Gene Expression Profiling (GEP) for Breast Cancer Recurrence Risk Prediction, Surveillance in Michigan, 2008-2012

Michigan Department of Community Health

Cancer Genomics Program

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Introduction

From 2008-2012, the Michigan Department of Community Health (MDCH) Cancer Genomics Program was awarded cooperative agreement funding from the Centers for Disease Control and Prevention (CDC) Office of Public Health Genomics (OPHG) to identify and promote cancer genomics best practices for appropriate translation of cancer genetic tests into clinical and public health practice. The primary goal was to develop and implement a model for surveillance of select cancer genetic tests, specifically breast tumor gene expression profiling (GEP) tests, *BRCA1/2* and Lynch syndrome. This report provides a summary of MDCH's surveillance methods and findings regarding three GEP tests that predict risk of breast cancer recurrence– Oncotype DX® Breast Cancer Assay, MammaPrint® Test, and Breast Cancer Gene Expression Ratio Assay (or H:I ratio test).

For women diagnosed with early stage (Stage I or Stage II), node negative breast cancer, the decision to undergo chemotherapy treatment to prevent breast cancer recurrence often presents a difficult dilemma. The majority of these women will not have a recurrence within 10 years. However, because some are at risk for a recurrence that may be prevented by chemotherapy, most women with early stage breast cancer are offered chemotherapy.[1] Standard risk stratification, which can be used to determine risks of recurrence, is typically based on clinical and pathological cancer features.

With the recent advent of GEP tests, new molecular information can now be added to assist women with early stage breast cancer and their providers with this decision. GEP tests evaluate the activity of genes within breast tumor tissue samples to estimate the risk of recurrence. These tests provide a recurrence risk score and interpretation (i.e. high, intermediate, low risk) to predict the chance of cancer recurrence within 5-10 years. The three manufacturers have slightly different guidelines for the intended use of these tests (**Table 1**). All three manufacturers recommend that the breast cancer be lymph node negative. The costs of these tests vary from $1,400-$4,000 based on the specific manufacturer and year of marketing.

Table 1: 2008 Published Manufacturer's Guidelines for Intended Use of GEP Testing Among Breast Cancer Patients

Test	Age at Diagnosis	Tumor Stage	Tumor Size	Estrogen Receptor
MammaPrint®	≤ 61	I or II	≤ 5 cm	Positive or Negative
Oncotype DX®	Any age	I or II	Not specified	Positive
H:I ratio test	Not specified	Not specified	Not specified	Positive

Note: this project utilized publicized information by manufacturers in 2008. In 2011, MammaPrint® revised their guidelines to exclude specific age criteria.

Evaluation of Genomic Applications in Practice and Prevention (EGAPP™)

The EGAPP™ Working Group is an independent, multidisciplinary panel of scientific and health care experts that utilize a systematic process for evaluating genomic applications for analytic validity, clinical validity and clinical utility.[1,2] In 2009, the EGAPP™ Working Group evaluated if GEP tests improved outcomes in patients with breast cancer, finding that:

2009 EGAPP™ Working Group Recommendation:

Can GEP Improve Outcomes in Patients With Breast Cancer?

There is insufficient evidence to make a recommendation for or against the use of tumor gene expression profiling tests. Further development and evaluation of these technologies is encouraged.[1,2]

The EGAPP™ Working Group found no direct evidence that GEP testing in women with breast cancer improved outcomes. More specifically, there was inadequate evidence of the analytic validity and clinical utility of all three of these tests. The Oncotype DX® Recurrence Score was found to have adequate evidence of clinical validity. However, MammaPrint® and the H:I ratio test were found to have inadequate evidence of their clinical validity.[1,2]

EGAPP™ concluded that further development and evaluation of these technologies was needed. The TAILORx Clinical Trial has been underway since 2006 to further address this issue.[3] The EGAPP™ Working Group also stated that providers should decide if the use of GEP testing is relevant and adds value on a case by case basis.[1,2] Additionally, any patient considering GEP testing for breast cancer should be provided with counseling and educational materials about the potential benefits and harms.[1,2]

Epidemiology of GEP Testing among Breast Cancer Patients in Michigan

Given the recent availability of these tests and the insufficient evidence for their utilization, activities were limited to investigating the feasibility of conducting surveillance on the uptake of GEP tests in Michigan breast cancer patients. Our key surveillance questions for GEP testing were:

