

Image analysis and Informatics

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WMIC, Sept. 5, 2012

Objectives

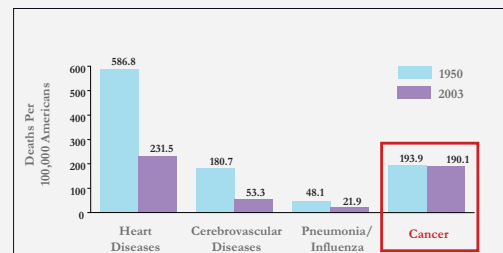
- Describe the motivation underlying analyses of tumor heterogeneity
- Describe the role of Image 'omics in Oncology
- List the different levels of biomarker qualification

The bad news

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

Cancer is not being "cured"

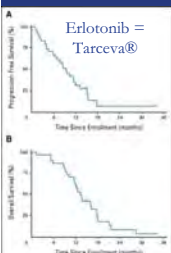
Unlike Other Major Disease Killers, Cancer Continues to
Take Nearly the Same Toll as it did in 1950



Sources for 2006 deaths and diagnoses: American Cancer Society (ACS) 2006 Cancer Facts & Figures, Atlanta, Georgia
Sources for 2003 age-adjusted death rates: National Center for Health Statistics, U.S. Department of Health and Human Services, NCHS Public use file for 2003 deaths.

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

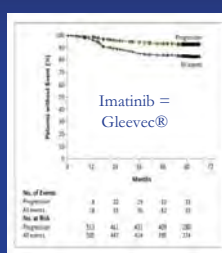
EGFR mut NSCLC



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

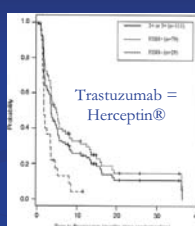


Cytogenetic CR=87%

Druker, B. et al. NEJM; 2006 Dec

7;35(23):2408-17

HER2 Pos BRCA

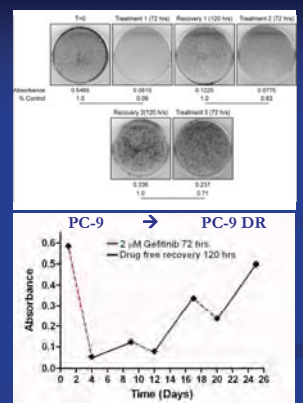


Clinical Benefit = 38%
3+ IHC = 48%
2+ IHC = 7%
FISH + = 48%
FISH - = 10%

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

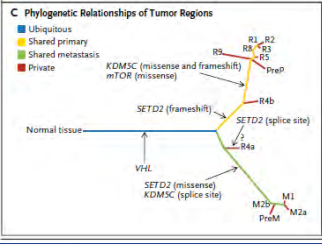
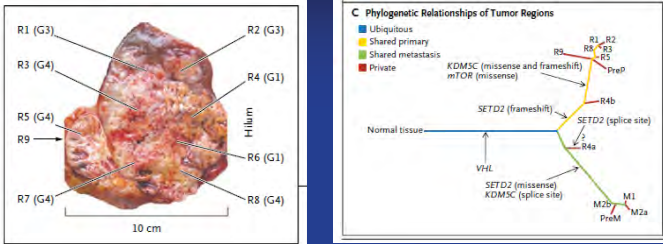
One of the problems...

- 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).



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 1939.)

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)

Die Meisereignisse Paris.
36. Chromosomenzahl: 28-33, wahrscheinlich 30. Der Zellkern ist in Anaphase gelegen, und etwa 20 Chromosomen bewegen sich nach jedem Pol.
37. Chromosomenzahl: 54-60, im Hohlkugelstadium, mehr oder minder der Länge nach gespalten.



Abb. 37a und b. 37-40. Hohlkugelstadium einer Tumorzelle. 38-40. Chromosomenzahl: 37-40, langgestreckt, total der Länge nach gespalten. Kein Hohlkugelstadium (Abb. 37a und b).
39. Chromosomenzahl: 47-49, auffällig klein, im Hohlkugelstadium.
40. Chromosomenzahl: 49-53, wahrscheinlich 51.

