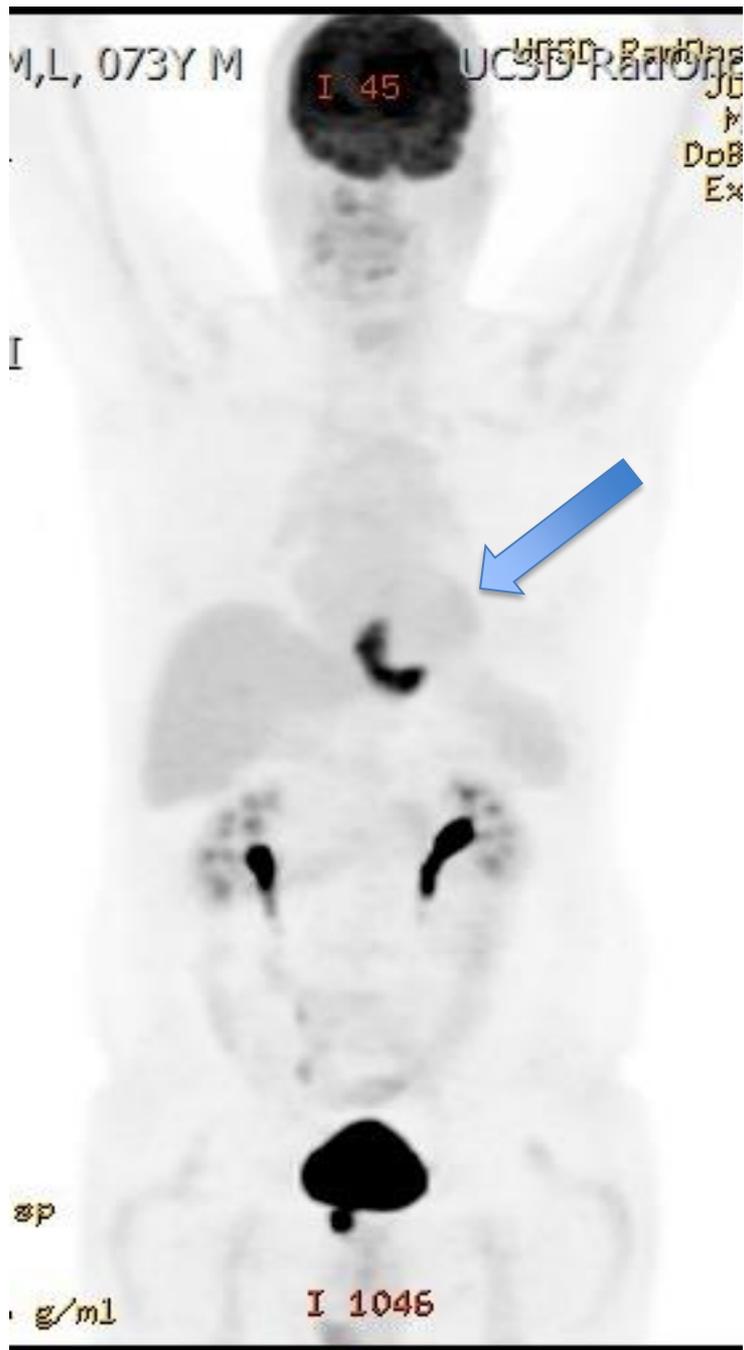
## Esophageal Cancer

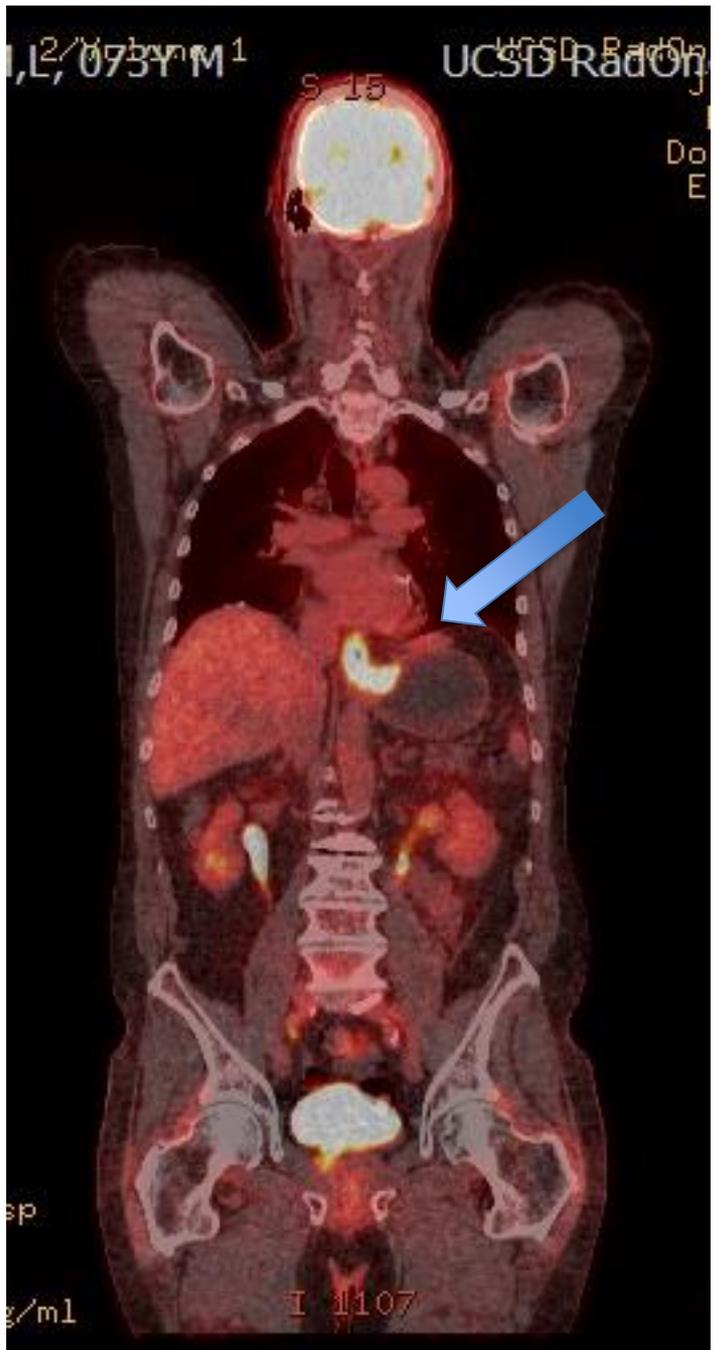
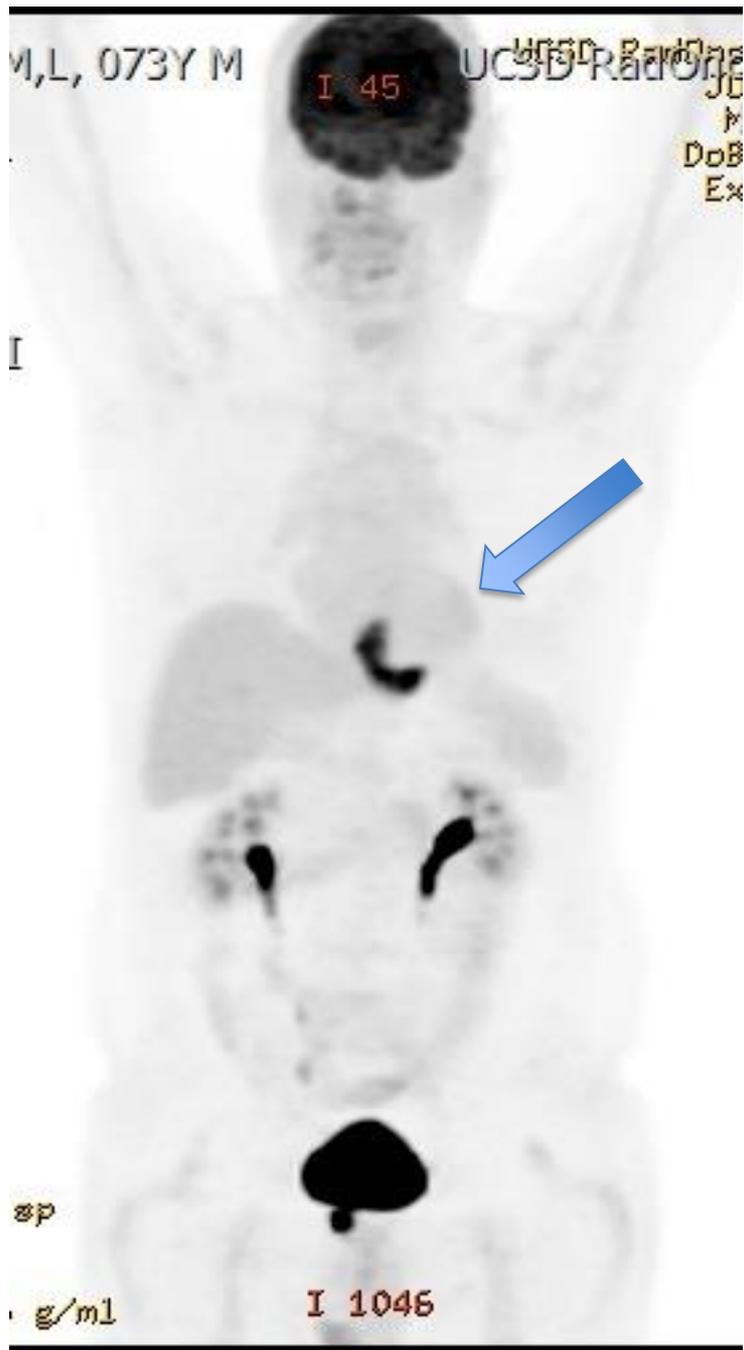
# Esophageal Cancer

- 73 year old male presented with dysphagia
- EGD shows mass in distal esophagus

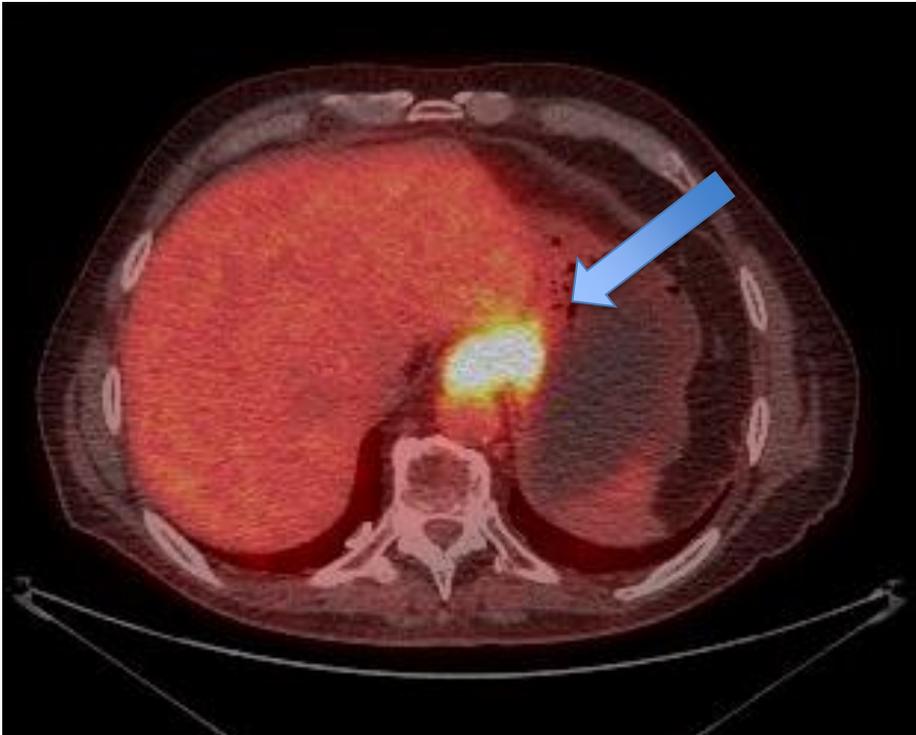




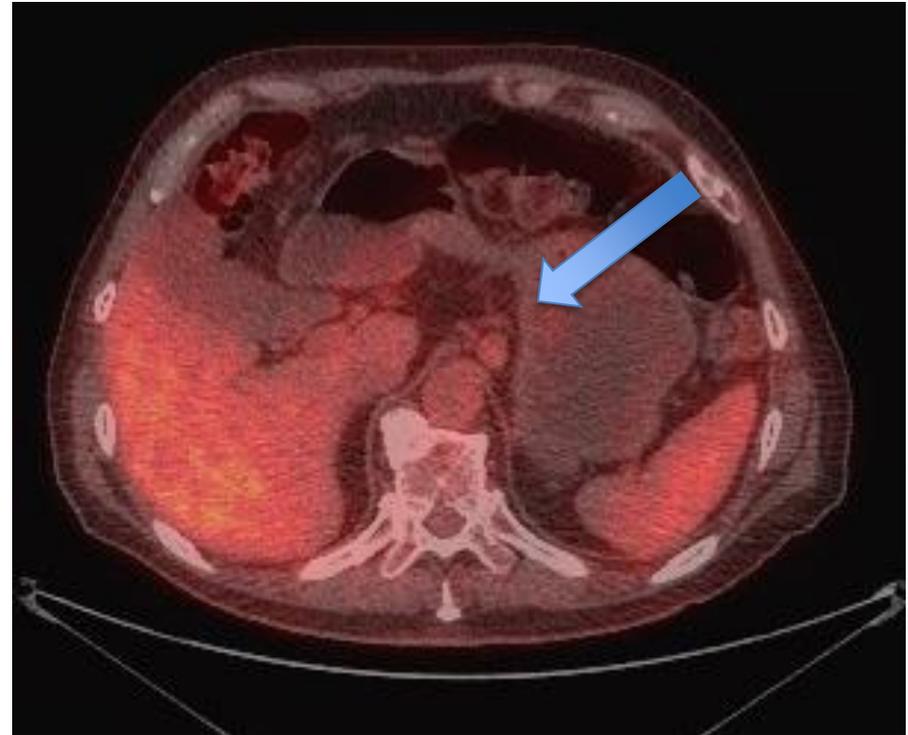




# PET/CT scan



SUV max 14.6  
Primary esophageal cancer



SUV max 1.4  
Left para-aortic lymph node

# Questions

- Can we do better than PET/CT imaging for staging of esophageal or other cancers?
- Would molecular imaging be more specific and give more information?

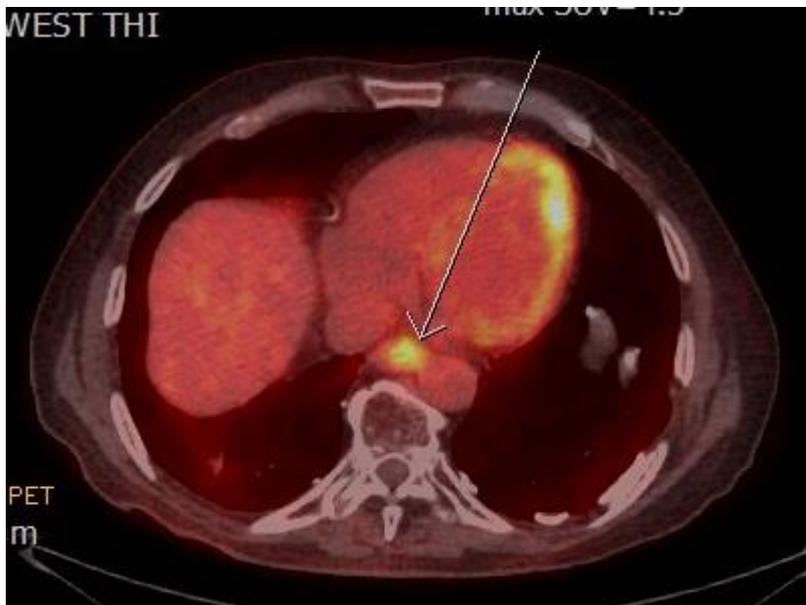
# Endoscopic Ultrasound

- EUS stage T3N2



# Case 1

- Patient undergoes neoadjuvant chemoradiation
- Restaged with PET/CT



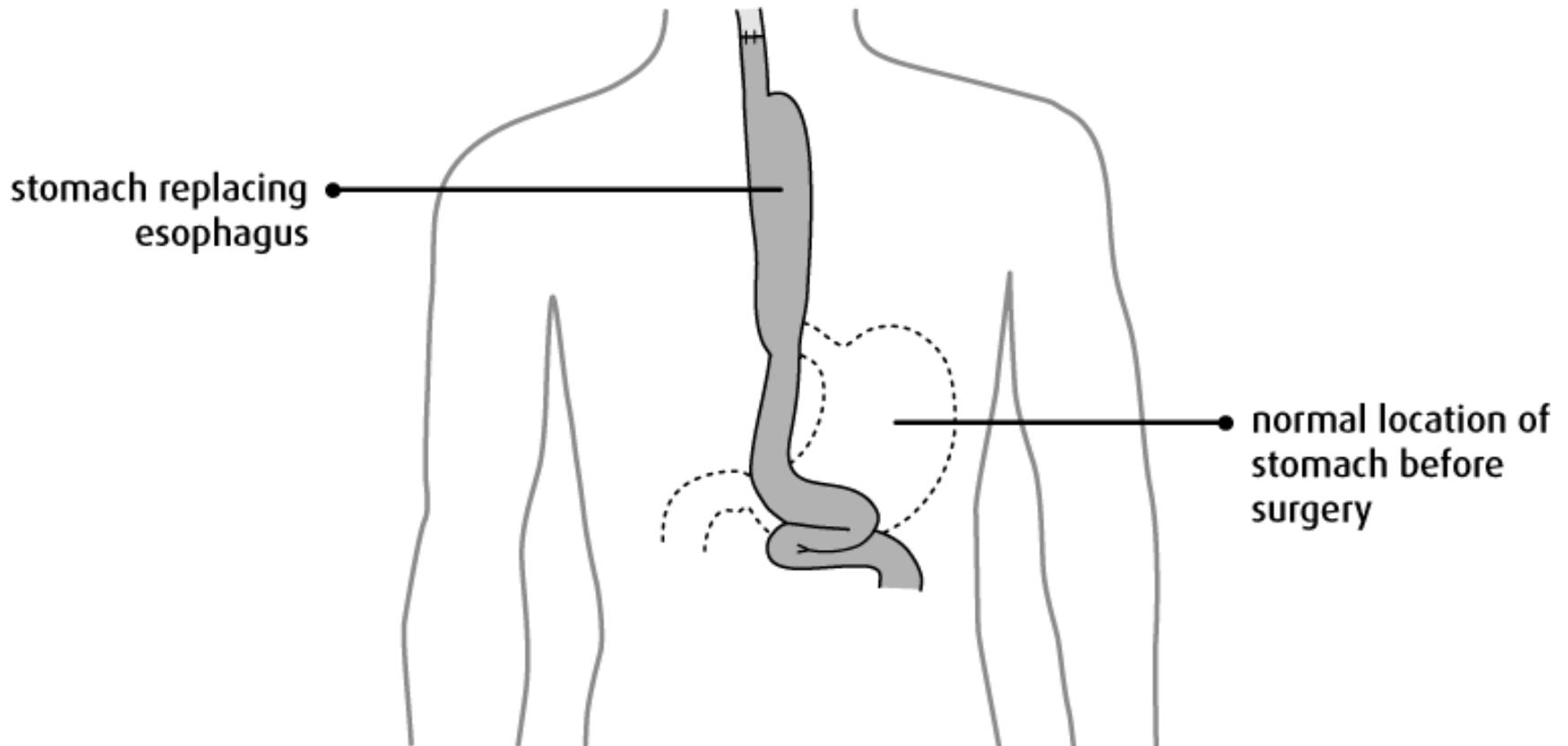
Primary esophageal cancer  
SUV max 4.5

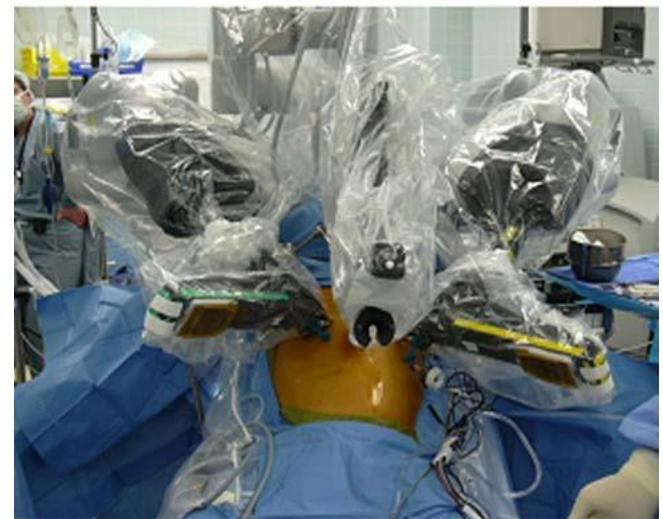
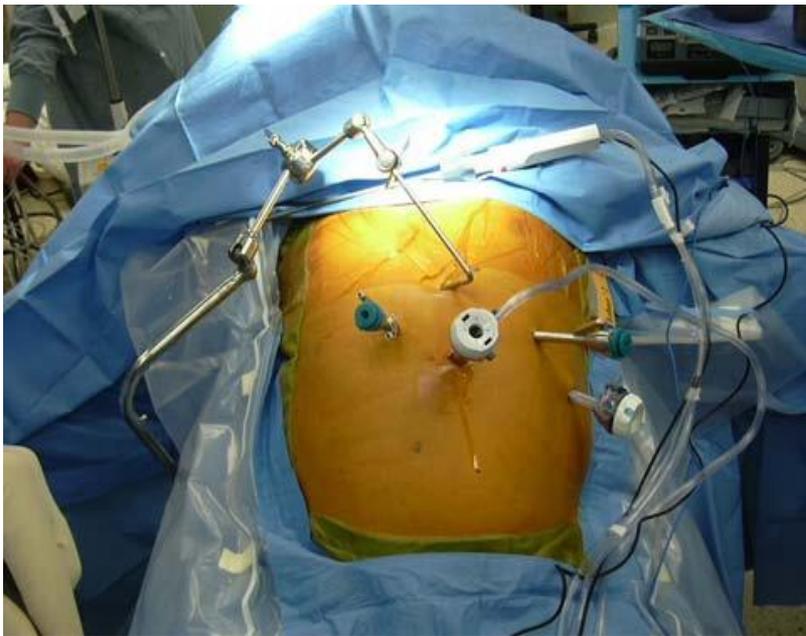
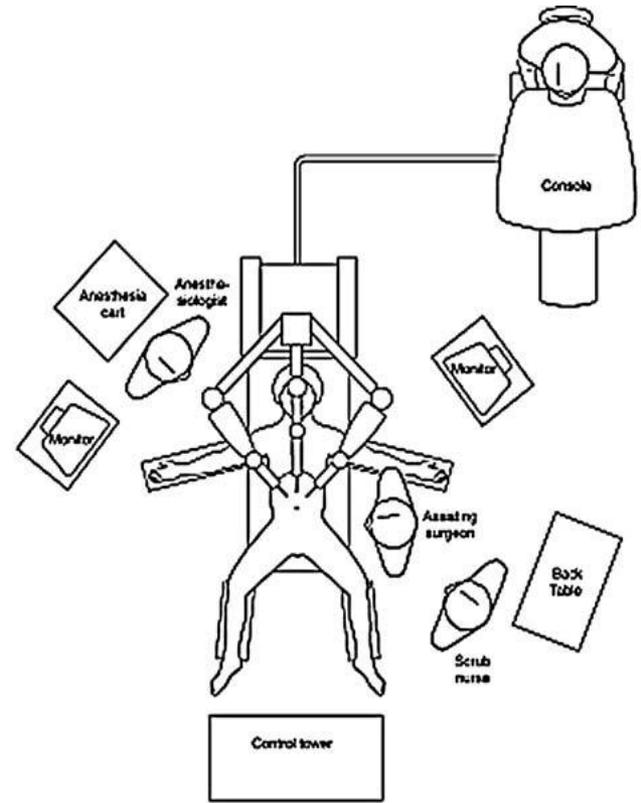


