ASU Complex Adaptive Systems
ARIZONA STATE UNIVERSITY

BIO 302:
MARCH 31, 2015

WEEK 11, LECTURE 1:
SYSTEMIC TREATMENT OF CANCER: PHARMACOLOGIC, BIOLOGICAL AND IMMUNOTHERAPEUTIC TREATMENTS

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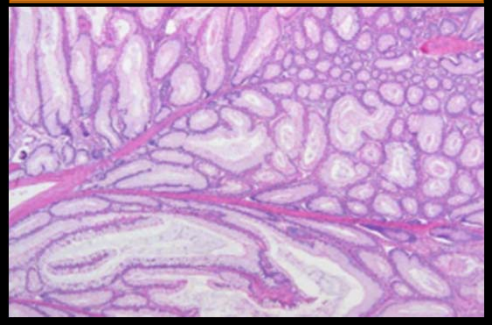
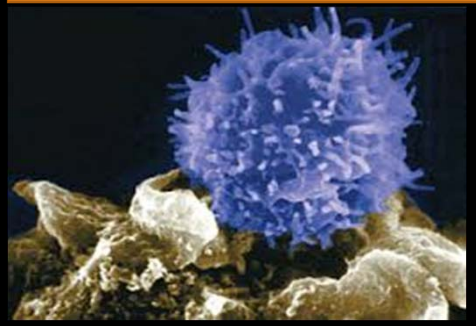
Cancer as a Complex Adaptive System: Emergent Phenomena and Tumor Progression (System State Shifts)

Escape From Controls for Normal Tissue Architecture

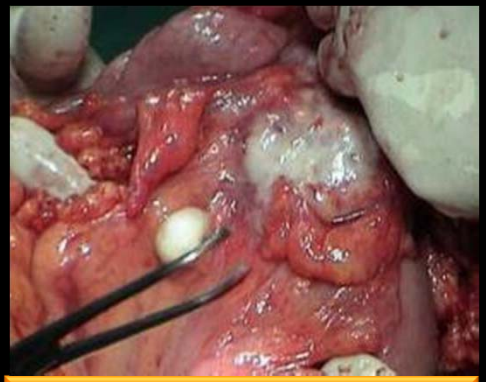


Genome Instability and Emergence of Clonal Variants

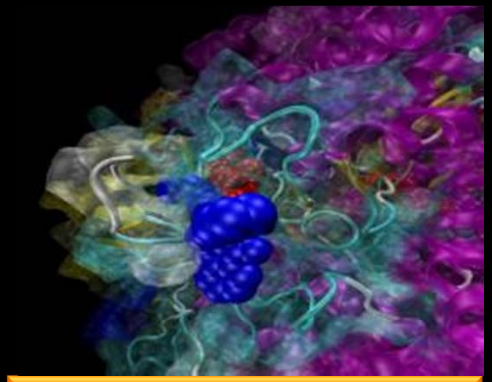
Evasion of Detection/Destruction by Host Immune System



Use of Host Systems to Promote Progression



Invasion and Metastasis



Emergence of Drug-Resistant Clones

Implications of Cancer as a Complex Adaptive System for the Development of More Effective Diagnostics and Therapies

Weeks 11 and 12

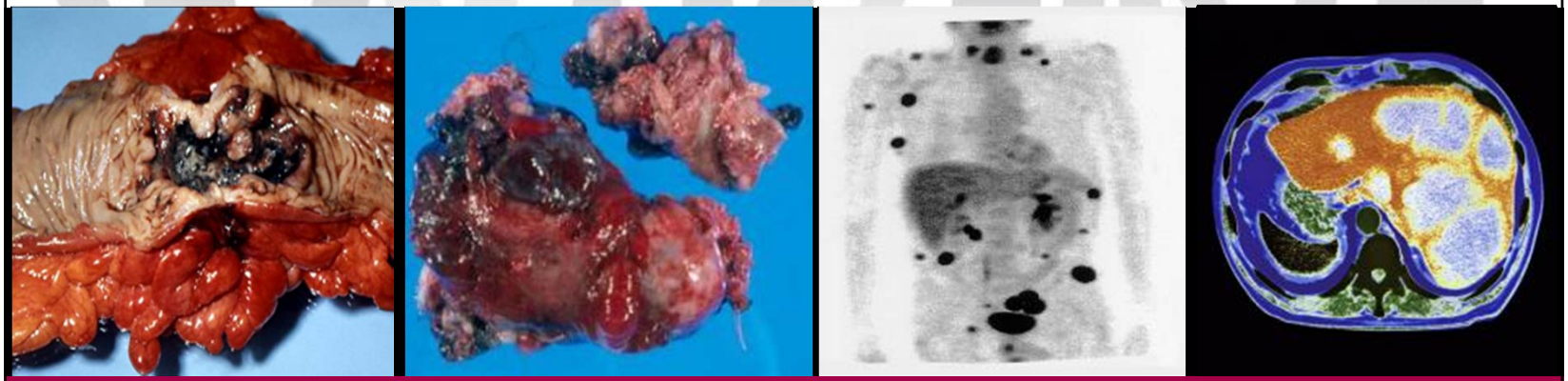
- current treatment practices and limitations
- confronting the tumor cell heterogeneity problem
- emerging treatment strategies to overcome tumor cell heterogeneity and rapid emergence of therapeutic resistance

Meeting The Cancer Challenge

The Ideal

- prevention
- cure

US Cancer Deaths 2014



The Biological Complexity of Cancer and the Design of Future Treatment Strategies

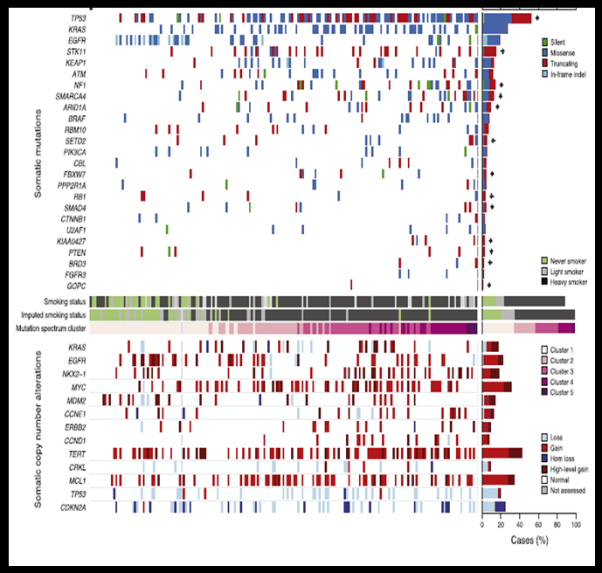
- successful surgical removal of primary tumor assumed (except brain tumors)
- targeting metastatic disease and circumventing Rx resistance
  - subclinical (adjuvant Rx)
  - advanced clinically evident metastases
  - minimal residual disease and tumor dormancy

Aspirations for Improved Cancer Diagnosis and Treatment

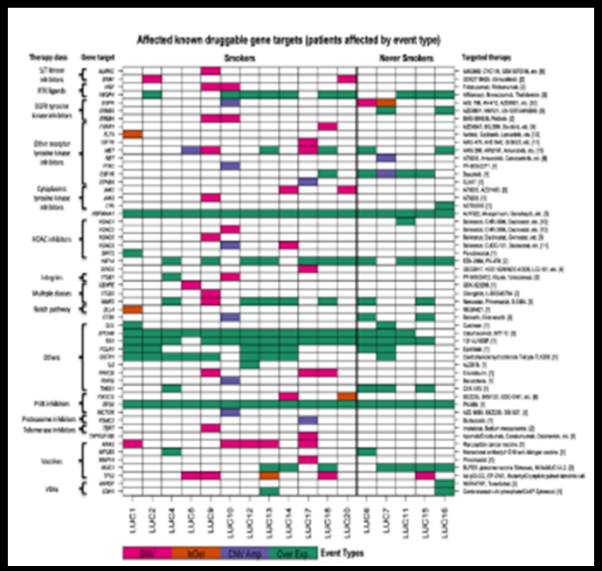
Better Approaches to Early Stage Disease

- earlier detection of subclinical disease
- earlier detection of clinical disease before metastasis occurs (surgery = cure)
- better methods to assess metastatic risk from primary tumor to evaluate need for exposure to adjuvant therapy
  - can tumors with metastatic potential be identified versus tumors that have low/no probability of metastatic spread?

The Extravagant Landscape of Genomic Alterations in Cancer (Cell 2012, 150, 1107 and 1121)



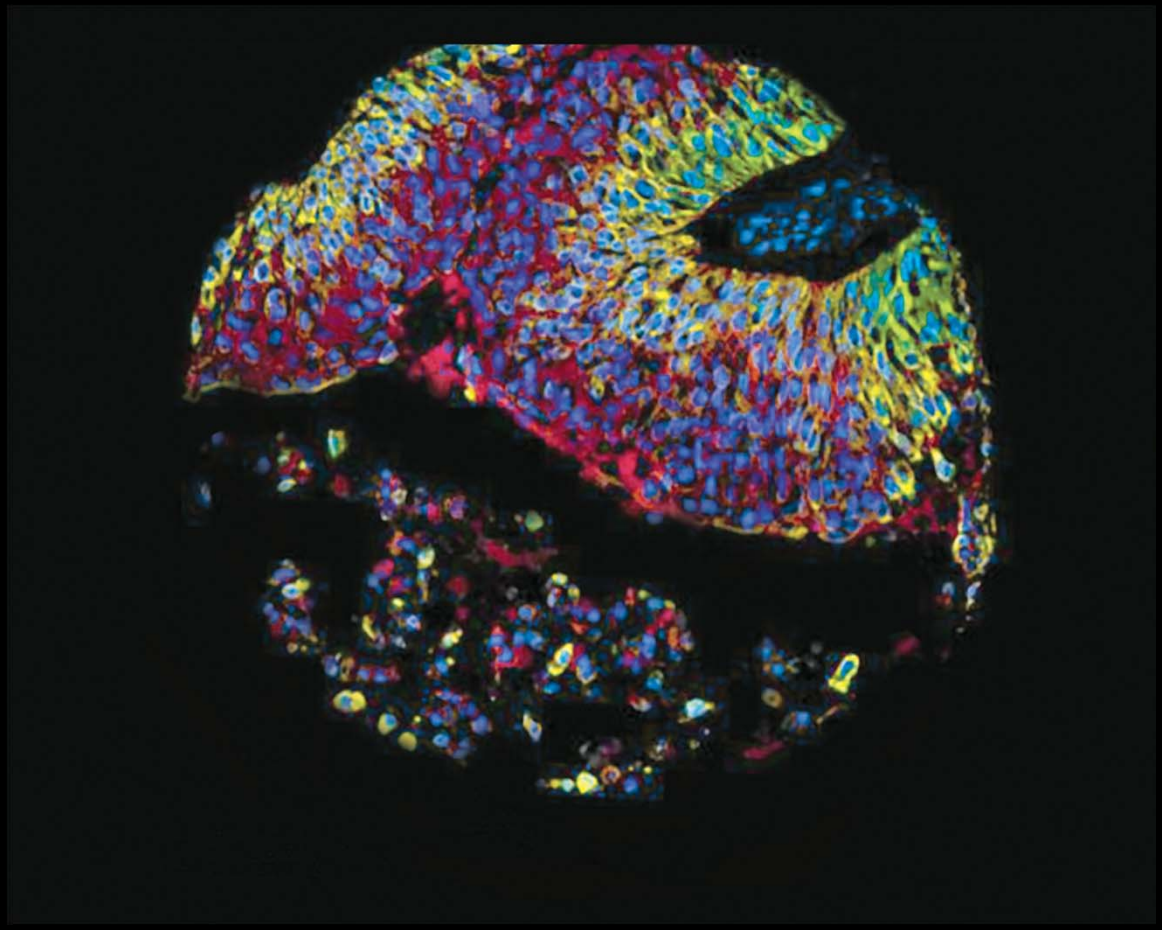
Mutations in Individual Non-small Cell Lung Cancer



Drug Targets in Individual Non-Small Cell Lung Cancers

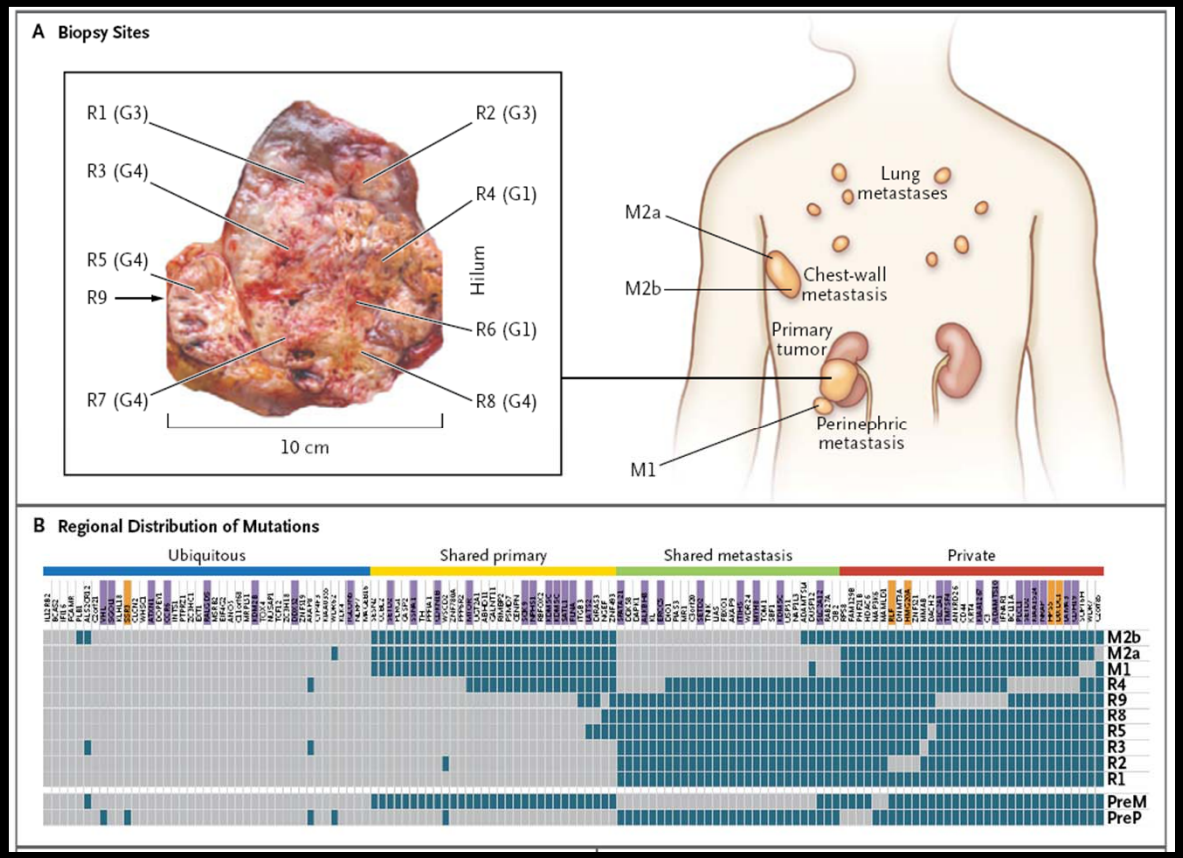
- "malignant snowflakes": each cancer carries multiple unique mutations and other genome perturbations
- disturbing implications for development of new Rx

Zonal Heterogeneity in Expression of Carbonic Anhydrase X in Renal Cell Carcinoma



From: Nature Biotechnol. (2015) 13, 215

Intratumor Genetic Heterogeneity in Multiple Regions of Primary Clear Cell Tumor and Three Metastases (Perinephric and Chest Wall) in RCC



From: M. Gerlinger et al. (2012) NEJM 366, 883

Aspirations for Improved Cancer Diagnosis and Treatment

Improved Outcomes

- **maximize the efficacy and safety of Rx interventions against advanced (metastatic) disease**
  - **circumventing variability in tumor cell clones to the selected Rx regimen (overcoming the heterogeneity problem)**
  - **dynamic monitoring of changing clonal dynamics during treatment for faster detection of drug-resistant clones**

Ensuring That the Patient's Voice is Heard

- what is my prognosis?
- what are the treatment options?
- what is the toxicity of the treatment?
- how will treatment impact my quality-of-life?
- what is likely course of my disease if I don't take treatment?

