Molecular Diagnostics Moving from the Teen Generation to the Next Generation

Facilitating Development and Utilization of Genome-Based Diagnostic Technologies: A Workshop

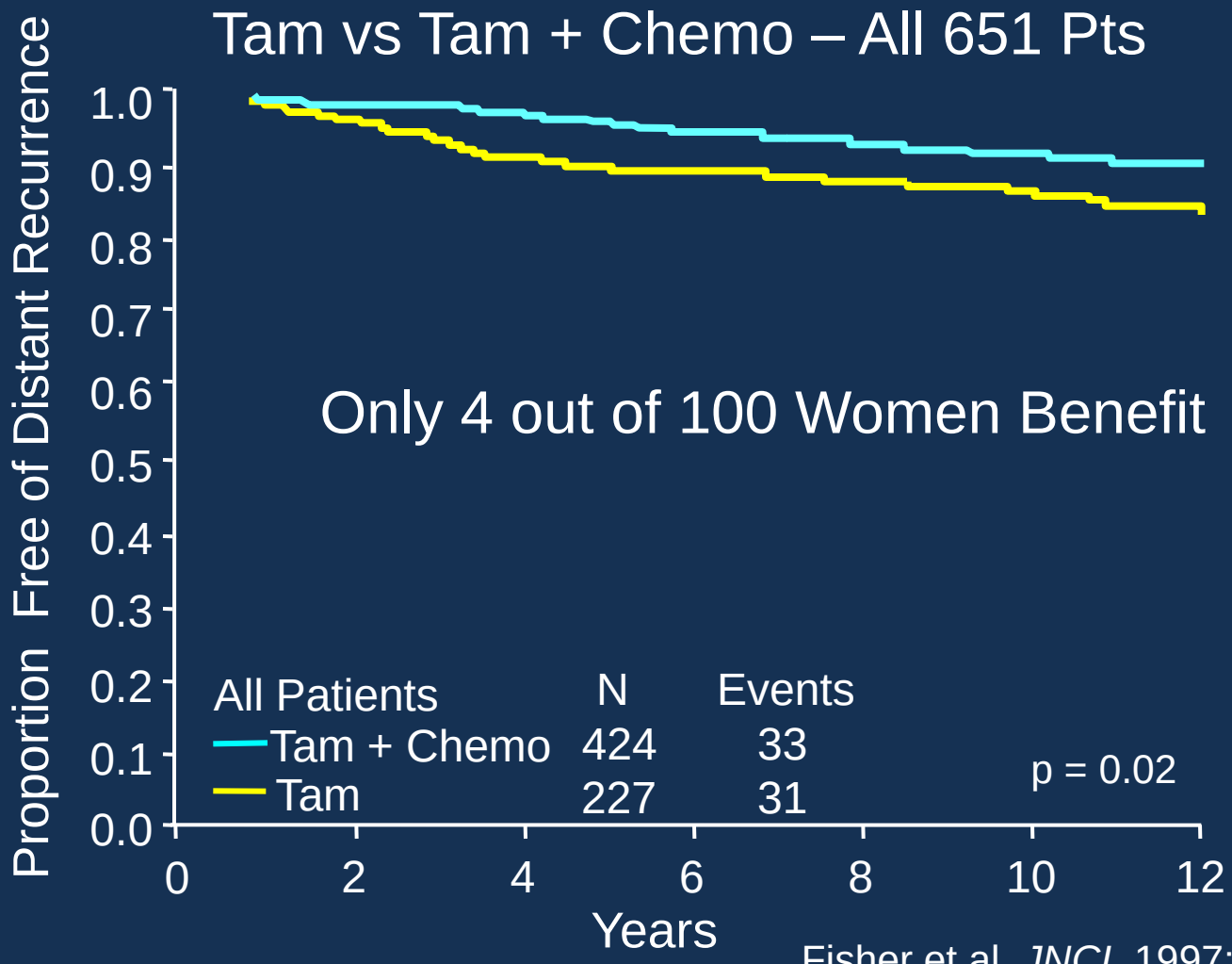
Steven Shak, MD

Chief Medical Officer, Genomic Health

November 15, 2011

- Cancer in the last century, and still too often today, is treated with limited clinical utility and with a one size fits all approach
- Over 550,000 people in the US will die this year

