

Welcome to the PHC Webinar Series

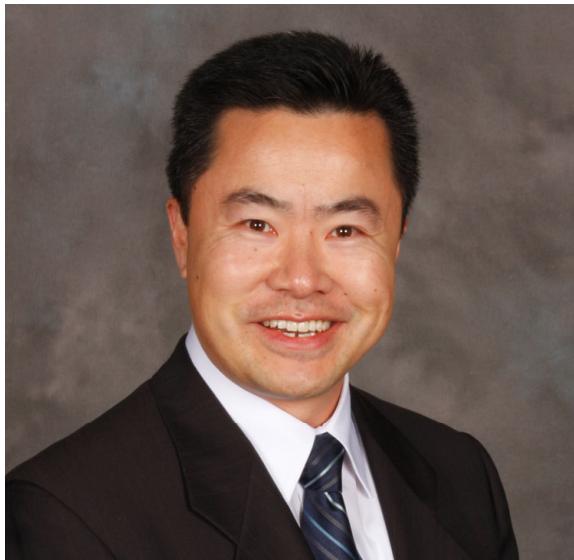
This lecture on “**Cancer: Critical Role of Pathology in Personalized Health Care**” is presented by Eric Walk, MD, FCAP



Your host is Jill Kaufman, PhD. For comments about this webinar or suggestions for upcoming webinars, please contact Jill Kaufman at jkaufma@cap.org

THE WEBINAR WILL BEGIN MOMENTARILY. ENJOY!

Eric Walk, MD, FCAP



- Senior Vice President and Chief Medical Officer at Ventana Medical Systems
- Head of the Department of Medical and Clinical Affairs as well as a member of the Executive Management Team
- Primary interests in the area of personalized health care



cap



Cancer: The Critical Role of Pathology in Personalized Health Care

Eric Walk, MD, FCAP

February 9, 2011

www.cap.org

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Opinions expressed by the speaker are the speaker's own and do not necessarily reflect an endorsement by CAP of any organizations, equipment, reagents, materials or services used by participating laboratories.

Disclosures

- I am a full-time employee of Ventana Medical Systems and Roche Diagnostics

Agenda

Personalized Healthcare (PHC): Emerging Reality

PHC and Pathology: The Need for Change

The Role of the Pathologist in PHC

Agenda

Personalized Healthcare (PHC): Emerging Reality

PHC and Pathology: The Need for Change

The Role of the Pathologist in PHC

Personalized Healthcare

Differential Medical Management of Patient Subsets

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Personalized medicine

From Wikipedia, the free encyclopedia

Personalized medicine is a medical model emphasizing in general the customization of healthcare, with all decisions and practices being tailored to individual patients in whatever ways possible. Recently, this has mainly involved the systematic use of genetic or other information about an individual patient to select or optimize that patient's preventative and therapeutic care.^[1]

Personalized medicine is a medical model emphasizing in general the customization of healthcare, with all decisions and practices being tailored to individual patients in whatever ways possible. Recently, this has mainly involved the systematic use of genetic or other information about an individual patient to select or optimize that patient's preventative and therapeutic care.^[1]

Main page
Contents
Featured content:
therapeutic care.^[1]
Current events
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NATIONAL CANCER INSTITUTE U.S. National Institutes of Health | www.cancer.gov

NCI Home Cancer Topics Clinical Trials Cancer Statistics Research & Funding

Dictionary of Cancer Terms

personalized medicine (PER-suh-nuh-LIZED MEH-dih-sin)

A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease.

HHS.gov Improving the health, safety and well-being of America

Personalized Health Care for informed and effective choices

Personalized Health Care

The Personalized Health Care Initiative will improve the safety, quality and effectiveness of healthcare for every patient in the US. By using "genomics", or the identification of genes and how they relate to drug treatment, personalized health care will enable medicine to be tailored to each person's needs.

Font Size - + Print Download Reader Secretary's Blog

Secretary Leavitt blogs about t year's Nobel Prize winner in medicine. [Oct. 12th posting](#)

Sec. Leavitt blogs about

Personalized Healthcare

Differential Medical Management of Patient Subsets

Prognostic Assays

Will the patient's disease have an aggressive or indolent course in the absence of therapy?

Is treatment needed or not and if so, should it be aggressive or conservative?

- Oncotype DX, Mammaprint: Need for chemotherapy in early stage breast cancer
- Aureon Prostate Px: Prostate cancer risk of disease progression

The collage consists of three screenshots of medical websites:

- Oncotype DX Breast Cancer Assay:** A screenshot of the official Oncotype DX website. It features a top navigation bar with links for "Login", "Press Room", "Register for Updates", "Contact Us", "Search", and "Choose a Language". Below the navigation is a horizontal menu with four options: "PATIENTS & CAREGIVERS", "HEALTHCARE PROFESSIONALS", "MANAGED CARE ORGANIZATIONS", and "CUSTOMER SUPPORT". The main content area contains a photograph of a hospital room with a patient chair and an IV stand, labeled "CHEMO? NO CHEMO?". To the right of the photo is the text: "The Oncotype DX® Breast Cancer Assay helps you find an answer". The logo "oncotype DX® Breast Cancer Assay" is at the bottom.
- Agendia:** A screenshot of the Agendia website. It features a logo with the word "agendia" and the tagline "decoding cancer.". Below the logo is a horizontal menu with three red buttons: "PATIENTS", "PHYSICIANS", and "ABOUT US". Underneath the menu is a banner with the text "MammaPrint® Identifies Early Metastatic Risk" and a photograph of two women, one in a lab coat and one in a white shirt.
- AUREON BIOSCIENCES:** A screenshot of the AUREON BIOSCIENCES website. It features a top navigation bar with links for "Physician Login", "Contact Us", "Site Map", "1.888.SYS.PATH", "Search", and "Go". Below the navigation is a horizontal menu with links for "ABOUT US", "WHO WE SERVE", "PROGNOSTIC TESTS", "NEWS & EVENTS", and "RESOURCE CENTER". The main content area features a section titled "Prognostic Tests" with a sub-section for "Prostate Px". It includes mathematical formulas, a diagram of a prostate biopsy, and a "About Prostate Px" section. On the right side, there is a "Do you have questions?" button with a link to "Click here if you would like us to call you". At the bottom, there is a "Contact Us" section with links for "Send an email" and "Give us a call".

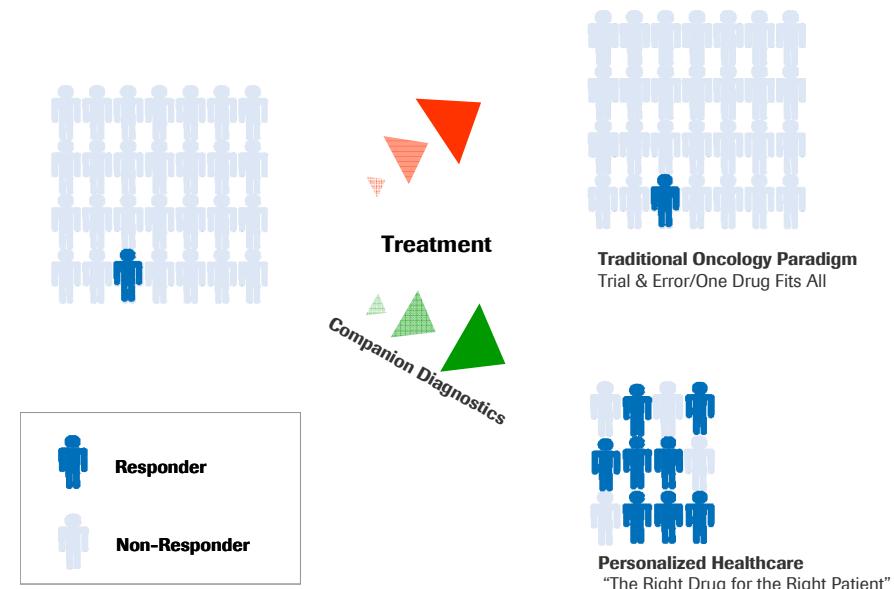
Differential Medical Management of Patient Subsets

Companion Diagnostics

Which specific therapies will be effective or ineffective in an individual patient?

"The Right Drug for the Right Patient"

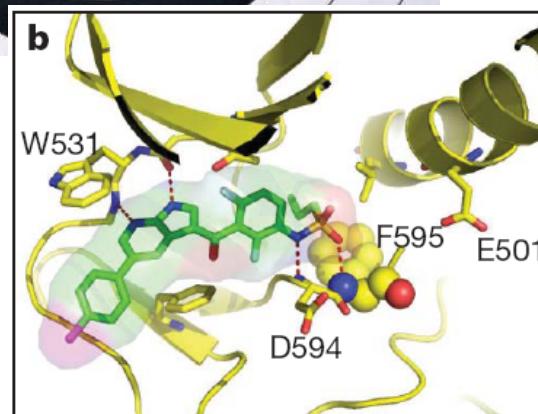
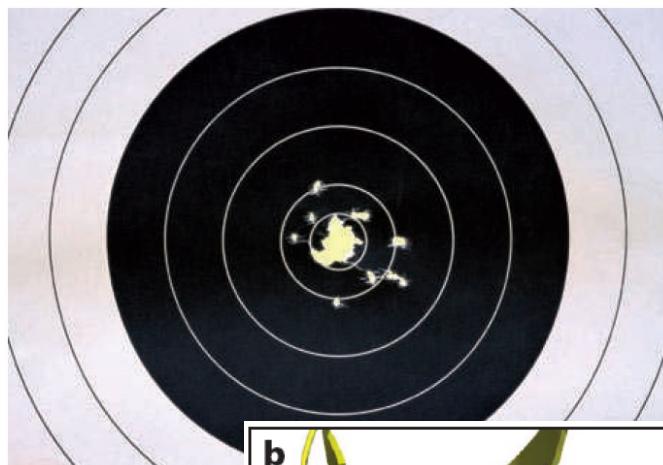
- HER2 – Herceptin for breast cancer and gastric cancer
- KIT – Gleevec for GIST
- ER/PR – Tamoxifen for breast cancer
- EGFR mutations – Tarceva/Iressa for NSCLC
- KRAS mutations – Erbitux resistance in CRC



Emerging PHC Companion Diagnostics *BRAF V600E/RAF Inhibitors in Melanoma*



Targeting mutant BRAF in metastatic melanoma



- **Current approved therapies for metastatic melanoma (interleukin-2 and dacarbazine) have response rates of only 10-20% with no improvement in OS**
- **40-60% of melanomas harbor activating mutations of BRAF, 90% of which are V600E**
- **RG7204/PLX4032 is a potent inhibitor of BRAF V600E, abrogating signaling through the MAP kinase pathway**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

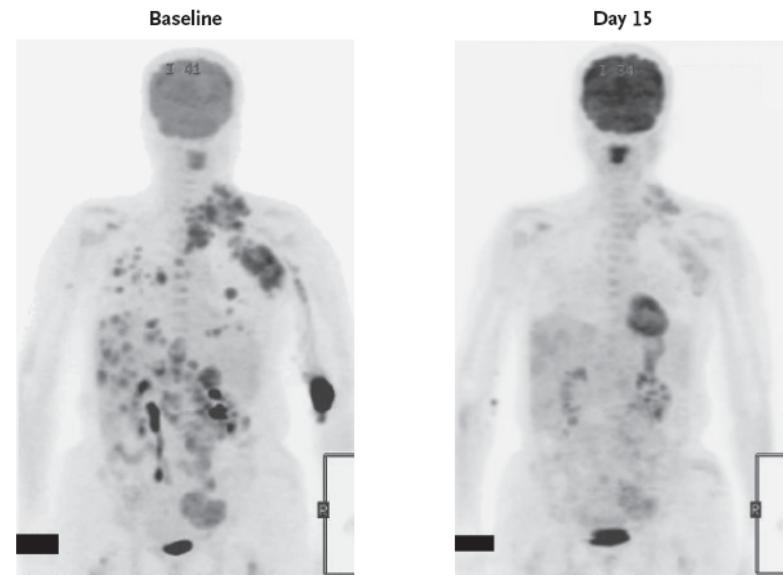
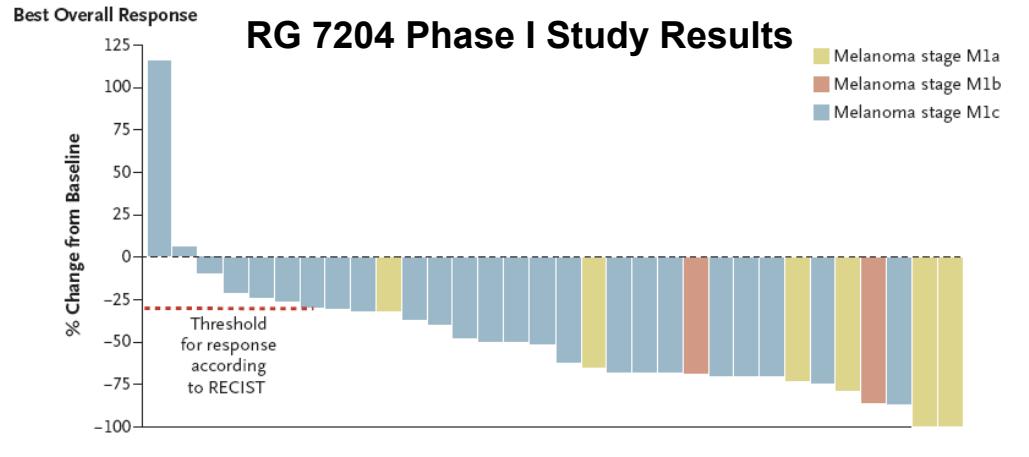
AUGUST 26, 2010

VOL. 363 NO. 9

Inhibition of Mutated, Activated BRAF in Metastatic Melanoma

Keith T. Flaherty, M.D., Igor Puzanov, M.D., Kevin B. Kim, M.D., Antoni Ribas, M.D.,
Grant A. McArthur, M.B., B.S., Ph.D., Jeffrey A. Sosman, M.D., Peter J. O'Dwyer, M.D., Richard J. Lee, M.D., Ph.D.,
Joseph F. Grippi, Ph.D., Keith Nolop, M.D., and Paul B. Chapman, M.D.

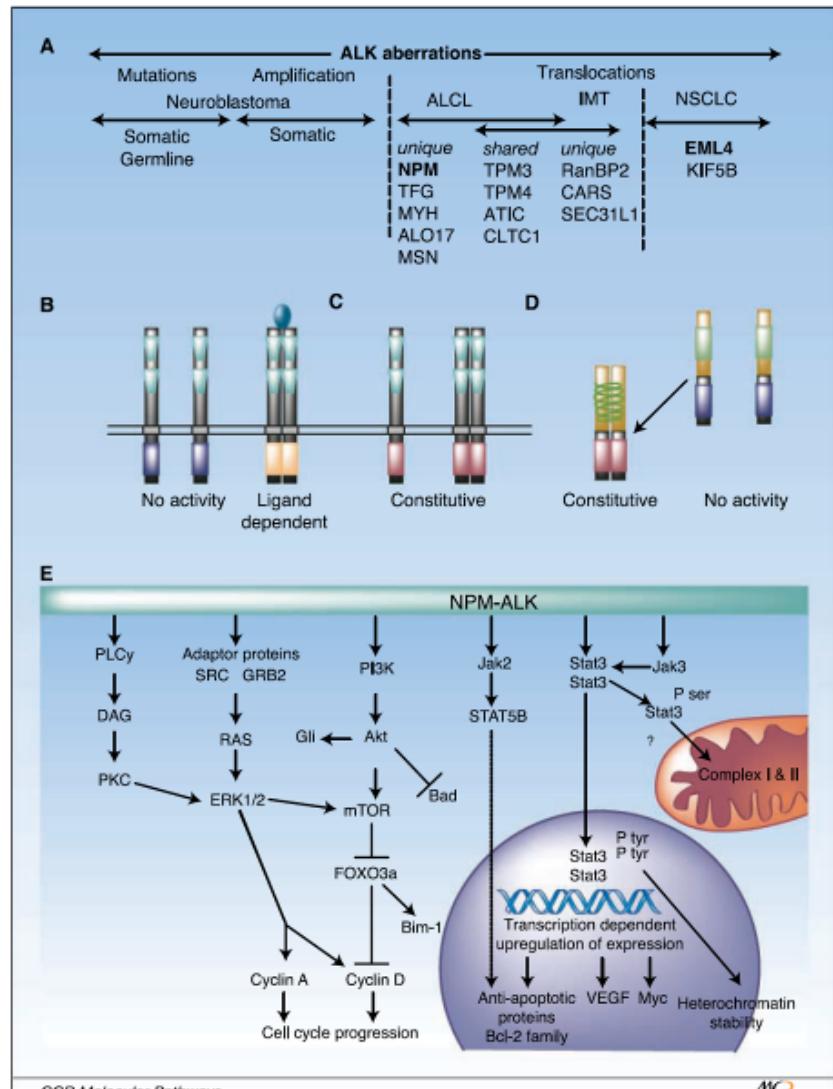
RG 7204 Phase I Study Results



- “Treatment of metastatic melanoma with PLX4032 (RG7204) in patients with tumors that carry the V600E BRAF mutation resulted in complete or partial tumor regression in the majority of patients.”