Clinical Standard-of-Care (SOC) Guidelines

- adjuvant therapy
  - (post-surgery/radiation)
- neoadjuvant therapy
  - (pre-surgery/radiation)
- palliative therapy
  - (non-curative Rx for advanced disease)
- end-of-life care
  - (last six months but more typically last month: ICU, hospice, in-home)

Drug Classes

Therapeutics

- small (heterocyclic) molecules <1500 Daltons Mw
- biologicals
  - recombinant (r)proteins, antibodies (natural/engineered)
  - nucleic acids: antisense, miRNAs, aptamers
- gene therapy (and delivery vectors)
- cell therapy
- vaccines
  - prophylactic, therapeutic
- novel drug formulations/drug delivery systems

(Bio) Pharmaceutical R&D

- small molecules (M_r typically <500 Daltons)
  - proprietary drugs (on patent) and generic versions (off-patent)
- biologicals (nucleic acids, genes, proteins, monoclonal antibodies, cells, vaccines)
  - proprietary biologicals (on-patent) and biosimilars (off patent)

FDA-Approved Anti-Cancer Drugs

DNA Damaging Agents

Generic Name	Trade Name	Approved Indication
altretamine	Hexalen	ovarian cancer
arsenic trioxide	Trisenox	certain leukemias
bendamustine	Treanda	multiple cancers
bleomycin sulfate	Blenoxane	certain lymphomas, squamous cell and testicular cancers
busulfan	Myleran, Busulfex	certain leukemias
carboplatin	Paraplatin, Paraplat	breast, lung and ovarian cancers
carmustine	BiCNU	brain tumors, certain lymphomas
chlorambucil	Leukeran	multiple cancers
cisplatin	Platinol-AQ	multiple cancers
cyclophosphamide	Cytoxan	multiple cancers
dacarbazine	DTIC-Dome	melanoma, certain brain cancers
dactinomycin	Cosmegen	multiple cancers
daunorubicin, daunomycin	Cerubidine	certain leukemias
doxorubicin hydrochloride	Adriamycin PFS, AdriamycinRDF	multiple cancers
epirubicin hydrochloride	Ellence	certain leukemias, breast and stomach cancers

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SUPPLEMENTAL MATERIALS

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Categories of Cancer Therapeutics

- expected to know different modes of action of anti-cancer drugs
- long lists of drugs posted on blackboard for reference only for those who want more information (no exam question on individual drugs)

Categories of Anti-Cancer Therapeutics

Cytotoxic Chemotherapy

- DNA synthesis inhibitors (anti-metabolites)
- DNA damaging agents
- cytoskeleton (microtubule) modifying agents

Hormonal Agents

- hormones (agonists)
- hormone blockers (antagonists)

Categories of Anti-Cancer Therapeutics

Targeted Chemotherapy

- small molecule cell signaling inhibitors
  - largely tyrosine kinase inhibitors (TKi's)
- angiogenesis inhibitors
  - again largely kinase inhibitors
- monoclonal antibodies
  - block growth factor receptors on tumor cells
  - induce tumor cell death
  - promote destruction by host defense cells (antibody dependent cellular cytotoxicity: ADCC)

Categories of Anti-Cancer Therapeutics

Epigenetic Modulators

- modify histones and gene expression

Proteasome Inhibitors

Cell Differentiation Agents

- induce terminal differentiation to non-replicating state (leukemias/lymphomas but not solid tumors to date)

Categories of Anti-Cancer Therapeutics

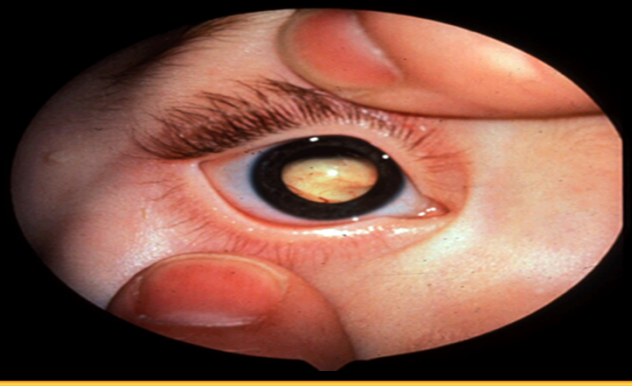
Immunotherapeutics

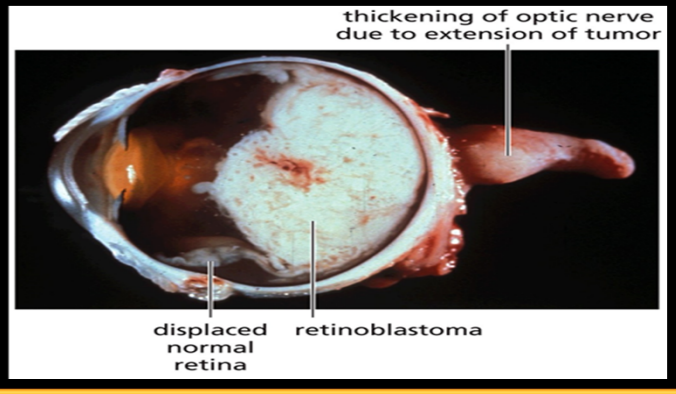
- anti-tumor monoclonal antibodies
- immune checkpoint modulators (overcome tumor-induced suppression of host defenses)
- immunomodulators (stimulate immune system)
- anti-cancer vaccines (prophylactic or therapeutic)
- immune cells with engineered anti-tumor activities

Week 11, Lecture 2

Cancer Predisposition Genes

Retinoblastoma (RB)





Adenomatosis Polyposis Coli (APC)

Inherited Cancer Risk

Cancer	Syndrome	Associated Gene
Leukemias and lymphomas	Ataxia telangiectasia	*ATM*
All cancers	Bloom syndrome	*BLM*
Breast, ovarian, pancreatic, and prostate cancers	Breast-ovarian cancer syndrome	*BRCA1, BRCA2*
Breast, thyroid and endometrial cancers	Cowden syndrome	*PTEN*
Colorectal cancer	Familial adenomatous polyposis (FAP)	*APC*
Melanoma	Familial atypical multiple mole–melanoma syndrome (FAMM)	*CDKN2A*
Retinal cancer	Familial retinoblastoma	*RB1*
Leukemia	Fanconi's anemia	*FACC, FACA*
Colorectal cancer	Hereditary nonpolyposis colorectal cancer/Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*
Pancreatic cancer	Hereditary pancreatitis/familial pancreatitis	*PRSS1, SPINK1*
Leukemias, breast, brain and soft tissue cancers	Li-Fraumeni	*TP53*
Pancreatic cancers, pituitary adenomas, benign skin and fat tumors	Multiple endocrine neoplasia 1	*MEN1*
Thyroid cancer, pheochromacytoma	Multiple endocrine neoplasia 2	*RET, NTRK1*
Pancreatic, liver, lung, breast, ovarian, uterine and testicular cancers	Peutz–Jeghers syndrome	*STK11/LKB1*
Tumors of the spinal cord, cerebellum, retina, adrenals, kidneys	von Hippel-Lindau syndrome	*VHL*
Kidney cancer	Wilms' tumor	*WT1*
Skin cancer	Xeroderma pigmentosum	*XPD, XPB, XPA*

AACR Cancer Progress Report 2013, pg31

BRCA 1 and 2 as Tumor Suppressor Genes: Different Mutations May Confer Different Risks

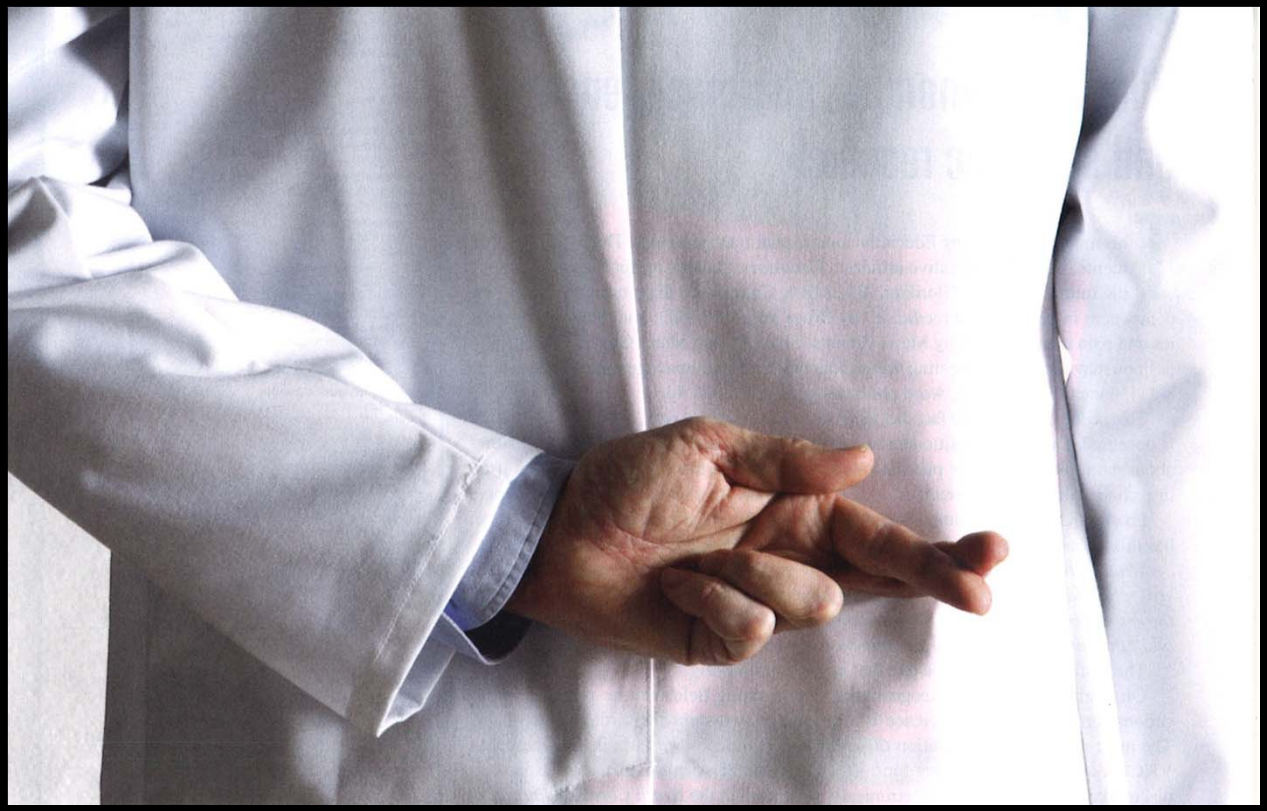
- substantially increased lifetime risks of breast and ovarian cancers but only small risk of increased pancreatic cancer
- loss-of-function mutations in central gene region confer higher risk of ovarian cancer versus breast cancer than mutations at gene end regions

Screening and Cancer Prevention in Individuals with Inherited Germline Mutations in Cancer Predisposing Genes

- surgical removal of 'at risk' organ in high risk patients
  - mastectomy, oophorectomy (BRCA-1/2 carriers)
  - stomach (CDH1 mutation)
  - thyroid (RET mutation)
  - colon (APC mutation)
- detection of early cancer and surgical resection
  - elevated catecholamines (phaeochromocytoma)
  - elevated calcitonin (thyroid cancer)

The Current Status of Cancer Care

Flying Blind:
One-Size-Fits All Rx Approaches to Complex Multigenic Diseases

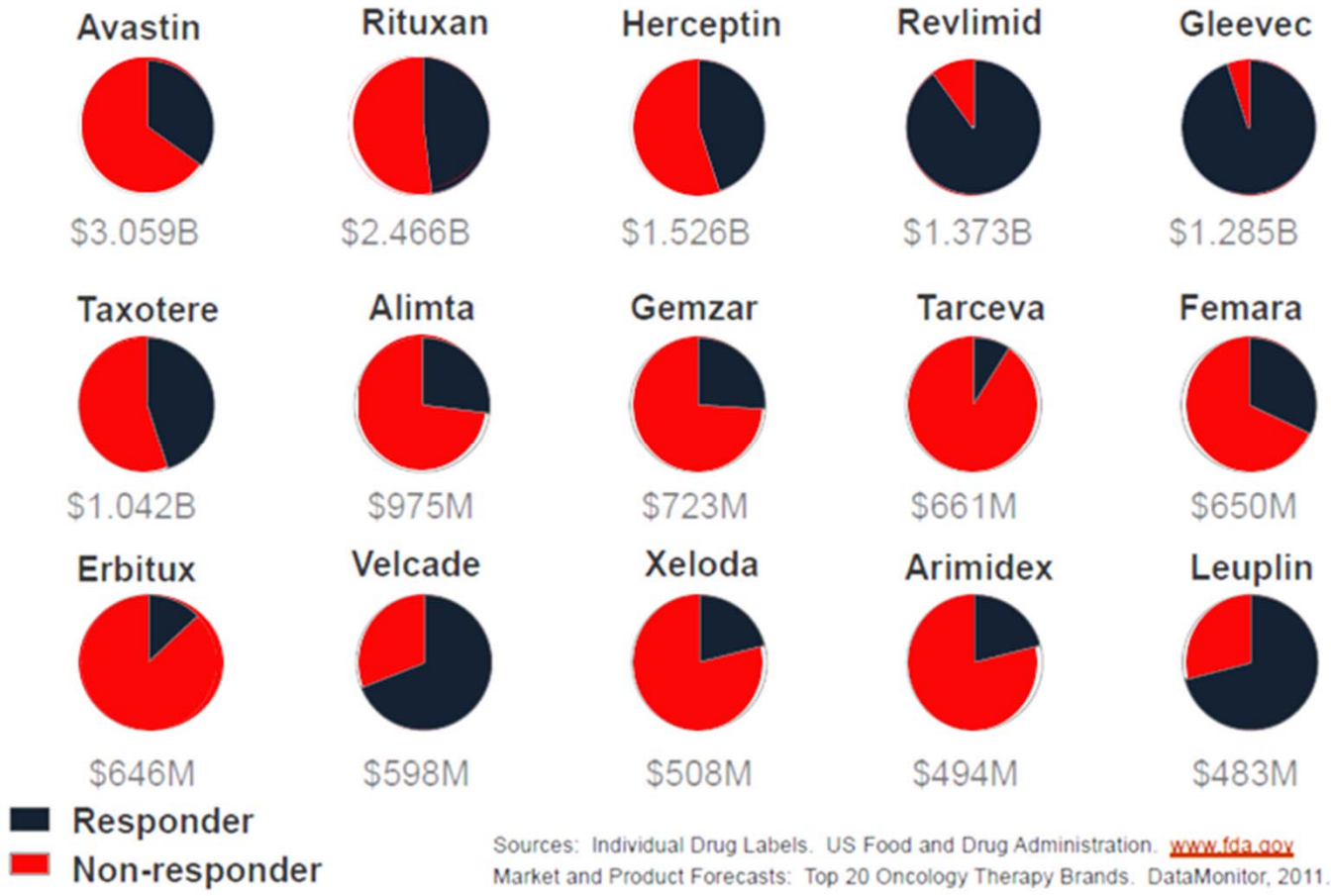


Ignoring The Obvious in Clinical Practice

- diseases are not uniform
- patients are not uniform
- a “one-size fits all” Rx approach cannot continue
- ignores known variation in disease progression and therapeutic responses

- inefficiency and waste caused by empirical Rx
- cost of futile therapy
- risk to patients via AE’s
- first rule of radical ethics: do no harm!

