

**2007
IOM NAS
National Cancer Policy Forum:
Cancer Clinical Trials Workshop**

Imaging Breakout Session Summary

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1) Separating imaging needs and requirements:

- Pre-clinical trials

- Phase I trials

- Phase II and III trials

 - Patient selection and treatment follow-up with quantitative biomarkers

- Clinical practice

 - Imaging as a biomarker to optimize patient selection

2) NCI-designated Cancer Centers should require clinical imaging core facilities

3) Request that FDA establish a pathway for qualification of imaging biomarkers

- Most urgent radiotracers

4) Validate methodology of a new technique before its use in clinical trials

5) Image-guided biopsies

- Standardization for genomic and proteomic correlation studies

6) Establish complementary nature of serum/urine/tumor biomarkers and

- imaging biomarkers

7) Change culture of imaging community and develop reward-based incentives

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The current utility of imaging is largely in Pre-clinical and Phase I studies, not Phase II or III

- However, imaging for pre-selection and patient population enrichment into phase II and III trials has the potential to improve trial outcomes

Reasons for conducting imaging in early trial design:

Determine if drug is hitting target (PD)

Confirm mechanism of action

Evaluate clinical response

Labeled drug for PK analysis

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Diagnostic Imaging Versus Imaging Therapeutic Response

-Diagnostic imaging

- Single target; quantification required

- May be too expensive to develop relative to market

- Targeted specificity equals small markets (disincentive)

-Imaging markers of therapeutic response

- Predictive/entry criteria versus monitoring response

- Monitoring response: relative change is relevant

 - Easier to implement

- Generalizable response targets

 - (e.g., apoptosis, DCE-MRI, FDG-PET, FLT PET)

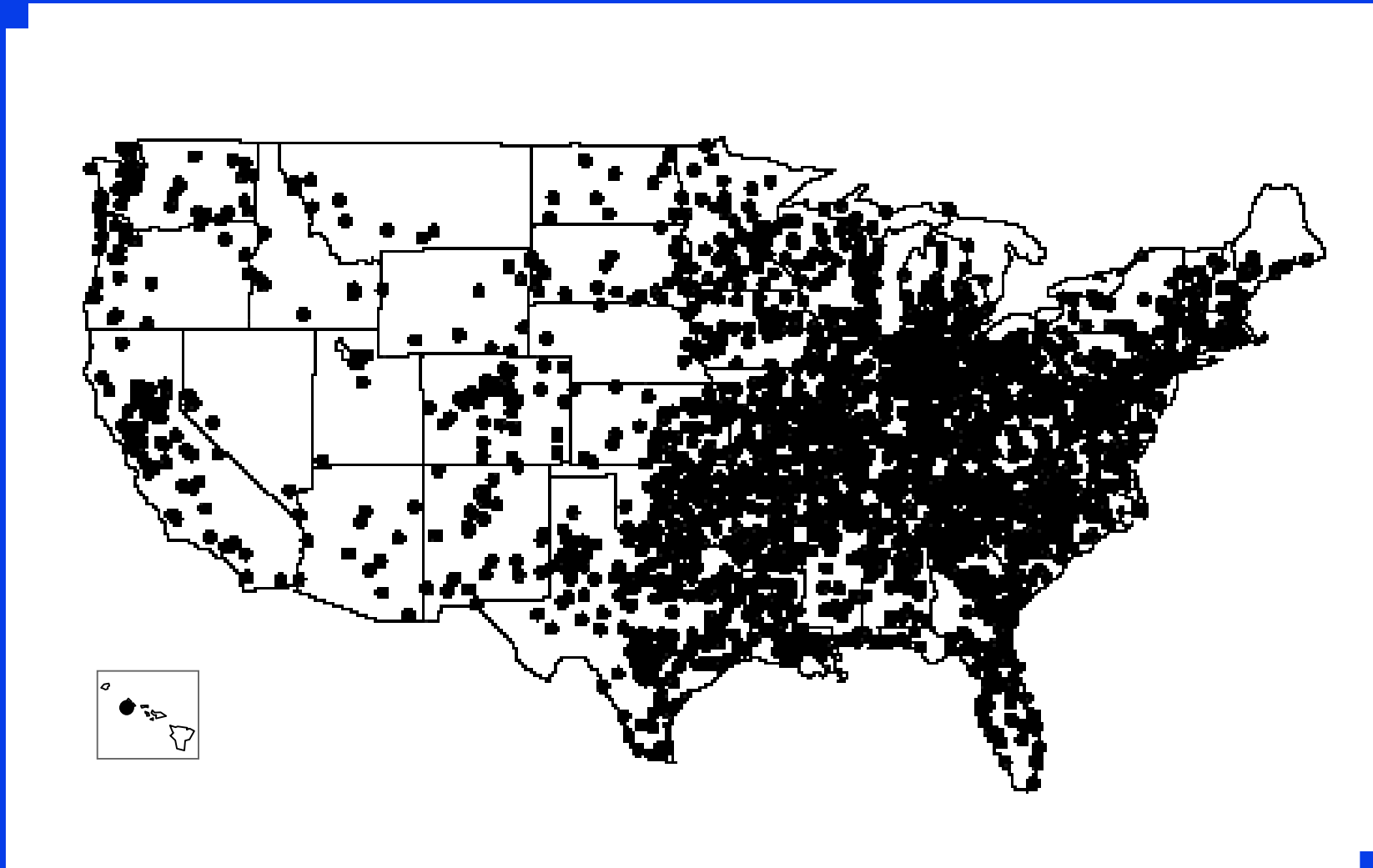
- Downstream mechanism-based probes that cross many cancer types