Left para-aortic lymph node  
SUV max not significant

# Transhiatal esophagectomy

## Gastric Pull-up





# Fluorescence Imaging Systems



NOVADAQ

SPY Elite

Open Surgery



NOVADAQ

PINPOINT

Minimally Invasive Surgery



NOVADAQ

LUNA

Diagnostic Imaging, Wound Care



INTUITIVE SURGICAL

FIREFLY

Robotic Surgery

# Robotic assisted transhiatal esophagectomy with ICG

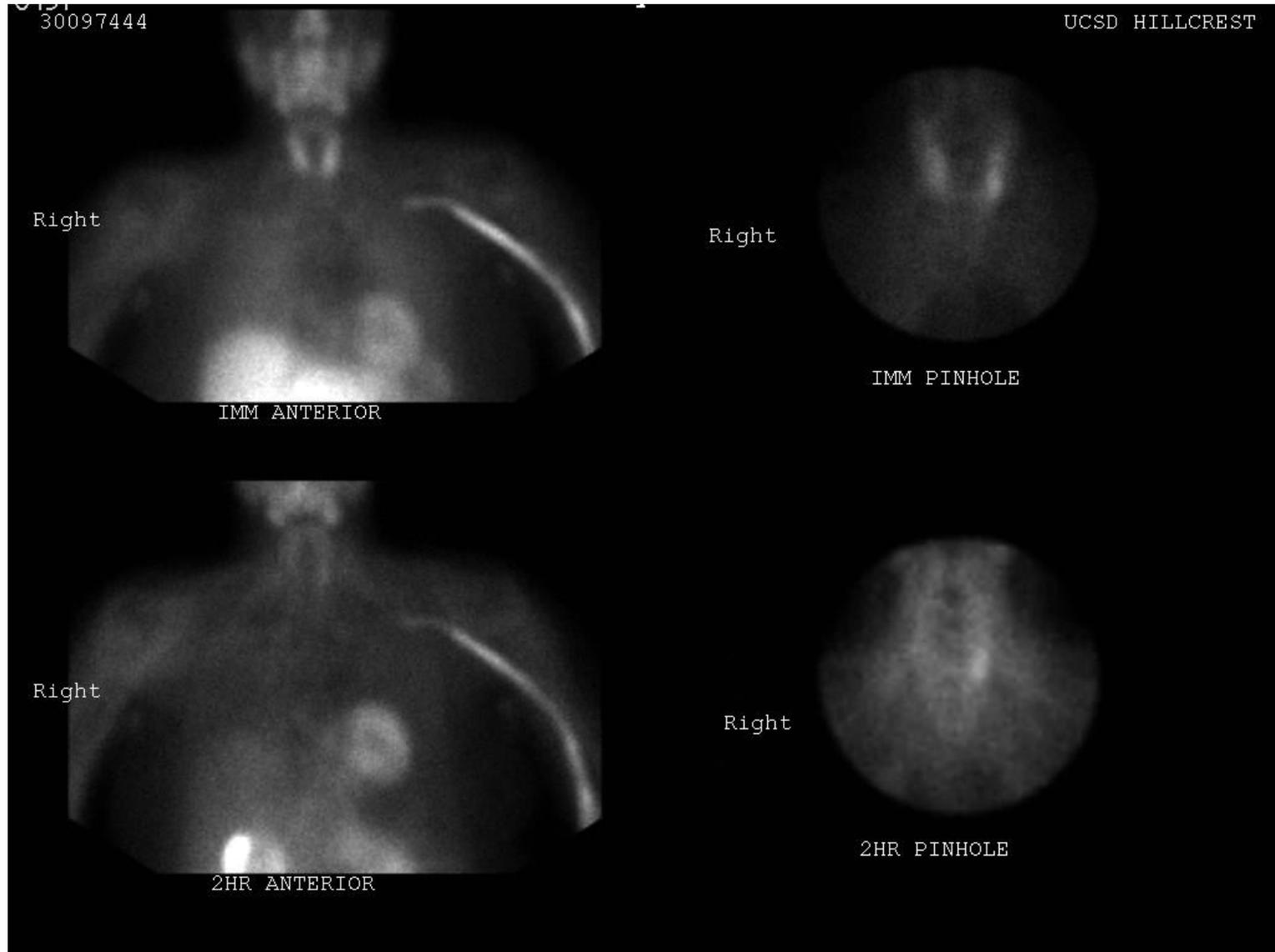
# Case 3

## Parathyroid adenoma

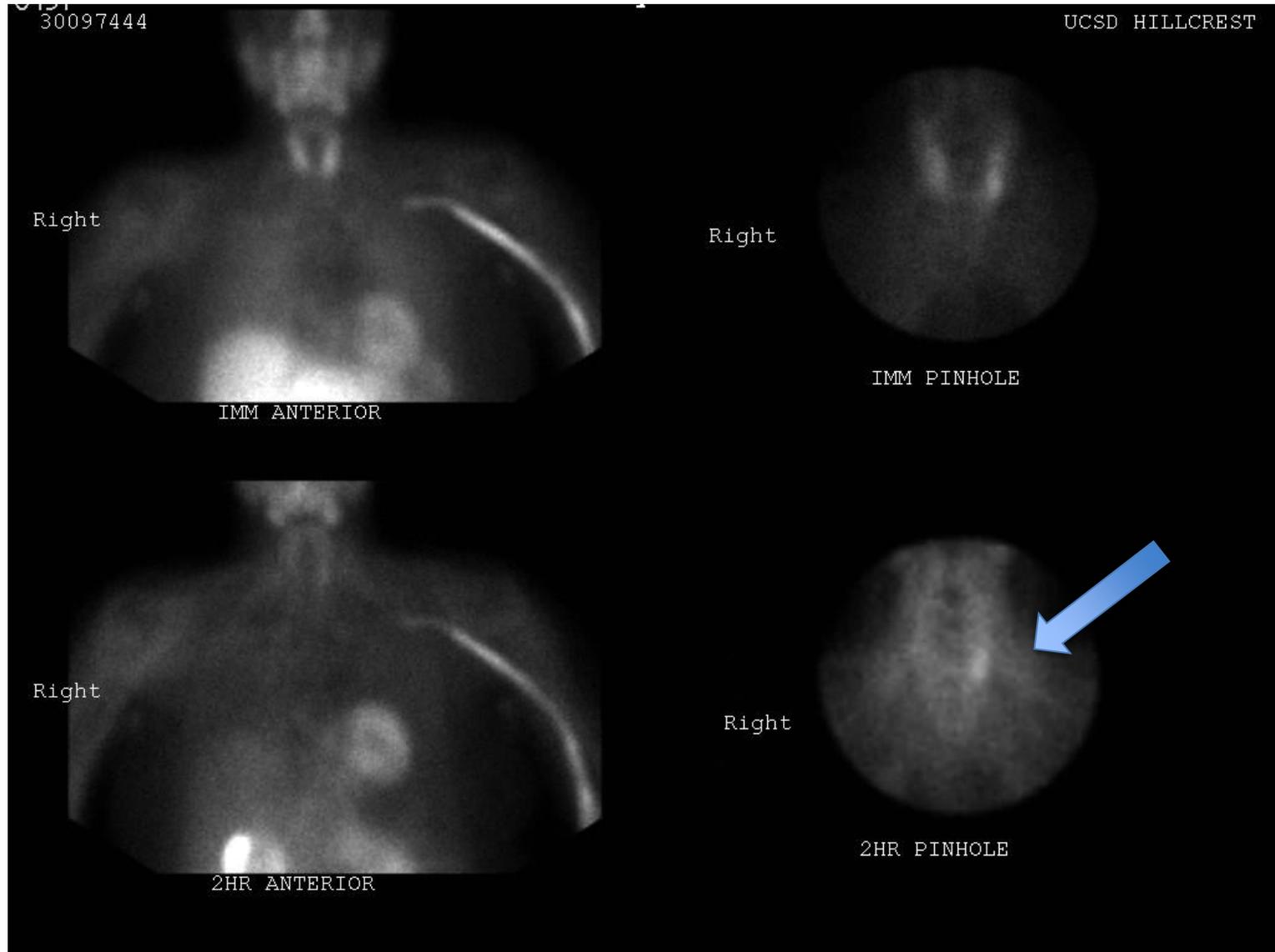
# Parathyroidectomy with ICG

- 49 year old woman with primary hyperparathyroidism
- Difficulty concentrating, fatigue, nausea, abdominal pain
- Calcium 11.1 mg/dL
- PTH 105 pg/dL
- 24 hour urinary calcium 421 mg

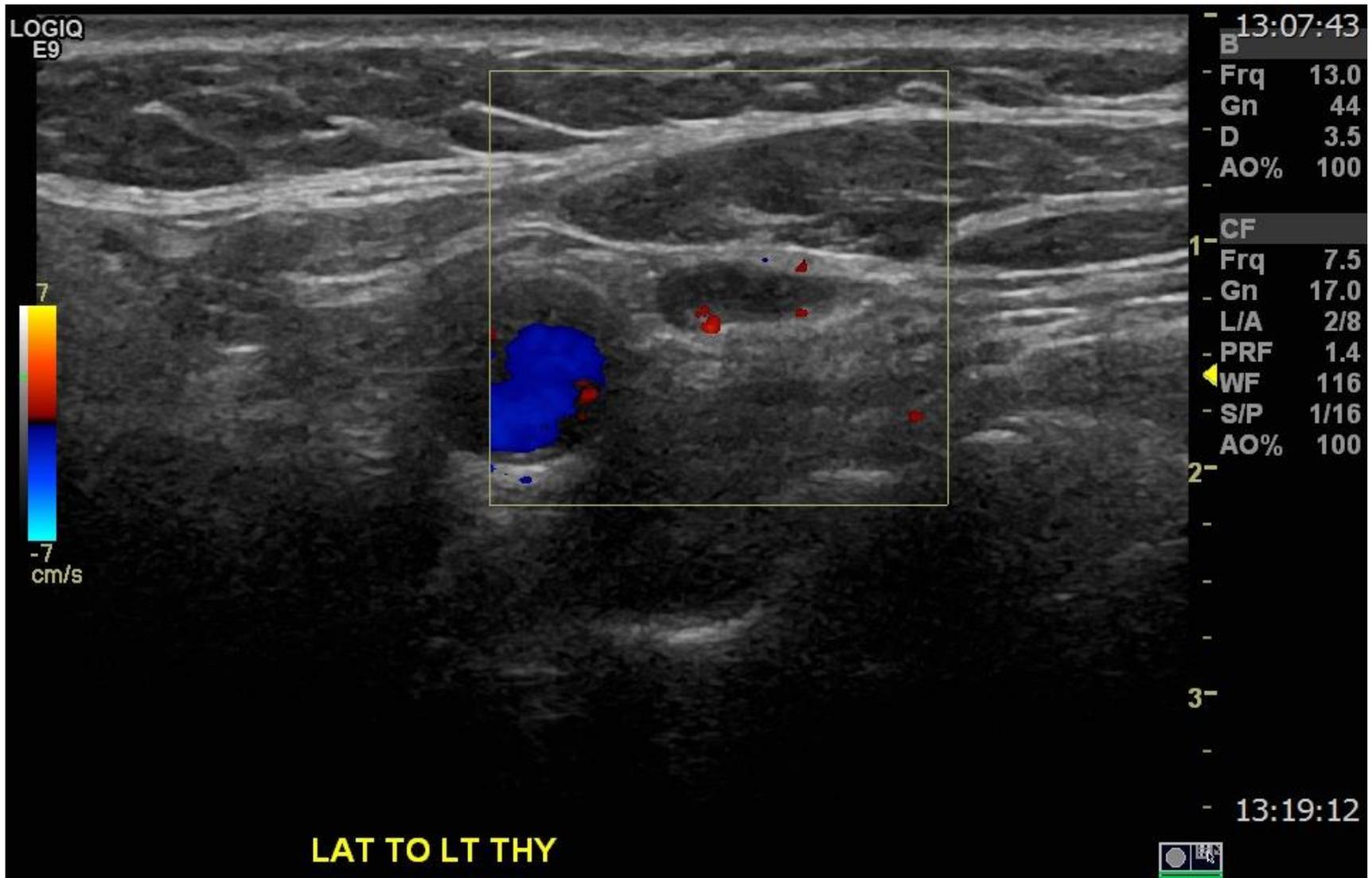
# Sestamibi nuclear scan



# Sestamibi nuclear scan

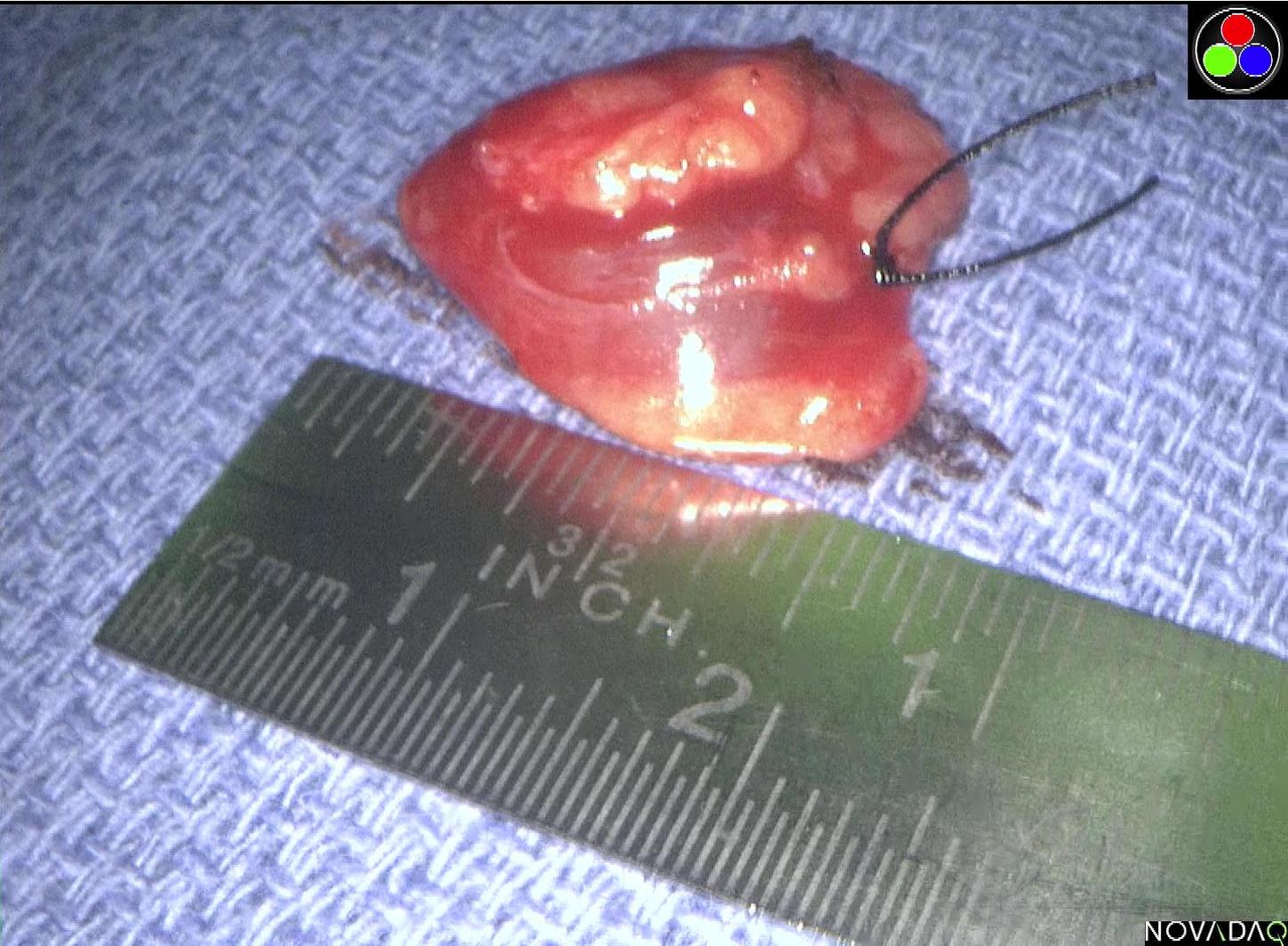
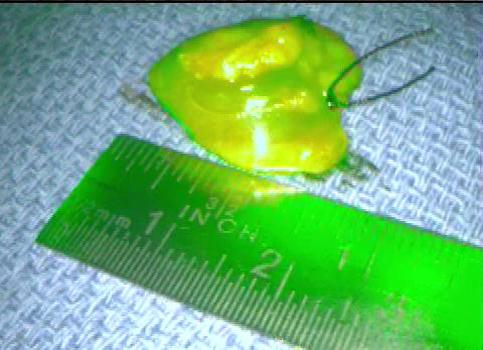


# Neck ultrasound



# Parathyroidectomy with ICG

# Parathyroid with ICG



# Questions

- Can we do better than sestamibi scanning for localization of parathyroid tumors?
- Are there better ways to light up parathyroid adenomas other than ICG?

# Topics to discuss

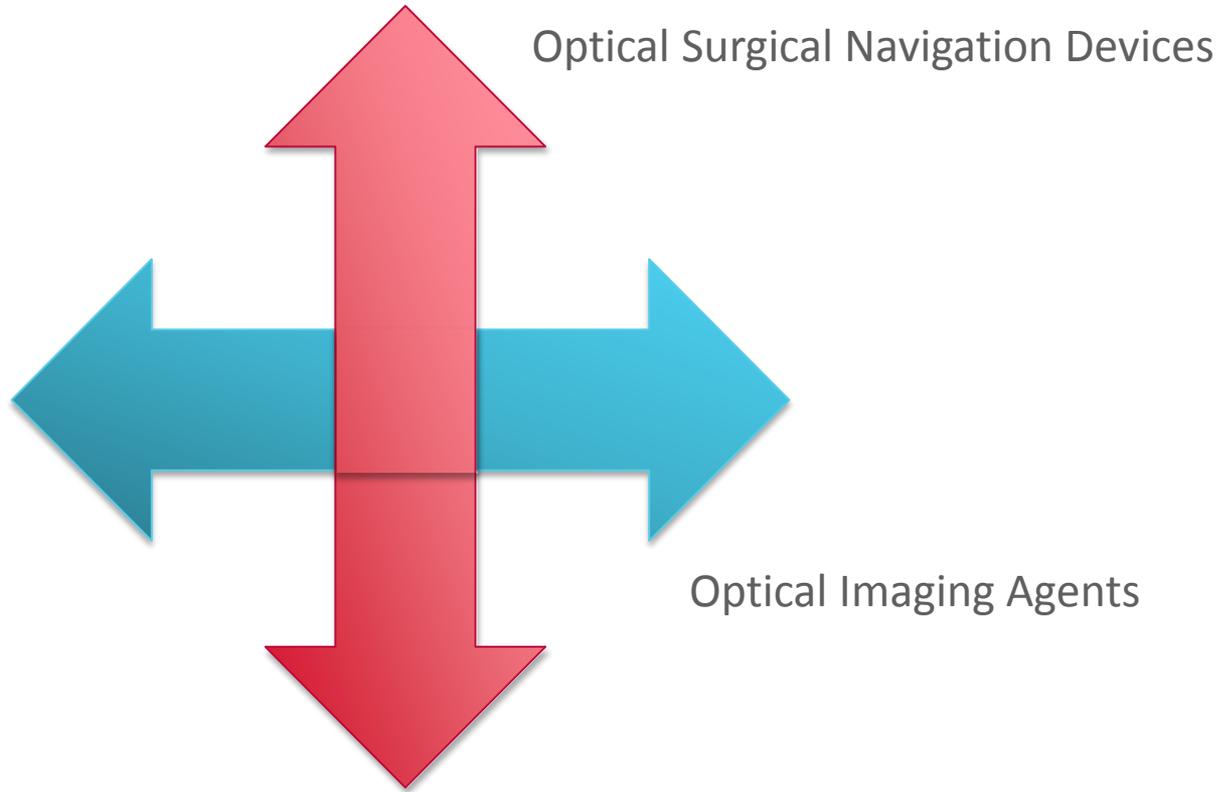
- Contrast agents to determine abnormal versus normal to guide intervention = CT-guided biopsy
- Molecular imaging – PET uses metabolic activity, not disease specific
- Agents that will improve standard of care by highlighting tumors for fluorescence guided surgery
- Using fluorescence for frozen sections to assess tumor margins

# Optical Methods and Exogenous Targets for Cancer Detection

*Overview of Devices*

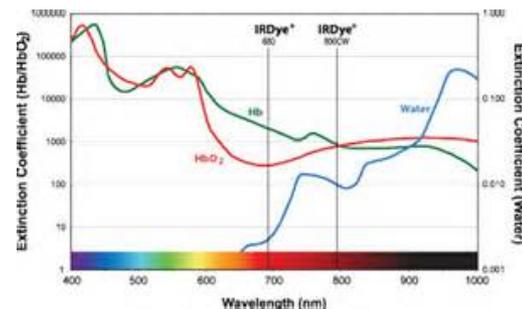
*Robert Nordstrom, Branch Chief: Image Guided Interventions NCI/CIP*

# Intersection of Technologies



# Augmenting Vision During Surgery

- Increasing the wavelength range of vision
  - NIR imaging
  - Increases depth penetration in tissue
- Increase contrast among tissue types
  - Fluorescence (endogenous and exogenous)
  - Targeted dyes and fluorophores
- Or Both



Dye	Solvent	$\lambda_{abs}^{max}$ (nm)	$\lambda_{em}^{max}$ (nm)	Stokes shift (nm)	$\epsilon_{max}^a$ ( $M^{-1} cm^{-1}$ )	$\phi^b$
CPCI	CH <sub>2</sub> Cl <sub>2</sub>	606	638	32	72,900	0.685
	CH <sub>3</sub> CN	593	644	51	56,250	0.242
	CH <sub>3</sub> OH <sup>c</sup>	591	640	49	54,450	0.166
	H <sub>2</sub> O	587	641	54	50,400	0.041
CPCIE	PBS	588	641	53	47,150	0.042
	CH <sub>2</sub> Cl <sub>2</sub>	606	637	31	75,300	0.469
	CH <sub>3</sub> CN	593	643	50	64,400	0.217
	CH <sub>3</sub> OH <sup>c</sup>	591	641	50	57,800	0.152
CPCZ	H <sub>2</sub> O	587	644	57	55,400	0.030
	PBS	587	644	57	35,717	0.028
	CH <sub>2</sub> Cl <sub>2</sub>	637	675	38	63,650	0.163
	CH <sub>3</sub> CN	619	683	64	50,650	0.025
CPCZE	CH <sub>3</sub> OH <sup>c</sup>	617	679	62	48,100	0.013
	H <sub>2</sub> O	608	684	76	36,700	0.003
	PBS	608	686	78	39,867	0.003
	CH <sub>2</sub> Cl <sub>2</sub>	638	676	38	76,650	0.125
CPCZE	CH <sub>3</sub> CN	620	687	67	67,700	0.024
	CH <sub>3</sub> OH <sup>c</sup>	618	681	63	64,400	0.017
	H <sub>2</sub> O	610	688	78	50,050	0.002
	PBS	610	689	79	27,000	0.002

<sup>a</sup> The molar extinction coefficients at maximum absorption.

