



Moving towards Personalized Cancer treatment: Future Vision or Urgent Necessity?

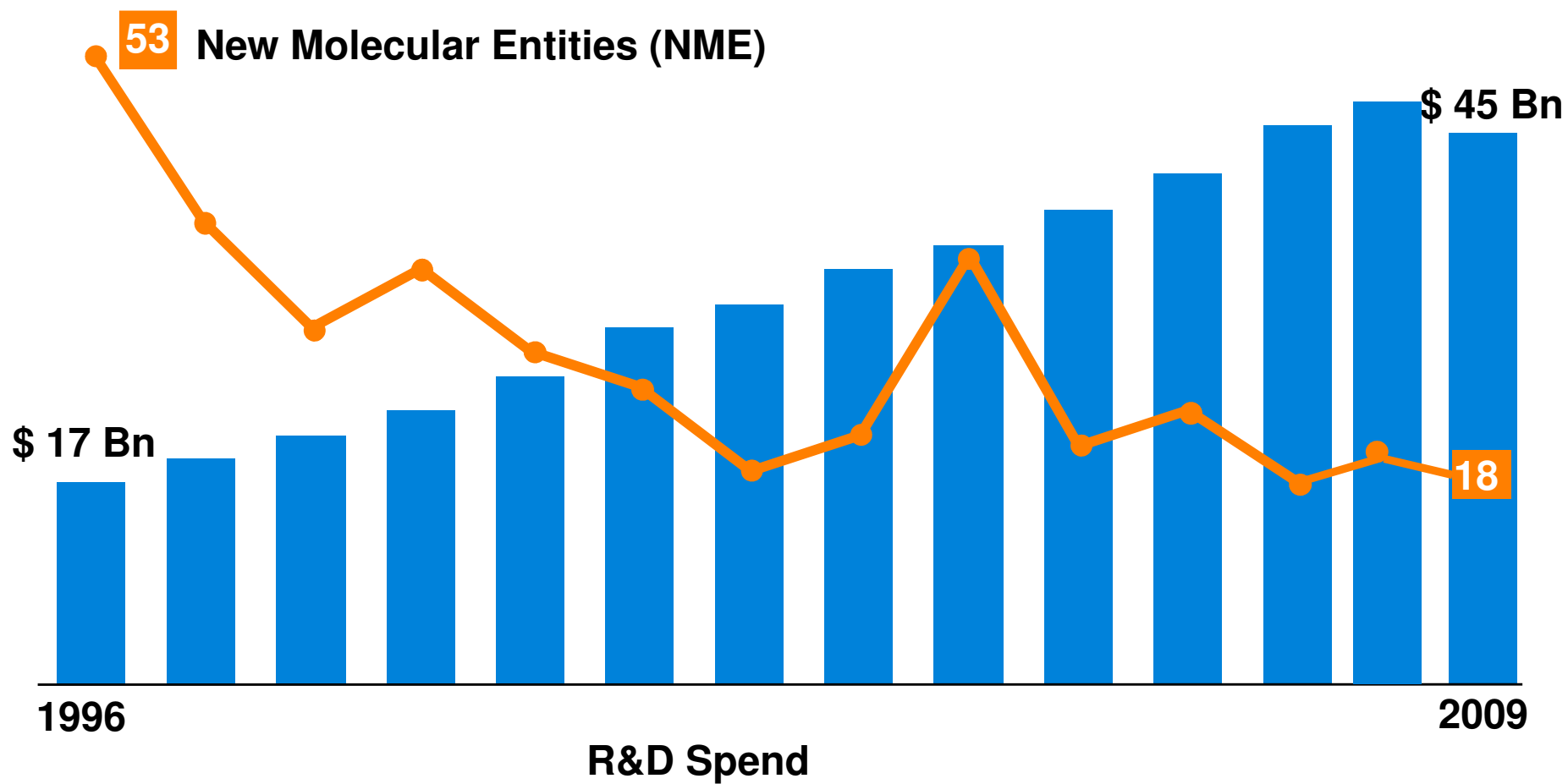
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Professor of Translational Medicine, EPFL Lausanne.