Emerging PHC Companion Diagnostics *ALK/ALK Inhibitors in NSCLC*

- The EML4-ALK gene fusion first identified in NSCLC in 2007 by Hiroyuki Mano
- Subsequent studies have shown frequencies of 3-7%
- EML4-ALK fusion-positive NSCLC appears to be a distinct subgroup, separate from NSCLC driven by EGFR or KRAS mutations.
- Several ALK tyrosine kinase inhibitors are in clinical development, the most advanced being crizotinib



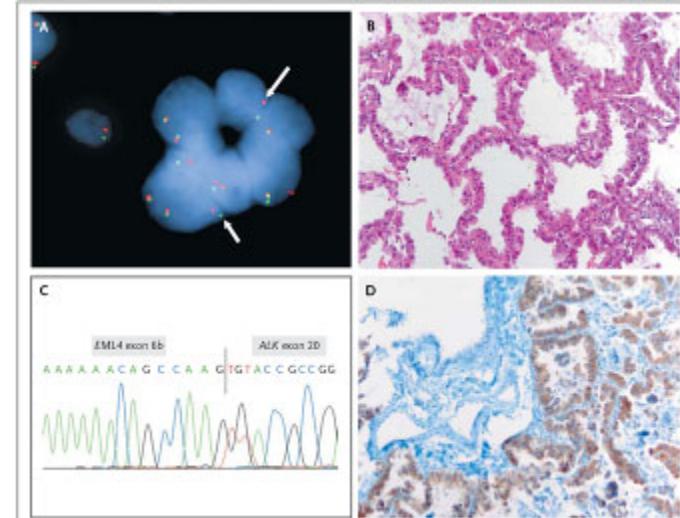
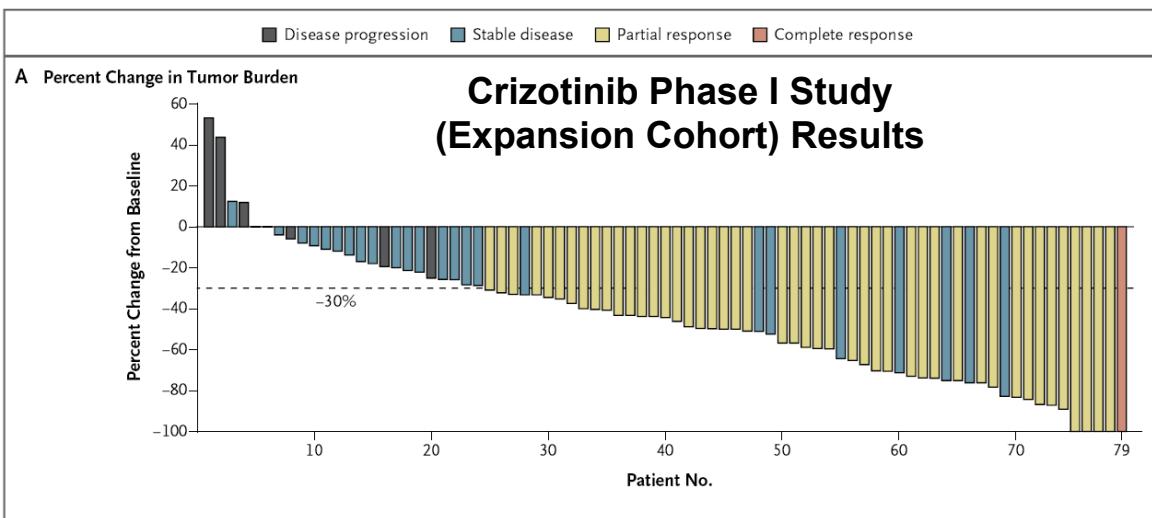
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ESTABLISHED IN 1812

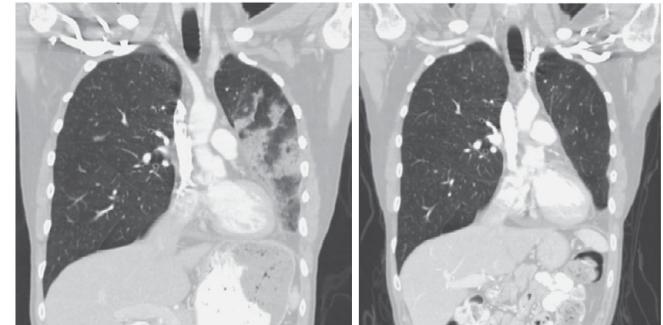
OCTOBER 28, 2010

VOL. 363 NO. 18

Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer

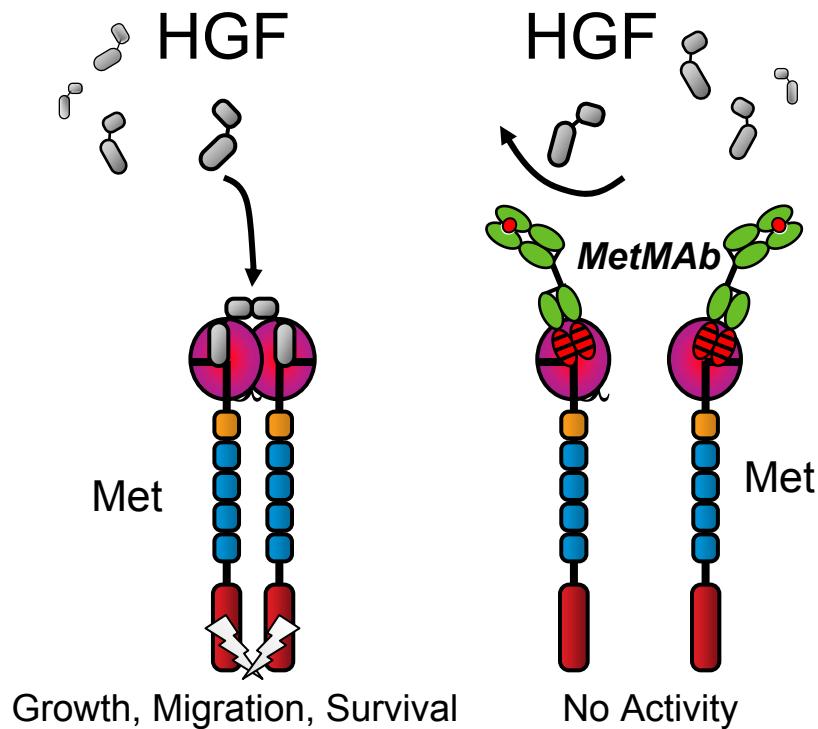


- Overall response rate was 57% (47 of 82 patients)
 - 46 confirmed partial responses
 - 1 confirmed complete response
 - 27 patients (33%) had stable disease
 - Mean treatment duration of 6.4 months



Emerging PHC Companion Diagnostics

MET/MetMAb in NSCLC

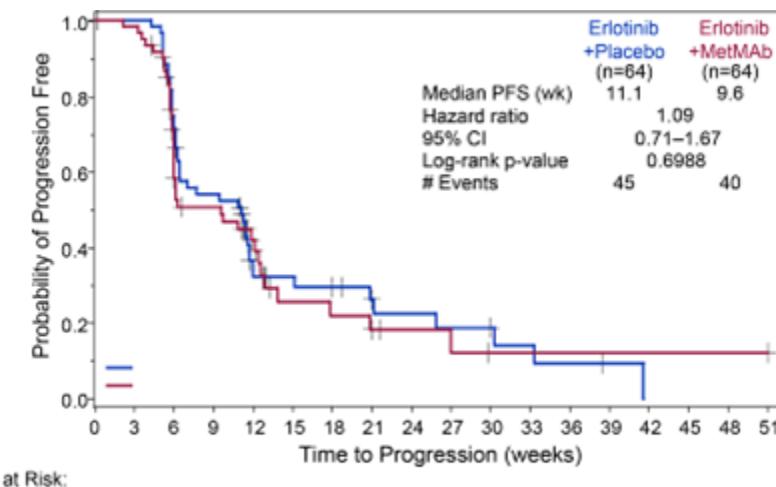


- **Rationale for targeting Met:**
 - Met is amplified, mutated, overexpressed or uniquely activated in many tumors
 - Met expression is associated with worse prognosis in many cancers including NSCLC
 - Met activation is implicated in resistance to erlotinib/gefitinib in pts with activating EGFR mutation
- **MetMAb:**
 - One-armed format designed to prevent HGF-mediated stimulation of pathway
 - Preclinical activity across multiple tumor models

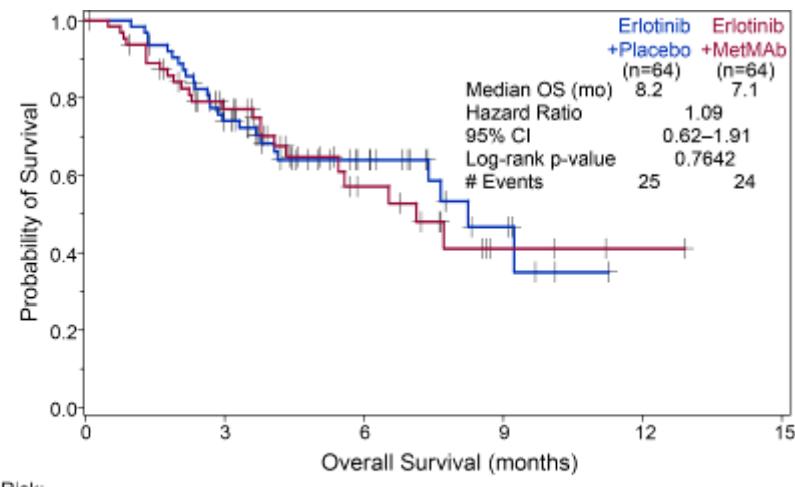
MetMAB + Tarceva (Erlotinib) vs. Tarceva + Placebo: Phase II Data

Analysis of All Patients: PFS and OS

PFS, HR=1.09



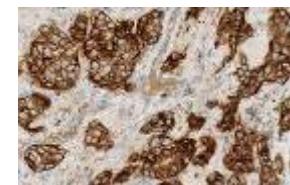
OS, HR=1.09



23 patients from the erlotinib+placebo arm crossed over to MetMAB.

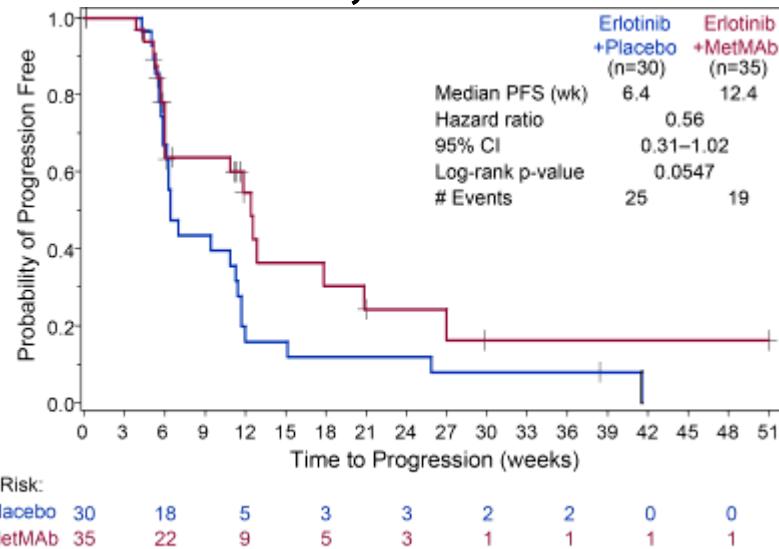
mPFS and mOS are consistent with previously reported findings in similar disease setting.

Met High NSCLC Patients Benefit from MetMAb+Erlotinib

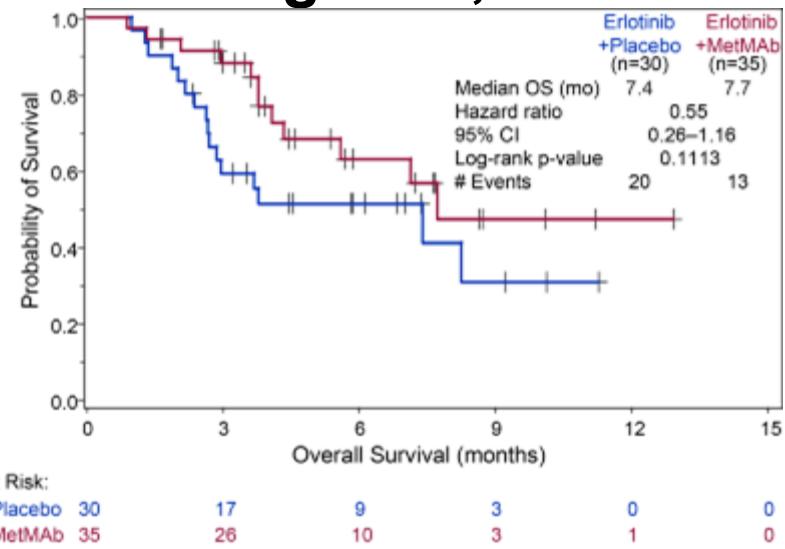


Analysis of Met High Patients

PFS, HR=0.56

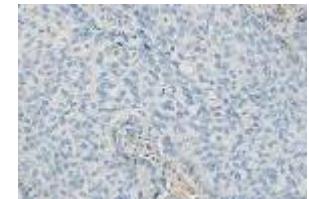


Met High OS, HR=0.55



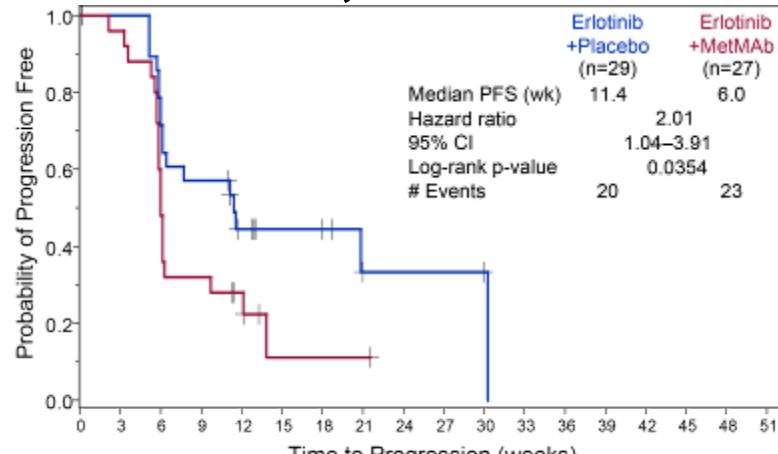
12/23 patients from the erlotinib+placebo arm who crossed over to MetMAb were Met High.

