



Biomarker as essential part of clinical development

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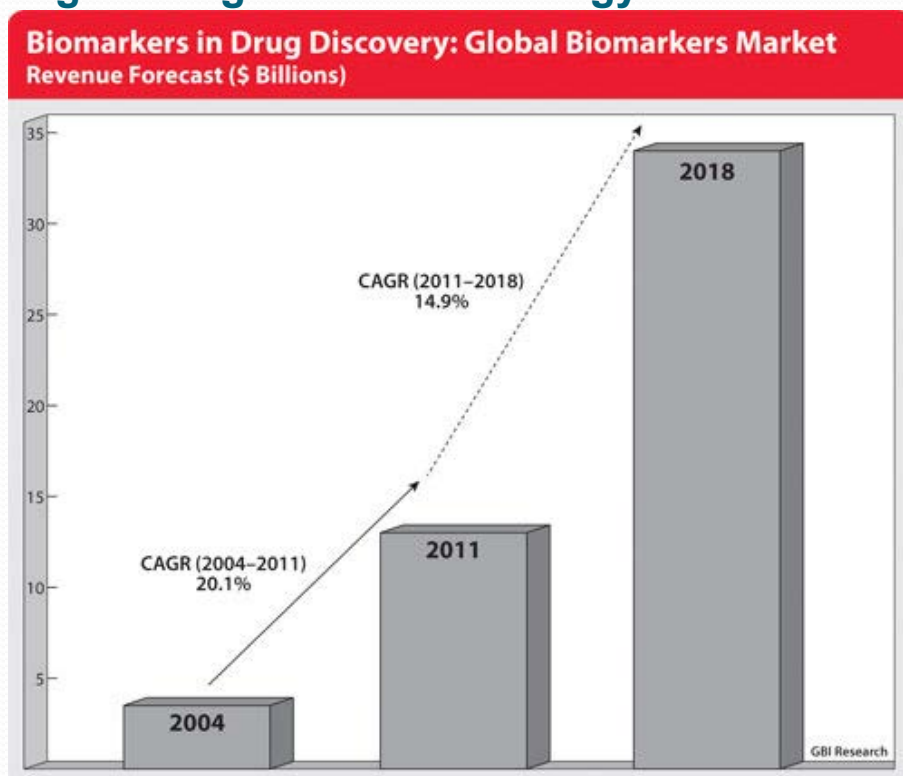
Agenda

- Why biomarkers in clinical development
- What is a Biomarker
- History of Biomarkers
- Biomarkers today
- Classification of biomarkers with examples
- Basic statistical techniques for evaluating biomarker
- Pitfalls and Future challenges
- Conclusion

Why Biomarkers in clinical trials

- Prediction of efficacy of drug early and accurately
- Predicts drug failures in earlier phases of clinical trials minimizing costs
- FDA estimate that 10% improvement in predicting drug failure would save \$100 million per drug.
- Biomarkers can be measured quantitatively to diagnose and assess the disease process and monitor treatment to response
- Difficult diagnosis is confirmed by biomarkers

Global Biomarkers market: Genetic Engineering and Biotechnology news



Current market value estimated is \$712 million which would double (\$1.38 billion) with next 5 years

Definition of biomarker

- Characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. (*Ref: Biomarkers definition working group: Biomarkers and surrogate endpoint: Preferred definitions and conceptual framework: K. Clin pharmacol ther 2001;69:89-95.*)
- *Biomarkers take the form of*
 - a. *Cellular characteristics –*
 - b. *Metabolites – sugars, lipids and hormones*
 - c. *Molecular and genetic variations – DNA, RNA*
 - d. *Physical features – clinical symptoms*