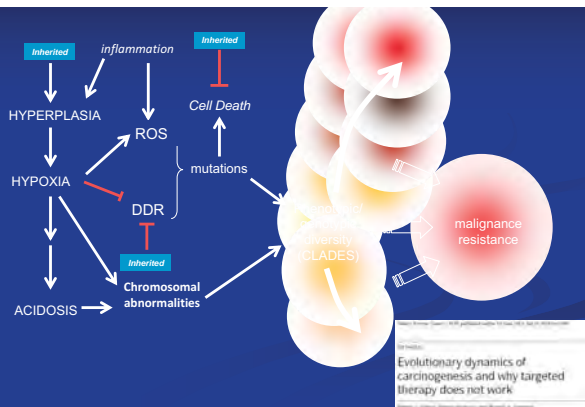
Winge, O. Z. Zellforsch. Mikrosk. Anat. 10, 683-735 (1930).

Evolutionary Dynamics of Carcinogenesis

Robert J. Gillies, Daniel Verduzco and Robert A. Gatenby

Nature Reviews | cancer

online 14 June, 2012



Evolutionary dynamics of carcinogenesis and why targeted therapy does not work

Evolutionary game theory



Rate of evolution

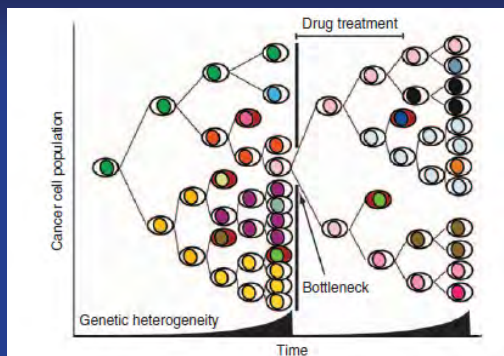
$$\dot{u} = \sigma^2 \left| \frac{\partial G}{\partial u} \right|$$

Phenotypic variance
Fitness, G
strategy, u

This can be imaged

Gatenby and Gillies (2007) *Cancer Metastasis Rev.* 26:311-317

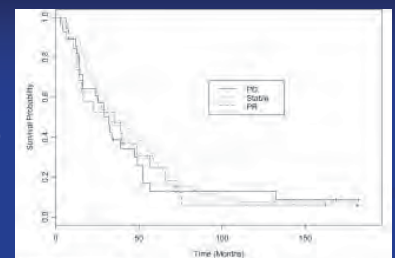
Evolutionary Dynamics in Therapy



Gerlinger and Swanton, 2010

Size (RECIST) does not matter!

- NSCLC
- Ted Patz
- Cancer (2009)



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 (13.8, 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

Metastatic Colorectal Cancer: Impact of Chemotherapy on Survival: A Meta-Analysis of Randomized Controlled Trials in the Adjuvant Setting
The Lancet • 374 • July 26, 2009

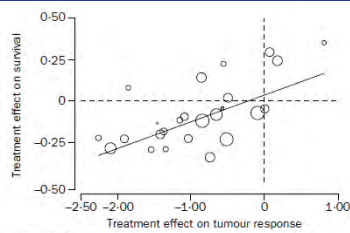
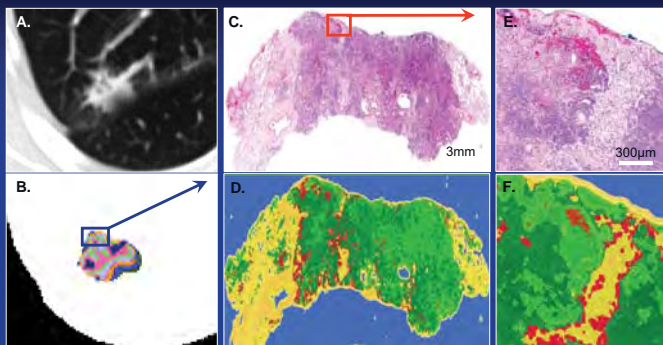


Figure 4: Treatment effects on survival versus treatment effects on tumour response
Each circle represents a trial, the area of which is proportional to the number of observations in the trial.