<sup>b</sup> Using cresyl violet in methanol as the reference ( $\Phi = 0.54$ ).

<sup>c</sup> CH<sub>3</sub>OH with 0.5% acetic acid.

# Augmenting Vision During Surgery

- Surgical Eye Loupes with specialty lamps
- Laparoscopic
- Colposcopes and more
- Surgical Microscopes
  - Digital, stereo, fluorescence
- Robotic



# A Useful Reference

*Theranostics* 2014, Vol. 4, Issue 11

1072



**Theranostics**

2014; 4(11): 1072-1084. doi: 10.7150/thno.9899

Review

## Intraoperative Imaging-Guided Cancer Surgery: From Current Fluorescence Molecular Imaging Methods to Future Multi-Modality Imaging Technology

Chongwei Chi<sup>1</sup>, Yang Du<sup>1</sup>, Jinzuo Ye<sup>1</sup>, Deqiang Kou<sup>3</sup>, Jingdan Qiu<sup>3</sup>, Jiandong Wang<sup>3</sup>, Jie Tian<sup>1</sup>✉ and Xiaoyuan Chen<sup>2</sup>✉

# More Devices

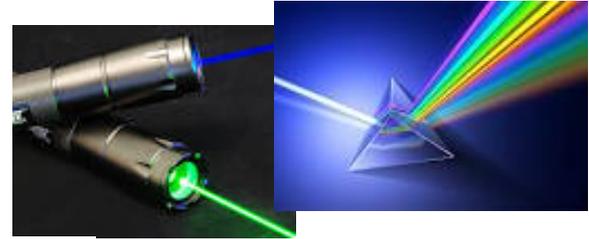


**Figure 1.** Portable intraoperative FMI systems: a) The Novadaq SPY™ system, b) Artemis™, c) Hamamatsu's Photodynamic Eye (PDE™), d) Fluoptics' Fluobeam®. Functional intraoperative FMI systems: e) FLARE™ imaging system, f) Multispectral FMI system from Technische Universität München & Helmholtz Zentrum, g) Surgical navigation system GXMI Navigator from the Institute of Automation, Chinese Academy of Sciences.

# Optical Device Components: Defining the Device

- Light source

- LED, halogen lamp, laser



- Detector

- Photodiode, CMOS, CCD, PMT, etc.



- Optical Train

- Lenses, mirrors, filters, fibers, dichroic components, etc.



Selection is determined by the mission of the optical device

Imaging agent must be compatible with the operation characteristics of the device.

# Devices

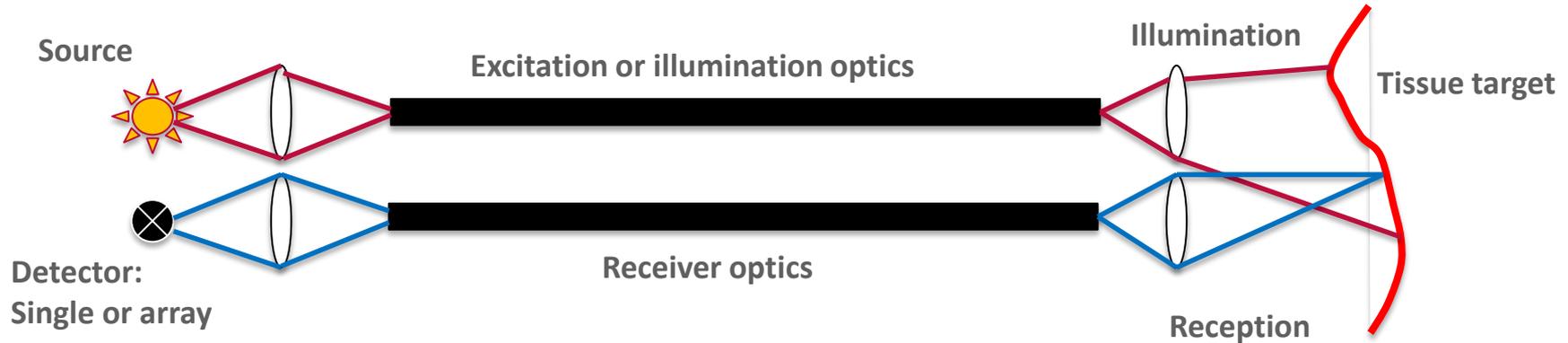
**Table 1.** Parameter comparison of image-guided systems.

N	Imaging systems	Manufacturer	Main application	Excitation wavelength (nm)	Field of view (mm)	Resolution	Display Refresh (Hz)	Dynamic range (bits)	Working distance (mm)	Color video	Light source	Clinical Status	Reference
1	SPY	Novodaq Technologies, Mississauga, Canada	Intraoperative Fluorescence Imaging	820	190*127	Not specified	30	8	300	No	Laser	FDA approved	www.novadaq.com
2	Artemis	O2view, Marken, The Netherlands	Stereoscopic Fluorescence Imaging	400-1000	22.5*22.5 at 50mm distance	659*494	5-60	14	≥50	Yes	Laser	FDA approved	www.o2view.com
3	Photodynamic Eye	Hamamatsu Photonics, Hamamatsu, Japan	Handheld Fluorescence Imaging	760	100*67	Not specified	Not specified	8	200	No	LED	FDA approved	www.hamamatsu.com
4	Fluobeam	Fluoptics, Grenoble, France	Handheld Fluorescence Imaging	690 or 780	128*94	640*480	30	12	150	No	Laser	Clinical trial	www.fluoptics.com
5	SurgOptix	SurgOptix, Redwood Shores, USA	Intraoperative Fluorescence Imaging	520	115*93	1392*1024	12	16	210	Yes	Laser	Clinical trial	www.surgoptix.com
6	FLARE	Frangioni Laboratory, Boston, USA	Intraoperative Fluorescence Imaging	670 or 760	150*113	1280*1024	15	12	450	Yes	LED	Clinical trial	www.centerformolecularimaging.org
7	GXMI Navigator	Institute of Automation, Beijing, China	Intraoperative Fluorescence Imaging	760nm	250*250	2456*2048	17	16	>300	Yes	LED	Clinical trial	www.3dmed.net

# A Few Typical Devices for ICG Fluorescence Trials

Device	Excitation Source	Fluorescence Collection	Detector	Working Distance	Field of View	Depth of Penetration	Integration Time or Frames Per Sec (FPS)
Photodynamic Eye (PDE) Hamamatsu	Light emitting diodes (LEDs) centered at 760 nm, incident power not specified	Bandpass filter >820 nm	CCD	20 cm	Not given, but limited	2 cm	Not specified
SPY (Novadaq)	Laser emitting at 806 nm, 2.0 – 2.7 W, incident power not specified	835 nm “camera,” not specified	CCD	30 cm	56 cm <sup>2</sup>	1 mm DOP	30 fps
FDPM imager (Texas)	Laser Diode, 785 ± 10 nm, <1.9mW/cm <sup>2</sup>	Notch filters at 785 nm, and at 830 nm	Gen III intensifier coupled to CCD, gain modulatable for tomography	Variable, but reported <76.2 cm	Max reported FOV 900 cm <sup>2</sup>	Estimated to be 4 cm	50 – 800 msec
IC-View (Pulsion Medical)	Laser Diode 780 nm (0.16W), incident power not specified	Not specified	CCD	Not specified	Not specified	Not specified	Not specified
FLARE (Beth Israel Deaconess Hospital)	LEDs emitting 745-779 nm, 14 mW/cm <sup>2</sup>	Bandpass filter 800-848 nm	CCD	45 cm	3.7 cm <sup>2</sup> – 169.5 cm <sup>2</sup>	Not specified	200 msec
Custom system (Kochi Medical School)	LEDs emitting light centered at 760 nm, incident power not specified	840 nm cut-on filter	Color CCD	~50 cm	78.5 cm <sup>2</sup>	Not specified	Not specified

# Dual or Common Channel Systems



## Advantages

- No “cross talk”
- Tailored optics

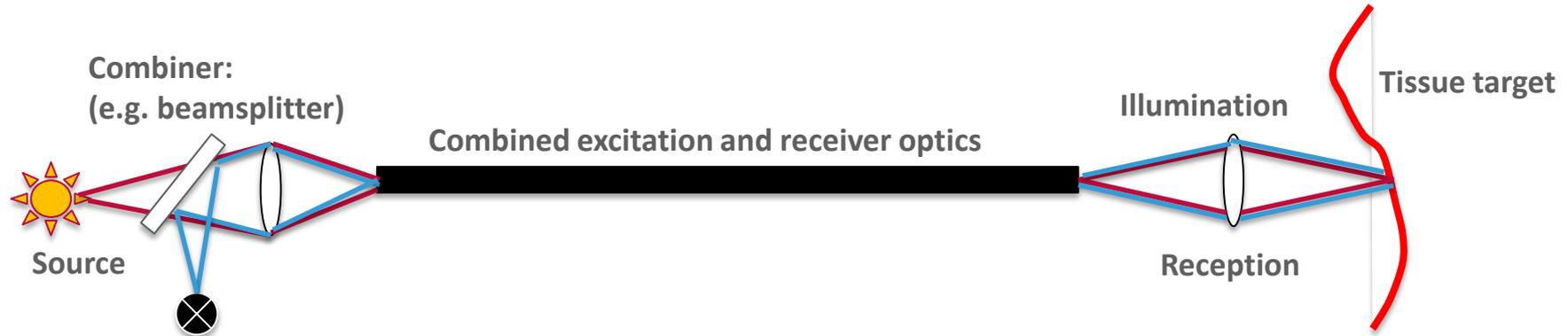
## Disadvantages

- Increased cost
- Device size

Selection of agents limited by optical properties of device

Conversely, the selection of the device components depends on the choice of imaging agent

# Dual or Common Channel Systems



Detector:  
Single or array

## Advantages

- Reduced size of device
- Possible cost savings

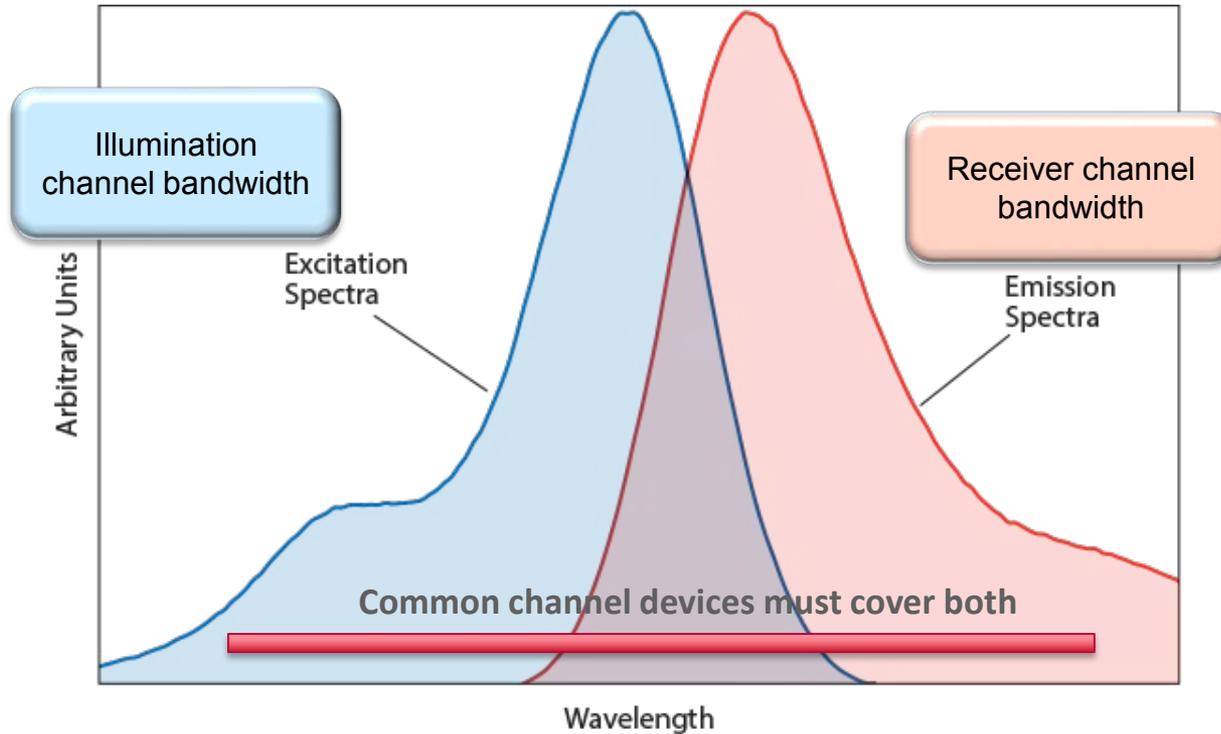
## Disadvantages

- Possible “cross talk”
- Tailored optics more complex

Selection of agents limited by optical properties of device

Conversely, the selection of the device components depends on the choice of imaging agent

# Emission and Excitation in Fluorescence



# Conclusions

- Optical Surgical Navigation is important to improve the ability to detect and circumscribe tumors
- Devices to augment navigation include those that expand useful “sensed” wavelengths or those that increase contrast between normal and diseased tissue.
  - Exogenous agents are very helpful in this process
  - The characteristics of the device will dictate the list of agents that can be used.
- Optics should be considered to be only one method. Pairing it with other imaging modalities in multimodal imaging should be considered.

# The Other Side of Things

## Label-free Optical Techniques for Biomedical Diagnostics & Imaging: Challenges and Opportunities for Clinical Translation

### Lead Authors:

**Paul French**, *Imperial College, United Kingdom*; **Laura Marcu**, *University of California - Davis, United States*;  
**Robert J. Nordstrom**, *National Institute of Health, United States*; **Juergen Popp**, *Leibniz Institute of Photonic  
Technology, Jena, Germany*; **Brian Wilson**, *University Health Network, Canada*

This white paper is based on the many contributions to an OSA Incubator held on 16-18 September 2015 at OSA Headquarters, 2010 Massachusetts Ave. NW, Washington, DC, USA. The Incubator ([osa.org/label\\_free\\_incubator](http://osa.org/label_free_incubator)) was organized by the lead authors, the following participants contributed to discussions at the Incubator and to this white paper.

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CANCER  
INSTITUTE**

[www.cancer.gov](http://www.cancer.gov)

[www.cancer.gov/espanol](http://www.cancer.gov/espanol)

# FDA and Optical Imaging Device/Combinations

Neil R.P. Ogden, BME  
Chief, General Surgery Devices Branch 1  
Division of Surgical Devices  
Office of Device Evaluation  
Food and Drug Administration  
10903 New Hampshire Ave.  
WO 66, Room G414  
Silver Spring, MD 20993      301 796-6397  
Neil.ogden@fda.hhs.gov      301 847-8117 (fax)

# Notice of Conflicts

None

I currently work for FDA.

MANAGING CONFLICT OF INTEREST



# Disclaimer

This talk represents the professional opinions of the author and is not an official document, guidance, or policy of the US government, the Department of Health and Human Services or the Food and Drug Administration, nor should any official endorsement be inferred.

# Presentation Overview

- **What we have done**
- What we want to do
- How we can do it
- Considerations

# Who does What at FDA?





**Center for  
Food  
Safety &  
Applied  
Nutrition**



**Center for  
Drug  
Evaluation &  
Research**



**Center for  
Biologics  
Evaluation &  
Research**



**Center for  
Devices &  
Radiological  
Health**



**Center for  
Veterinary  
Medicine**

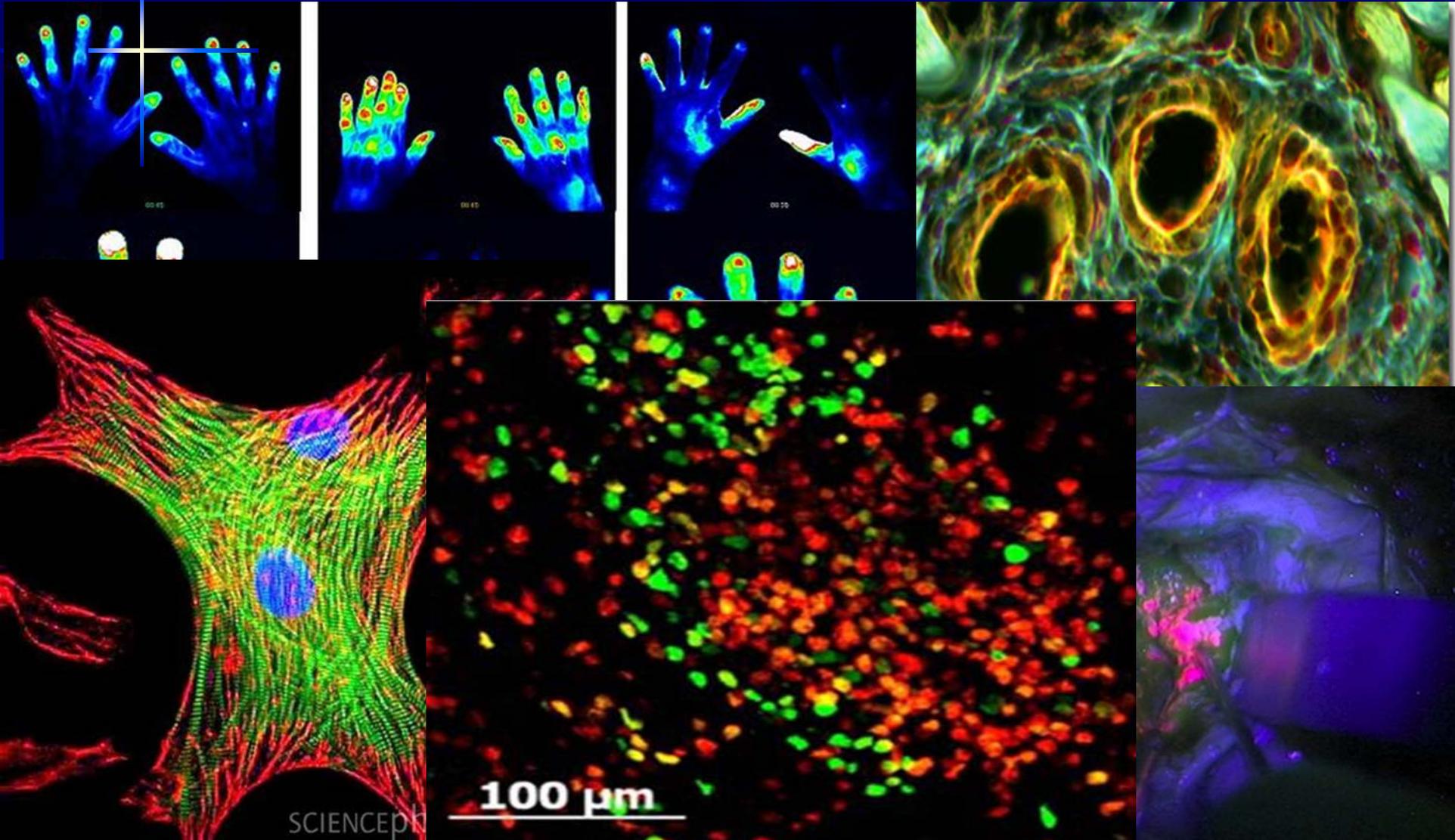


**Center for  
Tobacco  
Products**



**National  
Center for  
Toxicological  
Research**

# Light based Imaging and Combination products



# Cleared Device Indications with ICG

1. For use in intra-operative visual assessment of the coronary vasculature and bypass grafts during coronary artery bypass (CABG) surgery.
2. For visual assessment of blood flow and related tissue perfusion during cardiovascular surgical procedures.

# Cleared Device Indications with ICG, continued

3. For visual assessment of blood flow as an adjunctive method for the evaluation of tissue perfusion and related tissue-transfer circulation in tissue and free flaps used in plastic, micro- and reconstructive surgery.
4. For visual assessment of blood flow as an adjunctive method for the evaluation of flow in the native and anastomosed vessels, tissue perfusion and related tissue-transfer circulation in implanted and surrounding organs; to visualize blood flow indicative of perfusion of the donor implant prior to transplantation and to provide indication of organ function after transplantation

# Cleared Device Indications with ICG, continued

5. For visual assessment of vessels, blood flow and related tissue perfusion with near infrared fluorescence imaging during minimally invasive surgery.
6. For visual assessment of vessels, blood flow, and related tissue perfusion with near infrared fluorescence imaging during minimally invasive robotic surgery.
7. For visual assessment of blood flow and related tissue perfusion during gastrointestinal surgery.
8. For use as an imaging tool in the evaluation of human tissue microstructure by providing two-dimensional, cross-sectional, real-time depth visualization

# Cleared Device Indications, Cont'd

9. For use in diagnostic and operative arthroscopic and endoscopic procedures to provide illumination and visualization of an interior cavity of the body through either a natural or surgical opening.
10. Intended to allow confocal laser imaging of the internal microstructure of tissues in the anatomical tract; enables surgeons to perform minimally invasive surgery using standard endoscopic visible light as well as visual assessment of vessels, blood flow and related tissue perfusion.
11. The da Vinci Fluorescence Imaging Vision System is intended to provide real-time endoscopic visible and near-infrared fluorescence imaging. The da Vinci® Fluorescence Imaging Vision System enables surgeons to perform minimally invasive surgery using standard endoscopic visible light as well as visual assessment of vessels, blood flow and related tissue perfusion, and at least one of the major extrahepatic bile ducts (cystic duct, common bile duct and common hepatic duct), using near infrared imaging.

# Presentation Overview

- What we have done
- **What we want to do**
- How can we do it
- Considerations

# Questions about regulatory pathway

Does regulatory path depend upon how technology is used?

Intraoperative or endoscopic

Systemic vs. topical during surgery

Pathological assessment

Location of devices: OR (surgical field versus back table) vs. Pathology

Calibration and standard phantoms

Will the regulatory pathway vary with the type of device or agent?

Wavelength, sensitivity, speed, etc. (Cooling, maintenance, etc.)

Optical, Raman and photoacoustic imaging technologies

Contact based imaging

# What Imaging Clinical Strategy?

Complex issues dependent on many variables:

- General visualization alone
- Specific disease detection
- Combination products

# Devices indicated for imaging specific diseases

Device Indication drives data needs.

Stand alone clinical data showing S&E will be needed.

# Devices indicated for margin detection

When and where is margin detection occurring?

# Imaging Combination products

Device plus drug or biologic will be reviewed together.

Combination products: Complicated

Likely - stand alone clinical data showing Safety & Effectiveness.

If there's a predicate – technical comparison.

# Imaging Combination products, Continued

Regulatory Pathway experience:

- Established Drug, same dosing, admin. route - 510(k) or PMA. (ICG, Sodium Fluorescein)
- New Molecular Entity – New Drug Application (NDA) or PMA, co-package
- New drug indication - NDA or supplements, PMA co-package

# Combo Product - Which Center has lead - RFD?

Request For Designation (RFD) to our Office of Combination Products (OCP) will review Primary Mode of Action and how the combination achieves its Primary Intended Purpose(s) and what are the major FDA review challenges.