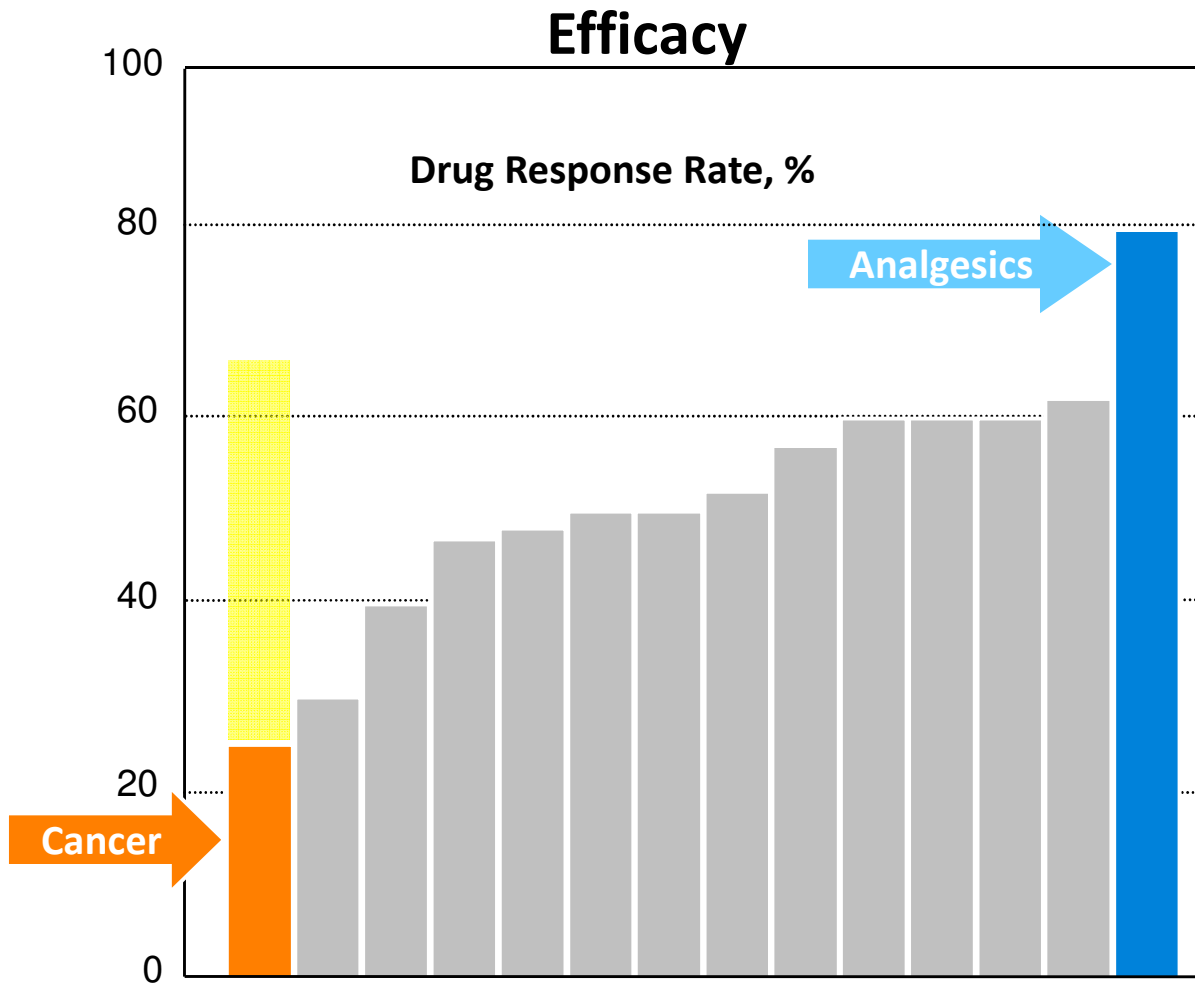
Vice Chairman, Caris Life Sciences

Decline in numbers of new Therapies



Sources: FDA/CDER Data, PhRMA data, Price Waterhouse Coopers analysis, Pharma 2020

More Effective and Safer Drugs requires a Redefinition of Disease



Safety

Avandia
rosiglitazone maleate

ACOMPLIA[®]
rimonabant

Mycograb[®]

TRASYLOL[®]
(aprotinin injection)

Zelnorm[®]
(tegaserod maleate) 1mg, 2mg tablets

Our Challenge!

“Diagnosis is a system of more or less accurate guessing in which the end-point achieved is a name. These names applied to disease come to assume the importance of specific entities, whereas they are for the most part no more than insecure and therefore temporary conceptions.”

T. Lewis: Reflections upon medical education

Lancet 1944 i:619-21

Novel Partnerships: The Innovative Medicines Initiative (IMI) in a nutshell



- Currently, the largest public-private partnership in the arena of medicine
- (2 Billion Euros)
- Innovative collaboration established between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA) as a Joint Technology Initiative
- Promotes medical innovation in Europe and addresses bottlenecks in the R&D process
- Public funding goes exclusively to academia, SME's, patient organisations and regulatory authorities

28 Company Members of the EFPIA RDG

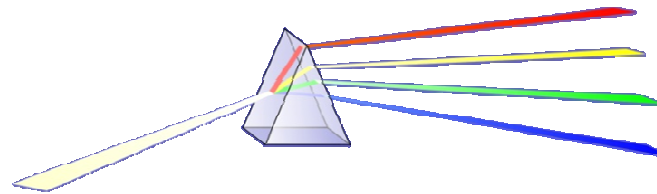


Personalized Healthcare

Use of Molecular Insights and Diagnostic Tests to Better Tailor Medicines and Manage a Patient's Disease

Today Most Patients are Treated the Same

- 25-80 % of patients receive effective treatment¹
- >100.000 deaths/yr from adverse drug reactions in US²



Molecular diagnosis



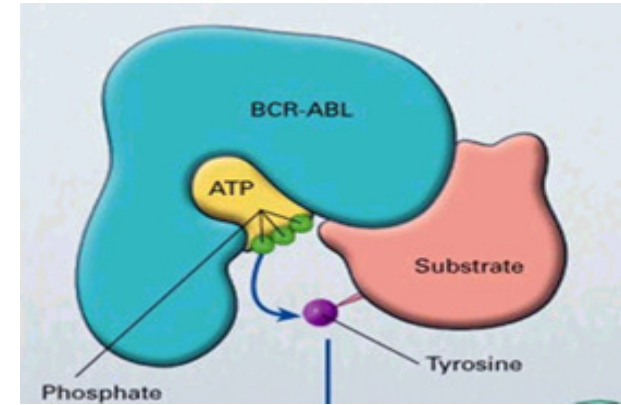
Increasingly, treatment will be tailored to **selected patient groups** defined by **molecular diagnostics**