How can Molecular Imaging inform oncology decision making?

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

Lung tumor heterogeneity

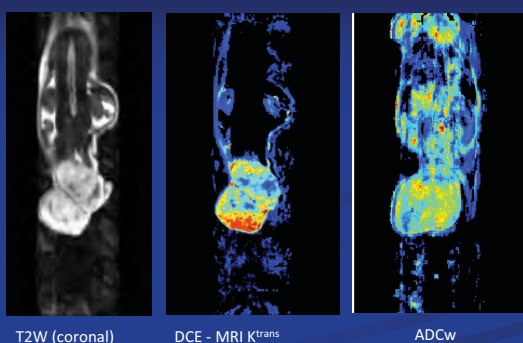


A) Lethal lung cancer CT with an; B) iso-attenuation map demonstrating regional heterogeneity at the tissue scale (cm). C) Whole slide digital imaging (3x) of a histology section of the same tumor at the mesoscopic scale (mm) coupled with; D) a masked image of regional morphological differences demonstrating 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

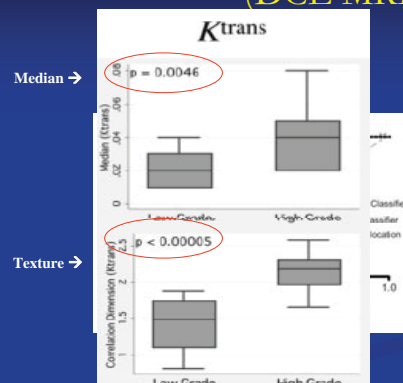
Quantitatively Characterize
Phenotypic Heterogeneity, σ ,
using advanced analyses of tumor
“textures”

Multiparametric MRI – Hs766t PanCan



Xiaomeng Zhang (in preparation)

Tumor Perfusion Heterogeneity (DCE MRI)



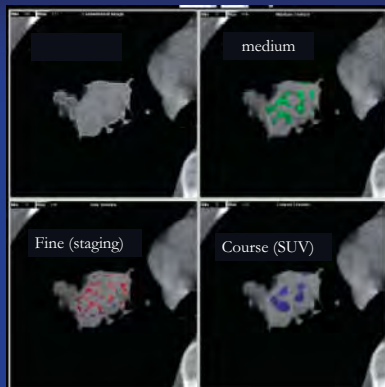
Glioma

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.

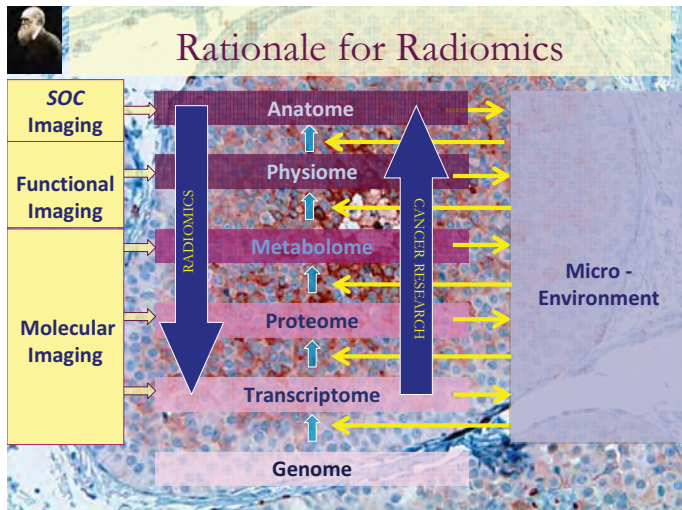
Ganeshan et al., Cancer Imaging (2010) 10,137

