Clinical Trial Using NIRS for Breast Imaging

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M-CERSI International Workshop on
Tissue Phantoms and Standardization in Biophotonics
Wednesday, May 21st 2014

Financial Disclosures

Nothing to disclose

Acknowledgements

DOSI Imaging: Anais LeProux, Albert Cerussi, Keunsik No, Brian Hill, Amanda Durkin, Tom O'Sullivan, Darren Roblyer, Sam Keene,Rob Warren, Alex Matlock, Soroush Zarandi, Hosain Hagany, Shigeto Ueda, Jing Liu, Ylenia Santoro, Shanshan Xu, Enrico Gratton, Bill Mantulin, Montana Compton, Sophie Chung, Tim Quang, Jason Ruth, Kia Koko, Natasha Shah, Dorota Jakubowski Wisner, Wendy Tanamai, Shwayta Kukreti, Ang Li

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Outline

- NIRS UC Irvine style (DOSI)
- What is the optical contrast of tumors?
- Why we care: What is the Clinical Need?
- What is the ACRIN #6691 Trial?
- How do we use phantoms in ACRIN 6691?
- What does the data look like?
- What are some future directions?

Just what in the world is DOSI?

What is DOSI?

DOSI Instrument

DOSI Measurement

like a MRS instrument with the spatial resolution and functionality of PET in the shape of an ultrasound

Bevilacqua, F., A. J. Berger, et al. (2000). Appl Opt ***39(34): 6498-507.***

Pham, T. H., O. Coquoz, et al. (2000). Review of Scientific Instruments ***71(6): 2500-13.***

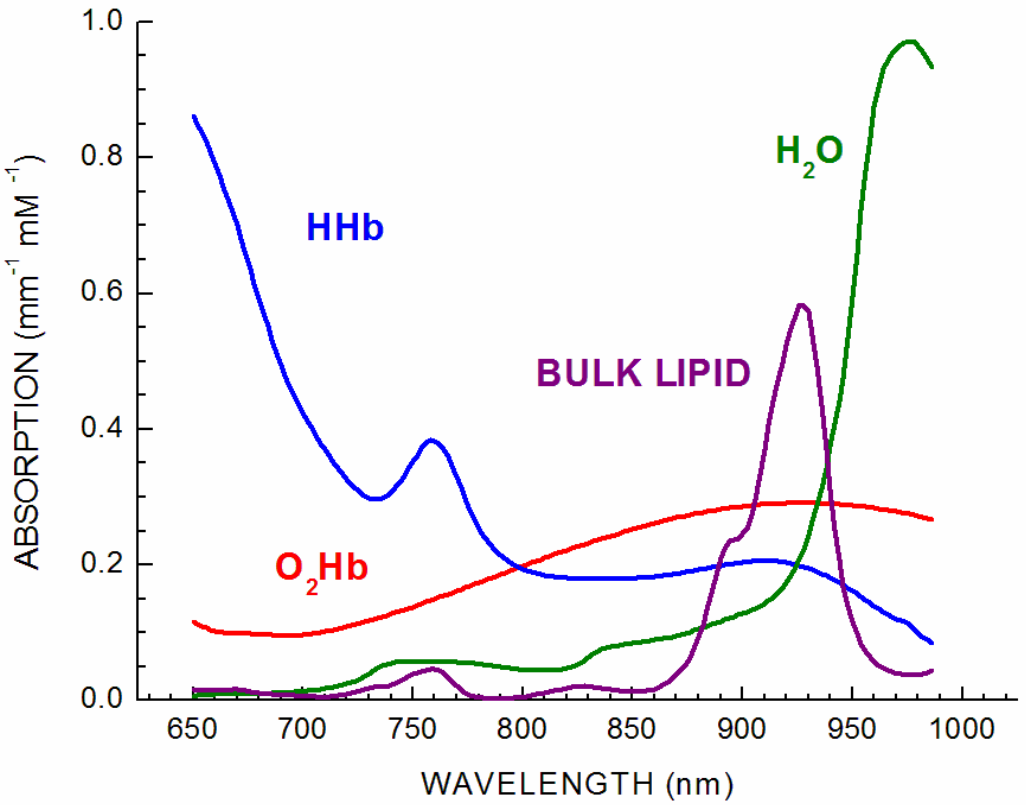
What is DOSI?

- **Diffuse**
- **Optical**
- Spectroscopic
- Imaging

Intense Multiple Scattering
“NIR” Window (650-1000 nm)

What is DOSI?

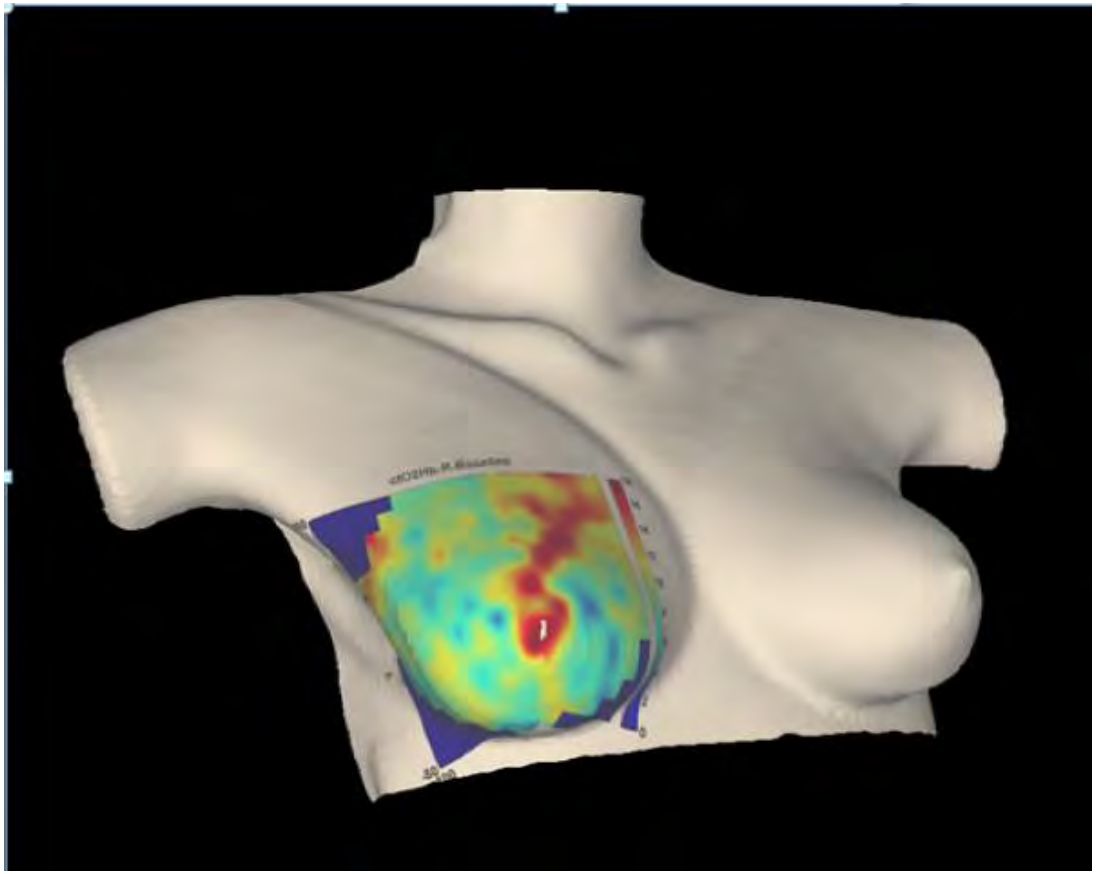
- Diffuse
- Optical
- **Spectroscopic**
- Imaging



Molecular targets
(concentration & disposition)

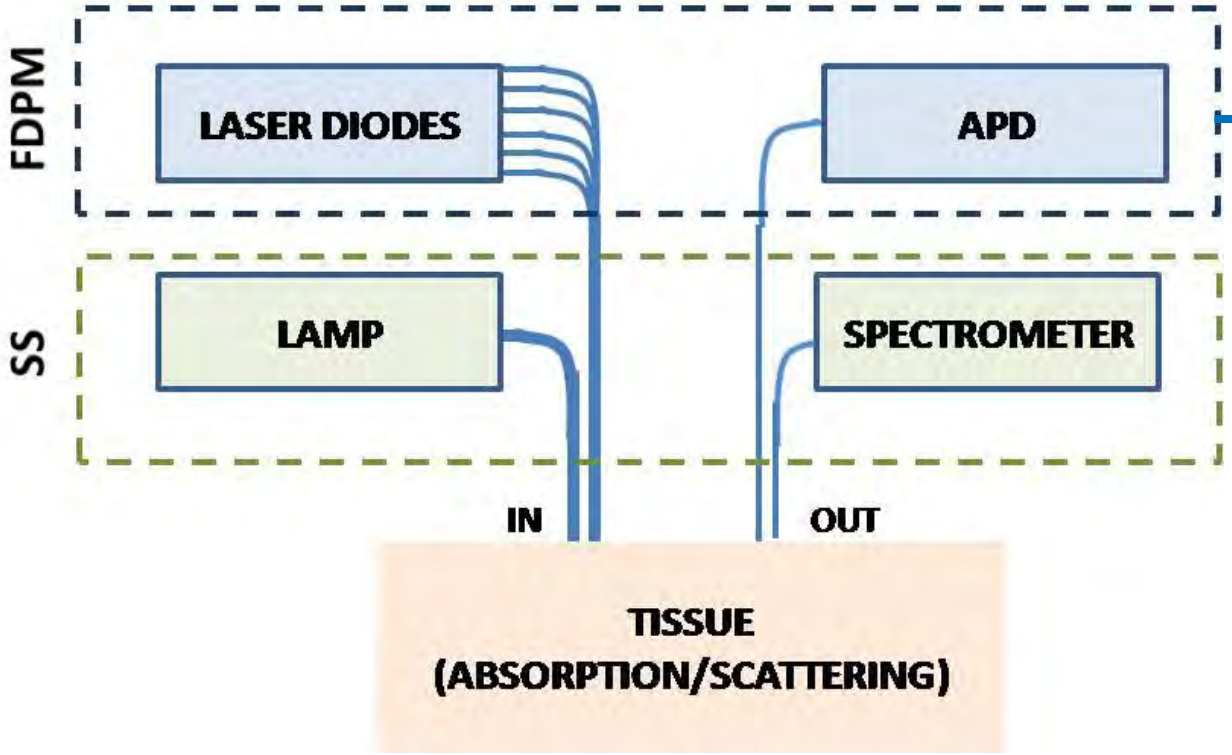
What is DOSI?

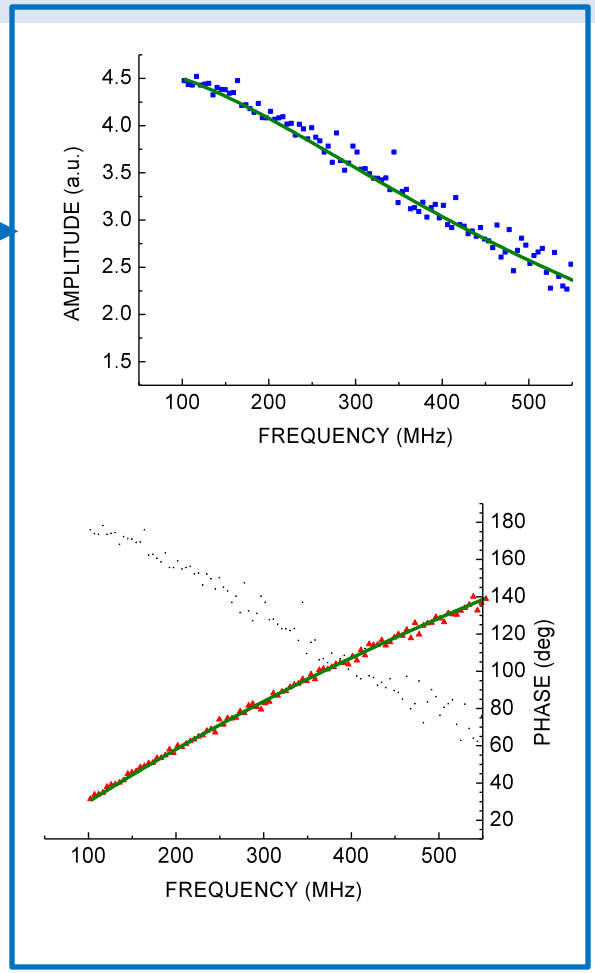
- Diffuse
- Optical
- Spectroscopic
- **Imaging**



How does DOSI work?

How does DOSI work?





