ADAM MICKIEWICZ UNIVERSITY IN POZNAŃ
Faculty of Biology

Prognostic & Predictive Medicine

AlloMap®

mammaprint

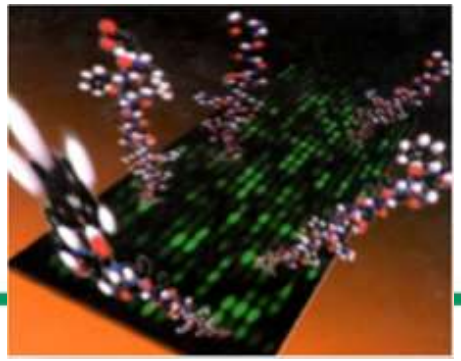
Tissue of Origin®

coloprint®

Hans Bluyssen, 18-11-2020

Clinically Available Molecular Diagnostics

Diagnostic Kits
Laboratory-developed-tests (LDTs)



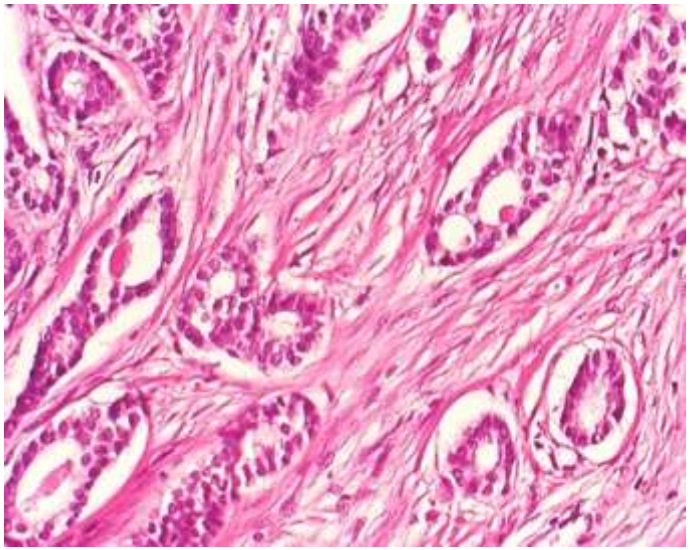
Time point in clinical decision making	Cancer		Cardiovascular disease	
	Test	Indication	Test	Indication
Risk/susceptibility	*BRCA1, BRCA2* *HNPCC, MLH1, MSH2* *TP53, PTEN*	Breast Colon Sarcomas	*KIF6, 9p21* Familion® 5-gene profile	CAD LQTS
Screening	HPV genotypes	Cervical	Corus™ CAD	CAD
Diagnosis	Lymphochip	Lymphoma	Corus CAD	CAD
Prognosis	Oncotype DX® (21-gene assay) MammaPrint® (70-gene assay) Her2/neu, ER, PR	Breast	TnI, BNP, CRP	ACS
Pharmacogenomics	Her2/neu *UGT1A1* *KRAS* *EGFR* Amplichip®; DMET™ *CYP2D6/CYP2C19*	Herceptin Irinotecan Cetuximab Erlotinib, gefitinib Various others (see Table 2)	*KIF6, SLCO1B1* Amplichip; DMET *CYP2D6/CYP2C19* *VKORC1*	Statins Warfarin Various others (see Table 2)
Monitoring	CTCs	Tumor recurrence or progression	AlloMap® gene profile	Transplant rejection

(Chan & Ginsburg, 2011)

Predicting disease outcome in cancer

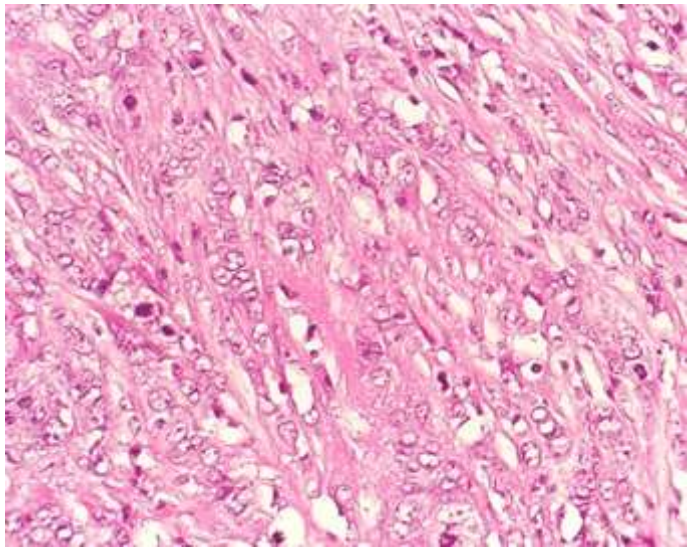
Histological grade

- Grade 1



Low risk

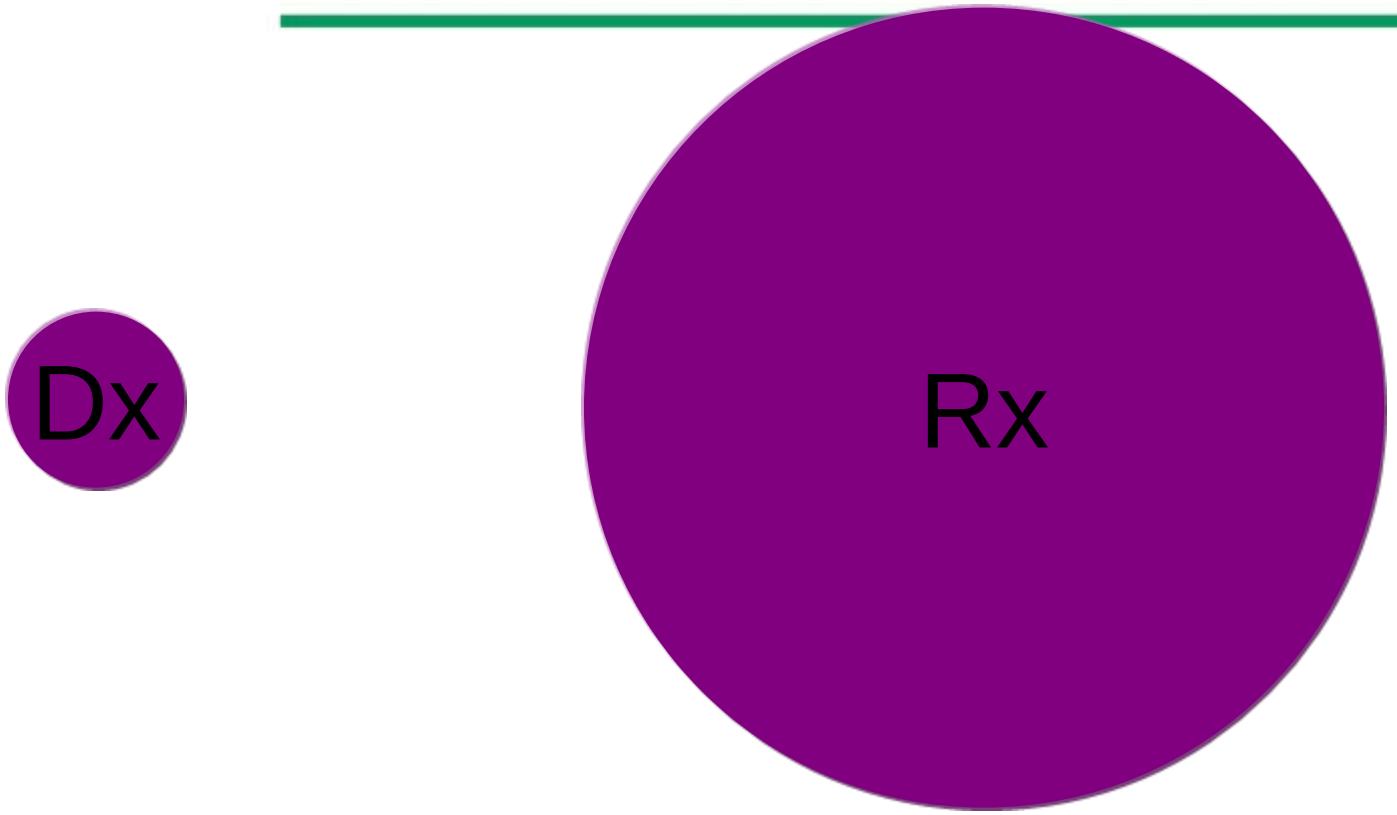
- Grade 3



High risk

Who to treat? & How to treat?

Conventional cancer treatment:



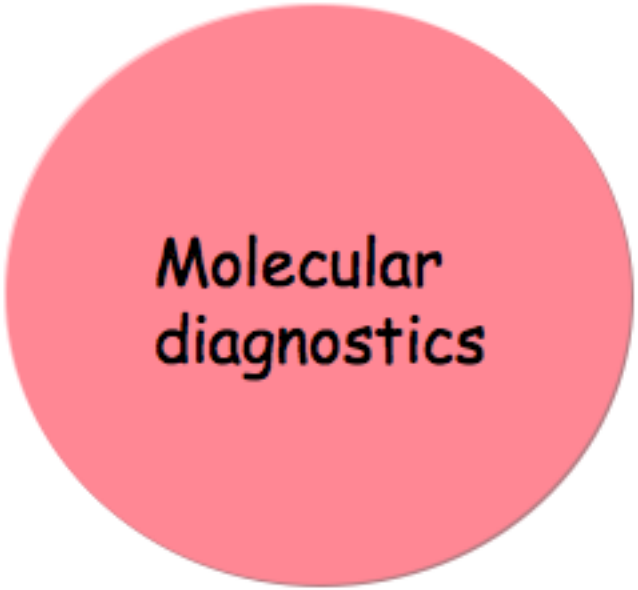
Diagnosis

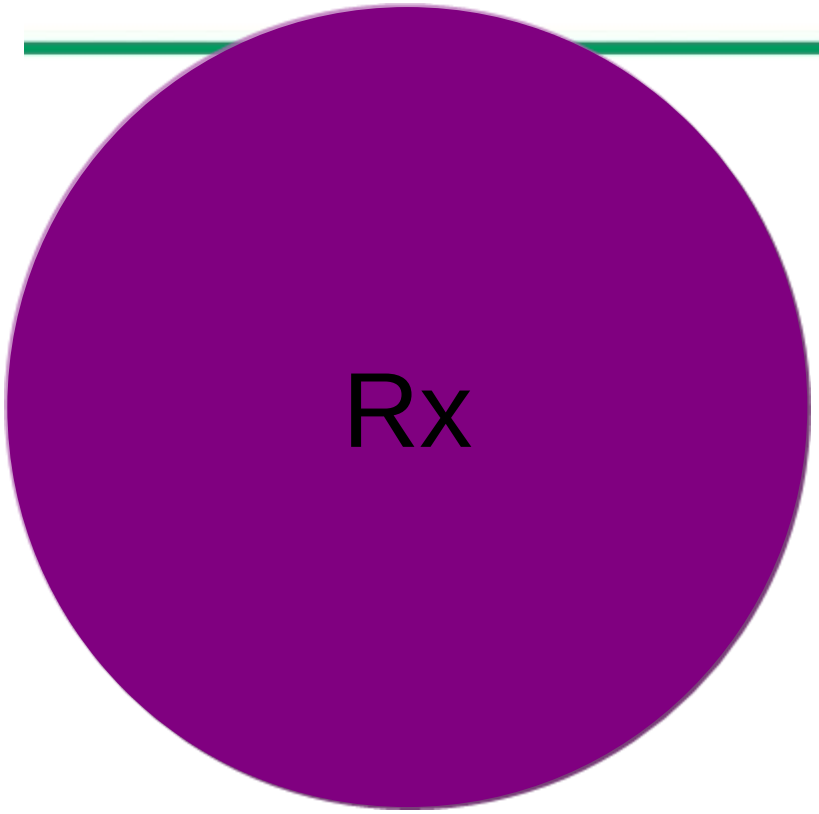
Stage, Grade, IHC

Treatment

Chemotherapy

Personalized cancer treatment:





Diagnosis:

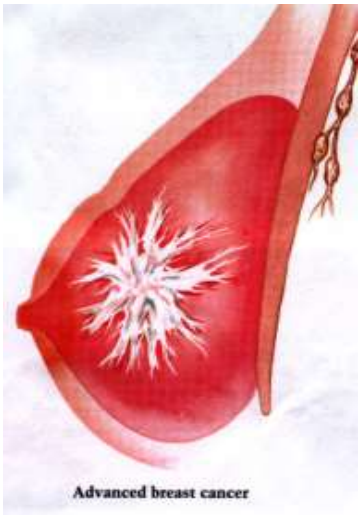
Which pathways are active?

Treatment:

Pathway targeted therapy

Goals of Breast Cancer Treatment

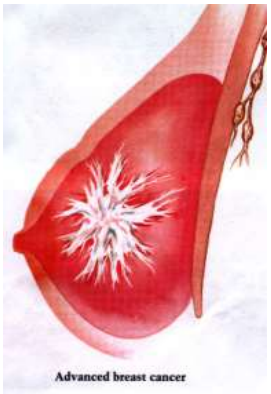
- Local/Regional Treatment: to control/ eliminate disease in breast and regional lymph nodes
  - Surgery
  - Radiation Therapy
- Systemic Treatment: to control/eliminate disease in distant organs
  - Chemotherapy
  - Endocrine/Hormonal Therapy
  - Other Targeted Therapy (e.g. Herceptin)



Systemic Therapy for Breast Cancer

- Chemotherapy
  - "generic" systemic therapy: kills any rapidly-dividing cells in the body
- Endocrine/Hormonally-active therapy
  - Tamoxifen; Aromatase Inhibitors
  - Target ER-positive and/or PR-positive breast cancer cells
- Herceptin/Trastuzamab
  - Targets HER2/neu-positive breast cancer

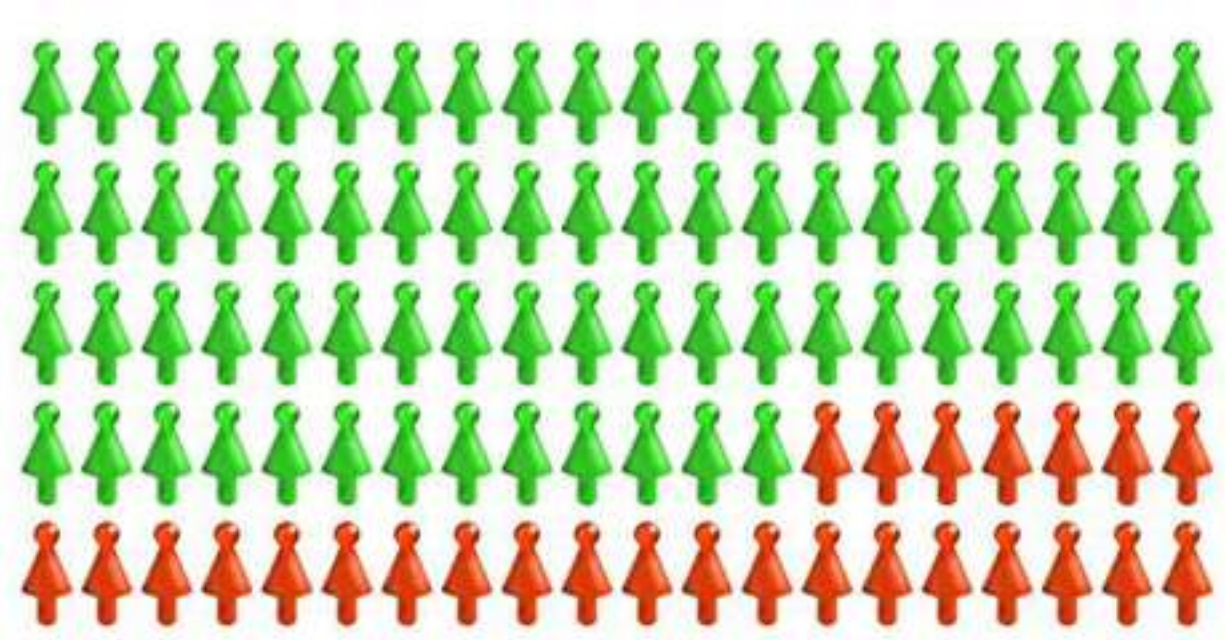
Systemic Therapy for Breast Cancer



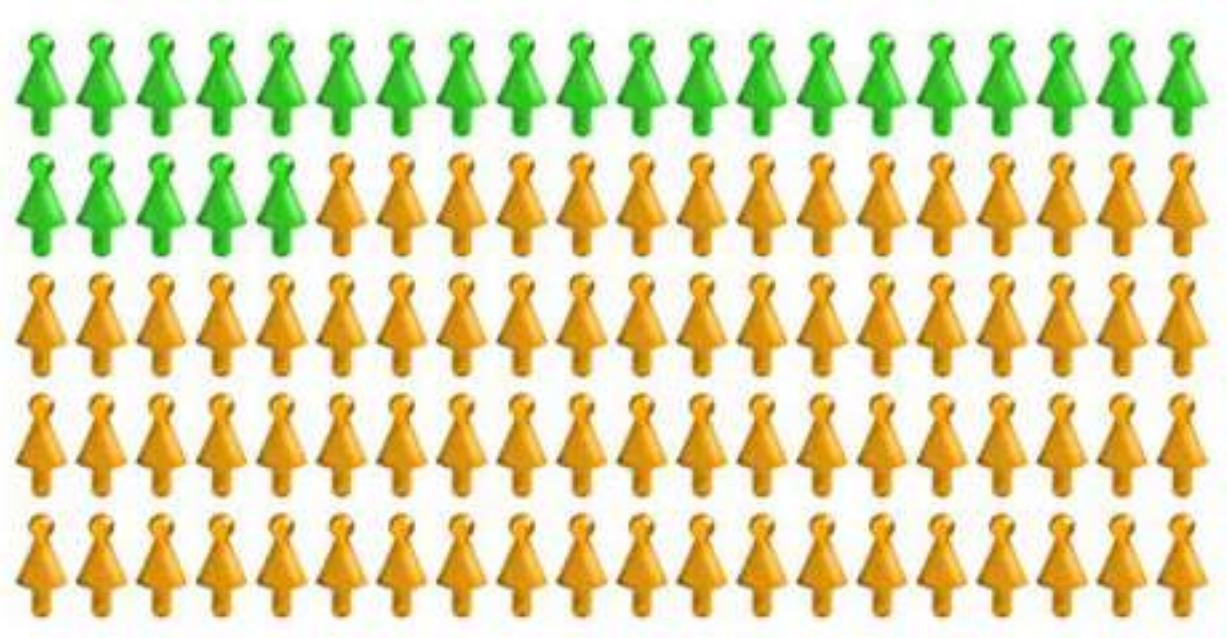
- Appropriate systemic therapy can improve breast cancer survival by 20-30%
- Preoperative (neoadjuvant) systemic therapy
  - can convert locally-advanced/inoperable breast cancer to resectable disease
  - can improve ease of surgery for any bulky cancer
- Success of systemic therapy:
  - ***COMPLETELY*** dependent upon having information regarding tumor markers (ER, PR, and HER2/neu)

