Multi-modal Image guided therapy: Novel personalized approaches in Oncology

Athens Greece

Clare Tempany MB BAO BCh
Ferenc Jolesz Chair of Radiology Research BWH
Professor of Radiology Harvard Medical School

NCIGT.ORG
Disclosures

loomberg

NIH support

- National Center for Image guided therapy (NCIGT) P41 EB 015898
  - 5R01CA160902-03
  - R01-CA111288 (JHU, WPI, Queens, AMS)
  - R25 Training grant NCI

Clinical trial & other support:

- Siemens, InSightec, Gilead, AdMeTech, DPH MA
- IMRIS, SMS, GEHC, Canon

Advanced Multimodality Image Guided Operating (AMIGO) Suite NIH P41 EB015898
Dedication: Ferenc Jolesz
Vision/Inspiration
Father of Modern day Image Guided Therapy

The use of any form of medical imaging to plan, perform, and evaluate surgical procedures and therapeutic interventions.*

*Jolesz F.A.
*Intraoperative Imaging and Image-guided Therapy.
Springer 2014 Jan;

Clinical Partners & Collaborators

Radiology, Radiation Oncology, Thoracic surgery, Chest imaging, IR radiology

Breast Surgery, Breast imaging, Neurosurgery,
Overview

• Healthcare challenges 2016
  ✷ Personalized Precision Medicine Era

• Imaging and image guided therapy (IGT) NCIGT
  ✷ Resources, Technology Tools & Infrastructure
  ✷ 5 Clinical translational programs:
    ▪ Background & History
    ▪ Prostate cancer
    ▪ Neurosurgery
    ▪ Breast cancer
    ▪ Gynecological malignancies
    ▪ Lung cancer

• Future directions
  ✷ Now: Non-invasive IGT
  ✷ Tomorrow Nano technology
5 forces driving Seismic change in US healthcare*

• Rise of consumerism
  - Retail, wearable's; Shift Doctor to patient
  - Patient/Doctor encounters > 50% Virtual visits

• Shift to value based care
  - Volume to value: FPS-Global bundle payments/ ACO’s;

• Tech advances and digitization

• Decentralization

• Growth in health management and wellness

*Pricewaterhousecooper’s health research institute report
5 forces driving Seismic change in US healthcare*

- Rise of consumerism

**Technology advances**
- Use of electronic medical records and other health data
- 3D printing
- The emergence of blockchain technology (Bitcoin)
- Development of –omics (Genomics, Metabolomics, Radiomics)
- Spread of machine learning and artificial intelligence

“*Digital enables the ability to shift the model from volume to value,*”

Andrew Thompson, President and CEO of Proteus Digital Health,
5 forces driving Seismic change in US healthcare*

• Rise of consumerism
  ✷ Retail, wearable's  Patient/Doctor Virtual visits

• Shift to value based care
  ✷ Volume to value:  FPS-Global bundle payments/ ACO’s;

• Tech advances and digitization
  ✷ 3D printing

• Decentralization

• Growth in health management and wellness

*Pricewaterhousecooper’s health research institute report
5 forces driving
Seismic change in US healthcare*

• Rise of consumerism
  ✧ Retail, wearable's Patient/Doctor Virtual visits

• Shift to value based care
  ✧ Volume to value: FPS-Global bundle payments/ ACO’s;

• Tech advances and digitization
  ✧ 3D printing

• Decentralization

• Growth in health management and wellness

*Pricewaterhousecooper’s health research institute report
Precision Medicine and Value

VALUE = Patient Experience + Outcomes

Cost

Improved consent process
Increased engagement

Tailor the treatment to risk
Increase consistency of care

Tailor Treatment to patient preference
Avoid treatment in patients with no benefit
Volume to Value

