

A Genomic Approach to Biomarker Discovery in Prostate Cancer

Case Study

GENE  LOGIC
An Ocimum Biosolutions Company

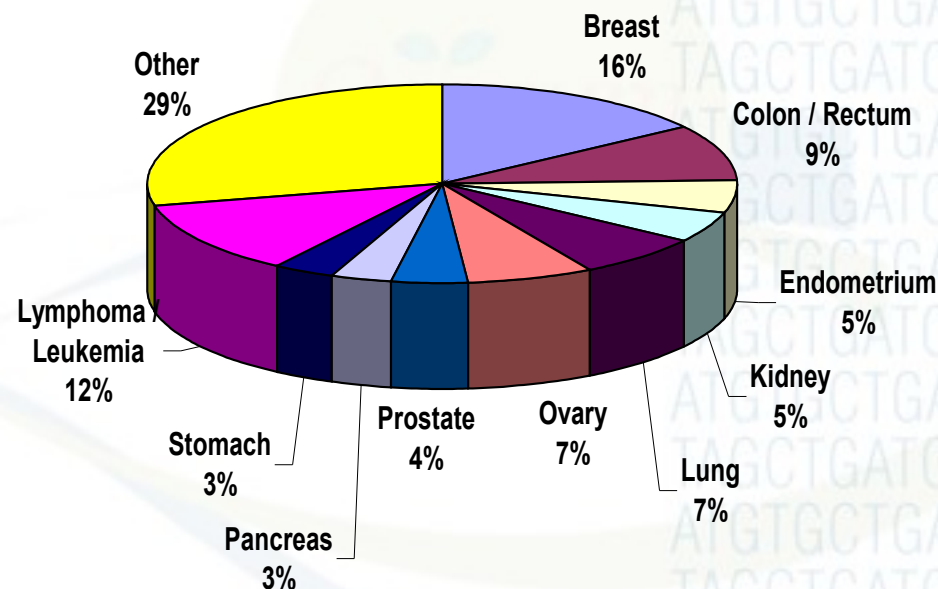
A Quick Introduction: Gene Logic Programs Overview

- **Gene Logic has developed one of the world's largest and most detailed knowledge bases of gene expression profiles using Affymetrix GeneChip® microarray technology.**
 - Over 36,000 human and animal samples significant to key therapeutic areas and with full clinical information are offered in our reference databases.
 - Over 200,000 microarrays have been processed in our high-throughput, GLP facility.
- **We offer a wide range of genomic products and services including:**
 - Genomic reference databases:
 - BioExpress® System
 - ToxExpress® System
 - The ASCENTA® System
 - Genomic data generation & bioinformatics analysis services:
 - Gene Expression including GeneChip® microarrays, miRNA, Exon, Q-RT PCR
 - SNP Genotyping
 - aCGH

The BioExpress® Oncology Program - Highlights

More than 6,000 samples, including:

- Primary tumors
- Secondary (metastatic) tumors
- Benign tumors
- Matched non-malignant tissue controls
- Extensive clinical annotation
- Various cell line studies
 - NCI-60 cell lines
 - Various drug-treated studies and cell culture experiments
- Human into mouse xenografts
- LCM samples



BioExpress Oncology® Program - Standard Clinical Data

- **Demographics**
 - Age
 - Gender
 - Race/Ethnicity
- **Health Risk Factors**
 - Height / weight / BMI
 - Allergies / exposures
 - Diet / supplements
 - Smoking history
 - Alcohol use
 - Recreational drug use
- **Medical History**
 - Primary disease
 - Concurrent disease(s)
 - Prior history
- **Treatment History**
 - Current and previous medications
 - Anesthetics / preoperative agents
 - Surgical procedure(s)
- **Family History**
 - Relative, disease, age of diagnosis
- **Diagnostic Tests**
 - Preoperative lab work
 - Disease-specific studies

Prostate Cancer | Epidemiology

- The most prevalent cancer in men (American Cancer Society)
- More than 220,000 new cases and nearly 30,000 deaths were reported in 2003 for the United States
- More than 40 Millions PSA tests are preformed worldwide each year and this number is expected to grow due to aging population

Prostate Cancer | PSA Testing Fact Sheet

- PSA Test is specific for prostate tissue not prostate cancer
 - Elevated PSA does not necessarily indicate prostate cancer
- Only 25% of patients found positive by PSA testing (> 4ng/ml) are confirmed by a biopsy to have cancer (high false positive rate)
- Urologists must then decide to
 - Conduct a biopsy or
 - Conduct additional PSA testing or
 - To delay follow-up
- It is being advocated to decrease the PSA threshold for biopsy in order to detect more cancer, the consequences are:
 - Increase number of expensive and uncomfortable biopsies
 - Increasing the rate of negative biopsies
- Not all prostate cancers release high levels of PSA in blood

Prostate Cancer | *In silico* Experimental Outline

- Curation of adenocarcinoma prostate, benign prostatic hypertrophy (BPH) and normal prostate sample sets
- Identifying candidate biomarkers that discriminate between prostate cancer, BPH or normal prostate
- Assess tissue specificity of selected gene in normal tissues as well as in other cancers and diseased tissues

