Clinical Utility: Lessons from Oncotype DX in Breast, Colon, and Prostate

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Genomic Health

Genomic Health Strategy in 2001 Was Founded on Four Strategic Imperatives

- Most important – “Fit for Purpose”
  - Delivering what patients, physicians, regulators, and payors need, relevant to a specific use
  - Actionable and patient oriented
  - Requires multiple studies
  - Clear value beyond existing measures
- Technical innovation brought to standardized implementation
- Collaboration, and the skills, processes, and resources to do it right – think industry-academic partnerships
- Commitment to continued research

2013 Perspectives: Approach to Deliver Clinical Utility Builds on Approach to Deliver Scientific Insights

Clinical and pathologic context greatly impacts biomarker clinical utility

- Alteration of the same gene(s) or pathway(s) in a different tumor context often has a significantly different clinical impact
  - K-Ras alterations in colon cancer and lung cancer
  - Oncotype DX Recurrence Score in ER- and ER+ breast cancer
  - Oncotype DX Proliferation gene group in breast cancer and colon cancer
  - Genomic Prostate Score needs to be integrated with biopsy Gleason Grade for appropriate interpretation
  - Too many other examples to count

2013 Perspectives: Approach to Deliver Clinical Utility Goes Beyond Approach to Deliver Scientific Insights

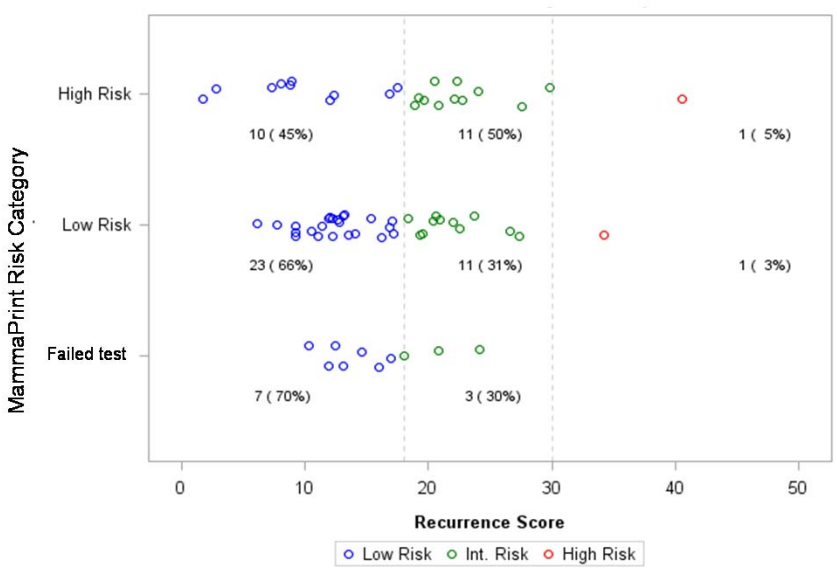
Three Examples Relevant to Clinical Practice

- Relevance to an actionable decision
  - Oncotype DX and MammaPrint clinical validation study populations and endpoints
- Assay reproducibility for individual patients
  - Oncotype DX Recurrence Score and Tumor Grade
- Documentation of change in physician behavior and value to the health care system
  - Treatment decision studies and health economic analysis

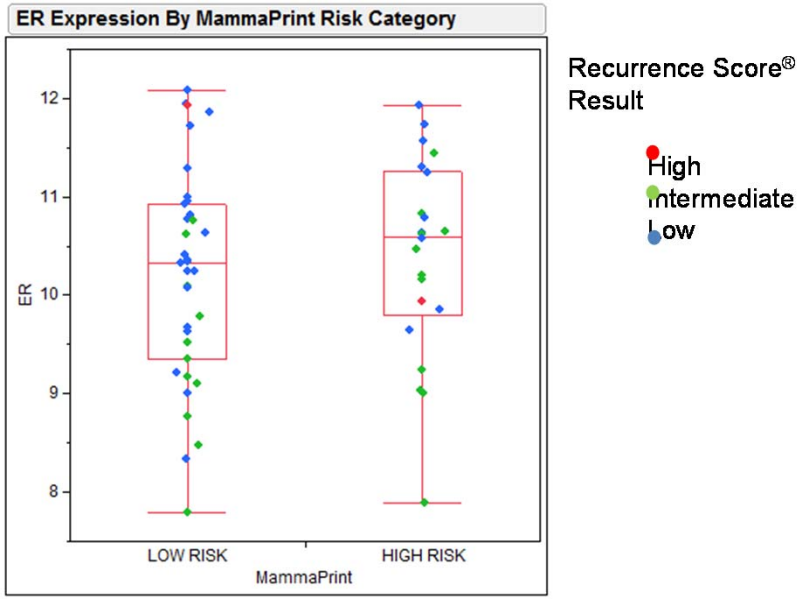
Clinical Utility: Relevance to an Actionable Decision

