Welcome to Genomic Health’s Quarterly Newsletter

Welcome to Genomic Health’s Quarterly Newsletter. The goal of this newsletter is to provide those who are speaking on genomics with updates on relevant information from Genomic Health. If you do not wish to receive this newsletter, please refer to the information listed at the bottom of this e-mail to unsubscribe.

FEATURED ARTICLES

- Genomic Health launches Oncotype DX Breast Cancer Assay
  With the increasing prevalence of ductal carcinoma in situ (DCIS), there is a significant unmet need to determine...

- Economic analysis of chemotherapy costs for adjuvant therapy in breast cancer in France
  In a poster presented at SABCS 2011, investigators from Hopital Tenon in Paris, France reported that using the Oncotype DX® assay in French...

- With over 200,000 assays performed, the Oncotype DX® Breast Cancer Assay is highly standardized
  In a report from Genomic Health presented at SABCS of 207,691 invasive breast cancer cases assayed between January 2005 and March 2011...

- Spotlight on Oncotype DX Colon Cancer Assay
  Gene: Cell Cycle and Ki67
  In contrast to the Oncotype DX Breast Cancer Assay, where higher expression of cell cycle genes (STK15, MYBL2, Ki-67 and CCNB1) is associated with increased risk of recurrence [1-2]...

ANNOUNCEMENTS

- Genomic Tools in Breast Cancer
  Leading the Way towards Personalized Treatment will be a featured official satellite during this year’s EBCC meeting in Vienna...

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  The Oncotype DX Colon Cancer Assay and MMR can now be ordered at the same time in a convenient...

- Step-by-Step Guide for Getting Oncotype DX assays available in English, German, French, and Italian
  Genomic Health has developed a new brochure to assist you and your office staff in ordering Oncotype DX tests
European School of Oncology – e-oncoreview

Expert: William Wood, Emory University Hospital, Atlanta, GA, USA
Discussant: Nigel Bundred, University Hospital of South Manchester, Manchester, United Kingdom

Now with the introduction of a genomic assay for DCIS, we should consider how this assay will be integrated with existing risk assessment tools for DCIS and ultimately treatment decisions.

A test to predict risk of recurrence in DCIS
Prof. Joseph Sparano, Albert Einstein Cancer Center, New York, USA, discusses a study validating a multigene test to predict risk of recurrence in breast cancer patients with ductal carcinoma in situ (DCIS).

Must All DCIS Patients Undergo Radiation?
Medscape Hematology-Oncology 2012

PATIENT CASE STUDIES

CHEMO/NO CHEMO: For which patient, would you recommend adjuvant chemotherapy+ hormonal therapy?

PATIENT A
61-year-old patient with 0.6-cm and 0.9-cm tumors

Menopausal Status: Postmenopausal
Tumor Type: Infiltrating Ductal Carcinoma (IDC), Ductal Carcinoma in Situ (DCIS)
Tumor Size: 0.6 cm, 0.9 cm
ER Status (IHC): Positive (95%)
PR Status (IHC): Positive (95%)
HER2/neu Status: Negative (FISH)
Histologic Grade: 2
Lymph Node Status: Negative (0/2 SLNs)
General Health: Excellent

Case submitted from: G. THOMAS Budd, MD

PATIENT B
62-year-old patient with 0.6 cm tumor

Menopausal Status: Postmenopausal
Tumor Type: Infiltrating Ductal Carcinoma (IDC)
Tumor Size: 0.6 cm
ER Status (IHC): Positive (strong)
PR Status (IHC): Positive (strong)
HER2/neu Status: Negative (IHC)
Histologic Grade: 2
Lymph Node Status: Negative (0/2 SLNs)
General Health: Bipolar, irritable bowel syndrome, hypertension, gastroesophageal reflux disease, hypothyroidism, asthma, cholecystectomy

Other Information: *Additional 1.2-cm and 1.3-cm tumors found on re-excision

Case submitted from: Terry P. Mamounas, MD. MPH

Recent publications Oncotype DX related articles:


For more information about Oncotype DX, please refer to [www.oncotypedx.com](http://www.oncotypedx.com) (now available in French, Spanish, and German)

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This e-newsletter contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, including statements relating to our plans to analyze, submit and present the complete data from this study at the 2011 San Antonio Breast Cancer Symposium; the expectation that these preliminary study results will be confirmed in the complete analysis of the study data; our plans to commercially launch Oncotype DX testing for DCIS patients by the end of 2011; the ability of Oncotype DX testing to individualize cancer treatment for DCIS patients; the ability of the company to develop additional tests in the future; the scope, success or results of clinical trials and the timing of such activities; the applicability of clinical study results to actual outcomes; the ability of the company's tests to impact clinical practice and, the ability of the company's test to be adequately reimbursed. Forward-looking statements are subject to risks and uncertainties that could cause actual results to differ materially and reported results should not be considered as an indication of future performance. These risks and uncertainties include, but are not limited to: the applicability of clinical study results to actual outcomes; the risks and potential delays associated with such studies; the risks and potential delays associated with the commercialization of current and future products; the risks and uncertainties associated with the regulation of our tests; the risks associated with competition; and the other risks set forth in the company's filings with the Securities and Exchange Commission, including the risks set forth in the company's Quarterly Report on Form 10-Q for the quarter ended March 31, 2011. These forward-looking statements speak only as of the date hereof. Genomic Health disclaims any obligation to update these forward-looking statements.
Genomic Health launches Oncotype DX Breast Cancer Assay

With the increasing prevalence of ductal carcinoma in situ (DCIS), there is a significant unmet need to determine which women with DCIS are at high risk of having either a DCIS or an invasive carcinoma local recurrence. The Oncotype DX® Breast Cancer Assay for DCIS patients is the first clinically validated genomic assay to provide an individualized prediction of the 10-year risk of local recurrence (DCIS or invasive carcinoma) to help guide treatment decision-making in women with ductal carcinoma in situ treated by local excision, with or without tamoxifen.

The Oncotype DX Assay for DCIS Patients is the first and only clinically-validated commercial genomic assay for patients with DCIS. This assay predicts the risk of local recurrence (DCIS or invasive carcinoma) and helps guide personalized treatment based on tumor biology as determined by the DCIS Score™. The DCIS Score was clinically validated in a prospectively designed study using patient samples from ECOG 5194. Besides the DCIS Score, the report includes quantitative ER and PR single gene expression values. The assay is run in Genomic Health's CLIA-certified, CAP-accredited reference laboratory.

Which Patients?

The Oncotype DX Breast Cancer Assay for DCIS can provide relevant information for women with ductal carcinoma in situ treated by local excision, with or without tamoxifen. The eligibility criteria for patients in the ECOG 5194 study was as follows:

- Patients with low/intermediate grade, size < 2.5 cm or high grade, size < 1 cm were a minimum of 3 mm negative margins, Patients were treated with surgical excision alone and no radiation therapy was administered
- Tamoxifen use was allowed at the investigator's discretion beginning after May 2000. There was no collection of duration of tamoxifen treatment. Approximately 30% of patients received tamoxifen at some point.
- 97% of the patients were ER positive.

DCIS Score Result

DCIS is a heterogeneous disease. Currently there is no objective method to identify patients who are at a high risk of local recurrence or determine which recurrences will be invasive. It is important to have an accurate and reproducible assay that predicts the risk of recurrence for DCIS patients. Reflective of the continuum of DCIS tumor biology, the DCIS Score quantifies: (1) the likelihood of local recurrence (DCIS or invasive carcinoma) at 10 years. The DCIS Score result provides physicians and their patients with an individualized score to help inform your treatment plan.
Economic analysis of chemotherapy costs for adjuvant therapy in breast cancer in France

In a poster presented at SABCS 2011, investigators from Hopital Tenon in Paris, France reported that using the Oncotype DX® assay in French clinical practice to inform chemotherapy decisions is expected to be cost-saving in the long term for ER+, N-, early stage invasive breast cancer patients.