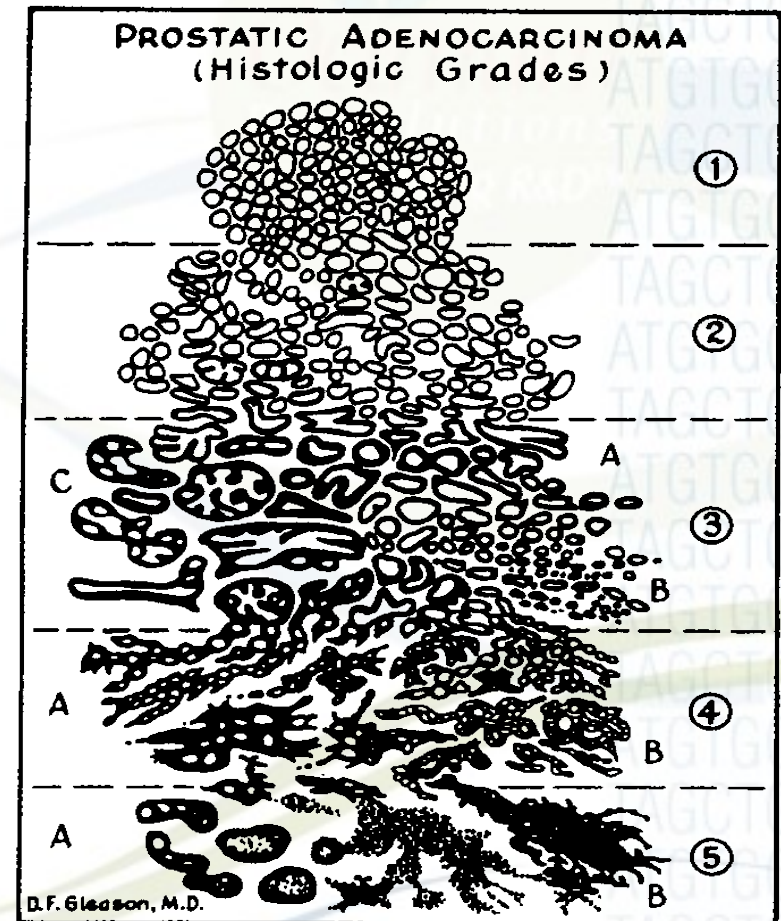
Prostate Cancer | Sample Set Curation

Sample sets defined by using specific pathological and clinical features available in the BioExpress® System.

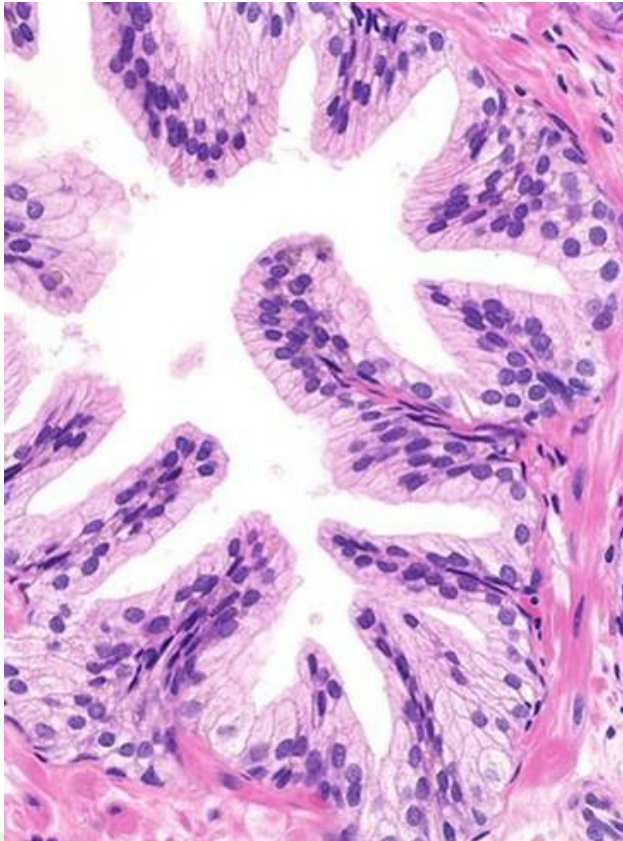
- Prostate Adenocarcinoma
 - Create sample sets based on Gleason score (5 or higher)
- Benign Prostatic Hypertrophy (BPH)
 - Select samples from patients with no malignancy in the prostate
- Normal Prostate
 - Samples from patients where the primary site of disease is not in the prostate or is elsewhere in the prostate