• How to change culture from Fee per Service to value for service

• Lee et al JAMA 2016
  ✷ Physicians were given access to a tool with information about outcomes, costs (not charges), and variation and partnered with process improvement experts.
  ✷ Total and component inpatient and outpatient direct costs across departments; cost variability for Medicare severity diagnosis related groups measured as coefficient of variation (CV); and care costs and composite quality indexes.
  ✷ Implementation of a multifaceted value-driven outcomes tool to identify high variability in costs and outcomes in a large single health care system was associated with reduced costs and improved quality
2 types of human decision making

Type 1
- Automatic
- Intuitive
- Exposed
- Easy to use
- Reflexive
- Not always right
- Strongly preferred

Type 2
- Logical
- Precise
- Analytical
- Hard
- Resource Intensive
- Almost always right
- Used only when forced
Advances in imaging technologies used in oncology

PET-MRI

Adapted from Condeelis J, Weissleder R Cold Spring Harb Perspect Biol 2010;2:a003848
Personalized Image-based Phenotyping

- Biomarker targeting
  - Specific
  - Non-specific
- Biochemical tissue characterization
  - Vascular/angiogenesis quantification
  - Ventilatory patterns
- Multi-modality and multi-parametric characterization
  - Image registration
- Treatment Guidance and monitoring
- Image-guided interventions

Combine genomics and imaging
Surgical Oncology

Surgery is:
- the most important cancer treatment
- cost-effective

Personalized Image guided surgery

Margins are critical
Define
Localize
Resect beyond

First course treatment of all sites Cancer Diagnosed in 2003-2013. From: National Cancer Data Base/Commission on Cancer, American College of Surgeons.
Clinical Test-bed for National Center for Image-Guided Therapy
Precise Localization of Tumor Boundaries for Therapy
The National Center for Image-Guided Therapy (NCIGT) is an NIH funded Biomedical Technology Resource Center. The NCIGT serves as a national resource for all aspects of research into medical procedures enhanced by imaging, with the common goal of providing more effective patient care.

Based at the Brigham and Women's Hospital and Harvard Medical School in Boston, Massachusetts, the NCIGT is lead by Ferenc A. Jolesz M.D. and Clare Tempany M.D. and includes the work of more than one hundred physicians, scientists, and technical staff members.

**About Us**
- Overview
- Research Labs
- Research Cores
- Research Projects
- DBPs/Collaborations
- People

**Resources**
- Publication DB
- Image Gallery
- Downloads
- AMIGO
- News and Events
- Contact Us

**Advanced Multimodality Image Guided Operating (AMIGO) Suite**
The Advanced Multimodality Image Guided Operating (AMIGO) Suite is an innovative surgical and interventional environment that is the clinical translational test bed of the National Center for Image-Guided Therapy (NCIGT) at the Brigham and Women's Hospital (BWH) and Harvard Medical School. The AMIGO is an integrated, 5,700 square foot area divided into three sterile procedure rooms in which a multidisciplinary team will treat patients with the benefit of intra-operative imaging using multiple modalities. More...

**In the Spotlight**
ISMIR 2011
19th Annual Meeting and Exhibition, May 7-13, 2011, Montreal, Quebec, Canada. NCIGT has a strong presence at ISMRM 2011 with presentations in imaging physics as well as image guided interventions.

**NIH Funded BTRC 2015**
P41 NIBIB - Now

Funds 45+ people

**PI** Clare Tempany, MD

**Executive Director**
Tina Kapur, PhD

**TRD Cores**
- Prostate (Tempany)
- Neurosurgery (Golby)
- Computation (Wells)
- Guidance (Hata)

**Major resources**
- AMIGO
- 3D SLICER
AMIGO History: A dream 20 years in the making

AMIGO represents the culmination of ground-breaking research at BWH in Image-guided Therapy (IGT) dating back to the early 1990’s.

- **1991**: BWH Image-guided Therapy program founded by Ferenc Jolesz
- **1994**: BWH develops first MR-guided Focused Ultrasound (MRgFUS) system
- **1997**: 3D Slicer
- **2005**: Creation of NIH-funded National Center for Image Guided Therapy
- **2011**: AMIGO: First suite to offer the full array of advanced imaging modalities in one operating theater (MRI, PET/CT, 3D US, Fluoro, Angio)

Since the early/mid-1990’s, over 100 intraoperative MRIs and close to 100 MRgFUS systems have been installed throughout the world.