Met Low NSCLC Patients Do Not Benefit from MetMAb+Erlotinib

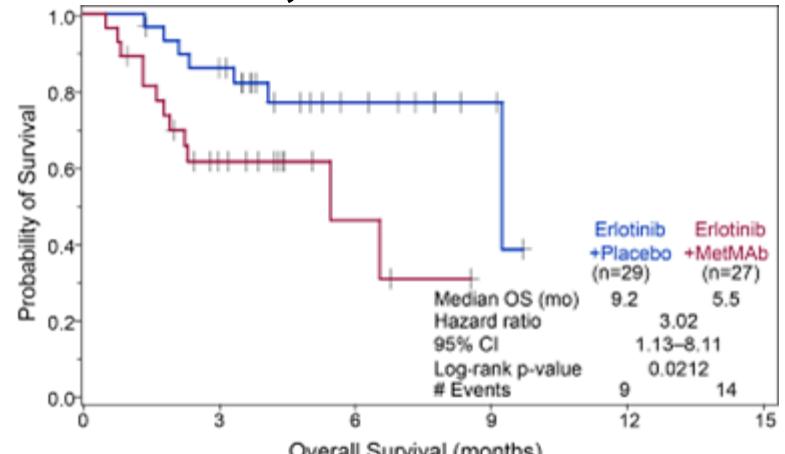


Analysis of Met Low Patients

PFS, HR=2.01



OS, HR=3.02



Number at Risk:									
Erlotinib+Placebo	29	22	9	6	2	2	0	0	0
Elotinib+MetMAb	27	15	5	1	0	0	0	0	0

Number at Risk:									
Erlotinib+Placebo	29	23	9	3	0	0	0	0	0
Elotinib+MetMAb	27	12	3	0	0	0	0	0	0

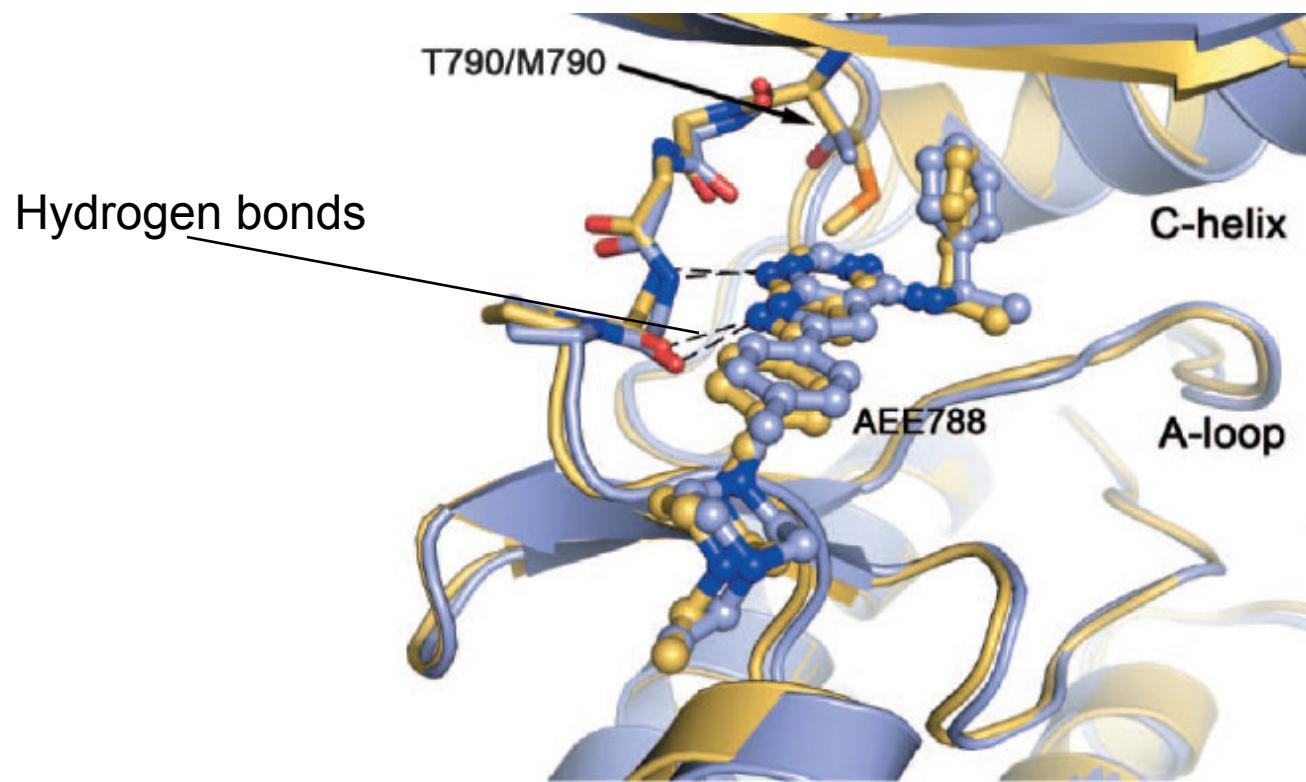
10/23 patients from the erlotinib+placebo arm crossed over to MetMAb were Met Low.

The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP

Cai-Hong Yun^{*†}, Kristen E. Mengwasser[†], Angela V. Toms^{*†}, Michele S. Woo[‡], Heidi Greulich^{‡§}, Kwok-Kin Wong^{#¶}, Matthew Meyerson^{‡§||}, and Michael J. Eck^{*†***}

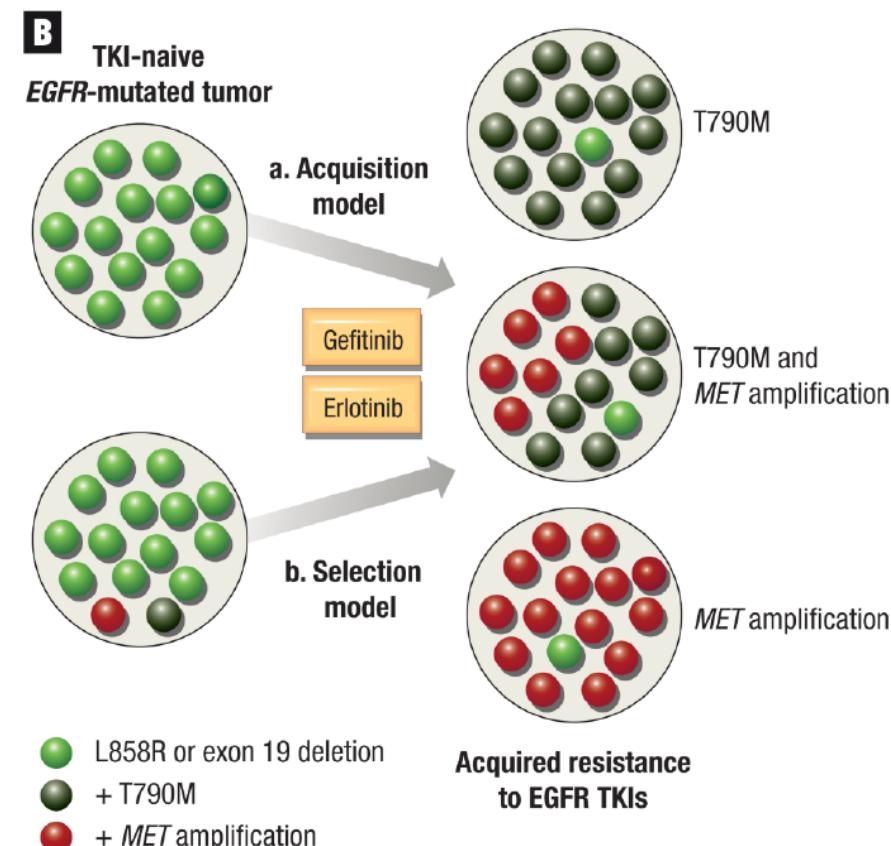
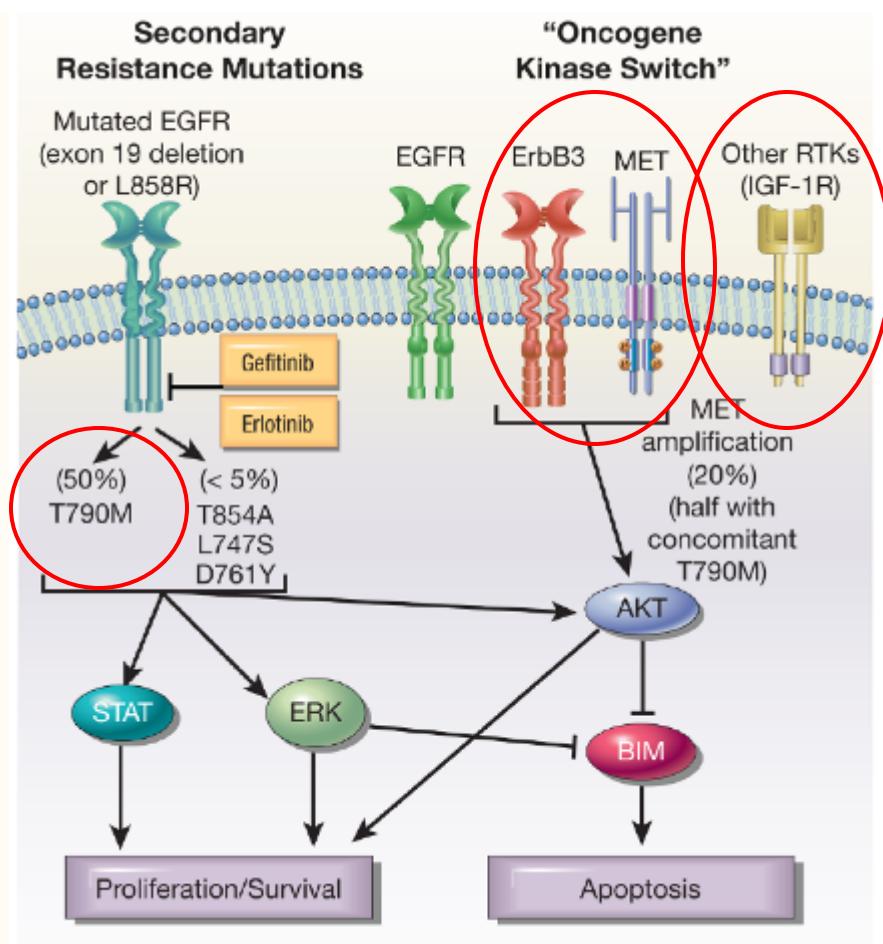
Departments of *Biological Chemistry and Molecular Pharmacology and †Pathology, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115; Departments of ‡Cancer Biology and §Medical Oncology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115; ¶Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115; and ||The Broad Institute of Harvard and Massachusetts Institute of Technology, 320 Charles Street, Cambridge, MA 02141

Edited by Harold E. Varmus, Memorial Sloan–Kettering Cancer Center, New York, NY, and approved December 13, 2007 (received for review October 11, 2007)



Three Known Acquired Resistance Mechanisms to EGFR Targeted Therapies in NSCLC

T790M, MET Amplification, IGF-1R Activation



Acquired Resistance to BRAF Inhibitors

RESEARCH ARTICLE

CANCER

Gatekeeper Mutations Mediate Resistance to BRAF-Targeted Therapies

Steven Whittaker,¹ Ruth Kirk,¹ Robert Hayward,¹ Alfonso Zambon,² Amaya Viros,¹ Neus Cantarino,¹ Annette Affolter,¹ Arnaud Nourry,² Dan Niculescu-Duvaz,² Caroline Springer,² Richard Marais^{1*}

(Published 9 June 2010; Volume 2 Issue 35 35ra41)

Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation

Ramin Nazarian^{1,2*}, Hubing Shi^{1,2*}, Qi Wang^{1,2}, Xiangju Kong^{1,2}, Richard C. Koya^{2,3}, Hane Lee^{2,4}, Zugen Chen^{2,4}, Mi-Kyung Lee^{1,2}, Narsis Attar^{2,5}, Hooman Sazegar^{2,5}, Thinle Chodon^{2,5}, Stanley F. Nelson^{2,4,6}, Grant McArthur⁷, Jeffrey A. Sosman⁸, Antoni Ribas^{2,3,5} & Roger S. Lo^{1,2}

Here we show that acquired resistance to PLX4032 develops by mutually exclusive PDGFRb upregulation or N-RAS (also known as NRAS) mutations but not through secondary mutations in B-RAF(V600E).

Acquired Resistance to ALK Inhibitors: Gatekeeper Mutations

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

EML4-ALK Mutations in Lung Cancer That Confer Resistance to ALK Inhibitors

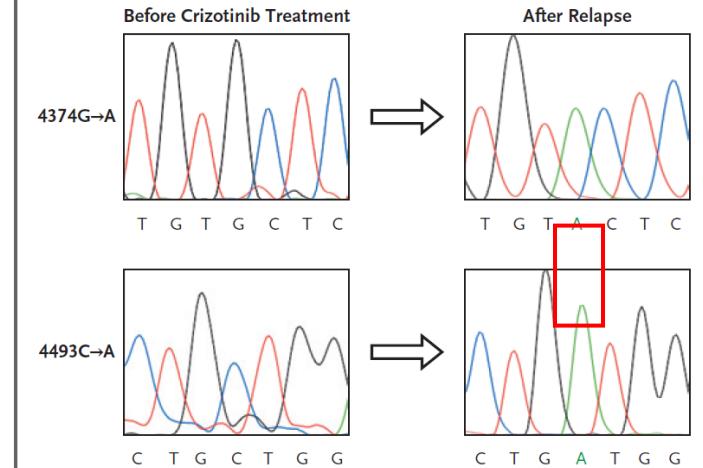
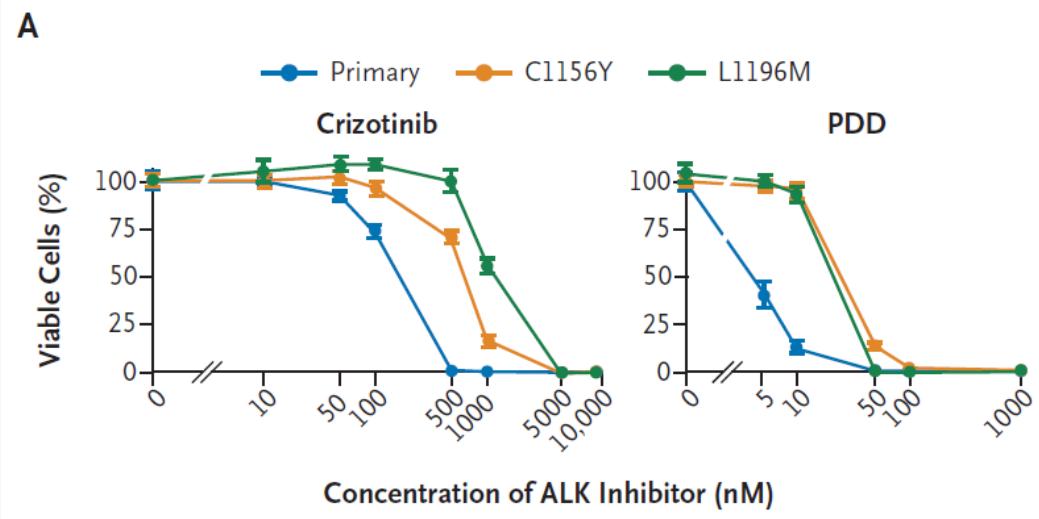
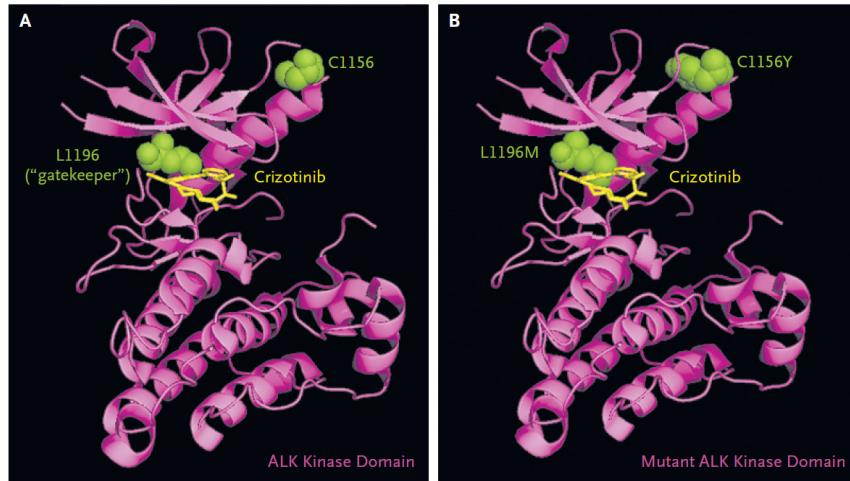
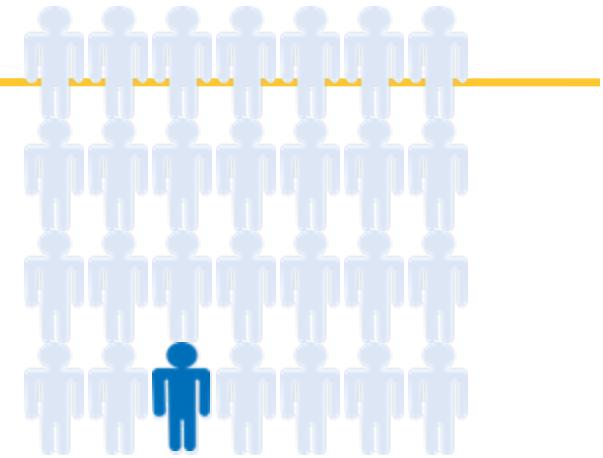
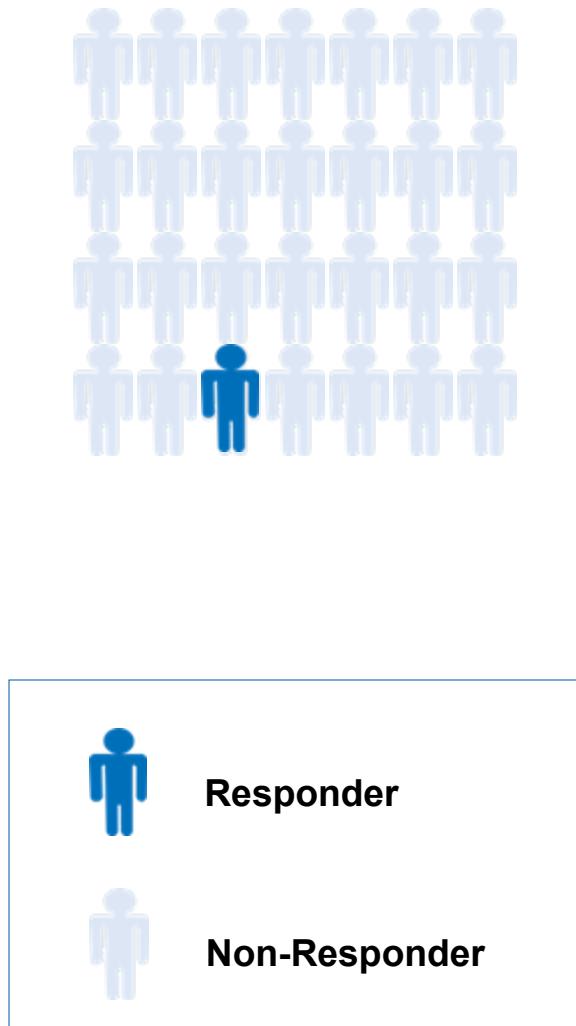


Figure 1. Secondary Mutations within EML4-ALK.

