The Role of Advanced Diagnostics in Cancer Care

September 20, 2012
Speakers

• **Amalia M. Issa**, PhD, MPH, University of the Sciences - Chair of the Department of Health Policy and Public Health; Director of the Program in Personalized Medicine and Targeted Therapeutics

• **Cesar Garcia**, President & CEO, IRIS

• **Walter Koch**, PhD, VP, Head of Global Research, Roche Diagnostics

• **Marcia Horn**, President & CEO, International Cancer Advocacy Network (ICAN)
AdvaMedDx

- Founded in 2010 as a division of AdvaMed, the medical technology manufacturers association.

- Dx = Diagnostics (medical diagnostic tests)

- AdvaMedDx functions as an “association within an association”, representing over 65 member companies from global industry leaders to early stage test developers.

- Our goals are to educate stakeholders on the value of diagnostics and advocate for public policies that advance patient care through the use of innovative, safe, and effective diagnostics.

- Diagnostics account for about 2% of Medicare spending, but influence 70% of medical decision making.
<table>
<thead>
<tr>
<th>Test Use</th>
<th>Purpose</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening, Early Disease Detection</td>
<td>To detect asymptomatic disease or a predisposition to disease in order to take action to prevent it by modifying a risk factor or to treat it earlier</td>
<td>• Blood cholesterol tests / heart disease&lt;br&gt;• Fecal occult blood tests / colorectal cancer&lt;br&gt;• Pap tests / cervical cancer&lt;br&gt;• Genetic tests&lt;br&gt;• Blood glucose tests / diabetes&lt;br&gt;• Blood glucose tests / diabetes</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>To make a diagnosis when symptoms, abnormalities on physical examination, or other evidence suggests, but does not prove, that a disease may be present</td>
<td>• Streptococcus / bacterial infection&lt;br&gt;• Brain natriuretic peptide (BNP) / heart failure</td>
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<tr>
<td>Disease Staging, Prognosis</td>
<td>To determine the extent of disease progression or severity and the likelihood of recovery or risk of future adverse health outcomes (e.g., cancer relapse)</td>
<td>• Testing for co-morbidities (e.g., hypertension, cardiovascular disease, acute respiratory infection)&lt;br&gt;• Blood clotting tests for pre-surgical risk assessment&lt;br&gt;• Cardiac marker testing (e.g., troponin, myoglobin) / rapid assessment of heart injury, heart attack</td>
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<tr>
<td>Drug Selection, Treatment Monitoring</td>
<td>To allow accurate and targeted treatment selection tailored to individual needs</td>
<td>• HER2/neu over-expression testing to identify patients who are more likely to respond to the breast cancer drug Herceptin&lt;br&gt;• Oncotype DX, a gene expression profile test, to quantify the likelihood of breast cancer recurrence and potential benefit from chemotherapy in women with newly diagnosed, early stage breast cancer</td>
</tr>
<tr>
<td>Disease or Condition Monitoring and Management</td>
<td>To understand the course of the disease or the effect of a therapy in order to evaluate the success of treatment and the need for additional testing or treatment</td>
<td>• Blood glucose tests and HbA1c tests for diabetes monitoring&lt;br&gt;• Viral load, CD4 count, complete blood count, blood chemistry tests to assess treatment response in HIV patients&lt;br&gt;• Cholesterol tests to monitor effectiveness of lipid-lowering drug therapy&lt;br&gt;• Alpha-fetoprotein tests to monitor effectiveness of therapy for patients with cancers of the liver, testes, or ovaries</td>
</tr>
<tr>
<td>Test Category</td>
<td>Test Purpose</td>
<td>Examples</td>
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<tr>
<td>General Chemistry</td>
<td>Measurements of base compounds in the body</td>
<td>• Urinalysis test strips</td>
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<td></td>
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<td>• Calcium level test</td>
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<td></td>
<td></td>
<td>• HbA1c tests</td>
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<td>• Fecal occult blood tests (FOBT)</td>
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<td>Immunochemistry</td>
<td>Match antibody-antigen response to indicate the presence or level of a protein</td>
<td>• Immunoassay test for troponin</td>
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<td>• Antibiotic susceptibility tests</td>
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<td></td>
<td></td>
<td>• Alpha-fetoprotein (AFP) tests</td>
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<td></td>
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<td>• HIV antibody tests</td>
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<td></td>
<td></td>
<td>• Substance abuse tests</td>
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<td>• Tumor marker tests</td>
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<tr>
<td>Hematology / Cytology</td>
<td>Study of the blood, blood-producing organs, and cells of the body</td>
<td>• Complete blood count</td>
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<td>• Coagulation tests (e.g., INR)</td>
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<td>• Papanicolaou (PAP) smear</td>
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<tr>
<td>Microbiology / Infectious Disease</td>
<td>Detection of disease-causing agents</td>
<td>• Streptococcal testing</td>
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<td>• Bacterial urine testing / urine culture</td>
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<td></td>
<td></td>
<td>• West Nile virus blood screening</td>
</tr>
<tr>
<td>Molecular</td>
<td>Study of DNA and RNA to detect genetic sequences that may indicate presence or susceptibility to disease</td>
<td>• HER2/neu over-expression testing to identify patients who are more likely to respond to the breast cancer drug Herceptin</td>
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<td>• BRCA-1 and BRCA-2 testing to indicate an individual’s risk of developing breast or ovarian cancer</td>
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<td></td>
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<td>• Nucleic acid hybridization tests and nucleic acid amplification tests</td>
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<td>• Pharmacogenomic profiling</td>
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<tr>
<td></td>
<td></td>
<td>• HIV viral load testing and other HIV assays</td>
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</table>
"Your weight problem is partly genetic and partly Boston Cream pie."
A Policy Primer on Diagnostics

