Image analysis and Informatics

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WMIC, Sept. 5, 2012

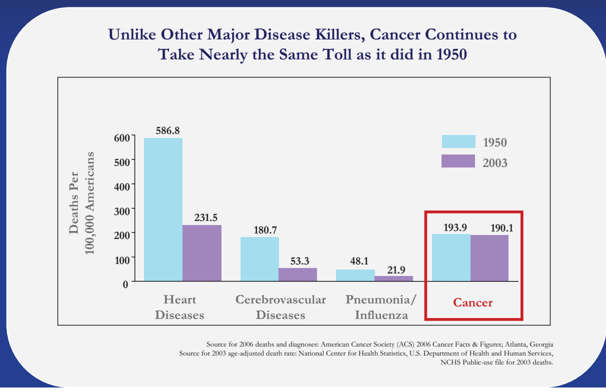
Objectives

- Describe the motivation underlying analyses of tumor heterogeneity
- Describe the role of Image 'omics in Oncology
- List the different levels of biomarker qualification

The bad news

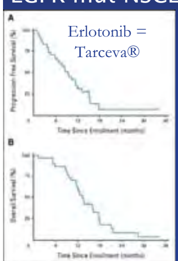
Despite advances in cancer genetics,
We are not "curing" cancer

Cancer is not being "cured"



Even when we know target and have a great drug, benefit is measured in months

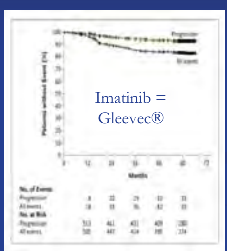
EGFR mut NSCLC



CR/PR=55%
SD =39%
PD = 6%
PFS = 9.2 mo

Sequist, L. V. et al. J Clin Oncol; 26:2442-2449 2008

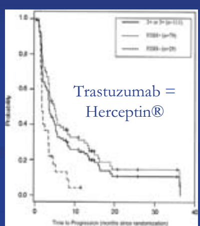
BCR- ABL CML



Cytogenetic CR =87%

Druker, B. et al. NEJM; 2006 Dec 7;355(23):2408-17

HER2 Pos BRCA

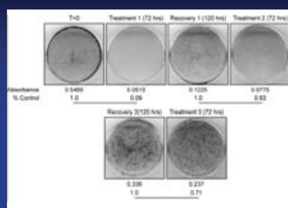


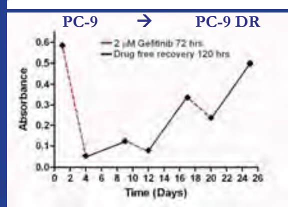
Clinical Benefit = 38%
3+ IHC = 48%
2+ IHC = 7%
FISH + = 48%
FISH - = 10%