Electropherograms are shown for *EML4-ALK* cDNA clones prepared from sputum specimens obtained from our patient before crizotinib treatment and from pleural-effusion specimens obtained after relapse. The 4374G→A and 4493C→A mutations are present in the specimens obtained after relapse.

PHC Companion Diagnostics Model

Conceptually Useful but Oversimplified



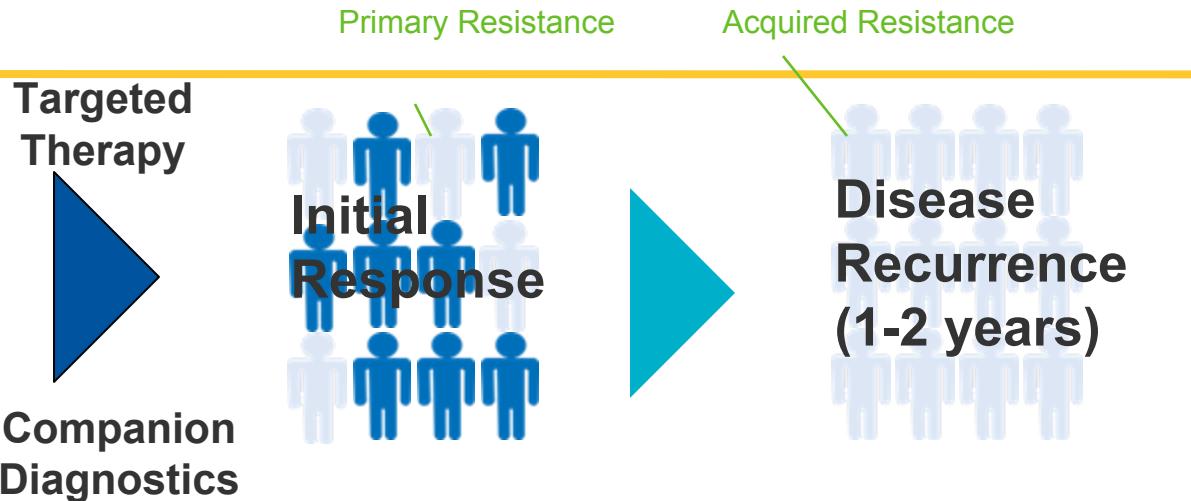
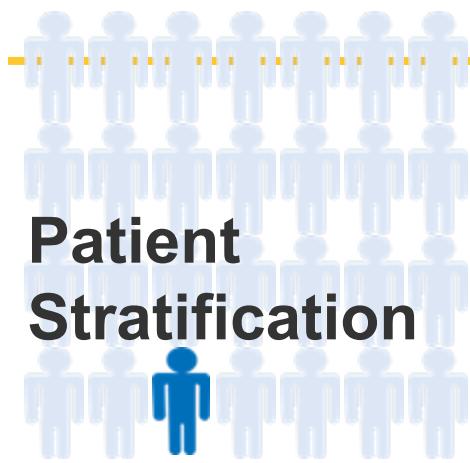
Traditional Oncology Paradigm
Trial & Error/One Drug Fits All



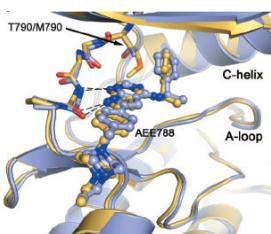
Personalized Healthcare
“The Right Drug for the Right Patient”

Personalized Healthcare Emerging Reality

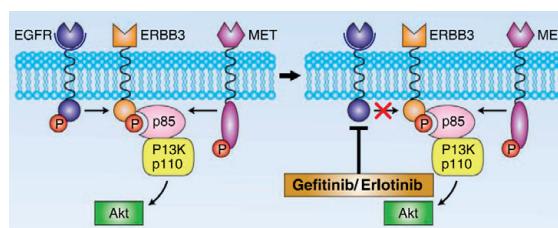
Primary and Acquired Resistance



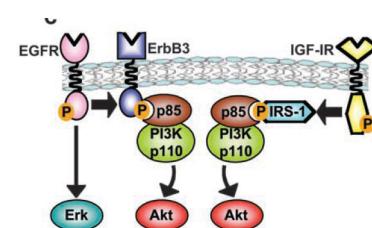
Resistance Mechanism #1



Resistance Mechanism #2



Resistance Mechanism #3



Multiple Molecular Mechanisms of Resistance

Structure-Aided Design (SAR) Delivers New Drugs to Address Acquired Resistance

Bioorganic & Medicinal Chemistry Letters 21 (2011) 638–643



Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl



Discovery of selective irreversible inhibitors for EGFR-T790M

Wenjun Zhou^a, Dalia Ercan^b, Pasi A. Jänne^{b,c}, Nathanael S. Gray^{a,*}

^aDepartment of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, and Department of Cancer Biology, Dana Farber Cancer Institute, Boston, MA 02115, United States

^bLowe Center for Thoracic Oncology, and Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA 02115, United States

^cDepartment of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, United States

Journal of
Medicinal
Chemistry
Article

J. Med. Chem. 2010, 53, 5439–5448 5439

DOI: 10.1021/jm901808w

A Type-II Kinase Inhibitor Capable of Inhibiting the T315I “Gatekeeper” Mutant of Bcr-Abl

Hwan Geun Choi,^{†,‡} Pingda Ren,[‡] Francisco Adrian,[‡] Fangxian Sun,[‡] Hyun Soo Lee,[‡] Xia Wang,[‡] Qiang Ding,[‡] Guobao Zhang,[‡] Yongping Xie,[‡] Jianming Zhang,[†] Yi Liu,[‡] Tove Tuntland,[‡] Markus Warmuth,[‡] Paul W. Manley,[§] Jürgen Mestan,[§] Nathanael S. Gray,^{*,†} and Taeko Sim^{*,‡,||}

[†]Dana Farber Cancer Institute, Harvard Medical School, Department of Cancer Biology and Department of Biological Chemistry and Molecular Pharmacology, 250 Longwood Avenue, Seely G. Mudd Building 628A, Boston, Massachusetts 02115, [‡]Genomics Institute of the Novartis Research Foundation, Department of Chemistry, 10675 John Jay Hopkins Drive, San Diego, California 92121, [§]Novartis Institutes for Biomedical Research, CH-4056 Basel, Switzerland, and ^{||}Life Sciences Research Division, Korea Institute of Science and Technology, 39-1 Hawolgok-dong, Seongbuk-gu, Seoul 136-791, Korea

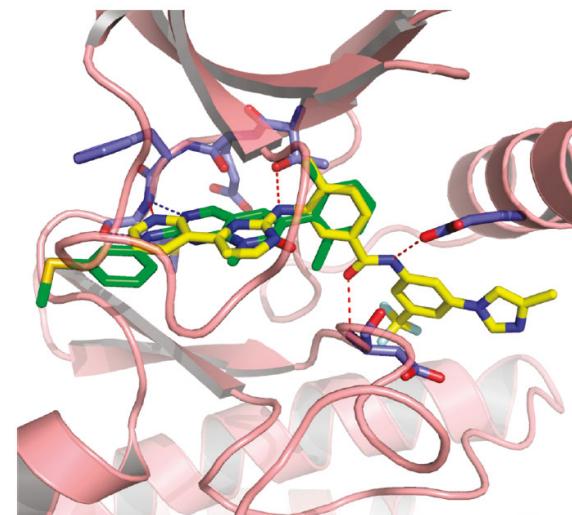


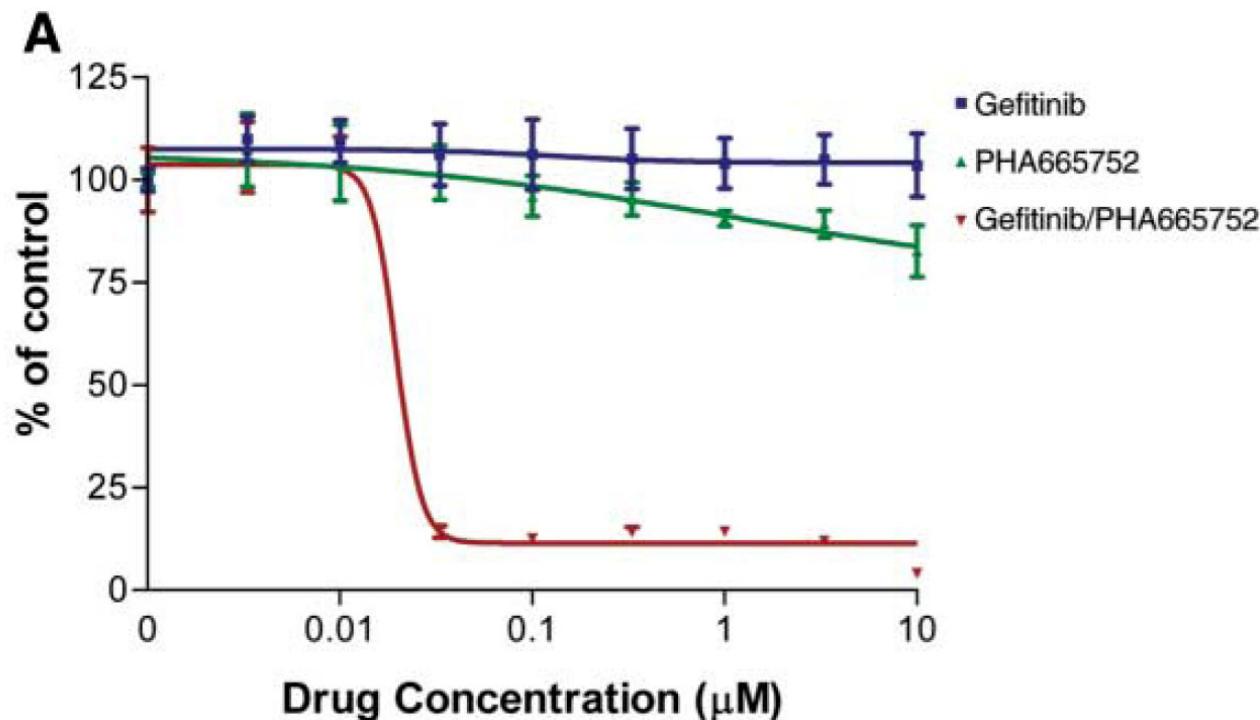
Figure 2. Superimposed structure of **20** (green sticks) bound to Abl (pink ribbon PDB: 1m52) and nilotinib (yellow sticks) bound to Abl (PDB: 3cs9). Hydrogen bonds are indicated by red hatched lines to key amino acids (blue sticks).

Targeted Therapy Combinations May be One Solution to Acquired Resistance

SCIENCE VOL 316 18 MAY 2007

MET Amplification Leads to Gefitinib Resistance in Lung Cancer by Activating ERBB3 Signaling

Jeffrey A. Engelman,^{1,2,3} Kreshnik Zejnullahu,^{4,5} Tetsuya Mitsudomi,⁶ Youngchul Song,^{2,3} Courtney Hyland,⁷ Joon Oh Park,^{4,5} Neal Lindeman,⁷ Christopher-Michael Gale,³ Xiaojun Zhao,⁵ James Christensen,⁸ Takayuki Kosaka,⁶ Alison J. Holmes,^{4,5} Andrew M. Rogers,⁵ Federico Cappuzzo,⁹ Tony Mok,¹⁰ Charles Lee,⁷ Bruce E. Johnson,^{4,5} Lewis C. Cantley,^{2,3} Pasi A. Jänne^{4,5*}



FDA Releases Guidance Document on Investigational Agent Combinations

Guidance for Industry Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Colleen Locicero 301-796-1114.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**December 2010
Clinical Medical**

Companion Diagnostics Today *One test, one drug*

Disease	Companion Diagnostic	1 st Line Drug
Breast Carcinoma	HER2 IHC/ISH	Herceptin/Trastuzumab

Companion Diagnostics Emerging Reality

Tumor marker profiles guiding rational targeted therapy combinations

Disease	Companion Diagnostic	Targeted Therapy	Primary Resistance Diagnostic	Secondary/Acquired Resistance Diagnostic	Rational Targeted Tx Combination
Breast Ca.	HER2 IHC/ISH	Herceptin/Trastuzumab	Unknown	Unknown ? PI3K Pathway activation	Unknown ? PI3K inhibitor
GIST	cKIT IHC	Gleevec/Imatinib	Unknown	KIT Mutation (e.g. exon 11)	Sunitinib (+ Imatinib)
CML	Bcr-Abl	Gleevec/Imatinib	Unknown	Abl Mutation	Dasatinib (+Imatinib)
Colon Ca.	?EGFR	Erbitux/Certuximab	KRAS Mutation	Unknown	Unknown
NSCLC	EGFR Mutation	Tarceva/Erlotinib	Unknown	Emerging 1. EGFR T790M 2. MET Amplification 3. IGF1R Activation (via IRS-1)	1. Irreversible EGFR TKIs 2. MET Inhibitor 3. IGF1R Inhibitor 4. PI3K Inhibitor

*For illustrative purposes only

Identification of Mutations as Predictors of Response and Resistance Will Become Increasingly Important for Clinical Management

The screenshot shows the TCGA homepage with the NCI and NHGRI logos at the top. The main header reads "THE CANCER GENOME ATLAS" with a globe icon. Below the header are navigation links for "About TCGA", "What We Do", "Publications", "News Center", and "Launch Data Portal". A search bar and a "Sign up for updates" button are also present. The central image features a DNA double helix with base pair mutations labeled (G, C, T, A). Below the image, a photograph shows two scientists in a lab setting. A call-to-action box on the right says "Looking for a Target on Every Tumor" with links to "Science Article" and "Podcast".

The Cancer Genome Atlas (TCGA) is a comprehensive and coordinated effort to accelerate our understanding of the genetics of cancer using innovative genome analysis technologies.

The screenshot shows the Sanger Institute's Cancer genome project page. The top navigation bar includes "Home", "Research", "Scientific resources", "Work & study", and "About us". Below this, a secondary navigation bar includes "Areas of research", "Projects", "Academic faculty", and "Scientific publications". A "Search" bar and the URL "www.sanger.ac.uk" are also present. The main content area is titled "Cancer genome project" and contains a paragraph about the project's goal to identify somatic mutations in cancer. It also states that one in three people in the Western world develop cancer and one in five die of the disease.

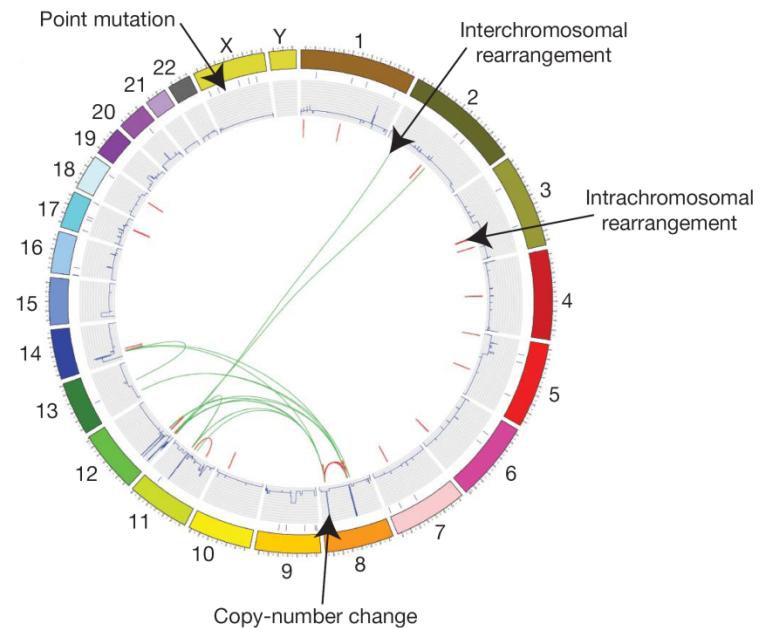
Cancer genome project

The Wellcome Trust Sanger Institute's Cancer Genome Project is led jointly by Professor Mike Stratton and Dr Andy Futreal. All cancers occur due to abnormalities in DNA sequence. Cancer affects people at all ages with the risk for most types increasing with age.

One in three people in the Western world develop cancer and one in five die of the disease. Cancer is therefore the most common genetic disease.