Click here to learn about the diagnostics industry and key policies affecting patient care.
The Role of Advanced Diagnostics in Cancer Care
Enabling Personalized Cancer Medicine: The Value of Molecular Diagnostics

Amalia M. Issa, PhD, MPH
Founding Director
Program in Personalized Medicine & Targeted Therapeutics
Professor & Chair
Dept of Health Policy & Public Health

US Capitol
Washington DC – Sept 20, 2012
Value of Molecular Diagnostics for Delivering Personalized Medicine

✦ **What** do we know about the adoption of molecular diagnostics in clinical practice?

✦ **What** needs to be done for molecular diagnostics to be more routinely adopted into clinical practice?
Molecular Diagnostics
Breast Cancer, 1992

Betty
Breast Cancer, 2011
Value of Molecular Diagnostics for Delivering Personalized Medicine

✧ **What** do we need to know?
✧ **When** do we need to know it?
✧ **What** difference does it make?
Understanding of the Human Genome Combined with Sequencing Technology Advances are Moving Us Toward Personalized Genomic Medicine

Human Genome Project

Completed 2003

1 Generic Genome

Technology & Knowledge Advances

Individual Patient Genomes

Direct Patient Care

Improve Outcomes

Genomic Medicine is made possible by ability to analyze individual patient genomes

Genomic Medicine (Personalized Medicine)
Breast Cancer, 1992

Course of Treatment

- Mastectomy
- Chemotherapy
- Radiotherapy
What do we know about Breast Cancer?
Breast Cancer, 2011

Gene Expression Profiling Test (e.g., Oncotype DX® or MammaPrint®)

ER PR Her 2
Molecular Diagnostics Can Lead to Better Decisions and Improved Outcomes

Questioning a $30,000-a-Month Cancer Drug

By ANDREW POLLACK
Published: December 4, 2009

A newly approved chemotherapy drug will cost about $30,000 a month, a sign that the prices of cancer medicines are continuing to rise despite growing concern about health care costs.
Breast Cancer, circa 2012 and beyond

Personalized Medicine
Drugs and Genes

Pharmacogenomics
Challenges to Implementation

- Validation
- Regulation (FDA)
- Interpretation
Crossing the Translational Chasm
✧ Standardization of Analytical Validity, Clinical Validity and Clinical Utility

✧ Is a clinical need being addressed?

✧ Is a clinical need being met?

✧ Is the application acceptable to patients?

✧ Is the application acceptable to health care providers?

✧ Is the application acceptable to society? How are patients best educated about the application?