Training and technology dissemination: eg, 3D slicer

A clinical and translational test bed for multi-modal IGT
AMIGO is an innovative surgical and interventional environment where real-time anatomical imaging modalities like x-ray and ultrasound are combined with cross-sectional digital imaging systems like CT, MRI, and PET.

AMIGO technology will improve the ability to define tumor margins to more completely excise or thermally ablate affected areas. **Multimodality, multidisciplinary, multivendor translational environment.**

**PET/CT Room**
Integration of anatomical info from CT and MRI with functional and metabolic info from PET informs surgical decision making during tumor resections and percutaneous thermal ablations.

**Operating Room**
The OR is outfitted with an electronically controlled patient table surrounded by imaging and therapy devices (ceiling-integrated navigation system, fluoroscopy, 3D ultrasound, and a microscope with near-infrared imaging system).

**MRI Room**
Room contains a 3T MRI and will be fully integrated with video monitors, surgical lights, therapy delivery equipment, an MRI-compatible anesthesia machine, and vital signs monitor. A ceiling mounted MRI scanner can be rotated or moved into/out of the OR and MR rooms.
Molecular imaging framework in AMIGO
Personal & precise voxel specific tissue sampling for pathological validation of imaging

A validation of multimodal imaging MR-PET registration
3D slicer: an Integral tool

- Key Features
- Integrated Display of What is Known About the Patient
  - Anatomical Space as Common Coordinate System
  - Multimodality Fusion
  - Segmented Anatomy and Volume Rendering
  - Statistical Volumes, Charts
  - Interactive Visualization (View, Visibility, Cropping, Slicing…)
  - Therapy Plans, Measurements, Annotations
  - Real-Time Updates
  - Linked Views

www.slicer.org

Plesniak, Aucoin et al - BWH
Jakab and Berenyi - University of Debrecen
Navigation & Guidance

- OpenIGTLink Standard
  - Tracked Instruments
  - Real-Time Images
  - Scanner and Robot Control
- BWH AMIGO
  - 3T MR + PET CT in OR
## AMIGO Procedures
### 8/30/2011 – 10/12/2016

<table>
<thead>
<tr>
<th>Neurosurgery</th>
<th>209</th>
<th>Interventional Radiology</th>
<th>913</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain tumor resection</td>
<td>112</td>
<td>Ablation</td>
<td>400</td>
</tr>
<tr>
<td>Deep brain stimulation</td>
<td>36</td>
<td>Cryoablation (MR, PET/CT)</td>
<td>309</td>
</tr>
<tr>
<td>Transphenoidal pituitary tumor resection</td>
<td>24</td>
<td>Kidney+</td>
<td></td>
</tr>
<tr>
<td>Laser brain ablation</td>
<td>11</td>
<td>Microwave (PET/CT, MR)</td>
<td>83</td>
</tr>
<tr>
<td>Brain biopsy</td>
<td>10</td>
<td>RF ablation</td>
<td>3</td>
</tr>
<tr>
<td>Skull base</td>
<td>7</td>
<td>IRE</td>
<td>4</td>
</tr>
<tr>
<td><strong>Endocrine Surgery</strong></td>
<td>9</td>
<td><strong>Biopsy</strong></td>
<td>508</td>
</tr>
<tr>
<td>Hemithyroidectomy</td>
<td>4</td>
<td>MRI Guided Prostate</td>
<td>427</td>
</tr>
<tr>
<td>Pheochromocytoma resection</td>
<td>3</td>
<td><strong>Radiation Oncology</strong></td>
<td>106</td>
</tr>
<tr>
<td>Parathyroidectomy</td>
<td>2</td>
<td>Gynecologic HDR Brachytherapy</td>
<td>96</td>
</tr>
<tr>
<td>Video-assisted Thoracoscopic Surgery</td>
<td>28</td>
<td>Prostate VLDR Brachytherapy</td>
<td>10</td>
</tr>
<tr>
<td>Spine Discectomy and Fusion</td>
<td>2</td>
<td><strong>Cardiac EP Ablation</strong></td>
<td>7</td>
</tr>
<tr>
<td>Breast Conserving Surgery</td>
<td>25</td>
<td><strong>N=1289</strong></td>
<td></td>
</tr>
</tbody>
</table>
Image-guided Prostate Cancer program

