New Research Horizons: Challenges and Opportunities

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What is "hot" in medicine (oncology)?

NCI Provocative Questions

- How do cancer-specific **subcellular pathognomonic structures** develop, what is their function, and can they be a source of novel therapeutic targets?
- What are the predictive biomarkers for the **onset of immune-related adverse events** associated with check-point inhibition, and are they related to markers for efficacy?
- Can we develop bifunctional small molecules that will couple **oncoproteins or other cancer causing molecules** of interest to inactivating processes such as degradation and achieve tissue-specific loss of function?
- How do **microbiota** affect response to cancer therapies?
- Through what mechanisms do **diet and nutritional interventions** affect the response to cancer treatment
- What are the molecular and/or cellular mechanisms that underlie the development of **cancer therapy-induced severe adverse sequelae**?

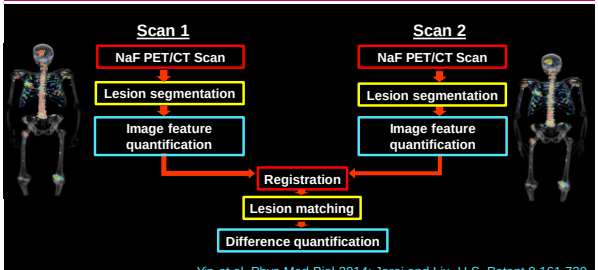
NCI Provocative Questions

- What molecular mechanism influence **disease penetrance** in individuals who inherit a cancer susceptibility gene?
- How do **variations in immune function** caused by comorbidities or observed among different populations affect response to cancer therapy?
- Do genetic **interactions between germline variations and somatic mutations** contribute to differences in tumor evolution or response to therapy?
- Can we develop tools to directly **change the expression or function of multiple chosen genes** simultaneously and use these tools to study range of changes important for human cancer?
- How can **mitochondrial heterogeneity** influence tumorigenesis or progression
- How do **circadian processes** affect tumor development, progression, and response to therapy?

Where is medical physics?

Shore et al 2012, Br J Urol Intl, 6: 22

Quantitative Total Bone Imaging (QTBI)



Yip et al, Phys Med Biol 2014; Jeraj and Liu, U.S. Patent 9,161,720

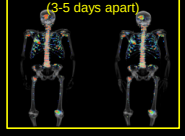
Quantitative Total Bone Imaging (QTBI)

Repeatability of NaF PET/CT

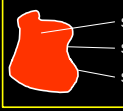
- Multicenter trial of metastatic castrate-resistant prostate cancer patients
  - received pre-treatment test-retest ^{18}F-NaF PET/CT scans

Site	Patients	Bone lesions
University of Wisconsin Carbone Cancer Center	18	265
Memorial Sloan Kettering Cancer Center	11	78
National Cancer Institute	6	68
All	35	411

Test/retest scans (3-5 days apart)



Standardized Uptake Value (SUV) metrics extracted from an ROI



SUV_{max} – maximum uptake

SUV_{mean} – average uptake

SUV_{total} – total uptake

What is our quantitative accuracy?

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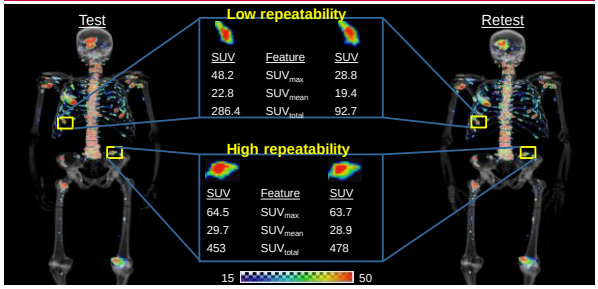


Limits of agreement define response

Test-retest limits of agreement (LOA) can be used to d… nificant changes in imaging features in individ…

Limits of agreement:

$$LOA_{95\%} = (e^{(B-RC)}, e^{(B+RC)})$$

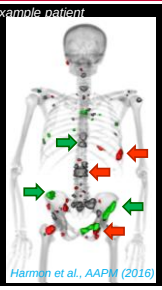
$$B = \frac{m_2}{m_1}$$

$RC = 1.$…

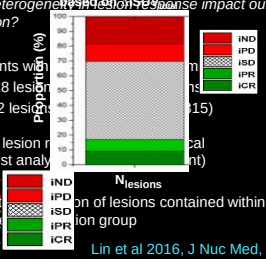
We can use our metrology skills!