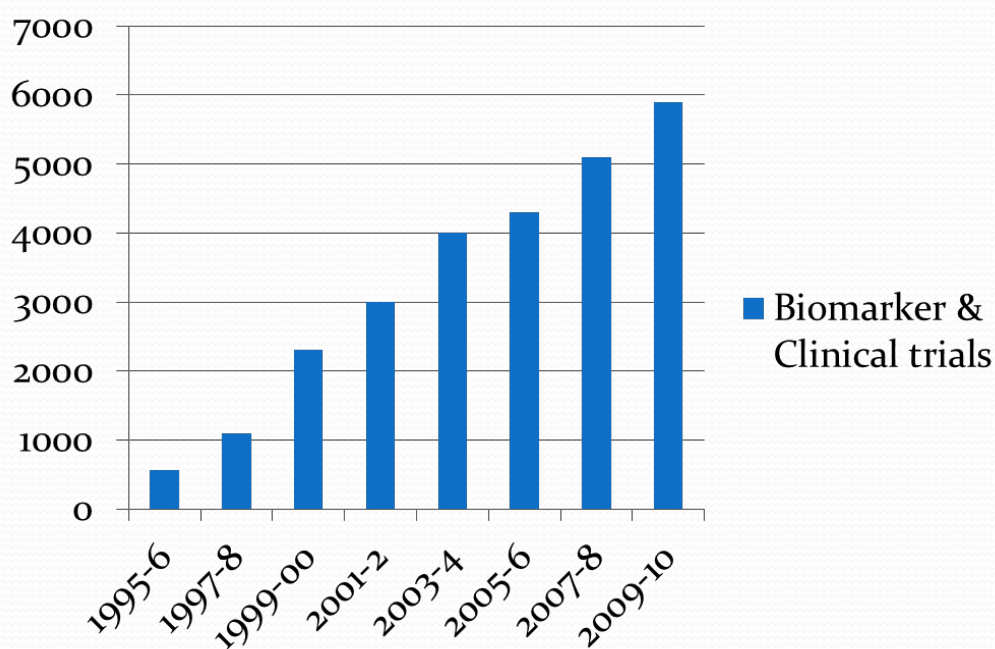
Biomarker purpose

- Detect specific disease as early as possible – diagnostic biomarker (HCV RNA after infection)
- The risk of developing a disease – susceptibility / risk biomarker (BRCA1) – Breast cancer
- Evolution of disease – prognostic biomarker (K-ras in NSCLC) – predictive marker too.
- The response and toxicity to given treatment – predictive biomarker (EGFR NSCLC)

Biomarker History

- Biomarkers were used from the beginning of medical treatment
- Urine examination – tested for color and precipitate- signs of disease
- Body temperature - fever
- Blood pressure - surrogate endpoint for stroke
- Philadelphia chromosome – benefit from drug candidates - chronic myelogenous leukemia
- HIV viral load - disease progression - antiretroviral treatment efficacy
- Overexpression of HER-2 in Breast cancer – prognostic and predictive marker