AMIGO

Slicer

Patient

Prostate Biopsy

Biomarker validation

Focal therapy

Guidance & Navigation

Prostate motion & deformation

iMRI
Prostate Cancer research team

• Clare Tempany MD
• Noby Hata
• Junichi Tokuda
• Kemal Tuncali
• Adam Kibel
• Andriy Fedorov
• Fiona Fennessy
• Gabor Fichtinger
• Iullian Iorchita
• Greg Fischer
• Clif Burdette
62 year old Male PSA 15, Biopsy 1: 5 on left 3 + 3

**THE SAMPLING PROBLEM**

**MR PIRADS 5**

**DCE Sub**

**ADC**

**AIF and tumor kinetic**

**MaxSlope** **Ktrans** **Kep** **Washout**
A Slicer module called MRProstateCare
1) Planning biopsy targets;
2) Controlling the scanner operations;
3) Guiding the prostate biopsy procedure.
MR guided transperineal prostate biopsy in bore at 3T

- Direct Transperineal sampling based on pre-biopsy MRI (Ecoil at 3T) to define targets
- Target sampling with 3D slicer, under IVCS- out patient
- Target MR abnormal areas
  - T2W/ADC/DCE
  - Site specific pathology

*Penzkofer et al* Transperineal in-bore 3-T MR imaging-guided prostate biopsy: a prospective clinical observational study Radiology. 2015
1995  MR guided prostate biopsy
       Transgluteal  n=3

1997-2007  MR guided brachytherapy
           Transperineal in bore 0.5T  BWH first  n=700

1999-2007  MR guided prostate biopsy*
           Transperineal in Bore  BWH first  n=50

2001:  1R01AG019513-01 (PI Tempany)
       MR GUIDED PROSTATE CANCER DIAGNOSIS AND BRACHYTHERAPY  n= 500

2005-present  P41 NCRR/NCI/NIBIB(Jolesz/Tempany-PROSTATE CORE)
2006:  RO1 (Tempany) BRP NCI
       Enabling technologies for MR guided prostate interventions

2008-present  MR guided prostate biopsy
              Transperineal in bore 3T (n>300)  BWH first

Now 18 years later MR targeted prostate biopsy is a routinely performed worldwide
Multiple approaches (TR/TP, in bore/out of bore), multiple devices/vendors, devices
How do we Diagnose Prostate Cancer?

Today: Transrectal Ultrasound Guided Biopsy
   Blind Systematic needle sticks

   Over diagnosed G6 Indolent dx
   Over treated

Today and tomorrow:
Magnetic Resonance Guided, Targeted
Prostate MR-Guided Biopsy

- Direct “in-bore” MRGB
  - Transperineal or transrectal

The solution: Find the target and hit it!
- Time MR used for image guidance during biopsy

- Indirect “out-of-bore” MRGB
  - TRUSGB
  - Pre-procedure mp-MRI is used to define targets for subsequent TRUSGB
    - “MRI-TRUS fusion” biopsy
      o Software based image co-registration
    - “Cognitive fusion” biopsy
      o Without automated image co-registration
Prostate Biopsy in-Bore MR robot with Higher degree of freedom

Collaboration with Fischer (WPI), Iordachita (JHU), Burdette (Acoustic Med), Fichtinger (Queens)

R01CA 111288 (PI Tempany/BWH)
Enabling Technologies for MRI-Guided Prostate Interventions
Overview of MR-US “fusion” biopsy systems
MR targeted US guided prostate biopsy