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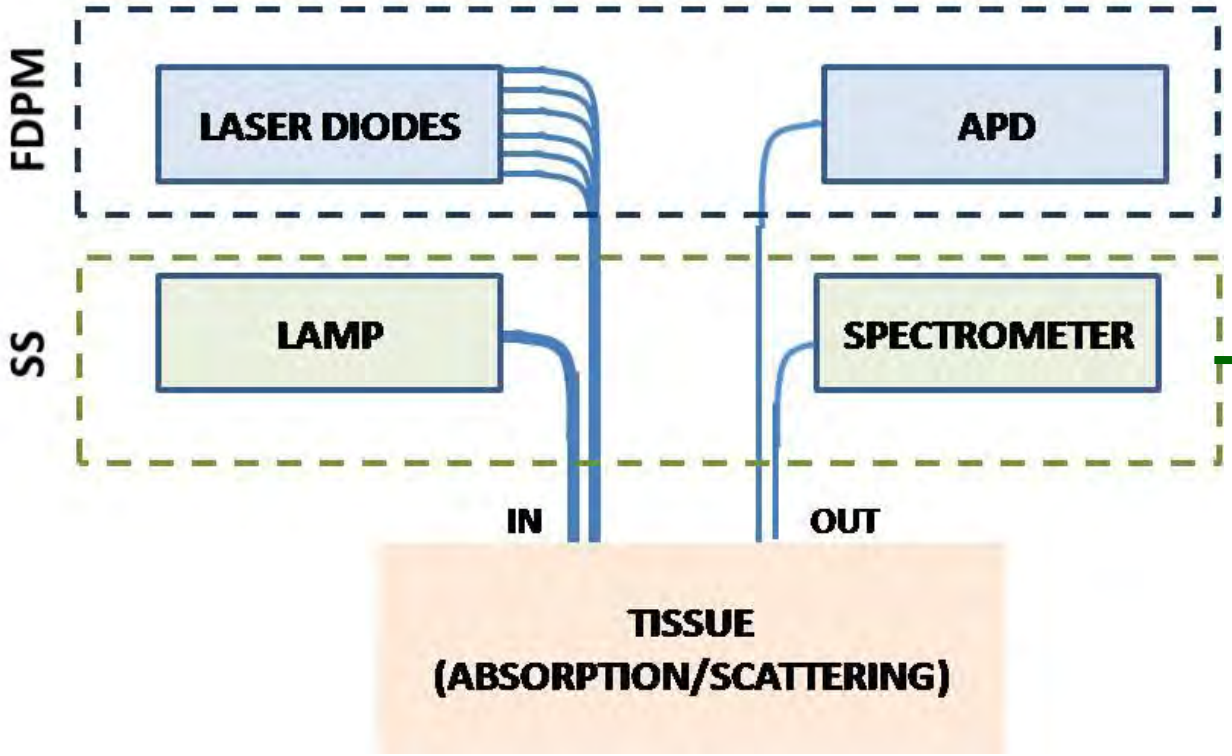

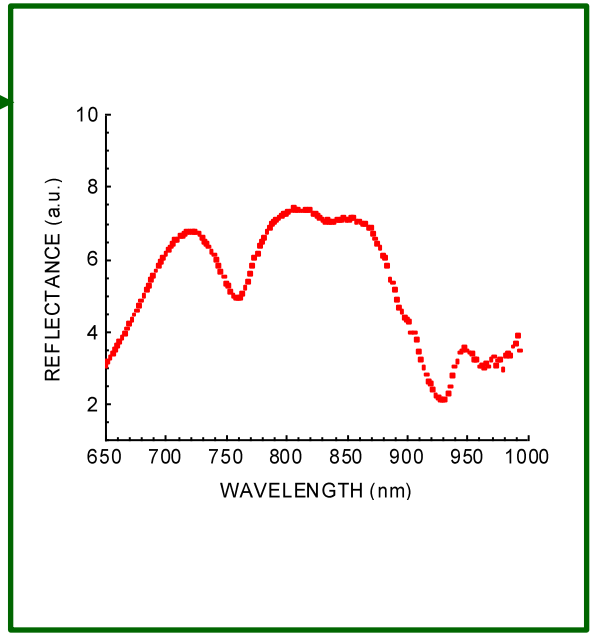

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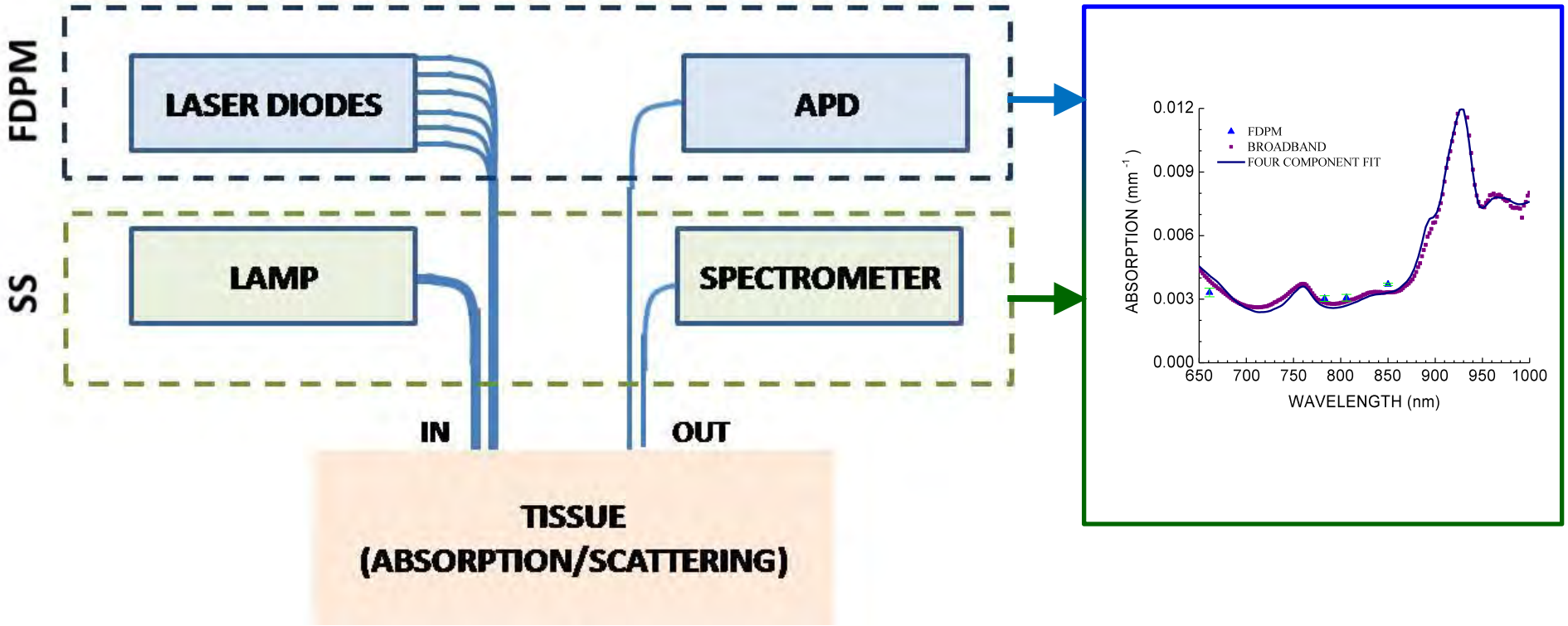
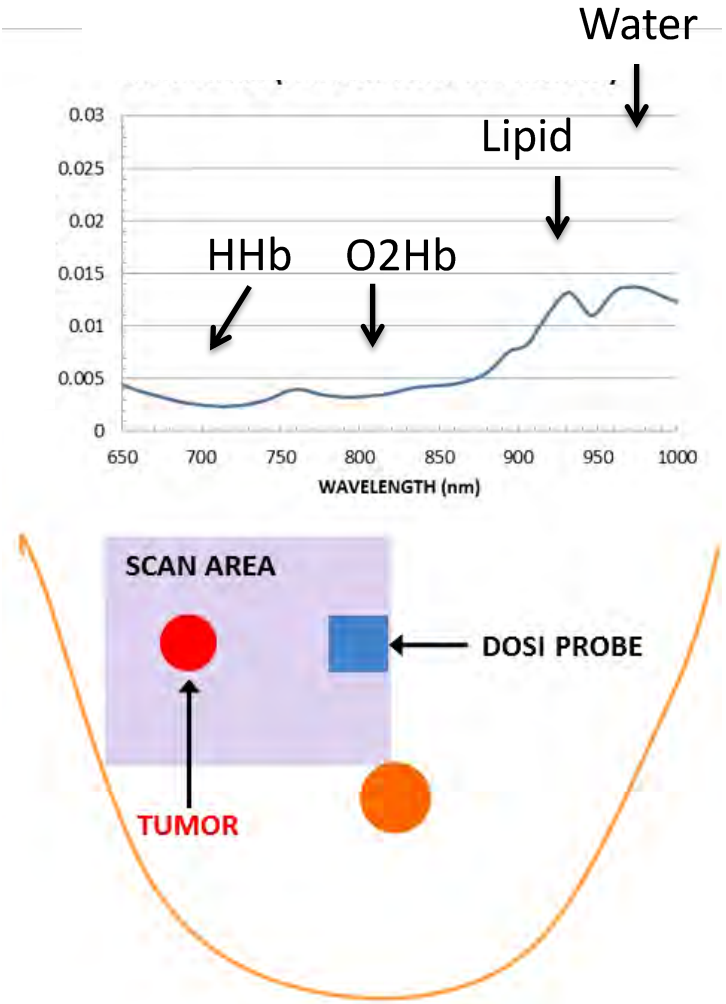


Bevilacqua, F., A. J. Berger, et al. (2000). Appl Opt ***39(34): 6498-507.***

How does DOSI work?

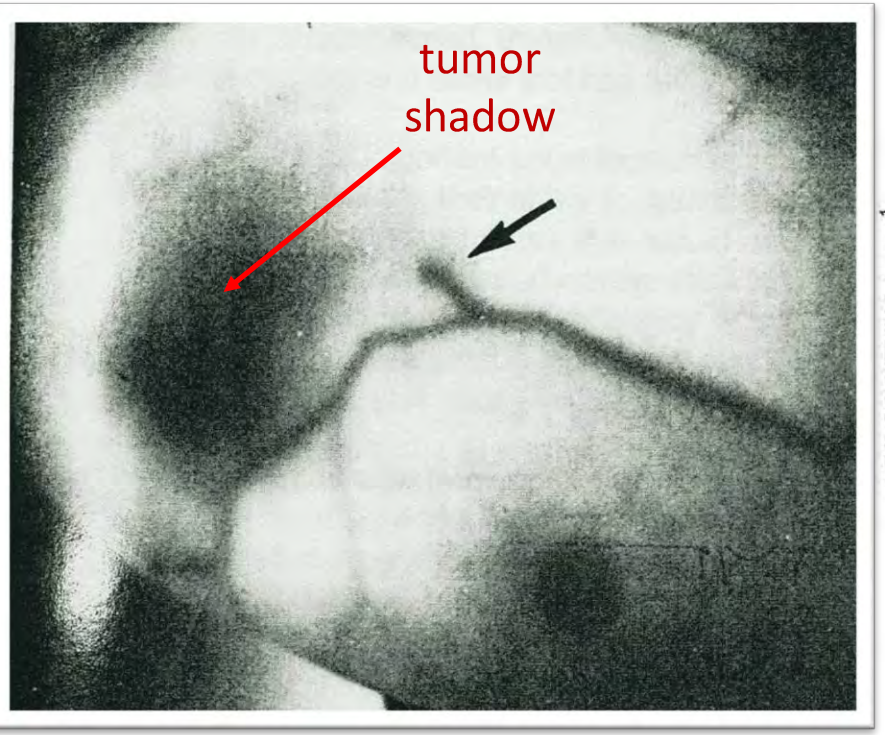
Making The Body a "Cuvette"



What is the optical contrast of tumors?

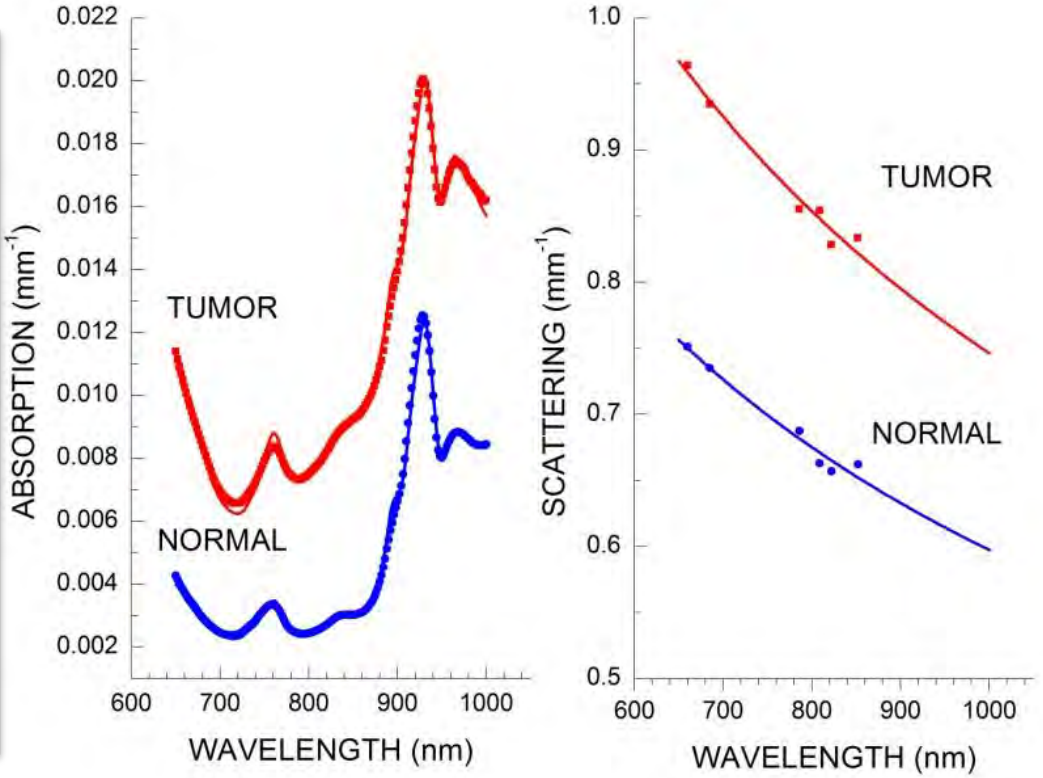
Tumors Generate Optical Contrast

Diaphanography



E. Sickels, AJR 142, 841-4 (1984)

DOSI



Cerussi, A., D. Hsiang, et al. (2007).
Proc Natl Acad Sci U S A ***104(10): 4014-9.***