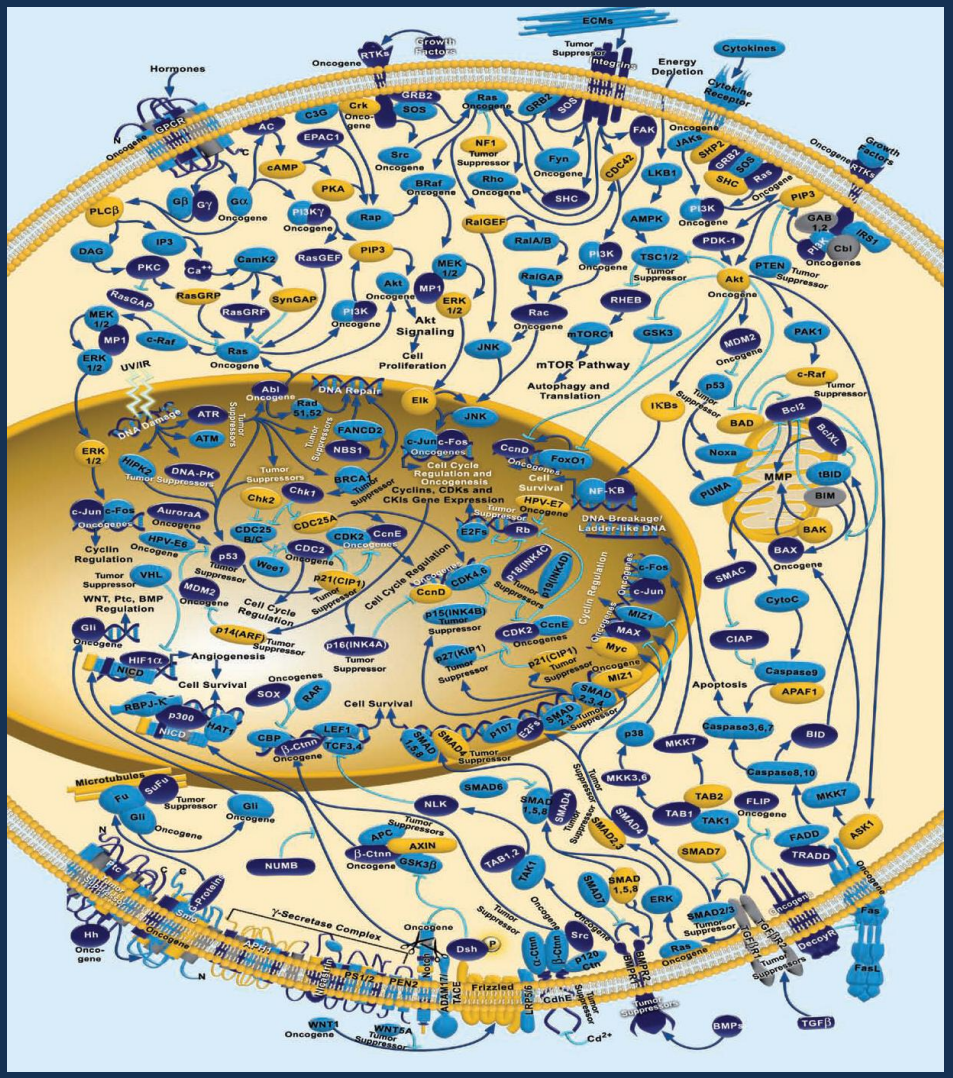
NSABP B-20 Clinical Study Established Benefit of Chemotherapy



Fisher et al. *JNCI.* 1997;89:1673-82.