Vogel, C. L. et al. J Clin Oncol; 20:719-726 2002

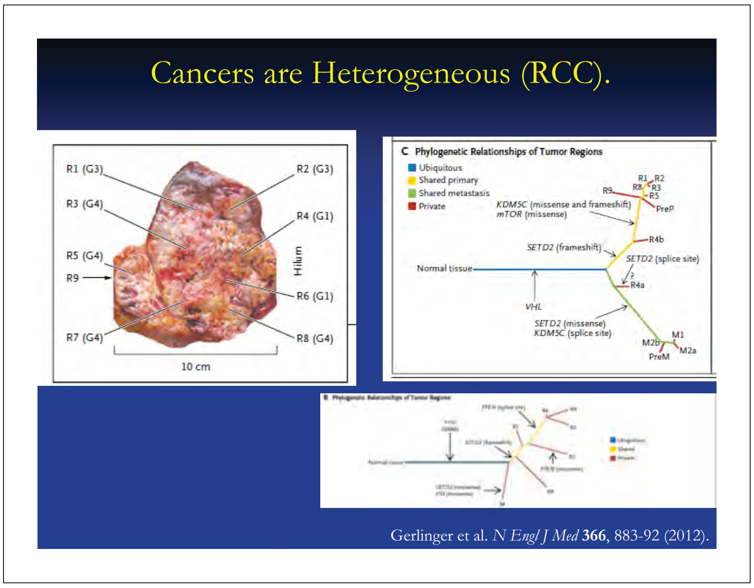
One of the problems…

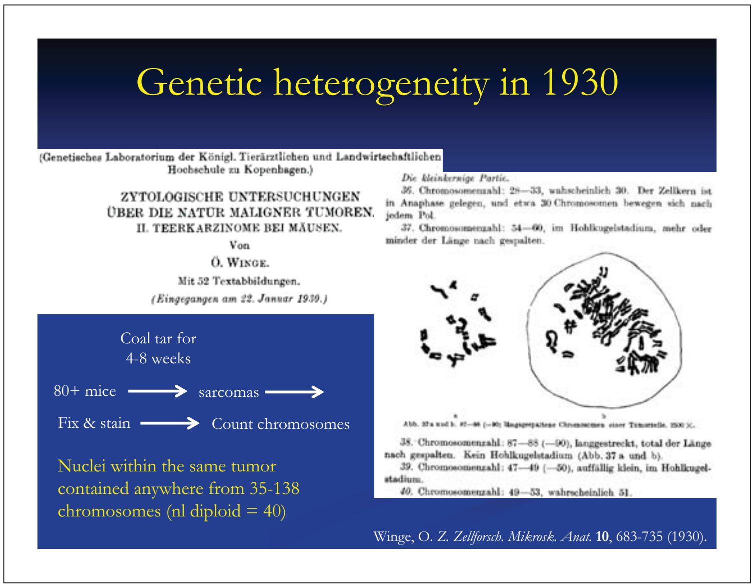
- Erlotinib: the $12 BB drug
- Treats 7-10% NSCLC (those with activating EGFR mutation)
- Over 12 known resistance mechanisms
- Resistance mechanisms can be pre-existing or can result from adaptive responses