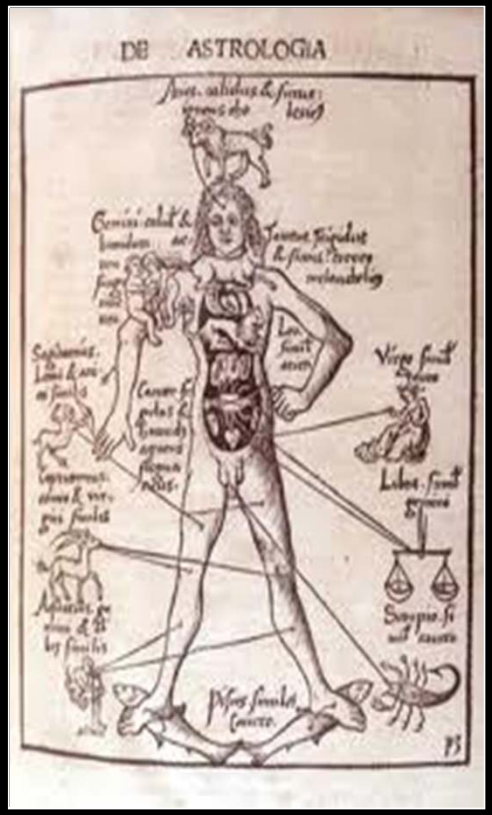
Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly

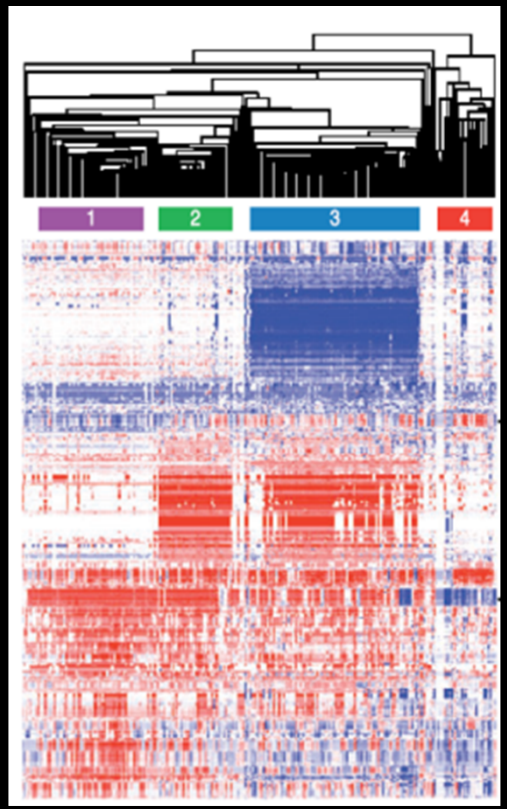


Sources: Individual Drug Labels. US Food and Drug Administration. www.fda.gov
Market and Product Forecasts: Top 20 Oncology Therapy Brands. DataMonitor, 2011.

The Path to Precision (Personalized) Therapy

Medical Progress:
From Superstitions to Symptoms to Signatures





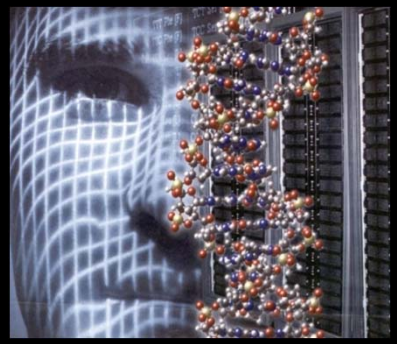
Precision (Personalized) Medicine

Mapping the Disruption in Molecular (Information) Signaling Pathways in Disease

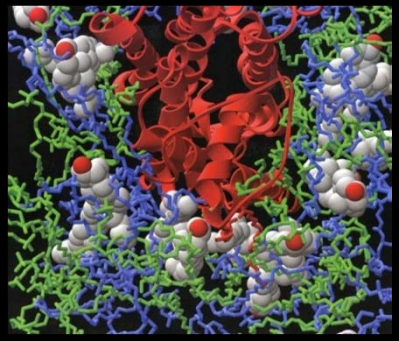
Foundation of Improved Diagnostic Accuracy Prognosis and Rational Selection of Rx Choice

Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

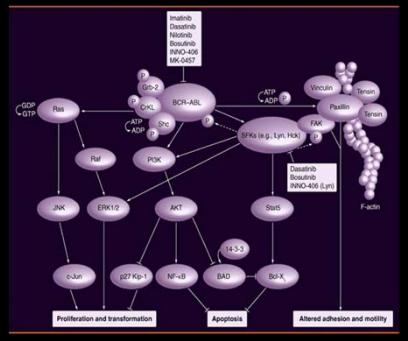
Genomics



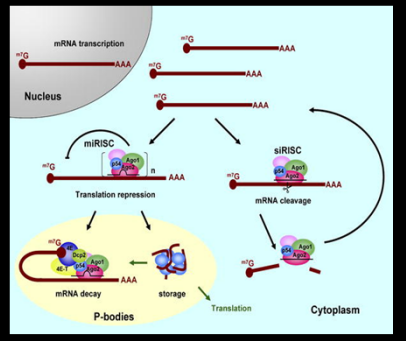
Proteomics

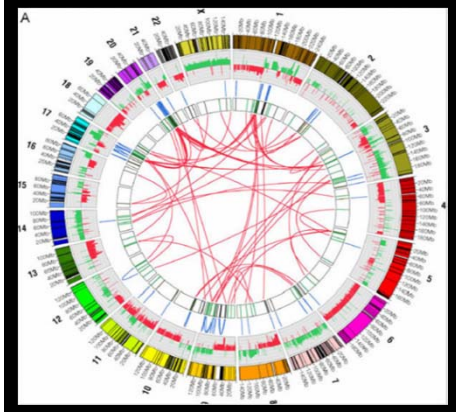


Molecular Pathways and Networks



Network Regulatory Mechanisms



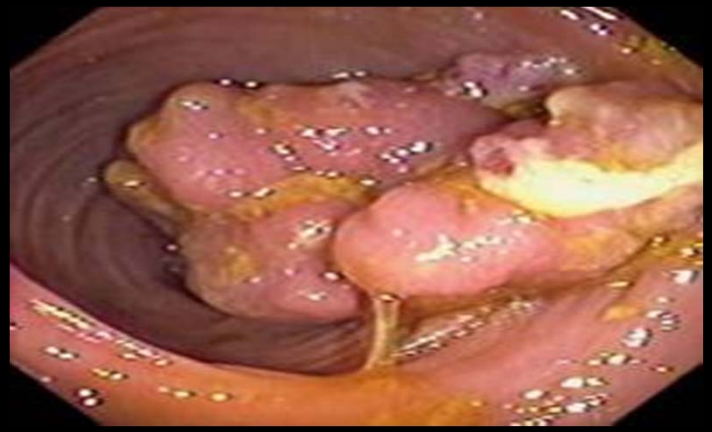


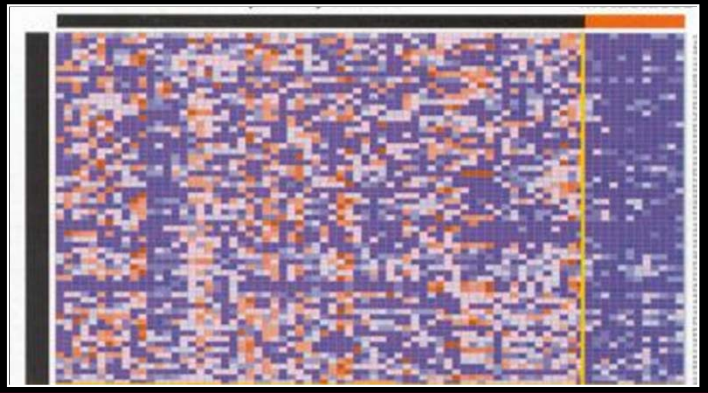
ID of Causal Relationships Between Network Perturbations and Disease

Patient-Specific Signals and Signatures of Disease or Predisposition to Disease

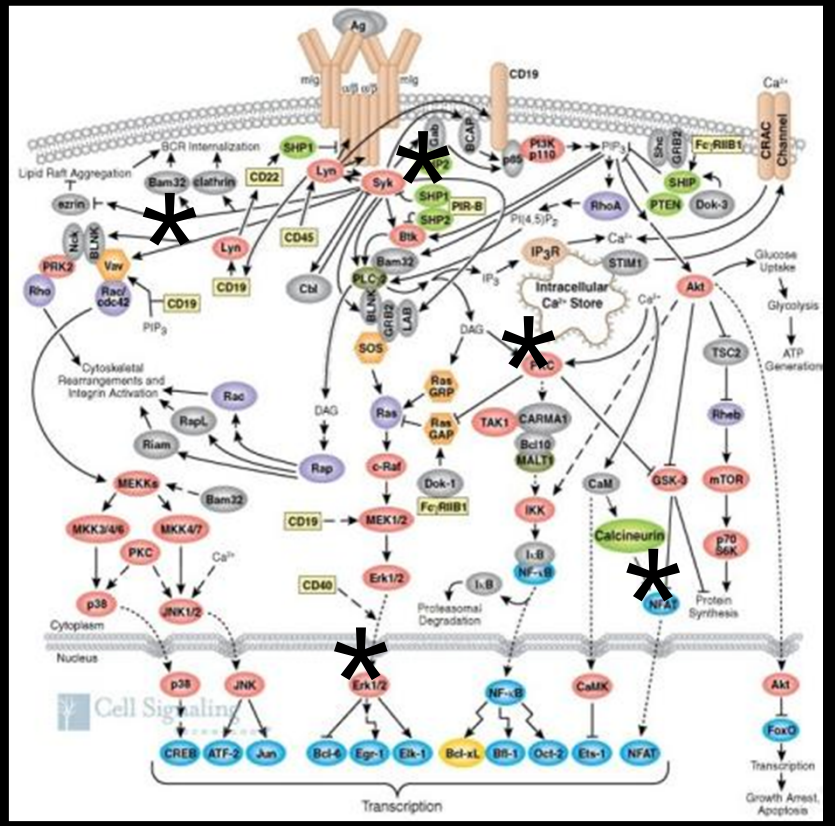
Mapping Causal Perturbations in Molecular Pathways and Networks in Disease: Defining a New Taxonomy for Disease

"Omics" Profiling to Identify Disease Subtypes (+ or - Rx Target)

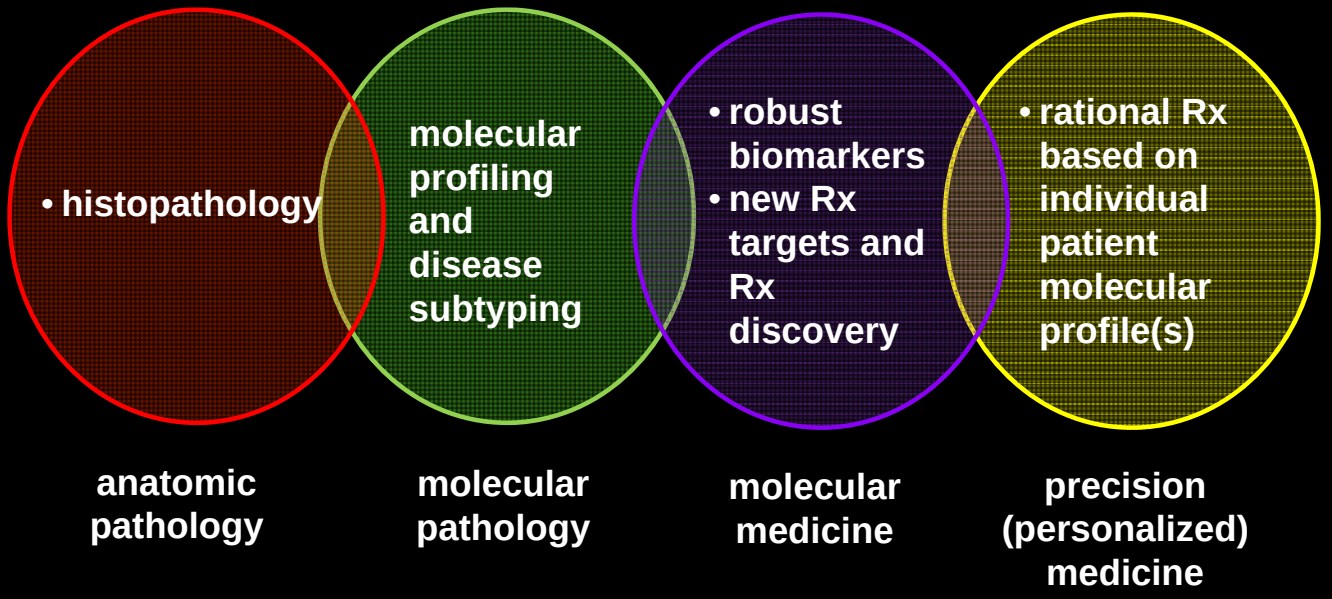




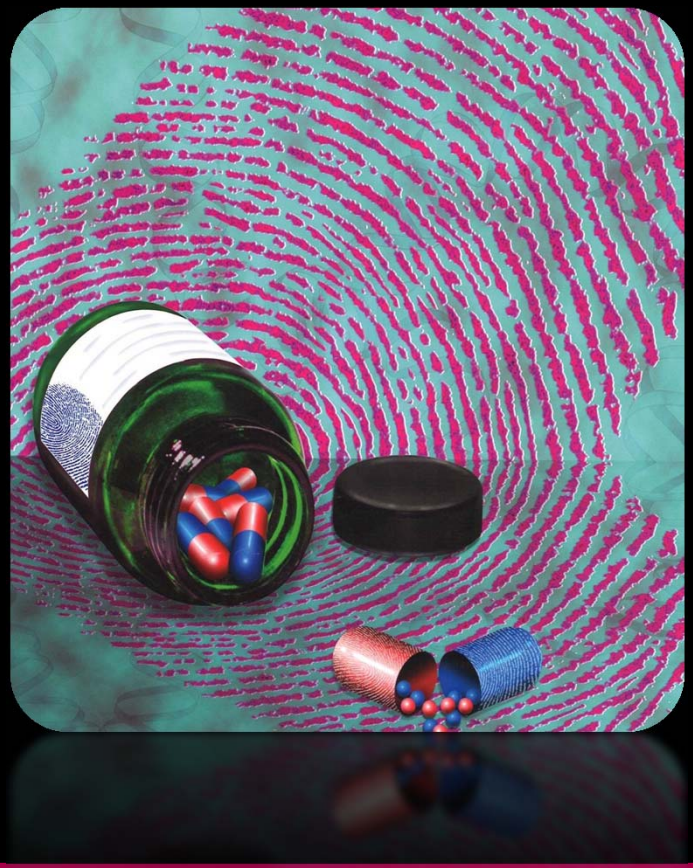
Altered Network Structure and ID of Molecular Targets for MDx and/or Rx Action