Tumors Generate Optical Contrast

Cancer

Elevated blood

- Increased tumor vascularity, metabolism detected by elevated THb, O2Hb and HHb

Elevated water

- Tumor edema and tumor cell proliferation lead to increased water content

Decreased lipid

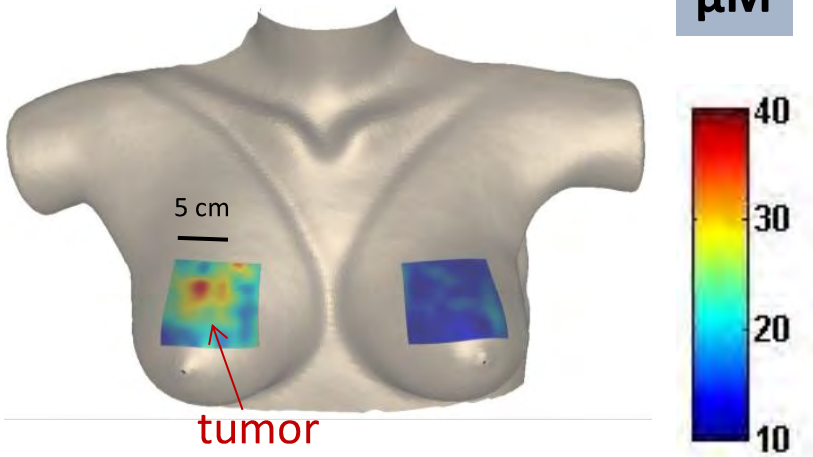
- Tumors displace bulk lipid when growing leading to decreased lipid content

Universal finding: THb increases

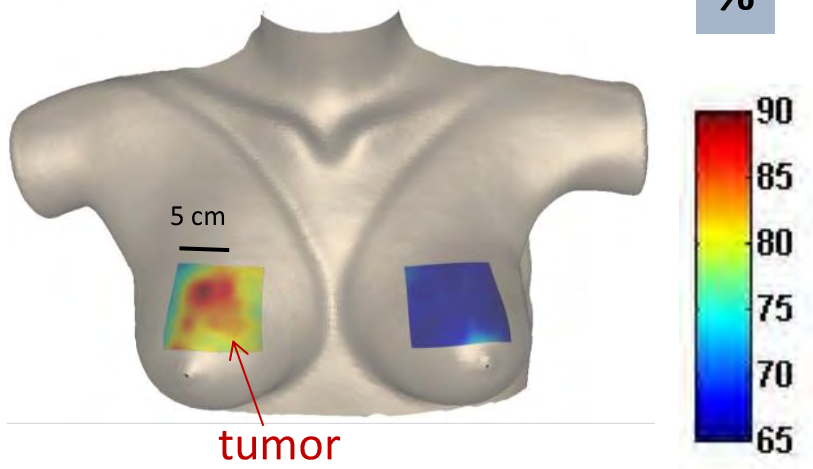
Tumors Create Optical Contrast

6691-09

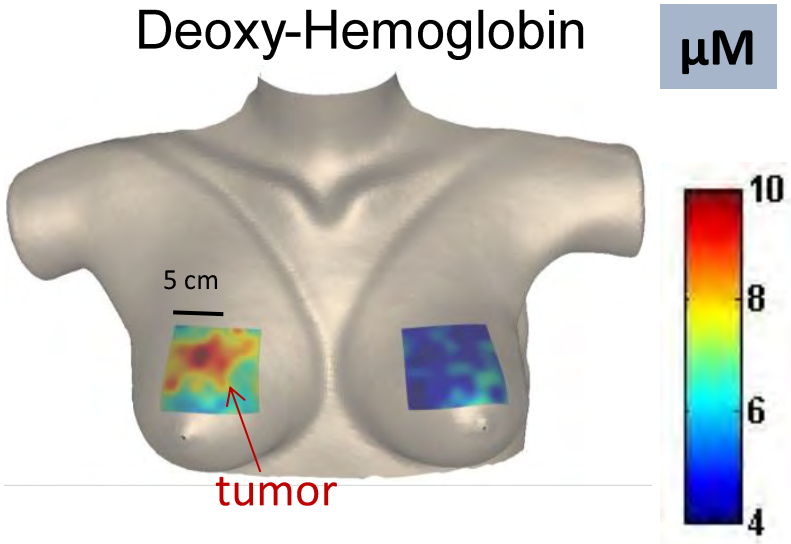
Oxy-Hemoglobin



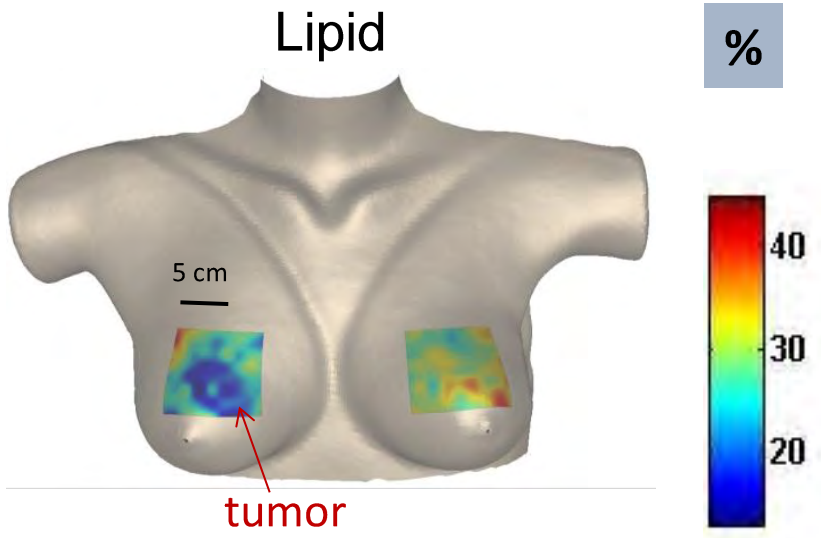
Water



Deoxy-Hemoglobin

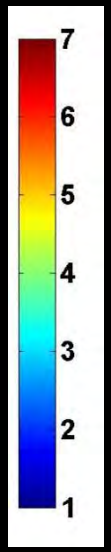


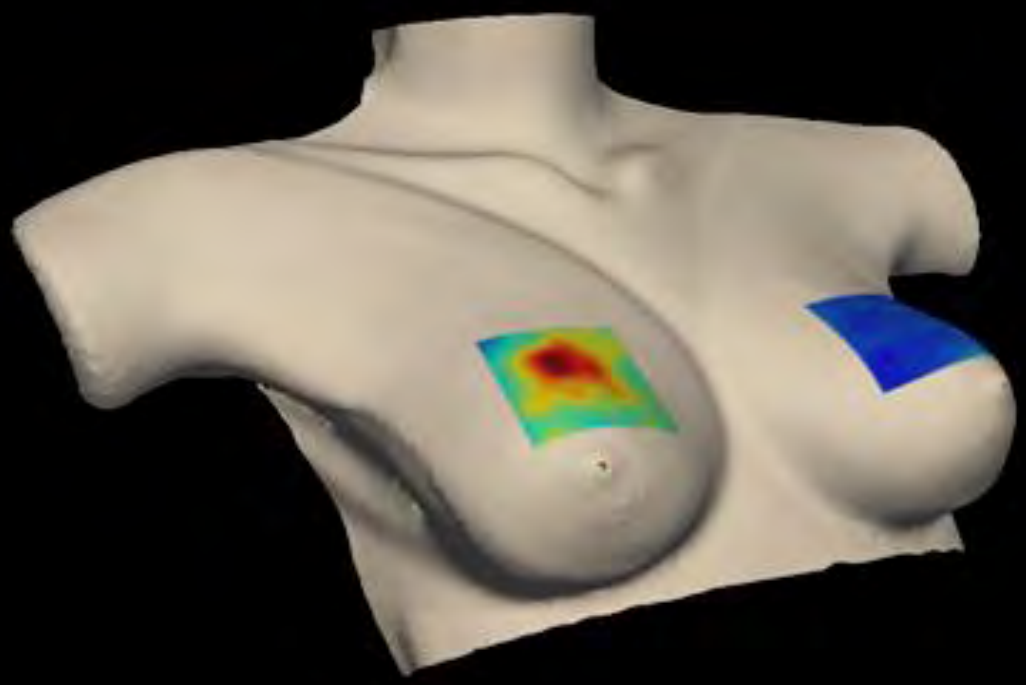
Lipid



Tumors Create Optical Contrast

Tissue Optical Index (TOI) = (HHb x H_2O)/lipid



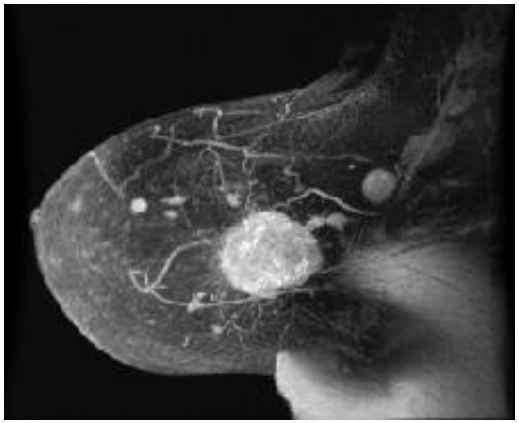


ACRIN 6691-09

Why does this matter?
What is the clinical need?

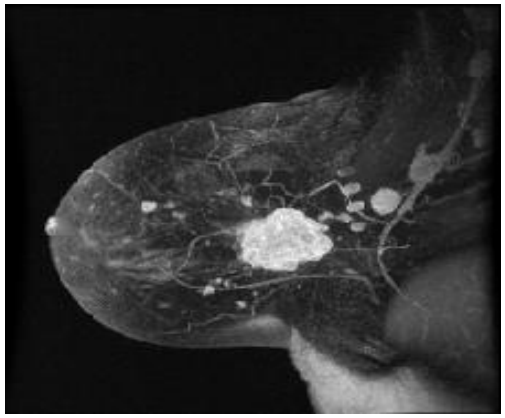
Pre-Surgical Neoadjuvant Chemotherapy

Treat Locally Advanced Disease



- Stage II-IV tumors
- ~20% of BrCa

~6 months Chemo →



DCE-MRI: *N. Hylton, UCSF*

- Shrink tumors: *improve surgical outcome*
- Begin Tx of possible nodes/metastasis
- **Complete path response (pCR): *increase 5 yr survival***

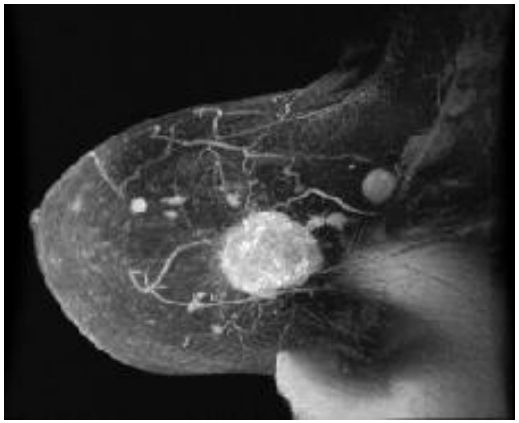
But…

~1/5 Don't Respond to Chemo

~1/3 achieve pCR

Pre-Surgical Neoadjuvant Chemotherapy

Treat Locally Advanced Disease



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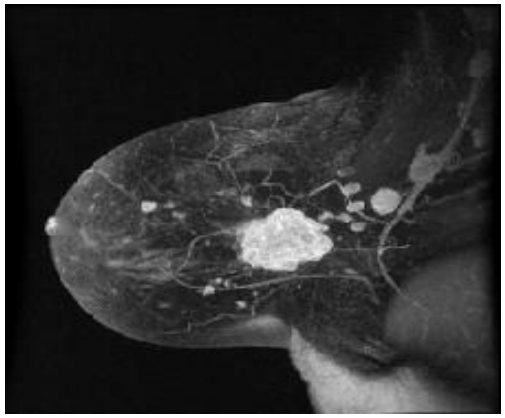


DCE-MRI: *N. Hylton, UCSF*

Clinical Need:

Predict path complete response (pCR) as early as possible

Impact:

Customize Treatment for Individuals

Cancer Imaging

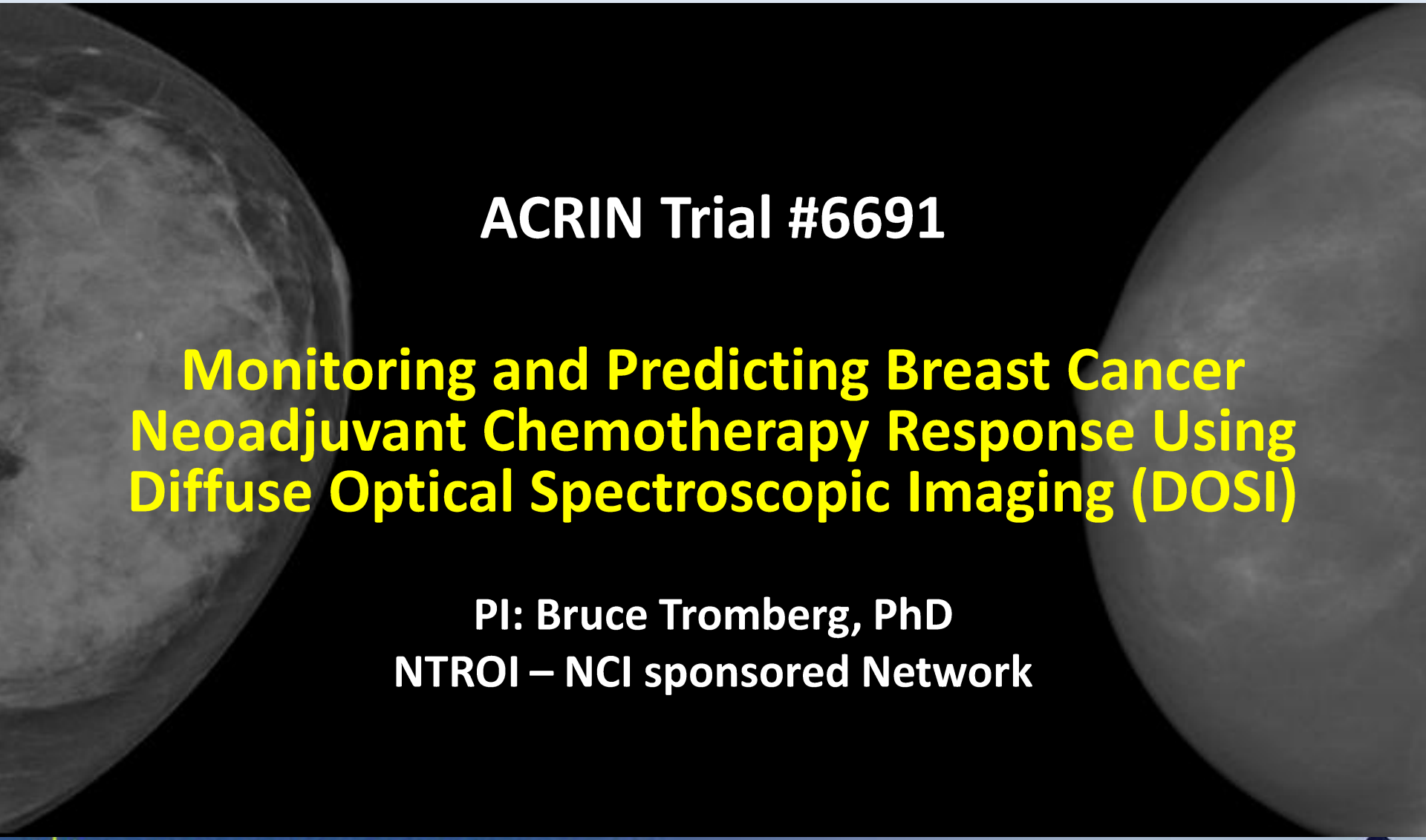
X-ray, MR, Nuclear, US…(Optical)

2004: D. B. Jakubowski, et al, 'Monitoring Neoadjuvant Chemotherapy in Breast Cancer Using Quantitative Diffuse Optical Spectroscopy: A Case Study', *Journal of Biomedical Optics,* 9 (2004), 230-38.

~10 yrs

~30 Publications: Penn, Dartmouth, MGH, UConn, Toronto, UC-London, UCI; (Saitama-Japan, Columbia-NYC, Berlin)

What is the ACRIN #6691 Trial?

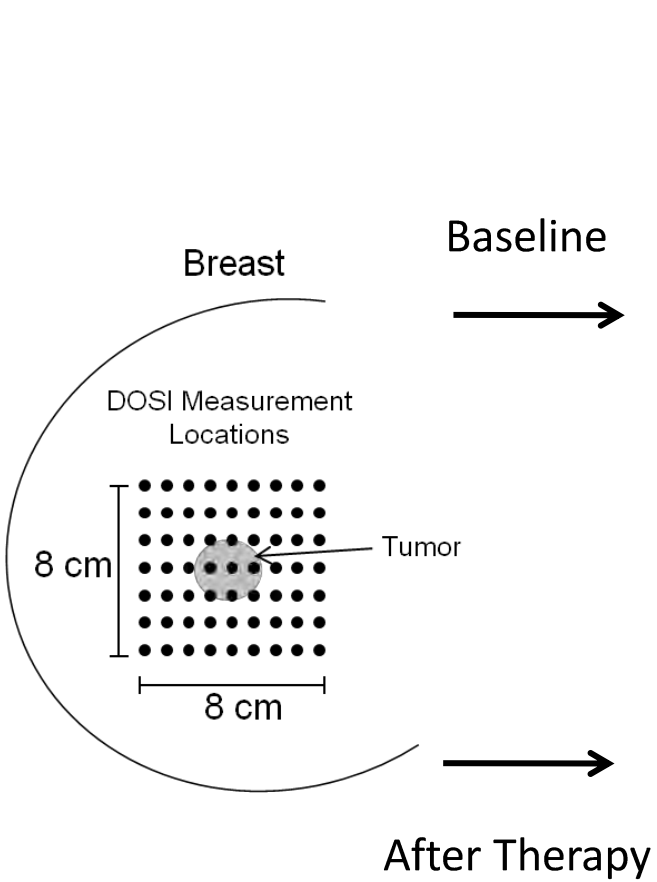


ACRIN Trial #6691

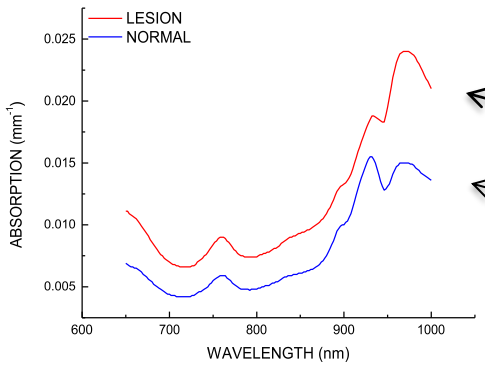
Monitoring and Predicting Breast Cancer Neoadjuvant Chemotherapy Response Using Diffuse Optical Spectroscopic Imaging (DOSI)

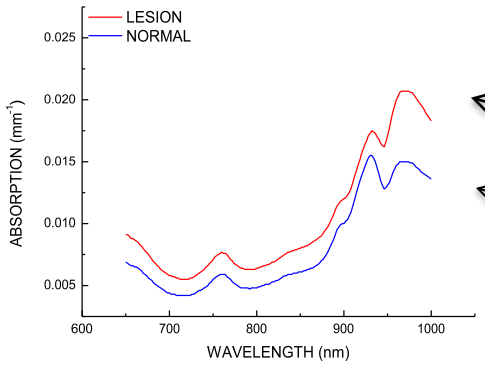
PI: Bruce Tromberg, PhD
NTROI – NCI sponsored Network

ACRIN #6691: Hypothesis



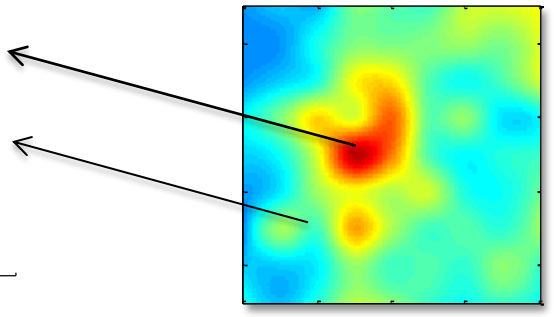
TISSUE SPECTRA





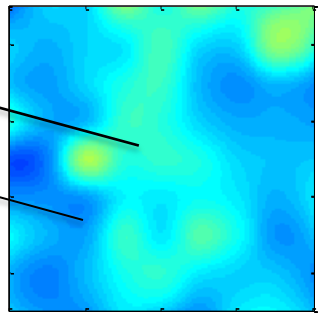
FUNCTIONAL IMAGES

Pre-treatment



Tissue Optical Index (TOI) = (HHb x H_2O)/lipid

3 weeks

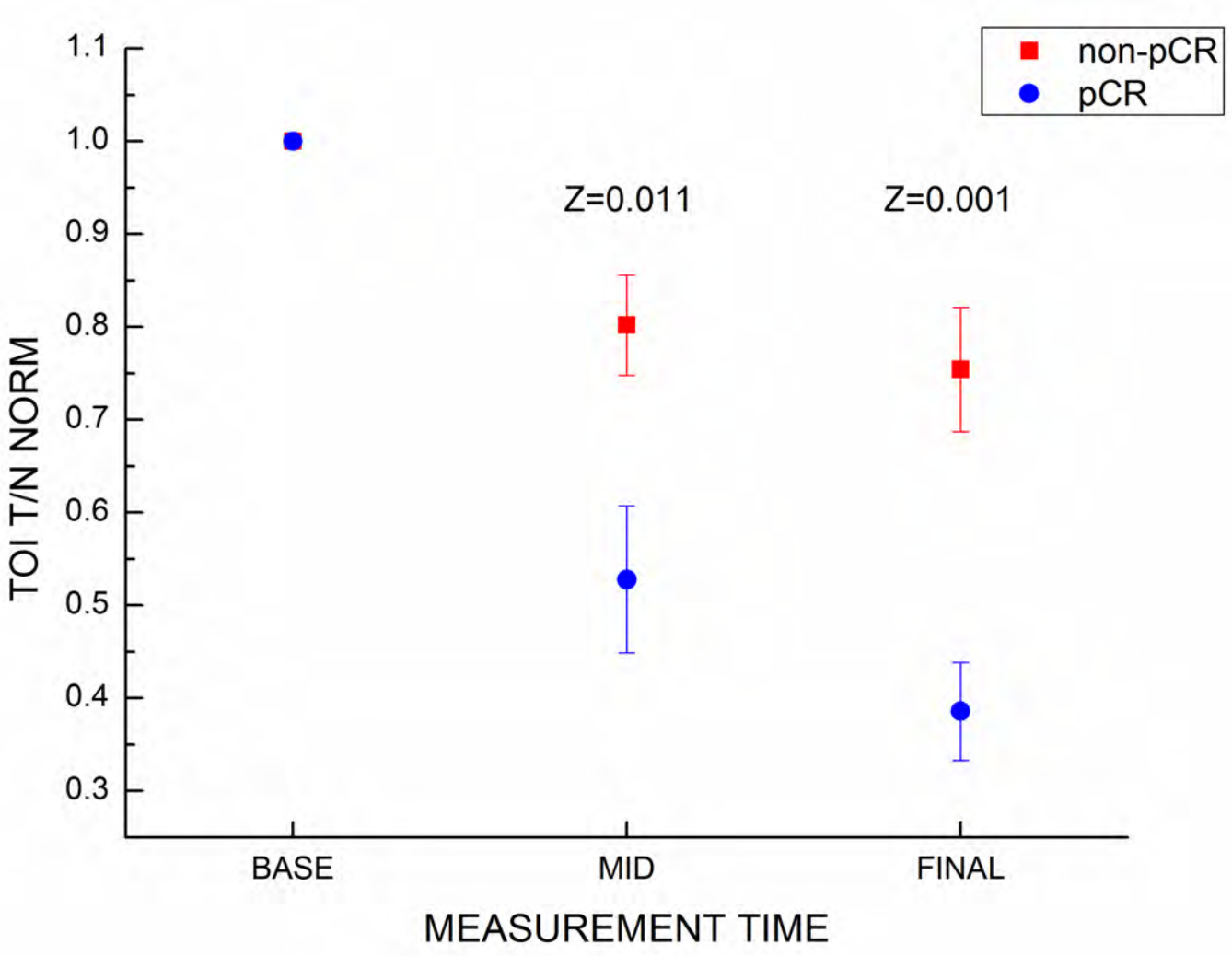


Seriously, they let you do this?

Supporting Data for ACRIN

ALL TREATMENTS (N=36)

$$\frac{\text{T/N @ Stage}}{\text{T/N @ BASE}}$$



Cerussi, A. E., D. Hsiang et al. Phil Trans Roy Soc A, 369(1995), 2011

ACRIN #6691: Study Aims

1st Standardized ACRIN Trial Using Optical Imaging
(New expertise to ACRIN; leverage MRI, PET experience)

1) Standardize DOSI measurements, analysis

- Determine inter-site "kappa"
- UCI, UCSF, Dartmouth, Penn, MGH (identical platforms)

2) Perform DOSI clinical measurements (open regimen)

- Multiple DOSI time points (*Base, 1 Week, Mid, Final*)
- Average ~6 subjects/site/yr = 30 x 2 yrs = 60 subjects
- **End point: Pathological response**

ACRIN 6691 NAC Trial

http://acrin.bli.uci.edu/ 6/11-6/13; 60 patients

ACRIN: David Mankoff, Zheng Zhang, Donna Hartfeill, Sharon Mallett

UCSF
Nola Hylton,
Dorota Wisner

U.C. Irvine
Albert Cerussi
Philip Carpenter
Rita Mehta,
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MGH
David Boas,
Stefan Carp
Steven Isakoff

Penn
Arjun Yodh
Mitch Schnall
Sophie Chung

DOSI Systems

LBS4 (UCSF)	LBS5 (UCI)	LBS7 (DART)	LBS8 (PENN)	LBS9 (MGH)
				


"HERE I COME
TO SAVE THE DAY."