⇒ **What is the estimated percentage of patients with breast cancer diagnosed in Michigan who have GEP testing?**

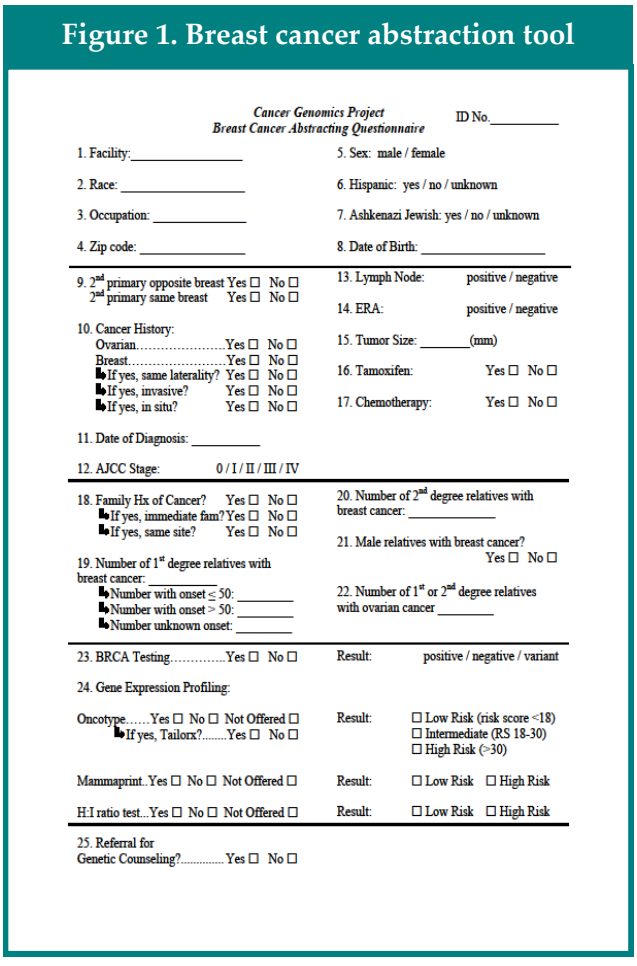
⇒ **Were those who had GEP testing appropriate candidates for testing based on the manufacturer's intended use guidelines?**

Michigan Cancer Surveillance Program Chart Abstraction of Breast Cancer Patients

The feasibility of conducting surveillance for GEP tests through existing state data was assessed using an existing quality assurance chart review process for cancer cases reported to the Michigan Cancer Surveillance Program (MCSP), in the MDCH Division for Vital Records and Health Statistics. MCSP is mandated by state law (Act 82 of 1984) to collect information on all cancer diagnoses and treatment. More specifically, the mandate established MCSP to:

"...record cases of cancer and other specified tumorous and precancerous diseases that occur in the state, and to record information concerning these cases as the department considers necessary and appropriate in order to conduct epidemiologic surveys of cancer and cancer-related diseases in the state." This mandate further states that "a reporting entity which meets the standards of quality and completeness set by the department shall be subject to inspection not more than once every 2 years for the purpose of assessing the quality and completeness of reporting from the entity."[4]

Figure 1. Breast cancer abstraction tool



Cancer Genomics Project
Breast Cancer Abstracting Questionnaire

ID No._____

1. Facility:_____
2. Race: _____
3. Occupation: _____
4. Zip code: _____
5. Sex: male / female
6. Hispanic: yes / no / unknown
7. Ashkenazi Jewish: yes / no / unknown
8. Date of Birth: _____
9. 2nd primary opposite breast Yes ☐ No ☐
   2nd primary same breast Yes ☐ No ☐
10. Cancer History:
    Ovarian……Yes ☐ No ☐
    Breast……Yes ☐ No ☐
    If yes, same laterality? Yes ☐ No ☐
    If yes, invasive? Yes ☐ No ☐
    If yes, in situ? Yes ☐ No ☐
11. Date of Diagnosis: _____
12. AJCC Stage: 0 / I / II / III / IV
13. Lymph Node: positive / negative
14. ERA: positive / negative
15. Tumor Size: _____(mm)
16. Tamoxifen: Yes ☐ No ☐
17. Chemotherapy: Yes ☐ No ☐
18. Family Hx of Cancer? Yes ☐ No ☐
    If yes, immediate fam? Yes ☐ No ☐
    If yes, same site? Yes ☐ No ☐
19. Number of 1st degree relatives with breast cancer: _____
    Number with onset ≤ 50: _____
    Number with onset > 50: _____
    Number unknown onset: _____
20. Number of 2nd degree relatives with breast cancer: _____
21. Male relatives with breast cancer? Yes ☐ No ☐
22. Number of 1st or 2nd degree relatives with ovarian cancer _____
23. BRCA Testing……Yes ☐ No ☐ Result: positive / negative / variant
24. Gene Expression Profiling:
    Oncotype……Yes ☐ No ☐ Not Offered ☐ Result: ☐ Low Risk (risk score <18) ☐ Intermediate (RS 18-30) ☐ High Risk (>30)
    If yes, Tailorx?……Yes ☐ No ☐
    Mammaprint..Yes ☐ No ☐ Not Offered ☐ Result: ☐ Low Risk ☐ High Risk
    H:I ratio test…Yes ☐ No ☐ Not Offered ☐ Result: ☐ Low Risk ☐ High Risk
25. Referral for Genetic Counseling?……Yes ☐ No ☐