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



CT

N = 30 (training) + 32 (test)

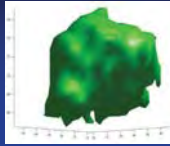
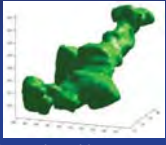
Radiomics

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

Maximilian Diehn^{1,2}, Christine Nardone¹, David S. Wang¹, Susan McGovern¹, Mahesh Jayaraman¹, Yu Liang¹, Kenneth Aldape¹, Soorena Chai¹, and Michael D. Kuo^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000,1001,1002,1003,1004,1005,1006,1007,1008,1009,1010,1011,1012,1013,1014,1015,1016,1017,1018,1019,1020,1021,1022,1023,1024,1025,1026,1027,1028,1029,1030,1031,1032,1033,1034,1035,1036,1037,1038,1039,1040,1041,1042,1043,1044,1045,1046,1047,1048,1049,1050,1051,1052,1053,1054,1055,1056,1057,1058,1059,1060,1061,1062,1063,1064,1065,1066,1067,1068,1069,1070,1071,1072,1073,1074,1075,1076,1077,1078,1079,1080,1081,1082,1083,1084,1085,1086,1087,1088,1089,1090,1091,1092,1093,1094,1095,1096,1097,1098,1099,1100,1101,1102,1103,1104,1105,1106,1107,1108,1109,1110,1111,1112,1113,1114,1115,1116,1117,1118,1119,1120,1121,1122,1123,1124,1125,1126,1127,1128,1129,1130,1131,1132,1133,1134,1135,1136,1137,1138,1139,1140,1141,1142,1143,1144,1145,1146,1147,1148,1149,1150,1151,1152,1153,1154,1155,1156,1157,1158,1159,1160,1161,1162,1163,1164,1165,1166,1167,1168,1169,1170,1171,1172,1173,1174,1175,1176,1177,1178,1179,1180,1181,1182,1183,1184,1185,1186,1187,1188,1189,1190,1191,1192,1193,1194,1195,1196,1197,1198,1199,1200,1201,1202,1203,1204,1205,1206,1207,1208,1209,1210,1211,1212,1213,1214,1215,1216,1217,1218,1219,1220,12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Shape and Texture CT Features

Shape based features:



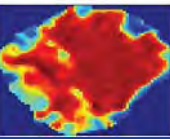
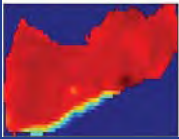
Sphericity:

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

Compactness:

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

Texture based features:



Skewness:

$$Skew = \frac{1}{N^{\frac{1}{2}} \sigma^3} \sum_{i=1}^N \sum_{j=1}^N \left[\frac{f(x, y) - \mu}{\sigma} \right]^3$$

Kurtosis:

$$Kurt = \frac{1}{N^{\frac{1}{2}} \sigma^4} \sum_{i=1}^N \sum_{j=1}^N \left[\frac{f(x, y) - \mu}{\sigma} \right]^4 - 3$$

Entropy:

$$H = - \sum_{i=1}^N \sum_{j=1}^N P(i) \log_2 P(i)$$

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

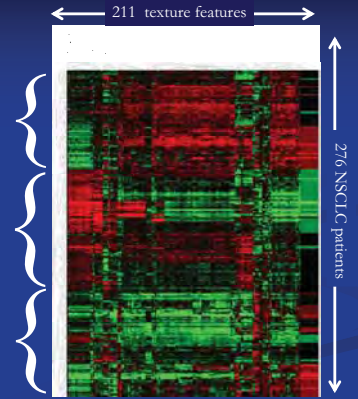
CT Image Texture Features of NSCLC

Unsupervised Hierarchical Clustering

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

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

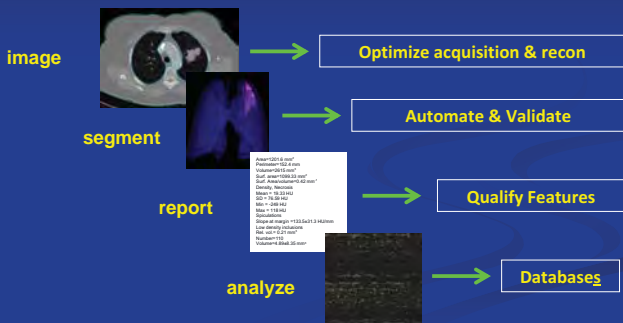
Recurrence 30%
of those who recur, the
median survival (months) = 15