The investigators conducted a retrospective analysis of medical records of patients having undergone surgery for breast cancer from January – July 2010 in their institution. Information on patient characteristics, pre-chemotherapy assessment, and relevant costs relating to treatment (chemotherapy, supportive care for adverse events, hospitalizations, laboratory tests, transport and sick leave) were collected. Patients were also interviewed, to collect data relating to transportation to and from the hospital as well as work absenteeism. Cost data was determined based on unit costs found in French insurance databases.

A Markov model was used to determine long term costs and clinical outcomes associated with the introduction of Oncotype DX to inform adjuvant chemotherapy decisions for ER+, N-, invasive breast cancer patients. The results showed that when compared to the conventional approach, using the Oncotype DX assay is estimated to decrease cost (-€ 630 per patient avg.) as a result of patients who are spared unnecessary chemotherapy, and improve outcomes (0.13 life years gained per patient) when patients are reclassified as likely to benefit from chemotherapy following Recurrence Score® assessment. Another interesting finding was that the chemotherapy drug costs only comprised 1/3 of the total cost associated with chemotherapy treatment. The breakdown of costs was as follows:

![Figure 1- Distribution of costs, according to specific areas](image)

The findings from France are consistent with studies from several other countries. In another study presented at SABCS which reviewed the published health economic studies on the Oncotype DX Breast Cancer Assay, Paolo Pronzato from Genoa, Italy reported that Oncotype DX was either cost savings or cost effective in studies from Australia, Canada, Hungary, Israel, Japan, Singapore and USA.

With over 200,000 assays performed, the Oncotype DX® Breast Cancer Assay is highly standardized

In a report from Genomic Health presented at SABCS of 207,691 invasive breast cancer cases assayed between January 2005 and March 2011, there were highly consistent distributions over time for the reference gene average and Recurrence Score® (RS) results. Additionally, quantitative single gene expression levels for ER, PR, and HER2 (reporting initiated in 2008) had highly consistent distributions and associations over time. The average and median RSs are 19.5 and 17, respectively.
Reference genes play an important role in normalizing the expression of the cancer-related genes. Normalization can compensate for sources of preanalytical variability such as delays to fixation, duration of fixation, different fixatives and sample age which can affect RNA quality.

The distribution of the average non-normalized level of expression for the five reference genes (which is related, in part, to the degree of RNA degradation in individual blocks) remained consistent over time, with non-systematic variation in the median value within approximately 0.5 units.

Strict quality control and quality assurance processes have resulted in consistent performance of the Oncotype DX Breast Cancer assay and consistent distributions over time for the Recurrence Score result, reference gene average, and quantitative single gene expression levels and their associations. All specimens, FFPE blocks, slides and tubes are bar-coded and tracked by our computer system from the moment they enter the GHI laboratory and they are tracked throughout the process all the way through to report generation. Also, routine monitoring of the ongoing performance of the Oncotype DX Breast Cancer assay shows that it continues to perform within the originally defined analytical parameters, which is critical for ensuring consistency with the studies that validated the Recurrence Score result as a predictor of breast cancer recurrence risk and anticipated hormone and chemotherapy benefit.
Spotlight on Oncotype DX Colon Cancer Assay Gene: Cell Cycle and Ki67

Cell Cycle Gene Group:

In contrast to the Oncotype DX Breast Cancer Assay, where higher expression of cell cycle genes (STK15, MYBL2, Ki-67 and CCNB1) is associated with increased risk of recurrence [1-2], higher expression of the colon cell cycle genes (cMYC and Ki-67 and MYBL2) is associated with a lower risk of recurrence [3-4]. This is consistent with other reported evidence that cell cycle gene expression correlates with a good prognosis in colon cancer [5-8]. Increased expression of these cell cycle genes in colon cancer may thus represent a different biological property than cell cycle gene expression in breast cancer, where it has been associated with proliferation. In colon cancer, increased expression of these genes may instead represent tightened control of various stages of the cell cycle in response to DNA damage or misalignment of chromosomes during mitosis. With tighter cell cycle control, a tumor could reduce the likelihood of chromosomal instability and aneuploidy [9], which are associated with poor outcome [10-13].