Understanding Cancer Biology and the Quest for Improvements in Cancer Care

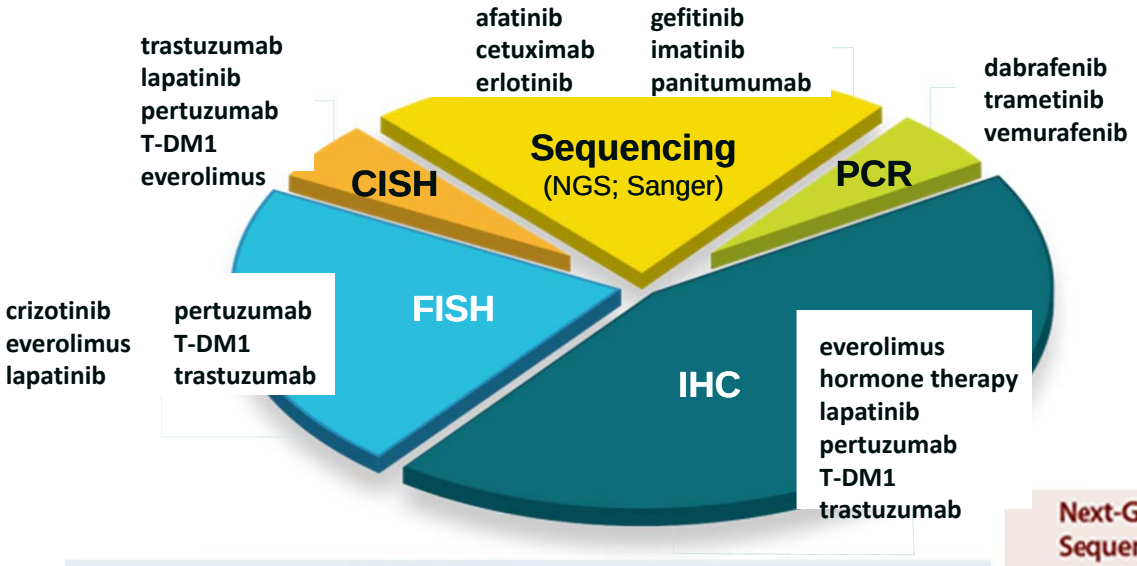


Precision Medicine



- right diagnosis and disease classification and subtyping by MDx
- right Rx for right disease subtype (efficacy)
- right Rx for right patient (efficacy and adverse event reduction)
- right dose, duration and timing (efficacy, safety and compliance)

The Need for Multiple Molecular Diagnostic Platforms for Comprehensive Profiling of Actionable Drug: Target Associations to Guide Therapeutic Decisions in Oncology



55 Actionable Drug/Target Associations

- Next-Generation Sequencing *(NGS)*
- Fluorescence in situ Hybridization *(FISH)*
- Chromogenic in situ Hybridization *(CISH)*
- Immunohistochemistry *(IHC)*
- Sanger Sequencing
- PryoSequencing
- Fragment Analysis
- Quantitative Polymerase Chain Reaction *(qPCR - cobas®)*

abarelix	ceritinib	docetaxel	fluorouracil	irinotecan	nab-paclitaxel	sunitinib	trametinib
abiraterone	cetuximab	doxorubicin	flutamide	lapatinib	oxaliplatin	tamoxifen	trastuzumab
afatinib	cisplatin	enzalutamide	fulvestrant	letrozole	paclitaxel	T-DM1	triptorelin
anastrozole	crizotinib	epirubicin	gefitinib	leuprolide	panitumumab	temozolomide	vandetanib
bicalutamide	dabrafenib	erlotinib	gemcitabine	liposomal-doxorubicin	pemetrexed	temsirolimus	vemurafenib
capecitabine	dacarbazine	everolimus	goserelin	lomustine	pertuzumab	topotecan	vincristine
carboplatin	degarelix	exemestane	imatinib	megestrol acetate	procarbazine	toremifene	

Next-Generation Sequencing *(NGS)*

19 Actionable Drug:Target Associations

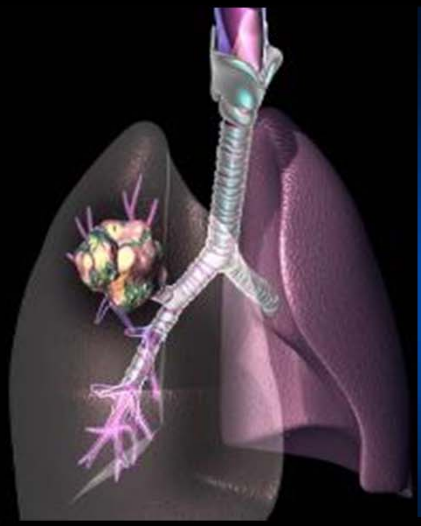
afatinib	oxaliplatin
carboplatin	panitumumab
cetuximab	sunitinib
cisplatin	temozolomide
dabrafenib	temsirolimus
dacarbazine	trametinib
erlotinib	trastuzumab
everolimus	vandetanib
gefitinib	vemurafenib
imatinib	

Oncogene Addiction and 'targeted' Cancer Therapies

- tumor cells become reliant on particular oncogene
- die if addictive oncogene is inhibited
- rationale for 'targeted' cancer therapy to selectivity inhibit the relevant oncogene

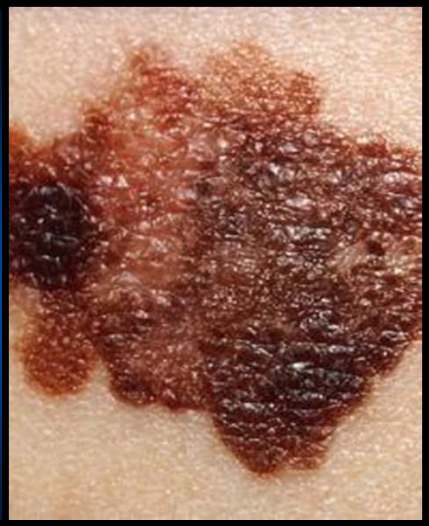
Biomarkers, Disease Subtyping and Targeted Therapy: Companion Diagnostics - the Right Rx for the Right Disease (Subtype)

Her-2+
(Herceptin)
(Perjeta)



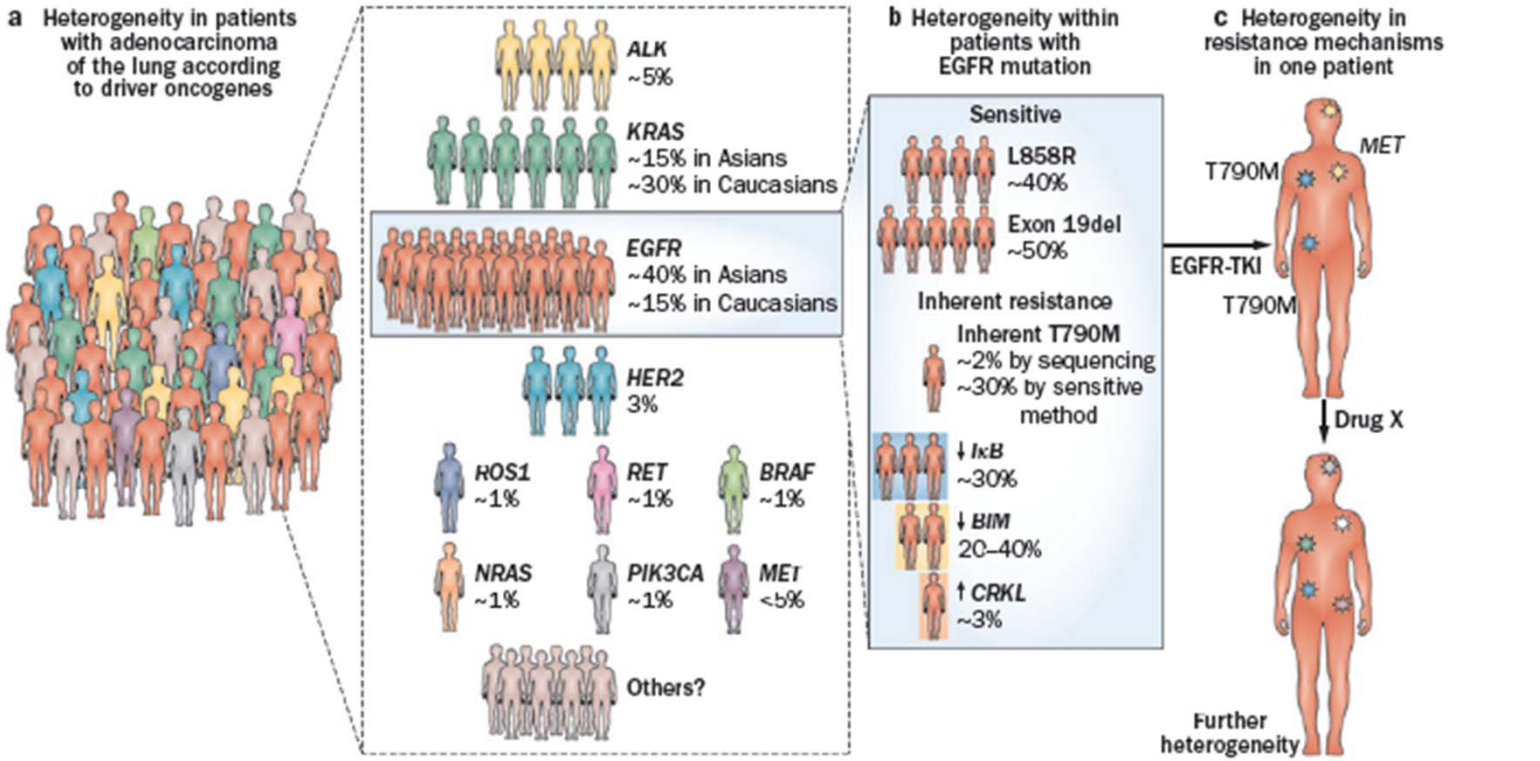
EML4-ALK
(Xalkori)

KRAS
(Erbitux)
(Vectibix)



BRAF-V600
(Zelboraf)

Heterogeneity of Driver Oncogenes in NSCLC



From: T. Mitsudomi et al. (2013) Nat. Rev. Clin. Oncol. 10, 235

Targeted Oncology Therapies in Molecularly Stratified Populations

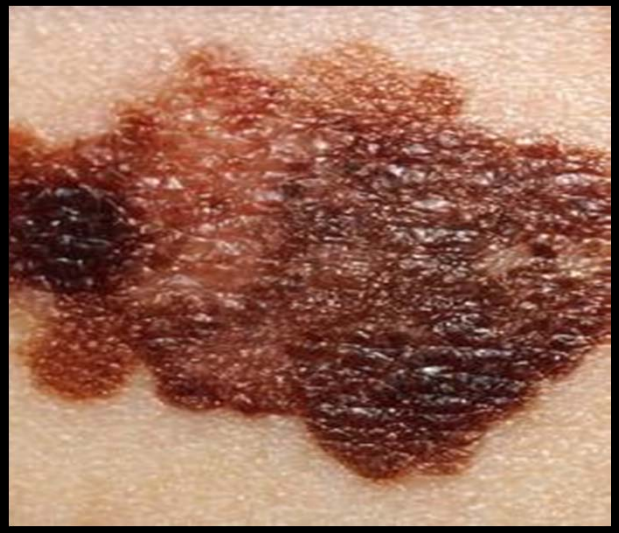
Cancer	Target	Agent
Breast carcinoma	HER2 amplification	trastuzumab, lapatinib
NSCLC (adenoCA)	EGFR mutations	EGFR TKIs (erlotinib, gefitinib)
NSCLC	EML-ALK	ALK inhibitors (crizotinib)
GIST	KIT and PDGFRA mutations	Imatinib
Melanoma	BRAF-V600 mutation	BRAF inhibitor (vemurafenib)
Ewing's sarcoma	EWS-FLI translocation	anti-IGF1R mab (figitumumab)
Medulloblastoma BCC	PTCH1 or SMO mutations	SMO inhibitors (vismodegib)
Ovarian/ breast CA	BRCA1/BRCA2 mutations	PARP inhibitors (olaparib)
PRCC	MET mutations	MET TKIs (ARQ197. XL880)

Context:

Alteration of Rx Target in One Cancer Cell Type
May Not Always Translate to Rx Efficacy
in Cancers Arising in Different Cell Types

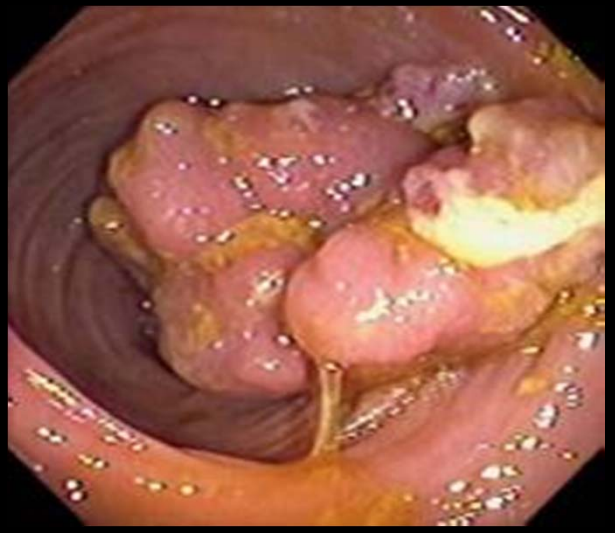
Expression of Same Mutation in Cancers Arising in Different Cell Lineages but with Different Response to Same Targeted Therapy