# OCP Guidance

*Copies are available from:*

*Office of Combination Products*

*Food and Drug Administration*

*WO32, Hub/Mail Room #5129*

*10903 New Hampshire Avenue*

*Silver Spring, MD 20993*

*(Tel) 301-796-8930 (Fax) 301-847-8619*

*<http://www.fda.gov/CombinationProducts/default.htm>*

# Informational needs for FDA device review

- Device Labeling
- Performance specifications
- Valid scientific evidence
- Tissue effects
- Mechanism-of-Action, like to have
- Clinical outcomes

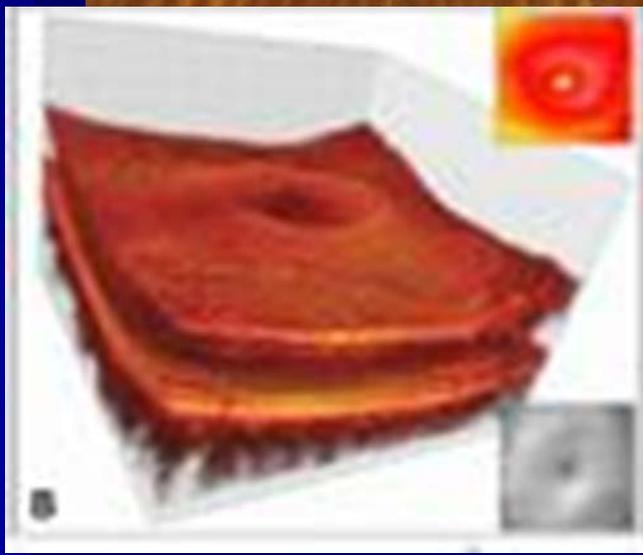
# VSE - 21 CFR 860.7

(2) Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.

# Presentation Overview

- What we have done
- What we want to do
- How can we do it
- **Considerations**

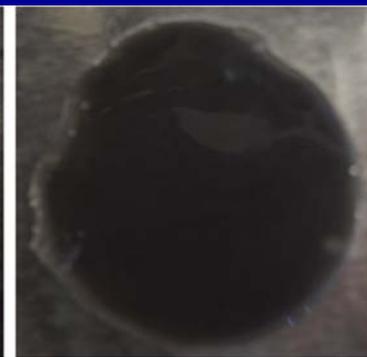
# Phantoms



(a)



(b)



(c)

# Standardization Efforts for Optical Imaging

Consensus standards are corner stones for other imaging modalities, serving both the industry and the government agencies

Increasing needs to standardize aspects of optical imaging - to facilitate product/clinical trial development

# What to standardize?

- Optical Image calibration and performance evaluation
- Optical Image quality, # pixels, color rendering
- Optical Image size, resolution, contrast, precision
- Optical Image capture, CCD, ICCD, ultrasound, OCT, photoacoustic
- Optical Image creation -photoshop

# Summary Comments

Optical imaging technology ---- non-ionizing, real-time microscopic observation

An emerging field in medical applications, particularly coupled with general surgery / minimally invasive surgery

Based on technologies and indications, regulated as Class I, II, and III devices

Specific disease detection, e.g., cancer, in screening and for intraoperative guidance

Challenges for combination products regulatory route with new drugs or approved drugs – across-Center efforts with CDER, CBER, and with Office of Combination Products

THANK  
YOU

For your Attention!

# Questions ?



# Development of Imaging Devices & FDA approval

## **Panel:**

Brian W Pogue PhD, John Frangioni MD, PhD,  
Christopher Contag PhD, Laura Marcu PhD,  
Vasilis Ntziachristos PhD, Ann Gillenwater MD,  
Josh Pfefer PhD, Betsy Ballard MD,  
Neil Ogden MS, Robert Nordstrom, PhD

# Issues

**Can we decouple Devices from Agents?** (advance the field, i.e. PET, CT, US)

## Order of magnitude variations:

**Device variety** – confocal (100X), microsc surg (10X), endoscopic, laparoscopic, surgery, pathology

**Large dynamic range differences** (vascular - mM, enzymes -  $\mu\text{M}$ , receptors – nM,  $\approx 10^6\text{X}$ )

**Wavelength variation between agents** ( $\approx 10\text{x}$  variation in excitation)

**Performance with room lights on** ( $\approx 10\text{x}$  variation in background rejection)

**Intensity variation with distance & camera dynamic range** ( $\approx 10\text{-}100\text{X}$  variation)

**Recognition of biological variability and spatial patterns to capture?**

**Depth sensing** – desired but hard to achieve without loss of sensitivity

**Technical performance standards to approve devices** – is this feasible?

(phantoms & standards)

# Idealized system

1. Real time operation - white light / fluorescence overlay
2. Seamless operation in room lights
3. High sensitivity –  $\mu\text{M}$  –  $\text{nM}$
4. Quantitative capabilities/pattern detection/augment
5. Ergonomics of use – real time decisions

# Imaging Agents: Targeting and Detection

Classes of Agents  
Safety and Toxicity  
PK and PD issues  
NCI Resources

# Thoughts

- Classes of Agents
  - Do they impart different qualities of detection, e.g. can topical applications see cells that are not yet vascularized
- Safety and Toxicity, PK/PD
  - Are they Drugs.....drugs are designed and dosed to modify biology, imaging agents are not
  - Are the regulatory requirements used now by default to drug requirements
  - Will there be evolution of the regulatory requirements for these “potentially safer” optical agents as there have been for nuclear, e.g. eIND
  - Cream for the skin...is that systemic; spray into the cavity , in vivo topical... is that systemic

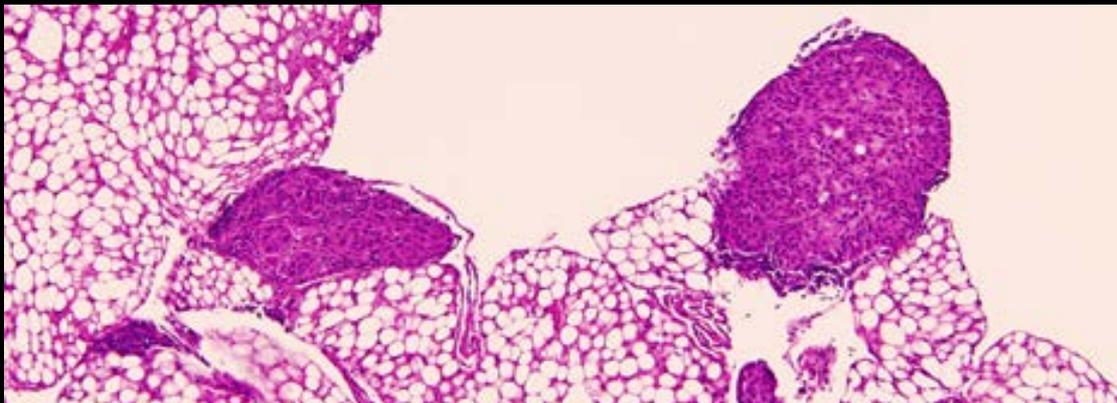


# Targeting and Detection: Classes of Agents

Peter L. Choyke, M.D.  
Molecular Imaging Program  
National Cancer Institute

# Background

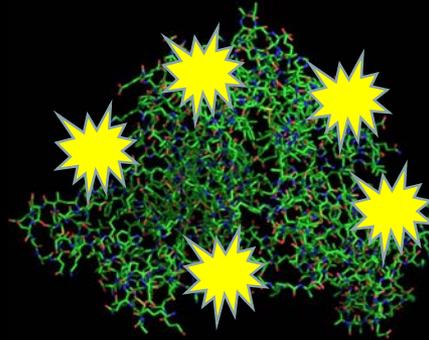
- Detection of small tumors on epithelial surfaces: peritoneum, bladder, GI tract, pleura, pericardium etc.
  - Screening
  - Optically enhanced surgery
- Lymphatics, vascularity, leakage
  - Sentinel node, lymphatic drainage
  - Vascularity of grafts, leakage of vessels, bowel
  - Angiography
- Goal is always high target to background ratio



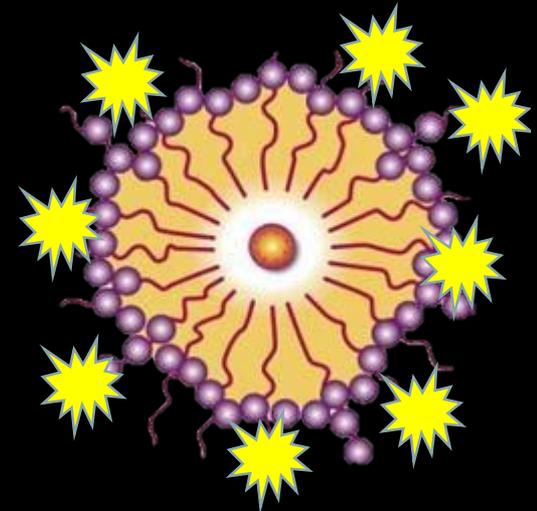
# Non-targeted Probes



Fluorescein  
Methylene Blue

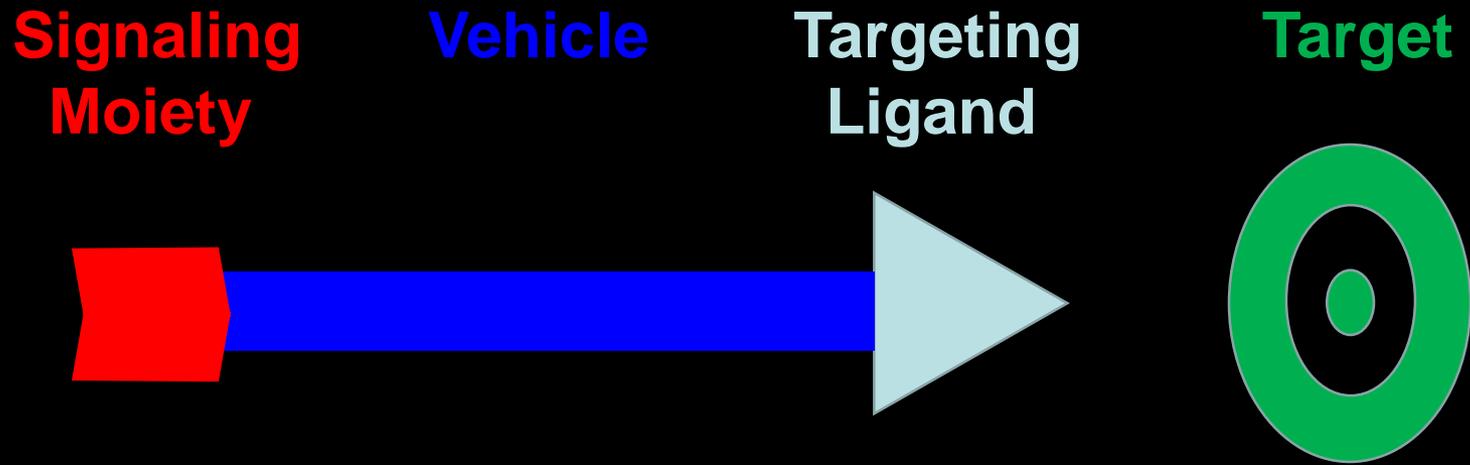


Indocyanine Green

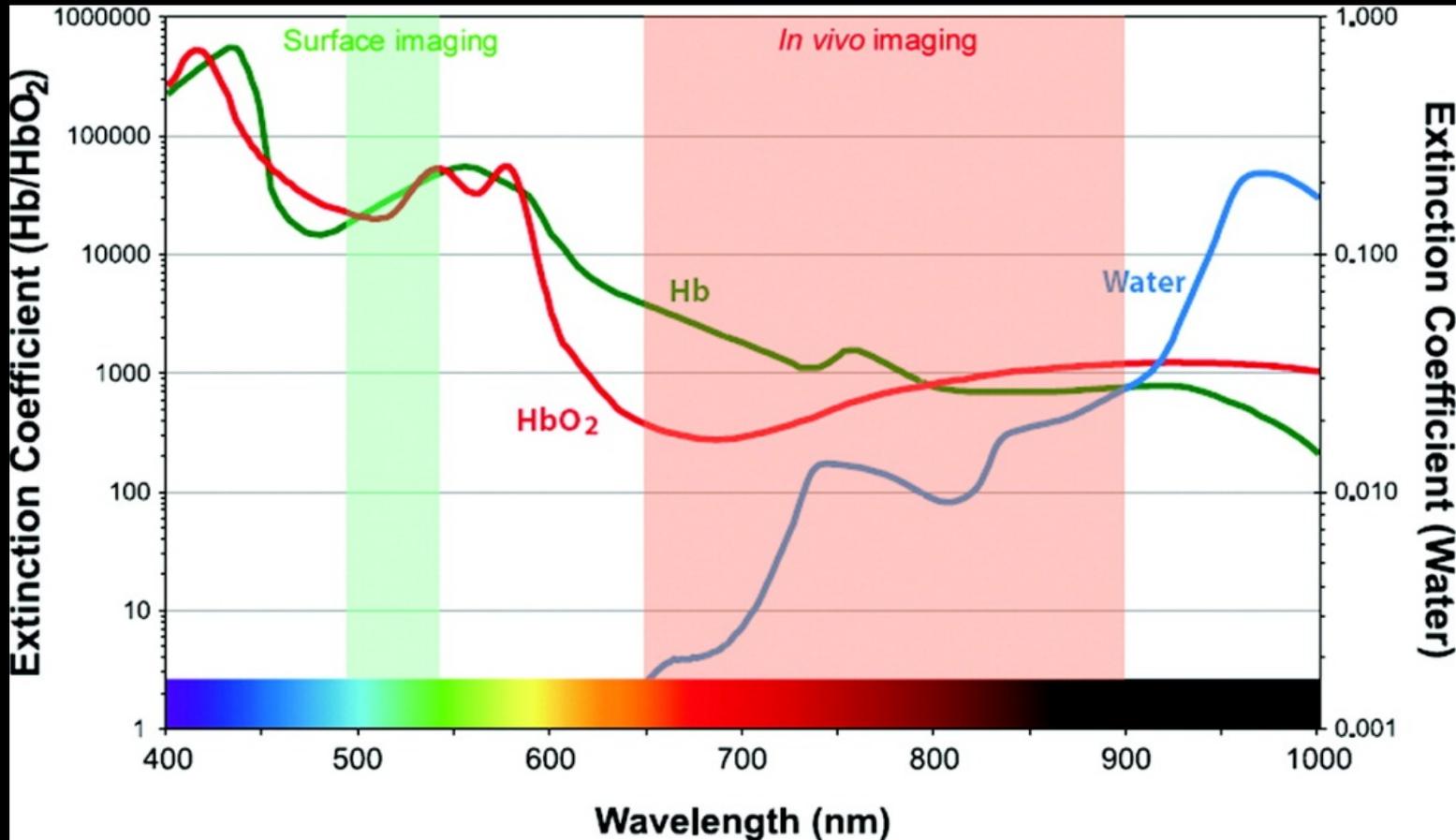


Dendrimers  
Liposomes

# Molecular Imaging Probes



# Signalling Moiety



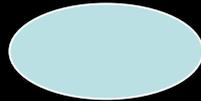
Visible fluorophores  
Sensitivity for human eye  
No camera

Near infrared fluorophore  
Depth of Penetration  
Fluorescence camera

# Always on Imaging of Peritoneum



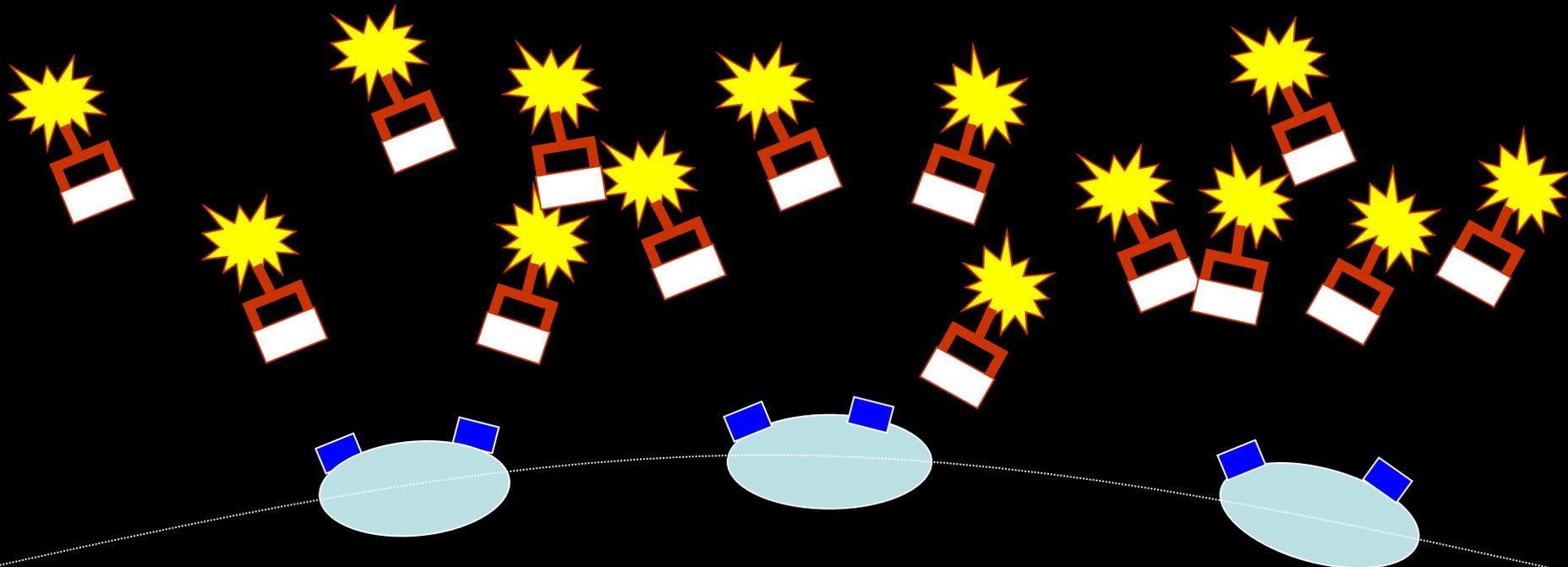
Avidin-FITC



Peritoneal  
Implant



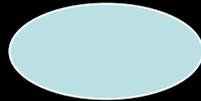
D-Galactose  
(a lectin)



# Activatable Imaging of Peritoneum



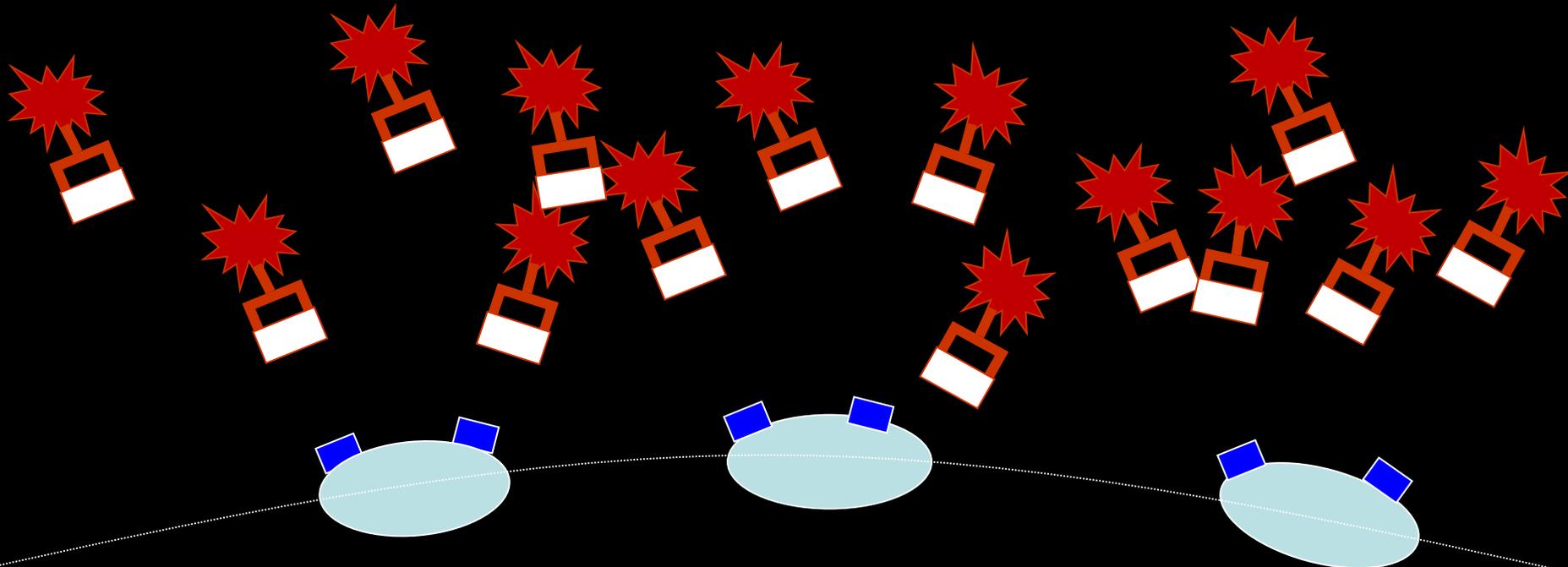
Avidin HMRG



Peritoneal Implant



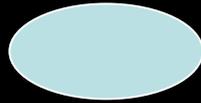
D-Galactose  
(a lectin)



# Activatable Imaging of Peritoneum



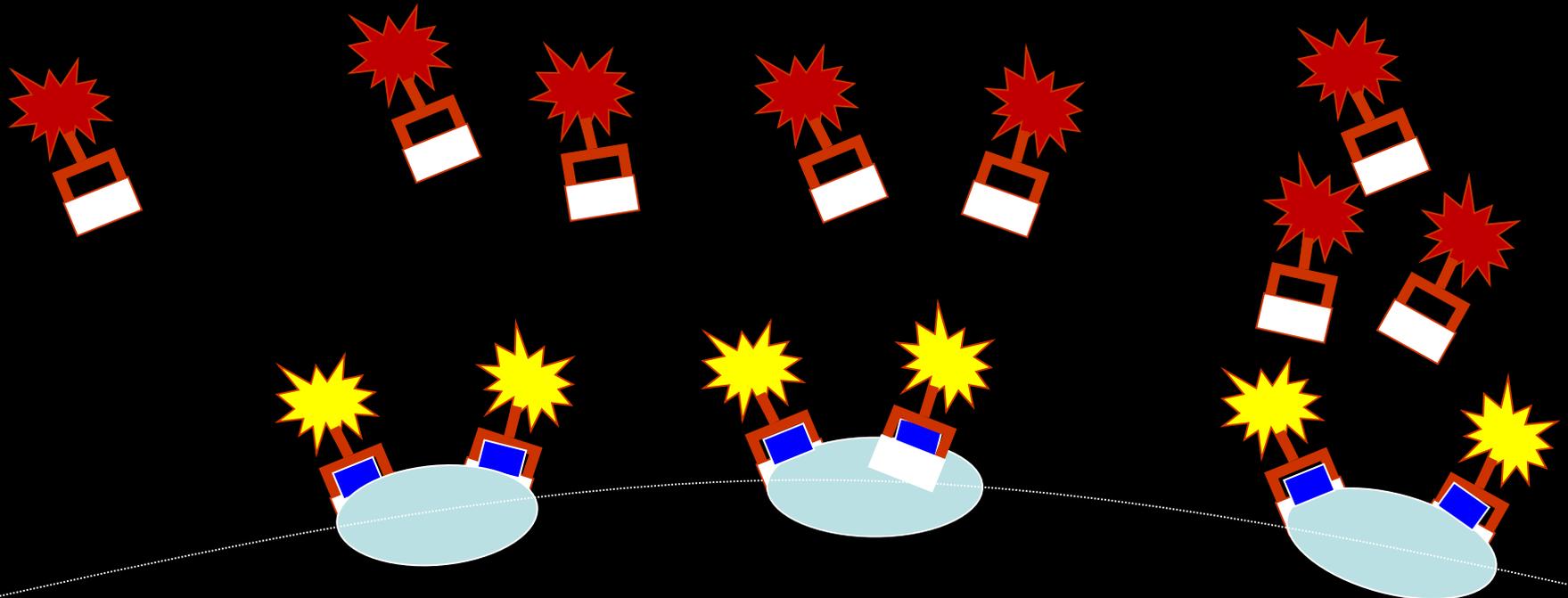
Avidin-gGluHMRG



Peritoneal  
Implant



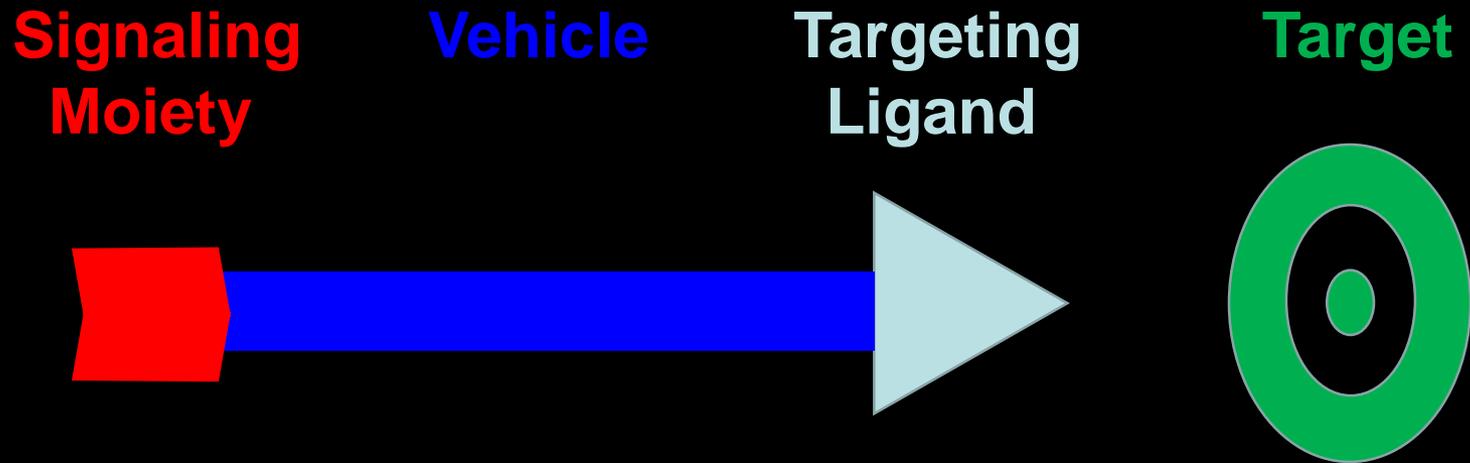
D-Galactose  
(a lectin)