Ki-67 (MK167; Antigen identified by monoclonal antibody Ki-67)

The Ki-67 gene encodes a protein which is synthesized from late G1 through M phase of the cell cycle, and is localized to the nucleus. There are several reports where high expression of Ki-67 in colon cancer is correlated with a lower risk of recurrence [6-8]. Although the Ki-67 antigen is the classic IHC marker for cell proliferation, Garrity et al. reported only a weak correlation in colon cancer between Ki-67 levels and S-phase (the standard measure of proliferation) [6]. Consequently, in colon cancer, expression of this gene may not actually signify rapidly dividing tumors, but rather represent part of an important cell cycle control mechanism.


**CHEMO/NO CHEMO:** For which patient, would you recommend adjuvant chemotherapy+ hormonal therapy?

**PATIENT A**

61-year-old patient with 0.6-cm and 0.9-cm tumors

- Menopausal Status: Postmenopausal
- Tumor Type: Infiltrating Ductal Carcinoma (IDC), Ductal Carcinoma in Situ (DCIS)
- Tumor Size: 0.6 cm, 0.9 cm
- ER Status (IHC): Positive (95%)
- PR Status (IHC): Positive (95%)
- HER2/neu Status: Negative (FISH)
- Histologic Grade: 2
- Lymph Node Status: Negative (0/2 SLNs)
- General Health: Excellent

**CASE SUBMITTED BY:**

G. Thomas Budd, MD

**PATIENT A RESULTS**

Clinical Experience

Patients with a Recurrence Score of 36 in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of 25% (95% CI: 19%-30%).

**PATIENT B**

62-year-old patient with 0.6-cm tumor*

- Menopausal Status: Postmenopausal
- Tumor Type: Infiltrating Ductal Carcinoma (IDC)
- Tumor Size: 0.6 cm
- ER Status (IHC): Positive (strong)
- PR Status (IHC): Positive (strong)
- HER2/neu Status: Negative (IHC)
- Histologic Grade: 2
- Lymph Node Status: Negative (0/2 SLNs)
- General Health: Bipolar, irritable bowel syndrome, hypertension, gastroesophageal reflux disease, hypothyroidism, asthma, cholecystectomy
- Other Information: *Additional 1.2-cm and 1.3-cm tumors found on re-excision

**CASE SUBMITTED BY:**

Terry P. Mamounas, MD, MPH

**PATIENT B RESULTS**

Clinical Experience

Patients with a Recurrence Score of 11 in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of 7% (95% CI: 5%-10%).
61 year old patient with 0.6-cm and 0.9-cm tumors:

**PATIENT A RESULTS**

**Clinical Experience**

Patients with a Recurrence Score of **36** in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of **25% (95% CI: 19%-30%)**.
62 year old with 0.6 cm tumor:

PATIENT B RESULTS
Clinical Experience
Patients with a Recurrence Score of 11 in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of 7% (95% CI: 5%-10%).
Recent Publications

Recently published Oncotype DX related articles:


European School of Oncology – e-oncoreview
Expert: William Wood, Emory University Hospital, Atlanta, GA, USA
Discussant: Nigel Bundred, University Hospital of South Manchester, Manchester, United Kingdom

Now with the introduction of a genomic assay for DCIS, we should consider how this assay will be integrated with existing risk assessment tools for DCIS and ultimately treatment decisions. This session will review the existing markers used for DCIS and how the added information from a genomic classifier predicting the individual risk of local recurrence may be relevant for treatment decisions.

This archived session can be accessed at: http://www.e-eso.net/egrandround.do?methodcall=details&id=234

E-cancer.TV
A test to predict risk of recurrence in DCIS

Prof. Joseph Sparano, Albert Einstein Cancer Center, New York, USA, discusses a study validating a multigene test to predict risk of recurrence in breast cancer patients with ductal carcinoma in situ (DCIS).