✧ How are providers best educated about the application?
Decision Making in the Clinical Setting is a Complex Affair!
After a short stay in America, Michelangelo’s David Returned to Europe
Decision analytic modeling of two GEP tests for breast cancer

Yang, M, Rajan S and Issa AM. Cancer, Feb 2012 (online) and October 2012 (in print)

Why this study is interesting:

USciences Study The First to Compare Gene Expression Profiling Tests for Breast Cancer

Results Point to Need for More Effective Assessment of Novel Personalized Genomic Diagnostics
Molecular Diagnostics Teaches Us About the Disease

RISK

DIAGNOSE

SCREEN

TREATMENT
Speed of Clinical Adoption Hinges on Several Factors

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreasing Costs</td>
<td>• Cost of genome analysis is rapidly decreasing</td>
</tr>
<tr>
<td></td>
<td>• Sequencing instruments now are clinically affordable</td>
</tr>
<tr>
<td>Increasing Speed</td>
<td>• Can generate sequencing data in 10-36 hour</td>
</tr>
<tr>
<td>Bioinformatics</td>
<td>• Need clinical quality databases and software tools</td>
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<td></td>
<td>• Pathologists must participate in development</td>
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<tr>
<td>Clinical Usefulness</td>
<td>• Genomic Analysis is in clinical use now (small but growing)</td>
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<tr>
<td></td>
<td>• Research/discovery will increase clinical applications</td>
</tr>
<tr>
<td>Payment Uncertainty</td>
<td>• Payers do not fully understand Genomic Analysis</td>
</tr>
<tr>
<td>Regulatory Uncertainty</td>
<td>• Federal regulatory uncertainty today</td>
</tr>
</tbody>
</table>
Molecular Diagnostics has the potential to transform Health Care
The Role of Advanced Diagnostics in Cancer Care
AdvaMedDx Capitol Hill Briefing
The Role of Advanced Diagnostics Testing in Cancer Care

César M. García
Chairman, President and CEO
September 20, 2012
Agenda

- Introduction to IRIS International
- Prostate Cancer Statistics
- New Patient Management Paradigm
- NADiA ProsVue - How it Works
- NADiA ProsVue - Performance
- Product Development Challenges
- Commercialization Challenges
IRIS International, Inc.

Sample Processing
Streamlines laboratory workflow with rapid cycle times and compact size

Morphology & Related Products
Leverages imaging expertise to identify cells in automation

Personalized Medicine
Early detection of disease relapse potentially providing better therapeutic outcomes

IRIS INTERNATIONAL
~$129mm Revenues
Prostate Cancer
Clinical Overview

- US incidence 228,000/year *

- Global incidence 680,000/year**

- Treatment options
  - Surgery (radical prostatectomy, RP)
  - External beam radiation therapy
  - Radioactive seed implants (brachytherapy)
  - Observation (active surveillance)

- 95,000 men undergo radical prostatectomy annually in the US
  - Number is increasing due to early detection (screening) and increasing availability of minimally invasive robotic instrumentation (e.g., Da Vinci)

** Globolscan 2002.
Risk Demographics

Post-RP

- Urologists choose to conduct a radical prostatectomy (RP) when they believe that the disease is confined to the prostate and the procedure has a high chance of curing or dramatically slowing the progress of the disease.

- Post RP, the surgical area and removed tissues are analyzed and patients are typically stratified into three risk groups.

<table>
<thead>
<tr>
<th>LOW</th>
<th>HIGH</th>
<th>MODERATE</th>
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<tbody>
<tr>
<td>Gleason Score</td>
<td>8 - 10</td>
<td>7</td>
</tr>
<tr>
<td>Disease Level</td>
<td>&gt;=T3</td>
<td>T2C / T2B</td>
</tr>
<tr>
<td>Pre RP PSA Level (ng/ml)</td>
<td>&gt;20</td>
<td>10&lt;x&lt;20</td>
</tr>
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</table>

- Patient distribution and potential for biochemical relapse (BCR) are as follows: 8%

  - Post-RP Risk Stratification*:
    - High: 63%
    - Mod: 23%
    - Low: 5%

Post-RP Patient Management

• The Solution
  - Create an ultra-sensitive diagnostic tool with sufficient specificity so that urologists can confidently make individualized patient management decisions

• Potential Benefits
  - Provide physicians with an objective tool that enables ‘clinical clarity’ to patients with high-risk features or adverse post-surgical pathology
  - Reduce the financial burden of prostate cancer on the healthcare system by optimizing treatment on a patient by patient basis
  - Provide “peace of mind” to patients with stable disease who may otherwise be concerned about the recurrence of their disease; and provide the information “at risk” patients may need to comply with the direction of their clinician to undergo adjuvant treatment post-RP
NADiA® Technology
Reproducible Sensitivity