Eigen/ Artemis

BiopSee®

Koelis
http://www.koelis.com/

Uro nav
http://www.artemis.shtml
Cost-effectiveness Prostate
mp-MRI and MRGB: The value

2013
• mp-MRI for PCa localization  *Mowatt et al*, UK

2014
• MRGB vs Systematic TRUSGB for PCa diagnosis  *De Rooij et al*, Netherlands

2014
• Mp-MRI and MRGB vs TRUSGB in PCa diagnosis  *Willis et al*, UK

2015
• Mp-MRI vs Repeat TRUSGB for PCa diagnosis in patients with prior negative TRUSGB  *Lotan et al*, US

2015
• MRGB vs Systematic TRUSGB for PCa diagnosis  *Cerantola et al*, Canada
Cost-effectiveness Ratio

\[ CER = \frac{C_i - C_{alt}}{E_i - E_{alt}} \]

Incremental resources required by the intervention

Incremental health effects gained with the intervention
Cost-effectiveness Analysis

• Decision analysis - a quantitative method for evaluating decisions between multiple alternatives in situations of uncertainty

• Steps include:
  ✷ Enumerate all relevant alternatives
  ✷ Identify important outcomes
  ✷ Determine relevant uncertain factors
  ✷ Encode probabilities for uncertain factors
  ✷ Specify the value of each outcome
  ✷ Combine these elements to analyze the decision

• CEA – a type of decision analysis which includes costs as one of it’s outcomes as a method for evaluating tradeoffs between health benefits and costs resulting from alternative courses of action
Sensitivity Analysis

• Systematically asking “what if” questions to see how the decision result changes

• Determines how “robust” the decision is
  - Threshold analysis: one parameter varied
  - Multi-way analysis: multiple parameters systematically varied

• Probabilistic Sensitivity Analysis (2nd order Monte Carlo)
  - Decision tree estimates of probabilities and utilities are replaced with probability distributions (e.g. logistic-normal)
  - The tree is evaluated many times with random values selected from each distribution
  - Results include means and standard deviations of the expected values of each strategy
**The problem:** Breast lumpectomy has 20-40% residual tumor left behind “Positive Margins”

**Solution pathway:** Demonstrated significant alternation in lesion from pre op prone to intra-op supine position. New supine breast imaging protocol has been added to accurately stage and plan surgical excision

- Second phase of the project has begun with intraoperative MRI and Mass Spectrometry.

- Gombos et al Radiology 2016
Breast Cancer Surgery

Pre-procedural imaging

Surgery

Post-procedural imaging

Re-excision

Golshan, Gombos, Jagadeesan
Pre-operative mapping and Intra-operative MRI for brain tumor resection

Alexandra J. Golby, M.D.
Associate Professor, Harvard Medical School
Associate Surgeon, Brigham and Women’s Hospital
Brain tumor surgery: two critical clinical challenges

- Identify critical brain structures:
  - fMRI, DTI, Electrophysiology

- Define extent of tumor
  - Intra-operative MRI
  - Mass Spectrometry
  - Ultrasound
Image guided Neurosurgery Platform

AMIGO

Slicer

Pathology

fMRI/DTI

Structure function map

Biomarker validation

Brain deformation

Tracked US

Mass Spect

Golby, Wells, O’Donnell, Westin, Frisken, Agar, Santagata
Genomics in Gliomas

BRAF

• BRAF is mutated in 3% of glioma cases (Horbinski 2012).

IDH

• IDH (1 or 2) mutations occur in over 30% of gliomas (Dang, Jin, and Su 2010).
• A IDH inhibitor is in a phase 1 clinical trial. The compound, AG-881, is an inhibitor of IDH and able to penetrate the BBB

MyCancerGenome.com
Intraoperative mass spectrometry mapping of an onco-metabolite to guide brain tumor surgery.

Desorption electrospray ionization (DESI) MS, to detect the tumor metabolite 2-hydroxyglutarate (2-HG) from tissue sections of surgically resected gliomas.