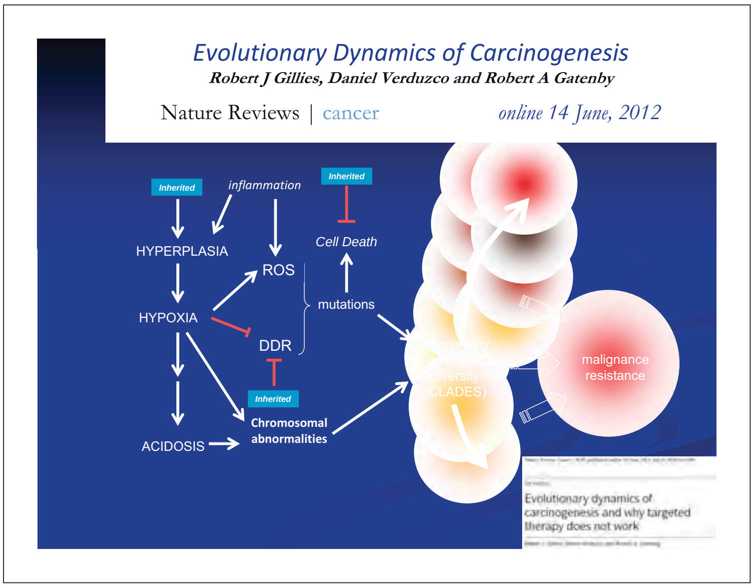


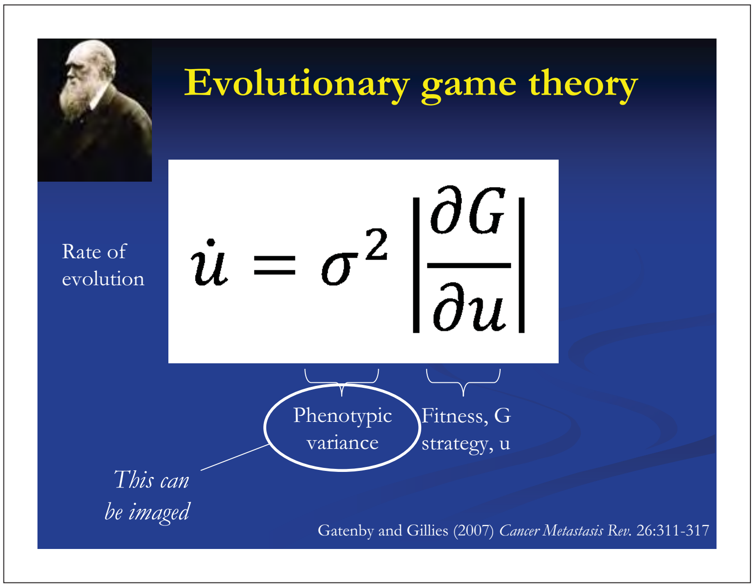


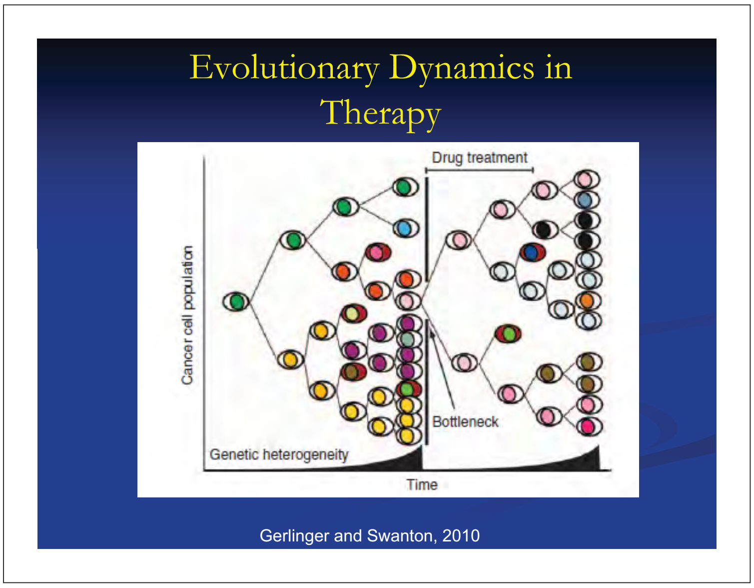
Jonathan Wojtkowiak

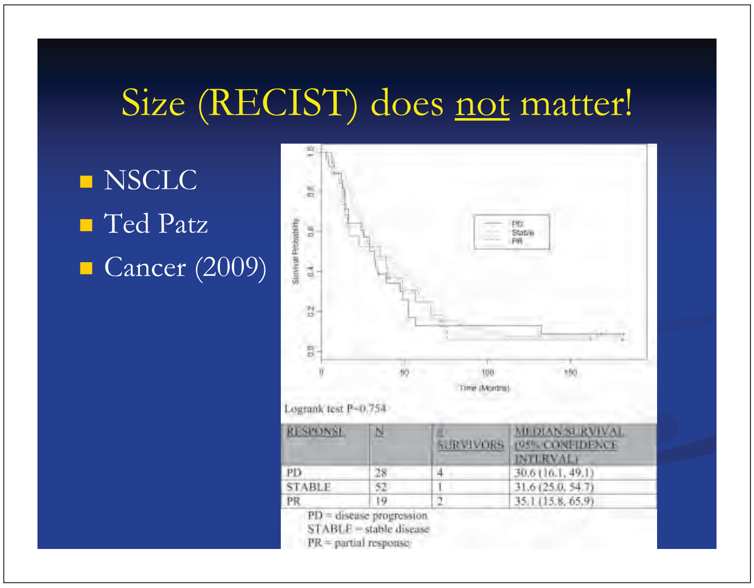

Cancers are Heterogeneous (RCC).
R1 (G3)
R2 (G3)
R3 (G4)
R4 (G1)
R5 (G4)
R9
Hilum
R6 (G1)
R7 (G4)
R8 (G4)
10 cm
C Phylogenetic Relationships of Tumor Regions
Ubiquitous
Shared primary
Shared metastasis
Private
KDM5C (missense and frameshift)
mTOR (missense)
SETD2 (frameshift)
SETD2 (splice site)
Normal tissue
VHL
SETD2 (missense)
KDM5C (splice site)
PreP
PreM
Gerlinger et al. N Engl J Med 366, 883-92 (2012).