ACRIN™
AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6691 NAC Trial

http://acrin.bli.uci.edu/ 6/11-6/13; 60 patients

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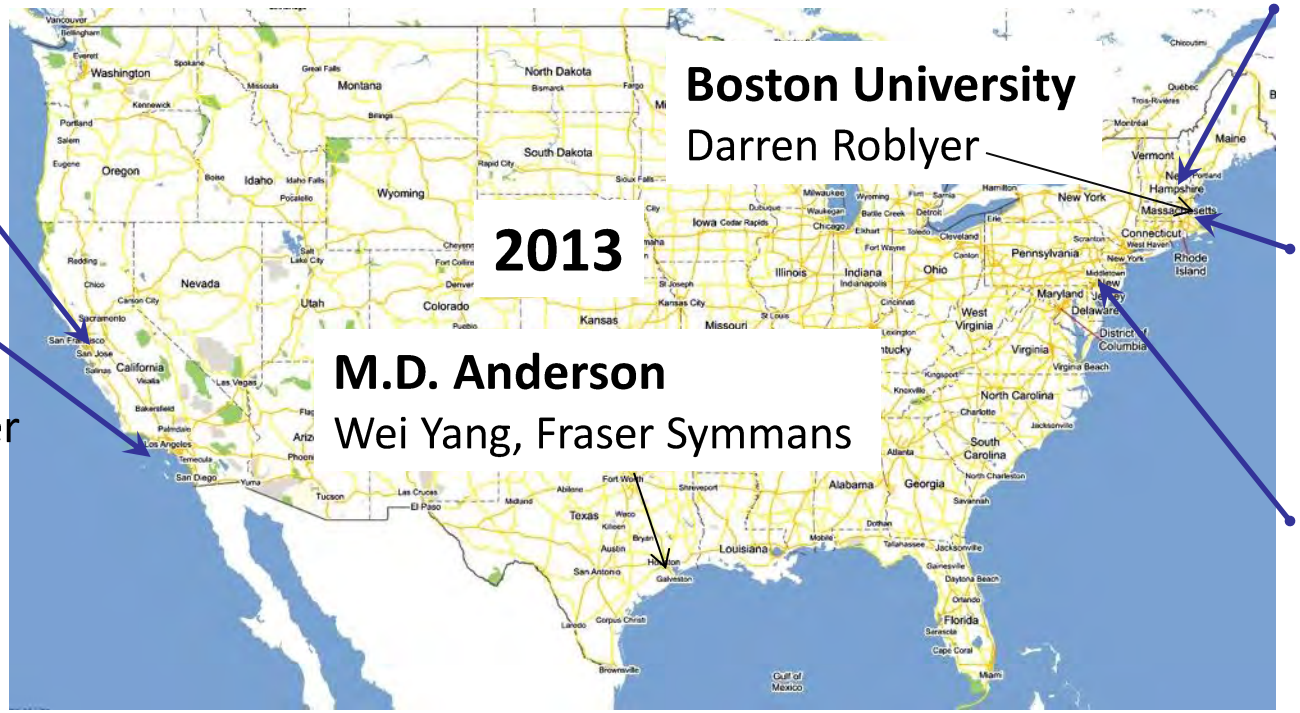


Dartmouth
Brian Pogue
Keith Paulsen
Shudong Jiang
Peter Kaufman

MGH
David Boas,
Stefan Carp
Steven Isakoff

Penn
Arjun Yodh
Mitch Schnall
Sophie Chung

DOSI Systems

LBS4 (UCSF) **LBS5 (UCI)** **LBS7 (DART)** **LBS8 (PENN)** **LBS9 (MGH)**



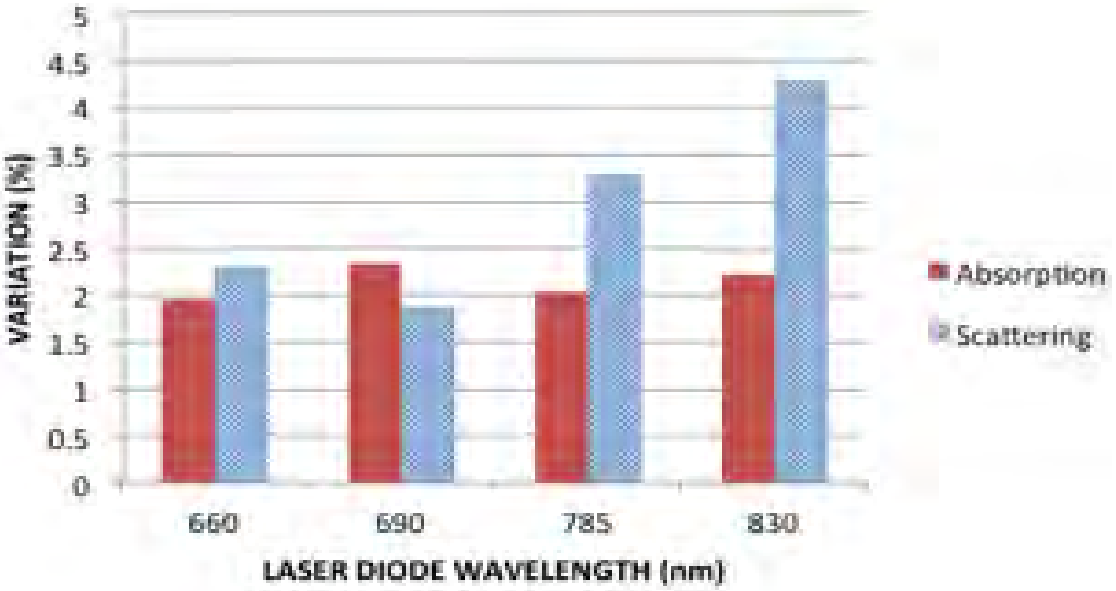

2013: in MDACC, BU, (Saitama Japan, Dankook)

2013: in Ivory Coast, Africa

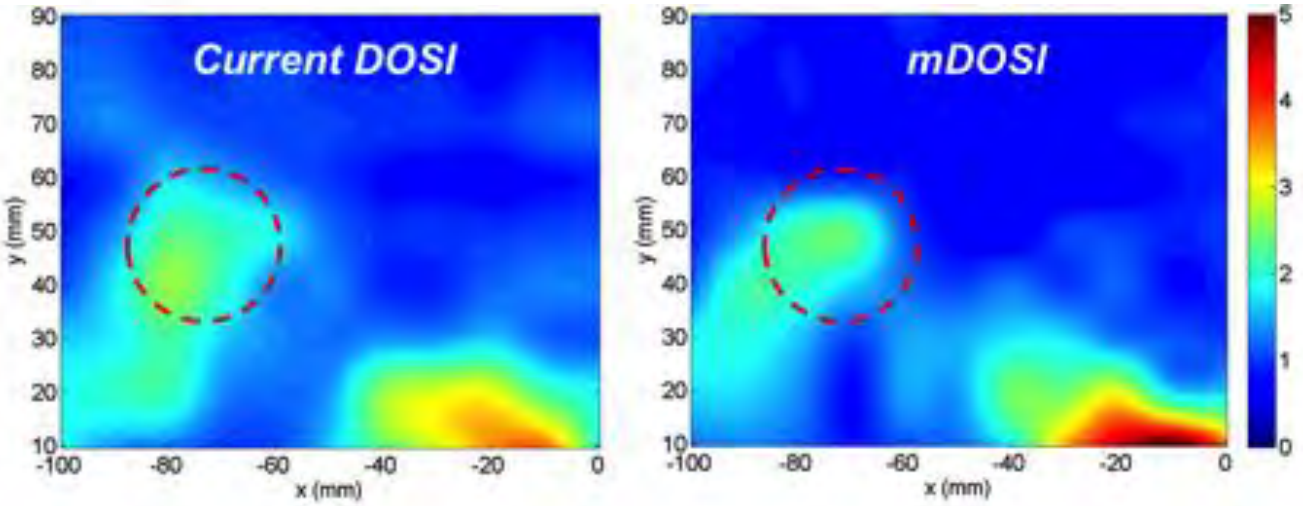
Seriously, they let you do this?

Comparison

FDPM OPTI CAL PROPERTIES



2D BREAST TUMOR MAPS



How we use phantoms in ACRIN 6691

How we use phantoms

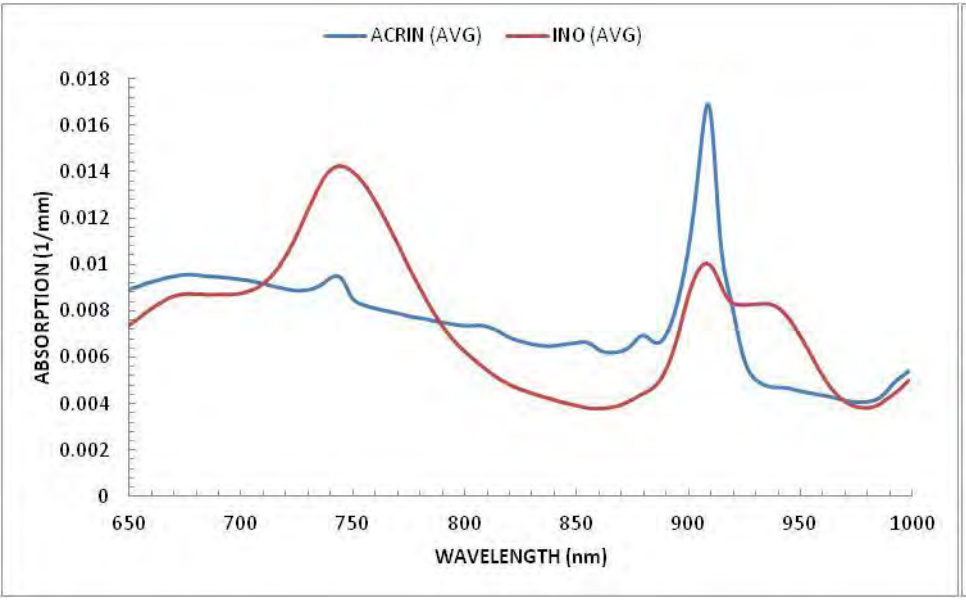
- System Calibration
- Instrument performance/validation
- training

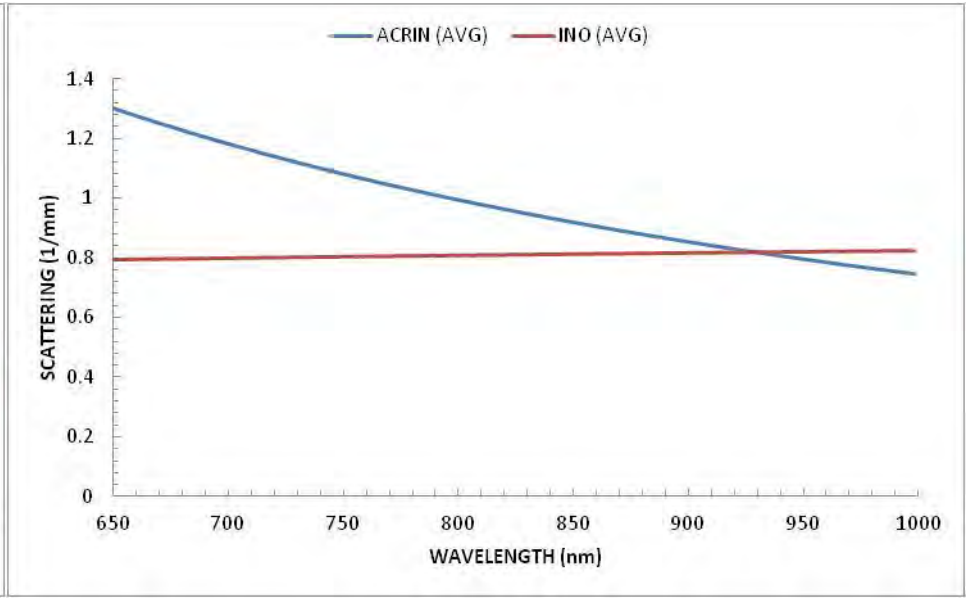
ACRIN 6691 Phantoms

- Phantom A
  - Calibration phantom (UC Irvine)

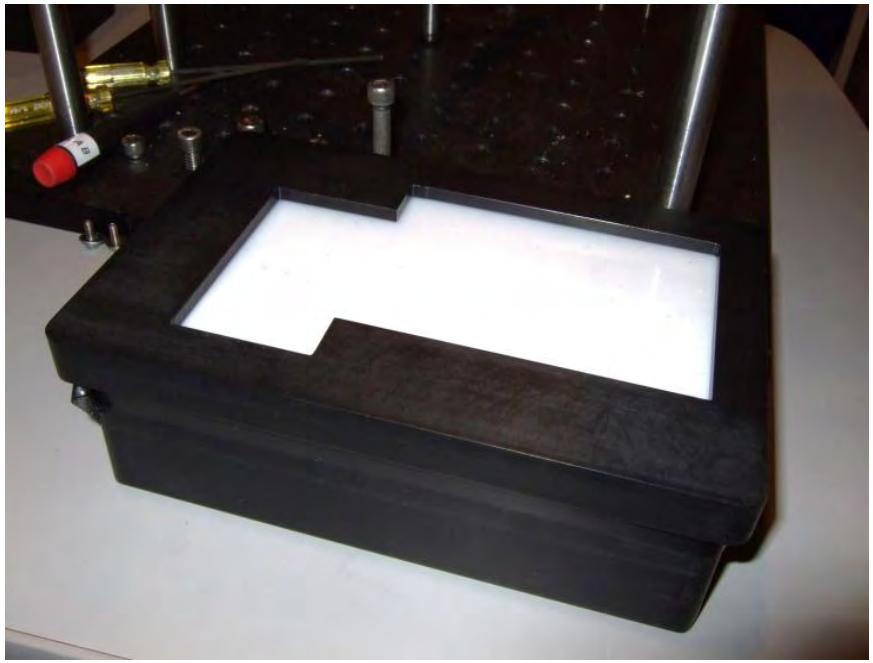
- Phantom B
  - Cross-check phantom (INO)
  - Backup calibration