Of 100 women with breast cancer

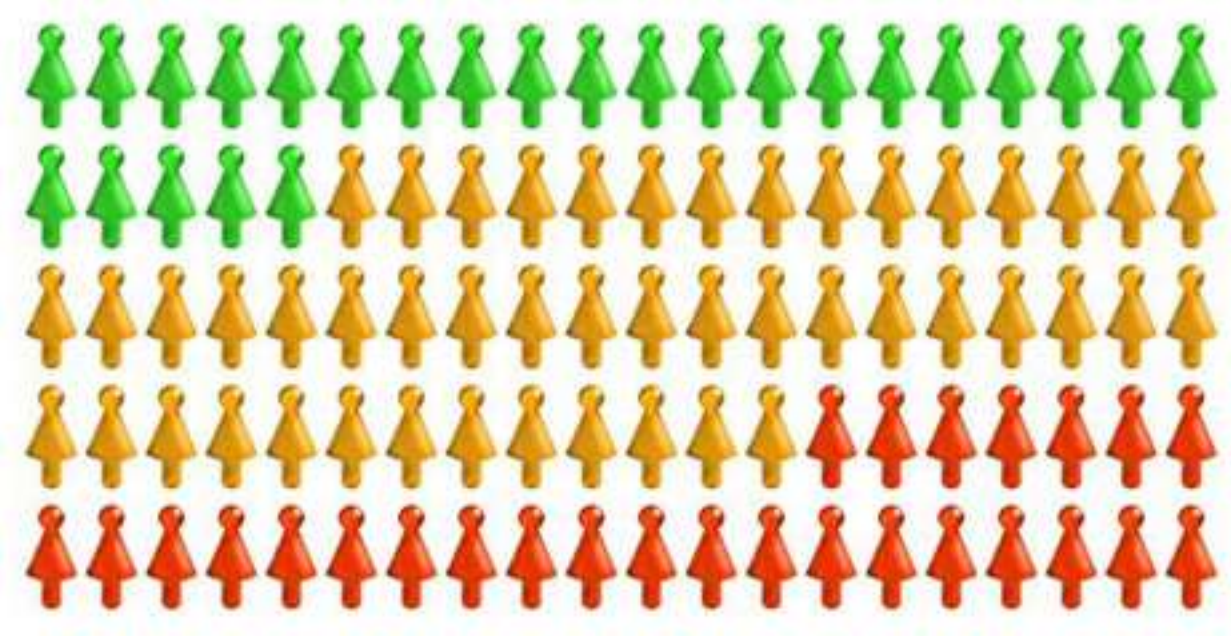
Only 25% will develop distant metastases



But we treat over 75% of all patients with chemotherapy



50% of all breast cancer patients get a toxic chemotherapy they did not need!

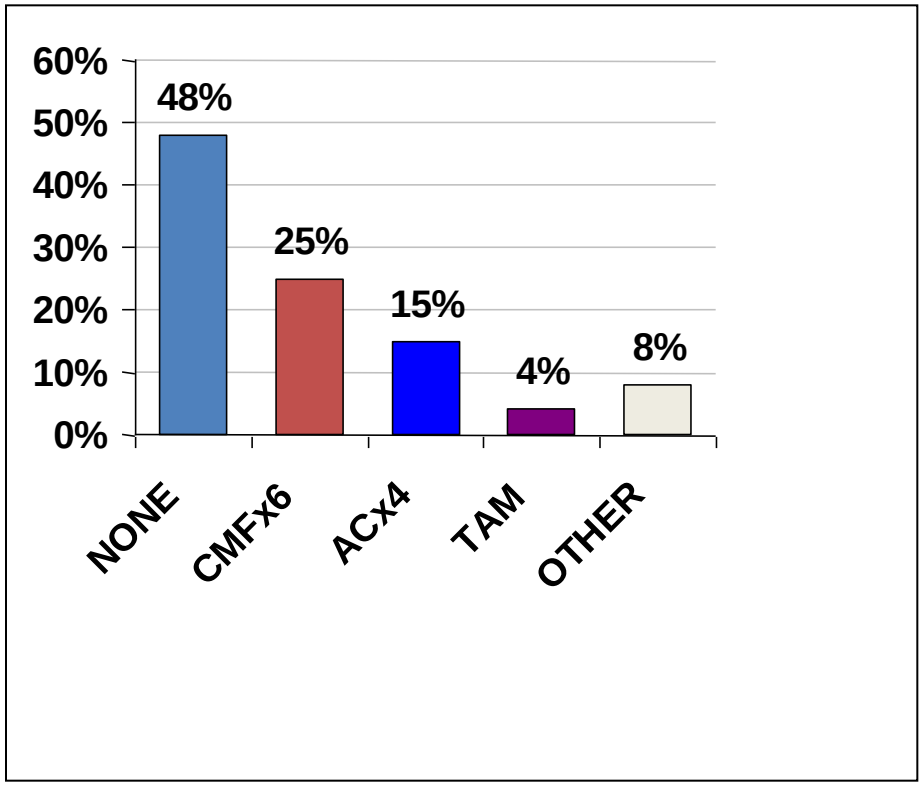


Breast Cancer: The Treatment Dilemma

61 y-old, fit, postmenopausal

Node negative
pT = 0.9 cm
ductal cancer
ER and PR negative
HER2 negative
Grade 2

Choices of 40 experts world-wide



Courtesy: Martine Piccart

Clinical applications of microarrays

Who to treat:

- Prognostic profiles as diagnostic tool
  -> improved selection for adjuvant therapy

How to treat:

- Predictive profiles for drug response
  -> selection of patients who will benefit most

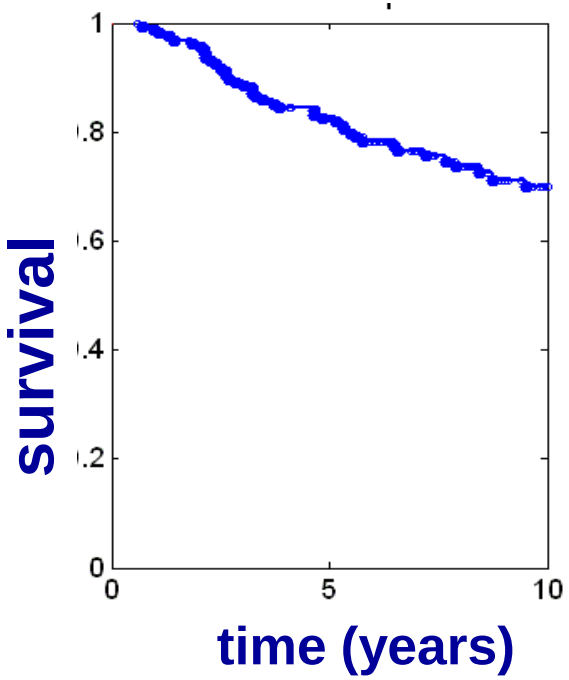
Gene expression profiling predicts clinical outcome of breast cancer

Van ‘t Veer, et. al., *Nature*, (415): 2002,530-536.

Aim:
to determine whether gene expression profiling could predict disease outcome and provide a strategy to select patients who would benefit from adjuvant therapy (metastasis)

Breast Cancer – Survival Pre-menopausal patients, lymph node negative

traditional diagnostics



~30% die <10 year

~70% survive >10 year

Everyone receives chemotherapy...!

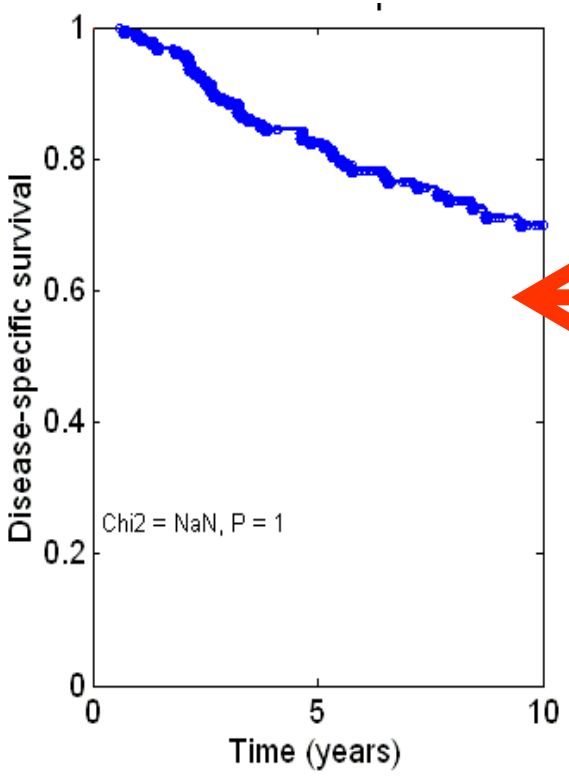
Breast Cancer – Survival Pre-menopausal patients, lymph node negative

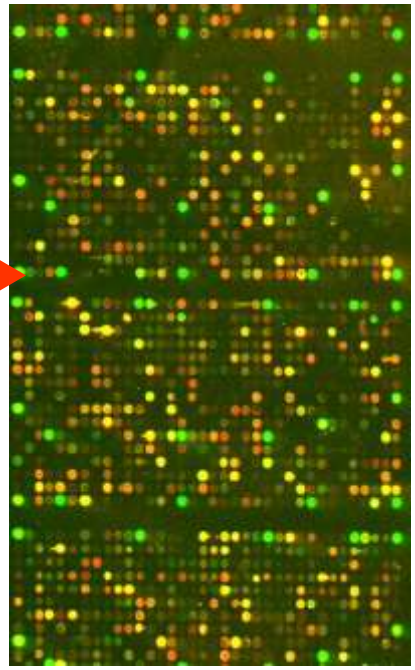
Current adjuvant treatment selection criteria:

- NIH (US) consensus criteria: > 95%
- St Gallen (EU) consensus criteria: > 80%
  receive adjuvant chemo- and hormonal therapy

As only 30% of these patients develop distant metastases, some 50-65% of patients are over-treated with adjuvant (chemo)therapy

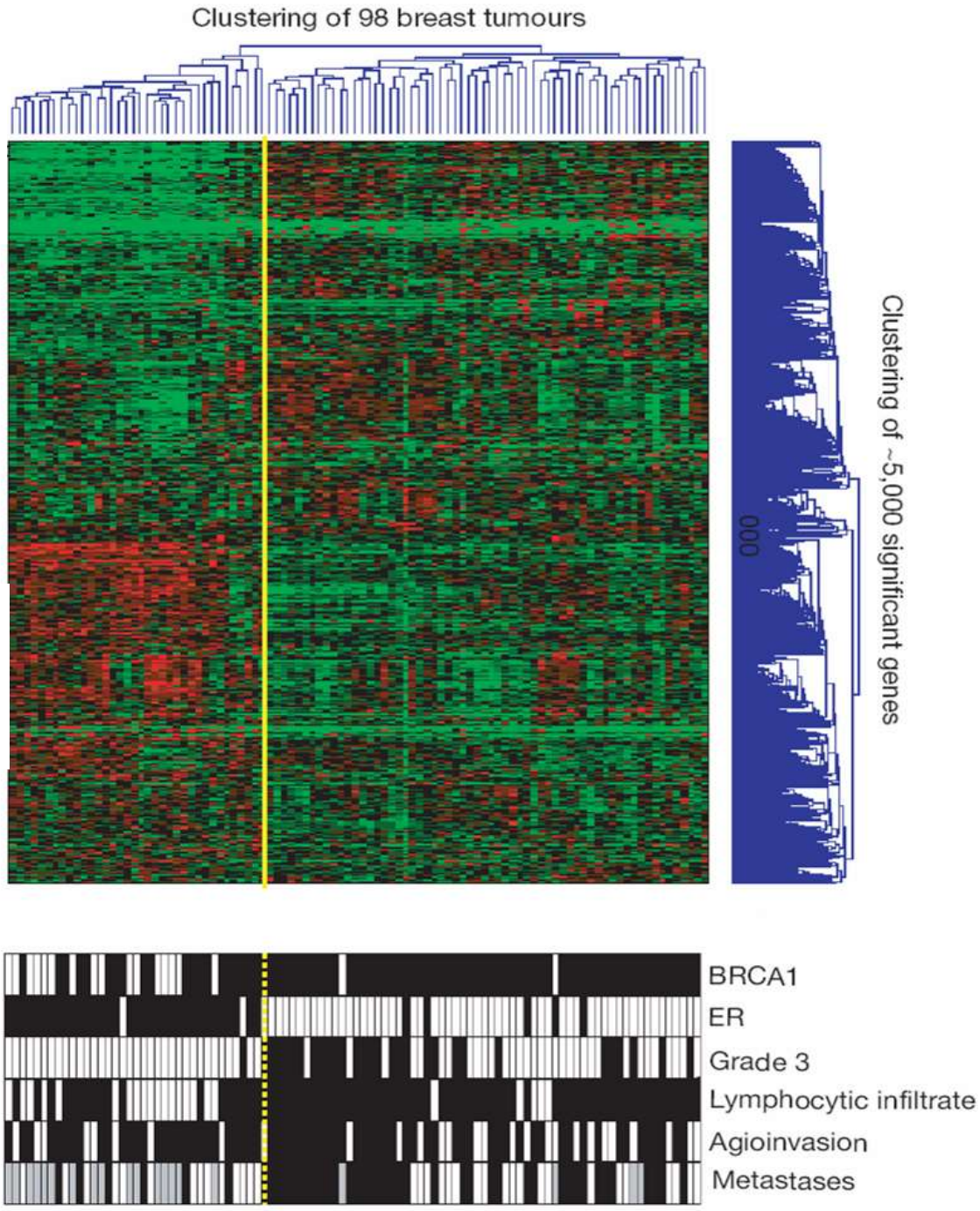
Identification of gene expression changes in breast cancer





- analyse 98 breast tumors
- 34 metastases-positive <5 year
  - bad prognosis
- 44 metastases-negative >5 year
  - good prognosis
- 18 BRCA1 +
- 2 BRCA2 +

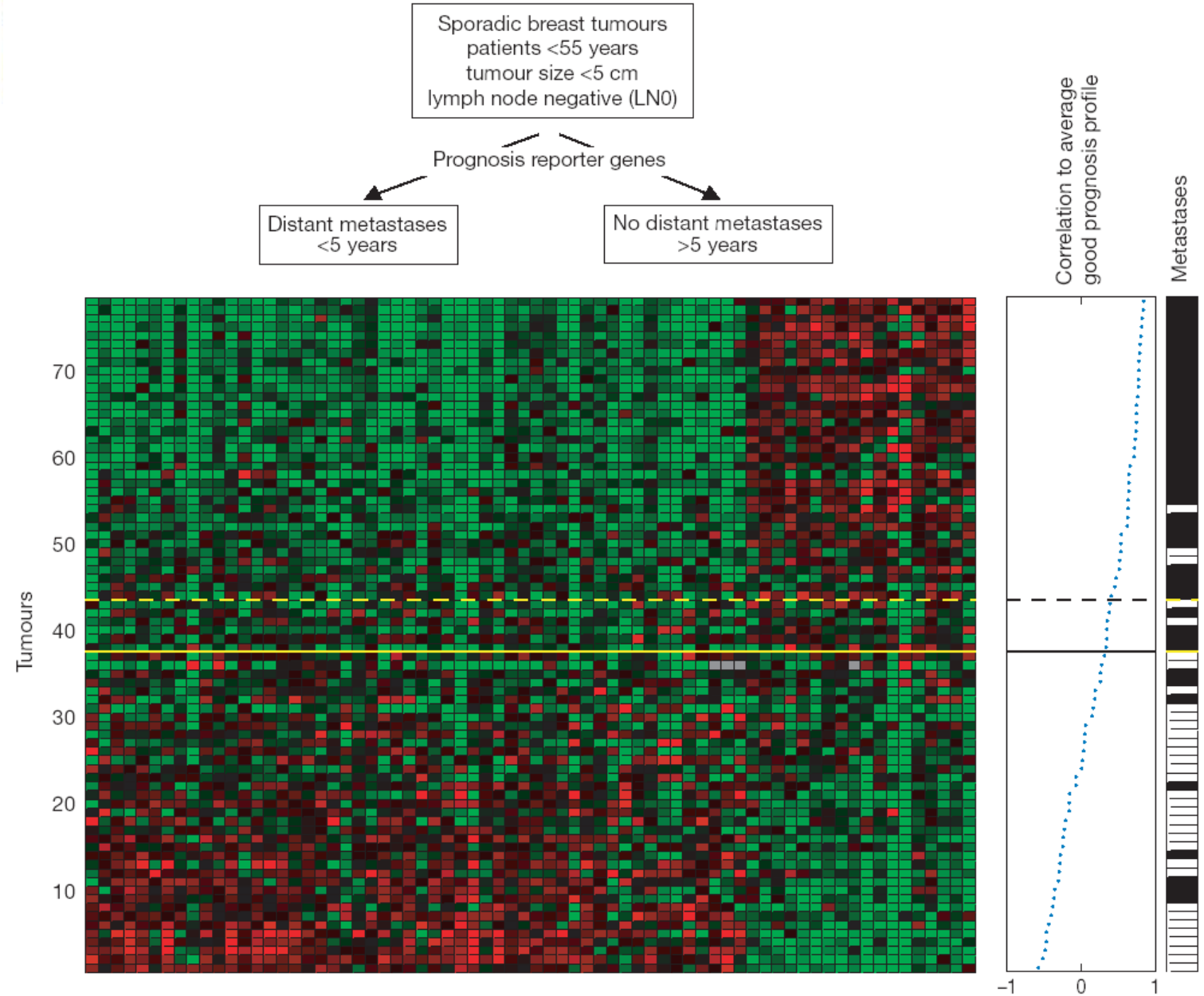
'sporadic'



- 98 breast tumors analysed
  - 34 ‘bad’ vs. 44 ‘good’
  - 18 BRCA1 +
  - 2 BRCA2 +
- microarray with 24.000 genes
- 5.000 genes showed expressional changes in tumors

Different classes of breast tumors...!