Genetic heterogeneity in 1930
(Genetisches Laboratorium der Königl. Tierärztlichen und Landwirtschaftlichen Hochschule zu Kopenhagen.)
ZYTOLOGISCHE UNTERSUCHUNGEN ÜBER DIE NATUR MALIGNER TUMOREN.
II. TEERKARZINOME BEI MÄUSEN.
Von
Ö. Winge.
Mit 52 Textabbildungen.
(Eingegangen am 22. Januar 1930.)
Coal tar for
4-8 weeks
80+ mice
sarcomas
Fix & stain
Count chromosomes
Nuclei within the same tumor contained anywhere from 35-138 chromosomes (nl diploid = 40)
Winge, O. Z. Zellforsch. Mikrosk. Anat. 10, 683-735 (1930).


Evolutionary Dynamics of Carcinogenesis
Robert J Gillies, Daniel Verduzco and Robert A Gatenby
Nature Reviews | cancer
online 14 June, 2012
Inherited
inflammation
Inherited
HYPERPLASIA
Cell Death
ROS
HYPOXIA
mutations
DDR
Inherited
Chromosomal abnormalities
ACIDOSIS
malignance
resistance
Evolutionary dynamics of carcinogenesis and why targeted therapy does not work


Evolutionary game theory
Rate of evolution
$$\dot{u} = \sigma^2 \left|\frac{\partial G}{\partial u}\right|$$
Phenotypic variance
Fitness, G
strategy, u
This can be imaged
Gatenby and Gillies (2007) Cancer Metastasis Rev. 26:311-317


Evolutionary Dynamics in Therapy
Drug treatment
Cancer cell population
Bottleneck
Genetic heterogeneity
Time
Gerlinger and Swanton, 2010


Size (RECIST) does not matter!
NSCLC
Ted Patz
Cancer (2009)
PD
Stable
PR
Time (Months)
Logrank test P=0.754
RESPONSE | N | # SURVIVORS | MEDIAN SURVIVAL (95% CONFIDENCE INTERVAL)
PD | 28 | 4 | 30.6 (16.1, 49.1)
STABLE | 52 | 1 | 31.6 (25.0, 54.7)
PR | 19 | 2 | 35.1 (15.8, 65.9)
PD = disease progression
STABLE = stable disease
PR = partial response

Size (RECIST) does not matter!

Relation between tumour response to first-line chemotherapy and survival in advanced colorectal cancer: a meta-analysis

THE LANCET

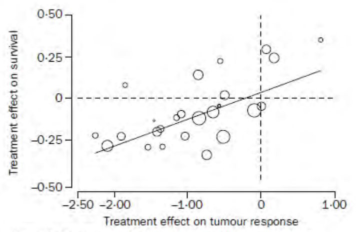
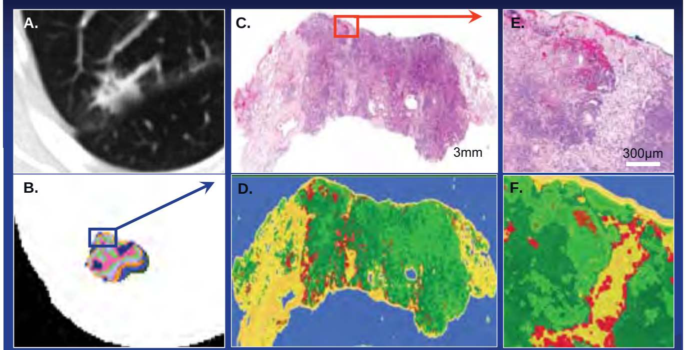


Figure 4: **Treatment effects on survival versus treatment effects on tumour response**
Each circle represents a trial, the area of which is proportional to the number of observations in the trial.