¹ Spears et al., Trends Mol Med, 2001

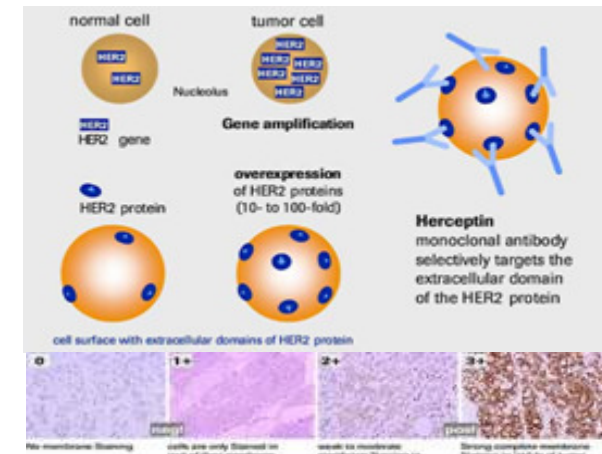
² Lazarou et al., JAMA, 1998

Cancer –Stratified Medicine – Efficacy through defining Responsive Populations

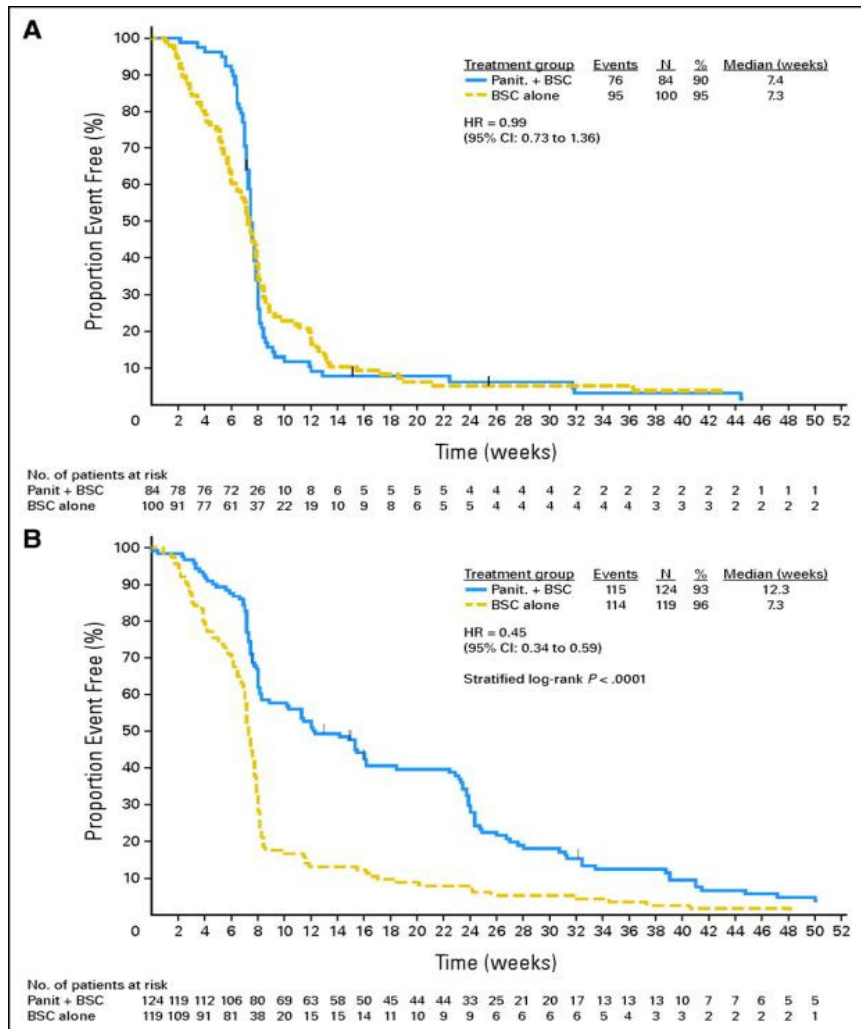
- Bcr-abl – Gleevec



- Her-2 – herceptin

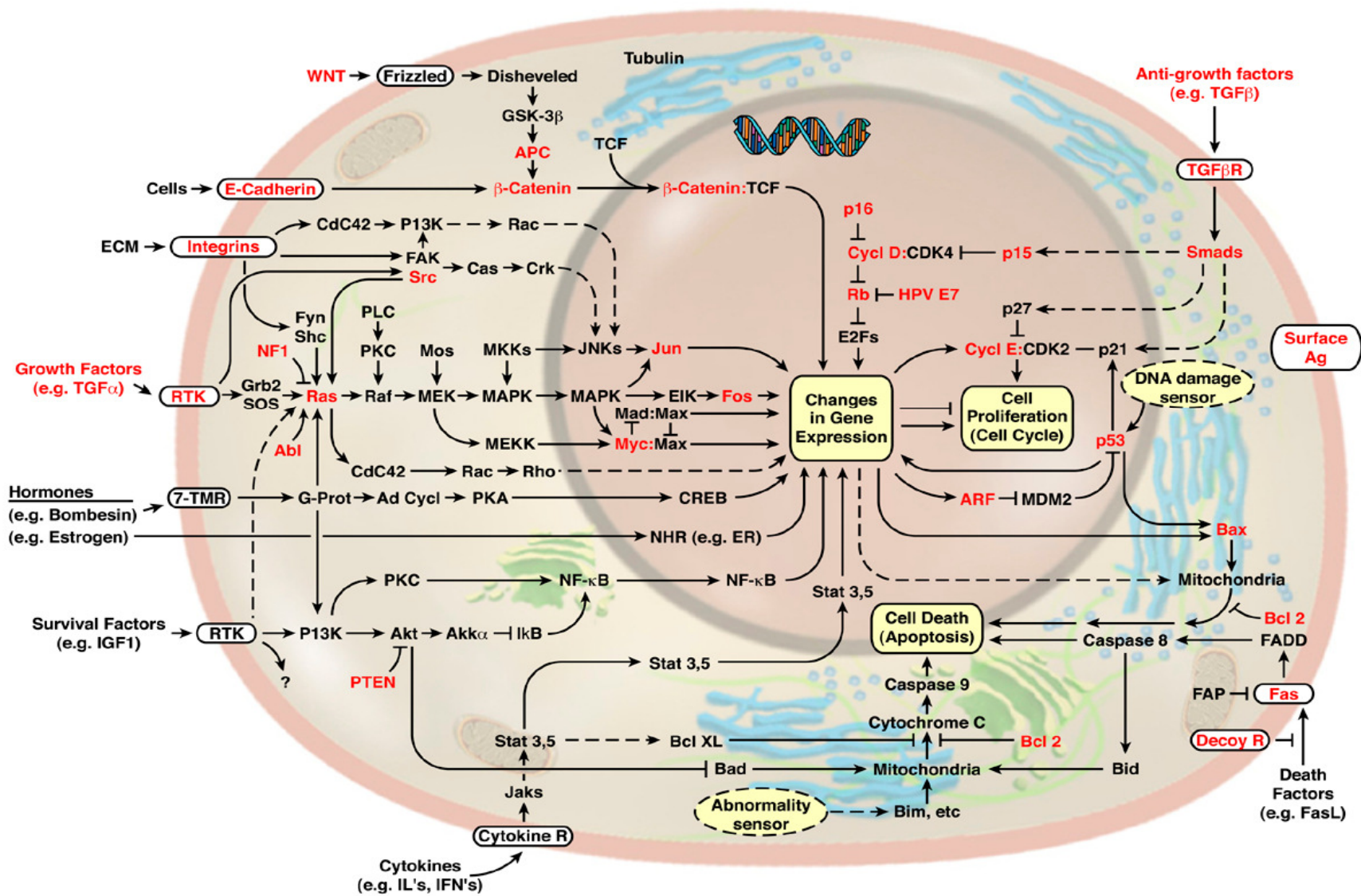


Stratified Medicine – Progression-free survival by treatment within KRAS groups



Wild-Type *KRAS* Is Required for Panitumumab Efficacy in Patients With Metastatic Colorectal Cancer
 Rafael G. Amado, Michael Wolf, Marc Peeters, Eric Van Cutsem, Salvatore Siena, Daniel J. Freeman, Todd Juan, Robert Sikorski, Sid Suggs, Robert Radinsky, Scott D. Patterson, David D. Chang
J Clin Oncol; 26:1626-1634 2008

The Magic Bullet problem-Cancer Cell Division Network



Driver Gene Classification

3142 genes mutated in human cancers

286 Tumor Suppressor Genes

33 Oncogenes

90% of drivers are suppressors