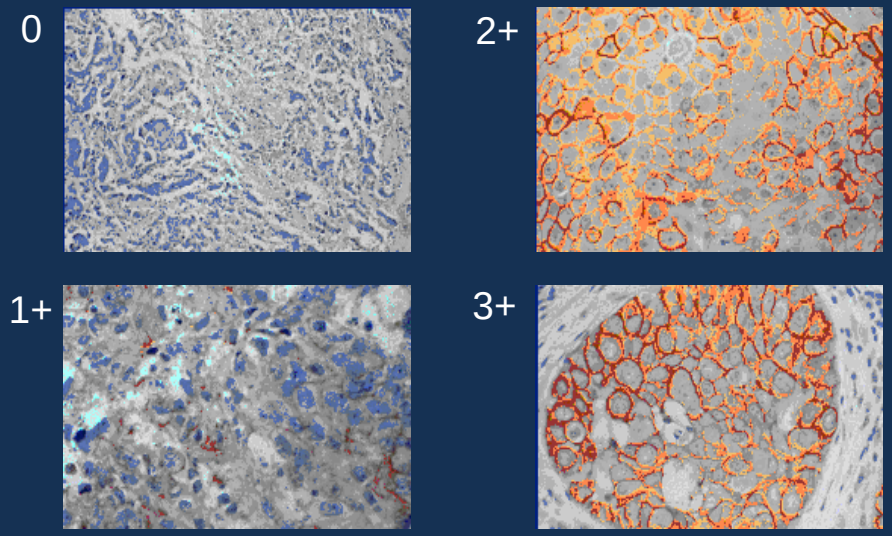
In the Last Century A New Generation of Technology Sequenced the Human Genome

Cancer Pathways



Trastuzumab For Herceptest Positive Breast Metastatic Breast Cancer (13 Years Ago)

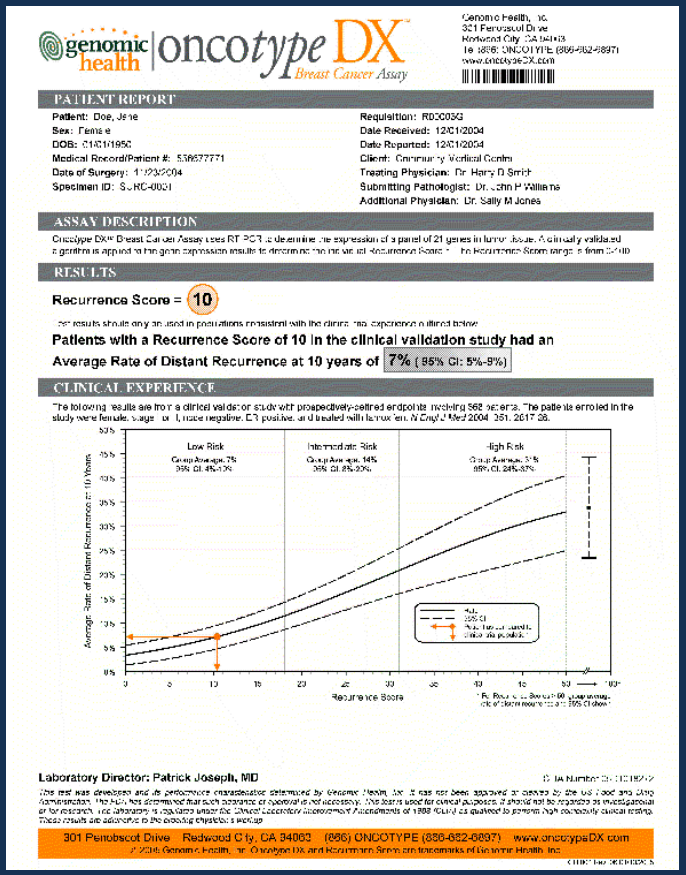
Humanized Anti-HER2 Antibody



Immunohistochemistry Assay for HER2 Protein

Oncotype DX® Breast Cancer Recurrence Score

- Recurrence Score® based on quantitative RT-PCR analysis of 21 genes
- Widely used and reimbursed
  - Over 250,000 tests since launch in 2004
  - Reimbursed by Medicare and major payers in US
  - Provided for patients in >65 countries
  - Incorporated in the published treatment guidelines


genomic health | oncotype DX Breast Cancer Assay

Genomic Health, Inc.
301 Penobscot Drive
Redwood City, CA 94063
Tel: (866) ONCOTYPE (866-662-6897)
www.oncotypeDX.com

PATIENT REPORT

Patient: Doe, Jane
Sex: Female
DOB: 01/01/1950
Medical Record/Patient #: 556677771
Date of Surgery: 11/23/2004
Specimen ID: SURG-0001

Requisition: RD0003G
Date Received: 12/01/2004
Date Reported: 12/01/2004
Client: Community Medical Center
Treating Physician: Dr. Harry D Smith
Submitting Pathologist: Dr. John P Williams
Additional Physician: Dr. Sally M Jones

ASSAY DESCRIPTION

Oncotype DX™ Breast Cancer Assay uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. A clinically validated algorithm applied to the gene expression results to determine the individual Recurrence Score® for the Recurrence Score range is from 0-100.