Number of publications in PUBMED: Increasing interest in Biomarkers



Ref:Drucker and Krapfenbauer The EPMA Journal 2013, 4:7

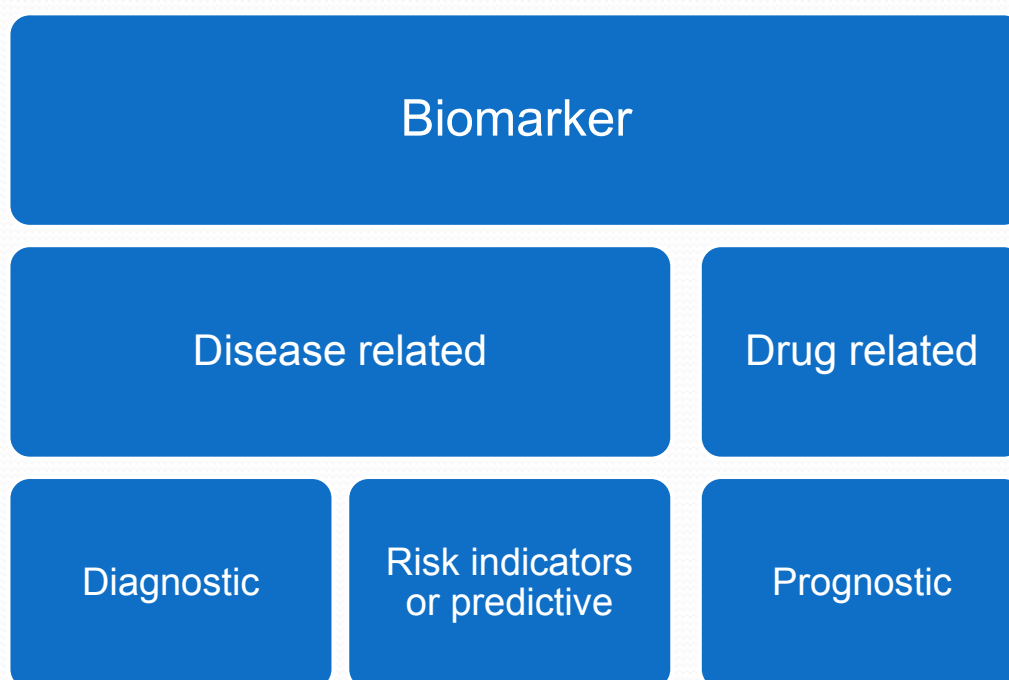
Biomarkers Today

- Alzheimer's disease or rheumatoid arthritis - begin with an early, symptom-free phase - diagnosis difficult – risk assessment is predicted
- Oncology - Circulating tumor cells (CTC) – Prognostic marker –early signal of efficacy
- Prevent drug development disasters
 - 34 drugs withdrawn due to hepatotoxic or cardio-toxic effects
 - anti-inflammatory drug rofecoxib withdrawn due to its increased risk of heart attack and stroke

Association of Biomarkers with disease and drug

- Biomarkers can be disease-related and drug-related
- Disease related biomarkers give an indication of :
 - the threat of disease (risk indicators or predictive biomarkers).
 - If a disease already exists (Diagnostic biomarkers)
 - How such a disease may develop in individual case regardless of the type of treatment (prognostic biomarker)
- Drug-related biomarkers indicate whether a drug will be effective in a specific patient and how the patient's body will process it
- Predictive biomarkers help to assess the most likely response to a particular treatment type
- Prognostic markers shows the progression of disease with or without treatment

Diagrammatic representation of biomarker relation with disease and drug



Prognostic biomarker: Evaluation of CEA and calcitonin

- CEA and calcitonin is evaluated as secondary objective in a phase III study in subjects with metastatic medullary thyroid cancer.
- Screening assessments performed within 28 days of randomization
- Each cycle of the treatment Period includes 4 weeks of daily administration of drug or placebo
- Patients had an end-of-treatment assessment at 30 days after the last dose of study treatment
- Serum levels of these prognostic markers were evaluated at week 12.
- Significant change in biomarker level is observed

Sample dataset with CEA biomarker dataset

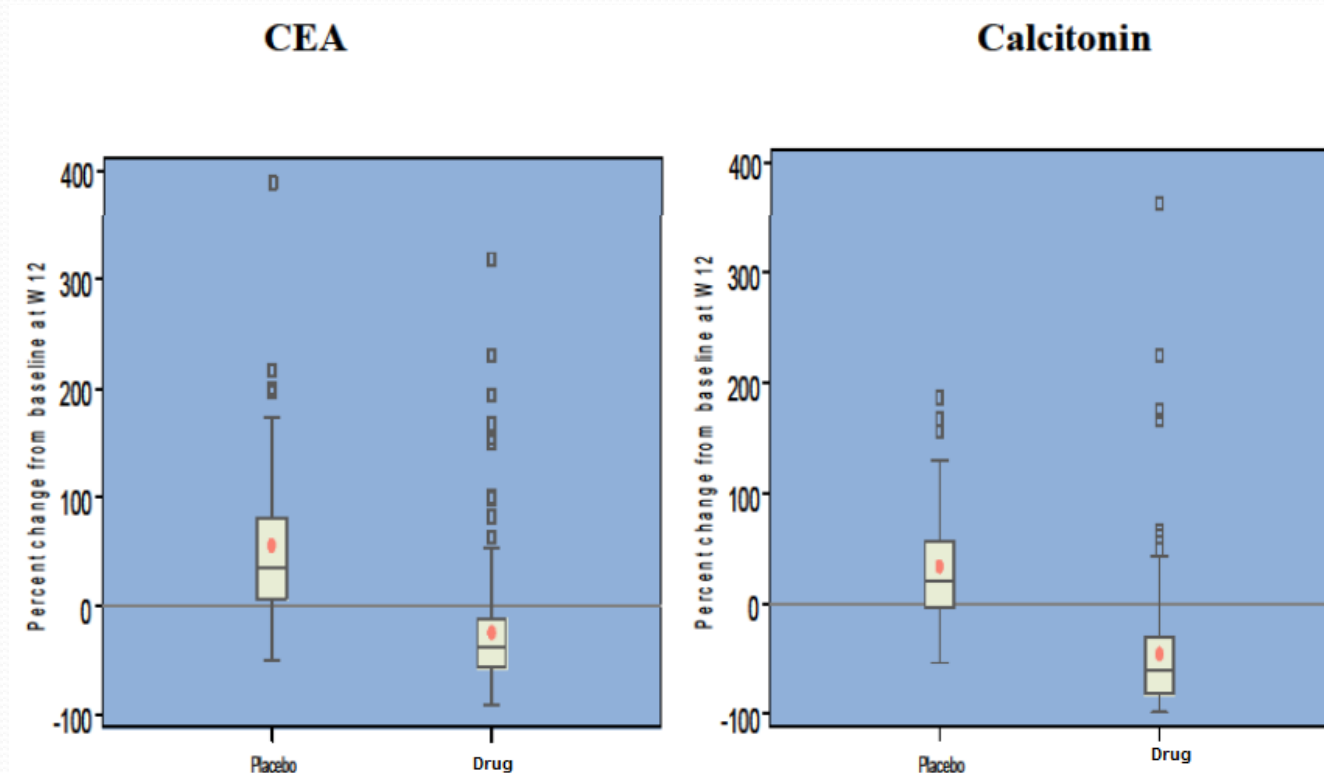
PT	Folder	InstanceName	VISITDT	CEA	CEA_raw	CEA_UN
001	D1PRE	Day 1 Predose (1)	4 Apr 2013	0.117	0.117	ug/L
001	D7HR1 POST	Day 7 Hour 1 Postdose	10 Apr 2013	0.118	0.118	ug/L
001	EOS	End of Study (1)	6 May 2013	0.055	0.055	ug/L
001	EOS	End of Study (1)	8 May 2013	0.019	0.019	ug/L