# Mechanisms of Activation

- Enzymatic cleavage
- Photochemical switches
- FRET
- Dimer formation
- Caged
- Quenching-Dequenching
- pH sensitivity

# Vehicle+targeting ligand



# Vehicle+targeting moiety



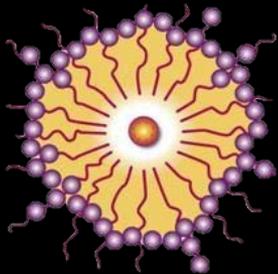
Small molecule:

High affinity, tissue penetration, high clearance rate



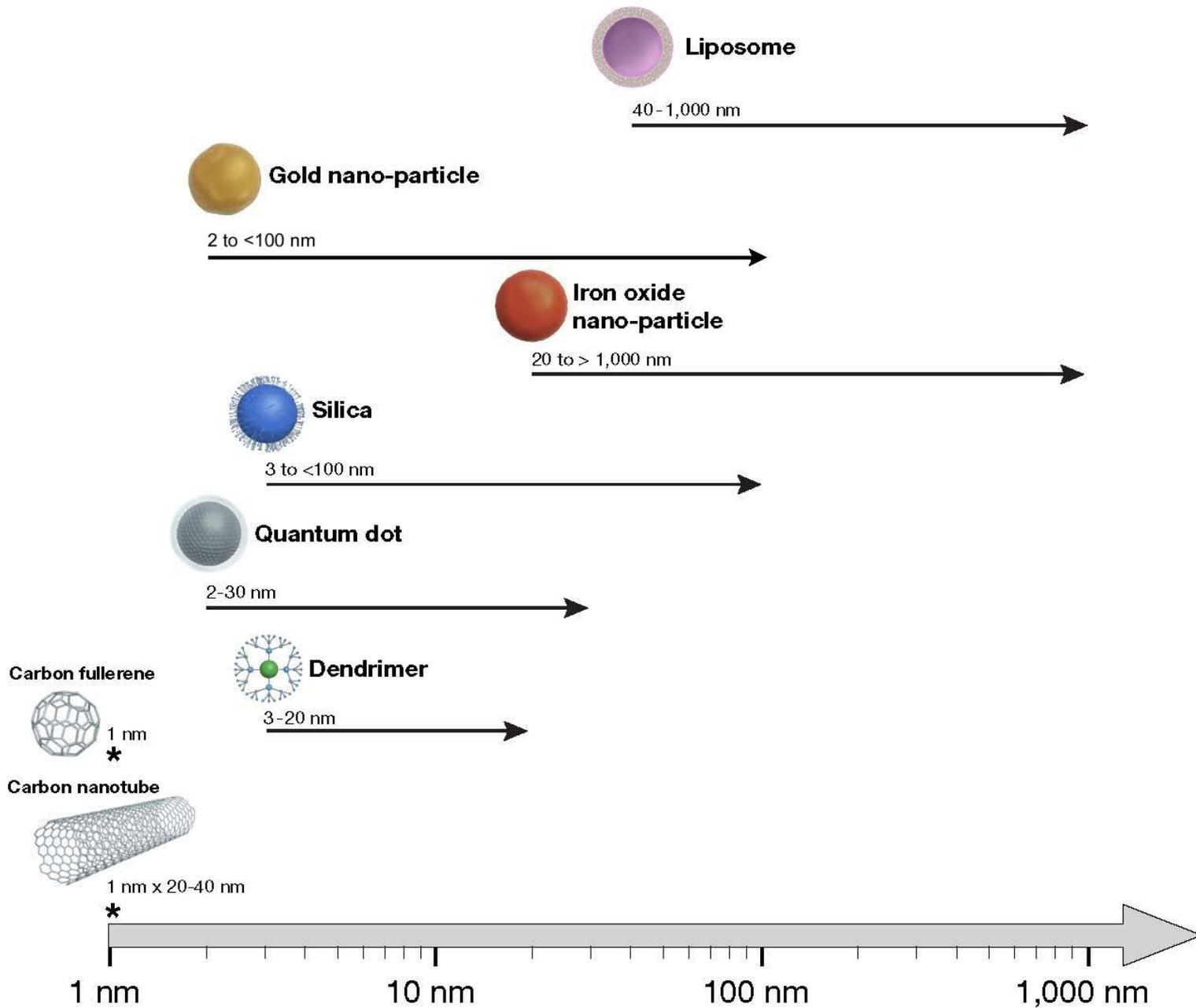
Macromolecules (e.g. antibodies):

Multiple fluorophores, slow clearance



Nanoparticle:

Polyvalent, multiple fluorophores, slower clearance



# Size of Carrier Molecule

- Biodistribution
- Clearance
- Tissue penetration/diffusion
- Affinity
- Signal to noise

# Routes of Administration

- Intravenous: Administer IV before or during surgery
- Intracavitary: Instill conjugate before or during surgery
- Topical: Applied during surgery

# Designing a Surgical Optical Probe

Visual Spectrum?  
Near Infrared?

Always on?  
Activatable?

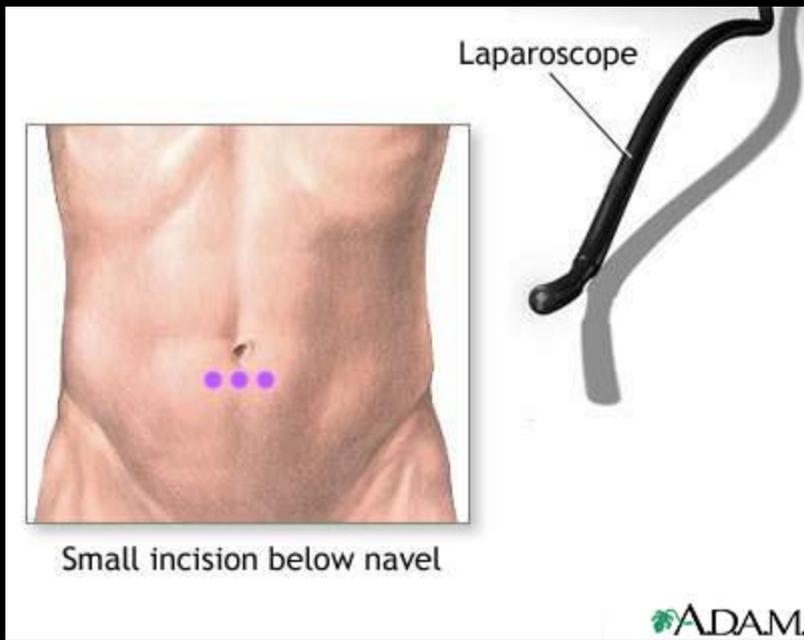
Surface tumor?

Small molecule?  
Macromolecule?  
Nanoparticle?

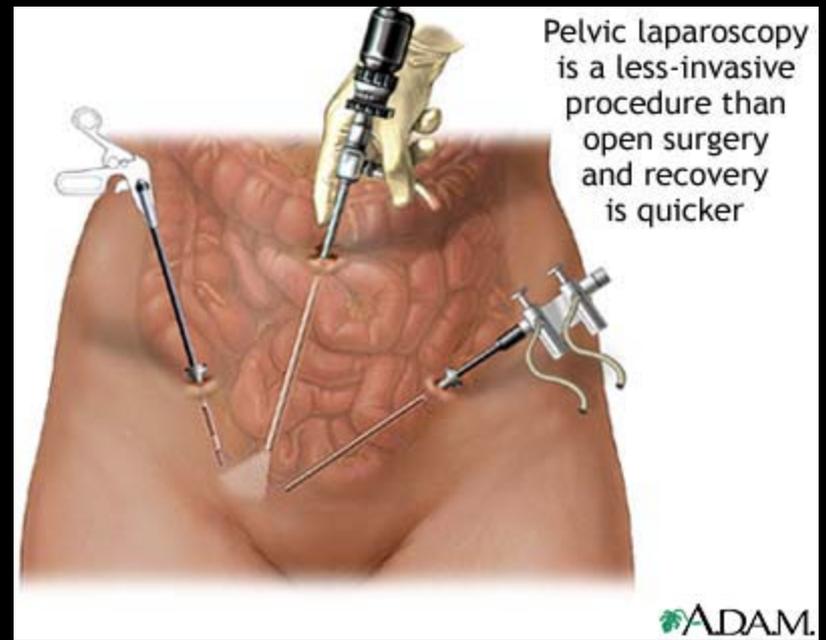
Need sensitivity?

Short or long acting?  
Intravenous?  
Intracavitary?  
Topical?

Workflow?



[http://health.allrefer.com/health/diagnostic\\_laparoscopy\\_incision\\_for\\_abdominal\\_laparoscopy.html](http://health.allrefer.com/health/diagnostic_laparoscopy_incision_for_abdominal_laparoscopy.html)



<http://health.allrefer.com/health/diagnostic-laparoscopy-pelvic-laparoscopy.html>



- Laparoscopic pictures of ovarian metastases
- From [www.laparoscopy.com/pictures/ovarymts.html](http://www.laparoscopy.com/pictures/ovarymts.html)

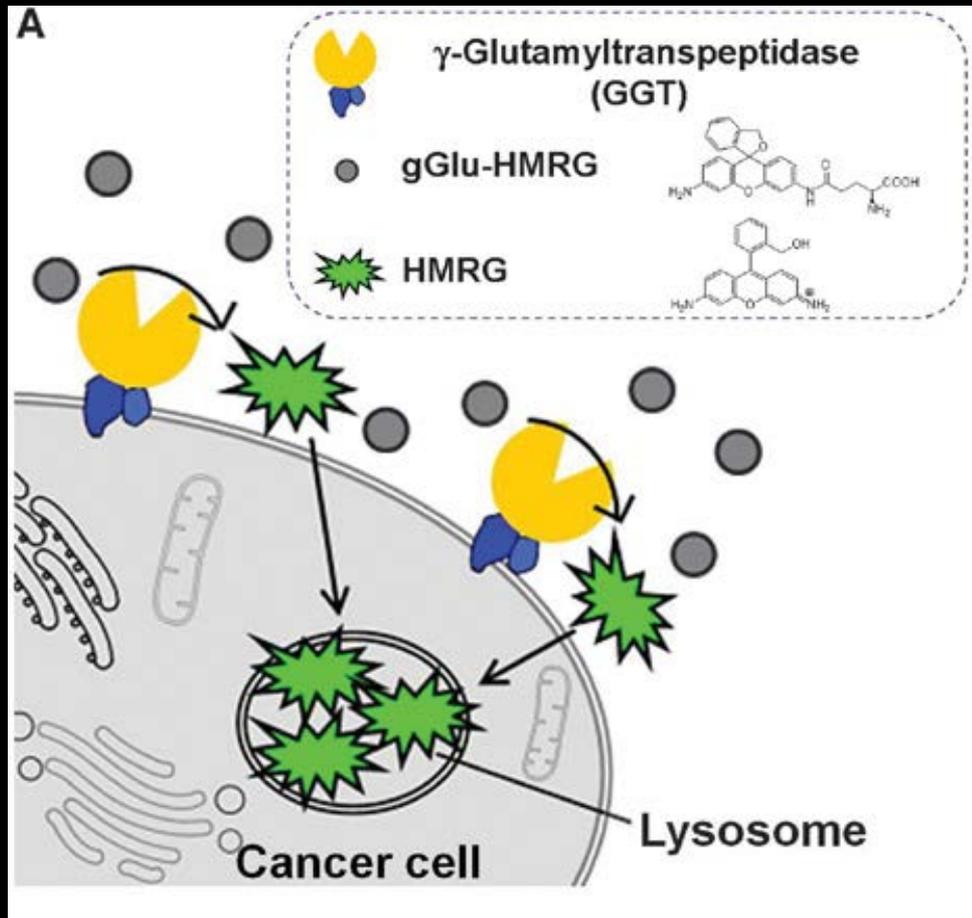
# Ultra-fast activatable probe :

$\gamma$ Glu-tamyltransferase probe

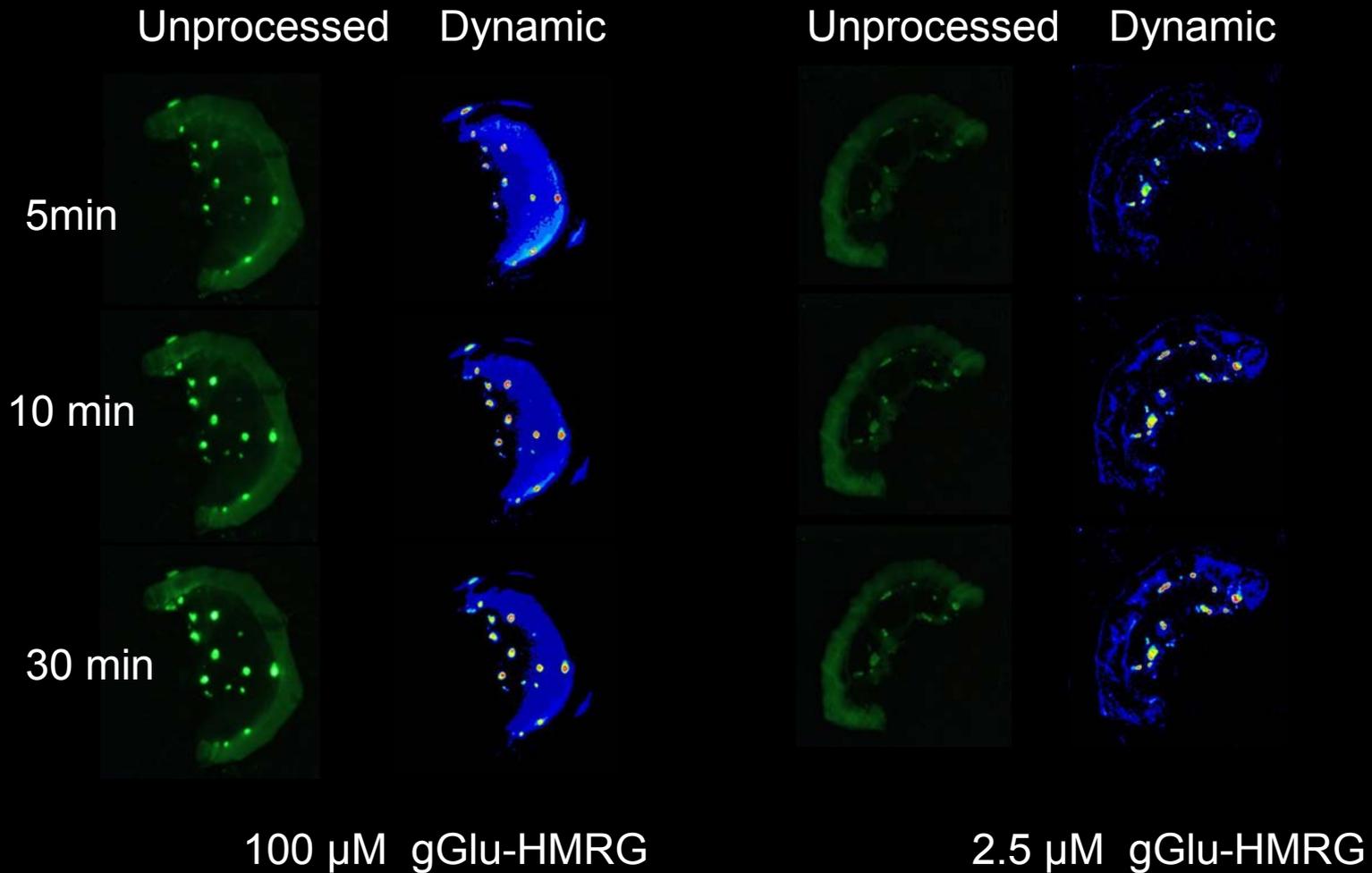
Urano, Kobayashi, et al.;  
Science Transl Med 2011 Nov 23



# $\gamma$ -Glutamyl hydroxymethyl rhodamine green (gGlu-HMRG)



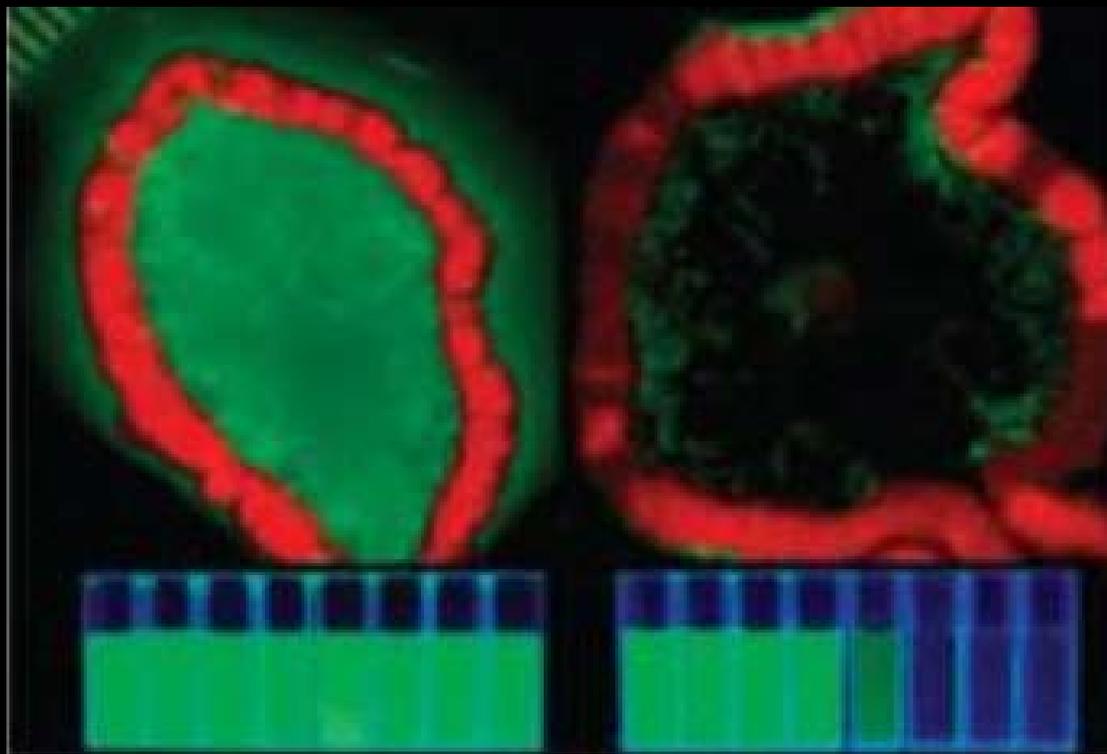
# Dilution and Dynamic Imaging



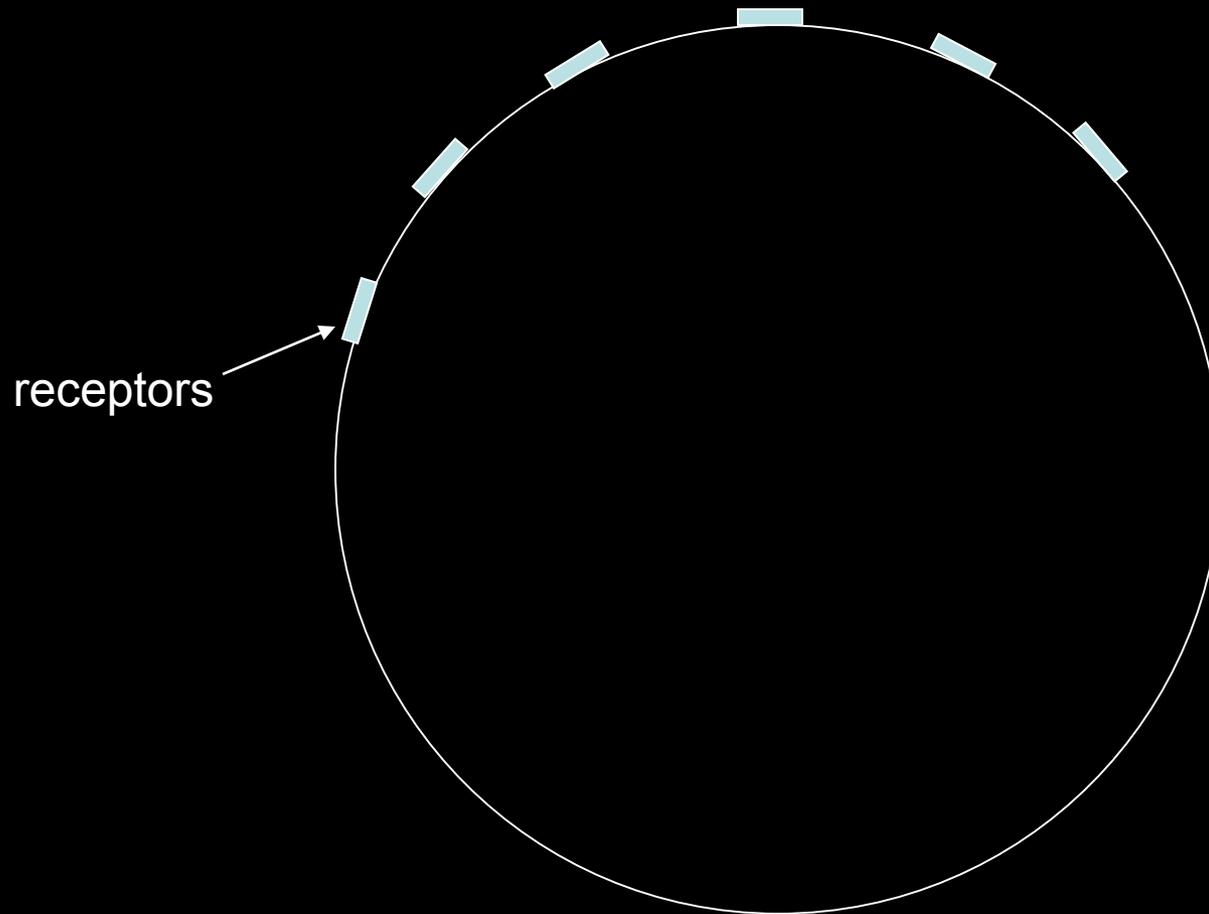
# Conclusion

- Optical imaging agents consist of:
  - Optical beacon (all)
  - Carrier molecule (all)
  - Targeting moiety (targeted only)
- These components can be combined in individual compounds
- Major design criteria for optical probes are
  - NIR? Size? Activatable? Route?