How can Molecular Imaging inform oncology decision making?

- (Quantification of Heterogeneity, σ)
- (Large Databases)

Lung tumor heterogeneity

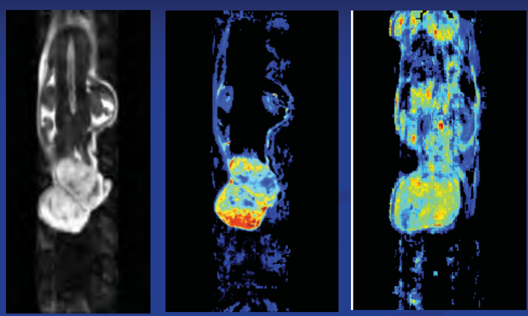


A) Lethal lung cancer CT with an; B) iso-attenuation map demonstrating regional heterogeneity at the tissue scale (cm). C) Whole slide digital imaging (3x) of a histology section of the same tumor at the mesoscopic scale (mm) coupled with; D) a masked image of regional morphological differences demonstrating spatial heterogeneity. E) 50x magnification sub segment of the whole slide image depicting the microscopic scale (µm) and; F) a pattern recognition masked image showing regional heterogeneity.

Opportunity 1: Image Analysis

Quantitatively Characterize Phenotypic Heterogeneity, σ, using advanced analyses of tumor "textures"

Multiparametric MRI – Hs766t PanCan



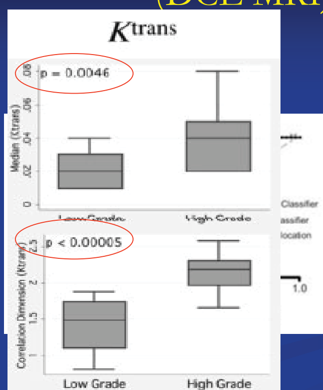
T2W (coronal) DCE - MRI K^{trans} ADCw

Xiaomeng Zhang (in preparation)

Tumor Perfusion Heterogeneity (DCE MRI)

Median →

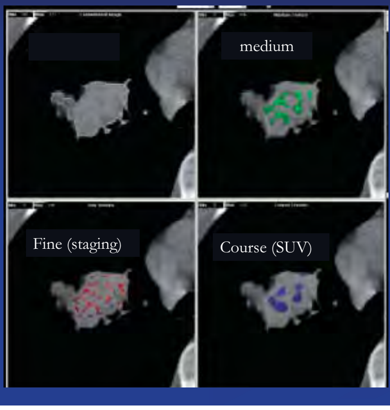
Texture →



Glioma
Rose et al., MRM 62, 2010
(Alan Jackson)

Lymphoma
Canuto et al., MRM 61, 2009
(Kevin Brindle)

Texture in NSCLC



Coarse texture features correlated with **SUV** of FDG uptake (p<0.03).

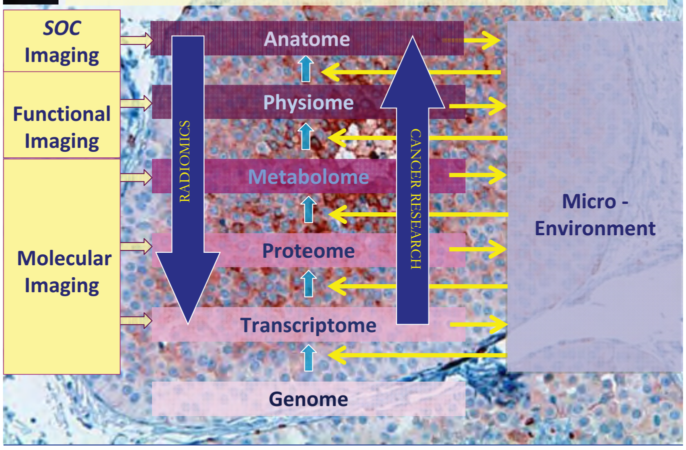
Fine texture features predicted tumour **stage** with 100% sensitivity and 87.5% specificity.