Melanoma
BRAF-V600



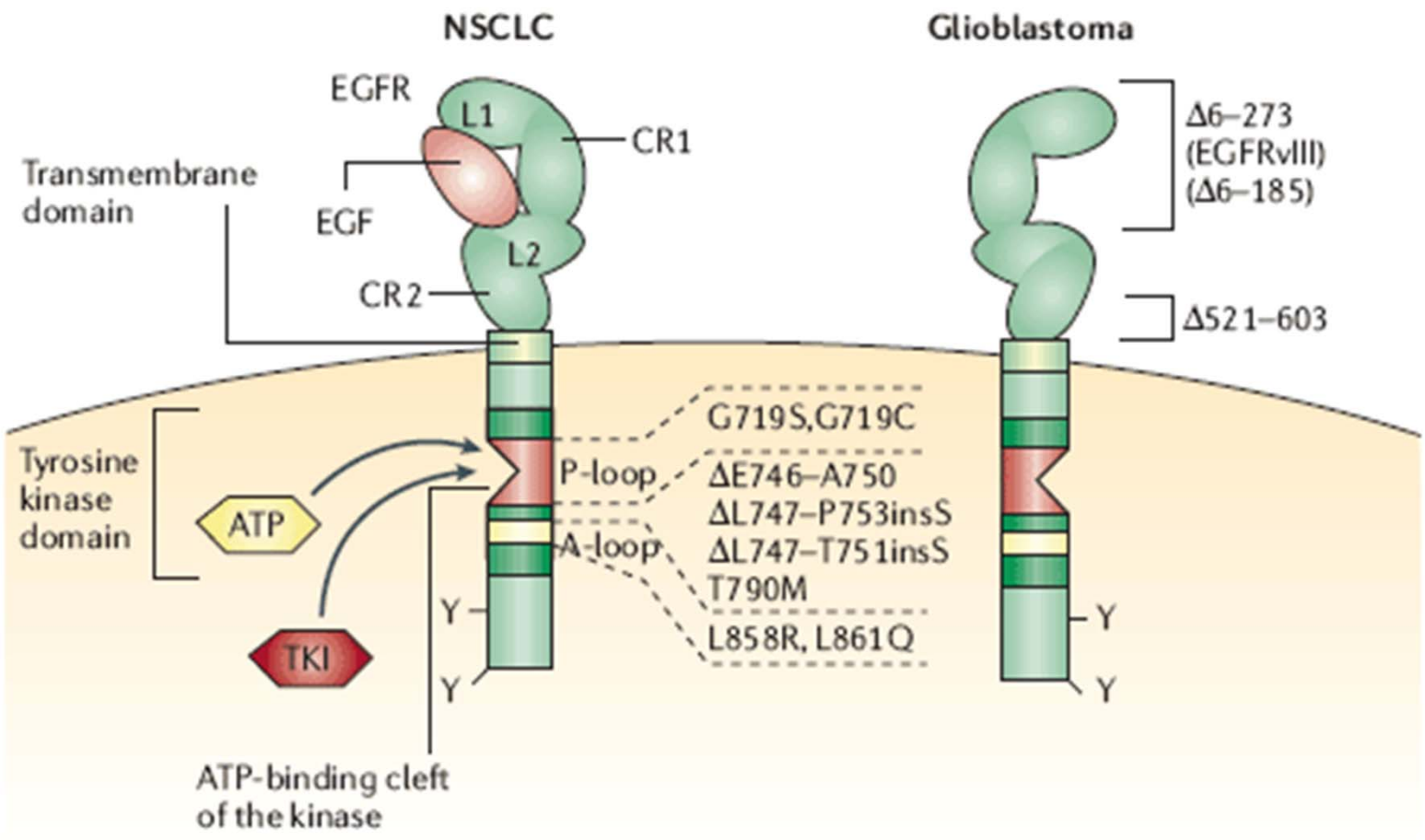
positive response to vemurafenib

Colorectal Cancer
BRAF-V600



10% patients carry mutation but unresponsive to vemurafenib due to compensatory activation of EGFR

EGFR Mutations in Different Structural Domains



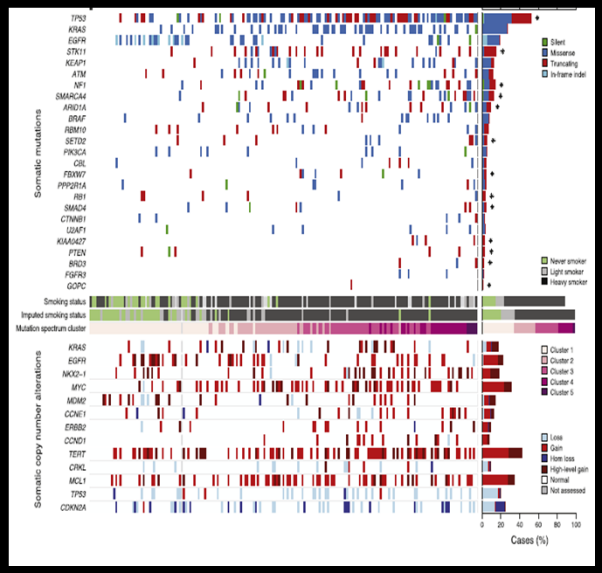
Source: Nat. Rev. Cancer 2006

Differential Sensitivity of Glioma-Versus Lung Cancer-Specific EGFR Mutations to EGFR Kinase Inhibitors

- EGFR mutations in lung cancer reside in the intracellular kinase domain
- EGFR mutations in glioblastoma multiforme (GBM) cluster in the extracellular domain
  - poor clinical results in GBM with erlotinib, gefitnib

Tumor Cell Heterogeneity: The Omnipresent and Greatest Challenge in Cancer Therapy

The Extravagant Landscape of Genomic Alterations in Cancer (Cell 2012, 150, 1107 and 1121)



Mutations in Individual Non-small Cell Lung Cancer

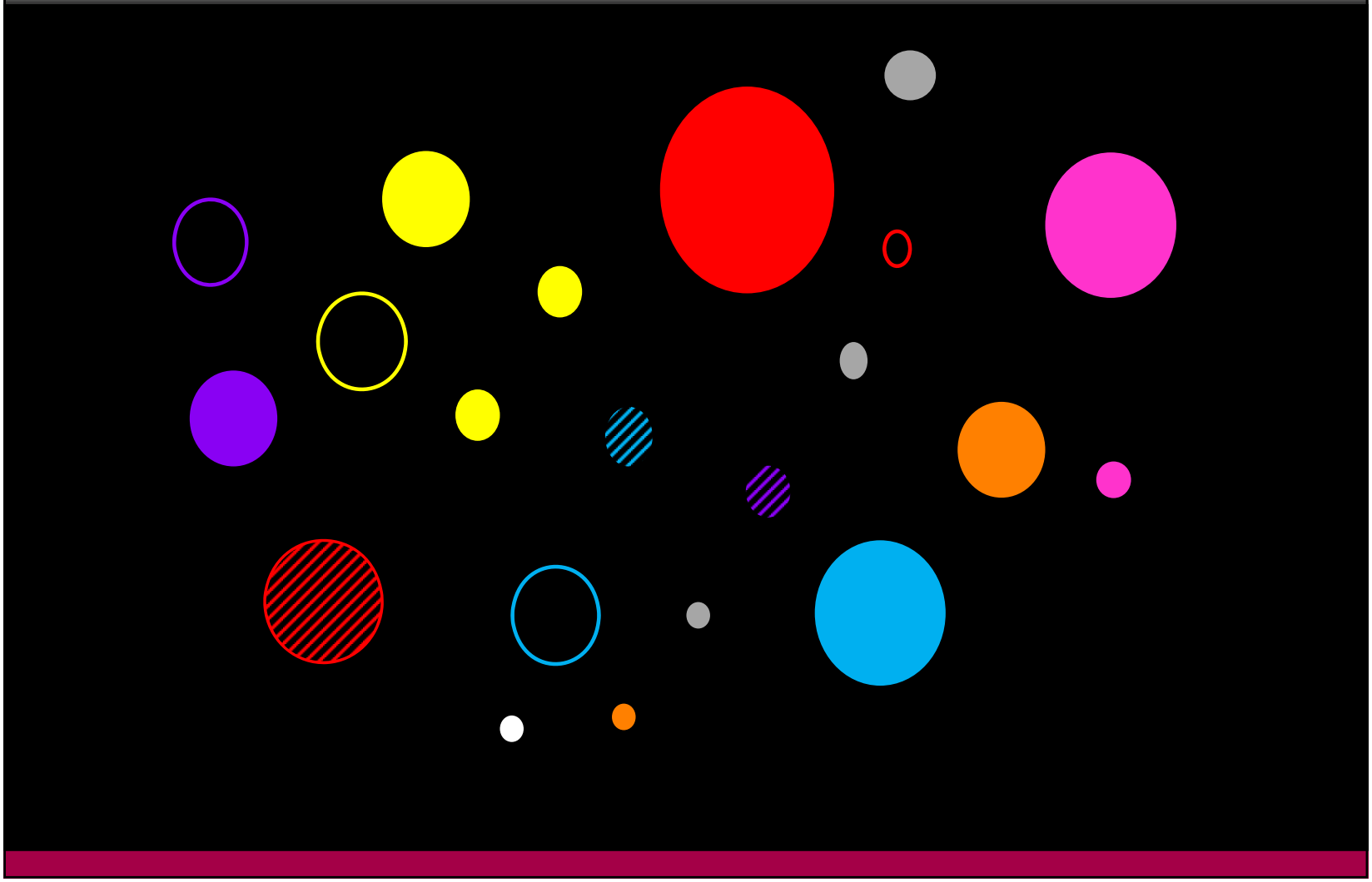
Drug Targets in Individual Non-Small Cell Lung Cancers

- "malignant snowflakes": each cancer carries multiple unique mutations and other genome perturbations
- disturbing implications for development of new Rx

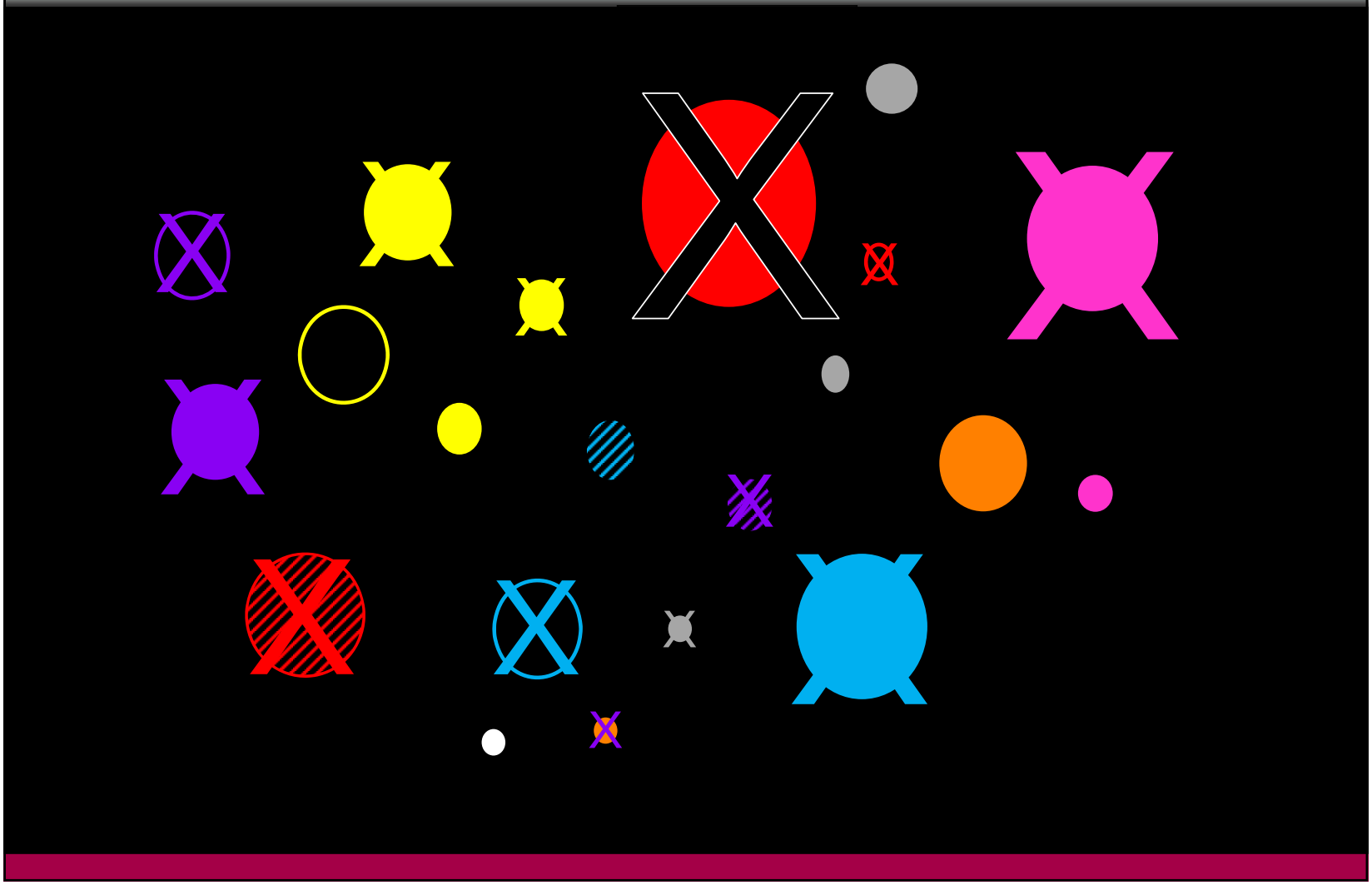
Cellular (Clonal) Heterogeneity: A Ubiquitous Feature of Cancer and the Largest Obstacle to Effective Treatment

- between patients (inter-patient heterogeneity)
- within the primary tumor (zonal heterogeneity)
- between different metastases in the same patient (inter-regional heterogeneity)

Tumor Cell Heterogeneity: The Omnipresent and Greatest Challenge in Cancer Therapy



Tumor Cell Heterogeneity: The Omnipresent and Greatest Challenge in Cancer Therapy



Drug Resistance:

The Principal Challenge in Cancer Rx Therapy

The Co-existence of Multiple Tumor Cell Clones with Varied Susceptibility to Different-Rx

Emergence of Drug-Resistance Mutations in Tumor Progression

mutation(s) in Rx-naïve patients

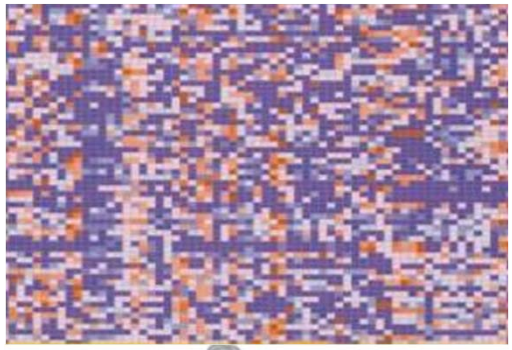
- "intrinsic resistance" to specific Rx
- exist prior to Rx