70-gene prognosis classifier for predicting risk of distant metastasis within 5 years



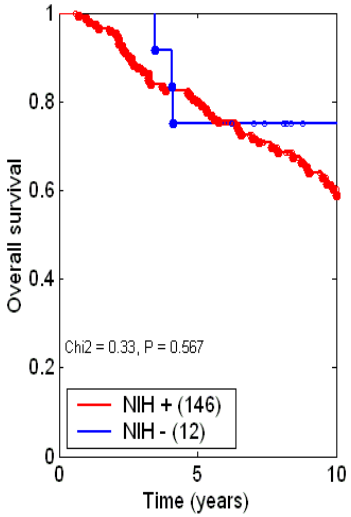
Supervised clustering

Good prognosis

Poor prognosis

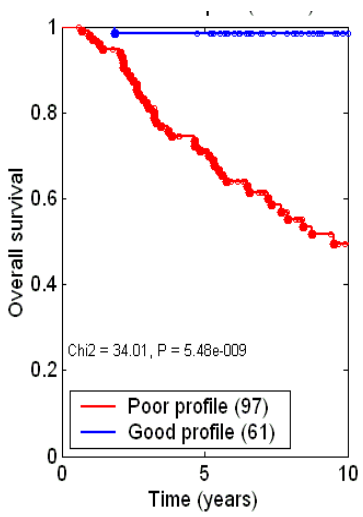
Microarray classification vs. NIH classification

5 % low risk
95 % high risk



Classical
NIH classification

39 % low risk
61 % high risk

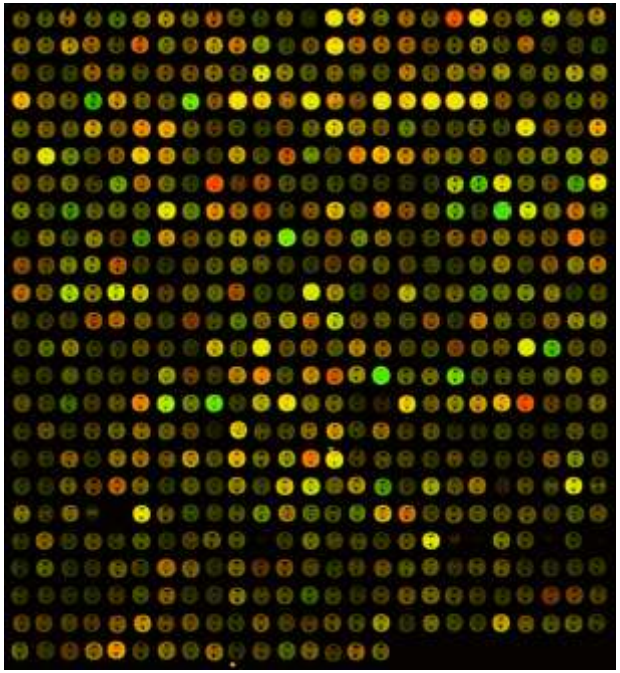


Classification based
on microarray

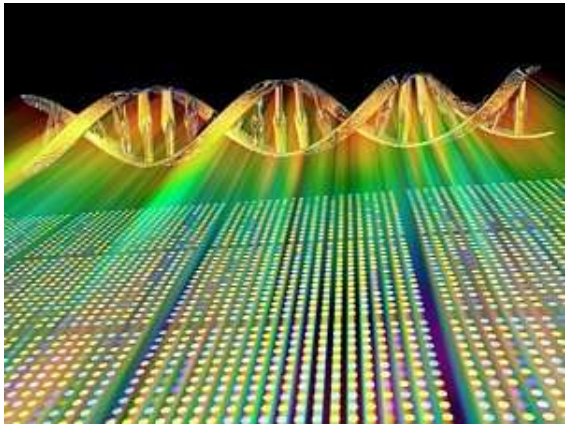
- Classification of 158 breast cancer tumors
- Less unnecessary chemo-therapy
- Identification of genes playing a role in breast cancer

Microarray to be used as routine clinical screen

by C. M. Schubert
Nature Medicine
9, ***9***, *2003.*



The Netherlands Cancer Institute in Amsterdam is the first institution in the world to use microarray techniques for the routine prognostic screening of cancer patients. Aiming for a June 2003 start date, the center will use a panoply of 70 genes to assess the tumor profile of breast cancer patients and to determine which women will receive adjuvant treatment after surgery.



Expression profiling & clinical application

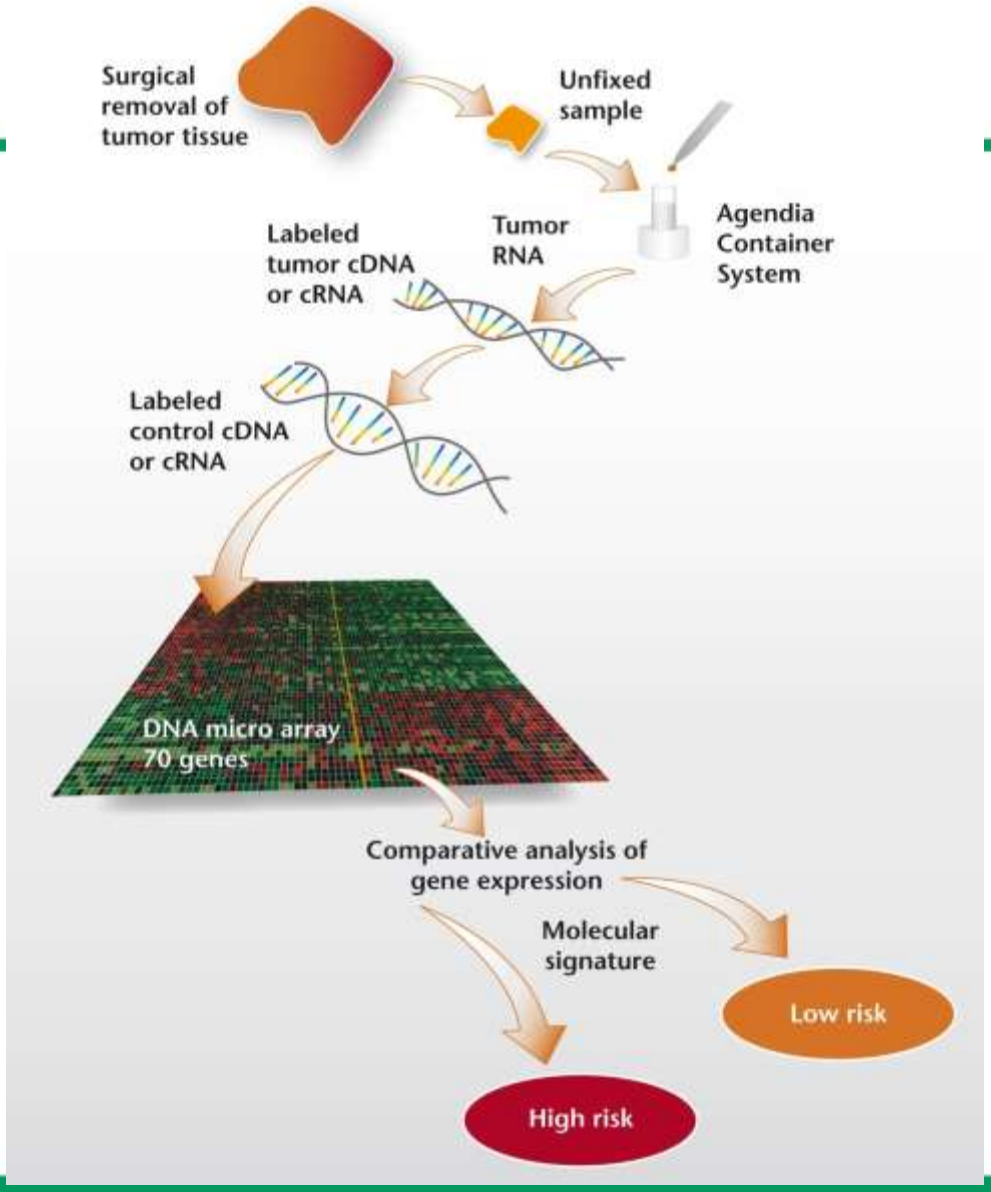
"Though each tumor is molecularly unique, there exist common transcriptional cassettes that underlie biological and clinical properties of tumors that may be of diagnostic, prognostic and therapeutic significance".

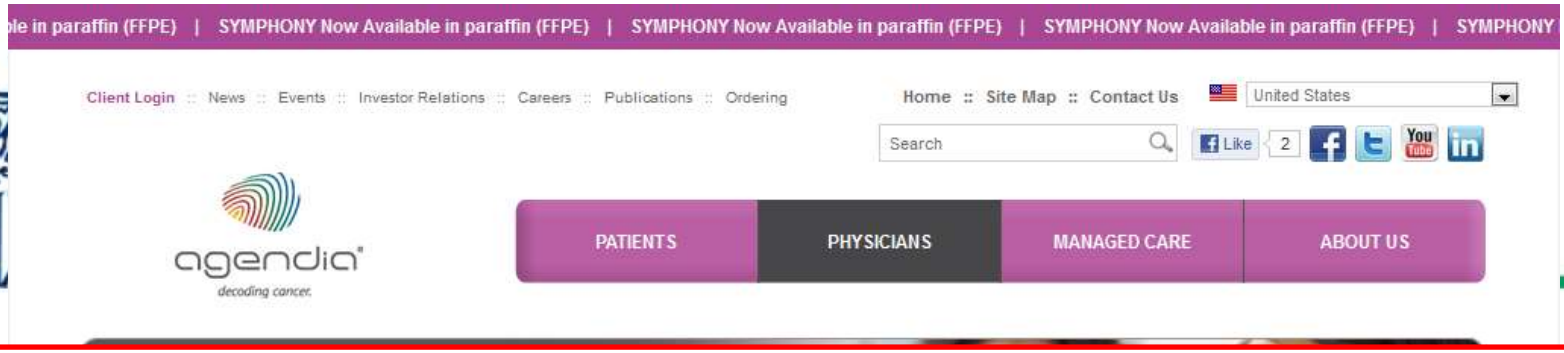
→ Also true for other complex diseases

agendia®

decoding cancer.

mammaprint



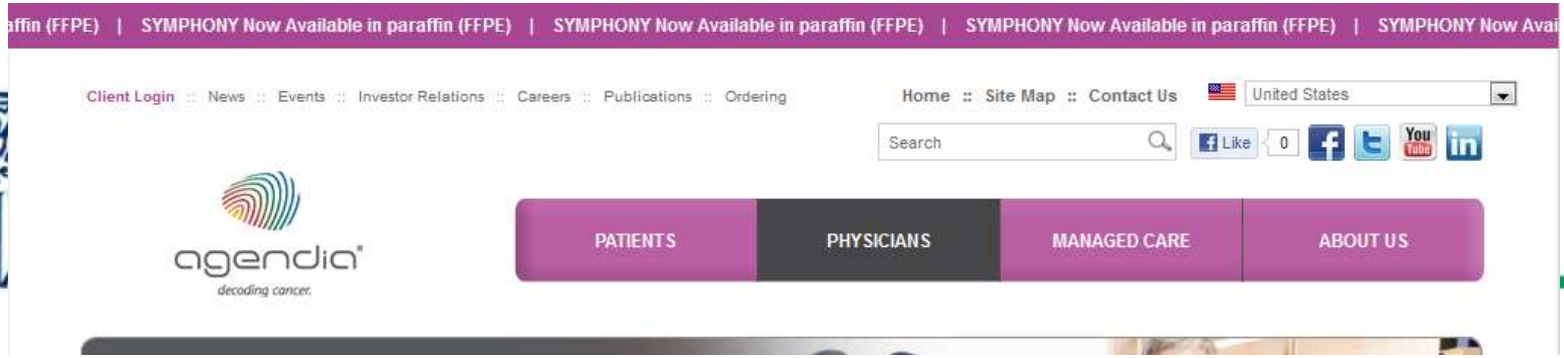


MammaPrint is the first and only FDA-cleared IVDMIA breast cancer recurrence assay. The unique 70-gene signature of MammaPrint provides you with the unprecedented ability to identify which early-stage breast cancer patients are at risk of distant recurrence following surgery, independent of Estrogen Receptor status and any prior treatment.

Unlike previous generation genomic tests, MammaPrint interrogates all of the critical molecular pathways involved in the breast cancer metastatic cascade. It analyzes 70 critical genes that comprise a definitive gene expression signature and stratifies patients into two distinct groups — low risk or high risk of distant recurrence. With MammaPrint, there are no intermediate results.

Hormonal therapy alone (e.g. Tamoxifen) may be sufficient to further reduce her risk if your patient is Low Risk by MammaPrint, when combined with traditional risk factors. Conversely, if she is High Risk by MammaPrint and has additional risk variables, more aggressive therapy including chemotherapy may be recommended.

With MammaPrint, you gain vital insights into the aggressiveness of your patient's tumor allowing you to tailor your treatment protocol to your patient's individual needs.

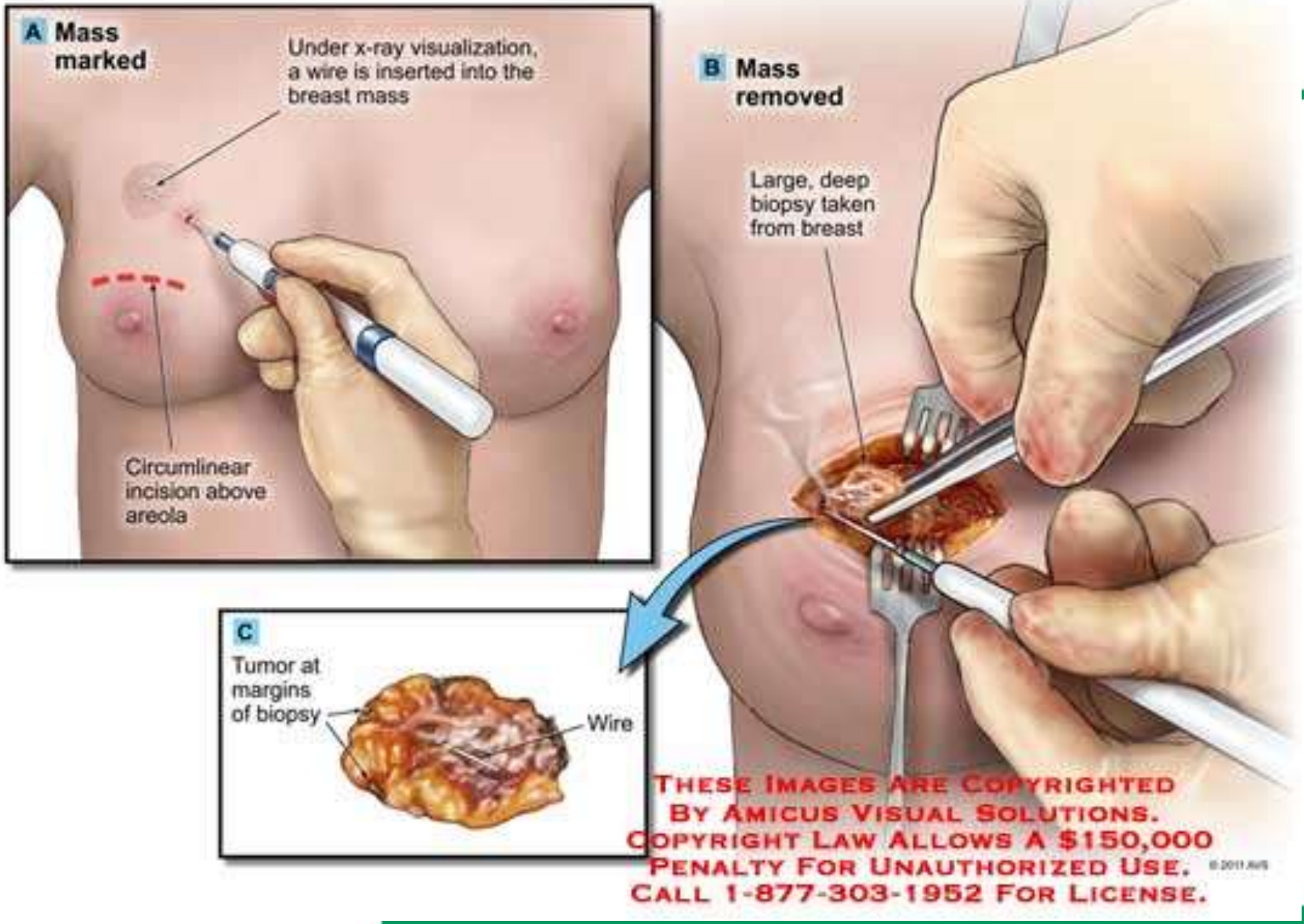


Agendia is at the forefront of the personalized medicine revolution, striving to bring more effective, individualized treatment within reach of cancer patients. Leveraging the advancements generated by the Human Genome Project and a cutting edge genomics platform for tumor gene expression profiling, Agendia's tests are designed to help physicians more accurately individualize cancer therapy. Agendia currently markets four products around the world, with several new genomic tests in development, and was the first to successfully achieve FDA clearance under the new IVDMIA guidance.