MammaPrint and Oncotype DX in 67 Patients (Poulet et al, SABCS 2012)

MammaPrint Risk vs RS



Oncotype DX ER vs MammaPrint Risk



Multi-gene assays are not the same

Assays developed on patients without systemic treatment may not be clinically useful when the need is to select between Rx's (eg, HT vs HT + CT)

Clinical Utility: Assay Reproducibility for Individual Patients

Tumor Grade[1]

Stanford, UCSF, and NSABP Pathologists

	Pathologist B		
Pathologist A	Well	Moderate	Poor
Well	**105**	114	5
Moderate	24	**241**	31
Poor	3	82	**63**

Concordance = 61%

	Pathologist A		
Pathologist C	Well	Moderate	Poor
Well	**76**	31	0
Moderate	140	**221**	52
Poor	8	44	**96**

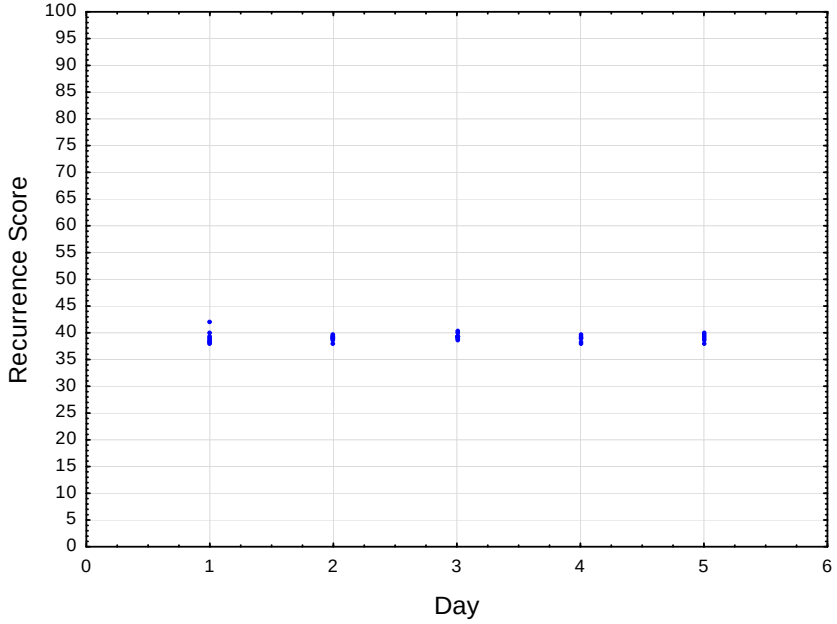
Concordance = 59%

	Pathologist B		
Pathologist C	Well	Moderate	Poor
Well	**56**	50	1
Moderate	74	**309**	30
Poor	2	78	**68**

Concordance = 65%

Standardized Oncotype DX[2]