MCSP agreed to conduct chart reviews on select 2007-2010 breast cancer diagnoses to determine: (1) if GEP tests were ordered; (2) what specific GEP tests were ordered; (3) GEP test results; and, (4) the types of breast cancer patients receiving (and not receiving) GEP testing. From the abstracted data, MDCH Cancer Genomics also determined if the affected individual met the manufacturer's criteria for GEP testing. The cancer's primary site was used to identify charts for abstraction. Breast cancer primaries were included if the ICD topography code was C59.9.[5]

MCSP staff were trained to abstract GEP testing information using a breast cancer chart abstraction tool **(Figure 1)**. Charts for 857 primary breast cancers diagnosed between 2007 and 2010 were reviewed with the majority of breast cancers diagnosed in 2008 and 2009. Breast cancer cases from 11 facilities were reviewed. Twenty breast cancer charts were found to be duplicated and excluded, leaving 837 breast cancer cases in the final review.

The majority of the reviewed cases were among women (99.2%) and white people (93.4%). The average age was 61 years, with 54.8% being between 25-61 years. Of the 837 breast cancer primaries, 373 (44.6%) were Stage I; 163 (19.5%) were Stage II; and 124 were Stage III or IV (14.8%). The cancer stage was not recorded in 177 cases (21.1%). The majority of cases were lymph node negative (n=612, 73.1%), estrogen receptor alpha (ERa) positive (n=643, 76.8%); and tumor size of 6 cm or greater (n=649; 77.5%).

Table 2. Number of GEP tests among breast cancer abstraction population, Michigan 2007-2010

Test type	Number of documented GEP tests
TAILORx study	8
OncotypeDX®	75
MammaPrint®	3
H:I ratio test	2
Total	88

Of the 837 cases review, there were 88 breast cancer cases that had documented GEP testing (9.6%). Eight cases participated in TAILORx. The most commonly ordered test was Oncotype DX® (n=75 breast cancer cases) (**Table 2**). Among these 75 Oncotype DX® tests, the most commonly reported result was 'low risk' (n=38), followed by 'intermediate risk' (n=26) and 'high risk' (n=11). The majority were white (94.6%) and 40 met the manufacturer's published criteria for the intended use of this testing (53.3%) (**Table 3**).

There were 3 cases that had documented MammaPrint® results; and, 2 that had H:I ratio testing. None of the breast cancer cases receiving MammaPrint® or H:I ratio testing met the manufacturer's published criteria for the intended use of this testing.

Among the 837 breast cancer cases reviewed, it appeared that 198 (23.7%) met the manufacturer's published criteria for intended use of the H:I ratio test; 166 met the criteria for intended use of Oncotype DX®; and, 26 met the criteria for intended use of MammaPrint®. None of the cases meeting the criteria for intended use of H:I ratio testing or MammaPrint® had documentation of receiving these tests.

Among the 11 facilities from which these cases were reviewed, 8 facilities had cases who had Oncotype DX® testing; 2 facilities had cases with MammaPrint® testing; and 2 facilities had cases with H:I ratio testing. There were 4 facilities who had cases with documented TAILORx participation.