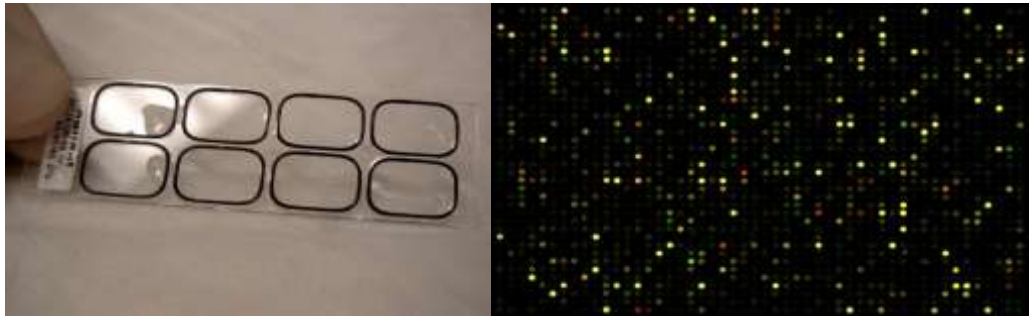
With MammaPrint®, you and your patients have an FDA-cleared test that can help deliver more personalized treatment. MammaPrint provides you with an accurate assessment of your patients' true risk of breast cancer metastases, thereby aiding you in determining the need for adjuvant chemotherapy. With TargetPrint®, you receive accurate quantitative results of Estrogen Receptor, Progesterone Receptor and HER2 gene expression levels, adding to traditional clinico-pathologic findings and allowing more informed prognosis and treatment decisions.

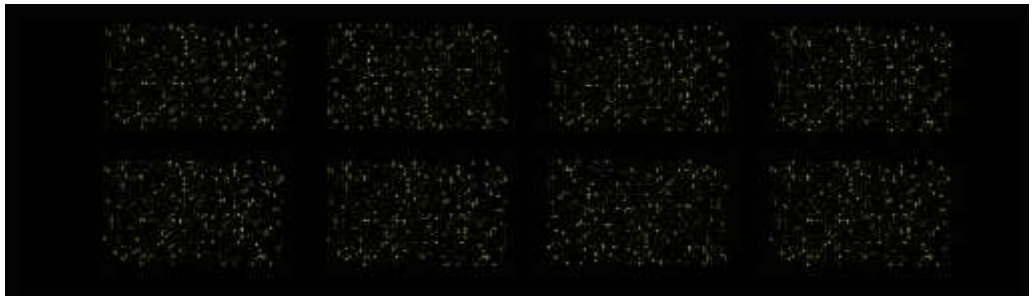
Agendia performs testing at its state-of-the-art CLIA (Clinical Laboratory Improvement Act) and CAP (College of American Pathologists) registered and compliant genomics laboratories in Irvine, California and Amsterdam, The Netherlands.

[redacted]'s 11/19/01 Right Breast Biopsy



Agendia's breast cancer prognosis test: MammaPrint





mammaprint™

decoding breast cancer.

The diagnostic microarray

- 8-pack custom array produced by *Agilent Technologies*
- Each subarrays has 15,000 genes
- Per subarray the genes of the prognostic profiles are printed 5-times
- Additionally, each subarray includes hundreds of normalization genes and data points for hybridization and quality control

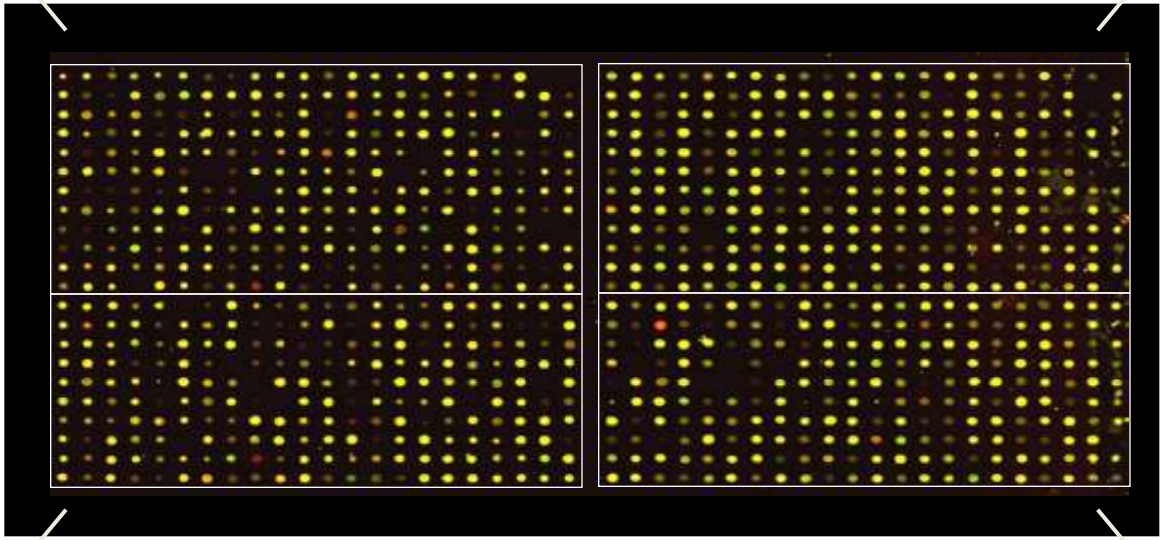
agendia

Personalized medicine:

multiple answers on a single microarray chip

Prognosis?

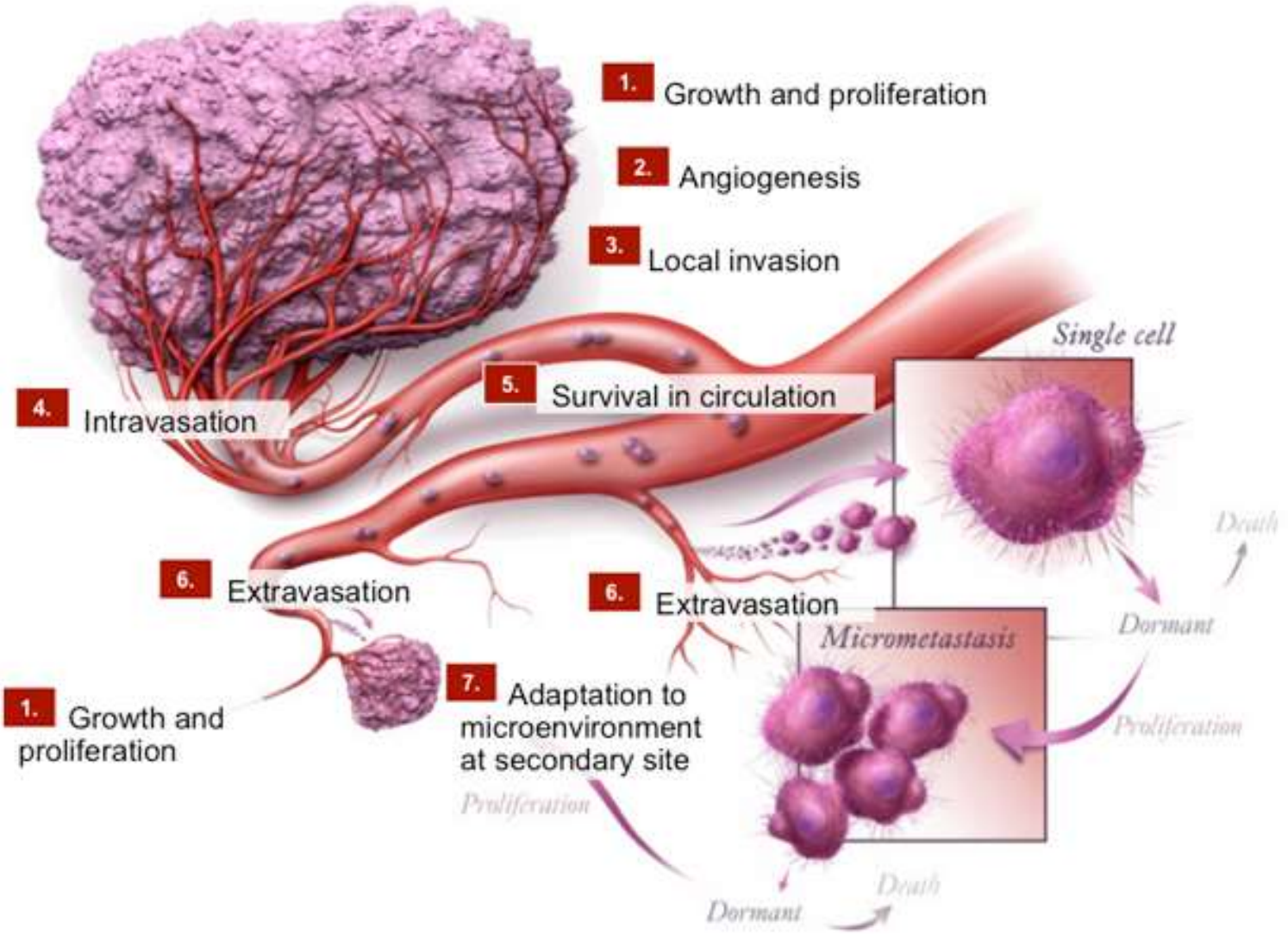
Is there a BRCA1 mutation?



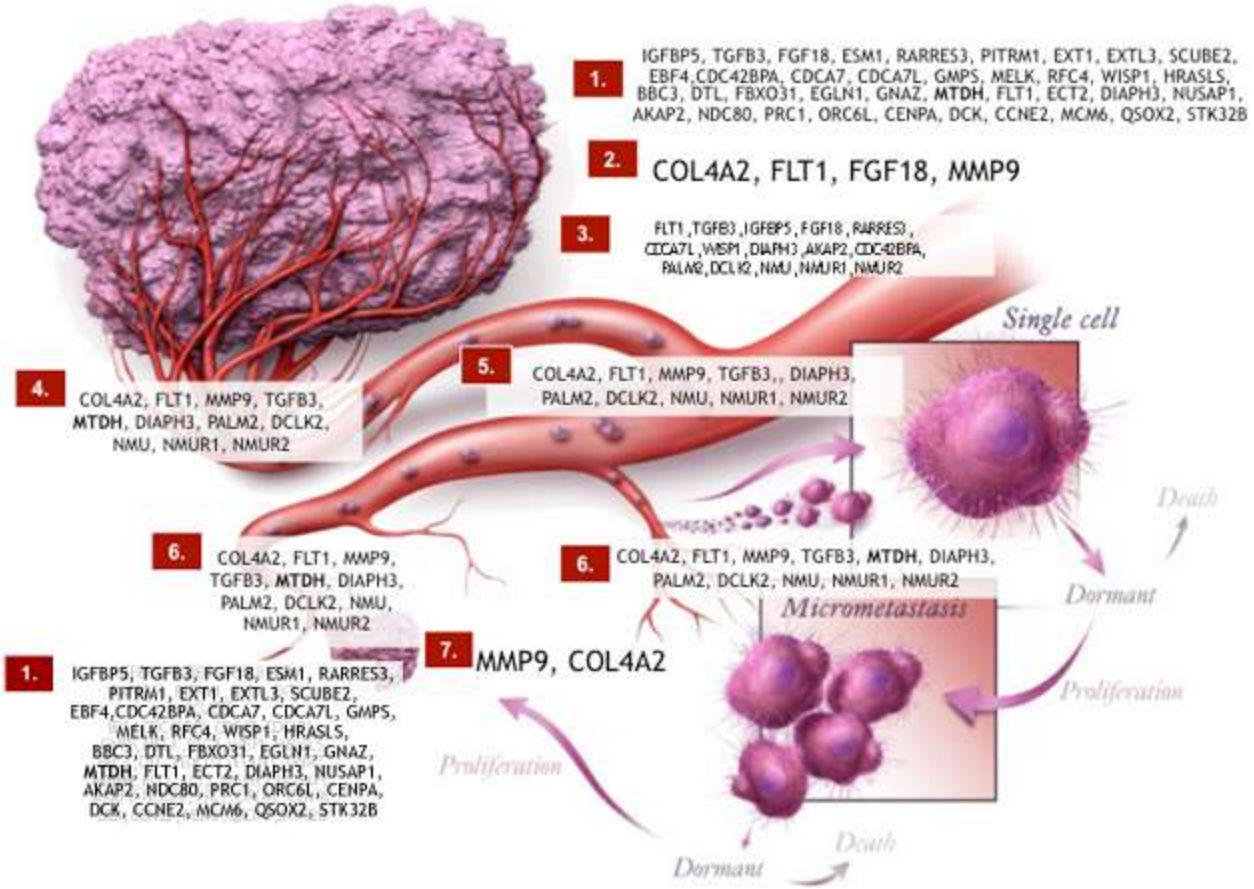
Will tumor respond to Herceptin?

Will tumor respond to crosslinking agents?

MammaPrint® interrogates critical genomic pathways



MammaPrint® interrogates critical genomic pathways



MammaPrint® has extensive clinical validation in an international patient cohort

Validation Study	Country	Reference	Years					
			2002	2004	2006	2007	2008	2009
MammaPrint Discovery		van 't Veer et al, Nature	78					
Primary Validation Study		van de Vijver et al, NEJM		295				
Independent European study		Buyse et al JNCI			302			
Dutch patient cohort		de Mesquita et al, Fur J Can			123			
Prospective Study		de Mesquita et al, Lancet Oncology				427		
Core Needle biopsies		Mayordomo et al, ESMO Meeting					35	
Validation in Older US patients		Wittner et al, Clin Cancer Res					100	
Validation in 1-3 LN+ patients		Mook et al, Breast Cancer Res Treat.					241	
Postmenopausal patients (>61)		Mook et al, (submitted) / SABCS					148	
Patients treated with Tamoxifen		Kok et al, (submitted)						192
German Patient Cohort		Kunz et al, St. Gallen Conference						140
Japenese patient cohort		Ishitobi et al, Jap Breast Cancer Symp						118
Validation in 4-9 LN+ patients		Saghastchian et al, St. Gallen Conf						167
Neoadjuvant predictive study		Straver et al, Breast Cancer Res Treat						162
Predictiveness (Meta-analysis) study		Bender et al, ASCO 2009 Conference						1,696

Validated on over 2,375 Patients

agendia

Regulatory Requirements: Lab

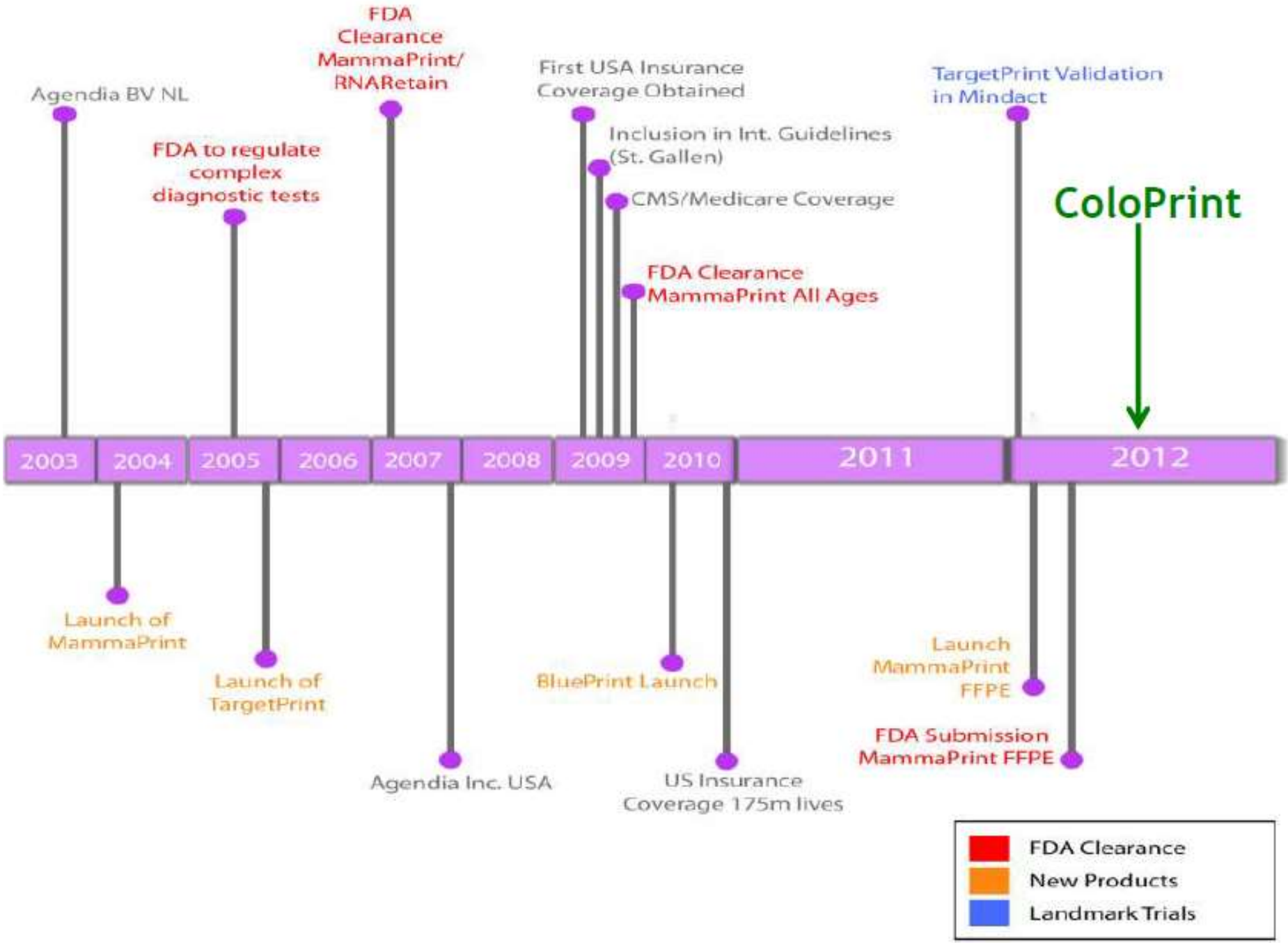
MammaPrint is the first multi-variate molecular diagnostic test cleared by FDA

ISO 17025 accredited and CE marked for European market

CLIA registered

College of American Pathologists (CAP) Accredited

agendia


Agendia BV NL
FDA to regulate complex diagnostic tests
FDA Clearance MammaPrint/ RNARetain
First USA Insurance Coverage Obtained
Inclusion in Int. Guidelines (St. Gallen)
CMS/Medicare Coverage
FDA Clearance MammaPrint All Ages
TargetPrint Validation in Mindact
ColoPrint
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
Launch of MammaPrint
Launch of TargetPrint
Agendia Inc. USA
BluePrint Launch
US Insurance Coverage 175m lives
Launch MammaPrint FFPE
FDA Submission MammaPrint FFPE
FDA Clearance
New Products
Landmark Trials

MammaPrint's FDA Indication – Patient Eligibility in the USA

Breast cancer recurrence and/or metastasis is partly dependent on the activation and suppression of certain genes located within the primary breast tumor. MammaPrint is a genomics test which uses the latest microarray technology to analyze a patient's breast tumor biology to predict whether existing cancer has the wherewithal to metastasize. This 70-gene profile is validated as an independent indicator for breast cancer prognosis for women with lymph node-negative, estrogen receptor positive and estrogen receptor negative disease.