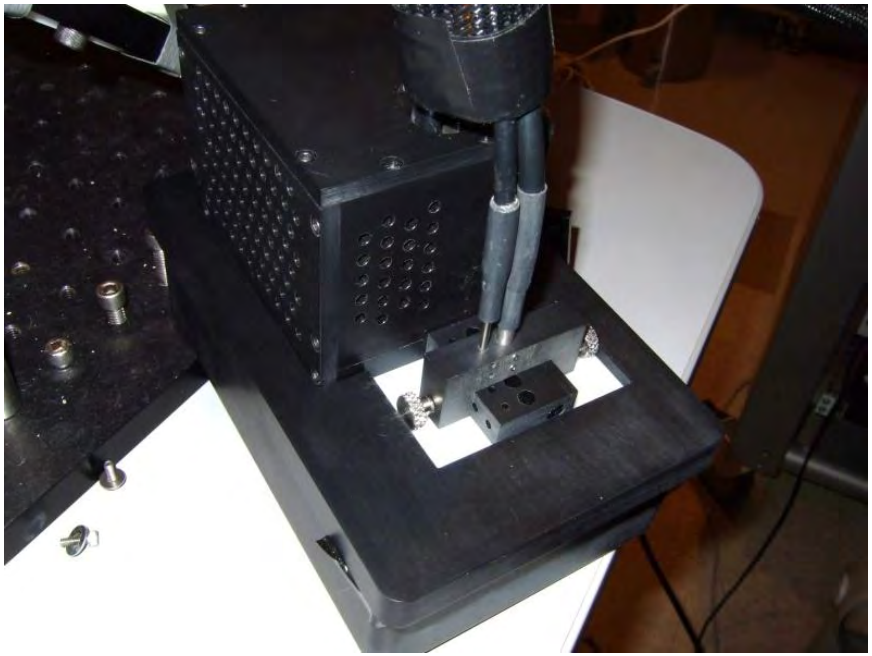
Meet our phantoms



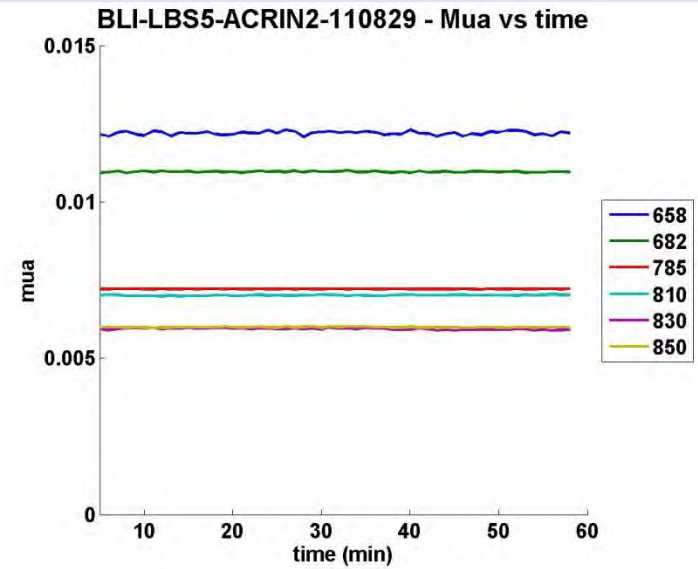


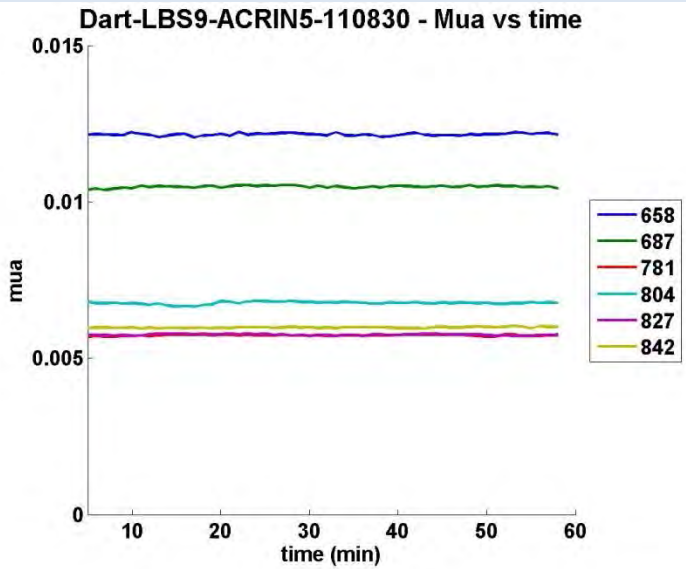
ACRIN 6691 Calibration

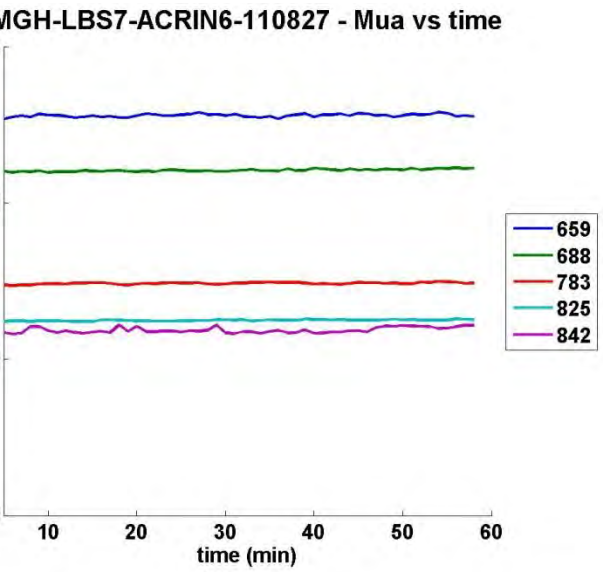


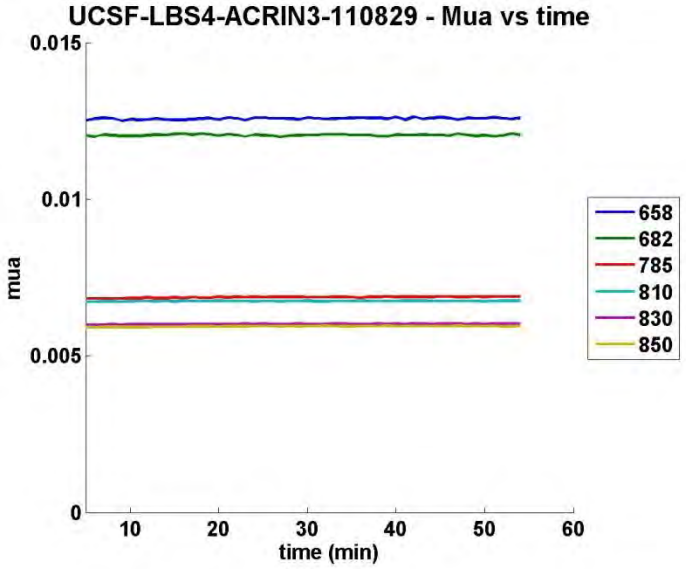


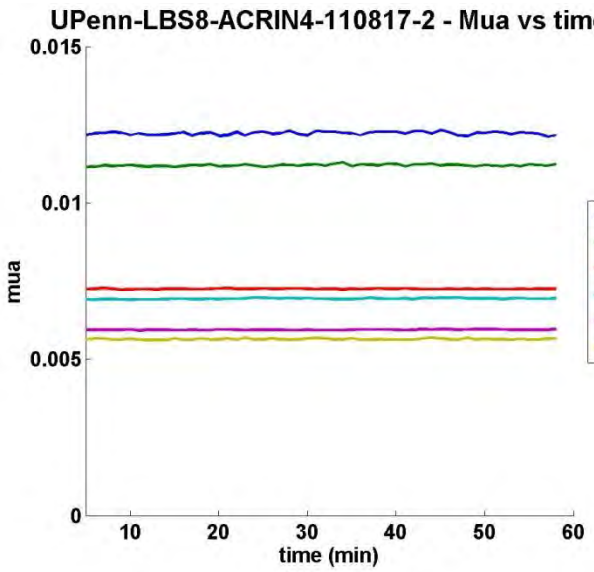
ACRIN 6691 Calibration





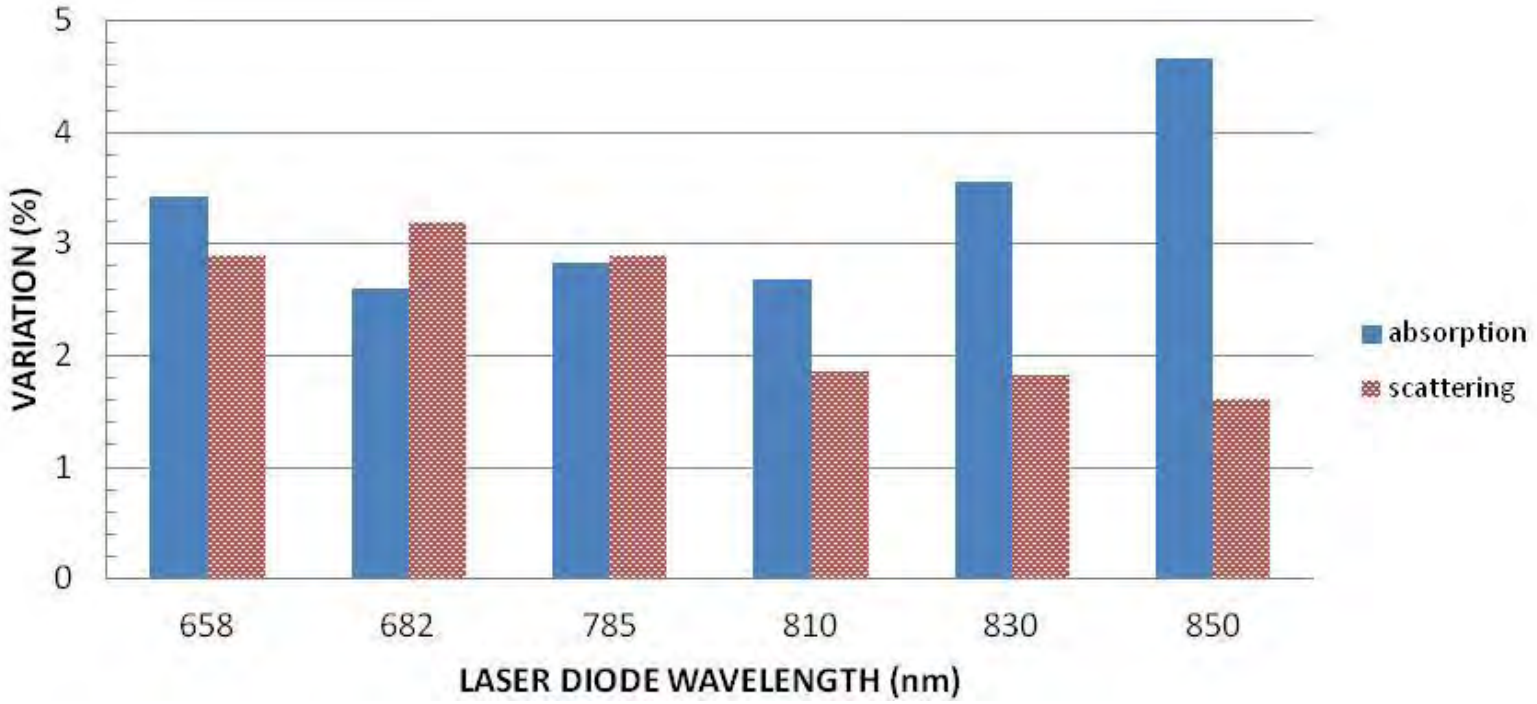






Multi-Site Validation

180 phantom measurements @ UC Irvine & Dartmouth



CITATION

Where can I get one of these cool phantoms?