Lin et al 2016, J Nuc Med, 57: 1872

Local disease heterogeneity



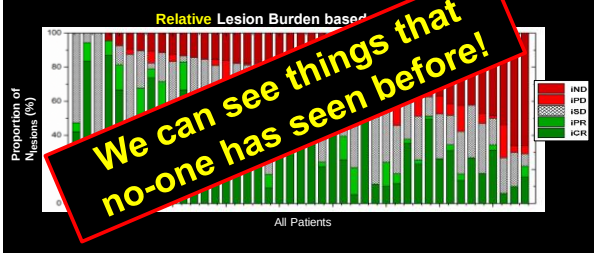
- *Does heterogeneity in lesion response impact our prediction?*
- 43 patients with …m
  - 3228 lesi…
  - 75.2 lesi… 315)
- Classify lesion r… cal test-retest analy… nt)
- Record t… on of lesions contained within each respons… ion group



Lin et al 2016, J Nuc Med, 57: 1872

Local disease heterogeneity

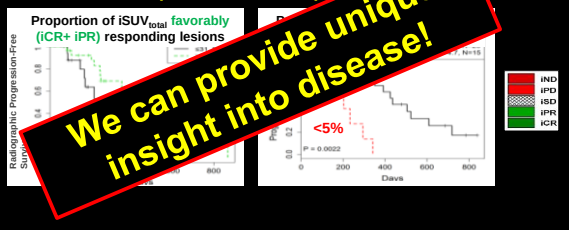
- 40/43 patients exhibit response heterogeneity rega… f burden



We can see things that no-one has seen before!

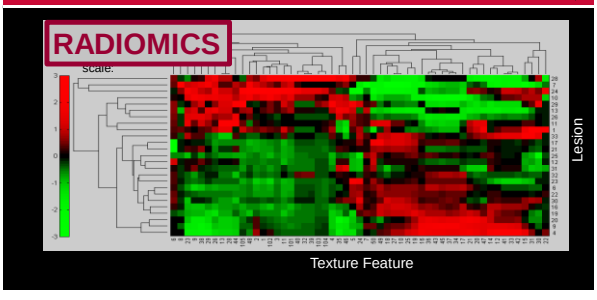
Local disease heterogeneity

- 40/43 patients exhibit response heterogeneity rega… f burden
- Non-favorable response dominates pro…



We can provide unique insight into disease!

From a single scan – LOTS of data!



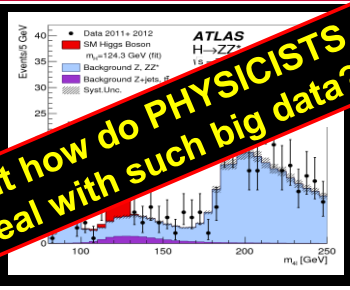
Data is the future…

We are getting to know how to deal with big data!

…herepeutics - 10% in 5 years

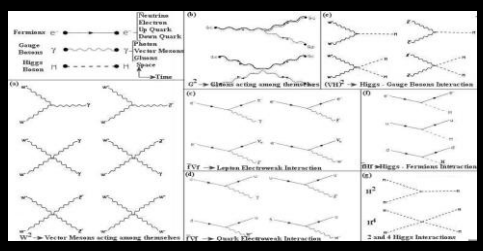
Informatics +150% in 5 years

Lots of data – we've seen it before…

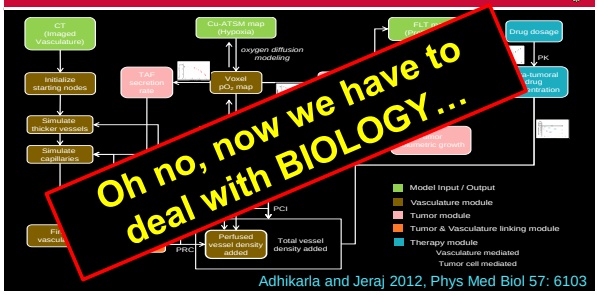


But how do PHYSICISTS deal with such big data?

Physicists want to understand!



What about medical physicists?



Adhikarla and Jeraj 2012, Phys Med Biol 57: 6103

But that is much harder…

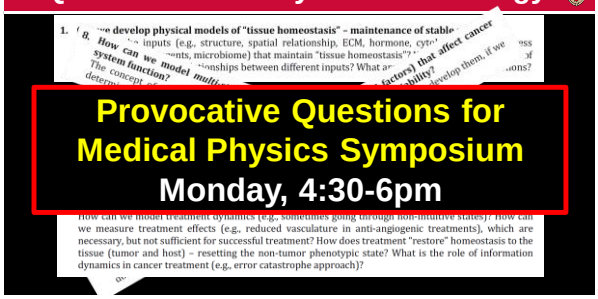
Biology enters the stage…
- Biological complexity by far exceeds physical complexity!
- "Bottom-Up" vs "Top-down" approach
- How and what can we approximate?
- We are not biologists…
- (how much of the biological language do we speak)?

It requires re-thinking **what medical physics is…**
- Should we expand beyond physics? How?
- Should we partner? How?

PQ for Med Phys (in Oncology)

- **Science Council/WG FUTURE initiative**
- **Goal:** to define highest-level problems in oncology that medical physics should attack
- Two-day meeting on Oct 31/Nov 1 2016 in Boston
- Modelled after **NCI's Provocative Questions**
- Very diverse panel
- Additional input from AAPM membership at large

PQs for Medical Physics in Oncology



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  - Tyler Bradshaw
  - Chris Jaskowiak
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- **Medical Physics**
  - Ed Jackson
- **UWCCC TIR, CTD2, DOTs**
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