The Killer in Context: A Pathologist's Perspective on Companion Diagnostics

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Ventana/Roche Tissue Diagnostics, Companion Diagnostics
Companion Diagnostics

FDA position:

Success of personalized medicine depends on safe and effective diagnostics.

FDA defines a companion diagnostic as a diagnostic where

- Therapeutic decisions will be made or optimized on the basis of the result
- Pivotal trial enrollment is based on a test result

FDA regulates companion diagnostics because

- Drug and diagnostic device are intended to be used together
- The diagnostic is essential to the therapeutic product being able to achieve the study established safety and efficacy
- Diagnostic tests are considered significant risk devices (carry the same risk profile as the drug)
Companion Diagnostics and Bio-targeted Therapy

Standard therapy means
same syndrome, same therapy.

Personalised Healthcare means
the right therapy for the right group
of patients at the right time.
Value of Personalized Healthcare

Physicians = easier prescription decision, and better prediction of treatment outcome

Payers = see the optimized use of resources and the potential reduction of co-treatments for side effects

Example = Instituting KRAS testing in Brazil would save that country $600 Million dollars annually in misdirected therapy.\(^1\)

\(^1\) www.personalizedmedicinecoalition.org (Oct 2011)
Value of Personalized Healthcare
Approval rates for bio-targeted strategies

*FDA approvals flat overall but 6x more likely with bio-target*

- **# of compounds being investigated**: +62%
- **Amount of R &D funding has doubled**
- **FDA approvals**: flat
- **Biomarker targeted therapies**: six-fold increase in clinical trial success

Market Conditions

Pharma’s & Dia’s need create ideal CDx environment

Rx - Challenges

- Rising costs vs. lowering program success
- Regulators mandate improved clinical outcomes
- Payors mandate better health economics

Dx - Challenges

- Increasing macro economic pressures drive decreasing reimbursement
- Low cost competitors drive pricing pressure
- Maturing business (decline in capital, automation saturation)

Targeted Therapy & Patient Selection

CDx

Differentiated Assays & Medical Value
Ventana Companion Diagnostics Solution

Prototype Assay Development and CAP/CLIA studies
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Current Case for Tissue

Immunotherapy

Future NGS

Q&A
Information embedded in the tissue

A DNA test would produce identical results at all three stages

Tissue context is required for diagnosis, IHC can not be displaced by molecular methods
Chemistry in Context

Intact

Extracted
## Medical Needs

<table>
<thead>
<tr>
<th>The Patient</th>
<th>The Lab/The MD</th>
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<tr>
<td>What do I have?</td>
<td>Diagnosis</td>
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<tr>
<td>What caused it?</td>
<td>Etiology: Infections/Genetic</td>
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<td>What explains my symptoms?</td>
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<td>What are my prospects?</td>
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<td>What is my treatment?</td>
<td>Therapeutic Targets</td>
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<td>Response Prediction</td>
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<td>How will I be followed?</td>
<td>Monitoring</td>
</tr>
<tr>
<td>Will it return?</td>
<td>Relapse</td>
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<tr>
<td>Will others in my family get it?</td>
<td>Predisposition Screening</td>
</tr>
<tr>
<td>How will you communicate the results?</td>
<td>Medical Report</td>
</tr>
</tbody>
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Objectives

Demonstrate how slide-based tissue chemistry innovations will change cancer care

Method

– Describe where we are today
– Describe our unsolved problems
– Describe innovative solutions
The Challenges

– Deliver more results relevant to patient prognosis and therapy.

– Deliver more molecular-based assays.

– Deliver more automated, standardized results.

– Communicate results better.
The Key Scientific Advances

Beyond diagnosis to **therapeutics**

Beyond single analyte to **multiplexing**

Beyond protein to **gene plus protein assays**

Beyond qualitative to **quantitative assays**

Beyond informatics to **cellular informatics**

Beyond written reports to **patient-centric reports**
Utility of Slide-Based Tissue Chemistry

*Simultaneous analysis of morphology, gene and protein status*

**Morphology**

**Gene status**

**Protein status**

**H&E:** Hematoxylin & Eosin (Dye)

**ISH:** in situ Hybridization (DNA/RNA Probe)

**IHC:** Immunohistochemistry (Antibody)
The Importance of Tissue Analysis in Morphologic Context

**Patient 1:** 48 year old female with 2 cm invasive ductal breast carcinoma (H&E).

Conflicting test results for Estrogen Receptor (IHC ER-neg/PCR ER-pos)
The Importance of Chemistry in Morphologic Context Breast Cancer: Heterogeneity of HER2 Expression

Predicts Therapy Failure
The Importance of Tissue Analysis in Morphologic Context

**Patient 2:** female with breast carcinoma and recurrent tumor despite anti hormone therapy.

Applying tests on various biomarkers helps explaining recurrence of HER2 positive tumor and allows appropriate therapy guidance.
Utility of Tissue-Based Chemistry

- Reveals functional morphology.

- Reveals microenvironment.

- Reveals driver events.
“Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing”

The Key Observations

In tumor heterogeneity there is genetic divergence with consequent phenotypic convergence which alters cell function at the protein level which undergoes Darwinian selection and evolutionary adaptation and probable therapy failure.

*Gerlinger et al, NEJM*
Loss of PTEN Expression in Prostate Cancer

Neutralizing Tumor-Promoting Chronic Inflammation: A Magic Bullet?

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Current Case for Tissue

Immunotherapy

Future NGS

Q&A
Immune Cell Modulators – A Class on its Own

A number of these receptors can be analyzed by IHC
PD-1/PD-L1: A Critical Immuno Checkpoint Pathway
PD-1/PD-L1: A Critical Immuno Checkpoint Pathway

anti-PD-1; NSCLC 40x

anti-PD-L1 (SP); NSCLC 40x
Surface Markers: Critical for Immune Cell Classification

anti-CD3 (SP7); anti-CD16 (SP96) NSCLC 40x

anti-CD3 (SP6) NSCLC 40x

anti-CD8 (SP16) NSCLC 40x

anti-CD3 (SP6)

anti-CD8 (SP16) NSCLC 40x
Role of IDO1 in Regulating Anti-Tumoral Immunity

anti-IDO1 (SP); NSCLC 10x
Other Immune Modulating Markers: B7H3

anti-B7-H3 (SP206); NSCLC 40x

Immunohistochemistry illustrates key interactions

– Summary points for IHC/ISH
  – Morphology
  – Interactions
  – Tumor vs. Infiltrate (or “inflamate”)
Where we are going ...

“We are leaving the world of commoditized diagnostic, \textit{what is it,}
and going to higher value tests linked to therapy, \textit{what to do.}”

Dr. Tom Grogan, Founder
Ventana Medical Systems, Inc.
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Q&A
Cancer Treatment in the Future?

"Here's my sequence"

A. Bacall, The New Yorker
Next Generation Cell Signaling Assays

Measuring Activation Status

- PI3k
- PTEN
- pAKT
- pPRAS40
- pS6K
- pERK1/2
- CARD11
- Proteosome
- IkappaB kinase
- PKC beta
- JAK/STAT
- Fostamatinib
- PCI32765
- CA-101
- rapalogs, small molecule
- Fostamatinib
- Bortezomib, carfilzomib
- PS1145
- Enzastaurin
- SB1518, INCB018424
Future

- Personalized medicine utilizing the best available technologies
- Clinically relevant, cohesive molecular information
- Broad patient access
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Future NGS

Q&A
Thank you.
Doing now what patients need next
Doing now what patients need next