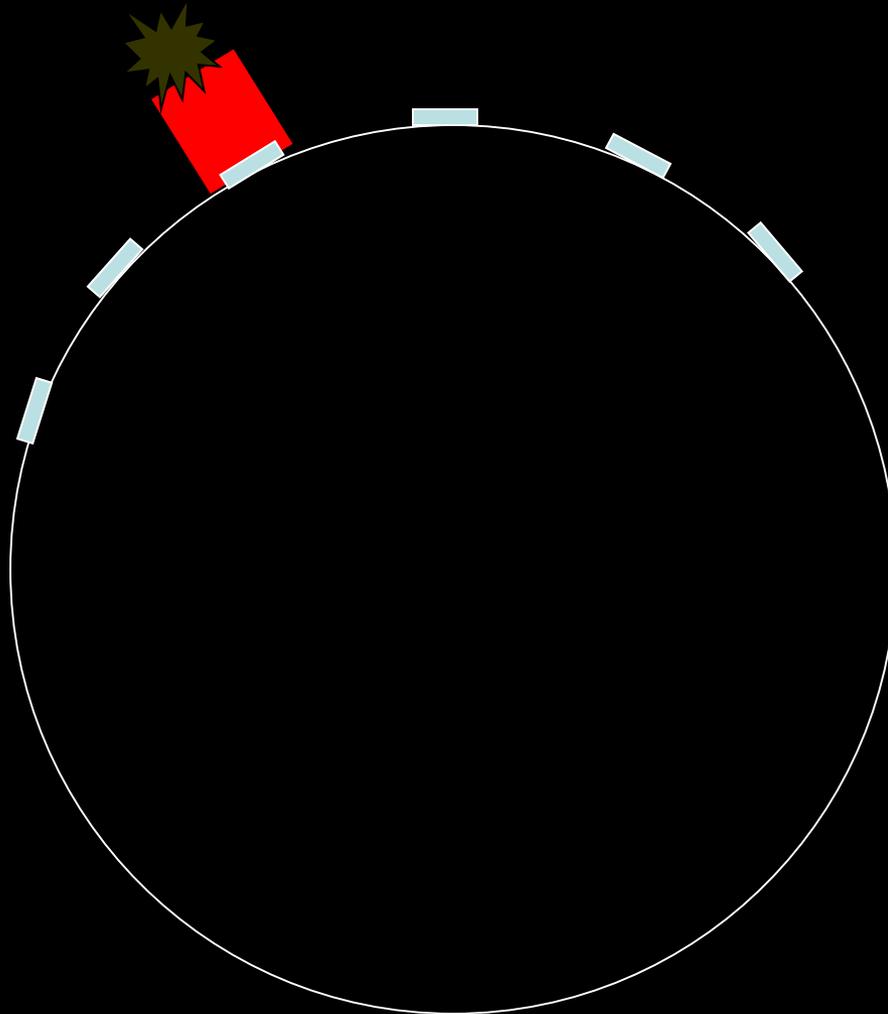
# Activatable Fluorophore (pH)



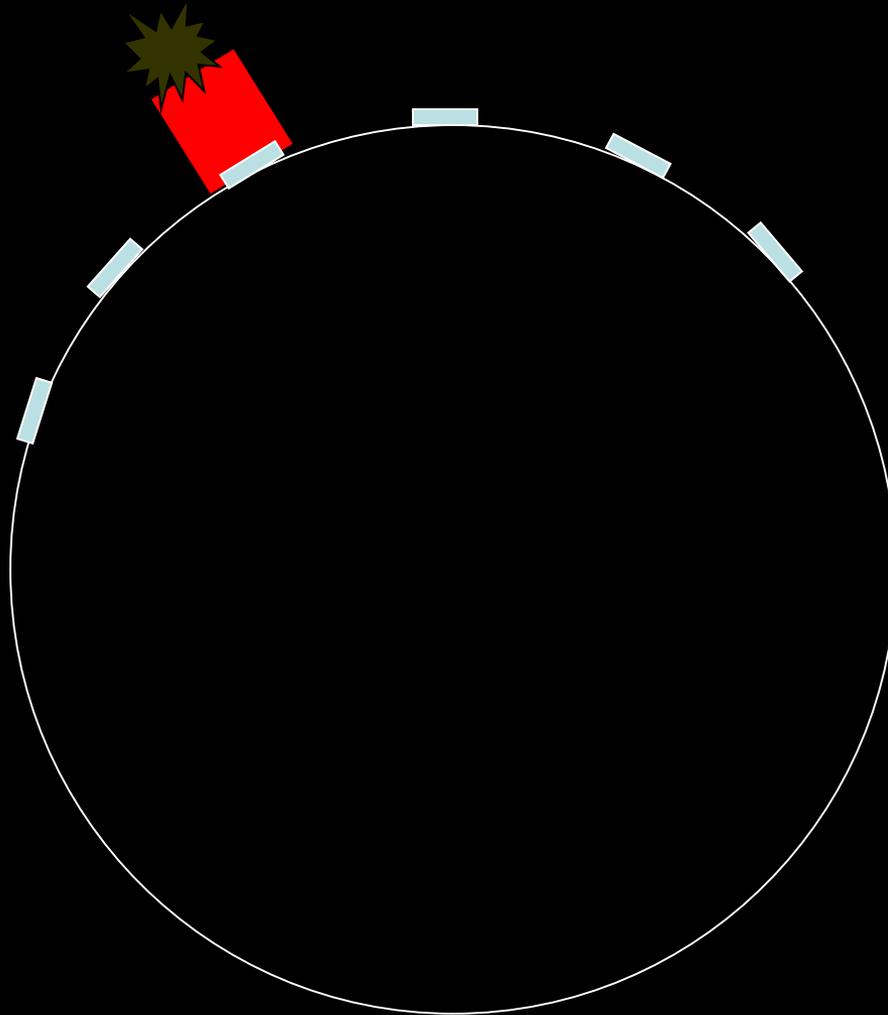
# Internalization

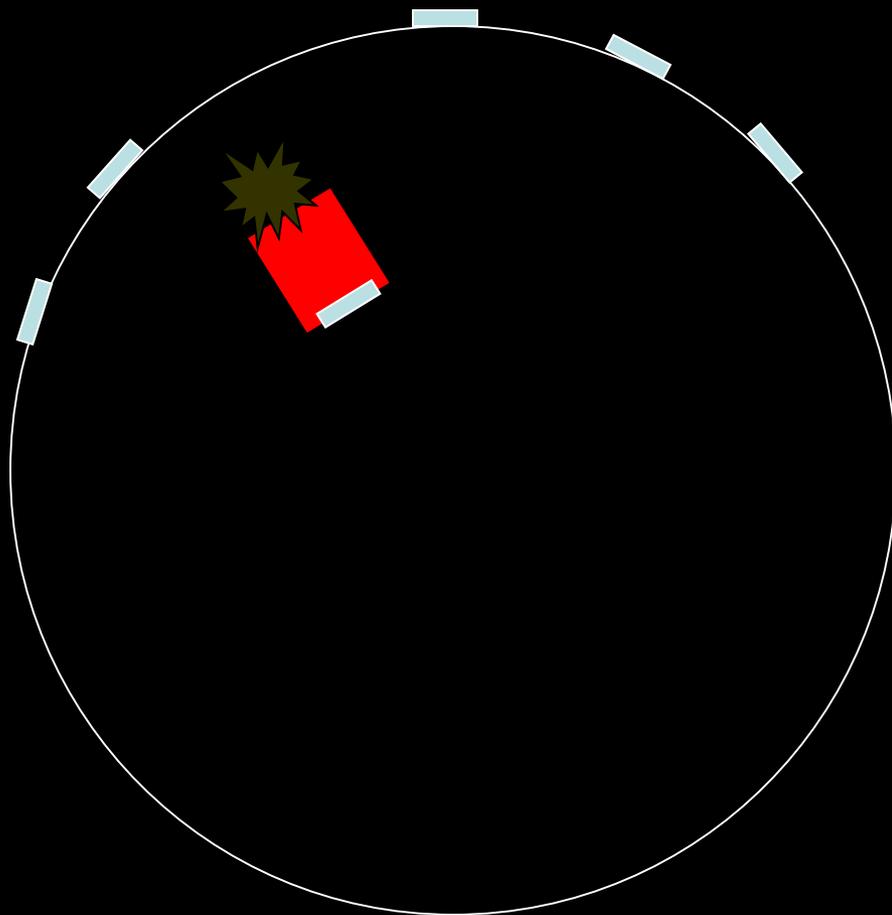


# Internalization

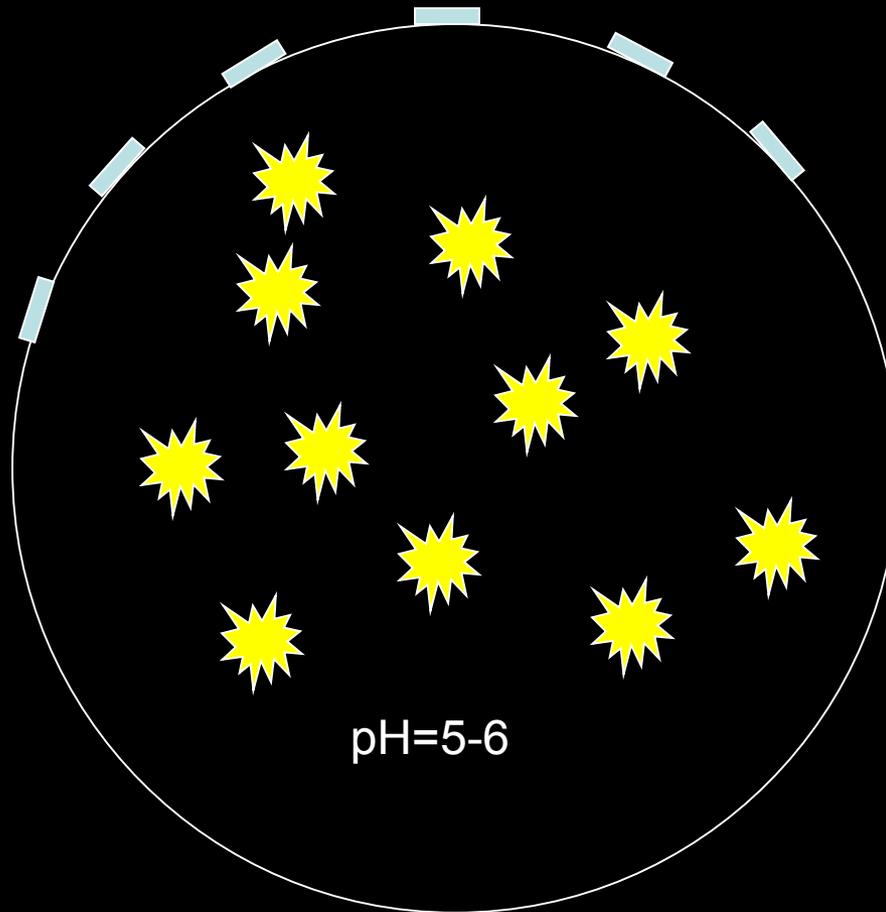


# Internalization





# Internalization







# Nonclinical Safety & Toxicity Assessment of New Molecular Entities & Modified Existing Agents

Adebayo Laniyonu, Ph.D.

Supervisory Pharmacologist

Division of Medical Imaging Products

# Focus

- Nonclinical studies needed to support clinical investigations under IND for optical imaging combination products
- Nonclinical perspectives on optical imaging agents combination products applications submitted by sponsors
- Potential device-related toxicities are evaluated by CDRH and will not be covered in this talk

# Goals of Nonclinical Investigation

- Identification of target organs
- Characterization of pharmacology and toxicology
- Specific outcomes
  - ✓ Initial starting dose
  - ✓ Dose escalation scheme
  - ✓ Monitoring schemes
  - ✓ Nonclinical studies tailored to meet the needs

# Fluorophore:

- Unapproved Dyes
- Approved/Unapproved Dyes combined with
  - Investigational New Molecular Entity
  - Approved small molecule/Biologics
  - Biologics at advanced stage of development
- Enzyme activated Products
- Nanoparticles (Gold, Silica, & Iron Oxide)

# Diverse Nature of Optical Imaging Combination Products is Self Evident

Therefore, nonclinical  
requirements have to be tailored  
to meet the needs

# Regulatory Flexibility

- Existing regulations allow for flexibility for nonclinical requirements
- Not often utilized
- ✓ Sponsors may not want to meet with FDA early in development
- ✓ FDA believes there is value in early dialog and agreement

# Please Note!

If a Sponsor determines that nonclinical pharmacology or toxicology studies are not needed, at any stage of development and provides adequate justification, FDA is prepared to grant a waiver (21 CFR 312.10)



# Nonclinical Assessment of New Molecular Entities

## Recommended Studies

# Studies Required Before Phase 1 for Optical Imaging IND (small molecules):

- Proof of Concept studies
- Safety Pharmacology: Major organs and organ systems
- TK/PK (ICH guidances)
- Expanded single dose toxicity study (may be combined with repeat dose toxicity study to save cost)
- Special toxicology (e.g. phototoxicity, route irritancy, blood compatibility)
- In vitro genotoxicity studies (not required for microdose)

# Studies Required Before Phase 2 for Optical Imaging IND (small molecules)

- Short Term Repeat Dose Toxicity Study
- Genotoxicity Studies (not required for microdose)
- Request for waiver of reproductive and developmental toxicity studies before phase 3 if applicable

# Nonclinical Assessment of Modified Existing Agents

To save time and resources, FDA strongly advises that sponsors communicate with the Agency prior to study initiation

# Nonclinical Requirements

- No new nonclinical study
- Bridging toxicity study (If issues with dye or other components)
- Letter of Authorization to reference nonclinical studies from other sponsors
- Public data (NCI, NIH)

# Biologics Optical Imaging Combination Products

- Most were previously investigated either as approved therapeutic biologics or as investigational therapeutic biologics at advanced stages of development hence relatively well characterized and may require fewer (or even no) new studies
- If not, immunogenicity, cross reactivity and other studies may be required. Best to contact review Division

# Nonclinical requirements for route, dose or population change for approved agents

Case by Case Basis, we strongly  
encourage early communication  
and dialog with review Division

# Outcome

- A more focused nonclinical safety evaluation
- Early communication with the Review Division to optimize nonclinical program
- A flexible approach that allows innovative products to move safely and quickly through nonclinical development

## Pertinent Guidances

- Developing Medical Imaging Drugs and Biological Products:

Part 1: Conducting Safety Assessment:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078930.pdf>

- Investigational New Drug Applications: Exploratory IND Studies

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078933.pdf>

- Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf>

- Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074957.pdf>



# Thank You!

[Adebayo.Laniyonu@fda.hhs.gov](mailto:Adebayo.Laniyonu@fda.hhs.gov)

301-796-1392



# Clinical Pharmacology

Gene Williams, Ph.D.

Team Leader, Division of Clinical Pharmacology V

Office of Clinical Pharmacology (OCP)

Office of Translational Sciences (OTS)

Center for Drug Evaluation and Research (CDER)



# Goals

- Approval
- High quality instructions for use: individualization of dose
- Avoid post-marketing requirements / commitments



# Developmental Milestones

- First-in-Human Trial
- Phase 2 Trial
- End-of-Phase 2 Meeting
- Phase 3 Trial
- Pre-NDA/BLA meeting

## First-in-Human Trial, 1 of 2

Safety = hold issues, recommendation to allow trial to proceed, microdose can make non-relevant add sub-bullets

- Entry criteria – e.g., renal impairment
- Monitoring of cardiac safety – e.g., QT<sub>C</sub>
- Drug-drug interactions (DDI) – drug as substrate/victim most often the concern
- Food effect (**not relevant for IV**)

## First-in-Human Trial, 2 of 2

Efficacy = non-hold issues, recommendations for trial design

- Goal is “near optimal” dose regimen and imaging conditions (timing, machine) prior to confirmatory trials
  - Process is completed in Phase 2, but begins in first trial
  - Superior images to alternatives which have been studied
    - Assured only when  $\geq 3$  doses and  $\geq 3$  imaging windows
    - Accuracy and precision impacts Phase 2 design / success
- Sufficient PK sampling
- DDI / food

# Pharmacokinetics

- Useful for drug development goals, not only package insert
- Phase 1/Phase 2: improve selection of imaging timing, timing of repeat dosing, and amount of repeat dose
- Eventual goal is to correlate concentrations with clinical outcomes: collect information in Phase 3
- Bioanalytical Method Validation
- Topicals
  - PK needed to correlate with safety outcomes
    - Demonstration of “non-absorption” may include acquiring PK in Phase 3

## Phase 2 Trial

- Safety = hold issues, recommendation to allow trial to proceed
  - Same as Phase 1 trial, but informed by Phase 1 information including use of PK for dose adjustments
- Efficacy = non-hold issues, recommendations for trial design
  - Completion of discovery of “near optimal” dose and imaging conditions for use in Phase 3
  - Sufficient PK sampling
    - linearity: issue for later specific population studies

## End-of-Phase 2 Meeting, 1 of 2

- Near Optimal Dose: efficacy as well as safety
  - Food Effect (**not relevant for IV**)
  
- Acquire Agency input on data to address Specific Populations in NDA/BLA

Q.: What to measure in future studies?

Info: Identity of major active (imaging, toxicity for non-microdose) metabolites

Q. What data in subjects with organs impairment are needed?

Info: Route of elimination and excretion of parent and major active metabolites

## End-of-Phase 2 Meeting, 2 of 2

- Acquire Agency input on data to address Specific Populations in NDA/BLA

Q. What in vivo drug interaction studies with new drug as victim are needed?

Info: parent and major metabolites as substrates (e.g., CYP enzymes and transporters)

Q. What future in vivo drug interaction studies with new drug as perpetrator are needed?

Info: Parent and major metabolites as inhibitors and inducers (CYP enzymes and transporters, not applicable to microdose)

## Phase 3 Trial, 1 of 2

Safety = hold issues, recommendation to allow trial to proceed

- Same as Phase 2 trial, but informed by Phase 2 information including use of PK for dose adjustments

## Phase 3 Trial, 2 of 2

Efficacy = non-hold issues, recommendations for trial design

- Evaluate if dose is near optimal (e.g., review EOP 2 meeting)
- Sufficient PK sampling to inform dose adjustment during or at end of trial; sampling all patients maximizes information (PK-imaging and PK-safety)
  - Adjust dose for “typical patient”
  - Adjust dose for specific population, or determine dose-adjustment not needed

## Pre-NDA/BLA Meeting

- Review of data acquired to fulfill recommendations made at the End-of-Phase 2 meeting
- Review of organization of future application: study reports, datasets

## Clinical Pharmacology Guidance Page

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm>

- This list is not comprehensive (e.g., pregnancy, pharmacogenomics, pediatrics)
  - Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications
  - Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling
  - Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling
  - Drug Interaction Studies--Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations

## **Biopharmaceutics Guidance Page**

**<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm>**

Below not comprehensive; biopharmaceutics often not relevant to IV

- Bioanalytical Method Validation
  - relevant to all PK
- Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations
  - case-by-case relevance for IVs
- Food-Effect Bioavailability and Fed Bioequivalence Studies Clinical Lactation Studies--Study Design, Data Analysis, and Recommendations for Labeling
  - not relevant for IVs

# Acknowledgments

- Brian Booth, Deputy Director, DCPV
- DMIP: Louis Marzella, Betsy Ballard, Adebayo(Bayo) Laniyonu, Kyong(Kaye) Kang, Nushin Todd



# End

- END

# Dose Adjustment Example

No dose change needed for renal impairment



american society of  
image guided surgery

It is all how you frame the question:  
**Contrast enhanced surgery**

**vs.**

A promotional image for Game of Thrones featuring Stannis Baratheon sitting on the Iron Throne. He is wearing dark, heavy armor and has a serious expression. The throne is made of dark, jagged metal. The background is dark and moody.

**GAME OF THRONES**

**Unenhanced Contrast-less Butchery**

GENERAL SURGERY IS TYWIN LANNISTER



MED STUDENT IS ARYA



Not able to be left on their own, asks a lot of questions, and will probably stab you with needle



A graduate always pays their debts....