Kumar et al., (in preparation)

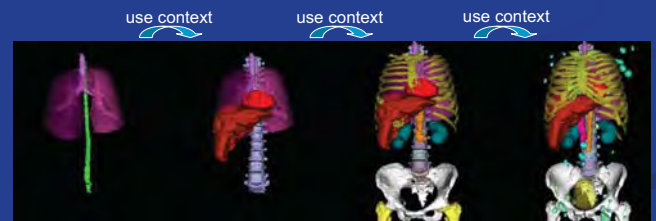
Radiomics: workflow & challenges

"Convert Images to mineable data"

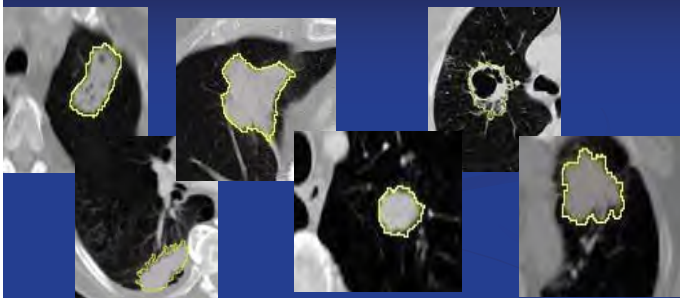


Kumar et al., MRI (in press) 2012

Context-dependent Automated Segmentation and Classification of organ systems



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	x
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 nanoparticles -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

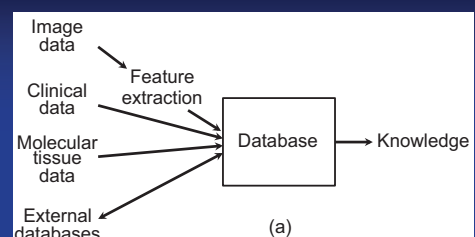
*Cancer Biomarkers, IOM, 2007

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.

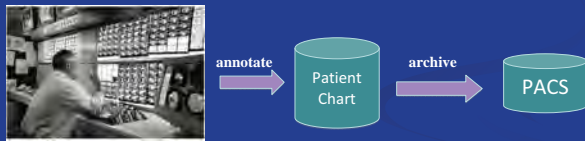
- Correlative observation in cells or animals
- Retrospective analysis with human samples
- Inter-lab cross validation
- Prospective Study
- Multi-center Prospective Study

Linking and Mining Image, Medical and Genomic Data

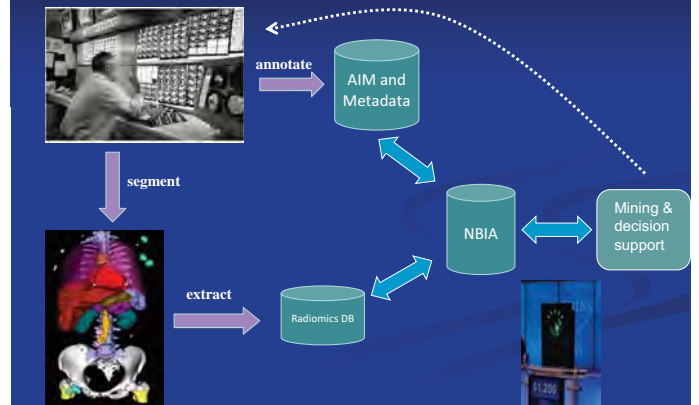


Courtesy Daniel Rubin, Stanford

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 technology 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