- NADiA Prosvue is **ultra-sensitive** (measures PSA in picograms - not nanograms)
- 1 nanogram = 1000 picograms
- 0.2ng/mL = 200 picograms/mL

**NADiA Combines Immunoassay Specificity with PCR Sensitivity**

**Sensitivity Comparison**

- **EIA**
- **Immuno-PCR**

Observed PSA (pg/mL)

Expected PSA (pg/mL)

Linear slope = 0.99
Pearson $R^2 = 0.994$
NADiA ProsVue™ Overview

- NADiA® ProsVue™ was cleared by the FDA in September 2011 and received CE Mark in October 2011
  - Not a Lab Developed Test (LDT)

- Recurrence is defined as clinically significant disease as demonstrated by positive imaging, biopsy results, or prostate cancer related death

- Utilizes a series of three blood samples taken post-radical prostatectomy to calculate the slope of the increase in tPSA levels over time
NADiA ProsVue™ Description

- NADiA ProsVue is indicated for use as a **prognostic marker** in conjunction with clinical evaluation as an aid in identifying those patients at **reduced risk for recurrence** of prostate cancer for the **eight year period following prostatectomy**.

Patients are classified as:
- “**At reduced risk for prostate cancer recurrence**”
- “**Not at reduced risk for prostate cancer recurrence**”

**Core Objective:** Avoid unnecessary treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient B</td>
<td><strong>Not At Reduced Risk for Recurrence</strong></td>
</tr>
<tr>
<td>Patient A</td>
<td><strong>At Reduced Risk for Recurrence</strong></td>
</tr>
</tbody>
</table>
A retrospective clinical study of 304 patients evaluated the slope of three successive NADiA ProsVue tests over a period of at least ten months after a prostatectomy as a prognostic marker for risk of clinical disease progression.

Recurrence of disease was determined by positive imaging, biopsy results, or prostate cancer related death.

A NADiA ProsVue slope of $\leq 2.0$ pg/ml/month was highly associated with low risk of clinical disease recurrence for a minimum of 8 years following prostatectomy.
Figure 1: Kaplan-Meier plot of probability of stable classification versus years after surgery. (Dashed line indicates patients with a slope ≤ 2 pg/mL/month [n=245] and solid line indicates patients with a slope > 2 pg/mL/month [n=59].)
Clinical Benefits

**NADiA ProsVue Provides Significant Benefits for Physicians and Patients**

- An objective tool that enables ‘clinical clarity’ to patients with high-risk features or adverse post-surgical pathology

- Significant aid to MDs in optimizing management strategies and follow-up treatment for men post RP
  - NADiA ProsVue may optimize the clinical and economic value of follow-up therapy (radiation, ADT, etc) and minimize the morbidity and costs associated with treating patients that may not benefit

- Provides “peace of mind” to patients with stable disease

- Potential to assist MDs in providing letters to patients to assist in receiving life insurance/medical coverage

- Potentially aid in decision of MDs considering testosterone replacement therapy

Summary
Cost Savings

Prostate Cancer Treatment Environment

- Approximately 25% of post-RP patients receive follow-up treatment in the form of radiation (ART), androgen deprivation (ADT), or both in a proactive effort by the MD to avoid potential metastasis and extend life for moderate and high-risk patients.
  - These treatments are expensive both in terms of direct costs for the therapy, and the costs for managing associated morbidity
    - Radiation Therapy: IMRT direct cost = $50,000
      - Co-morbidities not Quantified: Urinary incontinence, sexual dysfunction, bladder/rectal cancer, proctitis
    - Androgen Deprivation Therapy: Total patient 3yr management cost = $48,350
      - Co-morbidities quantified related to therapy treating bone abnormalities
  - Overall the treatment of men post-RP through death may cost $2.5B annually
    - Patients that either fail radiation/ADT, or are caught too late for adjuvant treatment often are treated with very expensive specialized drugs
      - Provenge: $93,000 course of treatment - Zytiga: $5000/month
      - Jevtana: $10,000/month - Medivation MDV3100: Expected to be Similar to Zytiga

- There is significant financial waste and overtreatment due to the performance (poor) of today’s risk stratification tools. Potential savings to the US healthcare system of $1.0B annually

ProsVue offers insurers the potential to reduce the cost of adjuvant therapy and possibly also reduce long-term costs through
Spent over 10 years and approximately $35 million in development of NADiA ProsVue and the technology platform.