# Clinical Endpoints

Eben Rosenthal, MD

# Clinical Trial Design: Endpoints beyond safety

## Moderator

Eben Rosenthal, MD

Ann and John Doerr Medical Director  
Stanford University

## Panel

Lalitha Shankar MD PhD, Jonathan Sorger PhD, Thomas Wang MD PhD, Barbara Smith MD PhD, Merrill Biel PhD MD MBA, Andrew Farb MD, Phillip Davis MD, Louis Marzella MD PhD

# Identify possible endpoints beyond safety

## Observational Endpoints

Abnormal vs. normal

Tumor to Background Ratio

## Endpoints to change practice

Change in number of positive margins

Quality of life (eg from reduction in normal tissue

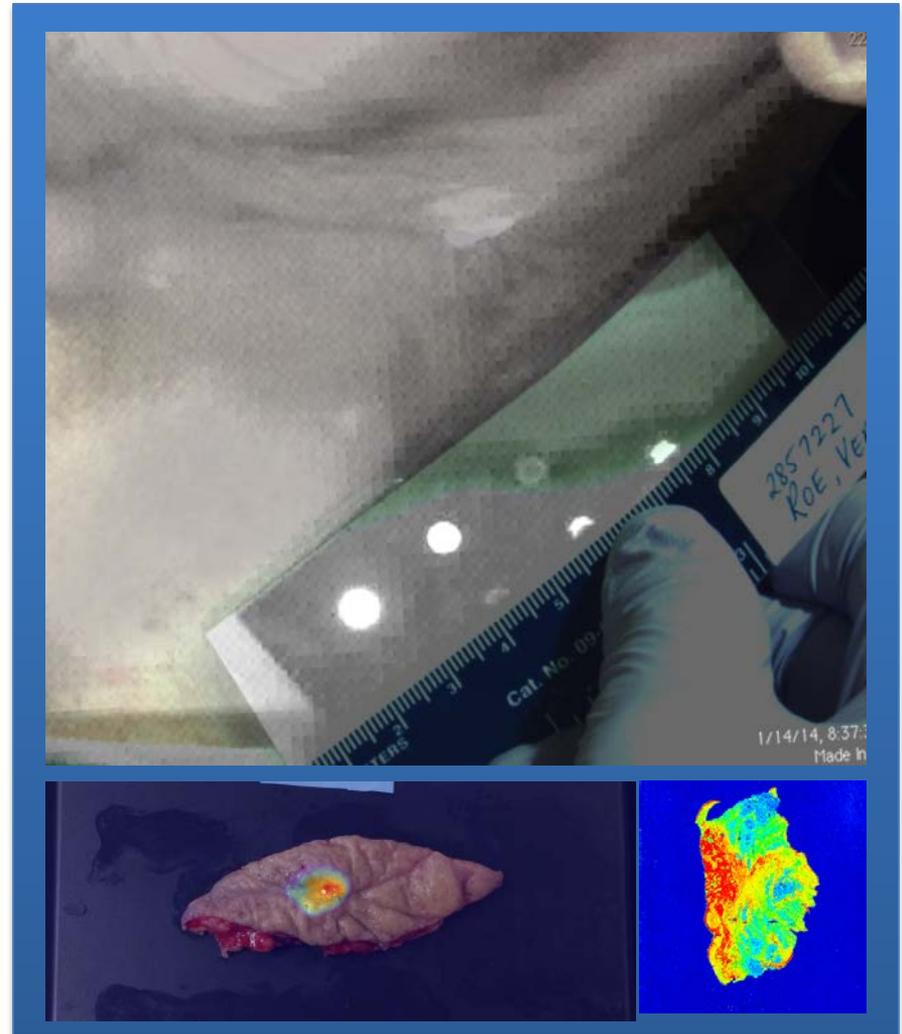
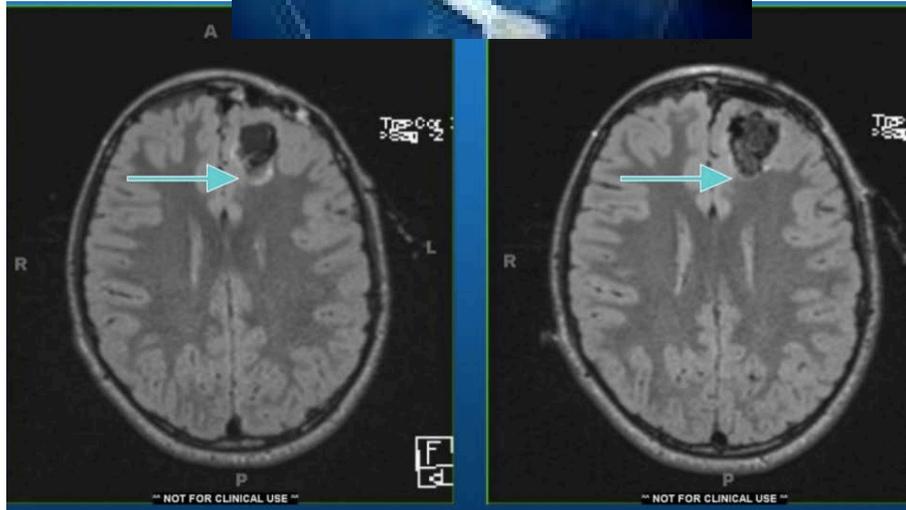
loss)

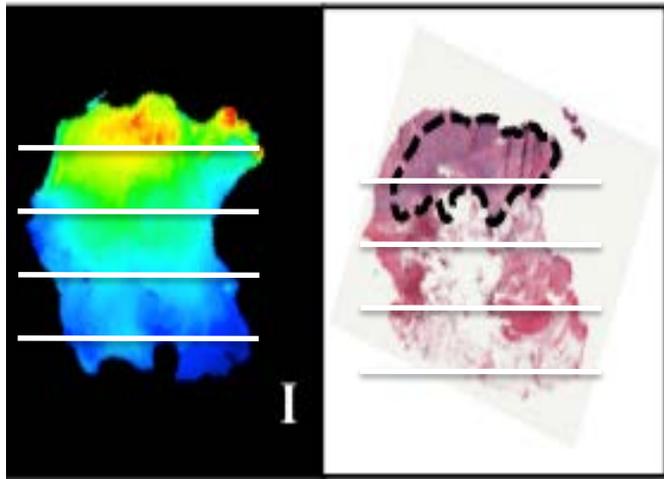
Change in the re-excision rate

Survival

# Abnormal from Normal

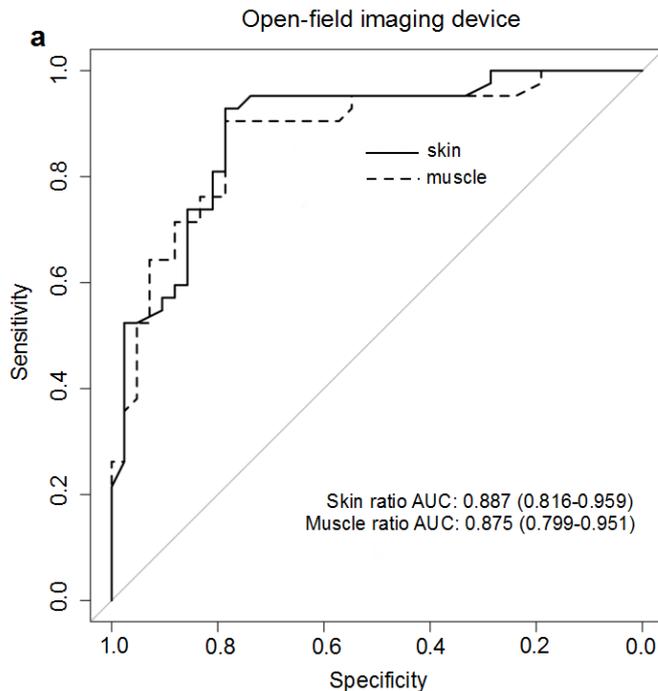
Objective: Exogenous contrast agent injected to identify areas of interest for further assessment





Can fluorescence be used to differentiate **normal** from **abnormal** tissue?

— 2 mm



SKIN NORMALIZED	
Sensitivity	92.9%
Specificity	81.0%
Positive predictive value	83.0%
Negative predictive value	92.0%

Should **sensitivity and specificity** be included as outcome measures for clinical trials?

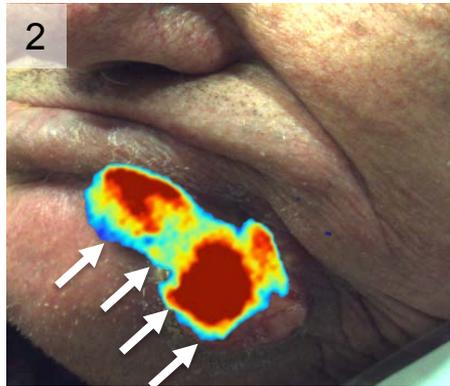
# Endpoint: Tumor to Background Ratio

**Hypothesis:** Optical imaging can be used to delineate tumor from non-malignant tissue *in situ*.

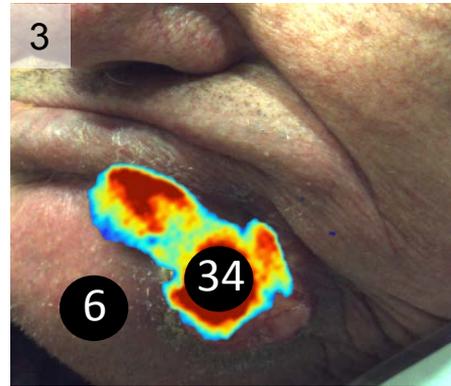
**Option 1:** The quality of contrast used to delineate normal from tumor tissue is determined.



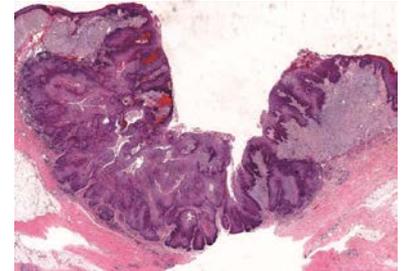
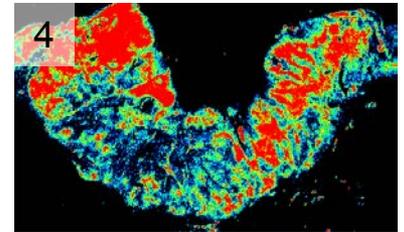
1  
Areas of normal and abnormal tissue are identified under normal light



2  
Fluorescence imaging is performed and tissues are evaluated



3  
Raw fluorescent counts are acquired for each area and a ratio is generated



4  
Abnormal tissue is correlated with histology

**Outcome measure:** Ratio of contrast generated from tumor tissue and normal tissue (Tumor to background ratio)

**Anticipated result:** TBR of  $>2$  for over 95% of tumors

# Observational Endpoints

How do these factor into the approval process?

Should these measurements be standardized?

# Identify possible endpoints beyond safety

## Observational Endpoints

Abnormal vs. normal

Tumor to Background Ratio

## Endpoints to change practice

Change in number of positive margins

Quality of life (eg from reduction in normal tissue

loss)

Change in the re-excision rate

Survival

# Change in Number of Positive Margins: *Wound Bed*

## Measure change in positive margin rate

Surgeons and/or pathologists using optical guidance will identify more positive margins compared to white light alone.

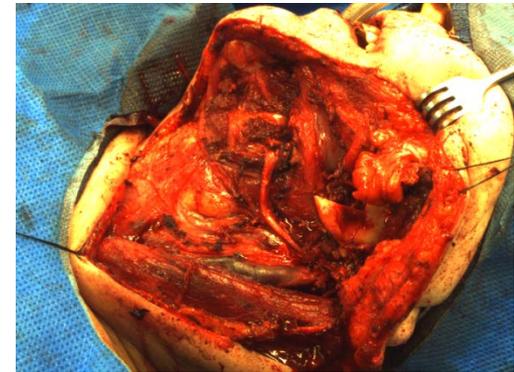
*Limitations?*

*Advantages?*

*Feasibility?*

*Value of information?*

*Thresholding*



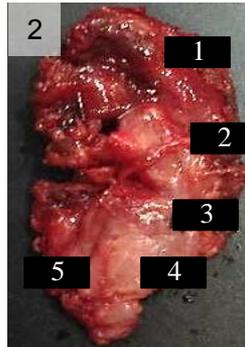
# Change in Number of Positive Margins: *Specimen*

*Optical imaging will increase detection of close or positive margins on the resected specimen in real time.*

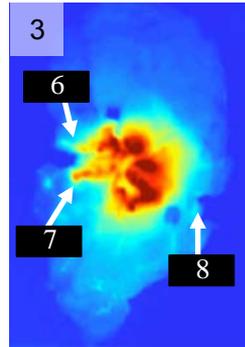
**Option 2:** Determine if ex vivo optical imaging of the ex vivo specimen improves detection of close or positive margin immediately after resection



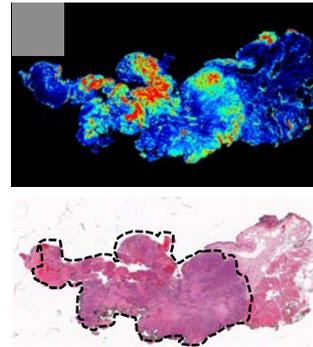
Tumor is excised



Identify specimen margins for pathological sampling using standard of care



Apply optical imaging and sample additional areas for pathological sampling



All samples are collected, catalogued, and sent to pathology.

**Outcome measure:**  
Number of additional positive margins taken due to fluorescence information.

# Improve quality of life

**Objective: Reduce normal tissue excised from breast during breast conserving surgery**

Measure volume of tissue removed using white light compared to surgical navigation after randomization.

*Limitations?*

*Advantages?*

*Feasibility?*

*Value of information?*

Volume (cm<sup>3</sup>) in surgical navigation

compared to

Volume in standard of care

# Return to OR

**Objective: Use of optical imaging to guide surgical to reduce need for re-excision of margins in breast surgery.**

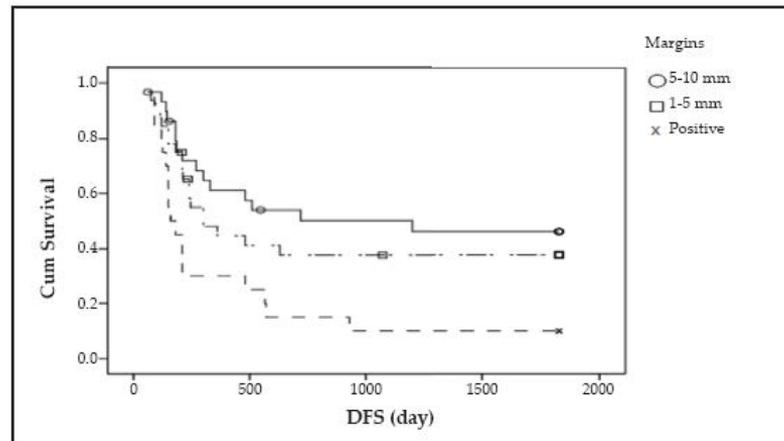
Randomize to use of optical navigation or standard of care and determine if the re-excision rate changes (vs. Historical control)

*Limitations?*

*Advantages?*

*Feasibility?*

*Value of information?*



# Local Recurrence Survival

**Objective: Improve local recurrence**

**Or improve survival**

Randomize patients to surgical guidance or white light alone and determine potential survival advantages.

*Randomized vs. historical controls?*

*Time to progression (palliative cases)*

*Local recurrence (local treatment)*

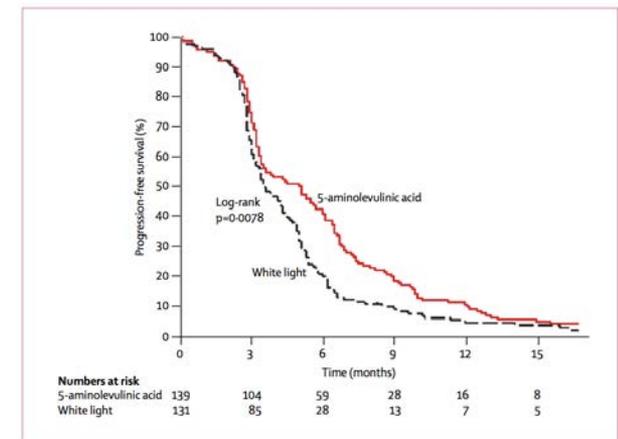


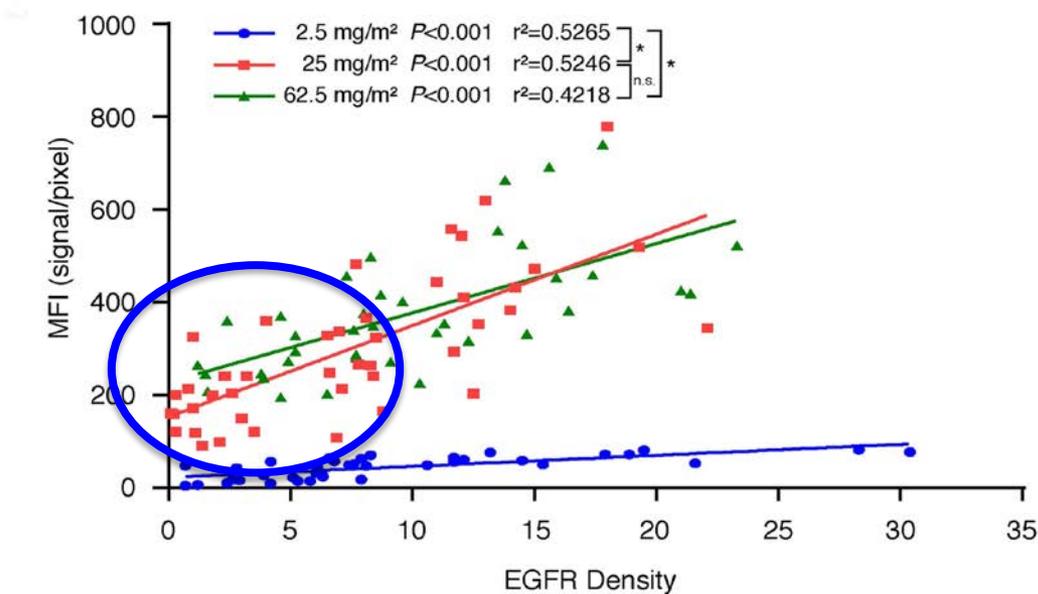
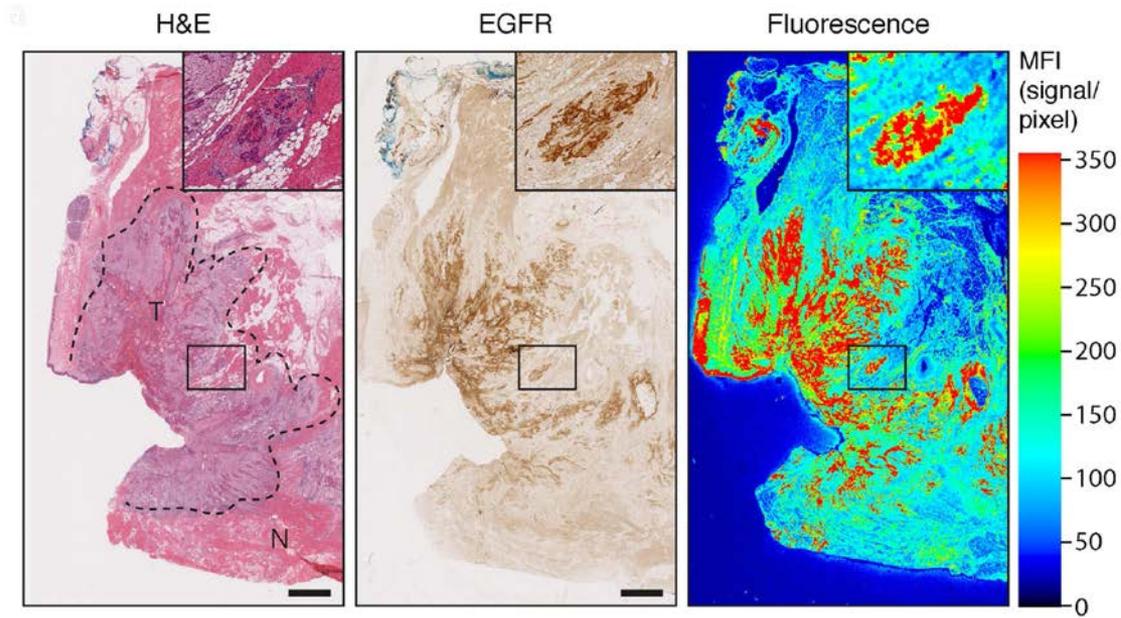
Figure 2: Progression-free survival by surgical group

# Discussion

# Diagnostic Testing for Molecular Agents

- Planned for use in invasive procedures
- Should tumors undergo interrogation for interventional diagnostic imaging?
- What data is required to avoid ligand testing for imaging requirements?

EGFR expression correlates with fluorescence intensity but low expression sufficient for intense signal





# Phase 1 and 2 Studies

*safety first...*

Phillip Davis, MD  
Medical Officer

**FDA/CDER/DMIP**

# Overview

- **Background**
  - FDA Mission
  - Drug Development Basics
  
- **Phase 1 Studies**
  
- **Phase 2 Studies**
  
- **Take Away Points**

# What We Do

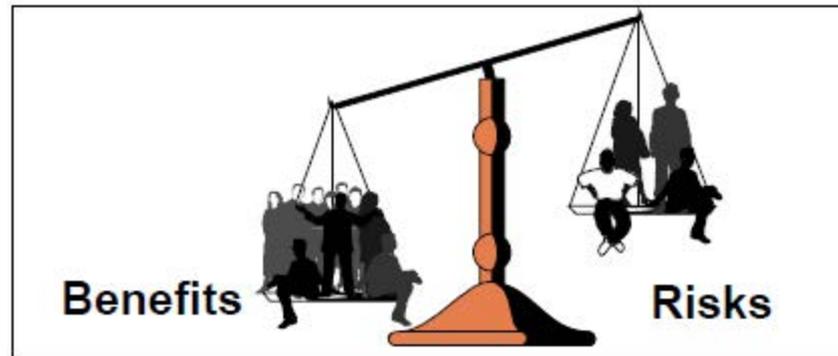
“The FDA is responsible for **protecting the public health** by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation.’

“The FDA is also responsible for **advancing the public health** by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and **helping the public get the accurate, science-based information** they need to use medicines and foods to improve their health.”

**Reference:** [www.fda.gov/aboutfda/whatwedo/default.htm](http://www.fda.gov/aboutfda/whatwedo/default.htm)

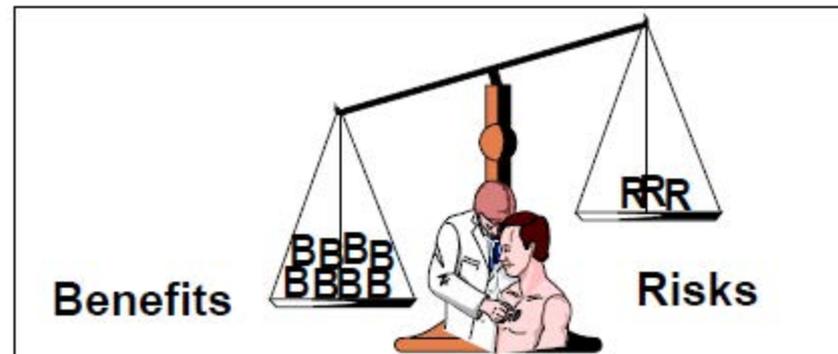
## FDA

Evaluates risks/benefits for a **population**



## Provider

Evaluates risks/benefits for a patient



## Patient

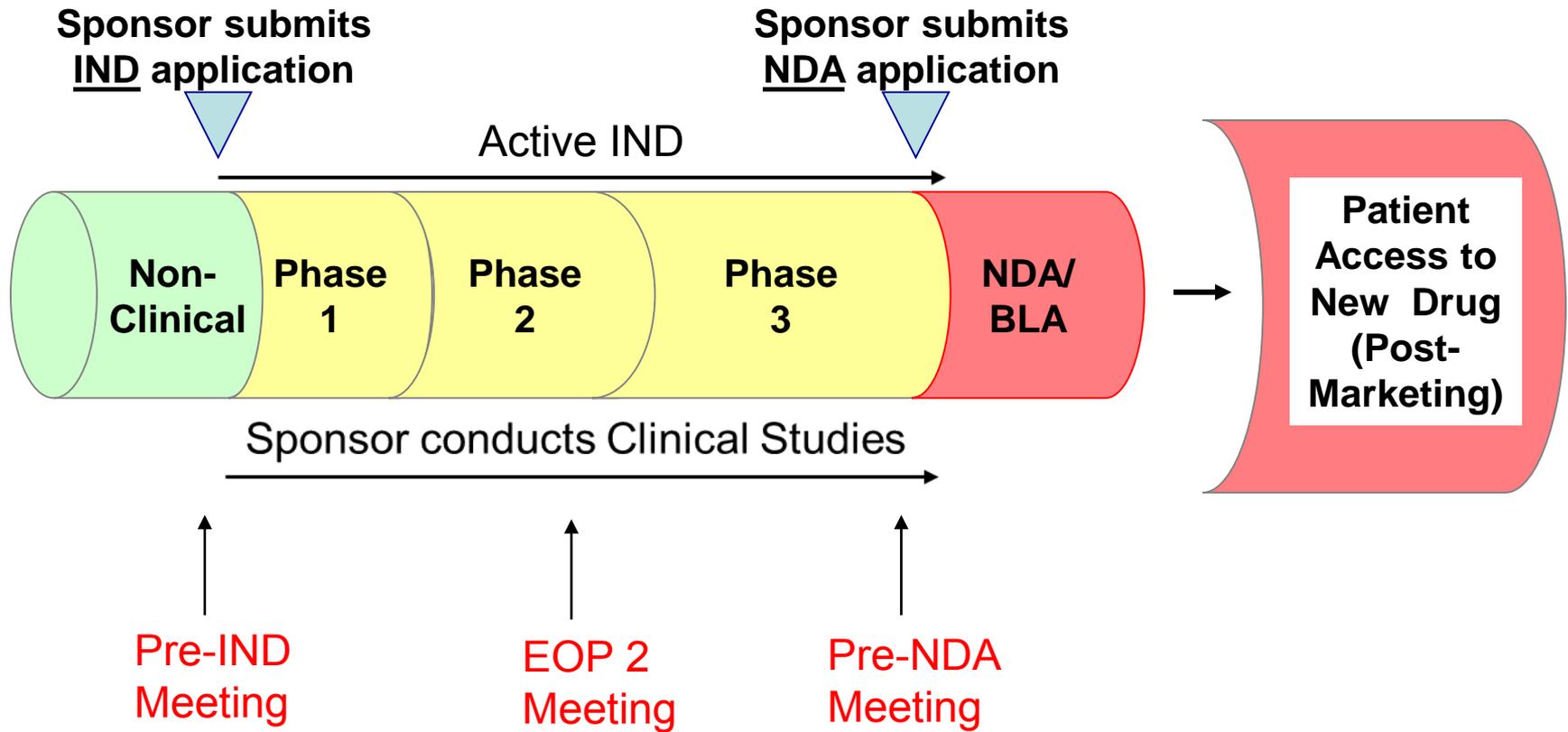
Evaluates risks/benefits for himself/herself



# FDA Roles in Drug Development

- Assuring the **safety** and **effectiveness** of drugs
- Safety of study participants
  - Human subject protection  
(consent, GCP, safety monitoring)
- “Speed innovations”
  - Helping in the development of more effective, safer and more affordable drugs – *promoting good science*
    - Involvement throughout all phases of drug development
    - Providing advise on the design of well controlled, safe investigations

# Milestone Meetings with FDA



## Phase 1 and 2

- *From a regulatory perspective:* Investigational diagnostic tests offer no advantage to study subjects: *drug and associated cameras/devices* must have acceptable safety threshold.
- Studies should collect sufficient data to allow for refinements at next step of develop pathway
- Begin thinking about clinical use early in order to develop indication statement and appropriately designed studies to test the proposed use.