Change from Baseline at week 12



	Drug XXX N=219 Median (q1 q3)	Placebo N=111 Median (q1 q3)
CEA µg/L[n (%)]	170 (78%)	71 (64%)
Baseline	120.7 (33.5,422.7)	153.1 (32.3,478.2)
W12	56.4 (21.4, 260.9)	221.8 (69.5, 962.7)
Change from baseline	-23.7 (-143.1, -3.2)	35.6 (4.1, 269.6)
Percent Change from baseline	-38.0 (-56.1, -11.5)	38.0 (8.9, 104.0)
Pvalue	<0.0001	
Calcitonin pmol/L[n (%)]	140 (64%)	61 (55%)
Baseline	2298.1 (544.5,5754.0)	3886.0(792.0,9237.4)
W12	584.8 (177.3, 2671.5)	4968.0 (1219.0,11716.0)
Change from baseline	-1188 (-3071.0,-135.4)	322 (-0.5, 3941.3)
Percent Change from baseline	-60.2 (-81.7, -29.5)	22.7 (-2.3, 67
Pvalue	<0.0001	

Box plots showing percent change from Baseline in CEA and Calcitonin level at Week 12



Predictive biomarker: Cognitive

- Cognitive biomarkers are used as predictive biomarkers to predict conversion of mild cognitive impairment (MCI) to Alzheimer disease.
- Cognition, a behavioral marker may be considered a surrogate for neural systems function.
- Verbal memory was assessed by the Alzheimer Disease Assessment Scale-Cognitive using a composite score for the memory tests - immediate recall, delayed recall, memory, non-memory and Clock Drawing Test
- All groups significantly differed from each other on each cognitive measure

Cognitive Test Scores at Baseline



Variable	Controls Mean (SD)	MCI Nonconverters Mean (SD)	MCI Converters Mean (SD)	Pvalue
Logical Memory, immediate recall	14.03 (3.44)	7.56 (3.00)	6.20 (3.16)	<0.001
Logical Memory, delayed recall	13.23 (3.48)	4.34 (2.65)	2.61 (2.26)	<0.001
ADAS memory domainA	8.15 (3.89)	14.39 (5.11)	18.09 (4.25)	<0.001
ADAS non- memory domainA	1.19 (1.22)	2.88 (2.24)	3.83 (2.55)	<0.001
Clock Drawing Test	4.70 (.61)	4.35 (0.86)	3.87 (1.12)	<0.001

Statistical techniques for biomarker assessment

Sensitivity and Specificity

- Diagnostic accuracy measured by sensitivity and specificity of marker.
- Sensitivity - true positive rate
- Specificity - true negative rate
- Specificity and sensitivity of CA19-9 tumor marker in pancreatic cancer is calculated using 2 x 2 table with the FREQ procedure.
- Predefined threshold was 37 U/ml
- In the sample dataset d is a dichotomous variable for the patient's cancer status and y1 is a continuous variable of the biomarker CA19-9
- Among the 90 cancer patients, 68 tested positive, giving us a sensitivity of 76%.
- 46 of the 51 non-cancer patients tested negative for a specificity of 90%