To be eligible for the MammaPrint gene expression profile, a breast cancer patient should fulfill the following criteria:

- Breast Cancer Stage 1 or Stage 2
- Invasive carcinoma (infiltrating carcinoma)
- Tumor size <5.0 cm
- Lymph node negative
- Estrogen receptor positive (ER+) or Estrogen receptor negative (ER-)
- Women of all ages

MammaPrint provides powerful insights into a patient's breast cancer risk of recurrence and need for adjuvant therapy. When making breast cancer treatment decisions for your patients, regarding hormone therapy (Tamoxifen) alone or in conjunction with chemotherapy, it is important to consider a woman's clinical and pathology related risk factors to determine the best treatment plan and potential response to systemic adjuvant therapy.

MammaPrint® – Patient Eligibility Internationally (Outside of the USA)

Breast cancer recurrence and/or metastasis is partly dependent on the activation and suppression of certain genes located within the primary breast tumor. MammaPrint is a genomics test which uses the latest microarray technology to analyze a patient's breast tumor biology to predict whether existing cancer has the wherewithal to metastasize. This 70-gene profile is validated as an independent indicator for breast cancer prognosis for women with invasive carcinoma tumors 5 cm or less, estrogen receptor positive and estrogen receptor negative disease up to 3 lymph nodes positive.

To be eligible for the MammaPrint gene expression profile, a breast cancer patient should fulfill the following criteria:

- Breast Cancer Stage 1 or Stage 2
- Invasive carcinoma (infiltrating carcinoma)
- Tumor size <5.0 cm
- Lymph node status: negative or positive (up to 3 nodes)
- ER+ or ER-

MammaPrint provides powerful insights into a patient's breast cancer risk of recurrence and need for adjuvant therapy. When making breast cancer treatment decisions for your patients, regarding hormone therapy (e.g. Tamoxifen) alone or in conjunction with chemotherapy, it is important to consider a woman's clinical and pathology related risk factors to determine the best treatment plan and potential response to systemic adjuvant therapy.

Select Country

- USA
- Austria
- Belgium
- Canada
- France
- Germany
- Israel
- Italy
- Japan
- Korea
- Luxemburg
- Mexico
- Netherlands
- New Zealand
- Portugal
- South Africa
- Spain
- Switzerland
- All Others

Specimen Requirements (Fresh)

- The Symphony profile tests can be performed on core needle biopsies or tissue taken from a surgical specimen.
- Fresh specimen (3x3mm, tic tac size) in RNARetain®

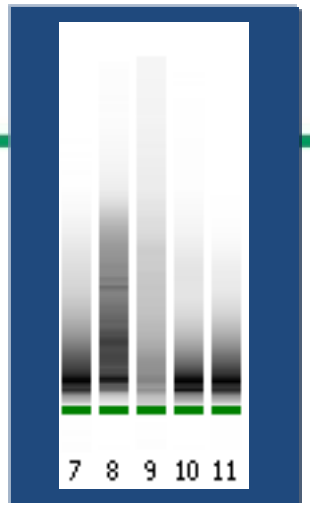
Specimen Requirements (FFPE...coming early 2012)

- Block with invasive tumor *OR*
- 10 unstained slides with 5µm section on each slide

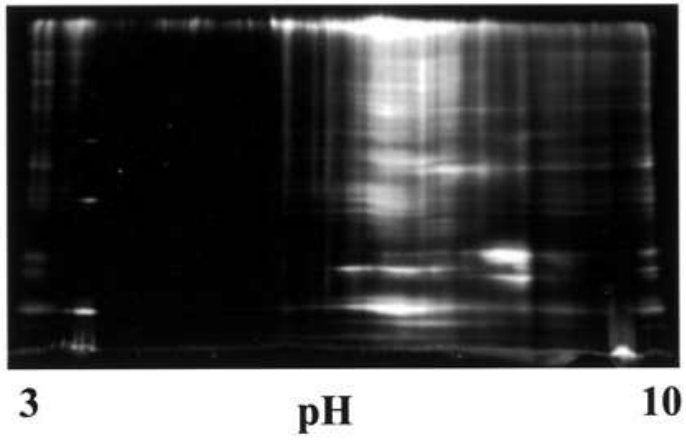
Formalin-Fixed Paraffin-Embedded

Poor quality biomolecules: poor quality biomarkers!

FFPE

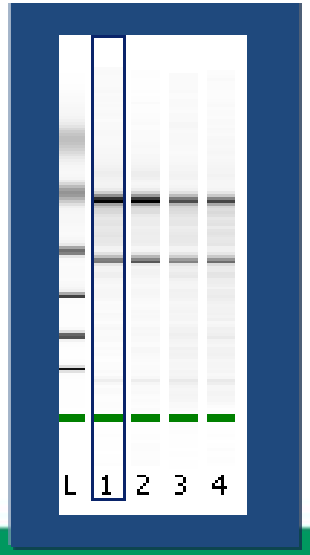


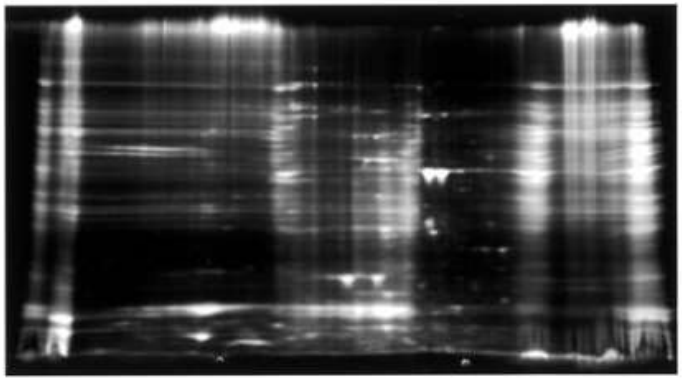
RNA integrity



Protein integrity

Frozen





Understanding Health Insurance Coverage for SYMPHONY™ in the USA

Making personalized medicine available for your breast cancer patients

Agendia's mission is to provide all breast cancer patients access to Agendia's Symphony™ Breast Cancer Decision Suite, which includes, MammaPrint®, BluePrint™, TargetPrint®, and TheraPrint®, to help physicians and patients make more informed, personalized therapy decisions. Agendia understands that costs associated with the patient's diagnosis, treatment, and management of their breast cancer can possibly pose a financial hardship and may influence a patient's decision in selecting diagnostic and treatment options.

Agendia has established excellent coverage for Symphony breast cancer tests and is billing insurance companies on behalf of insured patients throughout the United States. Based on the patient's specific benefit level, the insurance companies will pay a portion or all of the cost submitted for the Symphony tests. Patients are responsible for their co-insurance, co-pay, or deductible per their health insurance plan. For more information about medical insurance coverage questions, please review the Frequently Asked Questions (FAQ's) page.

financial needs:

- Uninsured patient assistance
- Indigent patient assistance
- Underinsured patient assistance
- Interest-free payment plans

Agendia remains dedicated to providing physicians and their patients the very best in diagnostic testing and customer support. For questions regarding a patient's specific level of coverage, please contact Agendia:

e: billing@agendia.com

p: 888-363-7868

mammaprint®

decoding breast cancer.

CUSTOMER		SPECIMEN		PATIENT	
Doctor:	Marian P. McDonald	Requisition #:	12345678	Patient:	(anonymized)
Account:	St. Luke's Hospital - Allentown	Collection Date:	Jun-01-2010	DOB:	(anonymized)
Address:	1901 Hamilton Street Suite 100	Date Received:	Jun-03-2010	Patient #:	(anonymized)
		Report Date:	Jul-21-2010	Gender:	(anonymized)
		Specimen Type:	FFPE, Core	SSN:	(anonymized)
City, St., Zip:	Allentown PA 18104	Customer Ref.:	MRN123456		

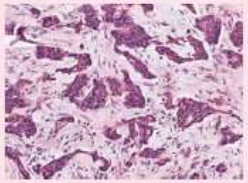
Gene Profile Test Result

HIGH RISK

The breast cancer tissue sample submitted was analyzed by MammaPrint, an IVDMIA 70-Gene Profile of Breast Cancer for Metastatic Risk that has been validated to correlate with high or low outcome risk for distant metastases in patients with invasive breast cancer.[1] In a consecutive series of 131 patients, "High Risk" means that a lymph node negative patient 61 years of age or older has a 22% (95% CI 12-38) chance that their cancer will recur within 5 years without any additional adjuvant treatment, either hormonal therapy or chemotherapy.

Clinicopathologic Findings

Tumor Cell Percentage: 30%



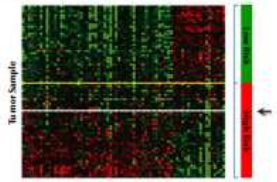
RNA Integrity Score: 5.0

The reported tumor cell percentage and pathology comments serve as a quality control for Agendia's genomic assays and should not be viewed as a diagnosis of the presence or absence of malignancy.

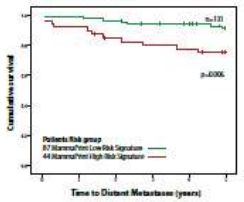
Assay Description

The U.S. Food and Drug Administration (FDA) has provided IVDMIA clearance of MammaPrint with fresh tissue for Stage I and II, lymph node negative, invasive breast cancer, for patients of all ages who have a tumor of 5 cm or less, independent of estrogen receptor status (ER+/-), based upon the development and validation of the assay as reported in *Nature, New England Journal of Medicine, Journal of the National Cancer Institute and BMC Genomics*.[2-5] The test is performed using a microarray-based gene expression profile that was independently validated on 10 year outcome data on an untreated patient cohort.[2] An unbiased, supervised analysis of the entire human genome, ~25,000 genes, followed by a leave-one-out cross-validation procedure, revealed the 70 critical genes that distinguish patients at High Risk vs. Low Risk of metastasis.[3] Based on the analytical performance of MammaPrint, the accuracy of classifying a sample as High Risk or Low Risk is 98.9% with reproducibility of the measurement being 98.5%.[1] MammaPrint has been validated in over 774 breast cancer patients and shown to provide information independent of clinicopathological risk assessment.[2,4,5]

MammaPrint® Breast Cancer Gene Profile[3]



Above 61 Years Validation Results



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mammaprint®

decoding breast cancer.

Sample Report

CUSTOMER		SPECIMEN		PATIENT	
Doctor:	Marian P. McDonald	Requisition #:	12345678	Patient:	(anonymized)
Account:	St. Luke's Hospital - Allentown	Collection Date:	Jun-01-2010	DOB:	(anonymized)
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		Report Date:	Jul-21-2010	Gender:	(anonymized)
		Specimen Type:	FFPE, Core	SSN:	(anonymized)
City, St., Zip:	Allentown PA 18104	Customer Ref.:	MRN123456		

Pathology/Additional Comments:

None

References:

1) FDA Label - USFDA Clearance; http://www.accessdata.fda.gov website.
2) Buyse M, Loi S, van 't Veer LJ, et. al., J Natl Cancer Inst 2006; 98(17):1183-1192
3) van 't Veer LJ, Dai H, van de Vijver MJ, et. al., Nature 2002; 415(31): 530-536
4) van de Vijver MJ, He YD, van 't Veer LJ, et. al., New Engl J Med 2002; 347(25): 1999-2009
5) Glas AM, Floore A, Delahaye LJ, et. al., BMC Genomics 2006; 7: 278

Sign Off

Chynel Hanning, MD.

Chynel F. Hanning, MD, PhD, FASCP, FCAP
Pathologist
Laboratory Director

For *In Vitro* Diagnostic Use

Caution: Federal law restricts this device to sale by or on the order of a physician.

Agendia, Inc (05D1089250) is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. MammaPrint is a Laboratory Developed Test regulated under CLIA by CMS. MammaPrint is an aid in estimating the prognosis of patients diagnosed with breast cancer. Decisions regarding care and treatment should not be based on a single test such as this test. Rather, decisions on care and treatment should be based on the independent medical judgment of the treating physician taking into consideration all available information concerning the patient's condition, including other pathological tests, in accordance with the standard of care in a given community. MammaPrint was developed using adjuvantly untreated lymph node negative, mainly European, patients to capture the biology of the primary tumor in a gene expression profile. The metastasis free survival data is from an independent external patient group in Europe.

This test was performed at Agendia's Irvine, California laboratory.

General information about MammaPrint can be found at www.agendia.com.

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mammaprint®

decoding breast cancer.

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City, St., Zip:	Allentown PA 18104	Report Date:	Jul-21-2010	Gender:	(anonymized)
		Specimen Type:	FFPE, Core	SSN:	(anonymized)
		Customer Ref.:	MRN123456		

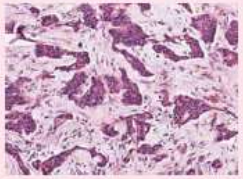
Gene Profile Test Result

LOW RISK

The breast cancer tissue sample submitted was analyzed by MammaPrint, an IVDMIA 70-Gene Profile of Breast Cancer for Metastatic Risk that has been validated to correlate with high or low outcome risk for distant metastases in patients with invasive breast cancer.[1] In a consecutive series of 131 patients, "Low Risk" means that a lymph node negative patient 61 years of age or older, has a 7% (95% CI 3-15) chance that their cancer will recur within 5 years without any additional adjuvant treatment, either hormonal therapy or chemotherapy.

Clinicopathologic Findings

Tumor Cell Percentage: 30%



RNA Integrity Score: 5.0

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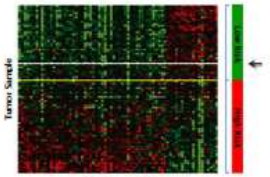
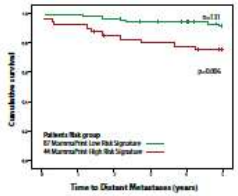
MammaPrint® Breast Cancer Gene Profile[3]



Above 61 Years Validation Results



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CUSTOMER		SPECIMEN		PATIENT	
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Account:	St. Lukes Hospital - Allentown	Collection Date:	Jun-01-2010	DOB:	(anonymized)
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		Specimen Type:	FFPE, Core	SSN:	(anonymized)
		Customer Ref.:	MRN123456		

Pathology/Additional Comments:

None

References:

1) FDA Label - USFDA Clearance; http://www.accessdata.fda.gov website.
2) Buyse M, Loi S, van 't Veer LJ, et. al., J Natl Cancer Inst 2006; 98(17):1183-1192
3) van 't Veer LJ, Dai H, van de Vijver MJ, et. al., Nature 2002; 415(31): 530-536
4) van de Vijver MJ, He YD, van 't Veer LJ, et. al., New Engl J Med 2002; 347(25): 1999-2009
5) Glas AM, Floore A, Delahaye LJ, et. al., BMC Genomics 2006; 7: 278

Sign Off

Chynel Henning, MD.

Chynel F. Henning, MD, PhD, FASCP, FCAP
Pathologist
Laboratory Director

For *in Vitro* Diagnostic Use

Caution: Federal law restricts this device to sale by or on the order of a physician.

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This test was performed at Agendia's Irvine, California laboratory.

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Tissue of Origin

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TISSUE OF ORIGIN®

Tissue of Origin®

The Tissue of Origin test, formally a Pathwork test, is a microarray-based gene expression test that aids in identifying challenging tumors, including metastatic, poorly differentiated, and undifferentiated cancers. TOO is the **ONLY** FDA-cleared test of its type and is a Medicare-reimbursed test.

Tissue of Origin® Overview

- The Tissue of Origin reports the most likely tissue of origin from 15 of the most common tumor types, representing 58 morphologies.
- 2000 genes, covering 15 tumors types and 90% of all solid tumors[1]
- Extensive analytical and clinical validation.
- Statistically significant improvement in accuracy over other methods, including IHC[2]
- Leads to a change in treatment 65% of the time.