Histopathology
Tumor cell concentration

DESI Mass Spectrometry
$m/z$ 768.3 +/- 0.5
Phosphatidylcholine 16:0/16:0

Image guided radiation therapy: Gynecological cancer

Guidance methods

- Traditional: XRAY- CT

- Emerging: MR-PET/MR/LINAC
MR g Gynecologic Brachytherapy

Viswanathan*, Wang, Kapur, Tempany, Schmidt
MRg Gynecologic Brachytherapy

Pre-brachytherapy 30 Gy (3.75 Gy x 8 fractions) After 5 month

Viswanathan, Wang, Tempany, Kapur, Schmidt
MRg Gyn implants: Active Needle Tracking

Magnetic Resonance-guided Active Catheter Tracking
Lung cancer 2016

• The National Lung Screening Trial with chest CT results in a 20% reduction in mortality.*
• USPSTF category B
• Most nodules detected are not cancer
• Biopsy and/or resection rec, for lesions > 1 cm
• Expect many < 2cm enlarging semi-solid nodules to be detected.
• Increase in demand for surgical resection

Challenges & Solutions

Nodules < 2cm

• Accurate imaging characterization
• Accurate biopsy
• Localization
• Palpation

Imaging & IGT solutions

• Radiomics*
• PET/CT guide biopsy
• Hybrid OR’s with cone beam CT
• T-bar in OR

Radiomics: Lung cancer

High throughput extraction of a large number of quantitative and minable imaging features, assuming that these features convey prognostic and predictive information.

Optimizing quantitative imaging feature extraction through computational approaches and developing decision support systems, to accurately estimate patient risk and improve individualized treatment selection and monitoring.

- Parmar et al PLoS ONE 2014
- Lambin et al. Eur J Cancer 2012
- Kumar et al. Magn Reson Imaging 2012
Representative CT images of Lung Cancer

Tumors are different
Medical imaging can capture these phenotypic differences
From “Common” lung cancer to “Rare Disease”

Example lung cancer

Specific molecular targets are identified for treatment using genetic analysis of tumor cells.

Histology: Lung cancer split into:

- Small cell lung cancer
- Non-small cell lung cancer (NSCLC)

Genetics: NSCLC split into:

- A family of rare diseases
- Potential for targeted treatment

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Frequency in NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKT1</td>
<td>Mutation</td>
<td>1%</td>
</tr>
<tr>
<td>ALK</td>
<td>Rearrangement</td>
<td>3–7%</td>
</tr>
<tr>
<td><strong>BRAF</strong></td>
<td>Mutation</td>
<td>1–3%</td>
</tr>
<tr>
<td>DDR2</td>
<td>Mutation</td>
<td>~4%</td>
</tr>
<tr>
<td>EGFR</td>
<td>Mutation</td>
<td>10–35%</td>
</tr>
<tr>
<td>FGFR1</td>
<td>Amplification</td>
<td>20%</td>
</tr>
<tr>
<td>HER2</td>
<td>Mutation</td>
<td>2–4%</td>
</tr>
<tr>
<td>KRAS</td>
<td>Mutation</td>
<td>15–25%</td>
</tr>
<tr>
<td>MEK1</td>
<td>Mutation</td>
<td>1%</td>
</tr>
<tr>
<td>METa</td>
<td>Amplification</td>
<td>2–4%</td>
</tr>
<tr>
<td>NRAS</td>
<td>Mutation</td>
<td>1%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Mutation</td>
<td>1–3%</td>
</tr>
<tr>
<td>PTEN</td>
<td>Mutation</td>
<td>4–8%</td>
</tr>
<tr>
<td>RET</td>
<td>Rearrangement</td>
<td>1%</td>
</tr>
<tr>
<td><strong>ROS1a</strong></td>
<td>Rearrangement</td>
<td>1%</td>
</tr>
</tbody>
</table>