# Phase 1

*Initial introduction of investigational drug into humans*

- Designed to collect safety data, determine metabolism, PK & early dosing information.
  
- Closely monitored for safety
  - Small numbers of subjects, sequential dose evaluation
  - Adverse event collection during imaging and follow up
  - Vital signs, EKG, clinical labs baseline and after imaging
  - Pregnancy testing prior to enrollment

# Phase 1

*Initial introduction of investigational drug into humans*

- Should collect sufficient information to design a well controlled hypothesis generating study
  - Early safety/tolerance issues
  - Imaging uptake characteristics
  - Best imaging time points
  
- Imaging characteristics at different dosing
  - *Begin thinking about optimal dose early*
    - *Although not typically determined until phase 2 or 3 studies.*

## Phase 2

- Controlled clinical study to collect early effectiveness data and generate hypotheses.
  - *Refine dosing* based on phase 1 safety/bio-distribution data
  - *Further develop*:
    - Imaging time points/procedures
    - Image interpretation standards
    - Hypotheses and reference standards
  
- Aids in early understanding of AE profile.
  - Well controlled, closely monitored
  - Relatively small numbers
  - Appropriate clinical laboratory and vital sign assessments<sup>10</sup>

## Phase 2 Example

- Optical imaging agent X given via IV injection.
- Objectives: Safety & early efficacy
- Population: Stage 4 cancer scheduled to undergo surgery
- Efficacy Endpoints: Imaging results as compared to reference standard (histology)<sup>11</sup>

## Phase 2 Example

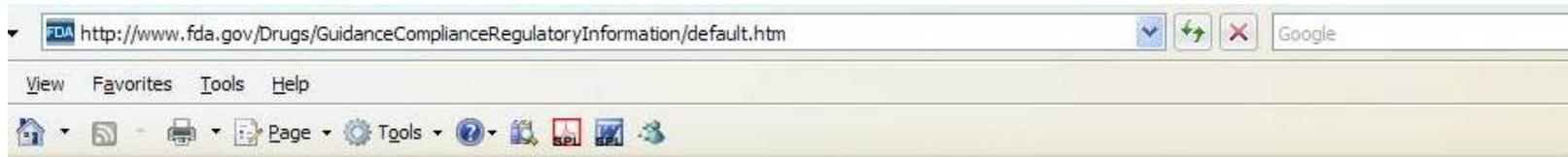
- Procedures: Standard of care (SOC) surgical resection/de-bulking with additional imaging using agent X and camera device
  - *Sponsor should ensure* SOC will be maintained and protect subjects from false imaging results/unwarranted surgical procedures
  
- Safety Monitoring: adverse events, vital signs, EKG, clinical labs at multiple time points; pregnancy testing at baseline.

# Take Away Points

- Investigational imaging agents offer no therapeutic advantage: high safety threshold should be supported by non-clinical studies to support clinical studies.
- Early studies should ensure SOC treatment.
- Appropriate monitoring and laboratory assessments should begin in phase 1 to allow for adjustments in phase 2.
- Collect sufficient information to refine at next step in development.



# Resources: www.fda.gov



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## Drugs

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Guidance, Compliance & Regulatory Information
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## Guidance, Compliance, & Regulatory Information

### Popular Items

- [Biologics Price Competition and Innovation Act of 2009](#)
- [Division of Drug Marketing, Advertising, and Communications \(DDMAC\)](#)
- [Drug Compliance Programs](#)
- [Guidances \(Drugs\)](#)
- [Newly Added Guidance Documents](#)
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### Contact Us

#### Human Drug Information

[\(888\) 463-6332](#)

[\(301\) 796-3400](#)

[druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov)

Division of Drug Information (CDER)

Office of Communications

Feedback Form

10001 New Hampshire Avenue

Hillandale Building, 4th Floor

Silver Spring, MD 20993

### Resources for You

- [Manual of Policies & Procedures \(CDER\)](#)
- [For Industry](#)
- [Small Business Assistance](#)



**Thank you!**



# Selection of Efficacy Endpoints for Optical Imaging Agents

May 4<sup>th</sup>

Betsy Ballard, MD, FACS

Division of Medical Imaging Products



# Overview

- Regulatory considerations for efficacy studies applicable to medical imaging drugs in general
- Efficacy endpoints for optical imaging drugs

# Device Considerations: Determination of Significant Risk

- Under 21 CFR 812.3(m) a significant risk device means that:
  - Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
  - Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
  - Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
  - Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

# 21CFR314.126

## New Drug Applications

- Adequate and well-controlled studies
  - Clear statement of objectives
  - Study design permits a valid comparison with a control to provide a quantitative assessment
  - Patients assigned in a way that minimizes bias
  - Well-defined methods of assessing response
  - Analysis should be adequate to assess the effect of the drug

# Truth Standards (Gold Standards)

- Demonstrate results are valid and reliable.
  - Test results obtained with the agent is evaluated without knowledge of the truth standard and knowledge of outcome
  - The true state of the subjects is determined with a truth standard without knowledge of the results obtained with the agent under review

# Indications for the Workshop Discussion

- Visualization/structure delineation
- Characterization
- Detection of disease, staging
- Response to therapy

# Lymphatic Mapping vs. Sentinel Node Biopsy

- Lymphatic mapping is a structure delineation claim. The product is used to locate nodes draining a primary tumor. Endpoint: number of histology confirmed lymph nodes detected by tracer
- Sentinel node biopsy is a diagnostic claim with therapeutic management implications (staging) Endpoint: patient-level false negative rates confirmed by pathologic assessment of regional lymph node

## Lesion Detection (e.g. tumor)

- Heterogeneity of disease
- Multifactorial etiology
- Heterogeneity of population affected
- Verification of detected abnormality with histology and/or clinical follow up
- Assessment of true negative rates
- Minimization of bias

## Lesion Detection

- Real-time during surgery versus pre-operative imaging and identification
- True positive and true negatives of the product-directed biopsy as confirmed by histology
- Truth standard: pathology (blinded to results of imaging, clinical follow up)

# Tumor Margin Detection

Single product approved through PMA process for ex-vivo margin detection in patients undergoing resection of primary breast cancer.

# Tumor Margin Detection

- Bias
  - Use of the product provides an additional opportunity that standard-of-care does not
  - Surgeon is not typically blinded to patient assignment
  - Non-randomness

# Tumor Margin Detection

- Panel Recommendations June 2012
  - Evaluate re-excision rate
  - Evaluate cosmesis postoperatively (6 and 12 months)
  - Prespecify diagnostic performance ( e.g. sensitivity and specificity)
  - Define meaningful improvement

# Optical Imaging Products

## Need for clinical outcomes

- Detection of gastrointestinal lesions
- Assessment of quality of revascularization in tissue reconstruction
- Planning for surgical resection; identification of viable tissue
- Visualization of anatomic structures at risk of inadvertent resection
- Debulking widely infiltrative tumors in critical organs
- Definition of tumor resection margins, decrease in reoperation
- Sentinel node detection

# Pertinent Guidances

- Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf>
- Developing Medical Imaging Drug and Biological Products: Conducting Safety Assessments  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071600.pdf>
- Developing Medical Imaging Drug and Biological Products: Clinical Indications  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071603.pdf>
- Developing Medical Imaging Drug and Biological Products: Design, Analysis and Interpretation of Clinical Studies  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071604.pdf>

# Pertinent Guidances

- Factors to Consider when Making Benefit-Risk Determinations  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf>
- Design Consideration for Pivotal Clinical Investigations for Medical Devices  
<http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm373750.htm>



# **Early Feasibility Study (EFS) IDEs**

## ***A Valuable Regulatory Tool for Medical Device Development***

**Carla M. Wiese**

Policy Analyst for the Early Feasibility Program  
Office of Device Evaluation  
Center for Devices and Radiological Health

Rockville, MD  
May 2016

# CDRH Led Submission

- Submission may be given the informal designation of “Early Feasibility Study” or “First in Human”
  - Similar to Phase 1 designation for drug development
  - Intent of this designation is to acknowledge the unique purpose of this early stage clinical study
- CDER will provide consultation for the drug component

# What is an EFS IDE?

## IDE - Investigational Device Exemption

- Clinical study of an investigational device

## EFS IDE - A standard IDE except...

- There are significant unknowns about how the device will perform
  - Device is generally early in development or
  - Device has a new intended use
- Small number of subjects in the clinical investigation
  - Initial indication of safety and/or effectiveness
  - Proof of concept

# Why the Focus?

- Clinical studies of novel technology are frequently conducted outside the US
- Devices may be approved outside the US only
- Device innovation may improve outside the US first

## Goal of EFS Program

FDA is dedicated to enhancing patient access to beneficial technology and supporting innovation in the US

# EFS Program Benefits

- Encourages **development of high quality products**
  - Allows for device and procedure changes early in the product development process
  
- Results in **high quality clinical data** that can...
  - demonstrate proof of concept which may be valuable to investors
  - allow for faster US market approval by building on EFS knowledge
  - be obtained for a device that has been used in compassionate use or emergency use cases and could support expanded device indications or a market application
  - And more!!

# Types of IDEs

EFS	Feasibility	Pivotal
<p>Small number of patients, &lt; 15 (approximate)</p>	<p>More patients than EFS</p>	<p>Number of patients determined by statistical needs</p>
<ul style="list-style-type: none"> <li>➤ <i>There are fundamental questions about device performance &amp; safety</i></li> <li>➤ <i>Device design may change.</i></li> <li>➤ <i>There may be limited nonclinical data available</i></li> </ul>	<p>Enough is known about the design, procedure or indication to justify clinical studies with more patients than EFS</p>	<p>Device is the final design and there is significant information known about the design, procedure and indication.</p>
<p>Purpose of study can be...</p> <ul style="list-style-type: none"> <li>➤ <i>to demonstrate a proof of concept</i></li> <li>➤ <i>get a very early look at safety/efficacy</i></li> <li>➤ <i>examine human factors</i></li> <li>➤ <i>determine what design or procedure changes could optimize the therapy</i></li> <li>➤ <i>Determine patient characteristics that may impact device performance</i></li> </ul>	<p>Purpose of study can be...</p> <ul style="list-style-type: none"> <li>➤ capture preliminary safety and effectiveness information and to adequately plan an appropriate pivotal study</li> </ul>	<p>Purpose of study can be...</p> <ul style="list-style-type: none"> <li>➤ Demonstrate safety and effectiveness to support a marketing application</li> </ul>

\*note: not all of these are required for market approval

# Key Elements of the EFS Guidance

- **Doing the “Right Testing at the Right Time”**
  - Comprehensive testing during early phases of device development may add cost without significant return (some testing may be deferred)
  - However, informative nonclinical testing should be completed
- **Unknowns and risk can be addressed by...**
  - Using clinical mitigations to provide patients with extra protection
  - The use of more frequent/detailed reporting
  - Informed consent recommendations

# Key Elements of the EFS Guidance continued...

- **Allows for timely device and clinical protocol changes**
  - More changes can be made through 5-day notification rather than FDA approval
  - Contingent approval: approval of anticipate or proposed device changes can be obtained contingent on the completion of an agreed upon test plan and acceptance criteria
- **Recommendations on pre-submission contents is provided**
  - High quality submissions are important

# Qualities of a Successful Submission

(for infrequent submitters in particular)

- 1. Sponsor uses available resources:** Use FDA guidance documents & CDRH Learn Modules, communicates with FDA staff, seeks assistance with regulatory, nonclinical testing and clinical trial issues if needed
- 2. Submissions are high quality**
  - Contents are well organized and navigable
  - High quality scientific discussion and evidence is provided
  - The sponsor is able to link together the information provided and tell the story of why an EFS is the right next step. (Why additional nonclinical testing will not be informative and a human clinical study is appropriate)

# Qualities of a Successful Submission Continued...

## 3. Submissions are well planned

- Sponsor reaches out to EFS rep or FDA team to discuss plan (informally)
  - Informational meeting may be useful (for novel ideas in particular)
- Initial pre-sub includes...
  - Design concept, clinical context & rationale for early feasibility study
  - Description of the risks and how they will be addressed
  - Investigational plan information – high level look (who will be treated, what type of information you want to collect...)
- Additional pre-submissions as needed (ex: if test requirements are uncertain/discuss clinical protocol)
- IDE submission contains all required information

## Note:

- Use of pre-submissions to discuss the test plan and the clinical protocol...
  - Can be useful when the nonclinical testing needed is unclear, can agree upon the test plan that will support an IDE submission with FDA
  - May avoid the need to re-do expensive and time consuming testing
  - May help determine appropriate clinical mitigations, reporting requirements and the patient population for whom the benefit-risk profile supports inclusion into the EFS

***Planning in Advance  
is Key***

# Qualities of a Successful Submission

Continued...

## 4. The decision to start human clinical work is well supported and explained

- There is a clear identification of potential risks & how they will be addressed
  - ✓ **Nonclinical testing:** Informative testing should be completed
  - ✓ **Clinical mitigations strategies** and appropriate reporting are proposed to protect patients - especially when nonclinical testing is uninformative
  - ✓ **Rationale is provided for why the plan is sufficient:** Explain what can/can not be learned from bench tests/animal models & why any information to be leveraged is directly applicable to the study
- List which tests will be done to support the EFS versus which will be done to support a later study if applicable



# We Would Like to Hear from You About your EFS Experience (good or bad)

- Test requirements do not seem appropriate for the EFS?
  - Review team doing a great job?
  - File progression is good/bad?

***Contact me:***

**Carla Wiese**

Policy Analyst for the Early Feasibility Program

301-796-0627

[Carla.wiese@fda.hhs.gov](mailto:Carla.wiese@fda.hhs.gov)

# Helpful Links

- **Early Feasibility Study Guidance**  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279103.pdf2>
- **EFS CDRH Learn Modules**  
[http://www.accessdata.fda.gov/cdrh\\_docs/presentations/EFS/story.html](http://www.accessdata.fda.gov/cdrh_docs/presentations/EFS/story.html)
- **Pre-Submission Guidance**  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>
- **IDE Submission Suggestions**  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046706.htm#regele>
- **Design Controls Guidance**  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070627.htm>
- **Electronic Submissions Guidance**  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf>



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# Selection of Efficacy Endpoints for Optical Imaging Agents

Louis Marzella, MD , PhD

Director

Division of Medical imaging Products

CDER/FDA

# Overview

- Regulatory considerations for efficacy studies applicable to medical imaging drugs in general
  - Strategic plan
  - Clinical trial development
  - Interactions with FDA
- Efficacy endpoints for optical imaging drugs

# Strategic Planning Objectives

- maximize efficiency of studies and value of data
  - minimize bias
- enhance communications with regulators
- expedite drug development process

# Clinical Development Plan

Overall strategy for clinical studies needed at the very early stages of drug development

- Begin with proposed indication for use
- Define indicated patient population, assessment of outcomes that demonstrate clinical utility
- Identify study population
  - Phase 1, 2 minimize heterogeneity, reduce variability
  - Phase 3 expand patient population , generalize

# Clinical Development Plan

## Clinical trial design and analysis considerations

- Selection of endpoints
  - efficacy e.g. precision and accuracy, diagnostic performance relative to reference standard
  - pharmacodynamic and biomarker of activity
- Pre-specified hypotheses, sample size, analysis plan

# Selection of Efficacy Endpoints

## Criteria to be considered

- Benefit: implied, shown through clinical outcomes
- Assay sensitivity
- Statistical efficiency
  - Variability of outcome, duration of assessment
- Trial phase

# Efficacy Trial Endpoints

- Exploratory
  - development of hypotheses, pharmacodynamic measurements
- Primary
  - demonstration of efficacy
- Secondary
  - supportive of efficacy, provide information in subgroups for safety and efficacy

# Considerations for Imaging in Phase 3 Clinical Trials

- Efficacy assessment
  - Anatomic or functional outcomes in trials of therapeutic drugs
    - ↓Radiologic joint space narrowing and erosions with DMARDS for RA
    - ↓Radiologically diagnosed fractures with therapeutics for osteoporosis
  - Performance (e.g. sensitivity, specificity) in trials of diagnostic drugs

# Considerations for Drug Approval: Imaging vs. Therapeutic drugs

## Similar regulatory process

- Evidence standards for safety and efficacy
- Risk-benefit considerations
- Marketing application
- Review procedures

## Unique efficacy consideration for imaging drugs

Ability to provide clinically useful information (no clinical outcome measures necessary)

# Efficacy of Optical Imaging Drugs: Unique Considerations?

Clinical value: Self-evident e.g.

- Increased conspicuity of poorly visualized structure in procedures associated with surgical complications. E.g. dye for visualization of ureters in laparoscopic procedures.
  - Historical control vs. parallel arm control
  - Primary Endpoint: objective measure of meaningful improvement in visualization
  - Secondary Endpoint: exclude an increase (define margin) in complication relative to historical experience or relative to parallel control

# Efficacy of Optical Imaging Drugs: Unique Considerations?

Clinical value: Self-evident e.g.

- Debulking widely infiltrative tumors
  - Intra-patient control vs. parallel arm control
  - Primary endpoints: superiority in tumor resection (tumor mass weight, residual tumor on imaging)
  - Secondary endpoints: non-inferiority (defined margin) for loss of organ function/disability, survival, superiority in patient reported outcomes



# NCI Optical Imaging Workshop

## Regulatory Pathway Considerations for Optical Imaging Drugs and Devices Used Together

Patricia Y. Love, MD, MBA  
Office of Combination Products,  
Deputy Director  
May 4, 2016

## Discussion Topics

- Pathway to market: blending the drug and device development
- Are optical imaging drug and devices combination products or not?
- What are the developmental implications?
- What practical considerations?

## Imaging Drugs in General

- Most general imaging drugs are not combination products
  - But there are some exceptions

## Optical Imaging Pathway to market

- Device alone?
- Drug alone?
- Device or Drug with limited reference labeling?
- Device - Drug with full reference to each other?

## Separately Provided Products: Labeling Jargon

- General labeling: Broad use; does not restrict to a particular drug or device
- One-way labeling:
  - Brand Drug A for use with Brand Device A
  - Brand Device A for use with drugs with certain characteristics
- Two-way labeling (cross-labeling; combination Product)
  - Brand Drug A for use with Brand Device A
  - Brand Device A for use with Brand Drug A

## Consistency Consideration for Safety & Effectiveness Labeling

- Indication for Use: differs from approved / cleared labeling
- Drug changes:
  - Dose, rate, route or method of administration; dosing regimen or frequency
  - Imaging method differences
- Device changes:
  - Modality or exposure differences,
  - Cleared for use with different drug
- Safety or other labeling revisions for new use

## What is a combination product?

- Combination product comprises 2 or more **differently** classified products\*
  - Drug + Device
  - Device + Biologic
  - Drug + Biologic
  - Drug + Device + Biologic

\*21 CFR Part 3

## Combination Product: Definition

- 21 CFR Part 3
  - Physically or chemically into a single entity; §3.2(e)(1)
  - Co-packaged (Kit); §3.2(e)(2)
  - Sold separately and **labeled for use together**; §3.2(e)(3) or (e)(4)

## 21 CFR Part 3.2(e) - continued

- (e)(3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended **for use only with an approved individually specified drug, device, or biological product** where both are required to achieve the intended use, indication, or effect and where **upon approval of the proposed product the labeling of the approved product would need to be changed**, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
- (e)(4) Any **investigational drug, device, or biological product** packaged separately that according to its proposed labeling is for **use only with another individually specified investigational drug, device, or biological product** where **both are required** to achieve the intended use, indication, or effect

## Assignment / Jurisdiction of CP

- Combination Product (CP)
  - CDER, CBER, or CDRH
  - Assigned based on the primary mode of action (**PMOA**)\* or algorithm\*\*

\*FD&C Act, Section 503(g);

\*\*21 CFR 3.2(m)

## Assignment / Jurisdiction of CP, Cont'd

- Mode of Action (MOA) – “the means by which a product achieves its **intended therapeutic effect or action, ...**” § 3.2(k)
  - Action is based on the drug, device, biologic definitions
- **PMOA** – “the **single mode** of action of a combination product that provides the **most important therapeutic action ...**
  - Most important therapeutic action is the mode of action expected to make the **greatest contribution to the overall intended therapeutic effects...;**” § 3.2(m)

## Useful Assignment Information

- Guidance documents and regulation\*
  - PMOA Rule, 21 CFR Part 3 revision – 2005
  - Chemical Action (draft) – 2011
  - Classification (draft) – 2011
  - How to Write an RFD - update 2011

\* <http://www.fda.gov/CombinationProducts/default.htm>

## What does it mean when CP is assigned?

- Lead center for industry contact
- Collaborative review with other center experts
- Product is still a combo once assigned, does not change classification to that of the type of products customarily in that center.
- Must comply with applicable regulations / requirements of **both constituent parts** without being contrary or confounding.

# Combination Product: General Regulatory Approach

- **Premarket**
  - Apply consistent standards to assess safety and effectiveness regardless of Center assignment
  - Use consistent and appropriate regulatory pathways
  - One investigational application (i.e., the one used by the lead center)
  - One marketing application for most combination products but might vary based on the marketing configuration
- **Postmarket**
  - Compliance with regulatory requirements for each constituent part while avoiding redundancy
  - Ensure consistent compliance and inspectional standards
  - Ensure consistent standards and pathways for postmarket<sup>14</sup> changes

## What is similar regardless of combination or non-combination status?

- Centers continue to work together to
  - Determine if the product is appropriately classified and in the appropriate center
  - Identify and assess the scientific and technical data
  - Consider the labeling that is appropriate to ensure safe and effective use of the product(s) for the proposed indication
  - Achieve consistency and transparency



## Contact Us – We're Here to Help!

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[www.fda.gov/CombinationProducts/default.htm](http://www.fda.gov/CombinationProducts/default.htm)

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