RESULTS

Recurrence Score = 10

Test results should only be used in populations consistent with the clinical trial experience outlined below.

Patients with a Recurrence Score of 10 in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of 7% (95% CI: 5%-9%)

CLINICAL EXPERIENCE

The following results are from a clinical validation study with prospectively-defined endpoints involving 668 patients. The patients enrolled in the study were female, stage I or II, node negative, ER positive, and treated with tamoxifen. N Engl J Med 2004; 351: 2817-26.

Laboratory Director: Patrick Joseph, MD

CLIA Number: 05D1057672

This test was developed and its performance characteristics determined by Genomic Health, Inc. It has not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational or for research. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical testing. These results are adjunctive to the existing physician's workup.

301 Penobscot Drive Redwood City, CA 94063 (866) ONCOTYPE (866-662-6897) www.oncotypeDX.com

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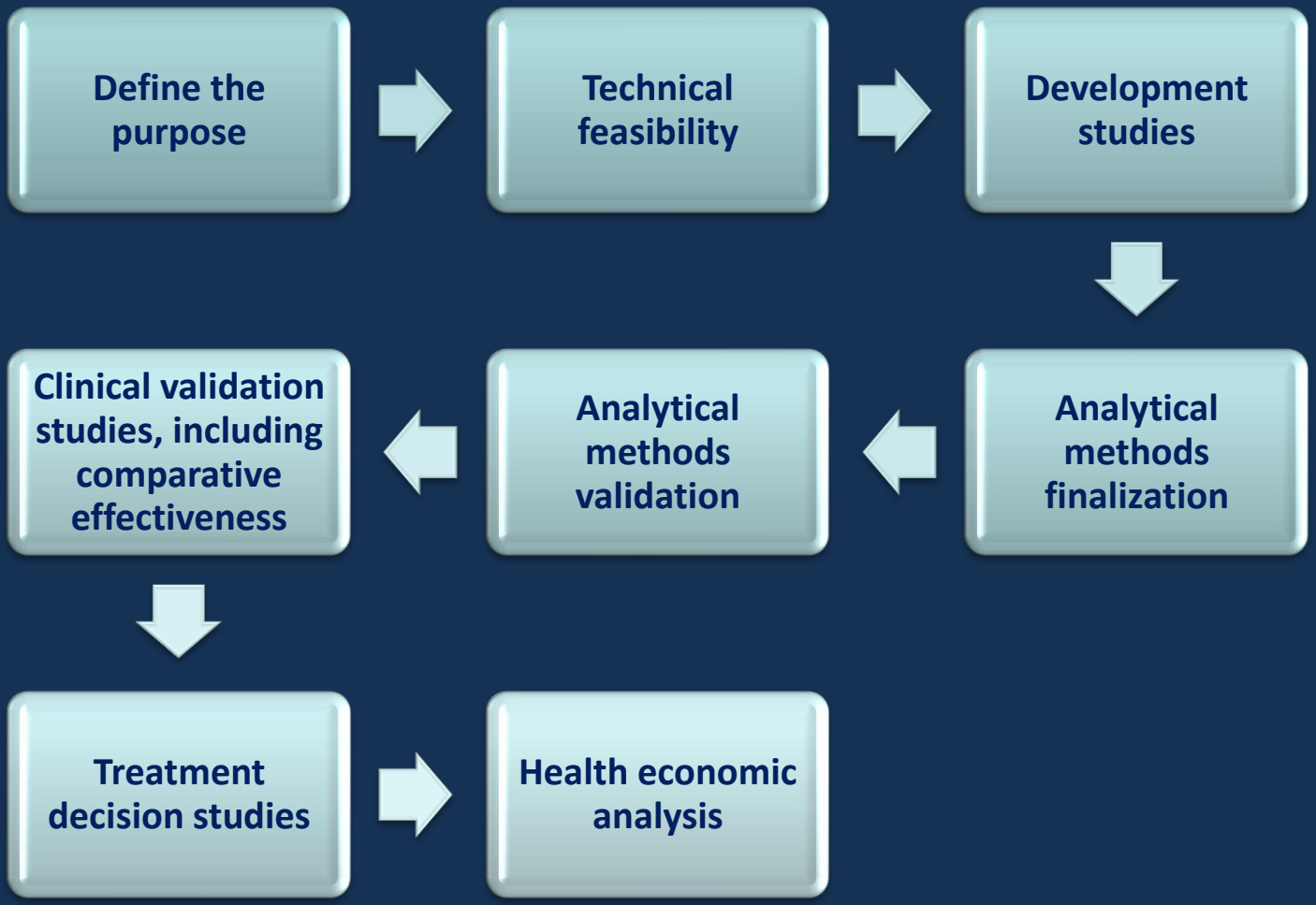
CLINICAL REPORT