Tissue of Origin® Overview

CHANGE IN DIAGNOSIS

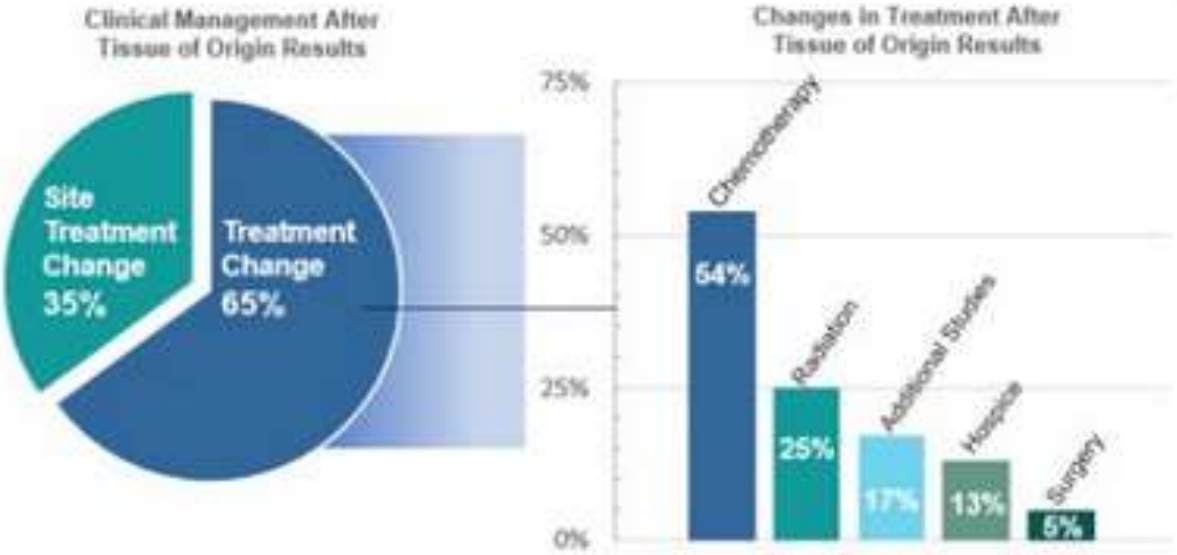
34% of the time CONFIRMS WORKING DIAGNOSIS

50% of the time IDENTIFIES A NEW SITE[3]

Tissue of Origin® Overview

CHANGE IN THERAPY

65% of the time LEADS TO CHANGE IN TREATMENT[3]



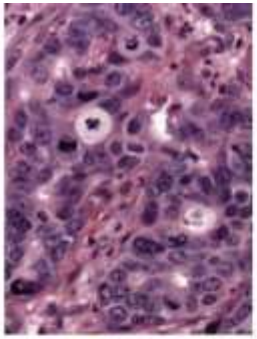
Methodology

CGI processes the specimen, runs the Tissue of Origin and reports the results to the ordering physician. Proprietary analytics are used to interpret the data, and a report is generated that provides clear, objective information on the Similarity Score for each of 15 tumor types, uniquely enabling the healthcare provider to rule in or rule out specific tumor types.

- Bladder
- Breast
- Colorectal
- Gastric
- Hepatocellular
- Kidney
- Melanoma
- Non-Hodgkin's Lymphoma
- Non-Small Cell Lung
- Ovarian
- Pancreas
- Prostate
- Sarcoma
- Testicular Germ Cell
- Thyroid

Each report includes a pathologist's interpretation of the test results.

How the Test Works



Tissue specimen

RNA extraction

cDNA synthesis

Labeled target preparation

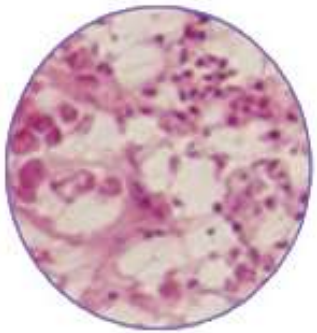
Hybridization to Pathchip microarray

Pathwork Analytic System

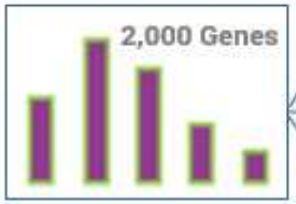
Tissue	Similarity Score	Low 0 5	High 100
Colorectal	88.2		◆
Pancreatic	4.4	◆	
Non-Small Cell Lung	2.3	◆	
Breast	2.1	◆	
Gastric	1.2	◆	
Kidney	0.6	◆	
Hepatocellular	0.3	◆	
Ovarian	0.3	◆	
Sarcoma	0.1	◆	
Non-Hodgkin's Lymphoma	0.1	◆	
Thyroid	0.1	◆	
Prostate	0.1	◆	
Melanoma	0.1	◆	
Bladder	0.1	◆	
Testicular Germ Cell	0.0	◆	

Report

How the Test Works



PATIENT RNA PROFILE GENERATED



PATIENT PROFILE COMPARED WITH KNOWN TISSUE PROFILES GENERATED

Similarity Scores Generated	
Colorectal	**88.2**
Pancreas	4.4
Non-small Cell Lung	2.3
Breast	2.1
Gastric	1.2
Kidney	0.6
Hepatocellular	0.3
Ovarian	0.3
Soft Tissue Sarcoma	0.1
Non-Hodgkin's Lymphoma	0.1
Thyroid	0.1
Prostate	0.1
Melanoma	0.1
Bladder	0.1
Testicular Germ Cell	0.0

Clinical Validation

The Tissue of Origin test is supported by extensive analytical and clinical validation data from robust, multi-center clinical studies.* The results of these studies are meaningful because they highlight the test's accuracy and reproducibility.

- A large-scale validation study was published in the January 2011 Journal of Molecular Diagnostics. The study comprised 462 metastatic, poorly differentiated, or undifferentiated tumor specimens that had been diagnosed using current methodologies: The test demonstrated 89% positive percent agreement (akin to sensitivity) with available diagnoses and 99% negative percent agreement (akin to specificity) using formalin-fixed, paraffin-embedded (FFPE) tumor specimens, the most common clinical specimen type.[1]
- In an independent validation study by the University of California, San Francisco published in Clinica Chimica Acta, 37 FFPE clinical specimens were tested using the Tissue of Origin test. In 95% of the cases, the test results were in agreement with the reference diagnosis.[2]
- The Tissue of Origin Endometrial test validation study was published in 2012 and looked at 75 specimens. Using 375 genes, the Test discriminated between Endometrial and Ovarian tissue with 95% accuracy. 14 histologic subtypes were included in the 75 specimens.[3]
- In 2013, the validation study for the Tissue of Origin Head & Neck test was published. The test uses 2,600 genes to discriminate between squamous lung and squamous Head & Neck cancer. 76 metastatic or poorly differentiated specimens were analyzed. The test was 83% accurate.[4]
- In a reproducibility analysis, the Tissue of Origin test demonstrated an average 89% overall concordance across three laboratories in a cross-laboratory comparison study of 149 metastatic and poorly differentiated and undifferentiated tissue specimens.[1]
- A study published in the journal Cancer Cytopathology demonstrated the capability of the Tissue of Origin test to be performed on a variety of body fluid cytology specimens preserved in FFPE. The test successfully yielded results in 89% of the specimens examined and correctly identified the available diagnosis with a 94.1% agreement.[5]

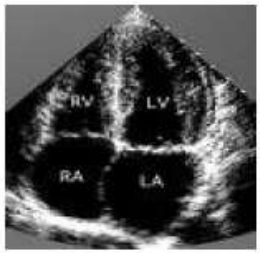
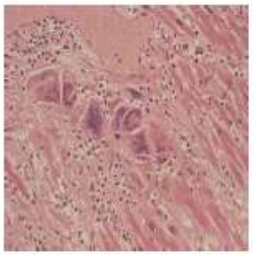
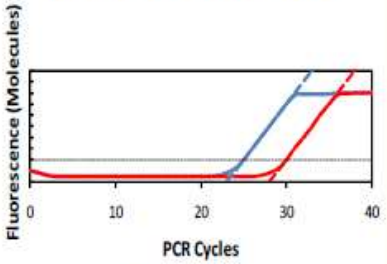
Tissue of Origin® Overview

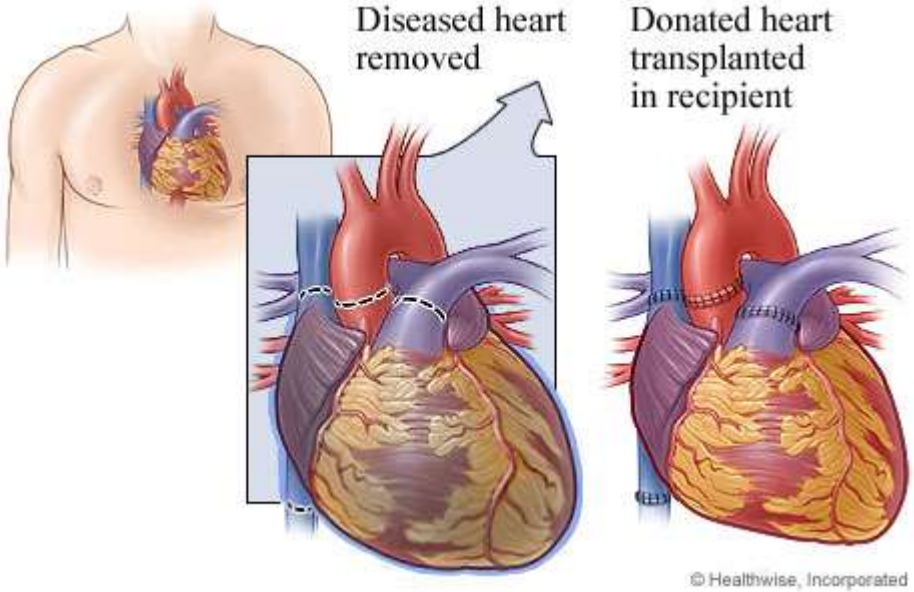
1. **Validation and Reproducibility of a Microarray-based Gene Expression Test for Identifying the Primary Site of Tumors in Formalin-Fixed Paraffin-Embedded Specimens**. *R Pillai, R Deeter, CT Rigl, JS Nystrom, M Halks Miller, L Buturovic, WD Henner. J Molec Diag 13 2011;13:48-56*
2. **A Multicenter Study Directly Comparing the Diagnostic Accuracy of Gene Expression Profiling and Immunohistochemistry for Primary Site Identification in Metastatic Tumors.** *CR Handorf, A Kulkarni, JP Grenert, L Weiss, W Rogers, O Kim, F Monzon, M Halks-Miller, G Anderson, M Walker, R Pillai, WD Henner. Am J Surg Pathol 2013;37:1067*
3. **Clinical Utility of Gene-Expression Profiling for Tumor-Site Origin in Patients with Metastatic or Poorly Differentiated Cancer: Impact on Diagnosis, Treatment, and Survival.** *JS Nystrom, J Hornberger, G Varadhachary, R Hornberger, H Gutierrez, WD Henner, S Becker, M Amin, M Walker. Oncotarget 2012 Jun;3(6):620-8*

AlloMap® Molecular Expression Testing

Subtitle

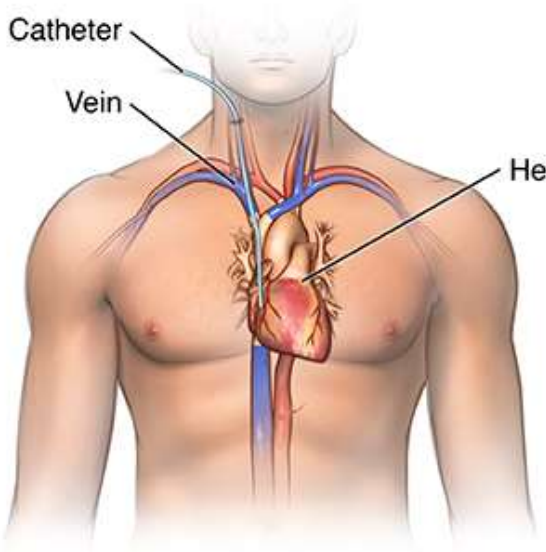
Management of the Heart Transplant Recipient

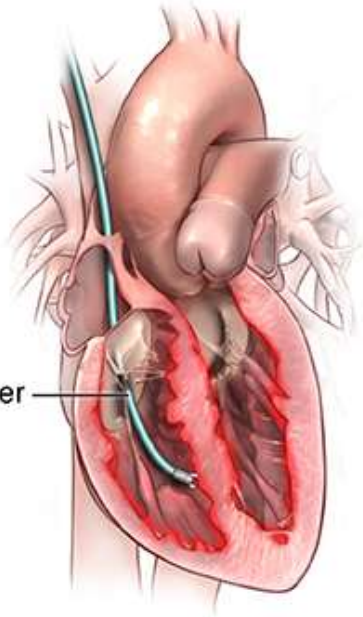
PATIENT	HEART	CELLULAR	MOLECULAR
			
History & Physical Exam	Hemodynamics	Endomyocardial Biopsy	AlloMap Molecular Expression Testing

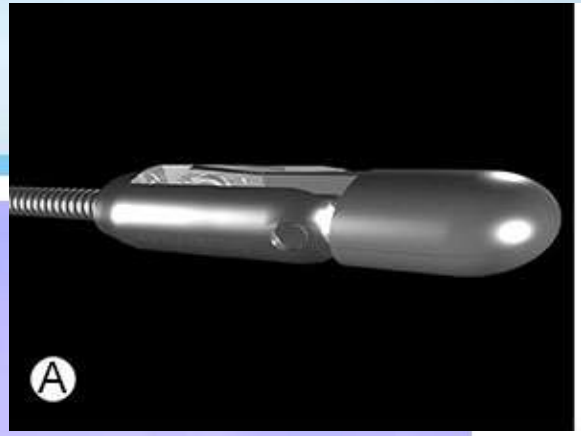


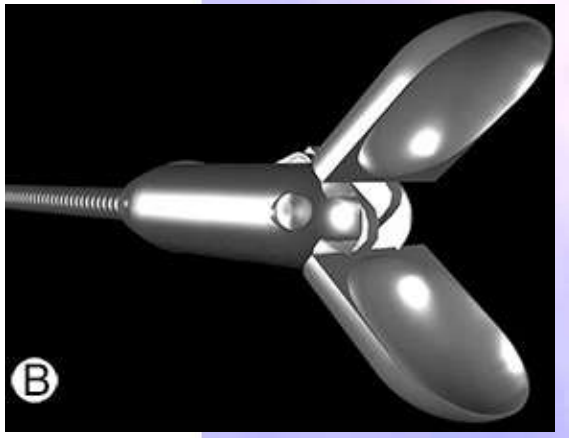
XDx
EXPRESSION DIAGNOSTICS

Heart biopsy









XDx
EXPRESSION DIAGNOSTICS

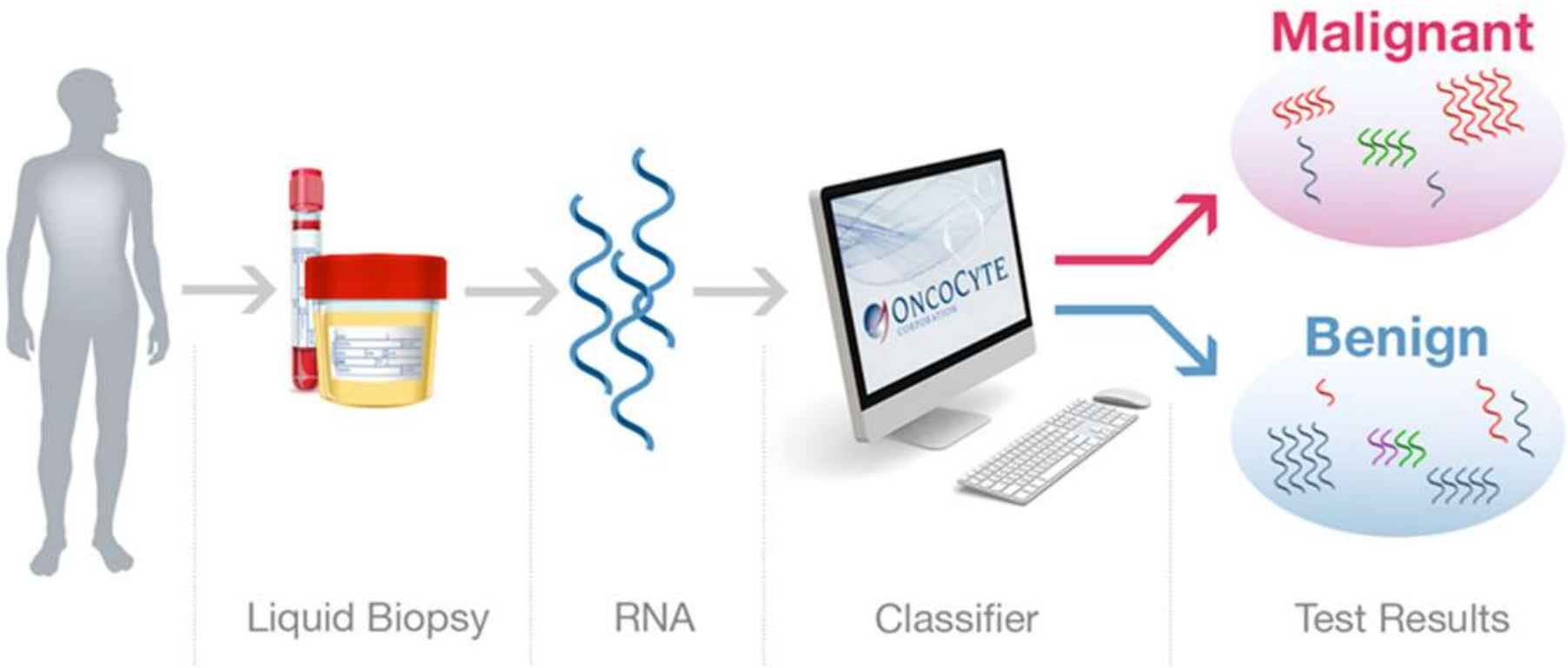
ISHLT Standardized Cardiac Biopsy Grading

(International Society of Heart and Lung Transplantation)

Grade		Histopathological Findings
2005	*1990*	
0R	0	No rejection
1R	1A	Focal perivascular and/or interstitial infiltrate without myocyte damage
	1B	Diffuse infiltrate without necrosis
	2	One focus of infiltrate with associated myocyte damage
2R	3A	Multifocal infiltrate with myocyte damage
3R	3B	Diffuse infiltrate with myocyte damage
	4	Diffuse, polymorphous infiltrate with extensive myocyte damage ± edema, ± hemorrhage, + vasculitis

Additional information (required when present): biopsy <4 pieces, humoral rejection, "Quilty" effect, ischemia, infection present, lymphoproliferative disorder, other.