Virtually all are components of
12 core pathways

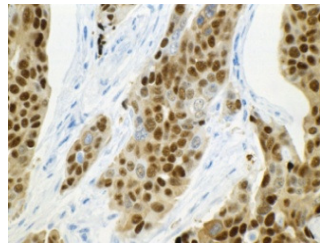
Bert Vogelstein: AACR 101st Annual meeting 2010

Personalised Therapy: Caris Target Now[®] Overview

A combination of the most clinically relevant technologies

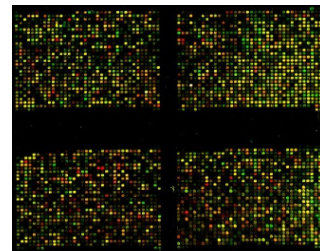
Delivers therapeutic guidance through molecular profiling

Analysis



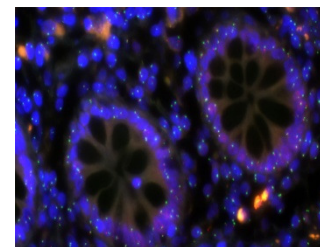
IHC

- Multiple profiles depending on tumor type with a total of over 30 different “protein targets”
- Additional 22 IHC validated



Microarray

- Looking at the over- or under-expression of RNA in a whole genome microarray for both fresh frozen and FFPE tissues
- Summarizing ~80 of the most significant or resistant targets



FISH

- Identifying gene copy number alterations in tumor tissue (EGFR, HER2, TOP2A, cMYC)

Mutational Analysis

- Identifying gene mutations in tumor tissue (e.g. KRAS, BRAF, EGFR, c-Kit, PIK3CA etc.)