The cancer genome

Michael R. Stratton^{1,2}, Peter J. Campbell^{1,3} & P. Andrew Futreal¹



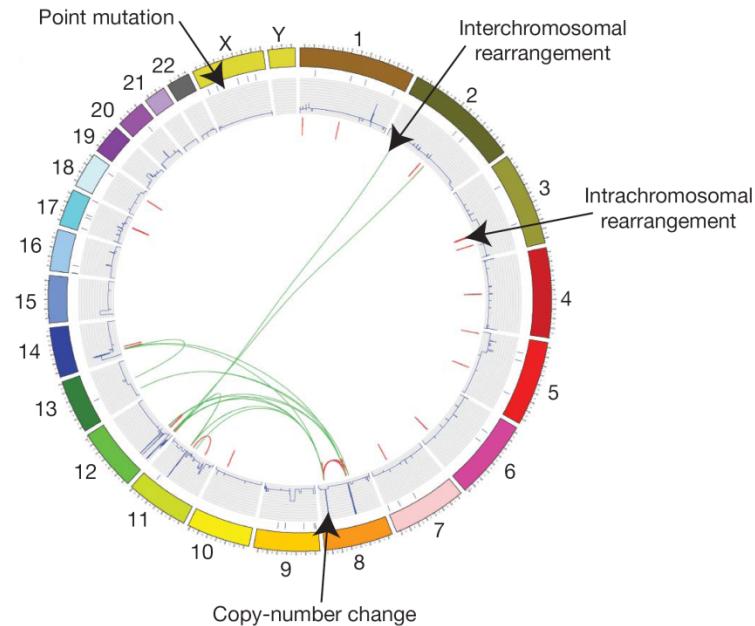
- Cancer genome 'landscape' map depicting > 40 somatic mutations present in a single small-cell lung cancer cell line (NCI-H2171)

Identification of Mutations as Predictors of Response and Resistance Will Become Increasingly Important for Clinical Management

- Catalog of Somatic Mutations in Cancer (COSMIC) Project
 - Tumors: 434,364
 - Genes: 13,634
 - Mutations: 101,866
 - Fusions: 3635
 - Structural Variants: 2250
- Publically available data
 - www.sanger.ac.uk/genetics/CGP/cosmic

The cancer genome

Michael R. Stratton^{1,2}, Peter J. Campbell^{1,3} & P. Andrew Futreal¹

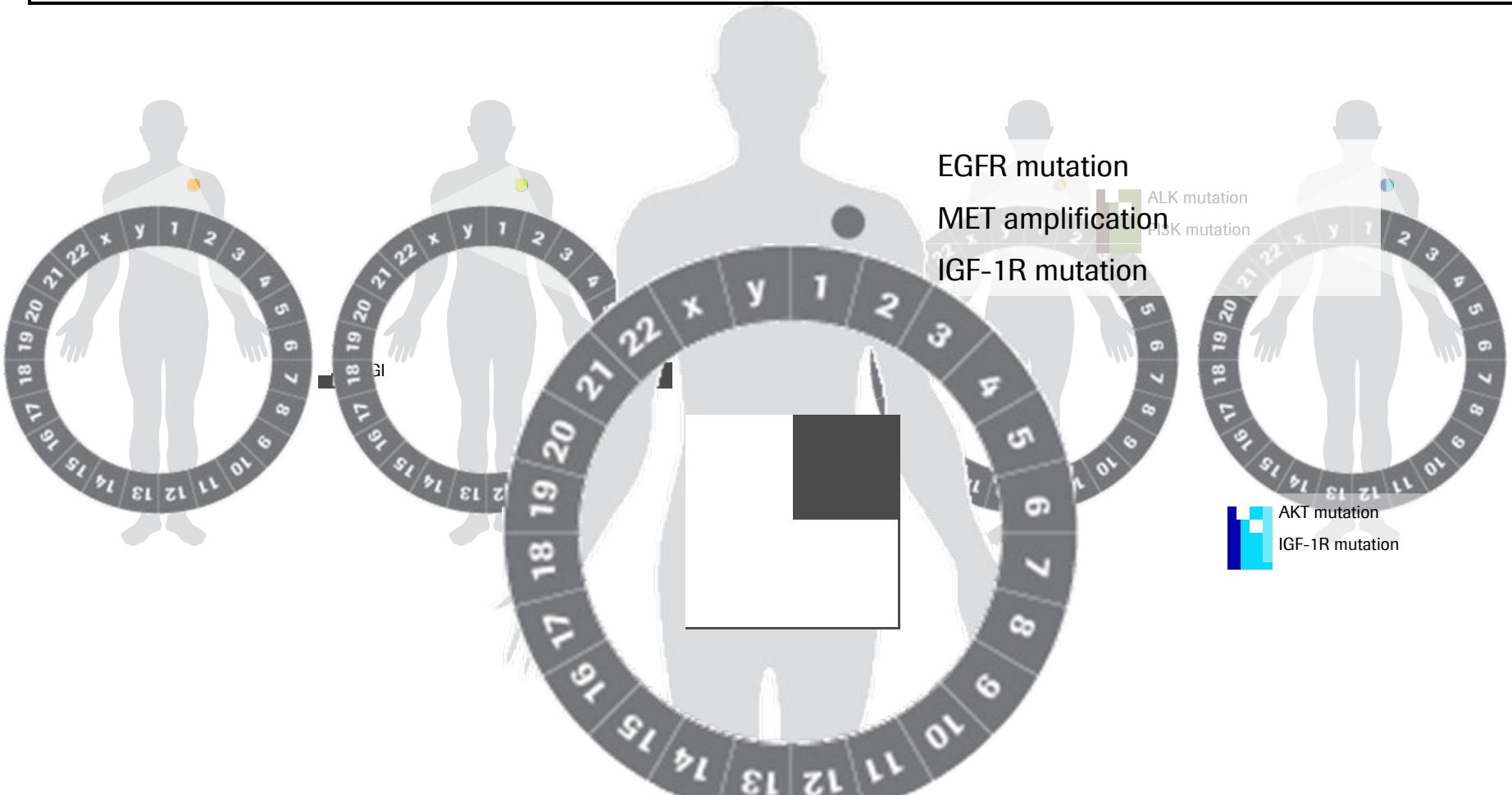


- Cancer genome ‘landscape’ map depicting > 40 somatic mutations present in a single small-cell lung cancer cell line (NCI-H2171)

Personalized Healthcare Emerging Reality

Therapies Matched to Specific Molecular Targets

Targeted Therapy Formulary



Agenda

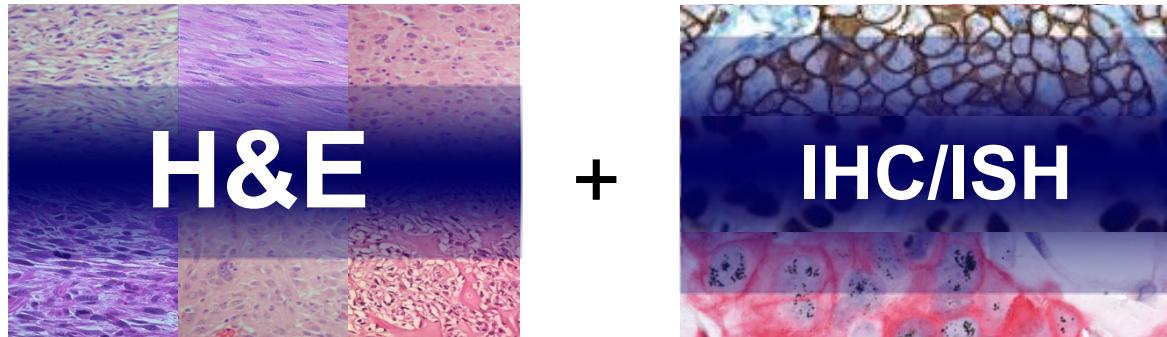
Personalized Healthcare (PHC): Emerging Reality

PHC and Pathology: The Need for Change

The Role of the Pathologist in PHC

Pathology Today

Diagnosis Focused



Anatomy/Morphology-Based Disease Classification



Neoplastic

- **Malignant**
- **Benign**
- **“Borderline”**

Non-Neoplastic

- Normal
- Physiologic
- Inflammatory

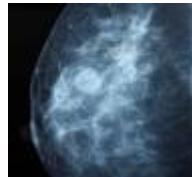
Pathology Needs to Embrace The Ongoing Paradigm Shift in Oncology

The Genomic View of Cancer

From anatomy



Lung



Breast



Prostate

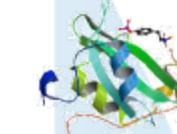


Colon



Brain

To molecular pathways



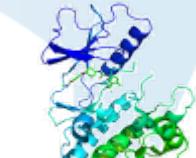
KIT



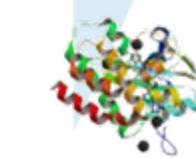
EGFR



HER2

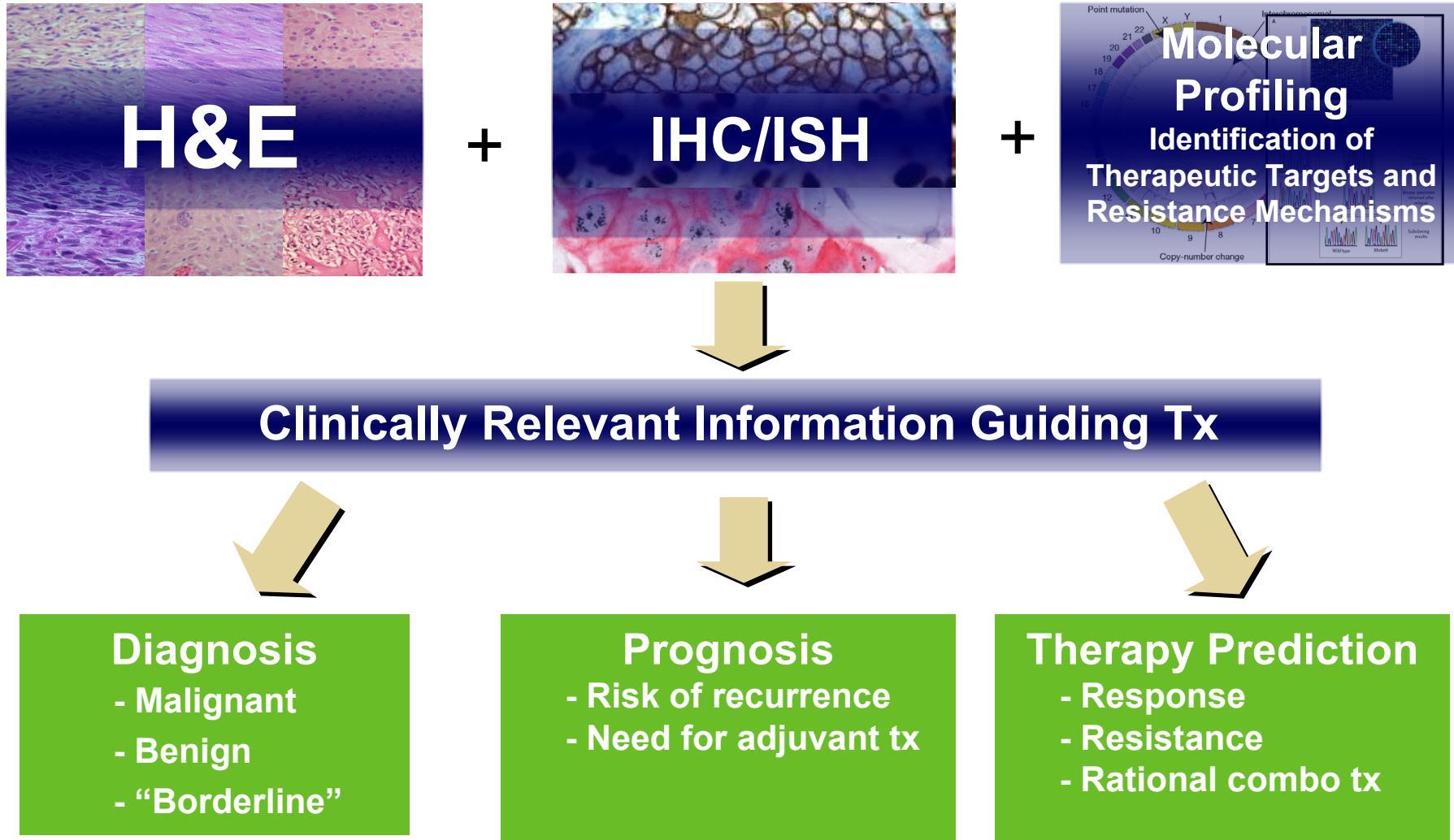


BRAF



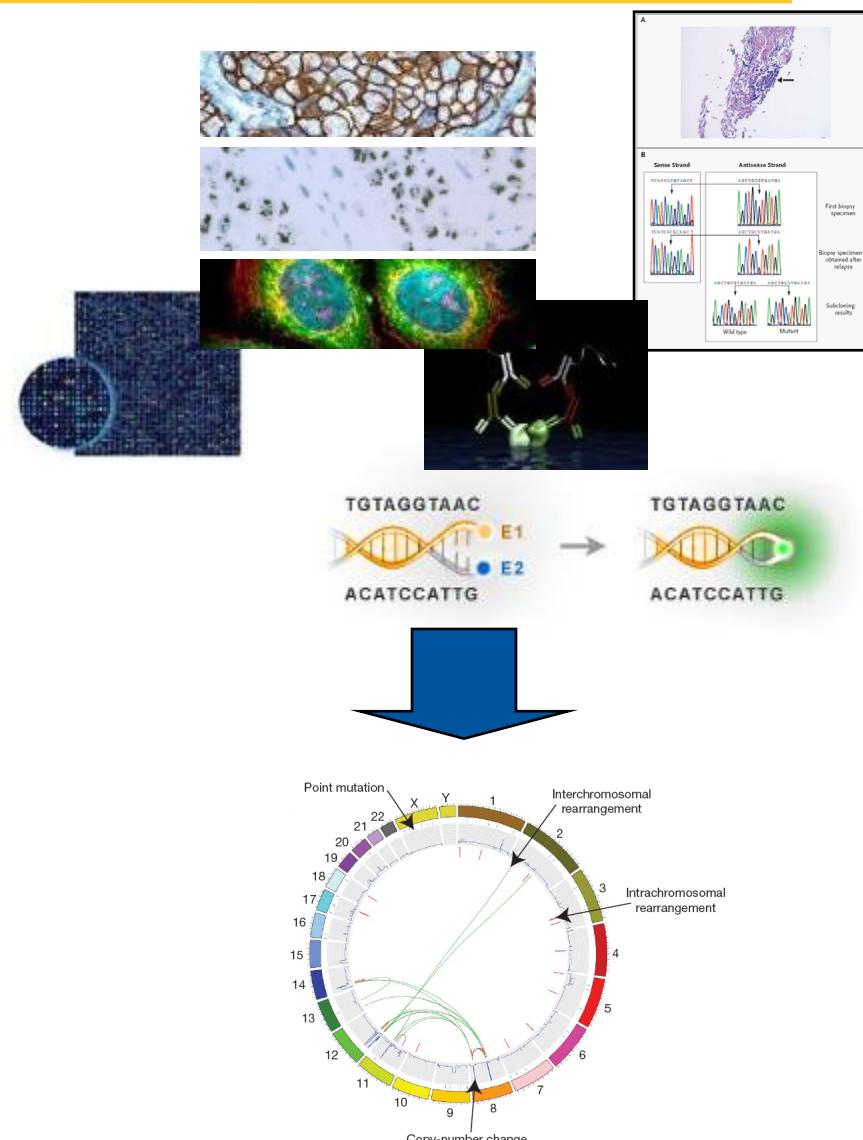
PIK3CA

The Opportunity For Pathology *Diagnosis + Tumor Profiling Focused*



Pathologists Need Next-Generation Tools To Embrace Genomics and Deliver **Comprehensive Tumor Profiling**

