

Presented by Dr. Steven Telschow, Associate Pathologist, Med Dir Lab, Bethlehem Campus, St Luke's Hospital & Health Network

## Personalized Cancer Care by Genomic Testing

... The Future is Now

A joint protocol developed by St. Luke's Regional Breast Center and the Departments of Medical Oncology, Surgical Oncology & Pathology, St. Luke's Hospital & Health Network centered in the Lehigh Valley.

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Our normal cells may become cancer cells by losing control of growth signals. When growth genes (proto-oncogenes) are mutated or overregulated, they become oncogenes, whose "out of control" expression accelerates the cell towards unregulated growth & transformation to cancer

### Abnormal Cell Growth: Oncogenes

Normal genes (regulate cell growth)

1st mutation leads to accelerated cell division

Proto-oncogene to oncogene

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To complete the transformation to cancer, a cell also acquires several additional key mutations in DNA repair genes (tumor suppressor genes) as well as in other genes which enable the cancer cell to invade neighboring tissue, evade immune system detection, recruit a new blood supply, and ultimately, to metastasize through blood & tissue fluid (lymph) to distant sites (e.g. bone & liver). Thus, abnormalities in many genes characterize a cancer cell.

Mammprint simultaneously measures the activity of the 70 genes found to be most predictive of breast cancer recurrence including genes which accelerate tumor cell growth (proliferation), invasion of other tissues (e.g. lymph nodes), immune system evasion & blood vessel necessary to nourish these more actively growing cancer cells.

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The Mammprint genomic test works by measuring activity signals in breast cancer cells (either decreased or increased mRNA) from 70 genes found most predictive of tumor recurrence. Each gene is represented by many single DNA strands which have been built at a precise location (dot) upon a glass slide by a nanotechnology device similar to an ink jet printer. Tumor mRNA which matches a particular gene, will stick (hybridize) to only that dot. An analyzer then measures the amount of mRNA sticking to each dot and colors the dot either green, red or black. Green is colored if less mRNA is present (down-regulated gene) than in benign breast epithelial cells (normal control), red if more mRNA is present (up-regulated gene) & black if about the same. The equipment & laboratory technical requirements necessary to perform Mammprint analyses are beyond the scope of most regional medical centers. Accordingly, tumor tissue in room temperature preservative must be sent to Agendia Labs in California where the test is performed.

Slide from presentation given by Dr. Rene Bernards, CSO, Agendia

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The test then computes the patient's risk of cancer recurrence (RS) in 10 years by comparing the patient's 70 gene signature (which genes are red or green) against signatures of reference patients, whose 10 year recurrence is known and who have not received either endocrine or chemotherapy. Mammprint's bioinformatic computation (RS) is cleared by the FDA. Low RS suggests ~10% risk (95% CI = 4-15%) whereas high RS suggests ~29% risk (95% CI = 22-35%). As we will see, surgeons & oncologists use RS in selected patients to make treatment decisions, most notably whether to offer chemotherapy. However, Mammprint requires fresh tumor cells not preserved in formaldehyde in the manner customary at most hospitals. This challenging requirement prompted our team to develop a novel protocol.

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### Fresh Tumor Acquisition for Mammprint Analysis – St. Luke's Protocol

St. Luke's Regional Breast Center Mammography & clinical considerations suggest a need for biopsy; patient agrees; radiologist performs biopsy in 615 women (3/1-9/22/11)

Pathologist evaluation & report: 55/526 (10.5%) have invasive CA

St. Luke's Electronic Medical Record (EMR) for surgeon & oncologist treatment planning, possibly before first patient visit

Radiologist's suspicion of cancer

If not high, e.g. BIRADS < 5: 526 cases (85%)

If high, e.g. BIRADS ≥ 5: 89 cases (15%)

All biopsy tissue sent to St. Luke's Path Lab

Mammprint high or low RS

Agendia Lab - if invasive CA & good quality RNA, perform Mammprint with Dr.'s order & report to EMR: 51/89 (57%). - if insufficient/no invasive CA or poor quality RNA, inform St. Luke's Lab, make slides available by telepathology: (43%)

St. Luke's Path Lab - if invasive CA, perform receptor studies (ER/PR/Her2) & report: 53/89 (60%) - if no invasive CA, report & reconcile with Agendia pathologist by telepathology, document this in pathology report: 40%

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**Surgery of breast cancer is determined by surgeon considering:**

- Patient's informed consent, after discussion of performance status, hormonal status, biopsy tumor characteristics & age.

**BIOPSY TUMOR CHARACTERISTICS INCLUDE:**

- histopathology including tumor type, size, grade
- ER and PR status by immunohistochemistry (IHC)
- HER2 status by IHC or FISH (fluorescence in situ hybridization)
- Recurrence score by genomic tests (e.g. MammaPrint).