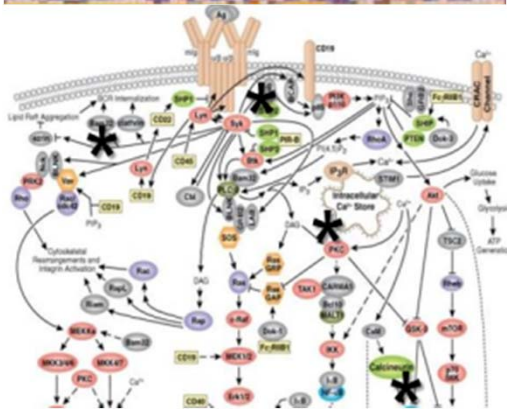
mutation(s) in Rx-treated patients

- "acquired resistance" to specific Rx
- Rx as selective pressure (cf. antibiotic resistance in bacteria)

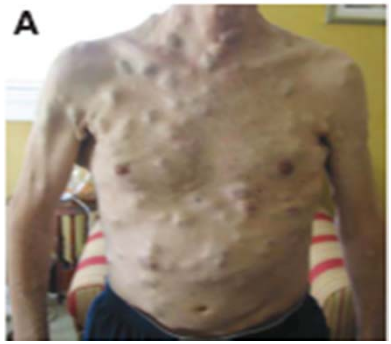
Targeted Therapeutics and Cancer

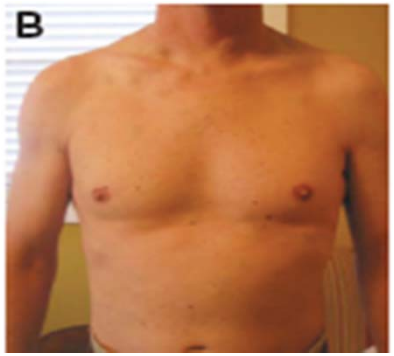
Molecular Subtyping and RX Targets



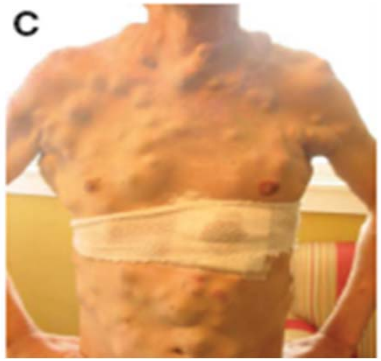


Initial Rx-Response to Targeted Rx





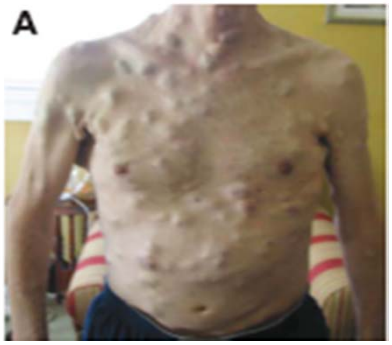
Rx-Resistance via Redundant Molecular Pathways

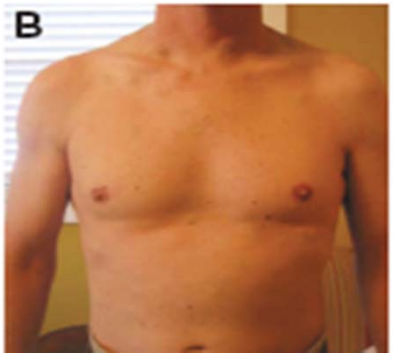


B = 15 weeks Rx (Zelboraf®)
C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011) JCO 29, 3085)

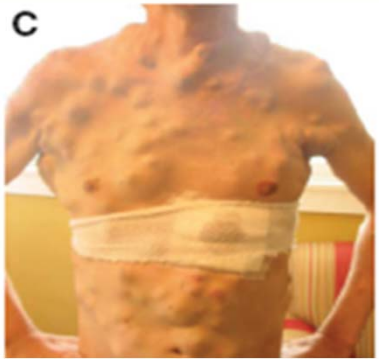
Emergence of Drug Resistance to Targeted Therapy in Melanoma

Initial Rx-Response to Targeted Rx



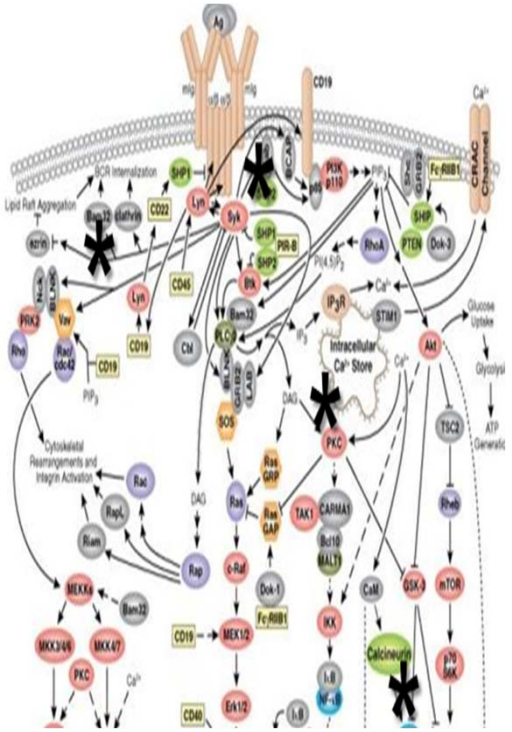


Rx-Resistance via Alternate Molecular Signaling Pathway (Network Redundancy)



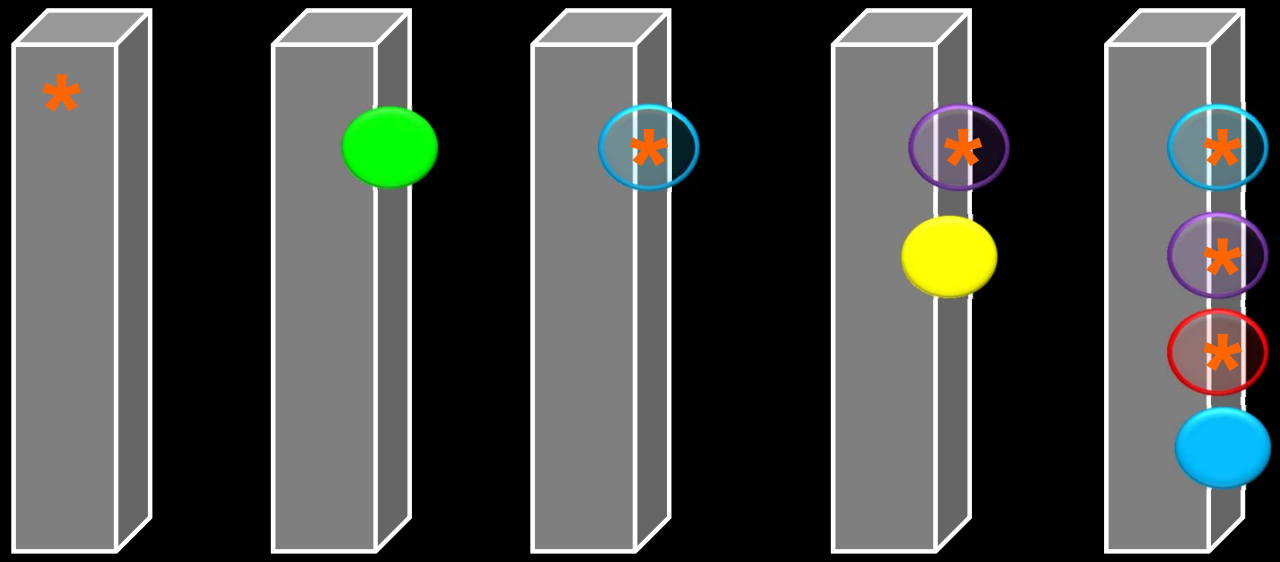
B = 15 weeks Rx (Zelboraf®)
C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011) JCO 29, 3085)

Circumvention of Rx-Resistance Requires Multi-site Blockade of Connected Signaling Pathways



Point Mutation$^{(M)}$-Driven Resistance to Targeted Anticancer Drugs

Evolution of Rx-Resistant Clones During Tumor Progression



Rx-sensitive Rx1

Rx-resistant

Rx-sensitive Rx2

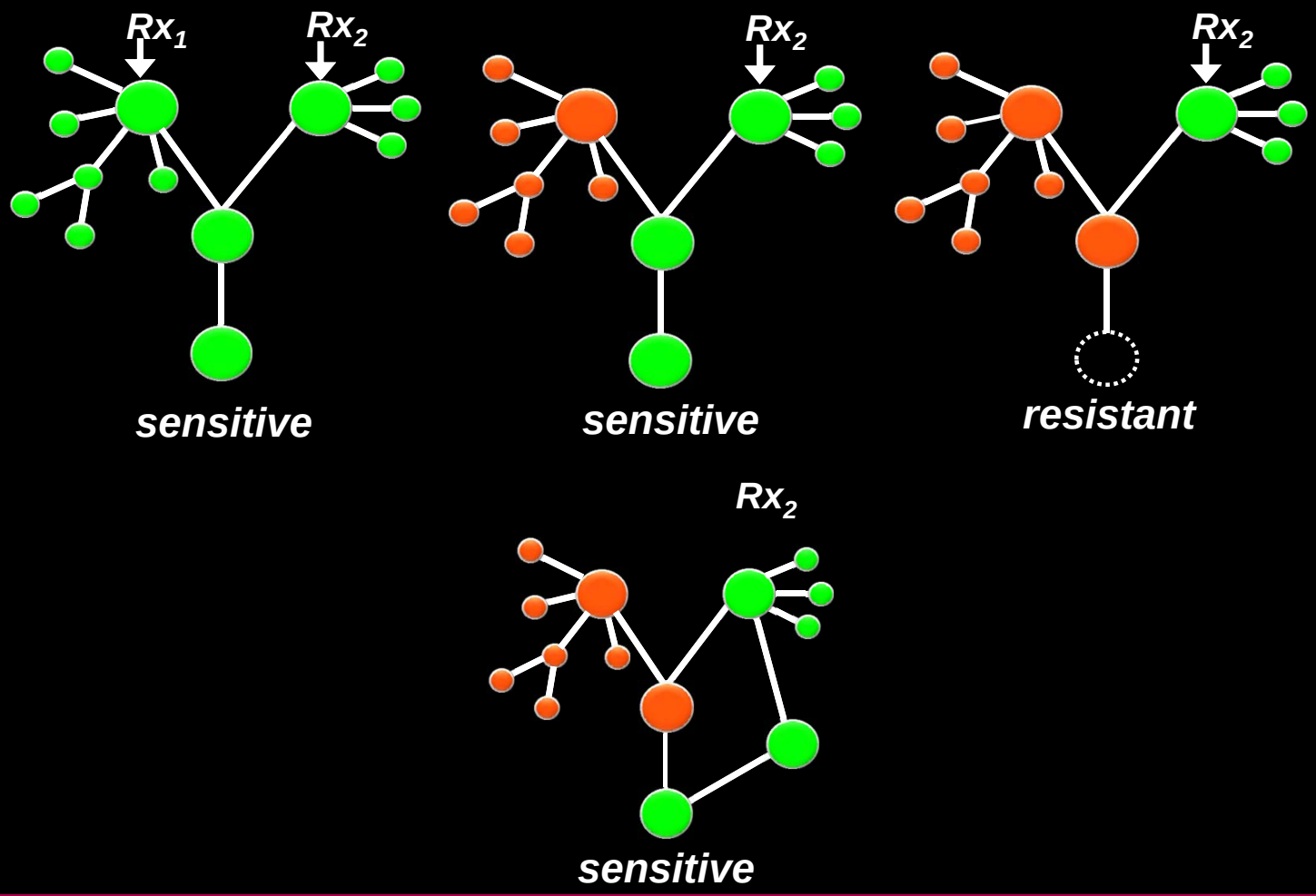
Rx-resistant

refractory resistant disease Rx^n

‘Compensatory’ Signaling Pathways and Drug Resistance

Linkage (Connections) Between Different Signaling Pathways Offers a Major By-Pass for Cancer Cells to Develop Rx Resistance

Redundancy and Robustness in Molecular Signaling Networks: The Biological Foundation of Rx Resistance



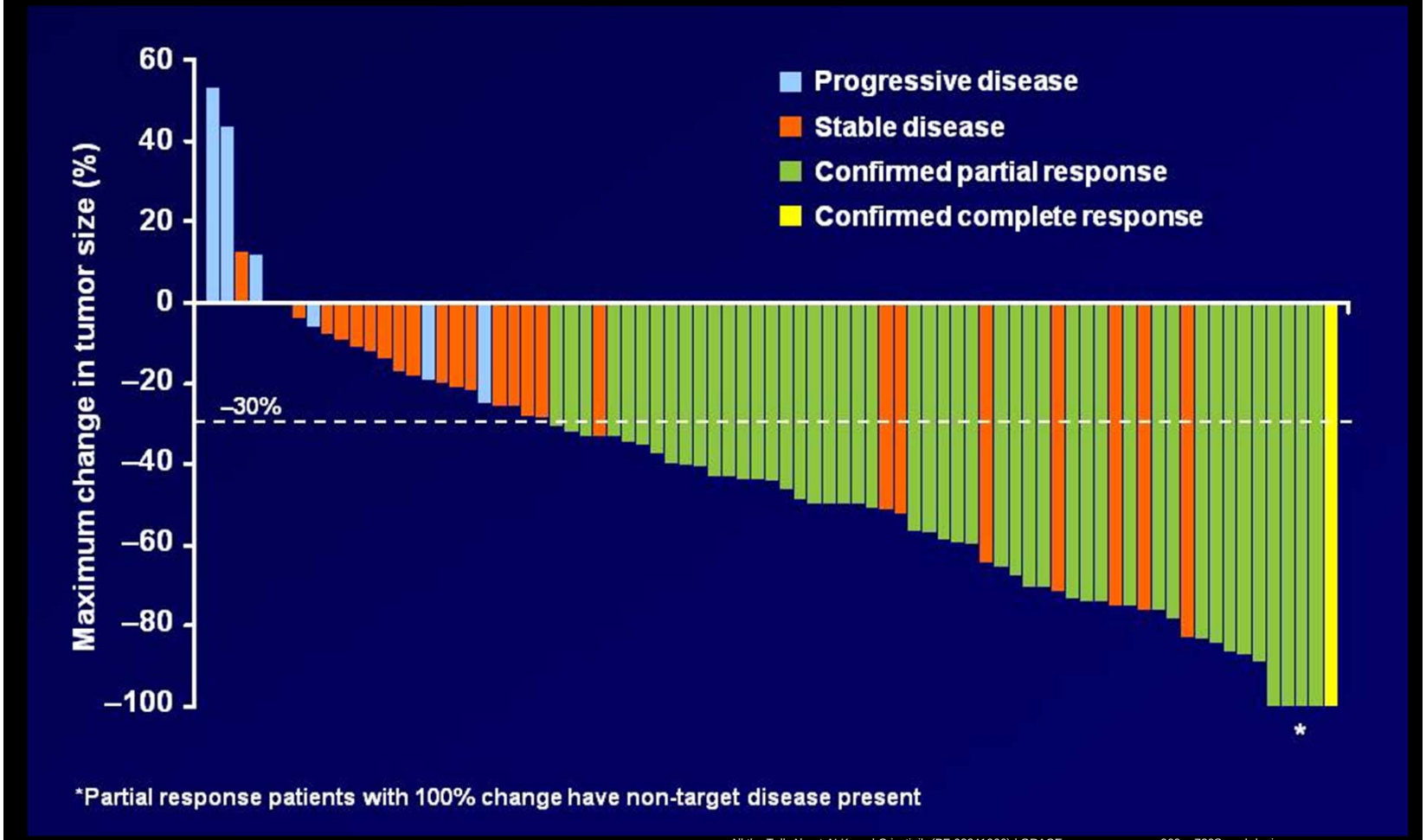
Drug Resistance Can Arise from Both Mutations in the Drug-Target Plus Use of By-Pass Pathways