- **DNA Level Testing**
 - Amplification (ISH) **Available**
 - **Mutations: insertions, deletions, point mutations/SNPs**
 - **Translocations**
 - Epigenetic events: methylation, acetylation, etc.
- **RNA Level Testing**
 - mRNA expression profiling
 - Micro RNA
- **Protein Level Testing**
 - Total proteins (IHC) **Available**
 - Phosphorylated proteins
 - Receptor dimerization
 - Stem cell markers
 - Protein fusions





transFORMation

CAP's vision is to transform the practice of pathology

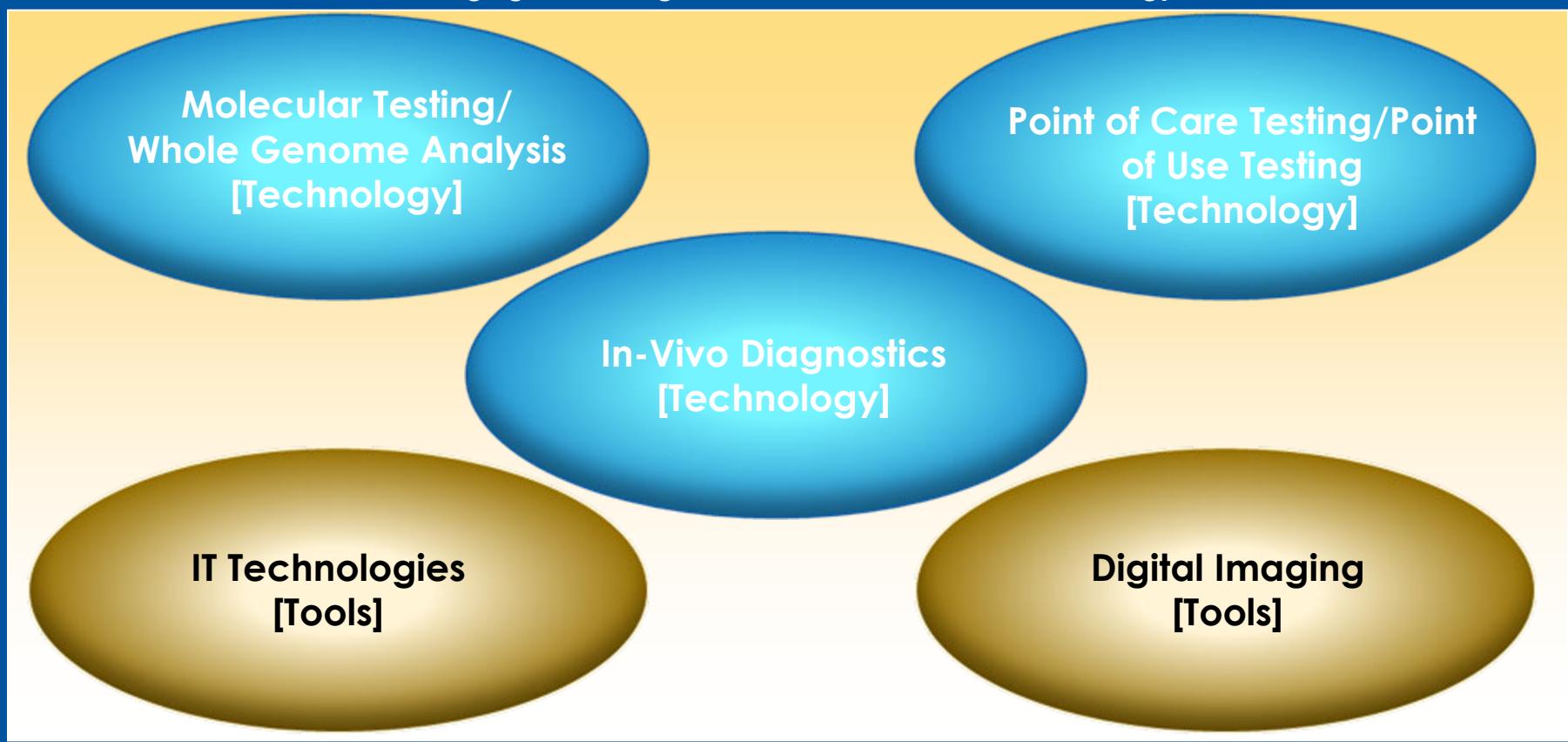
- Best practices/standards
 - Education
 - Better integration with the House of Medicine, especially in the era of personalized medicine
 - Emerging technology investigation
 - Strengthened advocacy
 - Laboratory improvement program expansion
 - Accreditation redesign
 - Membership growth and segmented services
- and more*



Transformation Case for Change Program

Emerging Technologies Framework

Emerging Technologies and Tools in the Field of Pathology



Emerging Tools

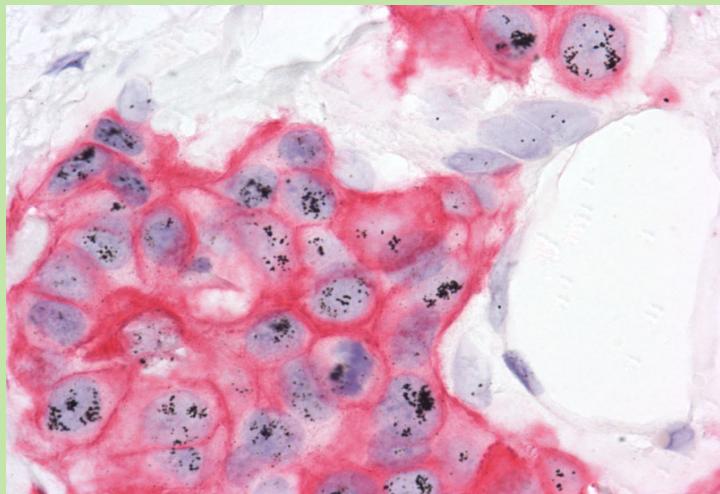
Potential New Tests that
Pathologists can Perform

Pathologists Must Respond to Provide Clinically Relevant Personalized Healthcare Solutions *Or Someone Else Will*

Embrace

Molecular diagnosis performed by pathologists

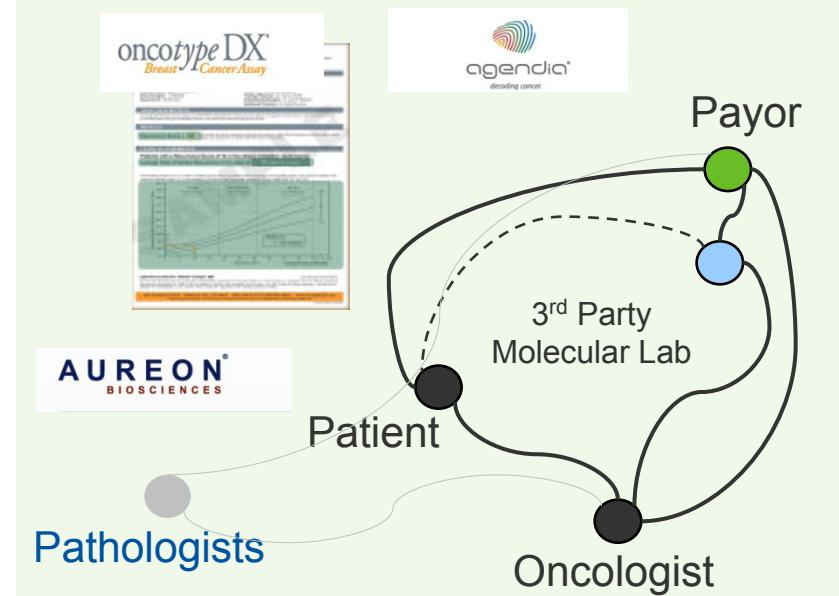
Preservation of morphologic information
High level of validation for FDA-approved/cleared assays
Work remains in pathology lab



Passive

Molecular diagnosis performed by 3rd party labs (e.g. LDT assays in CLIA labs)

Results lack morphologic context
Level of validation typically lower vs. IVDs
Pathologists cut out of the loop



Molecular Profiling Services are Emerging and Marketing Themselves Directly to Patients

NEWS

JNCI Vol. 103, Issue 2 | January 19, 2011

Ready or Not: Personal Tumor Profiling Tests Take Off

By Ken Garber

One vital goal of cancer research is a test that profiles individual tumors at the molecular level in order to guide treatment. Some single-marker predictive tests are now standard, as are two

that assumption is that the tests should be patients to clinical prove utility in theirical trials. Such trials

Commercial Tumor Profiling Tests

Test (company)	Main analytical method(s)	No. of genes interrogated	Validation/transparency	Turnaround time	Price
Target Now (Caris Life Sciences)	Biomarker rules	Varies by tumor subtype; ~100, by various methods	Pilot feasibility and efficacy study published; methods disclosed	10–14 business days	\$3,400
OnclnSights (Intervention Insights)	Biomarker rules, systems biology, connectivity map	Whole genome by expression microarray	Pilot feasibility study published as abstract; methods disclosed	≤10 business days	\$3,950
GeneKey (Formerly CollabRx)	Systems biology	Whole genome by expression microarray, whole-exome sequencing as add-on	No publications; proprietary methods	Varies; generally ≥3 wks	\$30,000–35,000 (does not include whole-exome sequencing)

The screenshot shows the CARIS LIFE SCIENCES homepage with a navigation bar for 'About Us', 'CarisPath™ Expert Pathology', 'Caris Target Now™ Molecular Profiling', 'Carisome™ Microarray Technology', and 'Clinical Services'. A main banner features a doctor and the text 'Now published in the Journal of Clinical Oncology'. Below it, a section for 'CARIS TARGET NOW™ MOLECULAR PROFILING' includes a 'Find a Doctor' button and a 'PATIENT STORY' link.

The screenshot shows the INTERVENTION INSIGHTS website with a navigation bar for 'Our Service', 'For Patients', 'For Physicians', 'About Us', 'Our Story', 'Guiding Principles', 'Contact', '23andMe', 'welcome', 'ancestry', 'health', 'how it works', and 'store'. A central banner features a doctor and the text 'Your cancer, your genomic signature, our insights...'. Below it, a section for 'Empowering community oncologists with the latest therapeutic and molecular services' includes a 'UPCOMING EVENT' button. To the right, a 'Learn From Your DNA' section details the 23andMe service, showing a flowchart from 'Get Your Kit' to 'Provide Saliva' to 'View Results and Learn About Yourself'.

For Illustrative Purposes Only - No Endorsements Implied

Recent Acquisitions of Molecular Pathology Testing Laboratories by Large Multinational Corporations

Monday, January 24, 2011 As of 2:00 PM EST New York 28° | 18°

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TOP STORIES IN Business

 1 of 12
CEO Says Nokia Needs Huge Transformation

Coca-Cola Profit Soars

HEALTH INDUSTRY | JANUARY 24, 2011, 2:00 P.M. ET

Novartis to Buy Genoptix for \$470 Million

GENOPTIX
MEDICAL LABORATORY

Genoptix Advantage

eCOMPASS®

Hematology

COMPASS™

CHART®

Solid Tumor

NexCourse™ CRC

NexCourse™ NSCLC

Test Directory

Technology Overview

Tests by Technology

Tests by Disease State

NexCourse™
SOLID TUMOR EVALUATIONS

NexCourse is our approach for solid tumor testing.

NexCourse tests can indicate whether or not a patient:

- Is likely to respond to certain treatments
- May be at risk for increased toxicity from certain treatments

NexCourse helps physicians make more informed clinical decisions.

Why NexCourse?

Molecular testing helps to predict patient response.

The stage of cancer broadly helps to determine treatment options. which treatments may be ineffective or toxic. This is where molecular t

NexCourse molecular markers can help indicate whether or not a p. and which treatments may be ineffective or toxic. This can help guic patient care

MARKETS

GE Healthcare Acquiring Clariant in \$580M Stock Deal

By Jennifer Brooten

Published October 22, 2010 | FOXBusiness

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[Text Size](#)



Reuters

Clariant InsightDx Mammostrat® N highly validated breast panel, provides clinicians a risk assessment, independent of proliferation and grade, and hormonal status. Learn More

Clariant InsightDx Pulmotype® Clariant's new lung cancer test helps physicians differentiate histologic sub-classes of non-small cell lung cancer (NSCLC), leading to better therapy selection for patients. Learn more about [InsightDx Pulmotype](#).

If you missed our Pulmotype webinar, see our playback.

Top Tests

ALK Gene Rearrangement

BRAF

EGFR Mutation Analysis

KRAS & BRAF

KRAS Mutation Analysis

Mammostrat

PI3K

Pulmotype

Our Focus

Breast Cancer Testing

Breast Cancer Recurrence Testing

Colon Cancer Testing

KRAS in Colorectal Cancer

KRAS & BRAF Testing in Colorectal

Cancer

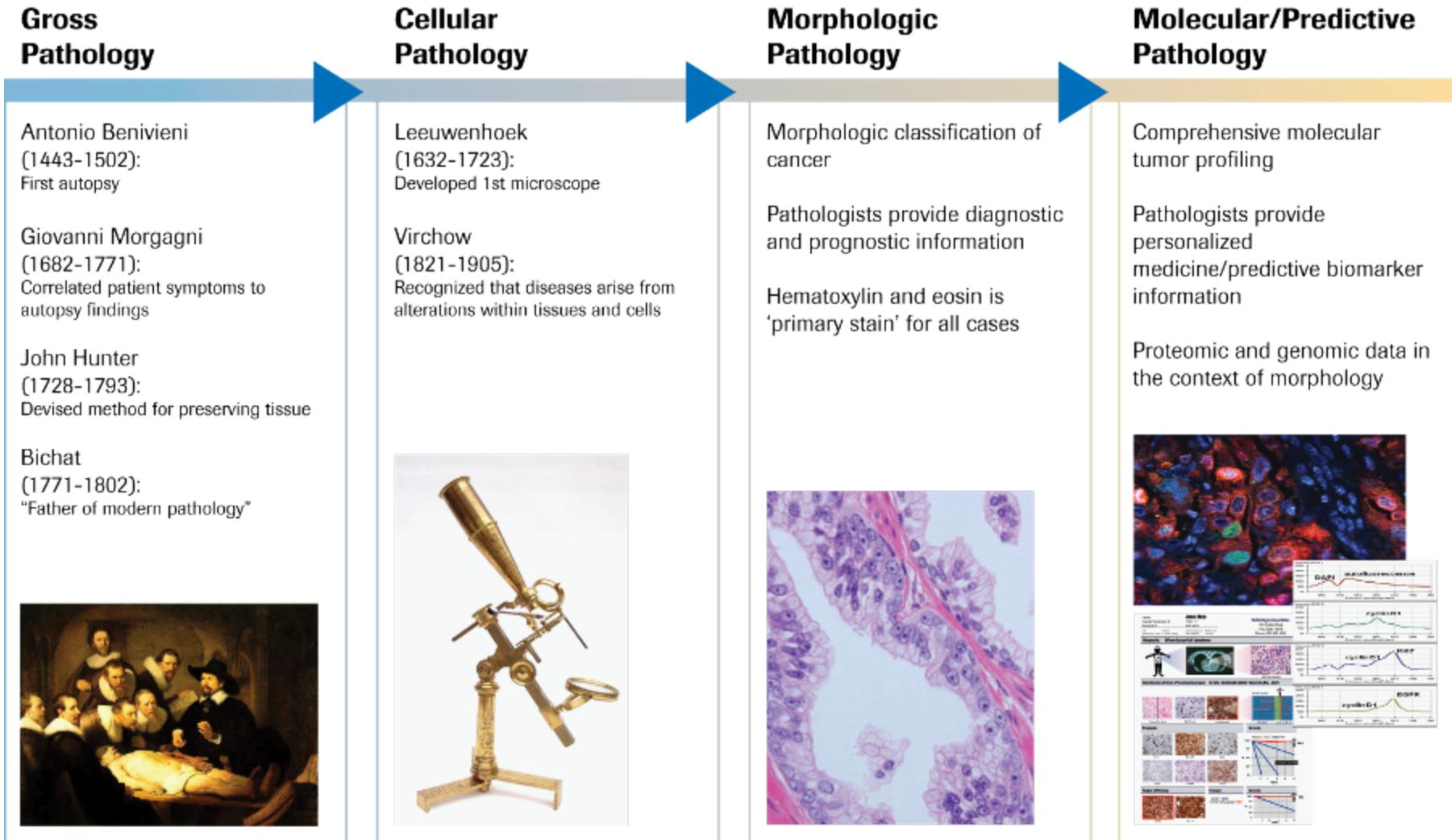
KRAS Mutation Analysis

KRAS Mutation Testing

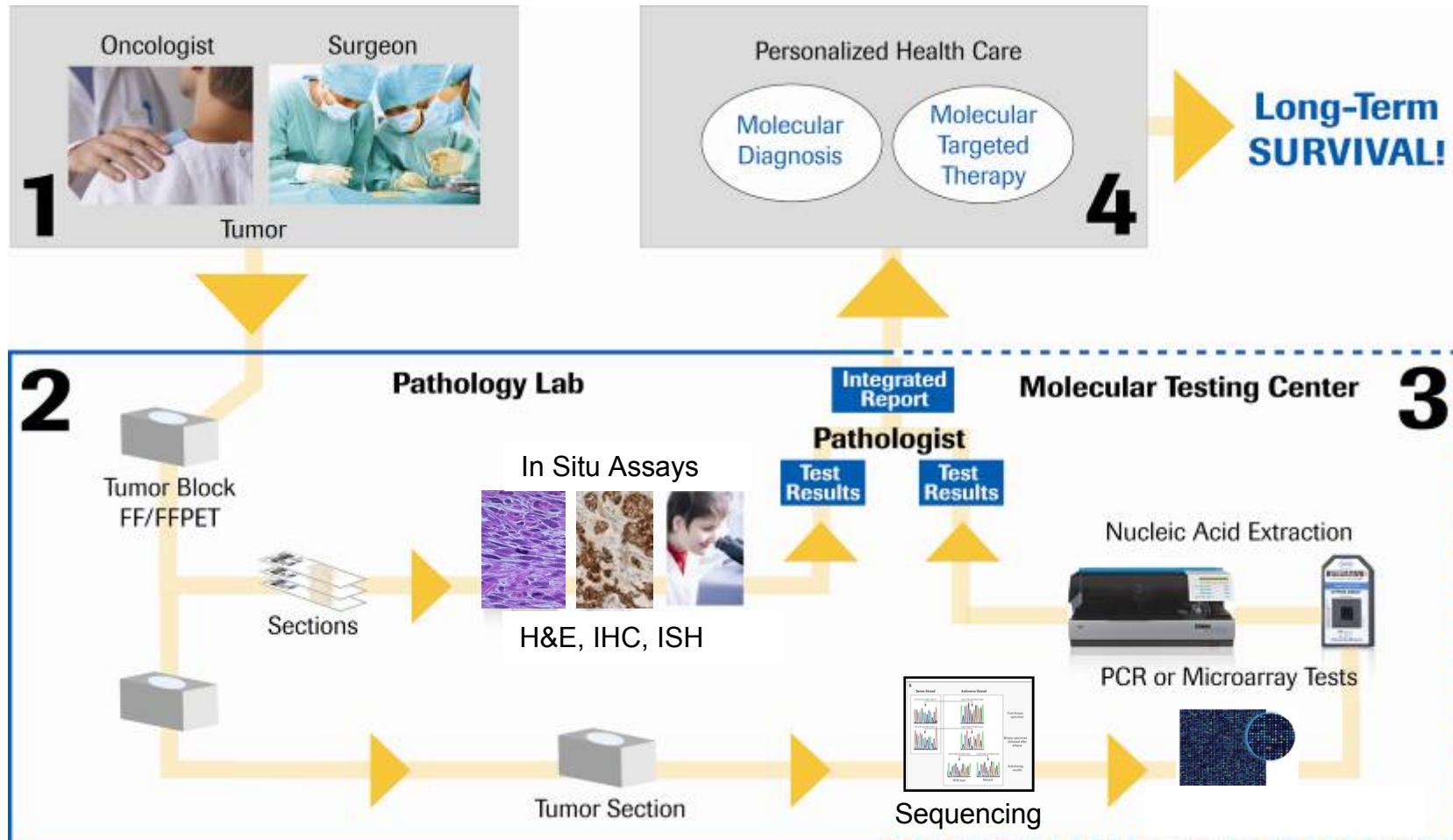
Pulmotype Test

For Illustrative Purposes Only - No Endorsements Implied

Pathology Will Evolve to Meet Patient Needs and Be a Central Driver of Personalized Healthcare