Known mutations in NSCLC

https://www.mycancergenome.org/content/disease/lung-cancer/
Image guided Lung Nodule Wedge Resection Surgery: iVATS

Bueno, Gill, Jagadeesan
Video-assisted Thoracic Surgery (VATS) – Current standard of care

Segmentectomy and Lobectomy

Wedge with tumor resected

Entire lobe with tumor resected

Video-assisted thoracoscopy
Results

• 25 enrolled in the study, 23 patients had successful resection
• 20 patients (87%) had successful placement of the T-bars to localize the lesion
• Median time
  ✴ Total = 212 min
  ✴ From anesthesia to VATS incision = 130 min
  ✴ Planning and placement of T-bars = 39 mins
• 22 nodules demonstrated malignancy, 1 was benign
• All nodules were completely resected

The ultimate non-invasive IGT
MR guided FUS

MR thermometry
Real-time feedback

focal heating

Transducer
Patient

Water interface

TEMPERATURE AFTER ONE SEC PULSE (°C)
MRI-guided FUS of the Brain

• Thermal Brain tumor treatment through the intact skull

• BBB opening Targeted drug delivery by FUS induced opening of blood-brain barrier

• Neuro-modulation Functional effect on nerve conduction
  ✧ Effect of CNS function
    ▪ Create focal lesions for control of Essential Tremor
      ○ FDA clearance & NEJM AUGUST 2016
    ▪ Parkinson’s Disease
    ▪ BBB- change protein environment – lower Amyloid Alzheimer's disease

MRgFUS focal ablation of prostate cancer

- Pre
- Intra
- Post

Tempany, Kibel, McDannold, Tuncali, InSightec Inc ExAblate
Look to the future

• Big Data, Deep Learning, Machine learning
  ✦ Tools: Watson, 3DSlicer, MR fingerprinting
    - IBM Watson ($4B EMR, MRI etc NLP) UNC N=1000, 99% agreement, 30% found Rx missed by MDs NYT 10-18-16

“Medicine is too important to be left to Doctors”
  ✦ Isaac Kohane TED MED talk 2013 (Est 160,000 cancer papers/yr)
  ✦ Over 50% of patient – doctor encounters are now virtual*

• Challenges and opportunities
  ✦ Data sharing vs Research Parasites vs Symbiotic/Collaborative*

D. Longo & J. Drazan NEJM

* Kaiser Permanent Annual report 2016
NIH – Biden Cancer Moon shot

• Blue ribbon panel report 8/2016

• “Development of new enabling cancer technologies. Support the development of promising new technologies that will accelerate testing of therapies and characterization of tumors. These include implantable micro dosing devices for testing drug effectiveness directly in tumors;”
Development of implantable device for high-throughput in vivo drug sensitivity testing

Multiple drugs or rational combinations of drugs are empirically tested in-vivo in each person’s tumor, enabling the best treatment decisions by the oncologist

- Test phenotypic response to drug inside the native tumor microenvironment
- For up to 30 drugs or combinations in parallel
- Within 1-2 days
- Minimally invasive
- No systemic exposure to any drugs
  - One millionth of systemic dose of each drug (removed)
Micro device to measure local drug effect & predict tumor sensitivity

- Delivery of multiple drugs into confined regions of tumor

- Efficacy readout for each drug using multiple markers

- Local readout is predictive of tumor sensitivity across models

Key Safety Considerations to support “non-significant risk” assessment by IRB

- Implantation with 18 or 19 g biopsy needle
- Device remains in tumor for ~ 1 day
- Up to 30 drug micro-doses
  - Each micro-dose ~ 1 millionth of systemic dose
- Retrieval with large coring needle
  - Removes entire region of drug exposure from body