Monitoring Treatment Efficacy

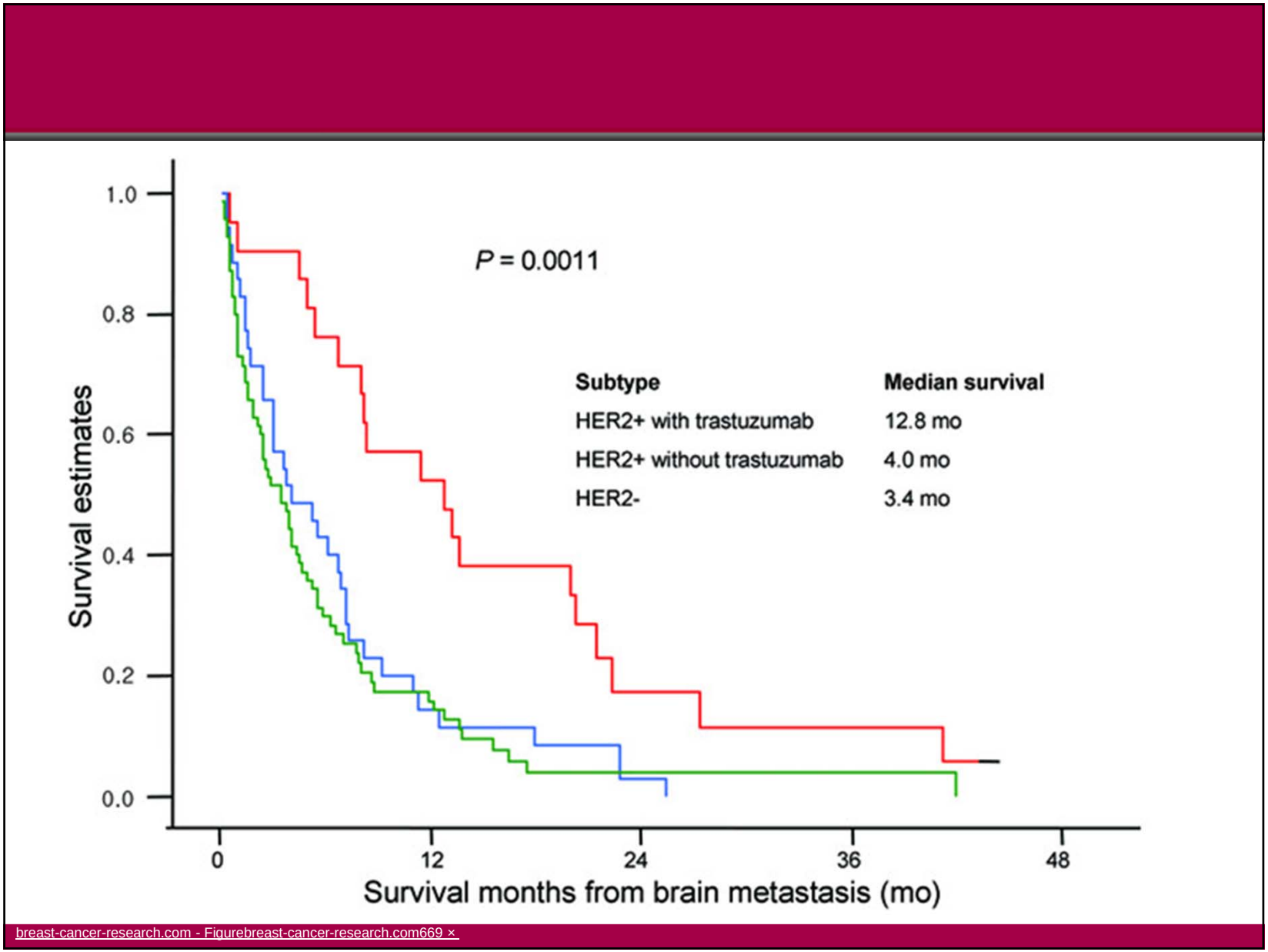
Monitoring Treatment Responses in Cancer Patients

- no, partial (PR) or complete (CR) responses
- progression-free survival (interval) (PFS)
- progressive disease
- chronic, stable disease
- regulatory parameters: PFS and overall survival (OS)
- recurrent disease in patients previously viewed as having no or minimal residual disease
- terminal disease

Tumor Responses to Crizotinib for Patients with ALK-positive NSCLC



All the Talk About ALK, and Crizotinib (PF-02341066) | GRACE ...cancergrace.org960 × 720Search by image


1.0
0.8
0.6
0.4
0.2
0.0
Survival estimates
P = 0.0011
Subtype
Median survival
HER2+ with trastuzumab
12.8 mo
HER2+ without trastuzumab
4.0 mo
HER2-
3.4 mo
0
12
24
36
48
Survival months from brain metastasis (mo)
breast-cancer-research.com - Figurebreast-cancer-research.com669 ×

RECIST
(Response Evaluation Criteria In Solid Tumors)

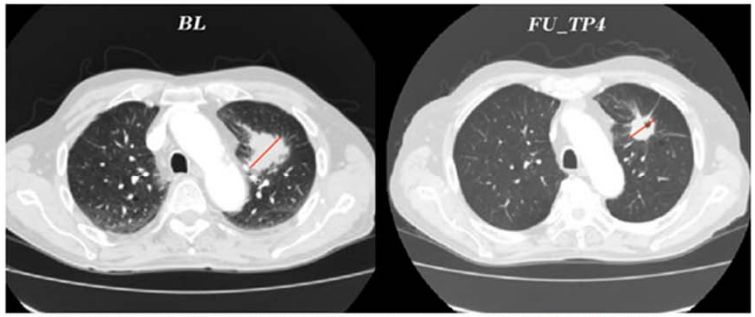
RECIST Version 1.1 Update | RECIST in Practice

Topics

1. RECIST - Definitions
2. Measure the longest in plane diameter
3. Target Measurement Rules
4. Selecting Target Lesions
5. Importance of Imaging Consistency
6. Importance of IV-Contrast
7. Importance of i.v.-contrast and proper timing, scanning delay
8. Imaging: Anatomy for CT/MRI
9. Target Measurement Rules at Follow-up
10. Progression by Non-Targets only
11. Reappearing Lesion
12. Splitting Lesions
13. Merging Lesions
14. Merging lesions example
15. Variable Enhancement
16. Lung Lesion develops cavity
17. Lymph Node Measurements, CT
18. Lymph Node Measurements, MRI
19. Bone mets
20. MRI
21. PET
22. Overview: RECIST vs. RECIST 1.1

Topic 16 < Prev Next >

Lung Lesion develops cavity



Continue measuring target lesions in their longest diameter, even when they develop central cavities or necrosis.

If the sum of diameters does not accurately reflect the patient's response assessment, a different assessment may be provided, accompanied by explanatory comments justifying so

< Prev Next >

Monitoring Treatment Responses in Cancer

RECIST

- **Response Evaluation Criteria In Solid Tumors**
- **imaging of size and volume of tumor metastases**
- **not sufficiently sensitive to detect emergence of treatment-resistant tumor cell clones in solid tumors**

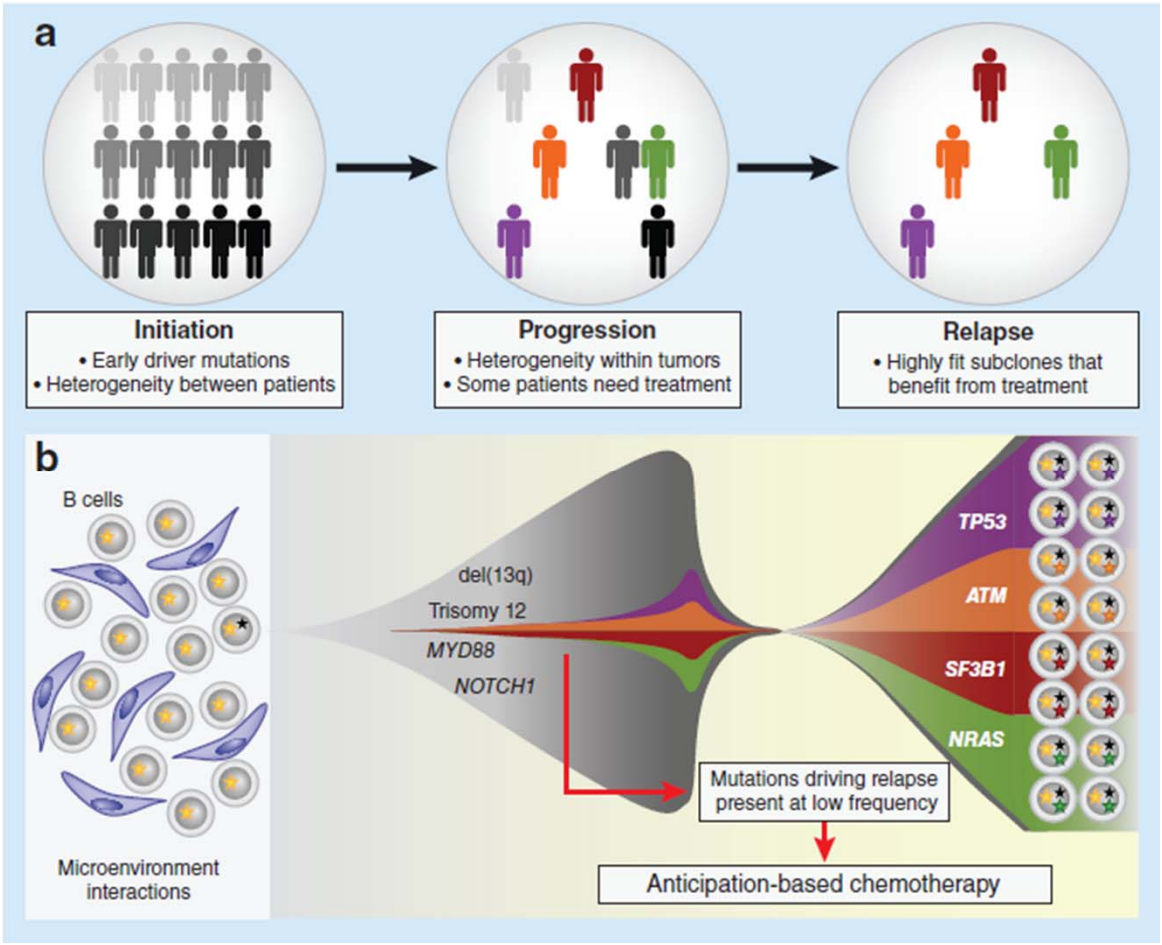
The Urgent Need for New Diagnostics and Molecular Profiling Tools for Improved Monitoring of Tumor Progression

From 'Static Snap Shot' at Initial Diagnosis to Dynamic Monitoring of Clonal Population Dynamics

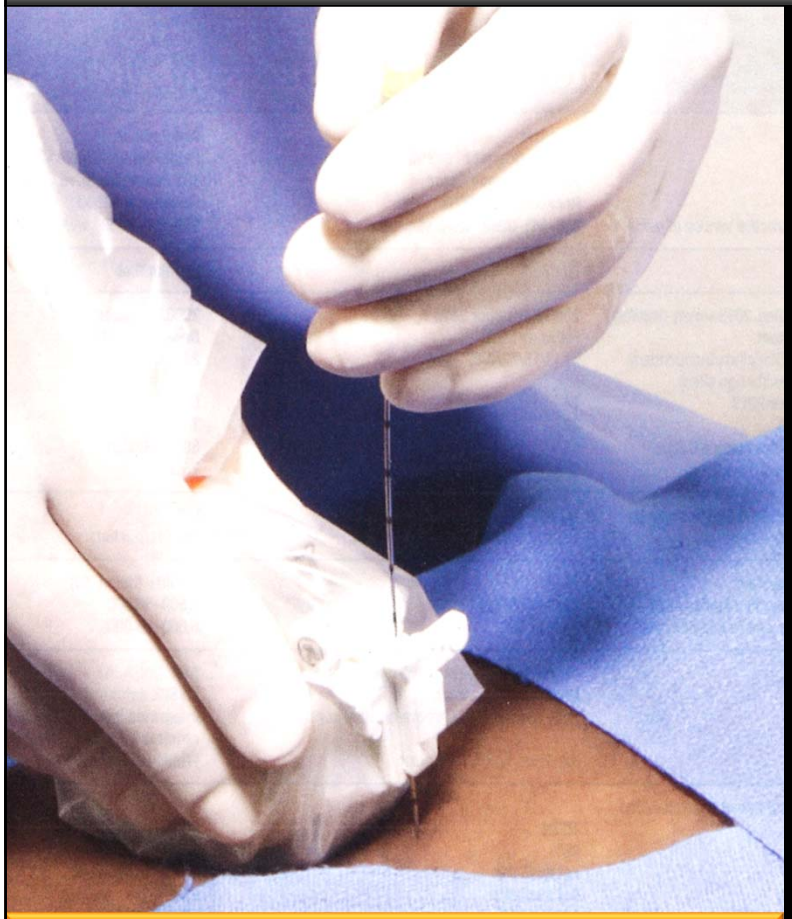
Tumor Profiling and Optimum Treatment Selection

- initial diagnosis ('static snapshot')
- longitudinal profiling during treatment for earlier detection of emergence of drug-resistant clones
- more agile shifts in Rx regiment to reflect changing clonal dynamics driven by Rx selection pressure(s)