Biomarker Field – Principles for Success

1. Delivering what patients, physicians, regulators, and payors need
   a) Most importantly, tests must be “Fit for Purpose” with evidence relevant to that specific purpose
   b) Consistent results across multiple well-designed studies
   c) Test must be shown to have value beyond traditional measures

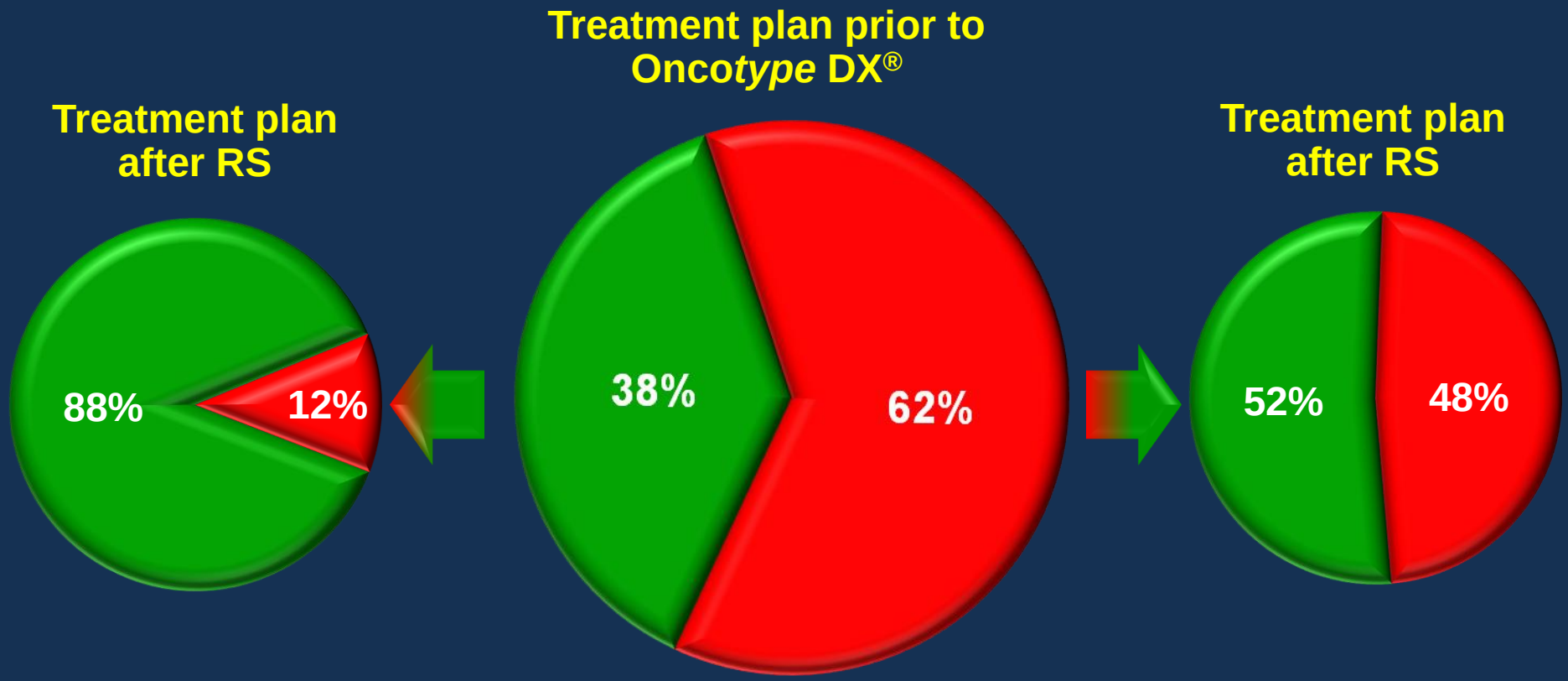
Roadmap to Establish Clinical Utility "Fit For Purpose"