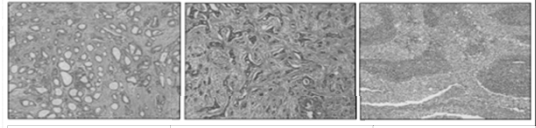
**Chemotherapy decisions are determined by medical oncologist considering all of the above, plus**

- Surgical specimen histopathology including number of involved lymph nodes & surgical margins

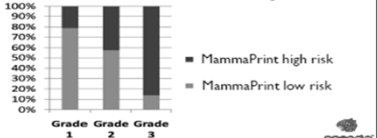
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**Biopsy histology characteristics read by the pathologist are only part of the story**

MammaPrint Recurrence Score (RS) has added prognostic information beyond routine histologic assessment of breast cancer – this information helps selected patients avoid chemotherapy when it is not likely to increase 10 year disease free survival



Grade 1 (low risk histology)    Grade 2 (intermediate risk histology)    Grade 3 (high risk histology)



Grade	MammaPrint high risk (%)	MammaPrint low risk (%)
Grade 1	~10%	~90%
Grade 2	~40%	~60%
Grade 3	~80%	~20%

Slide from presentation given by Dr. Rene Bernards, CSO, Agendia  
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**When the patient sees the Medical Oncologist, chemotherapy (chemo) as opposed to hormonal therapy is discussed**

**GOALS of Chemo:** Treat patients to make possible  $\leq 10\%$  chance of DISTANT metastasis in 10 years

- o Which patients receive no demonstrable incremental benefit from the addition of chemotherapy above and beyond that of hormonal therapy alone? This is controversial. At SLHNN we currently apply these guidelines:

- tumor size  $\leq 1$  cm (pT1a or pT1b) & hormone receptor positive, Her-2/neu negative.
- tumor size  $\leq 0.5$  cm (pT1a), hormone receptor AND Her-2/neu negative (triple negative).
- tumor size between  $> 1$  &  $\leq 5$  cm (pT1c – pT2), fewer than four positive lymph nodes, **LOW RECURRENCE SCORE** by MammaPrint or Oncotype & hormone receptor positive, Her-2/neu negative.

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**Who needs chemotherapy (continued)**

- o Which patients might benefit from systemic chemotherapy?  
At SLHNN we currently apply these guidelines:

- tumor size  $> 1$  cm (pT1c or above), **HIGH RECURRENCE SCORE** by MammaPrint or Oncotype, regardless of hormone receptor status.
- tumor size  $> 1$  cm (pT1c or above), hormone receptor negative
- tumor size  $> 0.5$  cm (pT1b or above), Her-2/neu positive
- tumor size  $> 0.5$  cm (pT1b or above), triple negative
- tumor of any size & grade with 4 or more positive lymph nodes

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**WHY NOT PERFORM MAMMAPRINT USING TUMOR TISSUE TAKEN FROM THE TUMOR EXCISION SPECIMEN AT TIME OF SURGERY ?**

We actually began with this approach, but found that the pathologist was less likely to find sufficient tumor tissue for MammaPrint analysis than the radiologist, who first biopsied the tumor utilizing mammographically directed techniques.

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Data from St. Luke's Pathology Lab, 3/1/2011 – 9/22/2011. In this time interval, MammaPrint analysis was requested by surgeons in 33 lumpectomy or mastectomy cases. The pathologist then attempts biopsy of fresh tumor by gross inspection of the lumpectomy or mastectomy specimen. Pathology findings of the tissue sent to Agendia Labs and of the St. Luke's pathology report are given below:

	Positive for invasive carcinoma by St. Luke's pathology report	Negative for invasive carcinoma by St. Luke's pathology report
<b>Agendia quality report:</b> Positive, MammaPrint analysis was performed for $> 30\%$ invasive cancer cells	21	1
<b>Agendia quality report:</b> Negative, MammaPrint analysis was not performed, $< 30\%$ invasive cancer cells	9	2

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Data from St. Luke's Regional Breast Center, 3/1/2011 – 9/22/2011. In this time interval, 89 (17.6%) highly suspicious biopsied lesions by mammography were sent to Agendia Labs from among 614 lesions biopsied.

	Positive for invasive carcinoma by St. Luke's pathology report	Negative for invasive carcinoma by St. Luke's pathology report
<u>Agendia quality report:</u> Positive, Mammaprint analysis was performed for > 30% invasive cancer cells	51	0
<u>Agendia quality report:</u> Negative, Mammaprint analysis was not performed, < 30% invasive cancer cells	2	36

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## CONCLUSION

**Personalized breast cancer care by genomic testing of mammographically-directed biopsy is feasible & offers several advantages to the patient & her care team:**

- Our protocol enabled Mammaprint analysis in 96% (51/53) of women receiving mammographic biopsy versus 70% (9/30) of women whose Mammaprint analysis was first attempted at lumpectomy or mastectomy.
- If promptly ordered by surgeon or medical oncologist, Mammaprint recurrence score can be posted to the EMR within 10 days of mammographic biopsy (MB) versus within > 27 days (average time to surgery following MB = 17 days) and could be available to both surgeon & oncologist at their first patient visit.

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**From our St. Luke's breast care team –**

**Thanks for your attention.**

**Here's wishing you a gentle breeze, calm waters & smooth sailing !**

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