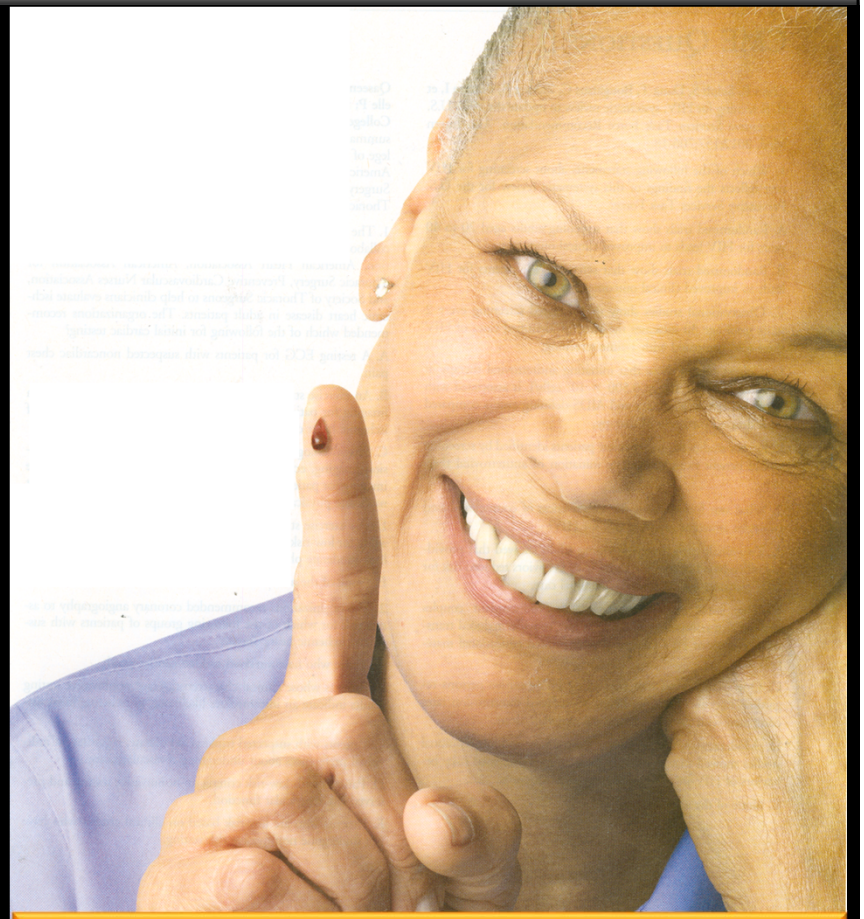
Anticipation-Based Chemotherapy in CLL



From: X. S. Puente and C. López-Otín (2013) Nature Genetics 45, 230



Fine Needle Aspiration (FNA) Biopsy

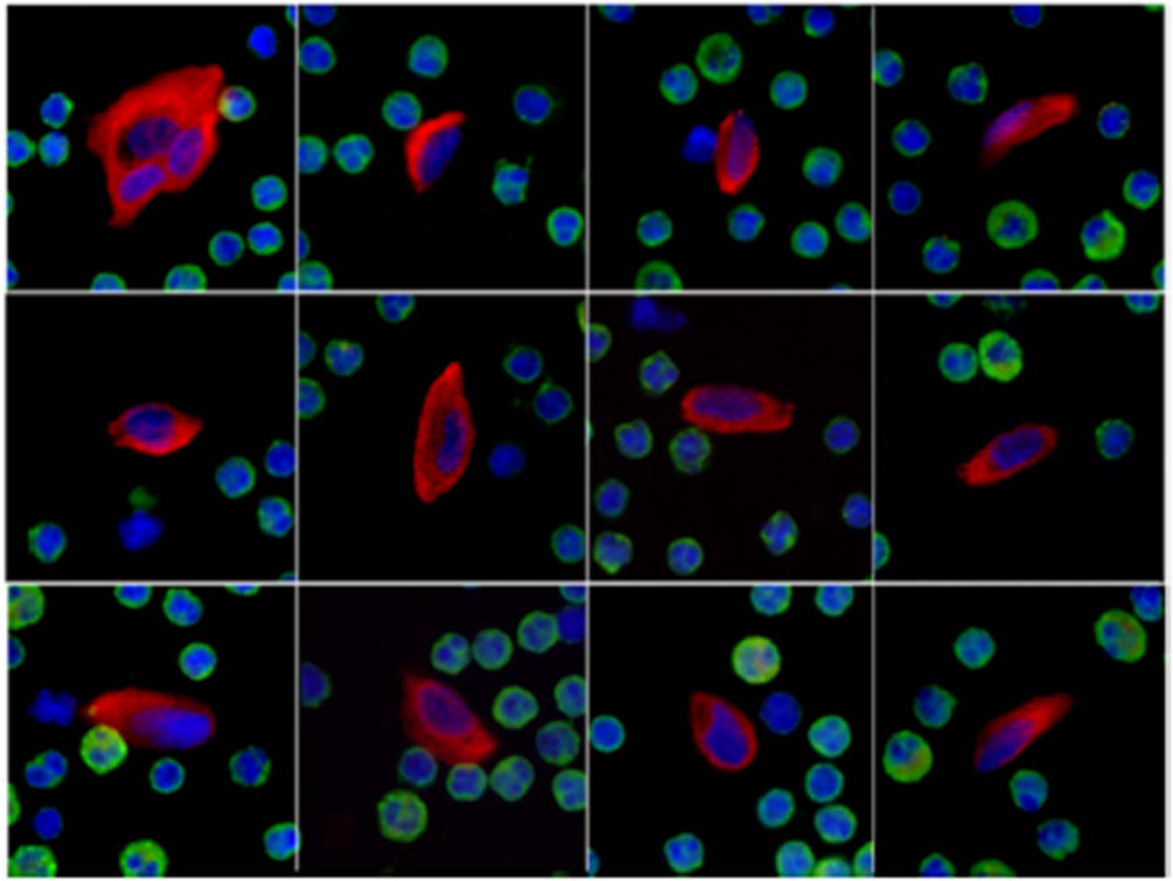


Minimally-Invasive Profiling
(Blood/Other Body Fluids)

Detection of Tumor-Associated Biomarkers in Blood: 'The Liquid Biopsy'

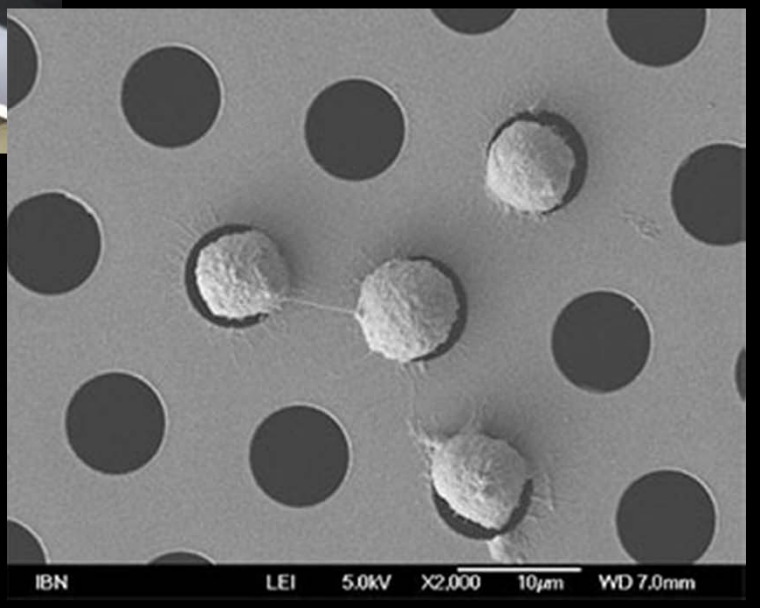
- cell-free nucleic acids
  - DNA, miRNAs
- circulating tumor cells(CTC)
- exosomes

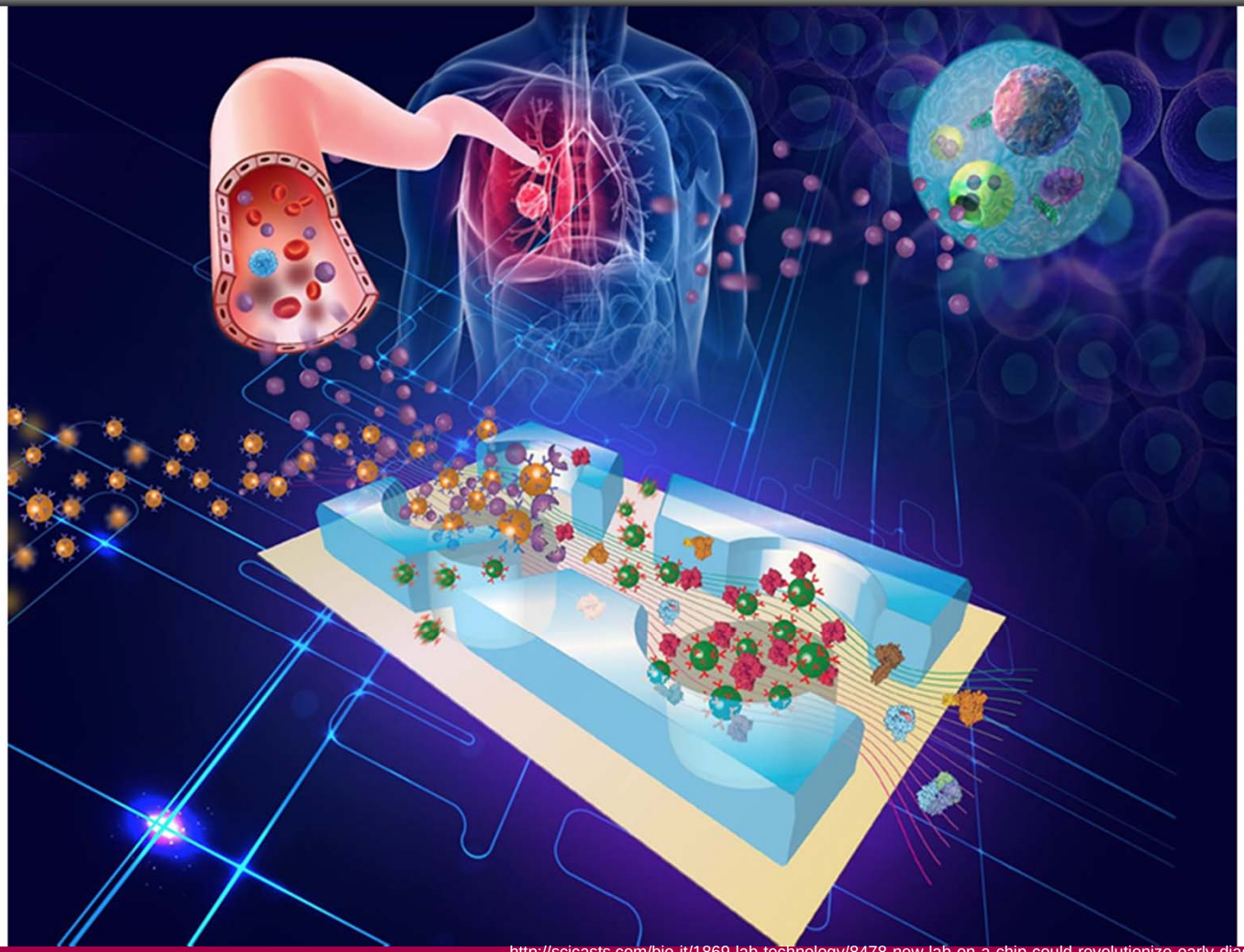
Gallery of representative HD-CTCs found in cancer patients. Each HD-CTC is cytokeratin positive (red), CD45 negative (green), contains a DAPI nucleus (blue), and is morphologically distinct from surrounding WBCs.



From: D. Marrinucci et al. (2012) Phys. Biol. 9, 016003

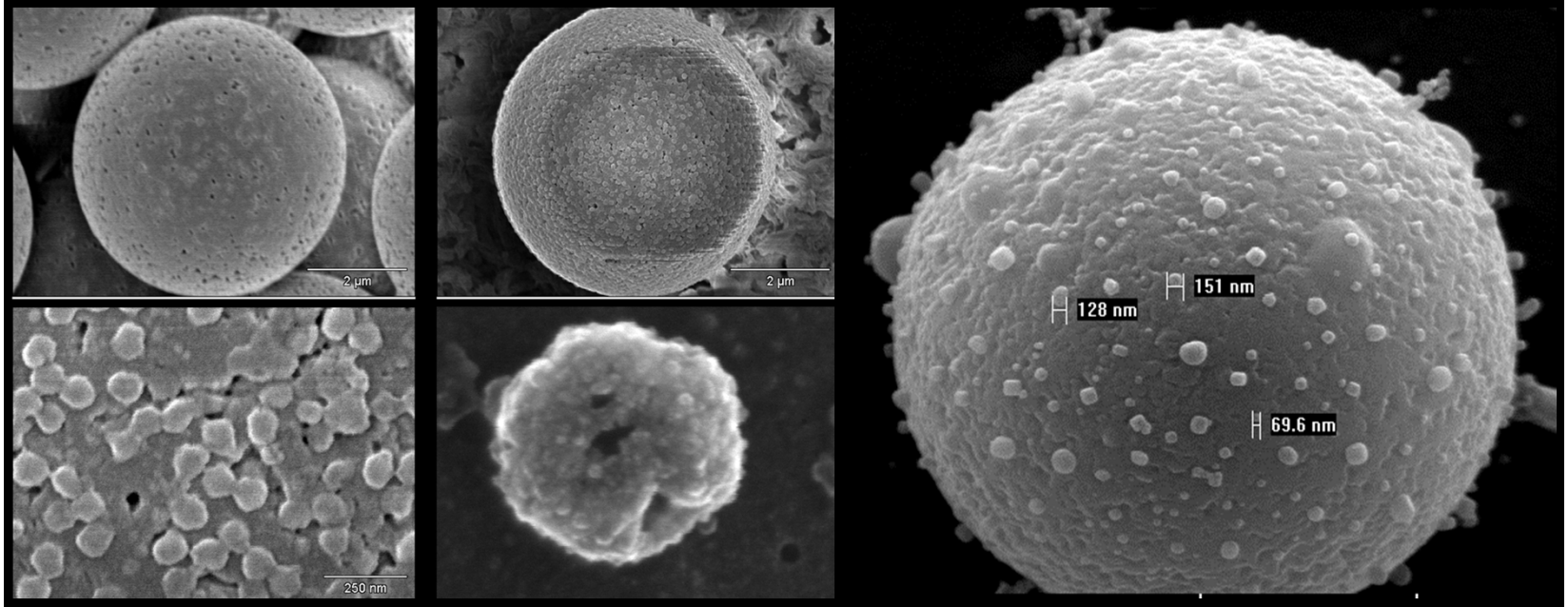
Liquid Biopsy:
Identifies Type of Cancer from Blood Draw





http://scicasts.com/bio-it/1869-lab-technology/8478-new-lab-on-a-chip-could-revolutionize-early-diagnosis-of-cancer/

Human plasma Carisome™ cMV isolated via Caris proprietary method captured on bead with anti-CD63 antibody



Lecture 2: Cancer Treatment

- rethinking current chemotherapeutic approaches
- the promise of immunotherapy
- post-treatment clinical challenges for cancer survivors
- the impact of advanced cancer on body function and quality-of-life
- palliative care (non-curative)
- end-of-life care