Extensive Clinical Study
More than 4,000 Patients Studied in 13 Trials

Study	Type	No. Pts	Nodal Status
Providence	Exploratory	136	Neg
Rush	Exploratory	78	Pos
NSABP B-20	Exploratory	233	Neg
NSABP B-14	Prospective	668	Neg
MD Anderson	Prospective	149	Neg
Kaiser Permanente	Prospective Case-Control	790 Cases/Controls	Neg
NSABP B-14	Prospective Placebo vs Tam	645	Neg
Milan	Exploratory	89	Neg/Pos
NSABP B-20	Prospective Tam vs Tam+Chemo	651	Neg
ECOG 2197	Exploratory and Prospective	776	Neg/Pos
SWOG 8814	Prospective Tam vs Tam+Chemo	367	Pos
ATAC	Prospective Tam vs AI	1231	Neg/Pos
Japan BCRG Study	Prospective	280	Neg/Pos

Treatment Decisions Are Changed: Overall Impact of RS on Treatment Decisions (7 Studies in 912 Patients)



Overall, the RS led to a 37% change in treatment decisions

- ***33% from CT+HT → HT***
- ***4% from HT → CT+HT***

Hornberger J, et al. SABCS 2010. Poster P2-09-06.

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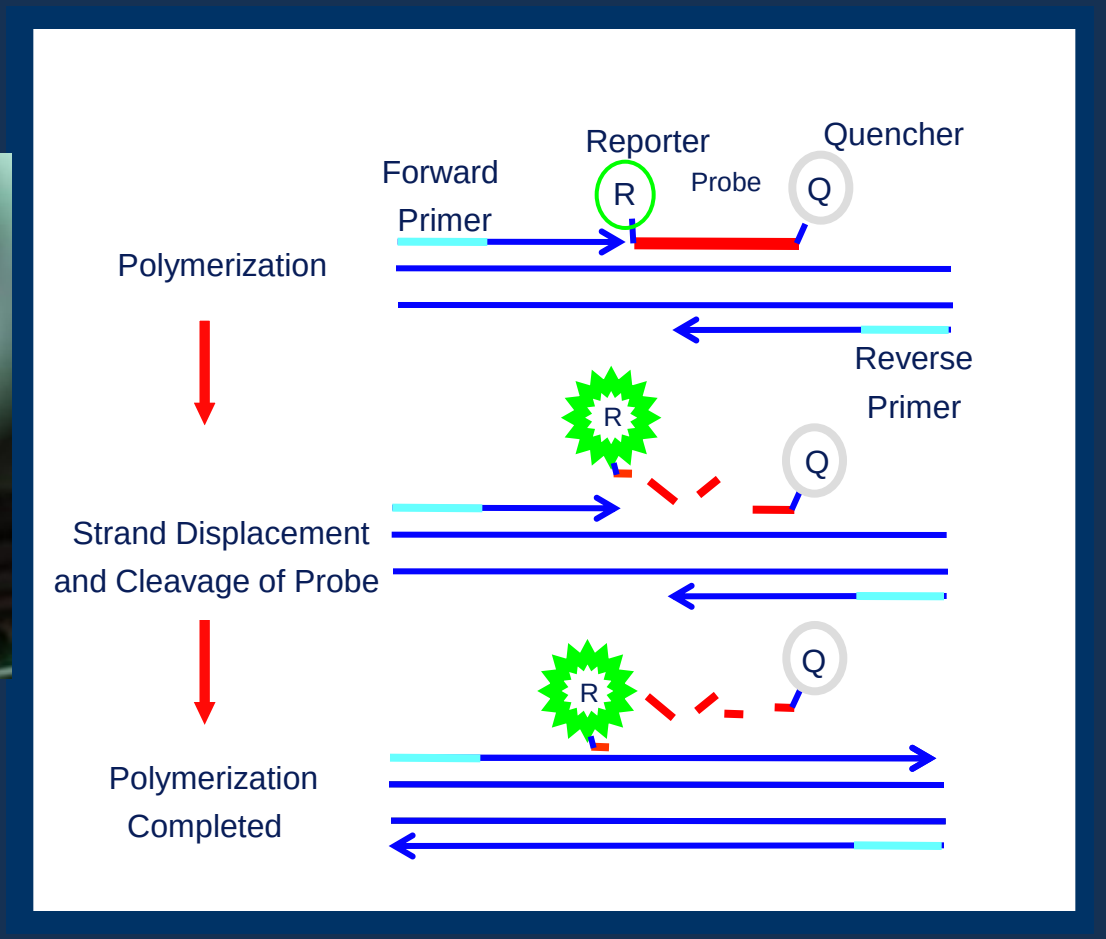
Technical Feasibility: Required Innovation to "Unlock the Block"