Ganeshan et al., Cancer Imaging (2010) 10,137

Can Imaging Features predict gene expression (and therapy response)?

Convert Images to mineable data in high throughput (radiomics)

Rationale for Radiomics



Radiomics

Segal et al. (2007). Nat Biotechnol **25**(6): 675-80

nature biotechnology

Decoding global gene expression programs in liver cancer by noninvasive imaging

Eran Segal[1], Claude B Sirlin[2], Clara Ooi[4], Adam S Adler[3], Jeremy Gollub[6], Xin Chen[8], Bryan K Chan[2], George R Matcuk[7], Christopher T Barry[3], Howard Y Chang[3] & Michael D Kuo[1]

CT

N = 30 (training) + 32 (test)

Radiomics

Identification of noninvasive imaging surrogates for brain tumor gene-expression modules

Maximilian Diehn*[†], Christine Nardini*, David S. Wang*, Susan McGovern[‡], Mahesh Jayaraman[§], Yu Liang[¶], Kenneth Aldape[‡], Soonmee Cha[||], and Michael D. Kuo*,**[††]

*Department of Radiology and **Center for Translational Medical Systems, University of California San Diego Medical Center, San Diego, CA 92103; [†]Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA 94305; [‡]Department of Neuropathology, University of Texas M. D. Anderson Cancer Center, Houston, TX 77030; [§]Department of Radiology, Brown University, Providence, RI 02912; [¶]Department of Neurological Surgery, Brain Tumor Research Center, University of California San Francisco Medical Center, San Francisco, CA 94143; and [||]Department of Radiology, University of California San Francisco Medical Center, San Francisco, CA 94143

Communicated by Helen M. Ranney, University of California at San Diego, La Jolla, CA, February 9, 2008 (received for review October 16, 2007)

MRI

N = 22 (training) + 110 (test)

Radiomics

AACR

Cancer Research

Prognostic PET 18F-FDG uptake imaging features are associated with major oncogenomic alterations in patients with resected non-small cell lung cancer

Viswam S. Nair, Olivier Gevaert, Guido Davidzon, et al.

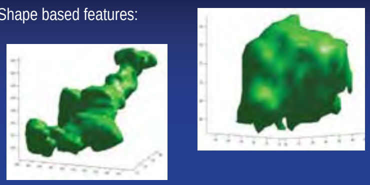
Cancer Res Published OnlineFirst June 19, 2012.

PET

N = 25 (training) + 63 (test)

Shape and Texture CT Features

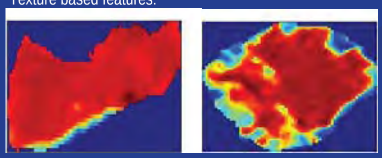
Shape based features:



Sphericity: $\Psi = \frac{\pi^{\frac{1}{3}}(6V)^{\frac{2}{3}}}{A}$

Compactness: $Comp = \frac{V}{\sqrt{\pi}A^{\frac{2}{3}}}$

Texture based features:



Skewness: $Skew = \frac{1}{XY}\sum_{x=1}^{X}\sum_{y=1}^{Y}\left[\frac{I(x,y)-\mu}{\sigma}\right]^3$

Kurtosis: $Kur = \frac{1}{XY}\sum_{x=1}^{X}\sum_{y=1}^{Y}\left\{\left[\frac{I(x,y)-\mu}{\sigma}\right]^4\right\}-3$

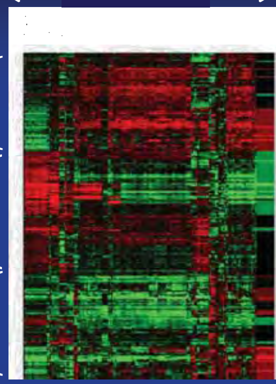
Entropy: $H = -\sum_{i=1}^{XY} P(i)\cdot \log_2 P(i)$