Table 3. Frequency of GEP testing among the breast cancer abstraction population (n=837), 2007-2010

	Number of Breast Cancer Cases		
	MammaPrint®	**Oncotype Dx®**	**H:I Ratio**
Met Intended Use Guidelines	26	166	198
Met Intended Use Guidelines and Received Test	0	40	0
Did Not Meet Intended Use Guidelines and Received Test	3	35	2

A limitation to the chart review process include the small number of facilities (n=11) that were included; this comprises less than 10% of all cancer reporting facilities in Michigan.

MCSP Young Breast Cancer Survivors Mail Survey

The MDCH Cancer Genomics Program, MCSP registry staff and partners also sought to assess the utilization of cancer genetic services (including GEP testing) among young female breast cancer survivors (under 50 years of age) through a mail survey. Five-hundred young female breast cancer survivors (YBCS) were identified using the MCSP cancer registry. The YBCS had been diagnosed in 2006-2007 in Michigan and were between the ages of 18-49 at the time of diagnosis. Of the 3,911 YBCS diagnosed in Michigan between 2006 and 2007, 500 women were selected by simple random selection from the eligible population. MDCH Vital Records were used to exclude cases known to have died. As part of the consent process, MCSP provided the local reporting facility and the physician on record with the potential study participant's name. Physicians of record were asked whether they knew of any reason that the selected participant should not be contacted, such as death, mental illness, or illness due to current cancer treatments. If the local reporting facility and diagnosing physician confirmed the case and did not indicate any medical contraindications to MCSP contacting the patient, the participant was mailed the MDCH-created survey with up to three attempts to obtain a response. Completed surveys and signed consent forms were received from 289 women (57.8%). The respondents were primarily white (86.2%), employed for wages (56.1%) and had private insurance (75.4%). The respondents' age ranged from 26-49 years with an average age of 43 years.

The mail survey included the following specific question, "Did you have a test called MammaPrint, OncotypeDx or H:I ratio after your breast cancer diagnosis? These would be done on a breast cancer tissue sample from surgery." If the respondent replied that she had any of these tests, she was asked to specify which test and recall the test results if possible.

Table 4. Number of GEP tests self-reported by Michigan YBCS (n=289)

Test type	Number of reported GEP tests
OncotypeDX®	50
MammaPrint®	11
H:I ratio test	19
Total	80

Of the 289 YBCS who responded, 69 (23.9%) reported that they had received GEP testing. There were 162 YBCS (56.1%) who responded that they did not know if they had GEP testing, and 56 (19.4%) reported hat they did not have GEP testing. Of the 69 YBCS who reported having GEP testing, 9 YBCS had more than one GEP test; and, 8 YBCS self-reported having all three GEP tests. Of the 80 reported GEP tests, 50 were Oncotype DX®; 11 were MammaPrint®, and 19 were H:I ratio testing (**Table 4**). For the 50 Oncotype DX® tests, 18 reported 'low risk' results; 9 reported 'intermediate' test results; and, 11 reported 'high risk' results. There were 8 respondents who did not recall their Oncotype DX® results, 2 who preferred not to answer, and 2 who chose not to respond to this question. Of the 19 H:I ratio tests, 6 reported 'low risk' and 6 reported 'high risk' results. There were 6 respondents who did not recall their H:I ratio test results and 1 who selected prefer not to share the results. Of the 11 MammaPrint® tests, 3 reported 'low risk' results and 3 reported 'high risk' results. There were 4 respondents who did not recall their MammaPrint® results and 1 who preferred not to share the results. Among the 8 YBCS who reported having all three tests, the test results were not consistent.

Conclusion

Surveillance of the utilization of GEP testing in Michigan revealed that most breast cancer patients for whom GEP testing is intended did not have documentation of receiving these tests. For the small number of breast cancer patients who had documented GEP testing. Oncotype DX® was the most common GEP test recorded with the majority of results showing 'low risk' recurrence risk scores. Of concern, our exploratory studies also revealed that among the relatively few patients who received these tests, many were conducted on those for whom they were not intended.

It is important to note that our studies were exploratory and only investigated breast cancer cases diagnosed in Michigan between 2007 and 2010. At that time, these three GEP tests had only recently become commercially available in the United States. Therefore, the level of provider and patient awareness of GEP testing at that time is not known. It is also unknown if counseling and education about the availability of GEP testing occurred and if there was a decision making process between the patient and provider to perhaps not pursue this testing. These are areas for future possible surveillance and investigation. The use of such costly molecular tests in patients for whom they were not intended requires further investigation and has potential educational and policy implications.

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