Phantom “eBay”

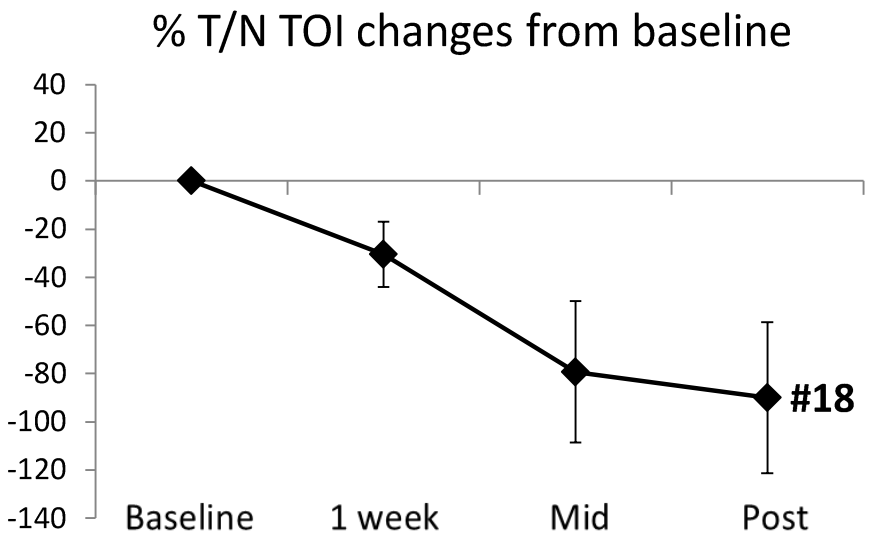
- We will train you (please come visit)
  - *lammp.bli.uci.edu*
- You can purchase via (Tony Durkin)
  - *lammp.bli.uci.edu/education/phantoms.php*
- You can purchase commercially
  - *www.ino.ca/en/products/biomimic-optical-phantoms/*

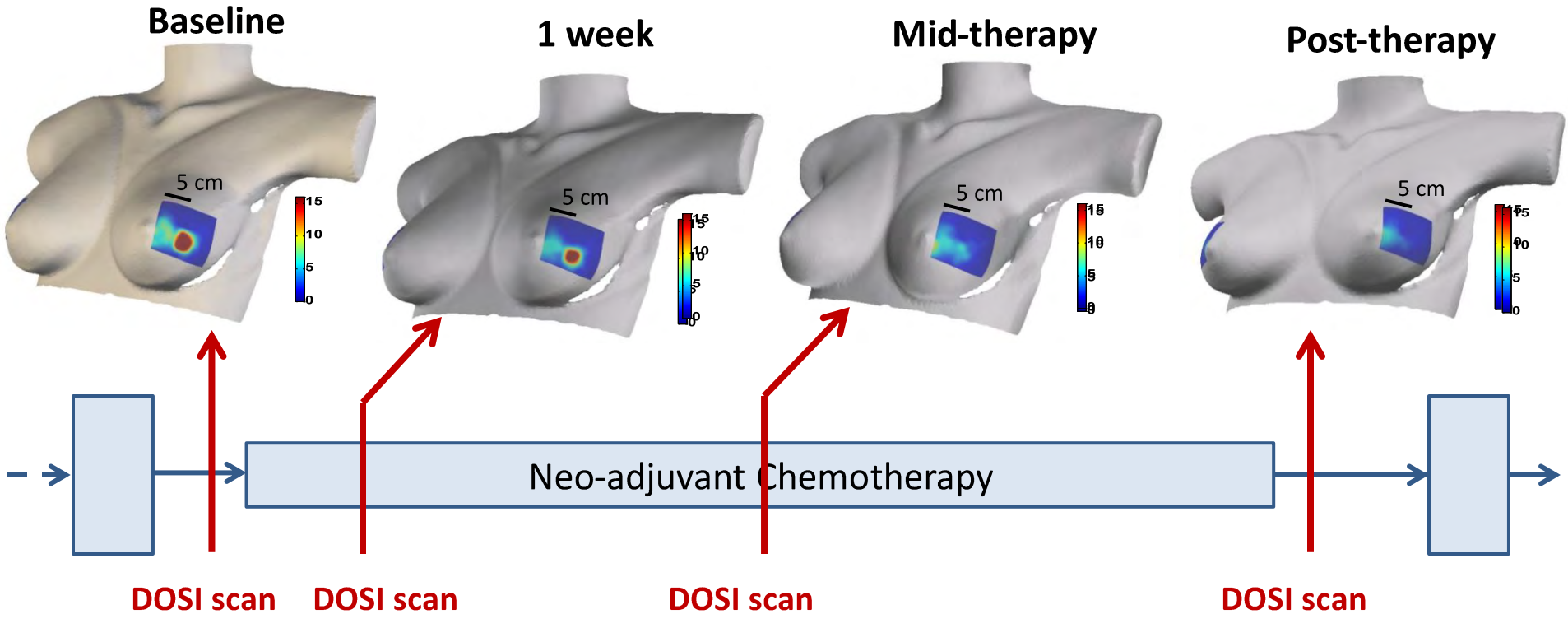
What does the ACRIN data look like?

ACRIN Endpoint Data

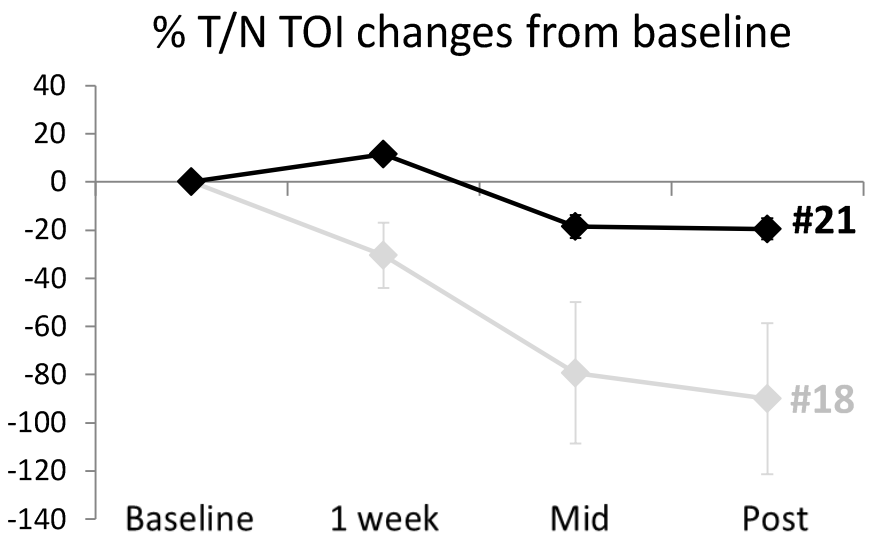
- Data locked by ACRIN (all completed)