Cronin et al. *Am J Pathol.* 2004;164:35-42.

Analytical Methods Finalization: CLIA Regulations

- All assay methods and procedures defined prior to clinical validation studies, for example:
  - Specimen eligibility
  - Reagent qualification
  - Instrument validation
  - Controls and calibrators
  - Linearity, precision, reproducibility

21 Gene Recurrence Score CLIA-Certified and CAP-Accredited Reference Laboratory Process

Oncotype DX
Number of Standard Operating Procedures (SOPs) and Forms

Category	Number of SOPs	Number of Forms
Equipment	33	18
Finance	1	0
Histopathology	6	6
IT	23	10
Materials Management	7	6
Pre and Post Analytical	13	3
Production and Quality Control	52	15
QA	15	36
Safety and Facilities	4	0
Total	**154**	**94**

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3. Requires collaboration and clinical research funding, and the skills, processes, resources, and incentives to do it right

All the Payors Need to be Addressed Individually

Florida, California, Michigan, Alabama, New York, Delaware, New Jersey, Pennsylvania, South Carolina, Arkansas, Idaho, Montana, North Dakota, Minnesota, Kansas, Arizona

Obstacles

- Knowledge and experience gaps of those working in and assessing this new field
  - Need continued education and training
- Incentives that encourage individual rather than team science
  - Need leadership, teamwork, academic-industry collaboration, way we recognize talent
- Reimbursement uncertainty
  - Need to continue to move to pricing based on “value”
- Regulatory uncertainty
  - Need regulations that are “fit for purpose”, suitable for continued rapid introduction of new and improved tests

Advances in Genome Biology and Technology
February 2 -5, 2011

Biomarker Discovery from Whole Transcriptome Analysis of Formalin-Fixed, Paraffin-Embedded Tumor and Normal Breast Specimens

Dominick Sinicropi; Kunbin Qu; John Morlan; Carl Millward; Francois Collin; James Stephans; Mei-Lan Liu; Mylan Pho; Jennie Jeong ; Ranjana Ambannavar; Aaron Scott; and Joffre Baker

Genomic Health, Inc., Redwood City, CA

Sample	Number of Reads (Millions)	Percent Mapped[a]	Percent rRNA
T1 (X3)	54.6	67.1	6.0
T2 (X3)	56.0	68.9	5.5
T3	17.2	69.5	3.9
T4	19.1	66.8	3.6
T5	19.2	65.5	6.5
T6	19.9	62.3	12.8
T7	20.3	70.8	5.5
T8	17.1	67.0	10.4
T9	23.2	71.5	3.6
T10	21.3	71.9	2.4
T11	19.8	64.3	5.6
T12	21.1	67.7	3.3
Average	19.1	67.8	5.7

Bringing the Promise of Genomics Into Clinical Practice

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