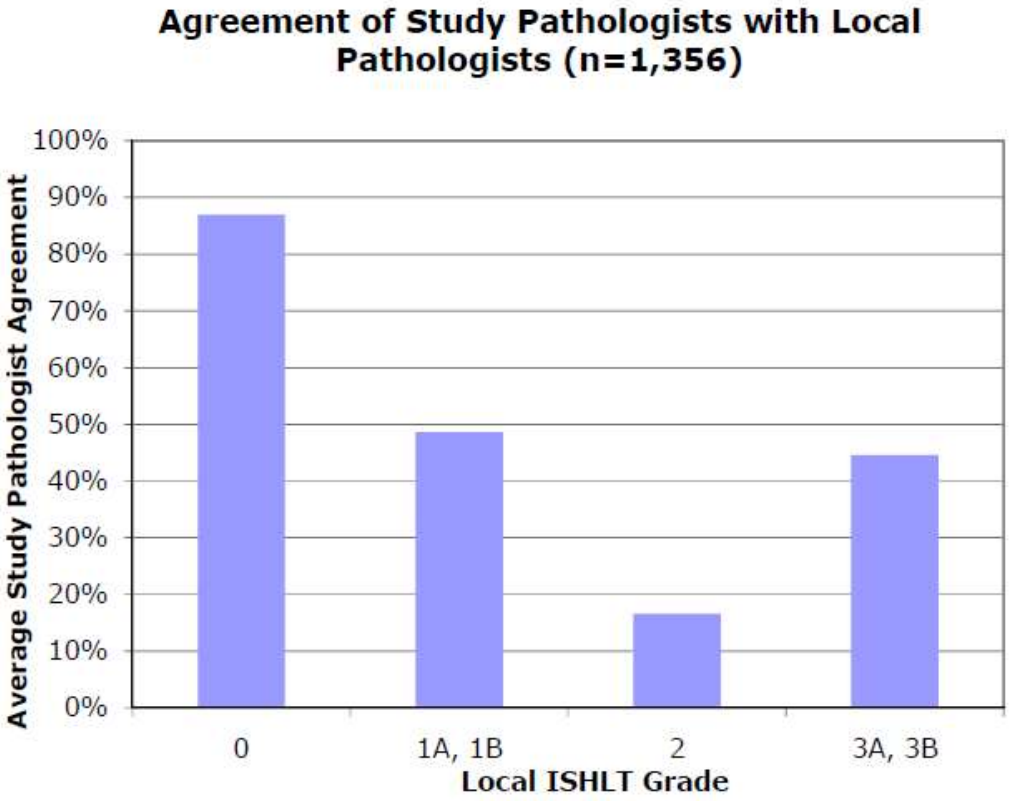
XDx
EXPRESSION DIAGNOSTICS


Malignant
ONCOCYTE
Benign
Liquid Biopsy
RNA
Classifier
Test Results

Limitations of Endomyocardial Biopsy

- Interpretive variability
  - Intra- and inter-reader variability
  - Over calling of ≥3A
- Tissue sample inadequacy
  - May miss focal areas of rejection
  - Repetitive biopsy leads to fibrosis
- Invasive
  - Percutaneous catheterization
  - Risk (0.2-2.3%) includes:
    - Right ventricular perforation
    - Tricuspid valve damage
    - Arrhythmias
    - Bleeding

Example of reader variability



CARGO Study

Cardiac Allograft Rejection Gene Expression Observational Study

- Columbia University (New York)
- Cleveland Clinic (Cleveland)
- Kaiser Permanente (San Jose)
- Ochsner Clinic (New Orleans)
- Stanford University (Palo Alto)
- Temple University (Philadelphia)
- UCLA (Los Angeles)
- University of Florida (Gainesville)
- University of Pittsburgh (Pittsburgh)

- **Hypothesis**
  - Peripheral blood gene expression profiles can differentiate between the absence and presence of acute cellular rejection
- **Study Overview**
  - 9 center observational study
    - Conducted 2001-2005
  - **737** subjects enrolled
  - **5,837** post transplant encounters
  - Centralized biopsy grading
    - 3 expert heart transplant pathologists read biopsies
    - Use of central reads to define Rejection/No rejection (R/NR)

XDx EXPRESSION DIAGNOSTICS

CARGO clinical study summary

I Discovery ~2 years (microarray)

II Development ~1 year (PCR)

III Clinical Validation ~1 year (Molecular Test)

- **Candidate gene selection**
  - 285 Leukocyte microarray
  - Database / literature mining
  - 252 candidate genes
- **Algorithm development**
  - Real-time PCR
  - 20-gene algorithm to distinguish rejection from quiescence (***AlloMap molecular testing***)
- **Validation**
  - Prospective, blinded, statistically-powered (n = 270)
  - Additional samples tested to further define performance (n > 1000)

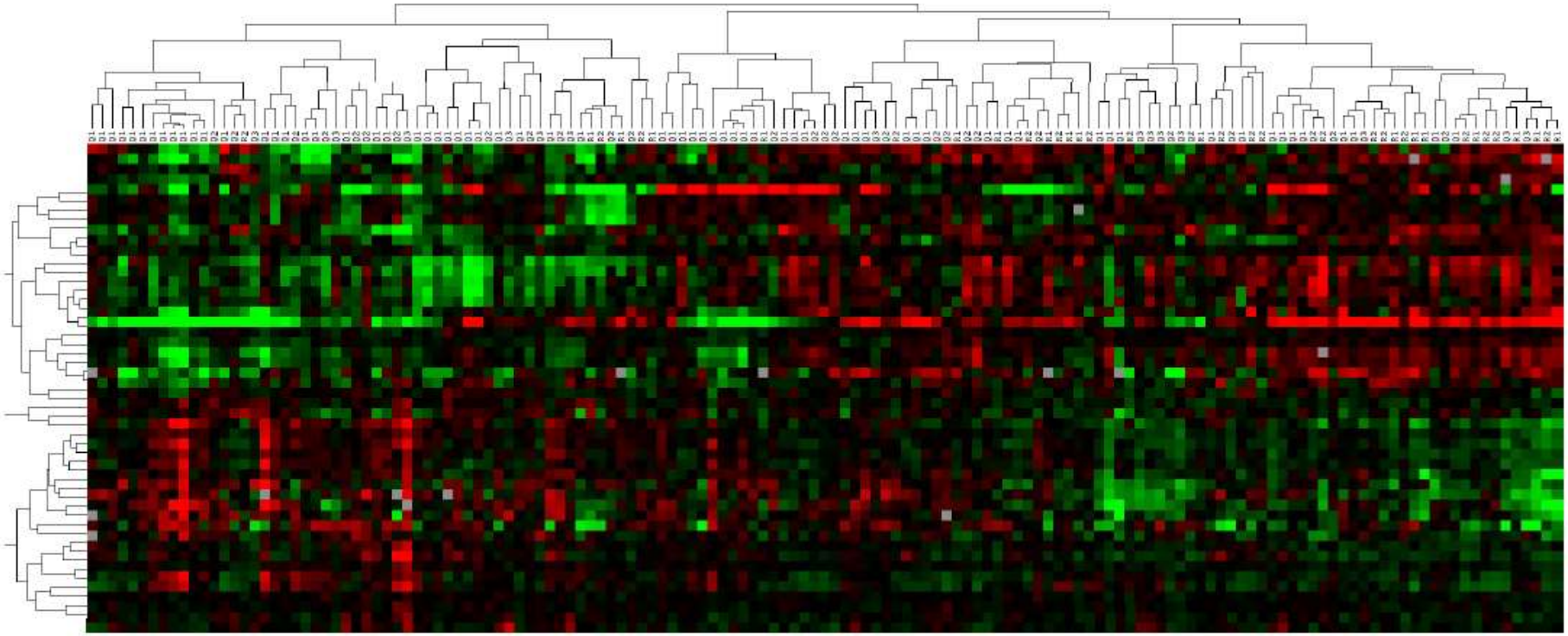
- Overview
  - Cardiac Allograft Rejection Gene expression Observational study = "CARGO"
  - 8 center, 4-year observational study initiated in 2001 (22% of US HTx).
  - 629 patients, 4917 post-transplant encounters
- Hypothesis
  - Gene expression profiling of peripheral blood mononuclear cells can discriminate ISHLT grade 0 rejection (quiescence) from moderate/severe (ISHLT grade ≥ 3A) rejection
- Design & Result

  Prospective, blinded validation study of 20 gene algorithm demonstrated ability to distinguish Grade 3A rejection from quiescence

Deng/Eisen/Mehra et al. Am J Transplant 2006;6:150

Genes that Distinguish Rejection

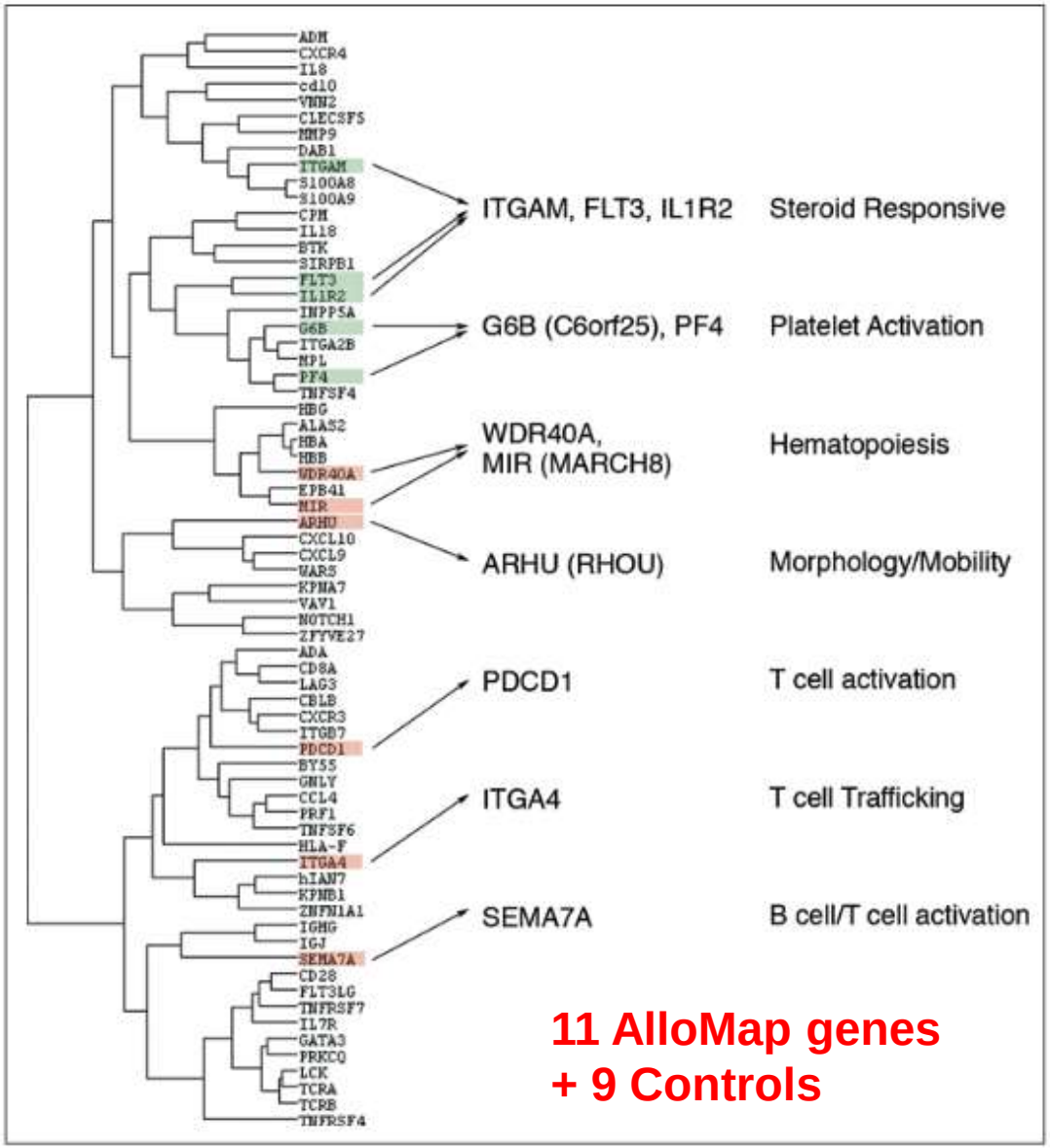
- Quantitative real-time PCR for 252 candidate genes
- 145 samples divided into ISHLT Grade 0 and ISHLT ≥3A by centralized pathologists
- 68 genes correlated with rejection ($p < 0.01$) or were more than 25% up- or down-regulated



Biopsy Grade 0 **Biopsy Grade 3A**

XDx
EXPRESSION DIAGNOSTICS

Targeting Specific Genes for the AlloMap Test

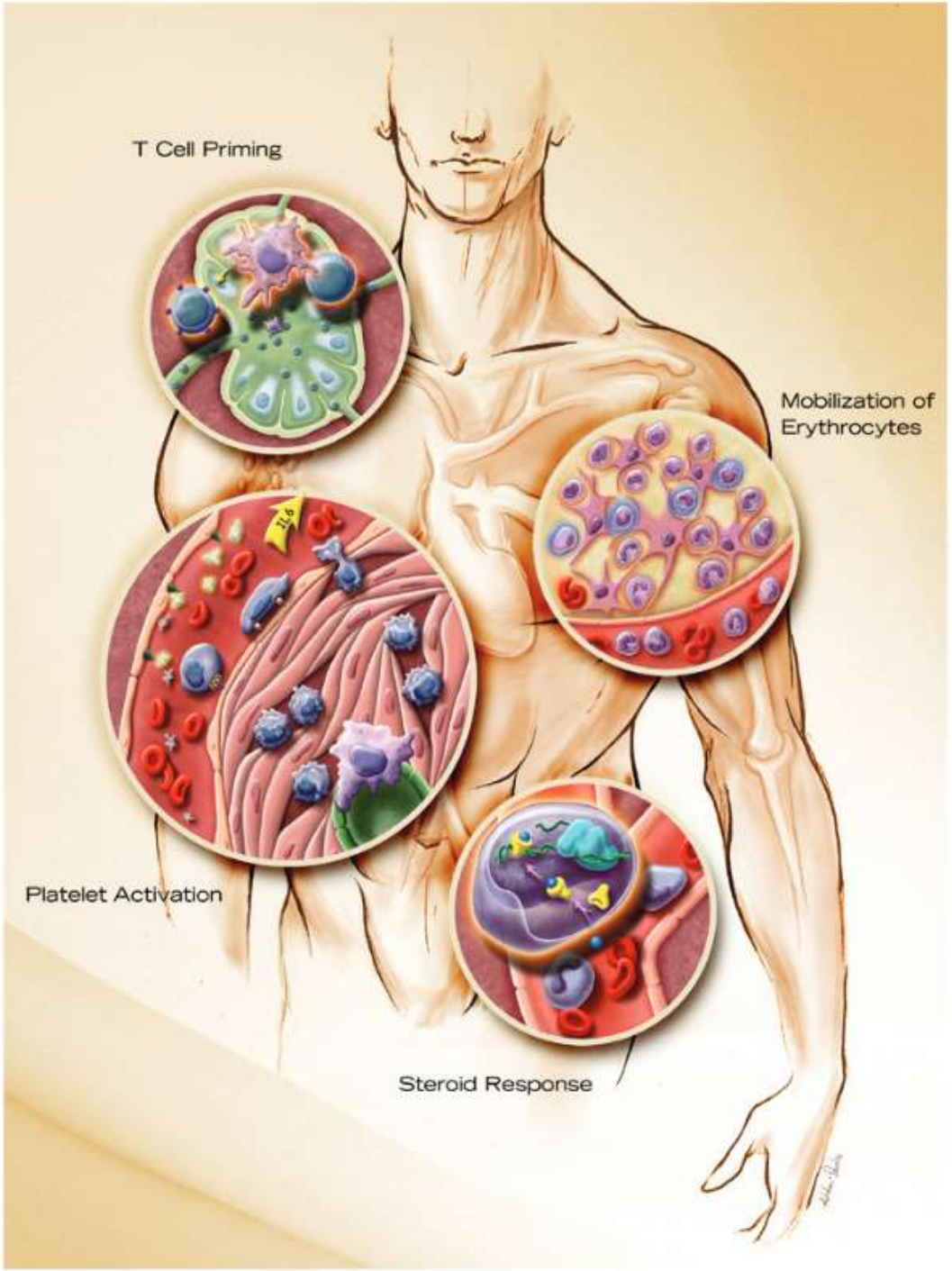


Using linear discriminant analysis, the expression levels of 11 genes were selected for the calculation of the AlloMap score (integer 0–40). This set of genes best distinguished between the presence and absence of rejection in the development of the AlloMap test.

Differential Expression of AlloMap Genes in Rejection Samples

Pathway and Gene	Gene Expression Level
T cell priming	
ITGA4 **Integrin alpha-4** α subunit of VLA-4; involved in T cell trafficking and adhesion	↑
PDCD1 **Programmed cell death** T cell costimulatory molecular (inhibitory); CD28 family	↑
Proliferation and mobilization of erythrocytes	
MARCH8 **Cellular mediator of immune response (MIR)** E3 ubiquitin ligase	↑
WDR40A **WD repeat domain 40A** Uncharacterized protein of the WD-repeat protein family	↑
Platelet activation	
PF4 **Platelet factor 4** Chemokine-like molecule expressed in platelets	↓
C6orf25 **G6b inhibitory receptor** Putative inhibitory receptor of the Ig superfamily expressed in platelets	↓
Steroid response	
IL1R2 **Interleukin-1 receptor type II** IL-1 decoy receptor inhibits cytokine signaling; steroid-dependent expression	↓
ITGAM **Integrin alpha-M** α subunit of MAC-1; involved in cell trafficking	↓
FLT3 **FMS-like tyrosine kinase** Signaling molecule expressed in monocytes	↓
Unknown role	
SEMA7A **Semaphorin 7A** Expressed by T cells, B cells, and immature granulocytes	↑
RHOU **Ras homolog gene family, member U** Member of the Rho GTPase family involved in the modulation of cytoskeleton organization	↑

Genes Represented in AlloMap Test Score: Multiple Rejection Pathways



Sample Collection and Preparation

The AlloMap test requires a blood sample obtained by routine phlebotomy and additional processing steps that enable the extraction and stabilization of RNA from peripheral blood mononuclear cells (PBMCs). As components of the immune system, PBMCs reflect the body's responses to the transplanted organ and have a distinct gene expression profile (i.e. individual RNA levels for each gene) associated with rejection that is assessed by the AlloMap test. After blood is collected, it is centrifuged to isolate the PBMCs. Further processing of the PBMCs releases the RNA from the cells and preserves it to ensure the recovery of high quality RNA for testing. The preserved sample is shipped together with the completed test requisition form to the clinical laboratory at CareDx.