How Will It Happen? *The Pathology Lab of the Future*



Next Generation In Situ Molecular Pathology

EGFR Mutation-specific Immunohistochemistry

Simonetti et al. *Journal of Translational Medicine* 2010, **8**:135
http://www.translational-medicine.com/content/8/1/135



JOURNAL OF
TRANSLATIONAL MEDICINE

RESEARCH

Open Access

Detection of EGFR mutations with mutation-specific antibodies in stage IV non-small-cell lung cancer

Sara Simonetti¹, Miguel Angel Molina¹, Cristina Queralt², Itziar de Aguirre², Clara Mayo¹, Jordi Bertran-Alamillo¹, José Javier Sanchez³, Jose Luis Gonzalez-Larriba⁴, Ulpiano Jimenez⁵, Dolores Isla⁶, Teresa Moran², Santiago Viteri¹, Carlos Camps⁷, Rosario Garcia-Campelo⁸, Bartomeu Massuti⁹, Susana Benlloch¹, Santiago Ramon y Cajal^{1,10},

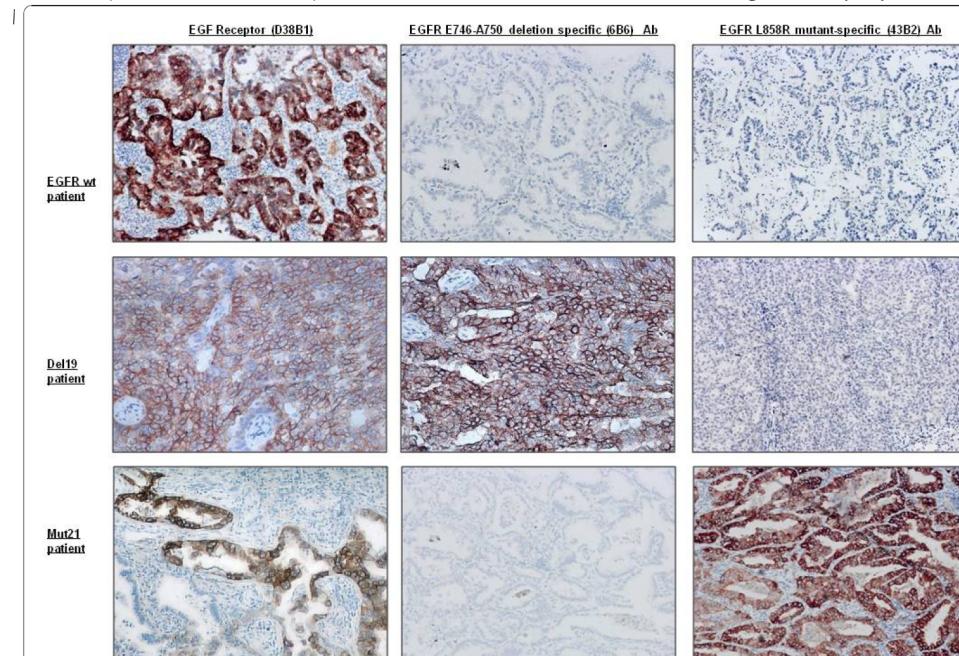
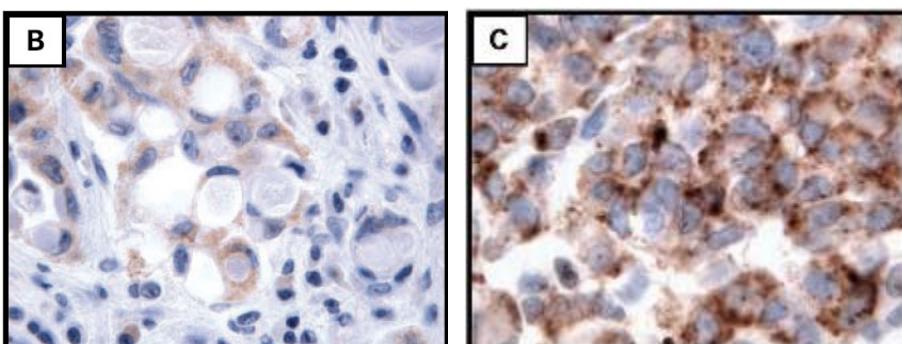
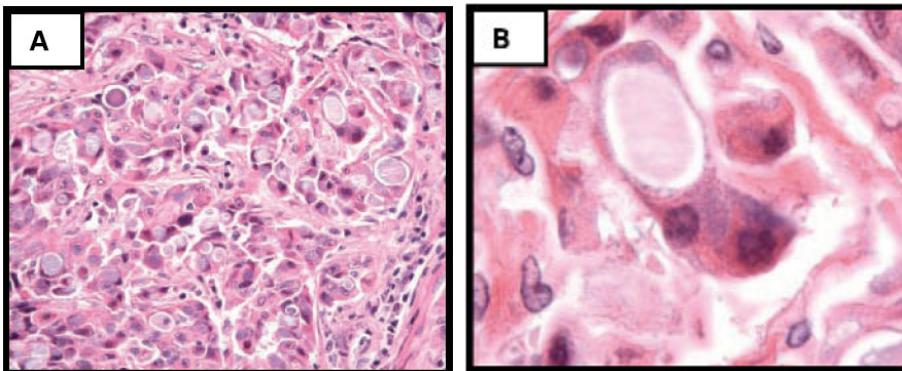


Figure 2 IHC staining of tumor samples from lung cancer patients. EGFR E746-A750 deletion specific (6B6) antibody detected 100% of cases with the 15-bp exon 19 deletion, and EGFR L858R mutant-specific (43B2) antibody detected 100% of cases harboring L858R mutation of exon 21.

Unique Clinicopathologic Features Characterize ALK-Rearranged Lung Adenocarcinoma in the Western Population

Scott J. Rodig,¹ Mari Mino-Kenudson,² Sanja Dacic,⁵ Beow Y. Yeap,³ Alice Shaw,³ Justine A. Barletta,¹ Hannah Stubbs,² Kenny Law,¹ Neal Lindeman,¹ Eugene Mark,² Pasi A. Janne,⁴ Thomas Lynch,³ Bruce E. Johnson,⁴ A. John Iafrate,² and Lucian R. Chirieac¹



Standard IHC

IHC with tyramide amp

- 5.6% lung adenocarcinomas with ALK rearrangements (Western population)
- ALK rearrangement associated with:
 - Younger age
 - Never smoking
 - Advanced clinical stage
 - Solid histology with signet-ring cells
- Sensitivity for ALK rearrangement
 - FISH: 95%
 - IHC standard: 40%
 - IHC with tyramide amp: 80%
 - Neither FISH nor IHC detected all cases of ALK rearrangement
- None of the ALK-rearranged tumors had coexisting EGFR mutations

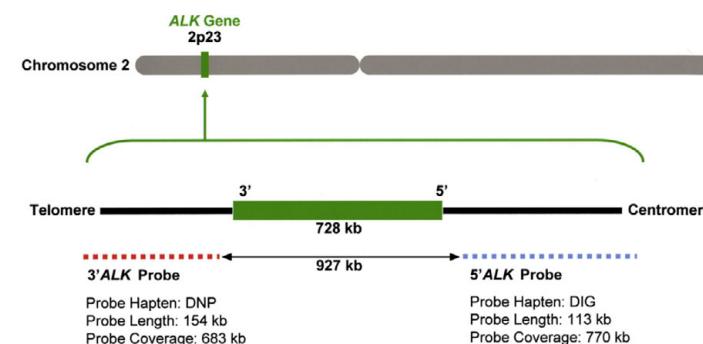
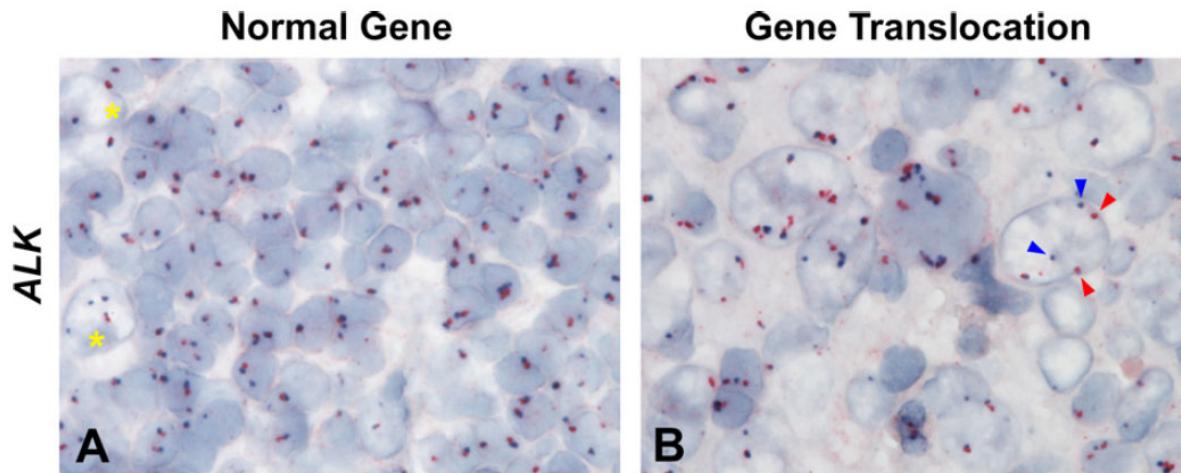


Methods

journal homepage: www.elsevier.com/locate/ymeth

Automated brightfield break-apart *in situ* hybridization (ba-ISH) application: ALK and MALT1 genes as models

Hiroaki Nitta ^{a,*}, Wenjun Zhang ^b, Brian D. Kelly ^c, Melanie Miller ^b, Lidija Pestic-Dragovich ^b, Christopher Bieniarz ^c, Thomas J. Vasicek ^d, Teresa Marafioti ^e, Lisa Rimsza ^f, Thomas M. Grogan ^a

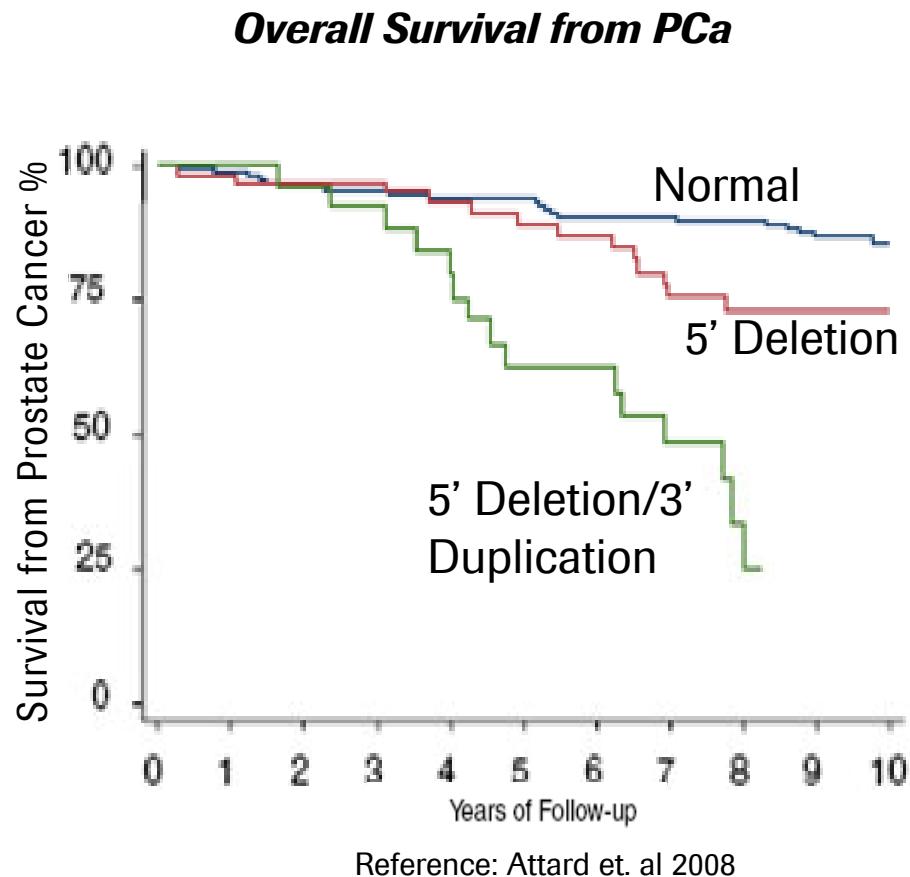
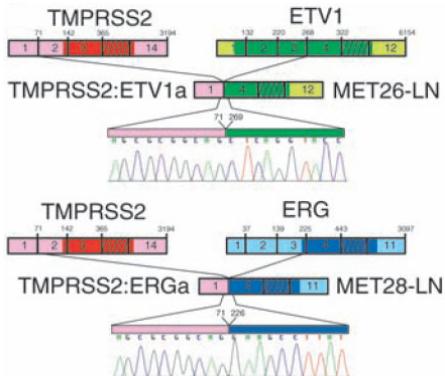