Output

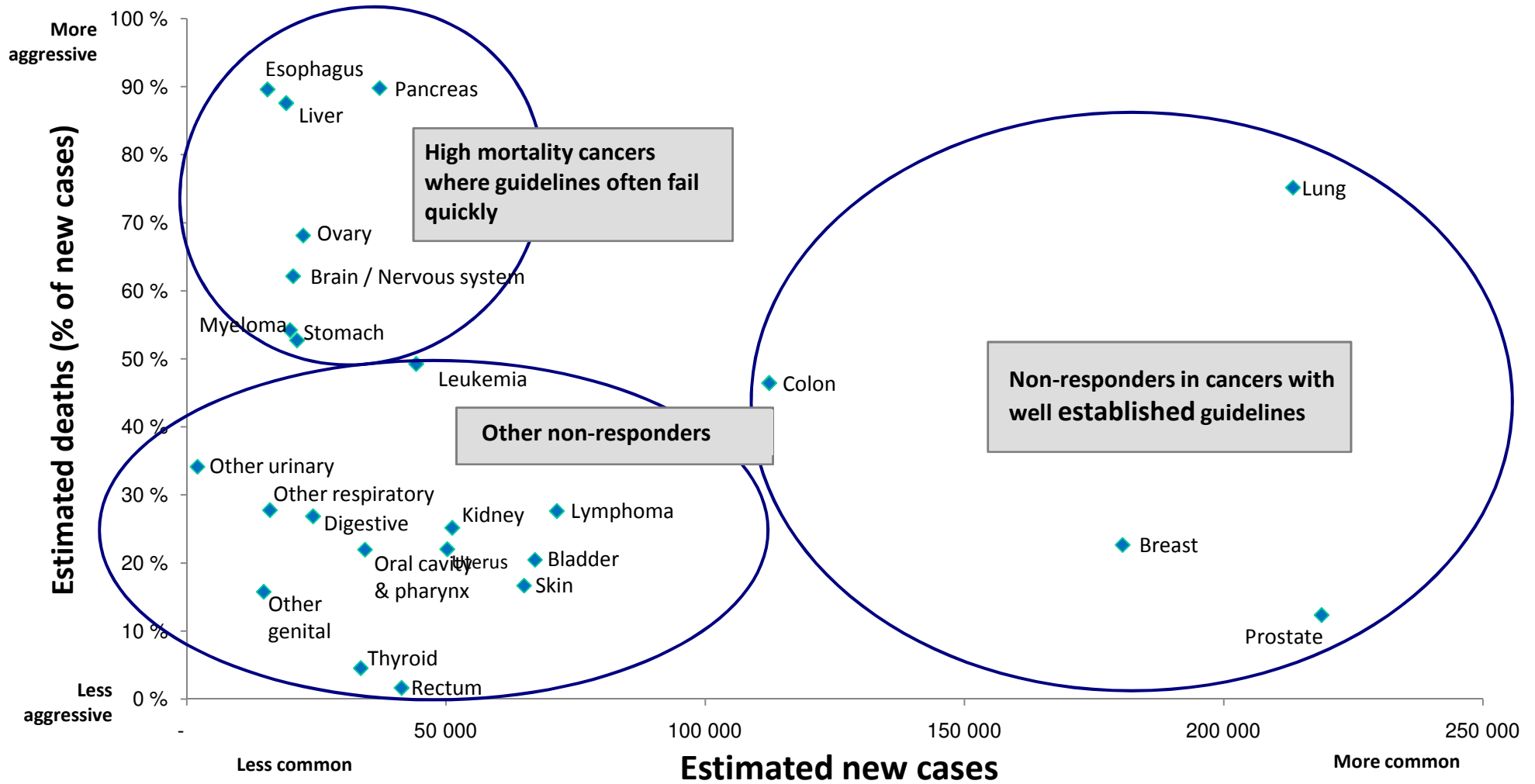
Unique molecular “blueprint” of patient tumor

- Gene Expression
- Quantitative Protein Expression
- Mutational Analysis
- Gene Copy Number Aberrations

Literature-based prioritized ranking of drug targets in tumor and their associated therapies

Information on therapies that might not otherwise have been considered based on the lineage of the tumor

Where Does Molecular Profiling Fit in Clinical Practice?



Target Now[®] Summary of Agents

Patient Information	Specimen Information	Ordered By
Test Patient Case Number: MP-TN10-00000 Date Of Birth: 09/05/1940 Sex: Female SSN: XXX-XX-XXXX	Primary Tumor Site: Colon: Cecum Specimen Site: Colon: Cecum Specimen Collected: 11/16/2007 Specimen Received: 1/30/2010 Date Reported: 2/8/2010	Test Ordering Physician The Cancer Center 1234 Main Street Dallas, TX 12345 123-456-7890

Target Now Summary

Clinical History: Per the submitted patient history, the patient is a 69-year-old female with a history of metastatic colon cancer. She underwent a right hemicolectomy in November 2007. The patient has received the following therapeutic agents/regimens: FOLFOX (12/07 - 05/08); 5-FU plus leucovorin (started 06/08); irinotecan (03/09 - 04/09); and capecitabine (05/09 - 08/09).

Clinical history
and prior
therapies

Agents Associated WITH CLINICAL BENEFIT

irinotecan

nab-paclitaxel

doxorubicin, liposomal-doxorubicin, epirubicin

octreotide

asparaginase, pegaspargase

sunitinib, sorafenib

azacitidine, decitabine

Agents Associated With LACK OF CLINICAL BENEFIT

cetuximab, panitumumab

trastuzumab

temozolomide

gemcitabine

cisplatin, carboplatin, oxaliplatin

erlotinib, gefitinib

lapatinib

Agents ranked.
See next slide.

Target Now[®] Details Agents Associated with Clinical Benefit

TARGET NOW[®] SUMMARY - AGENTS ASSOCIATED WITH CLINICAL BENEFIT

The role of Target Now is to identify biomarkers and therapies associated with clinical benefit or lack of clinical benefit for cancer patients. The selection of any, all or none of the matched agents resides with the discretion of the treating physician. If a patient's tumor has previously progressed on an agent identified as associated with clinical benefit on this report, the patient should not be re-treated with this agent.

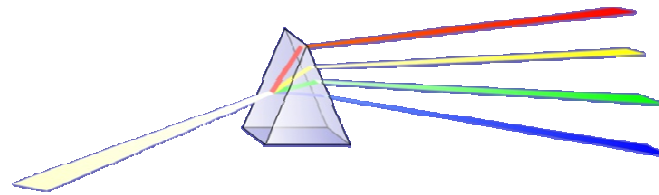
Agents Associated With CLINICAL BENEFIT	Summary Statement	Lineage of Evidence
irinotecan	High expression of TOPO1 has been associated with benefit from irinotecan.	CRC
nab-paclitaxel	High expression of SPARC has been associated with benefit from nab-Paclitaxel.	Breast cancer
doxorubicin, liposomal-doxorubicin, epirubicin	High expression of TOPO2A has been associated with benefit from anthracycline-based therapy.	
octreotide	High expression of SSTR2 and SSTR5 has been associated with benefit from somatostatin analogs.	
asparaginase, pegaspargase	Low expression of ASNS has been associated with benefit from asparaginase or pegaspargase.	
sunitinib, sorafenib	Over expression of c-Kit by DNA microarray has been associated with benefit from multi-targeted kinase inhibitors.	
azacitidine, decitabine	High expression of DNMT3A has been associated with benefit from DNA methyltransferase inhibitors.	