Customer Care
1-888-ALLOMAP
1-888-255-6627
caredxcustomercare@caredxinc.com

CareDx Customer Care is available to answer questions about AlloMap testing and to help resolve any problems regarding sample preparation, shipping, or test results.

AlloMap Testing Process at the Clinical Laboratory at CareDx

The testing procedure involves sequential steps beginning with purification of RNA from the sample received and finishing with the reporting of the AlloMap test score to the clinician. The intervening steps include analysis of the purified RNA by qRT-PCR, a proven methodology that yields sensitive, specific and reproducible gene expression measurements [Bustin, 2000]. The clinical laboratory at CareDx has optimized and standardized the performance of the AlloMap test processes. Comprehensive quality control ensures the reliability of the gene expression measurements used in the calculation of the AlloMap test score.

Testing Procedure

After purification, RNA is reverse transcribed into complementary DNA (cDNA), which is added to each of 60 wells containing gene-specific primers and probes. The expression of each gene is then measured by amplification and fluorescence detection using a qRT-PCR instrument.

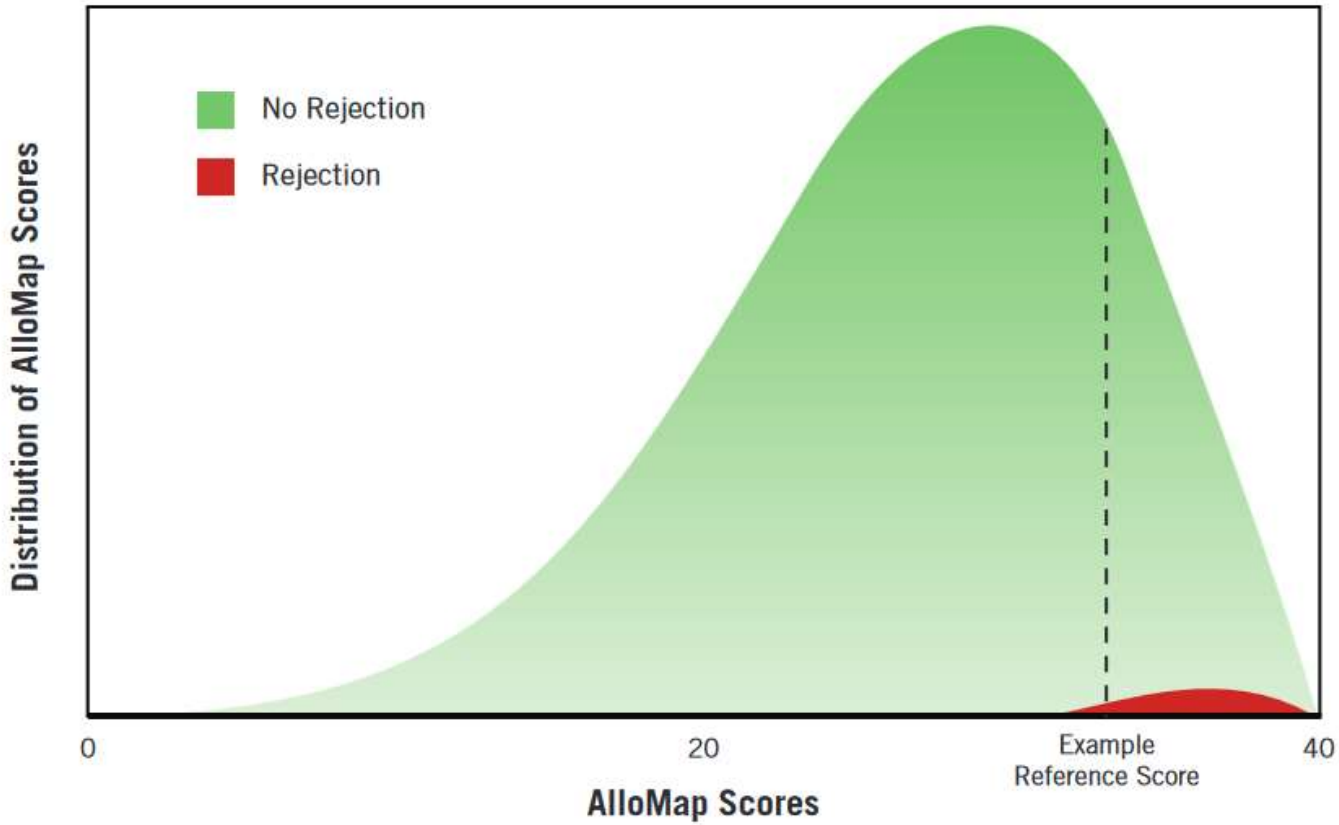
This procedure is performed in triplicate and normalized to provide the integrity and accuracy of the sample.

Quality Control and Normalization

The relative expression of the quality control genes used in AlloMap testing provides the data to assess the quality of all of the testing process. These include:

- Gene-specific measurement ranges
- Efficiency of the qRT-PCR
- Precision
- Accuracy and consistency

Understanding the Distribution of Scores Relative to a Reference Score*



AlloMap scores can be evaluated against a selected reference score to help identify the probability of acute cellular rejection (ACR) at the time of testing for an individual patient. When used in conjunction with standard clinical assessments, scores below the reference point can help indicate a lower probability of ACR; scores above the reference score can help indicate an increased probability of ACR.

*The distribution of scores in this figure is intended to be for graphic illustration purposes based upon a typical distribution of AlloMap Test scores and Rejection from a general transplant population.

AlloMap Testing Clinical Performance Characteristics*+

Post-Transplant Period >2 - 6 months (n=166 samples)			AlloMap Score**	Post-Transplant Period >6 months (n=134 samples)		
NPV <3A(2R) ± SE	% Pts Below	PPV ≥3A(2R) ± SE		NPV <3A(2R) ± SE	% Pts Below	PPV ≥3A(2R) ± SE
97.9% ± 0.0%	100.0%	—	**39**	**98.3%** ± 0.0%	97.7%	—
97.9% ± 0.0%	100.0%	—	**38**	**98.2%** ± 0.0%	96.5%	—
98.1% ± 0.2%	97.8%	**9.5%** ± 21.1%	**37**	**98.4%** ± 0.2%	91.7%	—
98.1% ± 0.2%	97.3%	**7.6%** ± 13.8%	**36**	**98.7%** ± 0.3%	90.2%	**5.4%** ± 3.2%
98.1% ± 0.2%	94.5%	**5.7%** ± 4.8%	**35**	**98.7%** ± 0.4%	84.1%	**4.0%** ± 2.2%
98.2% ± 0.3%	91.7%	**5.0%** ± 3.5%	**34**	**98.9%** ± 0.4%	79.1%	**4.1%** ± 1.7%
98.1% ± 0.3%	89.4%	**4.0%** ± 2.7%	**33**	**99.1%** ± 0.4%	72.4%	**3.8%** ± 1.3%
98.0% ± 0.3%	85.6%	**2.9%** ± 2.0%	**32**	**99.0%** ± 0.5%	63.1%	**2.9%** ± 0.9%
98.2% ± 0.4%	81.0%	**3.3%** ± 1.6%	**31**	**98.8%** ± 0.6%	54.1%	**2.3%** ± 0.7%
98.6% ± 0.4%	77.2%	**4.6%** ± 1.6%	**30**	**98.7%** ± 0.6%	50.6%	**2.1%** ± 0.6%
98.6% ± 0.4%	73.7%	**4.0%** ± 1.3%	**29**	**99.0%** ± 0.7%	40.8%	**2.1%** ± 0.5%
98.5% ± 0.5%	68.3%	**3.3%** ± 1.1%	**28**	**98.9%** ± 0.7%	39.1%	**2.1%** ± 0.5%
98.7% ± 0.5%	63.6%	**3.4%** ± 1.0%	**27**	**98.7%** ± 0.9%	31.6%	**1.9%** ± 0.4%
99.0% ± 0.5%	61.4%	**3.8%** ± 0.9%	**26**	**100.0%** ± 0.0%	26.8%	**2.3%** ± 0.1%
99.3% ± 0.5%	56.0%	**3.8%** ± 0.7%	**25**	**100.0%** ± 0.0%	22.1%	**2.2%** ± 0.1%
99.1% ± 0.6%	47.5%	**3.2%** ± 0.6%	**24**	**100.0%** ± 0.0%	18.4%	**2.1%** ± 0.1%
99.0% ± 0.6%	41.8%	**2.9%** ± 0.5%	**23**	**100.0%** ± 0.0%	14.1%	**2.0%** ± 0.1%
98.9% ± 0.7%	38.8%	**2.7%** ± 0.5%	**22**	**100.0%** ± 0.0%	11.0%	**1.9%** ± 0.1%
98.8% ± 0.8%	33.6%	**2.5%** ± 0.4%	**21**	**100.0%** ± 0.0%	9.8%	**1.9%** ± 0.1%
100.0% ± 0.0%	24.3%	**2.8%** ± 0.2%	**20**	**100.0%** ± 0.0%	8.1%	**1.8%** ± 0.1%
100.0% ± 0.0%	<22.4%	**≤2.7%** ± 0.1%	**≤19**	**100.0%** ± 0.0%	≤5.4%	**≤1.8%** ± 0.0%

Lower probability of ACR

+ (AlloMap Laboratory Services Guide - LQ-10004)

AlloMap Test Report

XDx Reference Laboratory
Lab Directors: Patrick Joseph, MD
Judith C. Wilber, PhD, D(ABMM)
CLIA No. 05D1029609

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www.allomap.com

Patient Name:	John Doe
Medical Record No.:	00998877
Date of Birth:	23 Nov 1953
Transplant Date:	03 Mar 2008
Referring Facility Sample ID:	

Test Results
Sample Date:
30 Jul 2008
AlloMap Score:
A **28**
B 95% CI: 24.7-31.3)
(range 0-40)

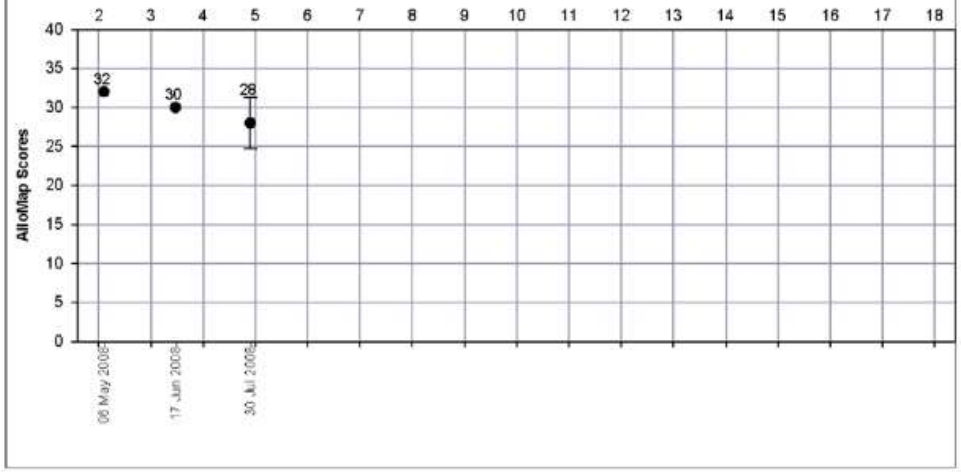
Accession ID No.: A01112 Report ID NO.: A01112

Ordered By:	Dr. John Smith
Client:	Medical Center
Test Comments:	

Longitudinal Results - First 18 Months

The graph shows AlloMap test results over the first 18 months post transplantation (sample date indicated on x-axis). Current result displays 95% confidence interval (CI). Prior scores within the 95% CI of the most recent score are not statistically different. C

Time Post-Transplant
4m 27d



D Interpretation of AlloMap Score E

D Interpretation of AlloMap Score E

AlloMap Score	Negative Predictive Value (NPV)*	Positive Predictive Value (PPV)**
28	98.5%	3.3%

The performance characteristics of the AlloMap test were established in patients who are 15 years of age or older, and at least 55 days post-transplant.
* The NPV is the probability of the absence of ISHLT grade >=3A (2R) acute cellular rejection for the AlloMap score below this score. The standard error for this NPV is 0.5%.
** The PPV is the probability of the presence of ISHLT grade >=3A (2R) acute cellular rejection for AlloMap scores at or above this score. The standard error for this PPV is 1.1%.

INDICATIONS FOR USE

AlloMap Molecular Expression Testing is an in vitro diagnostic multivariate index assay (IVDMIA) test service, performed in a single laboratory, assessing the gene expression profile of RNA isolated from peripheral blood mononuclear cells (PBMC). AlloMap testing is intended to aid in the identification of heart transplant recipients with stable allograft function who have a low probability of moderate/severe acute cellular rejection (ACR) at the time of testing in conjunction with standard clinical assessment.

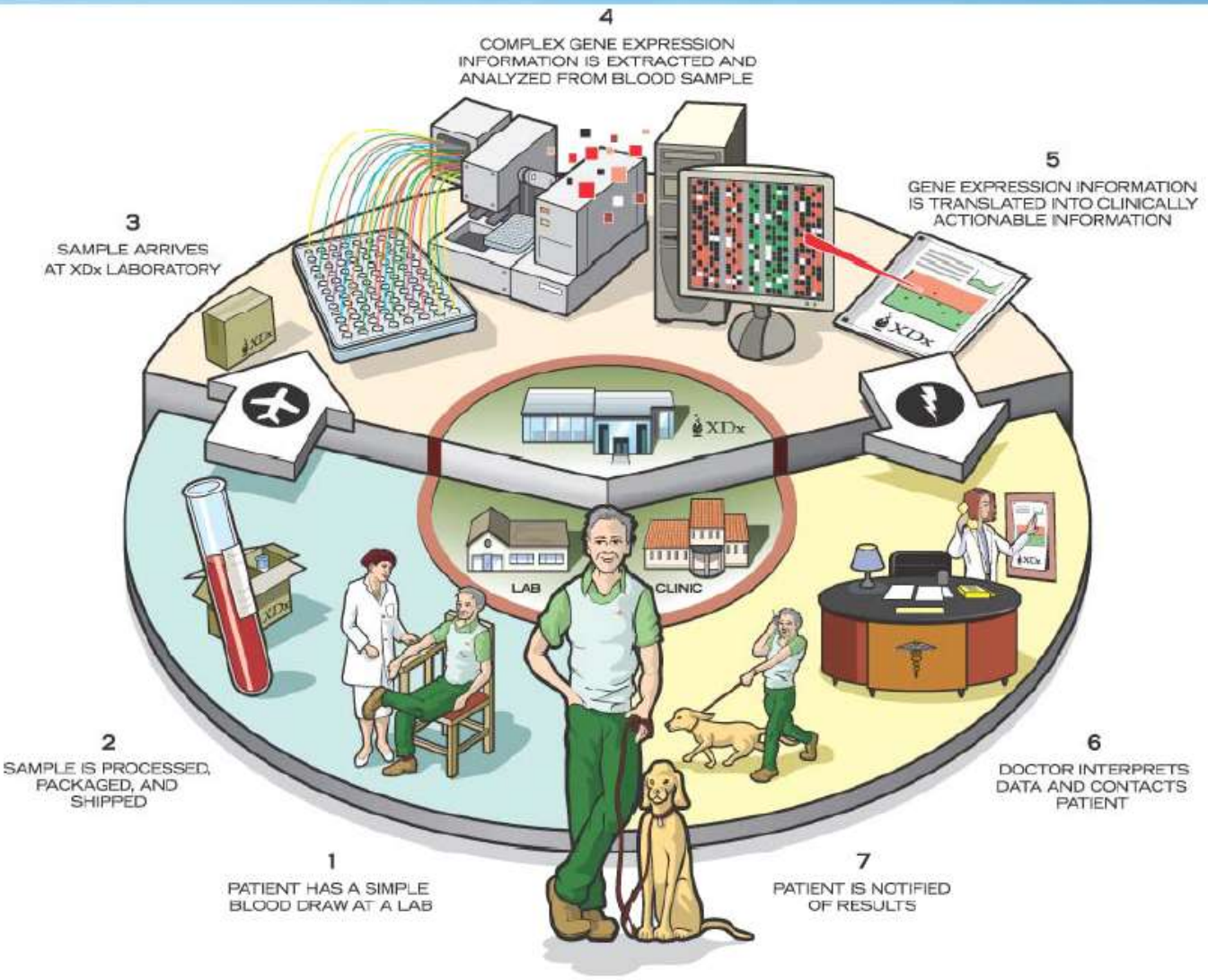
Note: Additional information about the AlloMap test, including performance characteristics, can be found at www.allomap.com.

XDx

Final Report Date: 10 Dec 2014

Legend: A AlloMap Score B 95% Confidence Interval C Post-Transplant Periods D NPV E PPV

AlloMap Workflow



XDx

Molecular diagnostics bring new challenges

- **Traditional diagnostics**
  - Methods developed over decades and centuries
  - Often used at local hospital
  - Single marker
  - cheap
  - Simple and understandable (patients, doctors, health care)
  - Established by tradition

- **Molecular Diagnostics**
  - Methods developed in less than 10 years
  - Often requires centralized lab
  - Multiple markers
  - Complex and complicated (method and application)
  - Requires new regulations and high quality control
  - Usefulness has to be demonstrated by clinical studies

agendia

Major challenges

- Society is willing to pay € 50.000 for treatment of patients
  - but not €5000 for a MDx that would help identifying those patients who will benefit from it
- Many Mdx have big influence on patient's life
  - but there are no validation standards and no stringent regulatory requirements for Mdx
- Validation, clinical studies, saftey data and education are required - similar to efforts required for new drugs
  - but this can not be provided without big costs for companies and support from community
  - and health insurances need to establish (better) rules how to reimburse Mdx

agendia

The future of cancer diagnosis: ¡Medicine!!