Region of tissue removed by coring needle
Region of exposure to drug A at 24h
Region of exposure to drug B at 24h
Device cross-section
Multi-modal Image registration MR-mass spectrometry & Image annotation

pre-biopsy mpMRI annotation

pre-biopsy analytics

post-biopsy analytics

validation

BWH
NATIONAL CENTER FOR IMAGE-GUIDED THERAPY

NATIONAL CENTER FOR IMAGE-GUIDED THERAPY
Hybrid OCM-MRI for Real-Time Imaging

- Ultrasound-based “organ-configuration motion” (OCM) sensor
- MR compatible, single-element, 5 Mhz center frequency, 8 mm diameter
- Patched on the abdomen
Machine-learning based synthetic real-time MRI, after less than 2 minutes of training

Synthetic MRI goes at the speed of OCM, here > 20 fps

F. Preiswerk et al., “Hybrid MRI ultrasound acquisitions, and scannerless real-time imaging,” Magnetic Resonance in Medicine, in press.

Machine-learning based synthetic real-time MRI, after less than 2 minutes of training

Synthetic MRI goes at the speed of OCM, here > 20 fps
Kalman filter-based optical and EMsensor fusion for MRI-guided nerve and tumor cryotherapy

MRI-guided Cryoablation

Current workflow and problem

1 Clinical background

• 1.1 Current workflow and problem

Needle Bending!!
Clinical background

• 1.2 Navigation system
Needle Tracking

**EM Tracking**
Gradient-based MRI tracking (Robin Medical)

- Track the needle
  Isocenter and entrance of the MRI
- Drive the scan plane
  Real-time BEAT-IRTTT sequence

Noisy and prone to errors
At the entrance of the MRI

**Optical Tracking**
(Polaris tracker from Symbowmed)

Accurate and less noisy
At entrance of the MRI

Line-of-sight problems

**Cannot track the needle at Isocenter**
(no scan plane control)
Method

Kalman filter-based sensor fusion
Future directions

• Tumor heterogeneity*
  ✷ Real-time intraprocedural detection and characterization
    ▪ Mass Spect, Raman, Optical probes in OR

• Precise sampling-mutation mapping
  ✷ Brain, breast, lung and prostate cancers

• Accurate surgical/ablation margins

*Gerlinger et al Nat Genet. 2014
New directions

• To increase accuracy of detection of clinically significant prostate cancer in vivo
  ✷ Better, smarter more precise biopsy
• To Characterize intra-tumoral heterogeneity
• To Improve surgical & Focal therapy outcomes
• Imaging: Mass Spect, Hyperpolarized C-13, PET PSMA
• Pathology Gleason Pattern 4
## The Clinical Impact

### Brain Tumor Resection
- **Today**
  - No way to evaluate whether the cancer has been completely removed
  - Complete excision vs postop morbidity
- **In AMIGO**
  - Intra-operative MRI scan identifies additional tissue requiring removal
  - Real-Time Mass Spect
- **Clinical Impact**
  - Optimize first surgery - best chance
  - Reduction in the need for repeat surgeries

### Lung Cancer Diagnosis
- **Today**
  - Low Dose CT scans
  - Long term follow up
  - Wide Excision
- **In AMIGO**
  - Entire procedure done in operating room
  - More accurate placement of T-bar for localization
  - Smaller wedge faster recovery
- **Clinical Impact**
  - Faster, more accurate, less invasive treatment

### Prostate Tumor Biopsies
- **Today**
  - Ultrasound-guided needle collects random samples from the gland
- **In AMIGO**
  - mpMR defines presence of suspicious targets
- **Clinical Impact**
  - Better detection of clinically significant cancer

---

**Bottom line motivator:**
Extra-ordinary rewards and benefits for our patients
On to the future!

- Healthcare challenges 2016 and beyond…
- Patient centric: information/preferences
- IT needs, machine & Deep learning

Strong long lasting infrastructure

Future directions
- Now: More Non-invasive IGT
- Tomorrow
- Nano technology
  - implantable. wearables
For More Information

National Center for Image Guided Therapy
- http://www.ncigt.org

Surgical Planning Laboratory
- http://www.spl.harvard.edu
- http://www.slicer.org

National Alliance for Medical Image Computing
- http://www.na-mic.org
New Collaborators!
Shogun and Obi