This validation study was a collaboration between the Eastern Cooperative Oncology Group (ECOG), North Central Cancer Treatment Group and Genomic Health. It analysed tumour samples from E5194, an ECOG-led, multi-institutional study of patients with low-, intermediate- or high-grade DCIS who had been treated surgically but had not received radiotherapy.

The study demonstrated that the test could predict the ten year risk of recurrence for both DCIS and invasive cancer.

This is the first time a multigene test has been has demonstrated an additional value beyond currently used prognostic markers in DCIS.

In this interview with Professor David Miles, a leading breast cancer expert from London, the role of Oncotype DX® in the management of invasive breast cancer was discussed.

Oncotype DX offers a novel and complimentary diagnostic test for women with node negative, ER positive and HER 2-, invasive breast cancer. It scores the breast tumour on 21 different genes involved in breast cancer, giving a Recurrence Score® (between 0 and 100), which shows the likelihood of breast cancer returning within 10 years of the original diagnosis. Early findings from prospective-retrospective trials indicate that a low Recurrence Score may determine which patients do not need chemotherapy. It is not meant to replace current diagnostic tools but to work in partnership with the likes of for instance Adjuvant on-line, to provide both the oncologist and patient a more complete picture of their disease and how best to treat it.

This programme was supported by sponsorship from Genomic Health.

A new test to determine risk of recurrence in DCIS breast cancer

Dr. Larry Solin, Albert Einstein Medical Center, Philadelphia, USA, talks to ecancer.tv about the development of a multigene test to predict risk of recurrence in breast cancer patients with ductal carcinoma in situ (DCIS).

This validation study was a collaboration between the Eastern Cooperative Oncology Group (ECOG), North Central Cancer Treatment Group and Genomic Health. It analysed tumour samples from E5194, an ECOG-led, multi-institutional study of patients with low-, intermediate- or high-grade DCIS who had been treated surgically but had not received radiation.
DCIS is an increasingly common non-invasive tumour. Dr Solin explains the significance of these findings, and outlines how they will help guide patients when deciding between surgery or a combination of surgery and radiotherapy. This is the first time a multigene test has been used to differentiate patients risk of recurrence after being diagnosed with DCIS and providing added value beyond traditional markers.

Medscape
Breast Cancer

Must All DCIS Patients Undergo Radiation?
Medscape Hematology-Oncology 2012

Slide Kits Available for download
Colon Cancer Core Slide Module
Breast Cancer Core Slide Module
Single Gene Slide Module
Ordering Oncotype DX Brochure #1
Announcements

Genomic Tools in Breast Cancer
Leading the Way towards Personalized Treatment will be a featured official satellite during this year’s EBCC meeting in Vienna. The program will held on Wednesday 21st of March 2012 from 18:45-20:15 at Vienna Exhibition Center, Hall F1.

MMR testing now offered to qualify patients for Oncotype DX® Colon Cancer Assay
The Oncotype DX Colon Cancer Assay and MMR can now be ordered at the same time in a convenient one-step process by selecting the Sequential Assay option on the Oncotype DX requisition form. We are pleased to announce the expansion of Genomic Health’s colon cancer laboratory services to include immunohistochemistry (IHC) testing to assess mismatch repair (MMR) status for stage II colon cancer recurrence risk. MMR testing also enables the identification of the patients with T3 MMR-Proficient (MMR-P) tumors, standard risk patients constituting the majority (~70%) of stage II colon cancer in whom the Recurrence Score® provides valuable recurrence risk discrimination not available with conventional clinical and pathologic factors. Results from the recently published QUASAR validation study strongly support a paradigm in which the Oncotype DX Colon Cancer Recurrence Score, MMR status, and T stage are used to determine recurrence risk for individual patients with stage II colon cancer. The QUASAR study results, which are highly consistent with several other published studies, demonstrate that MMR testing is clinically useful for identifying the ~15% of stage II patients with MMR-Deficient (MMR-D) tumor biology who have low recurrence risk.

Step-by-Step Guide for Getting Oncotype DX assays available in English, German, French, and Italian
Genomic Health has developed a new brochure to assist you and your office staff in ordering Oncotype DX tests

English | French | German | Italian