Summaries of biomarker associations

How might Personalized Clinical Trials in Cancer work!

Patient centric - not drug or treatment centric

2. Biotech and Pharma put new drugs into a pool with existing therapies and agree to Decision rules. (not just standard of care plus)



Cancer Clinic with
molecular Diagnostics



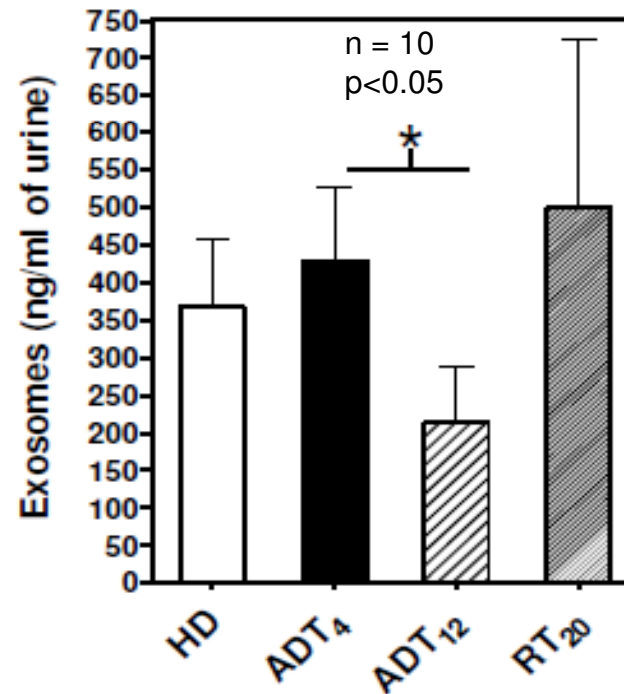
1. Give all patients entering clinic a complete modern diagnosis (all relevant parameters especially those predicting best therapy).

3. Treat patients with specifically chosen mono or combo therapy on the basis of the predicted efficacy

Prostate Cancer: Published studies demonstrate potential of microvesicles to be used as tools for monitoring PCa patient response to Androgen Deprivation Therapy.

Exosome Levels Decrease 2-fold Following 12 weeks Androgen Deprivation Therapy (ADT)

- Exosomes purified from urine of patients with locally advanced prostate cancer were quantified at 3 time points post therapy, and expression of prostate markers (PSA and PSMA) from exosomes were used