TMPRSS2:ERG Status Defines Prognostic Subgroups in Prostate Cancer

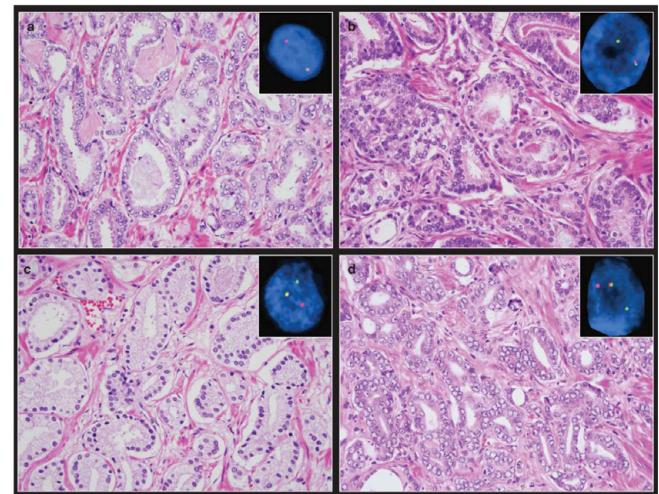
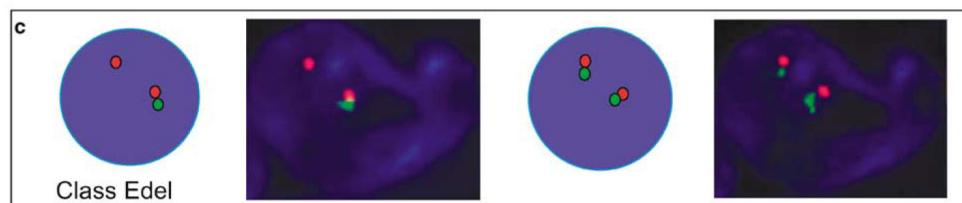
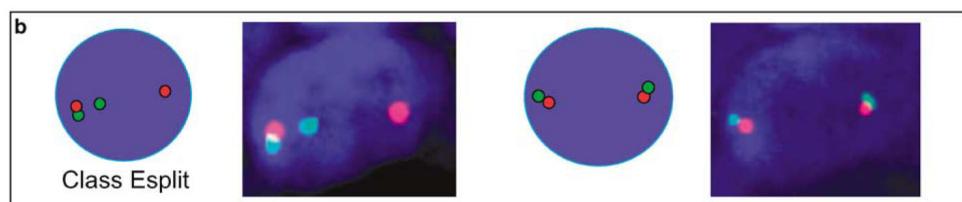
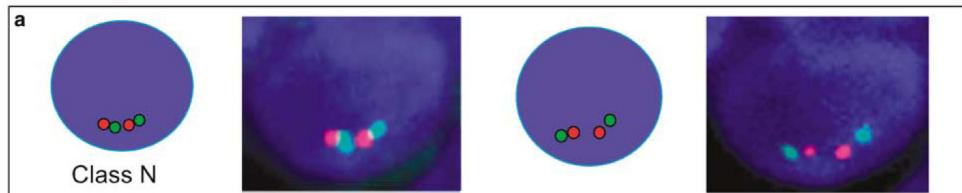
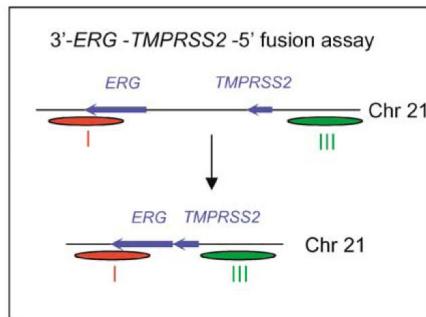
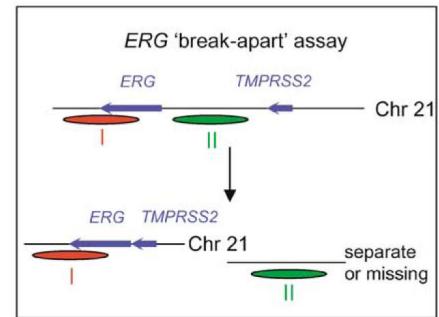
RESEARCH ARTICLE

Recurrent Fusion of *TMPRSS2* and ETS Transcription Factor Genes in Prostate Cancer

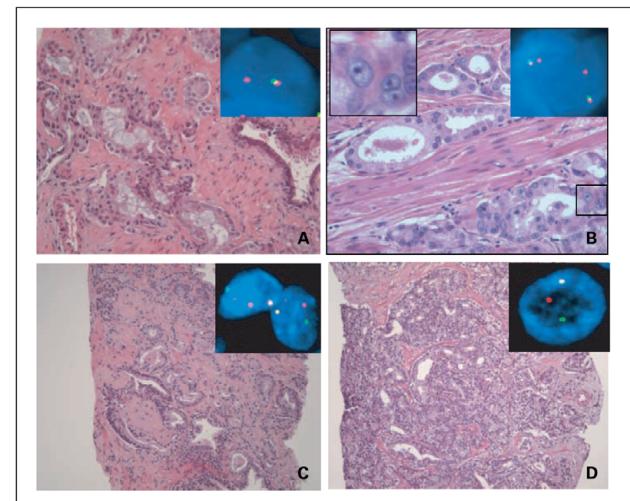
Scott A. Tomlins,¹ Daniel R. Rhodes,^{1,2} Sven Perner,^{7,9} Saravana M. Dhanasekaran,¹ Rohit Mehra,¹ Xiao-Wei Sun,⁷ Sooryanarayana Varambally,^{1,6} Xuhong Cao,¹ Joelle Tchinda,⁷ Rainer Kuefer,¹⁰ Charles Lee,⁷ James E. Montie,^{3,5,6} Rajal B. Shah,^{1,3,5,6} Kenneth J. Pienta,^{3,4,5,6} Mark A. Rubin,^{7,8} Arul M. Chinnaiyan^{1,2,3,5,6*}



FISH Detection of TMPRSS2 and ERG Gene Status



Esgueva et al. Mod Path (2010), 1-8

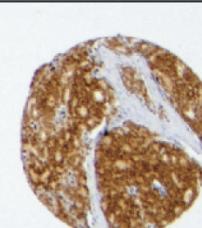
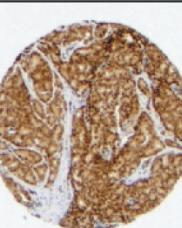
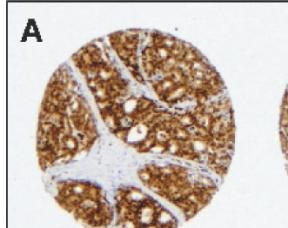


Detection of ERG Rearrangements By Immunohistochemistry

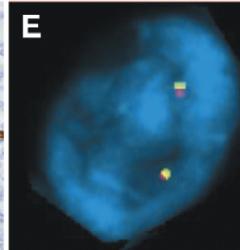
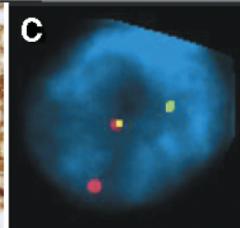
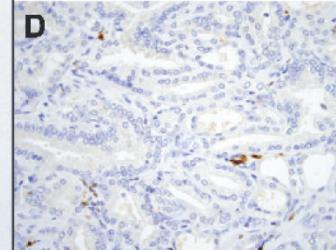
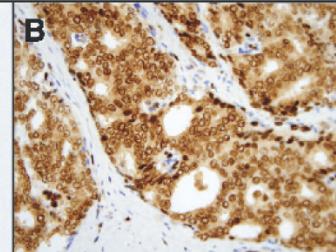
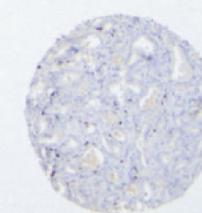
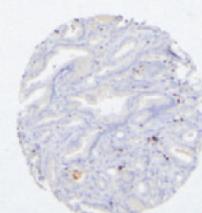
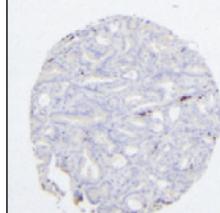
Antibody-Based Detection of ERG Rearrangement–Positive Prostate Cancer^{1,2}

Kyung Park^{*,3}, Scott A. Tomlins^{†,‡,3},
Kumaran M. Mudaliar^{*}, Ya-Lin Chiu[§],
Raquel Esgueva^{*}, Rohit Mehra^{†,‡},
Khalid Suleman^{†,‡}, Sooryanarayana Varambally^{†,‡},
John C. Brenner^{†,‡}, Theresa MacDonald^{*},
Abhishek Srivastava[¶], Ashutosh K. Tewari[¶],
Ubaradka Sathyanarayana[#], Dea Nagy[#],
Gary Pestano[#], Lakshmi P. Kunju^{†,‡},
Francesca Demichelis^{*,**},
Arul M. Chinnaian^{†,‡,¶,§§,4}
and Mark A. Rubin^{*,4}

Tumor
Area 1



Tumor
Area 2



Panel of 4 IHC Markers May Have Additional Prognostic Utility in Prostate Cancer: SMAD4, PTEN, CCND1, SPP1

LETTER

doi:10.1038/nature09677

SMAD4-dependent barrier constrains prostate cancer growth and metastatic progression

Zhihu Ding^{1,2,3,4}, Chang-Jiun Wu^{1,2,3,4*}, Gerald C. Chu^{1,2,5*}, Yonghong Xiao^{1,2}, Dennis Ho^{1,2,3,4}, Jingfang Zhang⁶, Samuel R. Perry^{1,2}, Emma S. Labrot^{1,2}, Xiaoqiu Wu^{2,7}, Rosina Lis^{2,7}, Yujin Hoshida^{8,9}, David Hiller¹⁰, Baoli Hu^{1,2}, Shan Jiang^{1,2}, Hongwu Zheng^{1,2,3,4}, Alexander H. Stegh^{1,2,3,4}, Kenneth L. Scott^{1,2,3,4}, Sabina Signoretti¹¹, Nabeel Bardeesy¹², Y. Alan Wang^{1,2}, David E. Hill^{3,13}, Todd R. Golub^{8,9}, Meir J. Stampfer^{15,16,17}, Wing H. Wong¹⁰, Massimo Loda^{2,5,7}, Lorelei Mucci^{15,17}, Lynda Chin^{1,2,3,4,14} & Ronald A. DePinho^{1,2,3,4}

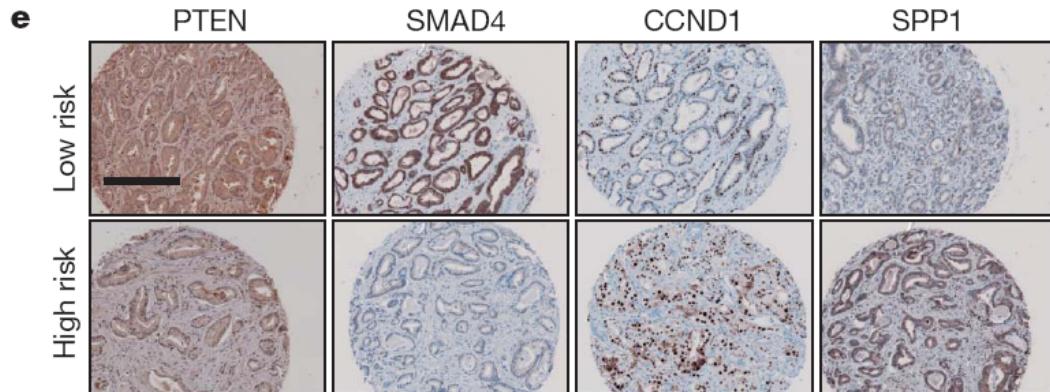
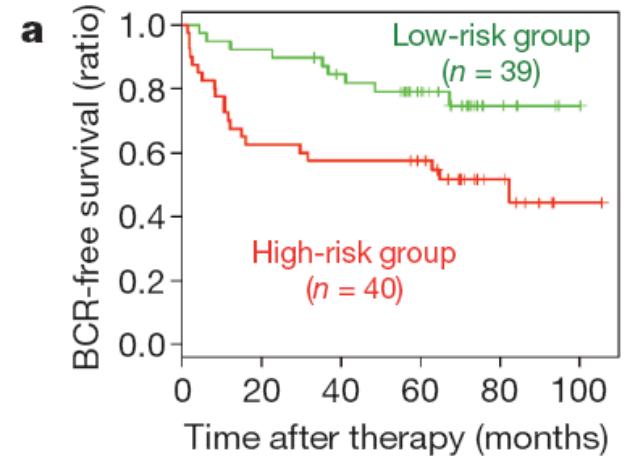


Figure 4 | Prognostic potential of a four-gene signature in human PCA.



Pathologists Don't Need to Be Limited to Tissue *In Situ Hybridization in Circulating Tumor Cells*

OPEN  ACCESS Freely available online

September 2010 | Volume 5 | Issue 9 | e12517

 PLOS ONE

Molecular Biomarker Analyses Using Circulating Tumor Cells

Elizabeth A. Punnoose^{1*}, Siminder K. Atwal¹, Jill M. Spoerke¹, Heidi Savage¹, Ajay Pandita², Ru-Fang Yeh³, Andrea Pirzkall⁴, Bernard M. Fine⁴, Lukas C. Amler¹, Daniel S. Chen⁴, Mark R. Lackner¹

D

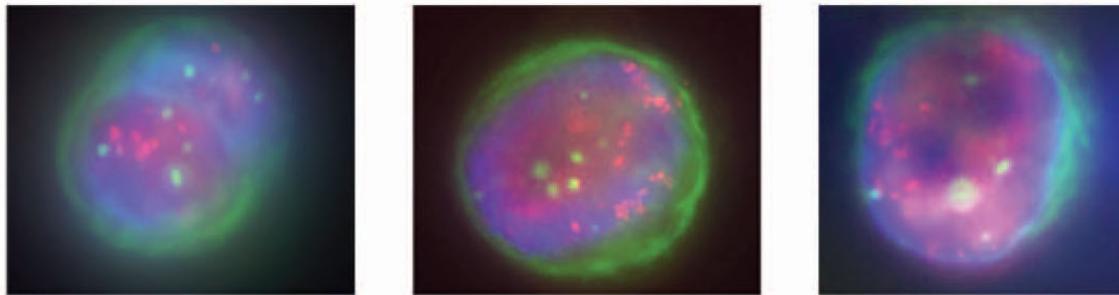


Figure 2. EGFR IF and HER2 FISH in CTCs. A. mRNA expression of EGFR (diamonds) or EpCAM (bars) in NSCLC cell lines. IHC scores for EGFR from tissue microarrays are indicated below. B. EGFR immunofluorescence (IF) scoring criteria for CTCs. For each scoring level, the range of high and low expression are shown. C. EGFR IF scoring of spiked tumor cells isolated from blood. The weighted H-score from CTC analysis and corresponding IHC score for that cell line is listed below for each sample. D. HER2 FISH assay in captured SKBR3 cells on the OncoCEE microchannel platform. Cells are stained with anti-cytokeratin antibody (green), DAPI (blue), FISH probes against HER2 (red dots) and a centromeric probe, CEP17 (green dots).
doi:10.1371/journal.pone.0012517.g002

Agenda

Personalized Healthcare (PHC): Emerging Reality

PHC and Pathology: The Need for Change

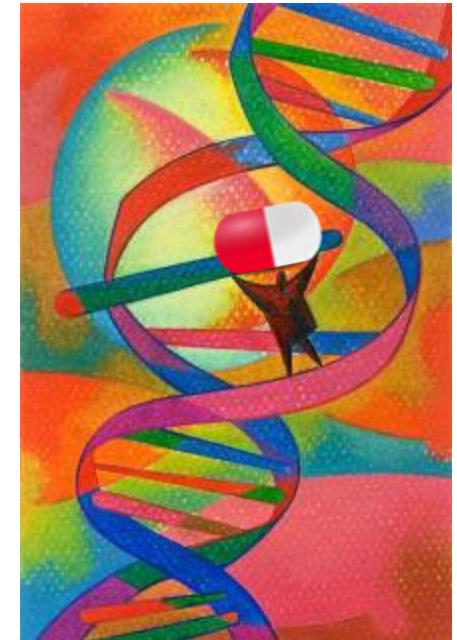
The Role of the Pathologist in PHC

Pathologists Have Critical Roles to Play as Personalized Healthcare Evolves

- Drug development process
 - Working in pharma/biotech on drug dev team, biomarker group or as CMO
 - Diagnostic development process
 - Working in dx industry on development team, medical group or as CMO
 - Companion Dx and Prognostic Assay validation trials
 - Principal Investigator based in hospitals, reference labs, academic labs
 - Assay adoption/usage
 - Interpretation of companion dx and prognostic assays
 - Integration of PHC/molecular data with other pathology and clinical data
 - Communication of PHC/molecular data to patients and clinicians
 - Assay standardization, QA/QC, sample quality/pre-analytical standardization
 - Biomarker Clinical/Translational Research [academia, pharma]
 - Novel markers
 - Better assays for existing targets
 - Novel technologies
- 
- Companion
Diagnostic (CDx)
Co-Development**

Summary

- **The effective application of personalized healthcare most certainly will become more complex as we learn more about tumor molecular biology**
 - detection of tumor-based mutations will be particularly important in the identification of molecular subsets of cancer patients responsive to specific targeted therapies
- **Pathologists have the opportunity to play a central and critical role as drivers of personalized healthcare via the delivery of tumor profiling information critical for therapy decisions**
- **Pathologists need to embrace this opportunity and actively pursue new roles, responsibilities and technologies for the benefit of patients in the era of personalized healthcare**



Next in the Series of Free PHC Webinars

- **How to Build and Fund a Financially Viable Molecular Lab**
March 16, 11 am-12 pm CT
 - Frederick Kiechle, MD, PhD, FCAP
- Go to www.cap.org/institute For All Upcoming Webinars!
- Past Webinars Available Now Online at www.cap.org/institute
 - Molecular Markers in Breast Cancer
 - The True Meaning of the Bethesda System: Integrating Cytology and HPV Molecular Testing to Individualize a Woman's Cancer Risk
 - Molecular Diagnosis for Lung Cancer
 - Molecular Diagnosis for Colorectal Cancer
 - Endoscopic Microscopy: Bridging the Radiology/Pathology Divide

Source: Century Gothic, 9 pt, sentence case

Upcoming CAP event of interest

- **Futurescape of Pathology—April 15-17, 2011 in Rosemont, IL**
- Futurescape of Pathology is an innovative forum designed to facilitate dialogue between decision-makers from pathology, business, technology and the financial industries. This exciting conference is the platform for a “two-way” conversation with the forces driving innovation to hear the ideas of, and gather information from practicing pathologists about the transformation of pathology.
- Experts will guide you through the exploration of the latest innovation theory, strategy, and case studies. Learn from these resources how to successfully implement and refine innovation to leverage and grow your practice.
- <http://www.cap.org/apps/docs/futurescape/index.html>