Three year regulatory pathway to receive 510(k) clearance.

Product Development Challenges

- 2H - 08
  - Submitted Pre-IDE: Collaborative approach optimizing study design and regulatory pathway.
- 2009
  - Protocol/IRB Approval at Duke to initiate first stage of clinical study.
  - Pre-IDE Meetings with FDA: Discussions reaching agreement on protocol for clinical studies.
  - Conducted 30 Patients Clinical Study: Results support prognostic claim.
- 2010
  - Pre-IDE Supplement Submitted & Reviewed by FDA: Additional FDA comments incorporated.

510(k) Received September 2011.
Reimbursement Strategy

- Initially, tests will be invoiced under “miscellaneous” code: list price of $3,500
- Approaching reimbursement through two routes
  1. Integrated Delivery Networks/ DOD/ VA
  2. CMS - CPT Code
- CMS Reimbursement Path: 2 + 2 + 2 needed
  - 2 Analytical Papers
  - 2 Clinical Papers
  - 2 Field Experience Trials (FETs) - Received Western IRB approval
    - A Field Experience Trial (n=600) is being initiated at key accounts across the country to validate the clinical utility and economic benefit of the assay
- Sponsor and participate in advocacy-driven activities

Through the combination of these activities and increasing utilization of ProsVue, IRIS will be in a position to request CMS coverage in 2013
NADiA® ProsVue™
Conclusions and Recommendations

- Advanced diagnostic tools like ProsVue are improving patient care and have significant potential to significantly reduce healthcare costs.

- Improvements to the regulatory and reimbursement systems are necessary to support and expedite the implementation of this kind of innovation throughout the diagnostics industry.
The Role of Advanced Diagnostics in Cancer Care
The Role of Diagnostics in Personalized Healthcare

ZELBORAF™ and cobas® BRAF test Co-Development

Walter H. Koch, Ph.D.
Roche Molecular Systems, Inc.
Progress in science and medicine

*From macroscopic to cellular to subcellular level*

**For more than 10,000 years**

Diagnosis and treatment based on what could be seen, smelled, tasted, palpated or intuited.

**The last 100 years**

Diagnosis and treatment has been based on increasing knowledge about biochemistry and cellular processes.

**Today**

Diagnosis and treatment increasingly based on rapidly growing insights into molecular processes and variations in our genes.
Molecular Diagnostics

*Working to improve medical value & testing efficiency*

Molecular Diagnostics tests...

... that provide rapid, precise, reliable actionable information

... to guide treatment for better patient outcome

... and provide more cost-effective healthcare
Personalized Healthcare is progressing

Every good therapy starts with a good diagnosis

**Personalized Healthcare:** Use of new molecular insights and molecular diagnostic tests to better tailor medicines and better manage a patient’s disease.

Most patients are treated in a few similar ways
- Only 25-80% of patients receive effective treatment $^1$
- >100,000 deaths / yr from adverse drug reactions in US $^2$

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

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$^1$ Spears et al., Trends Mol Med, 2001;
$^2$ Lazarou et al., JAMA, 1998
The Opportunities For Personalized Healthcare

An improved value proposition for all stakeholders:

- Patients
- Payers
- Physicians
- Drug Developers

More Effective Drugs
Fewer Failures
Shorter Development Cycles
Personalized Healthcare is becoming a necessity
An improved value proposition for all stakeholders

- Welcome any better medicine

- Increase efficacy, reduce toxicity
- Control healthcare costs

- Provide best care for patient
- Increase efficacy, reduce toxicity

- Rx: Clinically differentiated medicines
- Dx: Biomarkers to develop & choose therapies

- More cost-effective healthcare
Some Challenges for Personalized Healthcare

- Finding the **right selection marker(s)**
- Early and significant **investment** in diagnostic development
- Randomized **study designs** may be more difficult to conduct
- **Regulatory requirements** for diagnostics differ across the world, and are not widely known or fully appreciated
- **Coordination** between drug and diagnostic development
- No clear **incentive** for co-development of diagnostic with drug when Device regulatory oversight is inconsistent (PMA vs. Lab Developed Tests) and reimbursement environment is uncertain to recoup the substantial R&D investment for the diagnostic
Epidemiology of Melanoma