Mitchell et al., 2009 J. of Translational Medicine

Exosomes are one of the three key intercellular communication mechanisms

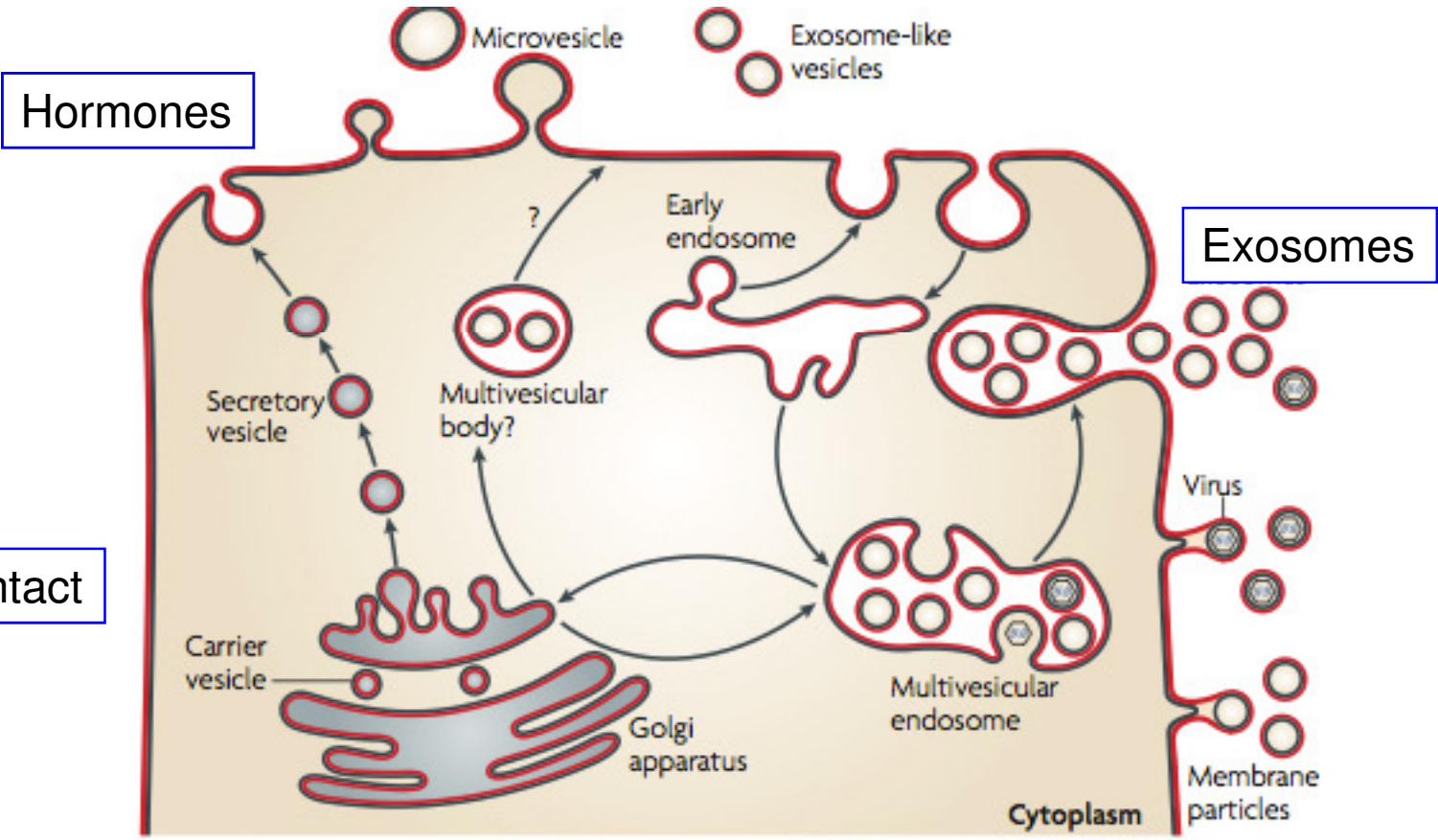


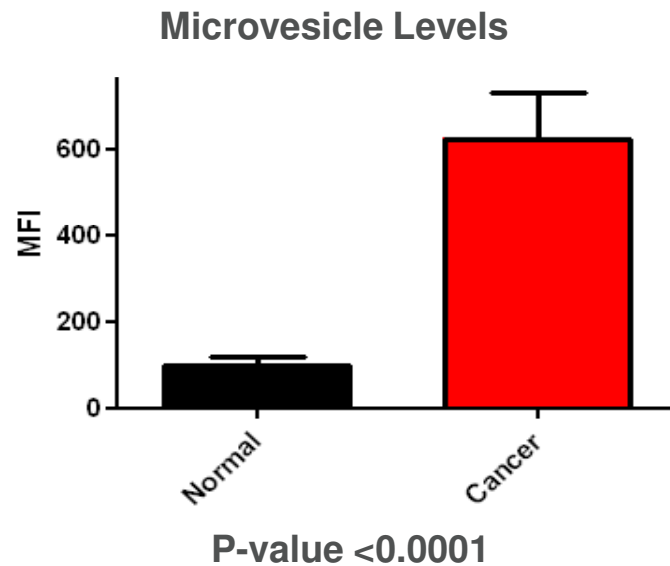
Figure 1 | Different types of secreted membrane vesicles.

Modified after

They, Ostrowski and Segura

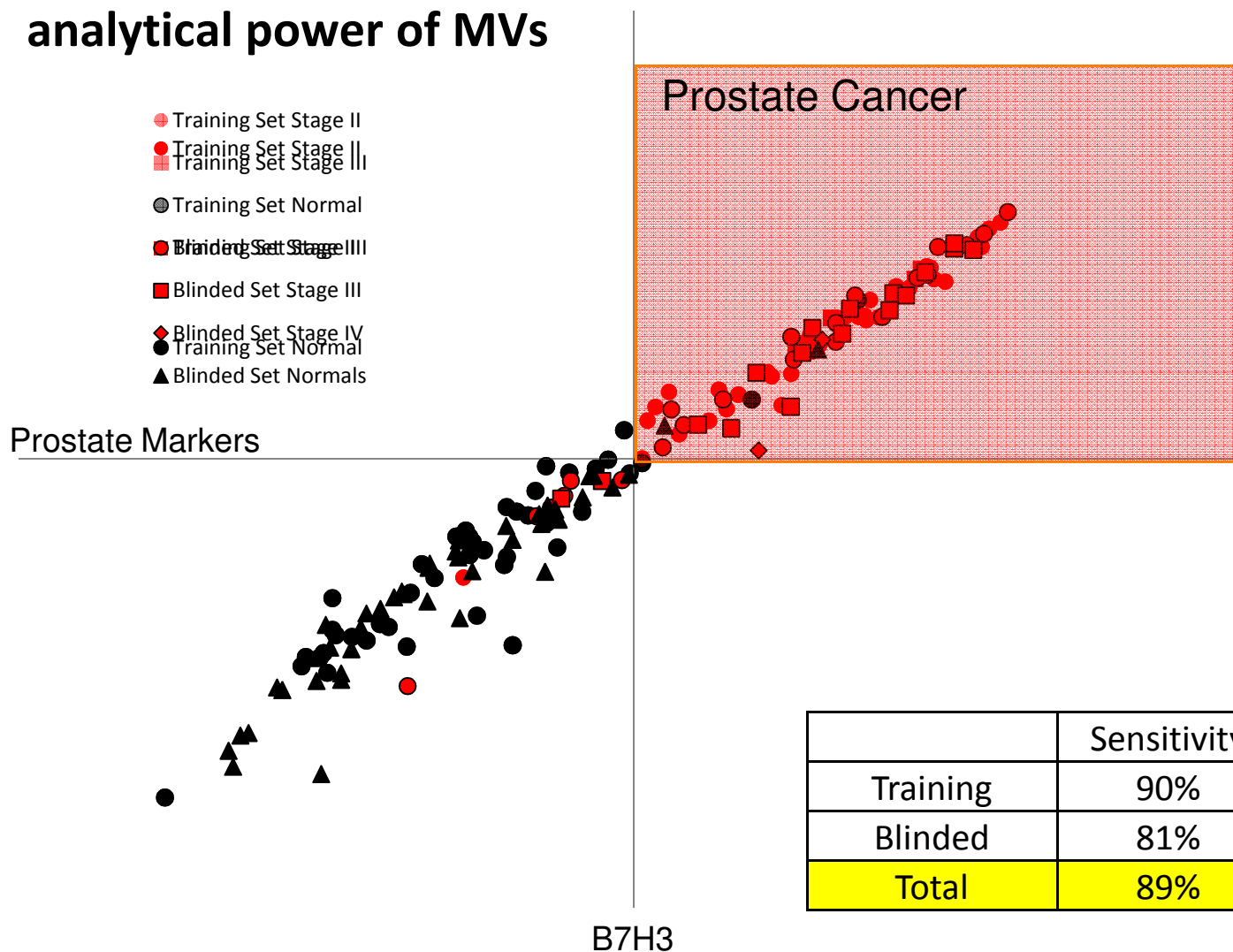
Nature Reviews Immunology Vol 9 August 2009 page 581