38 RS Measures on 5 Days



1 Paik et al, NEJM 2004 (supplemental data)

2 Genomic Health data on file

Clinical Utility: Importance of Treatment Decision Studies

Medicare

Department of Health Care Services Medi-Cal

UnitedHealthcare

HUMANA. Guidance when you need it most

Aetna

KAISER PERMANENTE

CIGNA

BlueCross BlueShield Association

Technology Evaluation Center

Excellus

CareFirst BlueCross BlueShield

Health Net A Better Decision

WELLPOINT

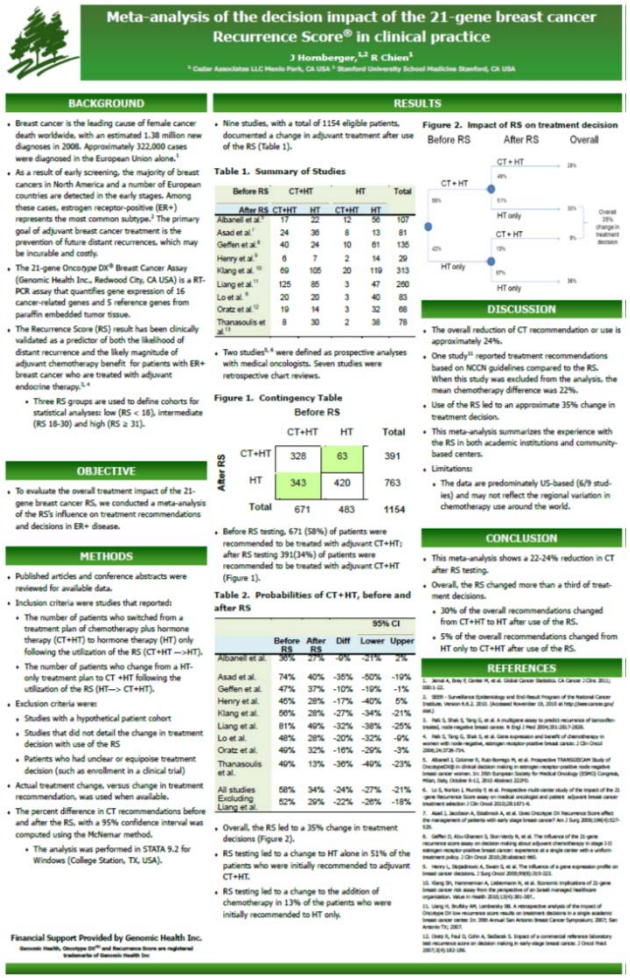
BlueCross BlueShield

CLALIT THE BEST FOR YOUR FAMILY

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

FEHB Federal Employees Health Benefits Program

Payors Want to Know – Will Test Change Clinical Practice?



Meta-analysis of the decision impact of the 21-gene breast cancer Recurrence Score® in clinical practice

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BACKGROUND

- Breast cancer is the leading cause of female cancer death worldwide, with an estimated 1.38 million new diagnoses in 2008. Approximately 322,000 cases were diagnosed in the European Union alone.[1]
- As a result of early screening, the majority of breast cancers in North America and a number of European countries are detected in the early stages. Among these cases, estrogen receptor-positive (ER+) represents the most common subtype.[2] The primary goal of adjuvant breast cancer treatment is the prevention of future distant recurrences, which may be incurable and costly.
- The 21-gene Oncotype DX® Breast Cancer Assay (Genomic Health Inc., Redwood City, CA USA) is a RT-PCR assay that quantifies gene expression of 16 cancer-related genes and 5 reference genes from paraffin embedded tumor tissue.
- The Recurrence Score (RS) result has been clinically validated as a predictor of both the likelihood of distant recurrence and the likely magnitude of adjuvant chemotherapy benefit for patients with ER+ breast cancer who are treated with adjuvant endocrine therapy.[3,4]
  - Three RS groups are used to define cohorts for statistical analyses: low (RS < 18), intermediate (RS 18-30) and high (RS ≥ 31).

OBJECTIVE

- To evaluate the overall treatment impact of the 21-gene breast cancer RS, we conducted a meta-analysis of the RS's influence on treatment recommendations and decisions in ER+ disease.