- 6th most common cancer in U.S.
- > 68,000 new cases in U.S. in 2009
- Incidence tripled in last 20 years
- ~1/50 people in the U.S. will have melanoma in their lifetime
- Amongst most common fatal cancers in young adults - > 8,000 deaths/year
- 1st risk factor – UV/sun
  - Burton et al. Int J Cancer 1993
  - Jemal et al. CA Cancer J Clin 2009
Treatment of Metastatic Melanoma - until 2011

- Grim prognosis – average survival 6-9 months
- Cytotoxic chemotherapy – Dacarbazine: < 15% response rate, no survival benefit
- Biologics/cytokines – high dose IL-2 and IFNα – low response rates, toxic and expensive, ? survival benefit
- Ipilimumab (anti-CTLA-4 Ab) – low response rates but improved survival; substantial toxicities
- Other targeted therapies in development

- High unmet medical need

Garbe C. et al. The Oncologist 2011;16:5-24
Melanoma

BRAF Mutations in Solid Tumors

Metastatic melanoma ~50%

Metastatic colon ~5-10%

Metastatic thyroid Papillary 40-70%

Metastatic serous low-grade ovarian BRAF 68%

H. Davies et al. Nature 2002
Mutated BRAF: A Driver of Disease in Melanoma

BRAF oncogenic mutations
- ~50% melanoma

Structure-Guided Discovery
Vemurafenib (RG7204, PLX4032) co-structure with kinase domain of BRAF<sup>V600E</sup>
(Bollag et al. Nature 2010)
Venurafenib-BRAF Co-development Effort

Early knowledge of biomarker enabled alignment

CoDx, companion diagnostic; IND, Investigational New Drug application;

PLX, Plexxikon, Inc.; RMS, Roche Molecular Systems, Inc.; Rx, pharmaceutical
RG7204 (ZELBORAF™)

Encouraging results in aggressive skin cancer

First clinical studies show significant medical benefits:

- Progression of cancer significantly slowed in up to 70% of patients
- Rapid response to treatment

Before treatment  After 15 days
A 38-year-old man with *BRAF* mutant melanoma and miliary, subcutaneous metastatic deposits. Photographs were taken (A) before initiation of PLX4032, (B) after 15 weeks of therapy with PLX4032

(*PLX4032 = Zelboraf*)

Evolving Co-development Timeline

Drug and device development aligned for pivotal trial

CoDx

Initial development
Prototype assay
Investigational assay

PLX4032 IND
Roche-Plexxikon Rx agreement
V600E assay initiated
Prototype used to screen for Phase I Extension

cobas® BRAF test used to screen for Phase II and Phase III

2005 2006 2007 2008 2009 2010

Preclinical Phase I Phase II and III

CoDx, companion diagnostic; IND, Investigational New Drug application; PLX, Plexxikon, Inc.; RMS, Roche Molecular Systems, Inc.; Rx, pharmaceutical
BRIM3 trial: A global study

104 clinical sites in 12 countries
5 BRAF testing sites in 3 countries

1998 patients screened in 12 months
Test result turnaround time \( \leq \) 5 days

47% cases BRAF V600 mutation-positive
Co-Development of Zelboraf and the cobas BRAF test

**CoDx**
- **Initial development**
  - V600E assay initiated
  - IDE approval for prototype assay
  - Prototype used to screen for Phase I Extension
  - cobas® BRAF test used to screen for Phase II and Phase III
- **Commercial assay**
  - FDA approval and CE-marking

**Rx**
- **Preclinical**
  - PLX4032 IND
  - Roche-Plexxikon Rx agreement
- **Phase I**
  - Phase I results
  - BRIM-2 results
- **Phase II and III**
  - BRIM-3 results
  - NDA and MAA
- **Commercial**
**Drug (Zelboraf™) and Diagnostic (cobas® BRAF test)**