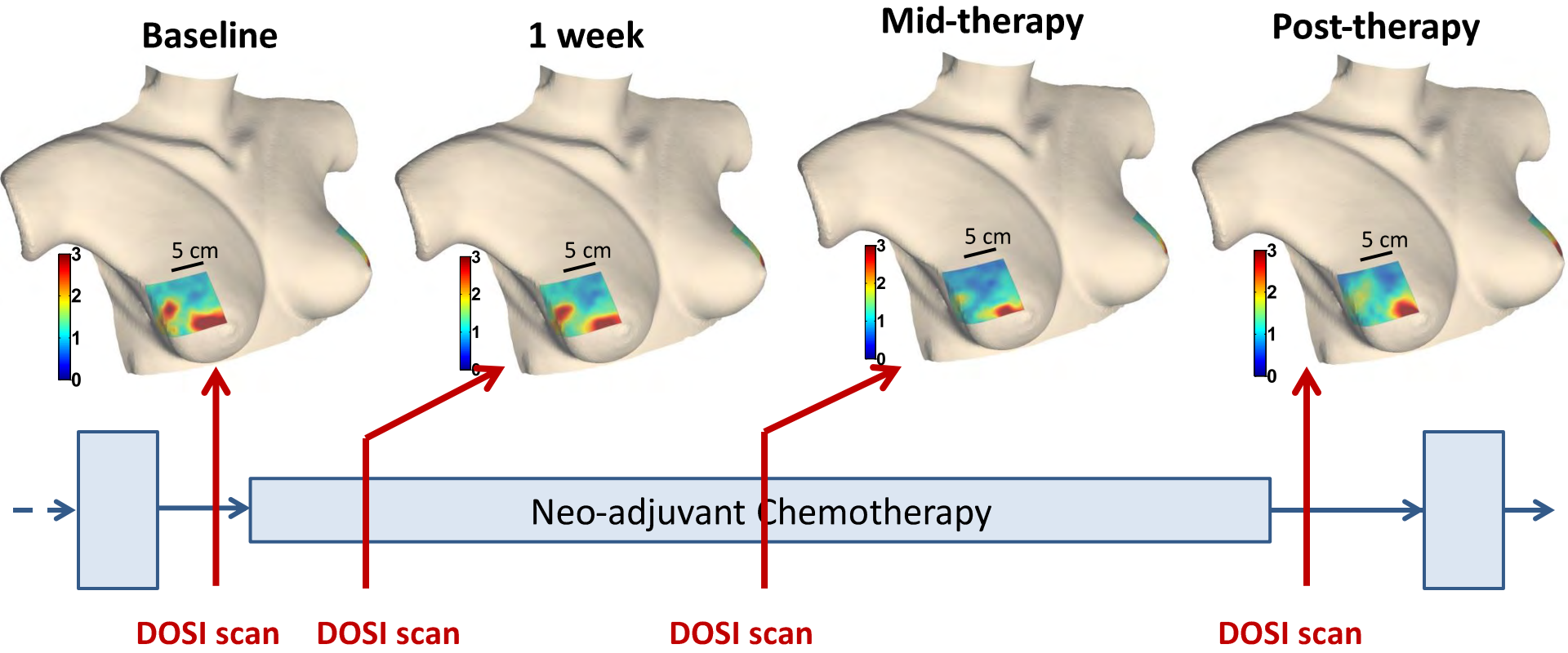
Clinical timeline 6691-18



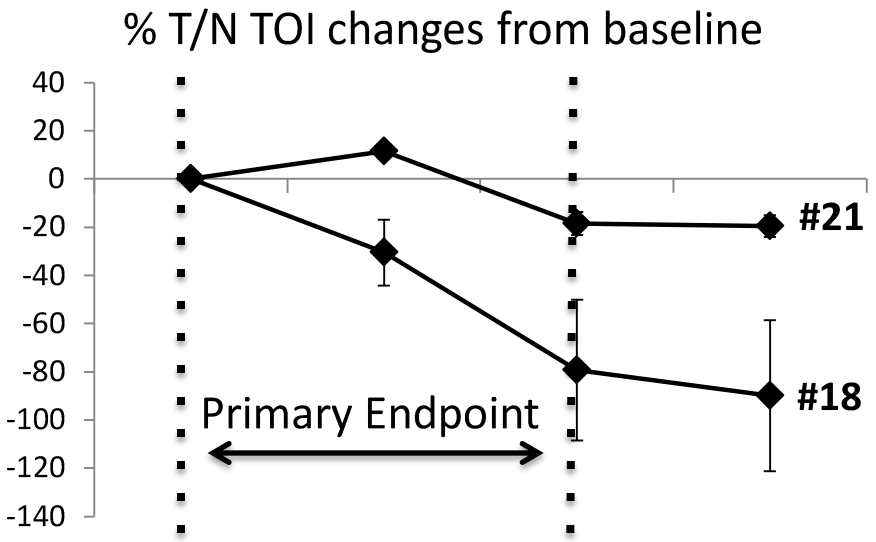


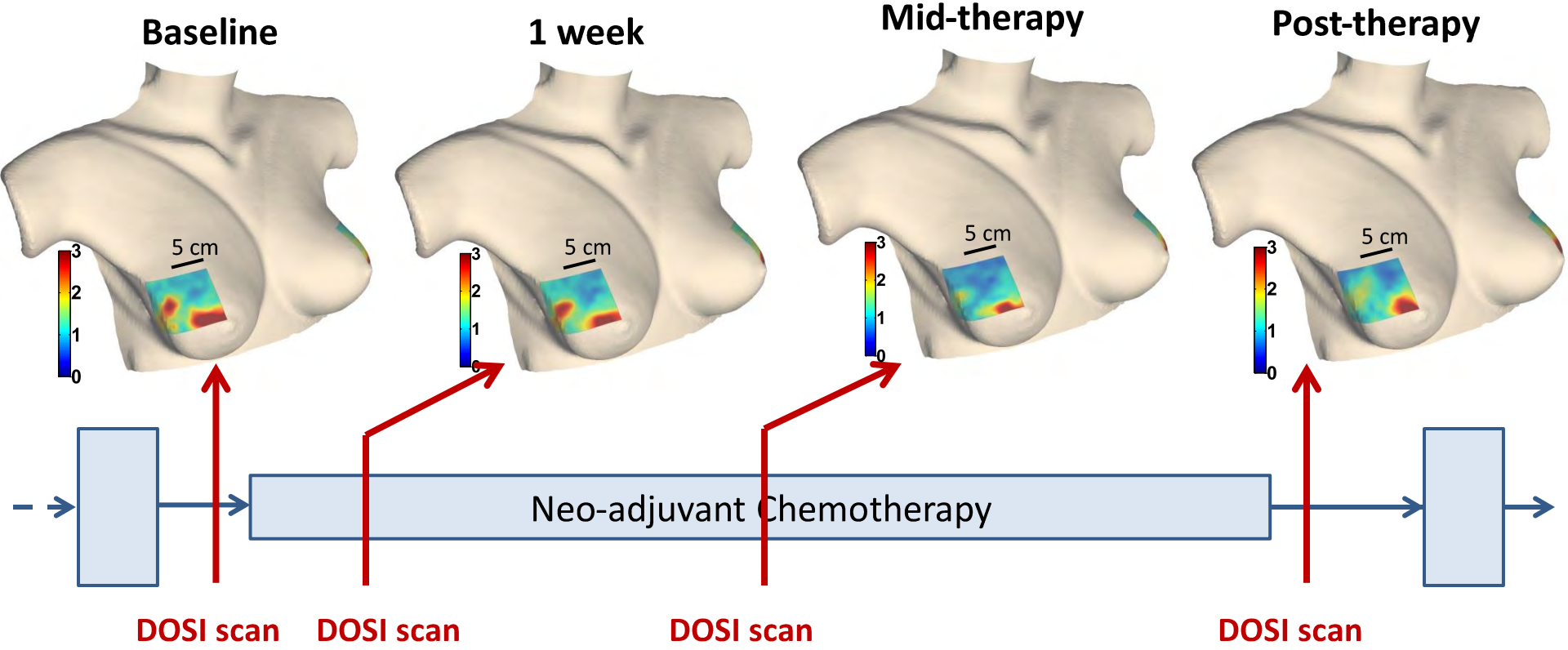
Clinical timeline 6691-21





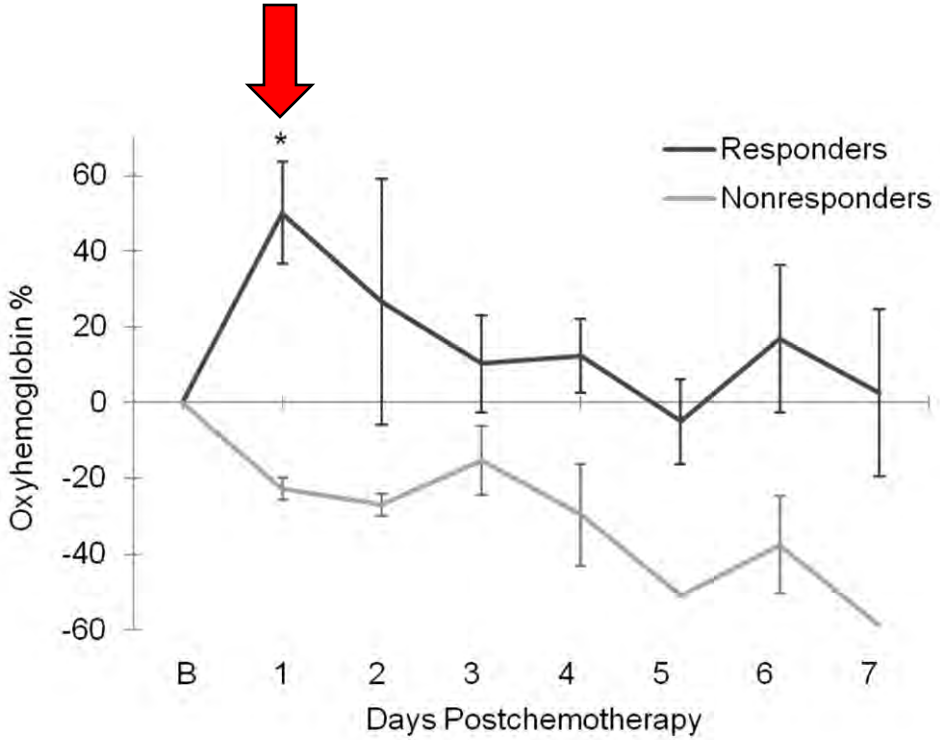
Clinical timeline 6691-21

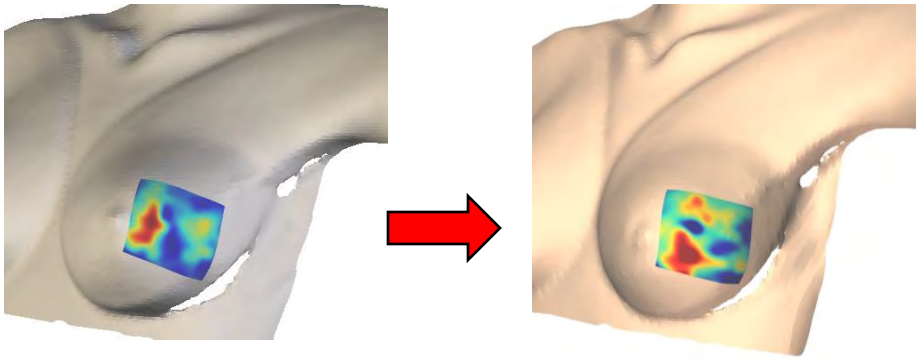




What are some future directions?

Week 1 Oxyhemoglobin





Baseline

Day 1

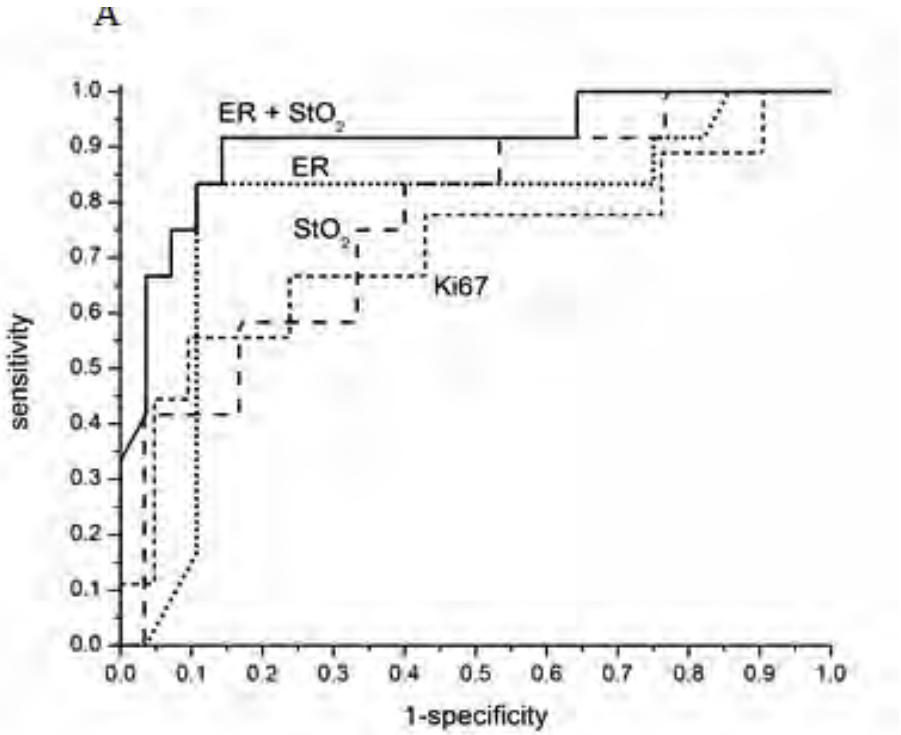
Roblyer *et al.*, PNAS, 2011. **108**(35): p. 14626-14631

17 subjects measured at least 3 times during the first 7 days of therapy

Clinical Impact:

Identify NON-Responders

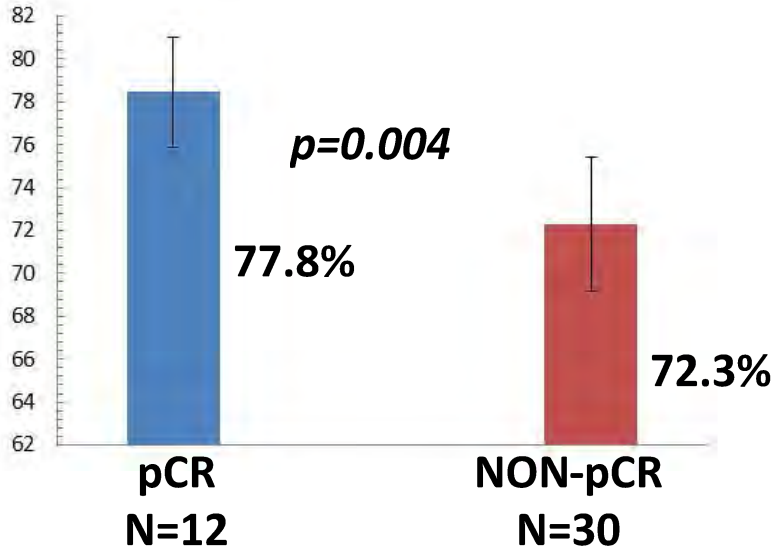
Pre-Treatment Biomarkers



stO2, Sense~ 75%, Spec ~ 68%

stO2+ER, Sense~ 100%, Spec ~ 86%

METABOLISM + MOLECULAR SUBTYPES PREDICTS RRESPONSE



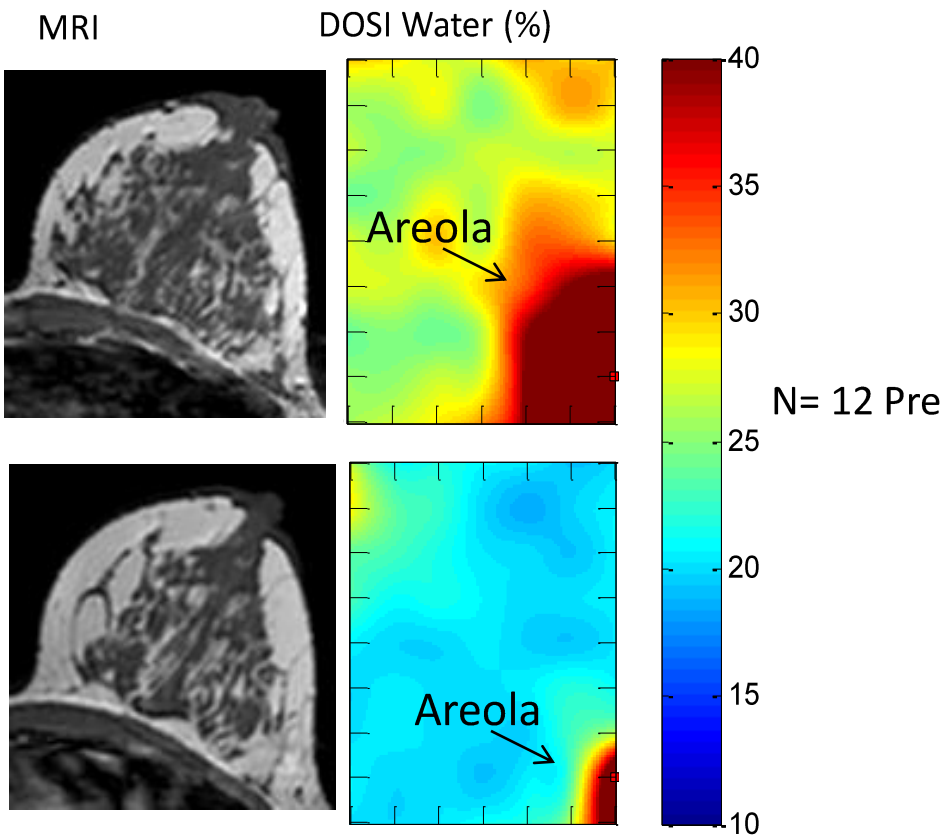
S. Ueda, D. Roblyer, et al, Can Res, (2012)

Quing Zhu, et al. Radiology 2013 (Total Hb)

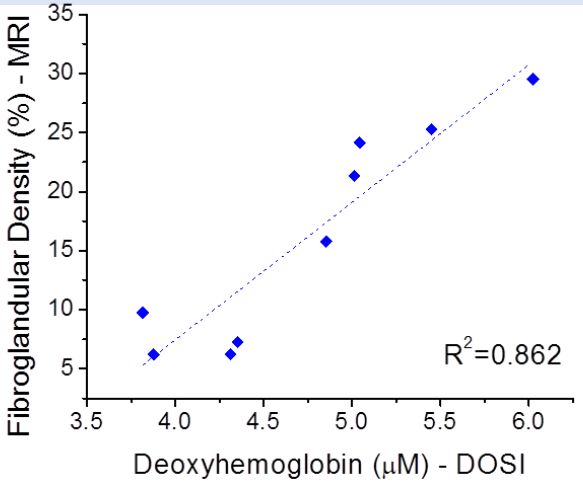
Clinical Impact:

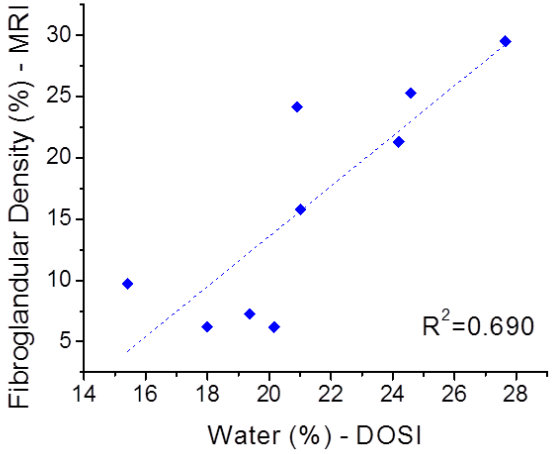
Predict Response before Therapy

Breast Density and Risk



T. O'Sullivan *et al*. Breast Cancer Research, 2012





Clinical Impact:

Risk assessment; Determine Response to Hormone Blocking (e.g. Tamoxifen) Therapy

Summary

- **DOSI sensitive to tumor perfusion, metabolism, composition**
  - *Potential Prognostic Biomarkers*
- **Therapy-induced changes monitored frequently at bedside**
  - *Feedback to guide treatment: Drug selection, Dosing schedule, New Drugs, Chemoprevention*
- **Principles Can be Generalized to Other Solid Tumors**
  - *Colo-rectal, Head and Neck, Sarcomas, etc.*
- **Clinical Adoption of Optics Requires Outcome-Based Studies**
  - *Evidence-based Medicine, Personalized Care*

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NCI *U54 Network for Translational Research;* **NCI** R01CA142989

NCI *Chao Family Comprehensive Cancer Center*

American College of Radiology Imaging Network **(ACRIN)**

DOD Breast Cancer Research Program

Beckman Foundation