METHODS

- Published articles and conference abstracts were reviewed for available data.
- Inclusion criteria were studies that reported:
  - The number of patients who switched from a treatment plan of chemotherapy plus hormone therapy (CT+HT) to hormone therapy (HT) only following the utilization of the RS (CT+HT —>HT).
  - The number of patients who change from a HT-only treatment plan to CT +HT following the utilization of the RS (HT—> CT+HT).
- Exclusion criteria were:
  - Studies with a hypothetical patient cohort
  - Studies that did not detail the change in treatment decision with use of the RS
  - Patients who had unclear or equipoise treatment decision (such as enrollment in a clinical trial)
- Actual treatment change, versus change in treatment recommendation, was used when available.
- The percent difference in CT recommendations before and after the RS, with a 95% confidence interval was computed using the McNemar method.
  - The analysis was performed in STATA 9.2 for Windows (College Station, TX, USA).

RESULTS

- Nine studies, with a total of 1154 eligible patients, documented a change in adjuvant treatment after use of the RS (Table 1).

Table 1. Summary of Studies

Before RS	CT+HT		HT		Total
After RS	CT+HT	HT	CT+HT	HT	
Albanell et al.[5]	17	22	12	56	107
Asad et al.[7]	24	36	8	13	81
Geffen et al.[8]	40	24	10	61	135
Henry et al.[9]	6	7	2	14	29
Klang et al.[10]	69	105	20	119	313
Liang et al.[11]	125	85	3	47	260
Lo et al.[6]	20	20	3	40	83
Oratz et al.[12]	19	14	3	32	68
Thanasoulis et al.[13]	8	30	2	38	78

- Two studies[5,6] were defined as prospective analyses with medical oncologists. Seven studies were retrospective chart reviews.

Figure 1. Contingency Table

	Before RS: CT+HT	Before RS: HT	Total
After RS: CT+HT	328	63	391
After RS: HT	343	420	763
Total	671	483	1154

- Before RS testing, 671 (58%) of patients were recommended to be treated with adjuvant CT+HT; after RS testing 391(34%) of patients were recommended to be treated with adjuvant CT+HT (Figure 1).

Table 2. Probabilities of CT+HT, before and after RS

	Before RS	After RS	Diff	95% CI Lower	95% CI Upper
Albanell et al.	38%	27%	-9%	-21%	2%
Asad et al.	74%	40%	-35%	-50%	-19%
Geffen et al.	47%	37%	-10%	-19%	-1%
Henry et al.	45%	28%	-17%	-40%	5%
Klang et al.	56%	28%	-27%	-34%	-21%
Liang et al.	81%	49%	-32%	-38%	-25%
Lo et al.	48%	28%	-20%	-32%	-9%
Oratz et al.	49%	32%	-16%	-29%	-3%
Thanasoulis et al.	49%	13%	-36%	-49%	-23%
All studies Excluding Liang et al.	58%	34%	-24%	-27%	-21%
	52%	29%	-22%	-28%	-18%

- Overall, the RS led to a 35% change in treatment decisions (Figure 2).
- RS testing led to a change to HT alone in 51% of the patients who were initially recommended to adjuvant CT+HT.
- RS testing led to a change to the addition of chemotherapy in 13% of the patients who were initially recommended to HT only.

Figure 2. Impact of RS on treatment decision

Before RS | After RS | Overall

CT + HT 48% 28%
58% 51% HT only 30%
CT + HT 8%
42% 13% HT only
87% 38%
HT only

Overall 35% change in treatment decision

DISCUSSION

- The overall reduction of CT recommendation or use is approximately 24%.
- One study[11] reported treatment recommendations based on NCCN guidelines compared to the RS. When this study was excluded from the analysis, the mean chemotherapy difference was 22%.
- Use of the RS led to an approximate 35% change in treatment decision.
- This meta-analysis summarizes the experience with the RS in both academic institutions and community-based centers.
- Limitations:
  - The data are predominately US-based (6/9 studies) and may not reflect the regional variation in chemotherapy use around the world.

CONCLUSION

- This meta-analysis shows a 22-24% reduction in CT after RS testing.
- Overall, the RS changed more than a third of treatment decisions.
  - 30% of the overall recommendations changed from CT+HT to HT after use of the RS.
  - 5% of the overall recommendations changed from HT only to CT+HT after use of the RS.

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Financial Support Provided by Genomic Health Inc.

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Hornberger et al, St. Gallen 2011

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