In our analyses, we have 211 3-D and 114 2-D texture and shape features

CT Image Texture Features of NSCLC

Unsupervised Hierarchical Clustering

← 211 texture features →



276 NSCLC patients

Recurrence 22%;
of those who recur, the
median survival (months) = 10

Recurrence 44%
of those who recur, the
median survival (months) = 17

Recurrence 30%
of those who recur, the
median survival (months) = = 15

Kumar et al., (in preparation)

Radiomics:
workflow & challenges

"Convert Images to mineable data"

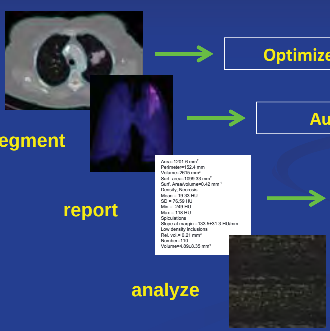


image → **Optimize acquisition & recon**

segment → **Automate & Validate**

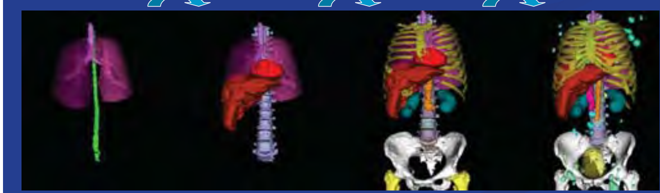
report → **Qualify Features**

analyze → **Databases**

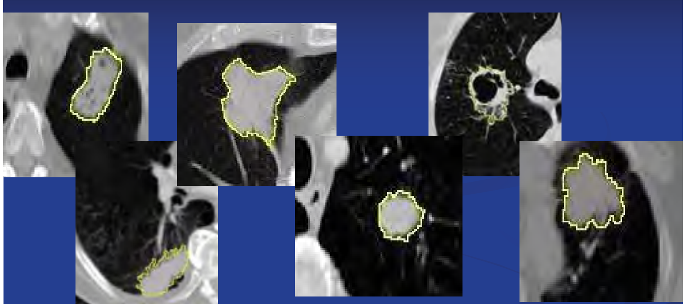
Kumar et al., MRI (in press) 2012

Context-dependent Automated Segmentation and Classification of organ systems

use context
use context
use context



Auto-segmentation of NSCLC



- *"Segmentation Challenge"*

Feature Selection

Qualify Features

Total # of 2D and 3D features is 324

report

Table 1: List of Customized Features

Feature name	2D	2D (No. of features)	3D	3D (No. of features)
Margin gradient	✓	2	x	X
Fractal dimension	✓	1	x	x
Fourier descriptor	✓	1	x	x
Co-occurrence matrix	✓	5	✓	6
Run-length analysis	✓	22	✓	11
Laws features	✓	25	✓	125
Wavelet decomposition	✓	30	✓	30
Fourier analysis	✓	5	x	4
Histogram features	✓	6	✓	6
Total # of customized features		97		178

(✓): Available (x): Not Available

Reducing Dimensionality

- 324 features are too many. Increased probability of over-fitting data
- Useful features can be identified by sequentially determining:
  - Their reproducibility in test-retest
  - Their uniqueness from correlation matrixes
  - Their dynamic range
- Goal is to reduce 324 features to ~40 that may be more useful.
- We have recently done this to identify 39 features that are non-redundant, robust and have high D.R. (*submitted*)

Clinical Imaging biomarkers

- PAST: anatomy (RECIST)
- PRESENT: DCE-MRI, FdG-PET, volumes.
- FUTURE:
  - Functional imaging endpoints:
    - Doppler US -Diffusion MRI
    - Magn Trans MRI -Macromolecule contrast (CT, MR)
  - Molecular imaging endpoints:
    - Receptor PET -Metabolic PET (FDG, FLT, cho)
    - Targeted nparticles -Magn. Reson. Spectroscopy
    - pH imaging -Hypoxia (PET, BOLD MRI)
    - CEST MRI -hyperpolarized (e.g.^{13}C pyruvate)

Biomarkers

- **Biomarkers** are characteristics that are **objectively and quantitatively measured** and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
- In therapeutic applications:
  - Prognostic biomarkers predict response regardless of therapy
  - Predictive biomarkers predict response to specific therapies
  - Response biomarkers measure change in response to therapy and may be related to clinical outcome
- Biomarkers are not surrogates! Surrogate markers can substitute for clinical endpoint.