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Imaging has and continues to have a growing impact on drug development

- Pfizer has used PET measures of receptor occupancy to stop clinical programs
- Used PET (FDG & FLT) and DCE-MRI measures to confirm mechanism of action in novel therapeutics
 - Contributed to go/no go decisions regarding further development
- Most tangible measures are cost savings
- Imaging biomarkers provided Amgen critical information
 - FDG-PET data demonstrated metabolic effect even in absence of traditional clinical response

Clinical PET Centers in the USA in 2007



Courtesy M. Phelps

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Imaging saves drug development costs by helping to kill compounds early in development

- Failures are expected: kill them early, kill them fast

- Avoid phase II/III, or repeat phase II failures

Opportunity cost

- For positive imaging signals, may get to registration sooner (confidence increased)

- Shortening drug development timeline (months = \$M)

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NCI-designated Cancer Centers should have imaging core and image analysis core laboratories for clinical trials

- Standardization, harmonization, training
- Cores useful in the conduct of Phase I trials and will save money down the road by improved quality of data.
- Need for more research protocol assistants who assure protocol logistics/execution
- Image Response Assessment Team (IRAT)

For oncology trials, patient access is key and imaging technology has to be realistic for multi-site trials

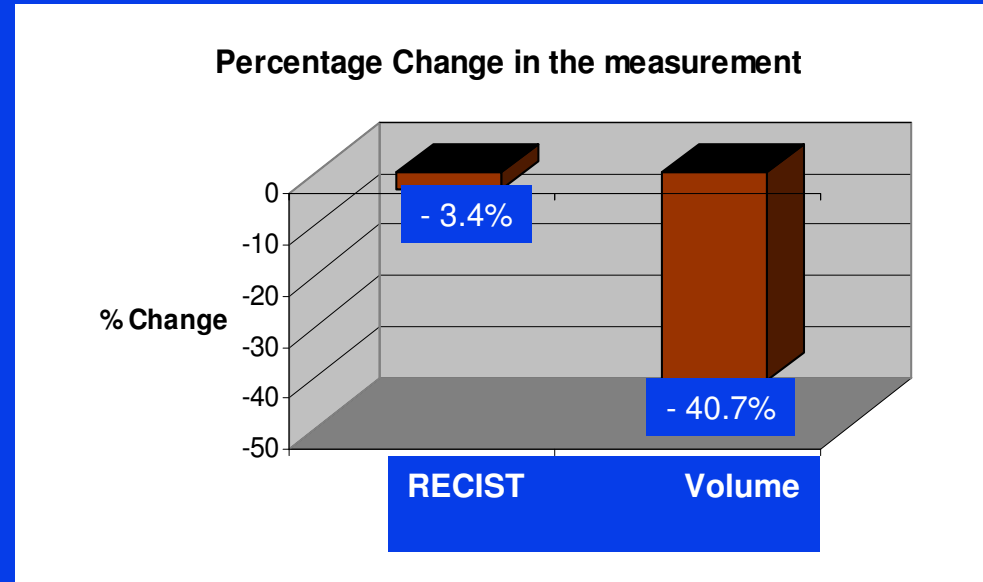
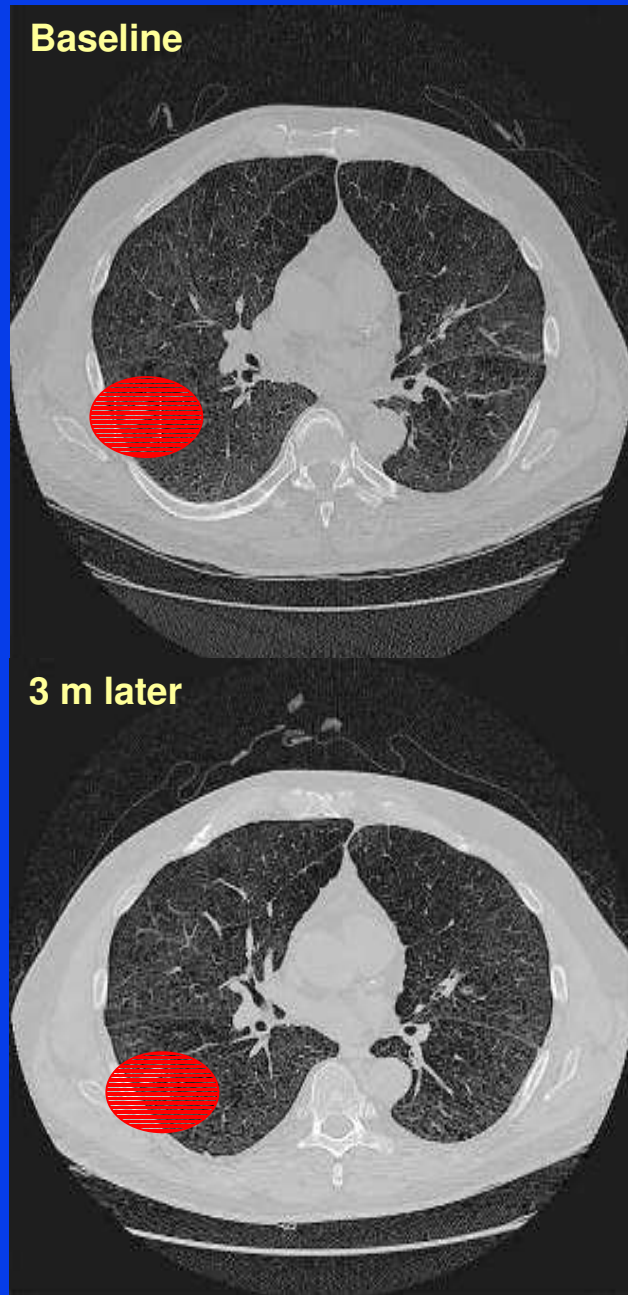
- Central reading is the only efficient path forward

Engaging intellectual involvement of academic imagers (radiologists) at starting point of trial design process will produce better trial results

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- When selecting imaging biomarkers, one needs to precisely define the question that you want the biomarker to answer
- Identified need for use of control positives and control negatives in imaging agent/protocol design
 - Qualifying biomarkers
- RECIST versus CT volume to monitor response

Monitoring Treatment Response: *RECIST* vs. *Volumetrics*



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Request that FDA establish a pathway for qualification of imaging biomarkers

- As with FDG-PET, enable mechanism-based utility for imaging agents
- Tracers as research tools

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Image-guided biopsies

Standardization for genomic and proteomic correlation studies

Establish complementary nature of serum/urine/tumor biomarkers and imaging biomarkers

Change culture of imaging community toward research

Develop reward-based practice environment to engage in clinical research

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Caveats:

- Note that neither hitting the target nor impacting the expected mechanism of action imply clinical benefit.
- It is necessary to recognize the regulatory and financial barriers involved with imaging biomarkers
- Threats to U.S. trials infrastructure (big pharma are global enterprises):
 - Moving imaging trials overseas
 - Competition for patients to enroll on protocol
 - Regulatory barriers impede use of imaging