**US package inserts are cross-labeled regarding BRAF mutation testing**

<table>
<thead>
<tr>
<th>Indications and usage</th>
<th>ZELBORAF™ is a kinase inhibitor for the treatment of patients with unresectable or metastatic melanoma with BRAF(^{V600E}) mutation as detected by an FDA-approved test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZELBORAF is not recommended for use in patients with wild-type BRAF melanoma</td>
</tr>
<tr>
<td>BRAF(^{V600E}) testing</td>
<td>Confirmation of BRAF(^{V600E}) mutation-positive melanoma as detected by an FDA-approved test is required for selection of patients for ZELBORAF because these are the only patients studied and for whom benefit has been shown</td>
</tr>
<tr>
<td>Intended Use</td>
<td>Intended to be used as an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with ZELBORAF</td>
</tr>
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</table>

cobas BRAF test considered high risk class III device

Highest R&D investment hurdle to gain FDA approval

<table>
<thead>
<tr>
<th>PMA Requirement</th>
<th>Description of studies and requirements</th>
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<tbody>
<tr>
<td>Analytically verified</td>
<td>25 assay performance verification studies using &gt;600 specimens to support label claims. specimens to support label claims.</td>
</tr>
<tr>
<td>Clinically validated</td>
<td>&gt;2300 metastatic melanoma patients in phase II and III clinical trials; patients that tested positive by cobas® BRAF test were shown to derive benefit from Zelboraf.</td>
</tr>
<tr>
<td>Highly reproducible</td>
<td>98.8% reproducibility achieved in 1440 samples in 3 external labs, 2 operators/lab, 3 reagent lots over 5 non-consecutive days.</td>
</tr>
<tr>
<td>Quality controlled system</td>
<td>System, reagents, software &amp; hardware must meet GMP. Ongoing quality assessment through required annual reporting and FDA inspections of facilities.</td>
</tr>
</tbody>
</table>

Source: cobas 4800 BRAF V600 Mutation Test Package Insert and Halait et al.
Analytical performance in the clinical utility (BRIM-2/3) studies

Discordant resolution: cobas test vs. “Gold Standard” Sanger sequencing

<table>
<thead>
<tr>
<th>Metric</th>
<th>cobas® test</th>
<th>Sanger sequencing</th>
<th>Clinical implication of using Sanger sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invalid rate</td>
<td>1 (0.2%)</td>
<td>44 (9.2%)</td>
<td>• Patient denied access to Zelboraf™ or Zelboraf™ or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• New biopsy needed, delaying time to therapy</td>
</tr>
<tr>
<td>V600E misclassified as wild type as wild type</td>
<td>3 (0.7%)</td>
<td>17 (3.9%)</td>
<td>False negative: Zelboraf™ would have been appropriately been withheld</td>
</tr>
<tr>
<td>Wild type misclassified as misclassified as V600E V600E</td>
<td>0 (0%)</td>
<td>2 (0.5%)</td>
<td>False positive: Patients would have been appropriately received Zelboraf™</td>
</tr>
</tbody>
</table>

Invalid rate, V600E misclassified as wild type as wild type, and Wild type misclassified as misclassified as V600E V600E are all instances where the cobas test results were different from the Sanger sequencing results, leading to potential clinical implications.
Conclusions

- The ability to select the appropriate patient population makes the development of targeted therapies more effective, more efficient, and commercially attractive, and *it’s the right thing to do for patients*

- Early and broad collaboration between Pharma and Diagnostics teams and integration of development plans is critical in setting common goals and overcoming challenges along the way, enabling simultaneous approval & launch

- Despite this achievement, Rx-CoDx co-development is far from routine

- cobas® BRAF V600 mutation test is considered a high risk device by FDA because of the high risk to patient safety of an erroneous test result. Rigorous analytical and clinical utility studies are required for a CDx test to receive FDA (PMA) approval

- The cobas® BRAF V600 mutation test is currently the only FDA-approved BRAF mutation diagnostic; test performance claims have been reviewed by independent experts (CDRH) and made transparent to the public through the package insert

- LDTs are not reviewed by FDA and performance data *may* not be available; typically do not conduct the level of validation FDA requires for a high risk device
Thank you

To the dedicated cobas® BRAF test team at Roche Molecular Systems, the vemurafenib team at Roche Pharmaceuticals, Genentech and Plexxikon, the clinical sites and testing laboratories, the investigators and their patients.
The Role of Advanced Diagnostics in Cancer Care