(clinical) Uses of Cancer Biomarkers*

- Prognosis – predict the probable outcome regardless of therapy
- Prediction – predict response to particular therapies
- Therapy monitoring – determine if therapy is having intended effect
- Screening – Detect and treat early-stage cancers in asymptomatic populations
- Risk stratification – assess likelihood that cancer will occur or recur
- Diagnosis – Definitively establish presence of cancer
- Classification – classify by disease subset
- Risk management – identify probability of adverse effects
- Surveillance – detect and treat recurrent disease

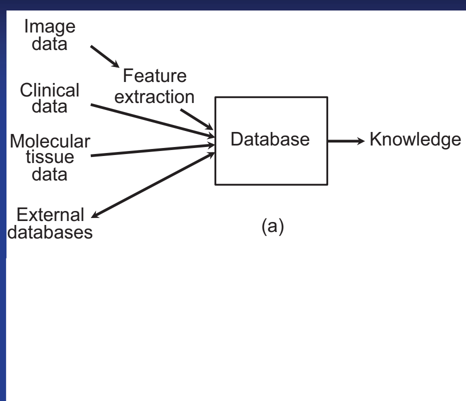
*Cancer Biomarkers, IOM, 2007

What does it take to be a 'biomarker'?

One biomarker validated for >1,000 literature mentions of the word "biomarker". To validate and qualify, 5 levels must be met.

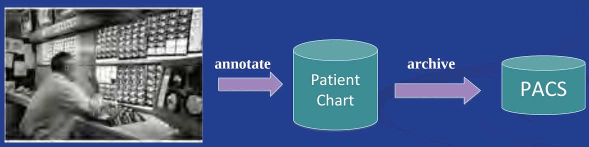
- Correlative observation in cells or animals
- Retrospective analysis with human samples
- Inter-lab cross validation
- Prospective Study
- Multi-center Prospective Study

Linking and Mining Image, Medical and Genomic Data

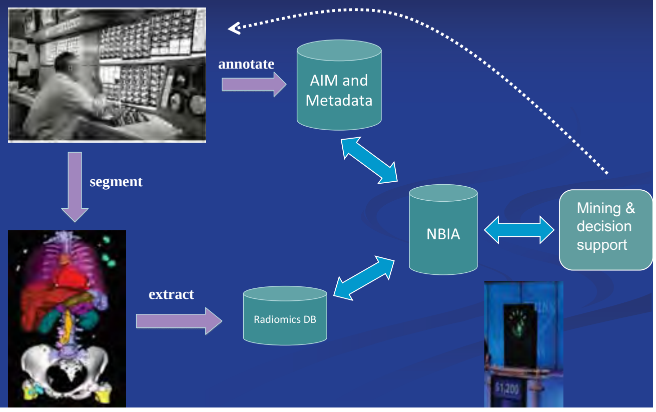


Courtesy Daniel Rubin, Stanford

Current Radiology



Reading rooms of the future



Conclusions

- Cancer Research is in a state of crisis at the moment because *targeted therapies are not curing cancer.*
- A major factor in the ineffectiveness of targeted therapy is *emergence of resistance*
- This is predictable with Evolutionary Game Theory, give tumor heterogeneity
- Imaging is the best-equipped techology to assess tumor heterogeneity in all patients.
- This requires advanced image analysis
- This requires high-throughput feature extraction
- This requires large data bases from multiple centers.

Objectives

- Describe the motivation underlying analyses of tumor heterogeneity
- Describe the role of Image 'omics in Oncology
- List the different levels of biomarker qualification