Microvesicle Levels are Increased in Cancer Plasma Samples Compared to Samples from Unaffected Individuals



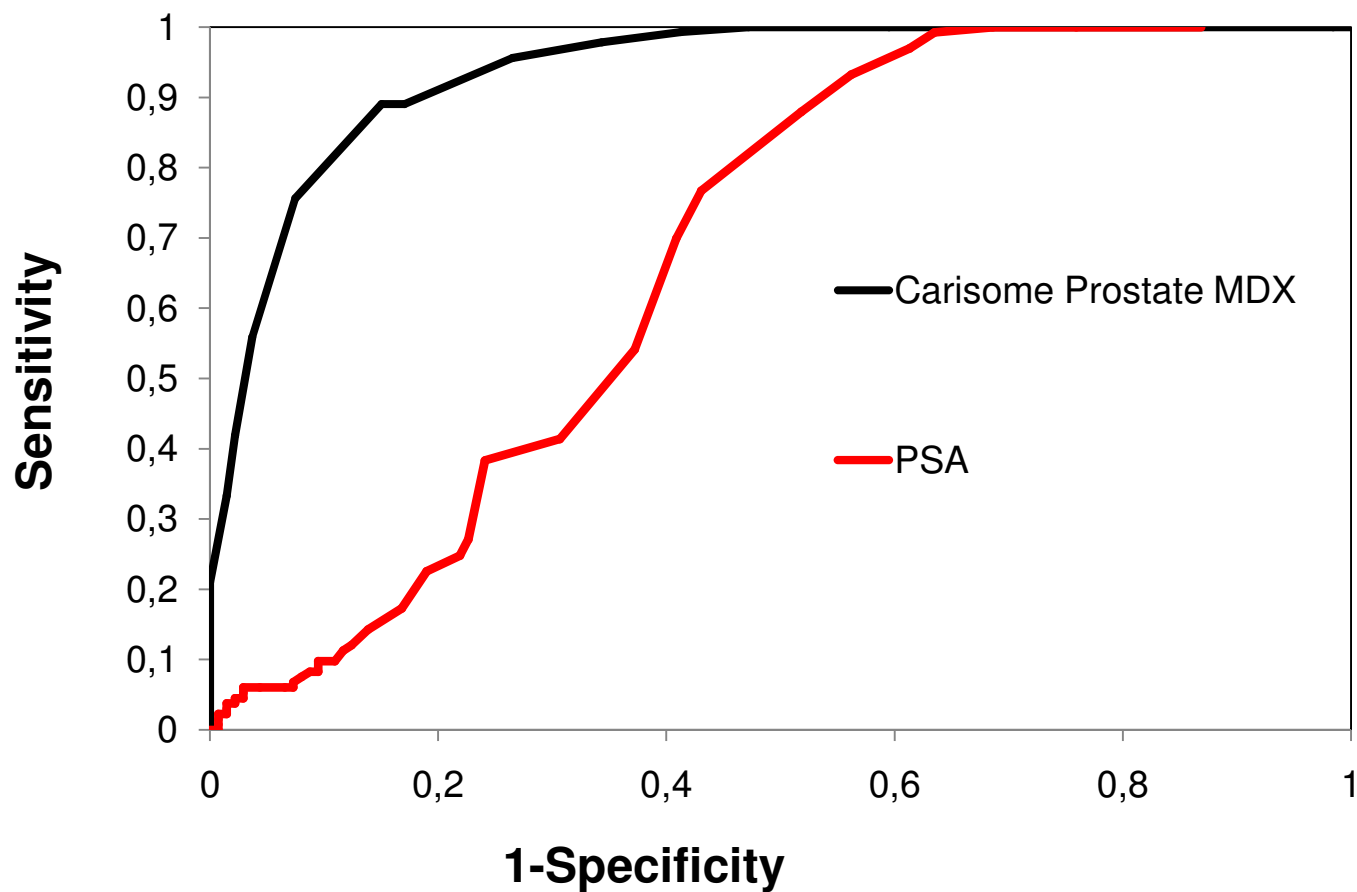
Pooled cancer patient samples: 17 prostate cancer patients, 18 colon cancer patients, 5 esophagus cancer patients, 3 pancreas cancer patients, 1 liver cancer patient, 1 rectal cancer patient sample (unpublished Caris data)

Training and Initial Blinded Validation of Prostate MDx 1.0 demonstrates analytical power of MVs



	Sensitivity	Specificity	No. Samples
Training	90%	79%	57
Blinded	81%	95%	78
Total	89%	95%	160

Carisome Prostate MDx 1.0: Significant improvement over PSA



	Carisome Prostate MDX	PSA
AUC	94%	68%

In summary,

from one ml of blood from a cancer patient
- it is likely that in 2011 we can:

Detect Cancers 1cm in diameter - (Prostate, CRC, Breast and Lung)

Detect response of each cancer to therapy very rapidly

Determine if cancer is metastatic

Determine optimal therapy from Exosome proteins and ONCO snips

6 Key Stakeholders in Healthcare

Benefits and contributions

- Patients
- Doctors
- Health care providers/payers
- Regulators
- Basic (biomedical) Researchers
- Private Sector

Personalized Therapies Require A MAJOR Mindset Change



Academia



Pharma



Hospitals/Physicians

- Re-classification of diseases on a molecular level
- Focus on efficacy for defined patients, not patient numbers
- Major innovation in how we demonstrate clinical efficacy
- Move on from companion diagnostics for each therapy to definition of the right therapeutic combination from personalized diagnosis
- Change in the way patient information is generated/used
- Encourage novel partnerships and collaborations