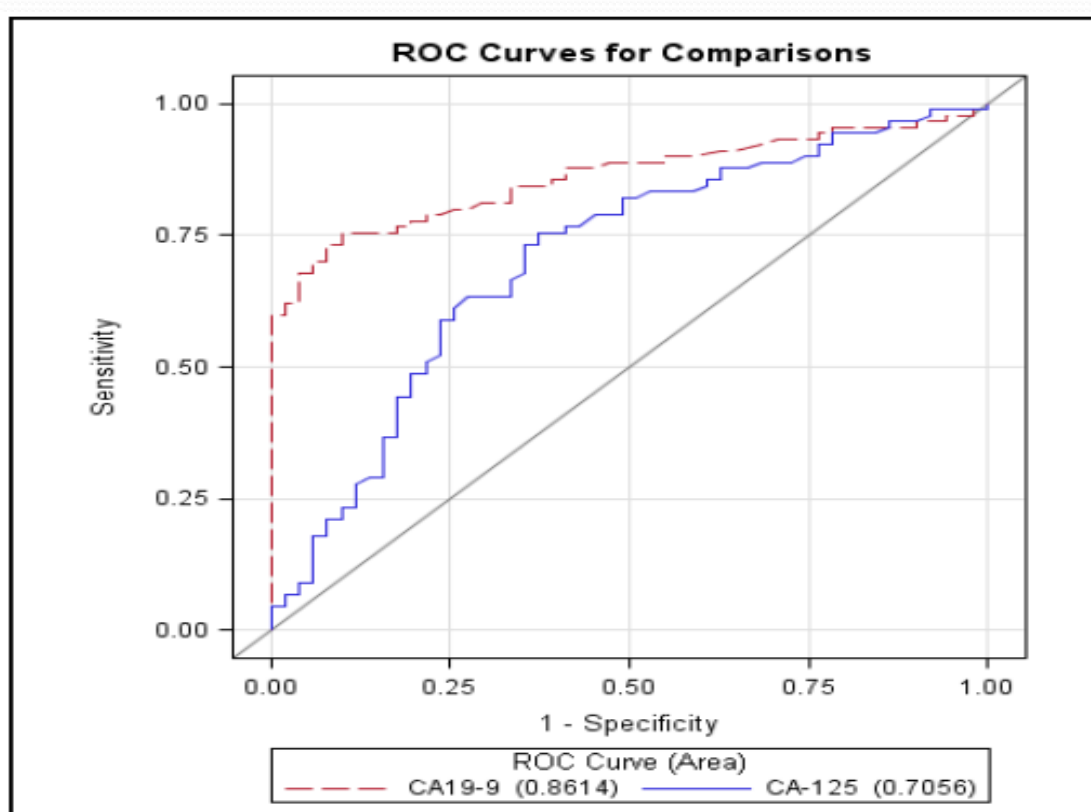
2 x 2 Freq output

Table of y1 by d				
y1(CA19-9)		d(Pancreatic Cancer)		
Frequency				
Col Pct	Cancer	No Cancer	Total	
37+ U/ml	68 75.56	5 9.80	73	
<37 U/ml	22 24.44	46 90.20	68	
Total	90	51	141	

ROC Analysis

- ROC (Receivers operating characteristic) curve used to assess the overall performance of the biomarker.
- Plot of sensitivity on the vertical axis and 1-specificity on the horizontal axis for all possible thresholds in the study data set.
- The area under the ROC curve (AUC) is the average sensitivity of the biomarker over the range of specificities.
- A biomarker with no predictive value have an AUC of 0.5 while a biomarker with perfect ability to predict disease would have an AUC of 1.
- CA19-9 biomarker has an AUC of 0.86

ROC curves for biomarker CA19-9 and CA-125



Pitfalls and Future Challenges

- Estimates show the total biomarkers of interest at about more than 1 crore (1,133,00020)
- Selection of Biomarker of clinical utility
 - Sensitivity, specificity and predictive value of biomarker
 - Understanding of pathophysiology of disease
- Lack in biomarker characterization/validation strategies.
- Analysis techniques used in clinical trials - advanced

Conclusion

- Biomarkers play a vital role in drug development
 - to monitor drug toxicity
 - prove a compound mechanism of action
 - Predict safety and efficacy of drug
- The ultimate vision is to have access to biomarkers in all therapeutic fields for which you need industry, academia and clinicians working together
- Biomarkers could have such a huge impact, because you could reduce the time of your trials and improve internal decision making.

Questions?