Gleason Grading Scheme

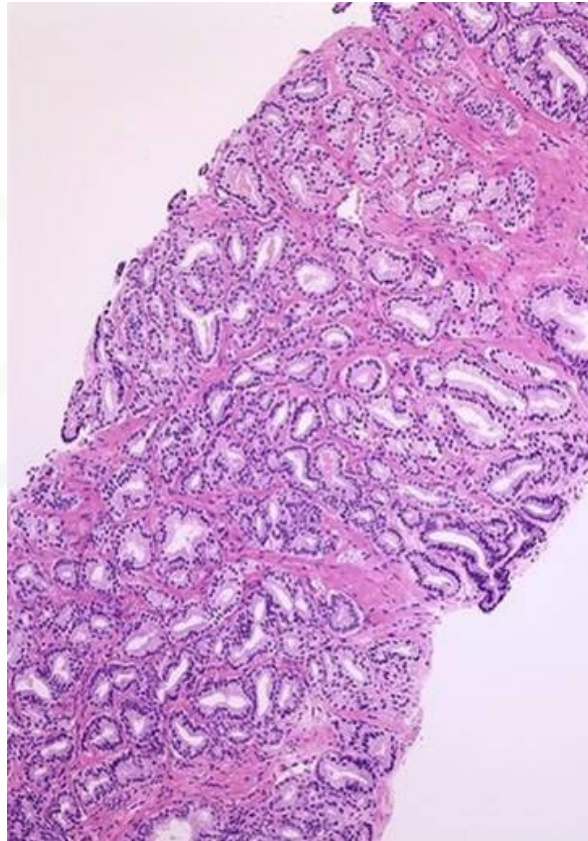
- A value from 1 to 5 is assigned to the microscopic architecture of the cancer.
- Two values are assigned to incorporate the two predominant patterns. The values are added to form a score.
- Gleason Scoring:
 - 2 to 4 is considered low grade;
 - 5 to 7 an intermediate grade; and
 - 8 to 10 a high grade.



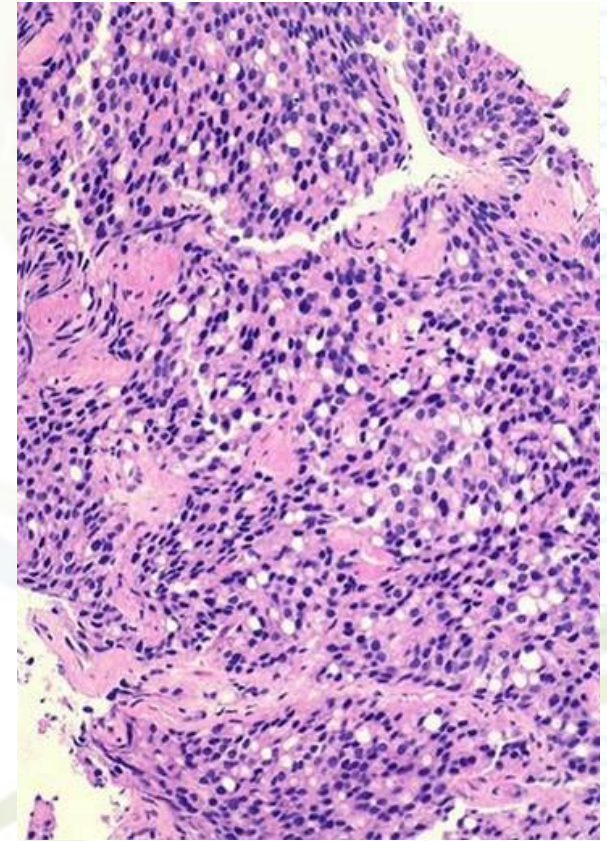
Gleason Grading Examples



Normal Prostate



Gleason Pattern 3



Gleason Pattern 5

Prostate Cancer | Sample Set Selection



Sample Table 1

#	Genomics ID	Sample Type	Sample Site	Pathology/Morphology	Sample Specific Pathologic Type	General Sample Description
46	10304	Tissue	Prostate	Adenocarcinoma	Primary malignant neoplasm of prostate	RADICAL PROSTATECTOMY: ADENOCARCINOMA, GLEASON SCORE 3+4=7, INVOL...
47	10308	Tissue	Prostate	Adenocarcinoma	Primary malignant neoplasm of prostate	RADICAL PROSTATECTOMY: ADENOCARCINOMA, GLEASON SCORE 3+3=6, INVOL...
48	10311	Tissue	Prostate	Normal tissue	Disease type AND/OR category not ass...	NORMAL PROSTATE, FROM PROSTATECTOMY FOR ADENOCARCINOMA.
49	10312	Tissue	Prostate	Adenocarcinoma	Primary malignant neoplasm of prostate	RADICAL PROSTATECTOMY: ADENOCARCINOMA, GLEASON SCORE 2+3=5, INVOL...
50	10313	Tissue	Prostate	Normal tissue	Disease type AND/OR category not ass...	NORMAL PROSTATE, FROM PROSTATECTOMY FOR ADENOCARCINOMA.
51	10314	Tissue	Prostate	Adenocarcinoma	Primary malignant neoplasm of prostate	RADICAL PROSTATECTOMY: ADENOCARCINOMA, GLEASON SCORE 4+5=9, INVOL...
52	10315	Tissue	Prostate	Adenocarcinoma	Primary malignant neoplasm of prostate	RADICAL PROSTATECTOMY: ADENOCARCINOMA, GLEASON SCORE 3+3=6, INVOL...
53	10317	Tissue	Prostate	Adenocarcinoma	Primary malignant neoplasm of prostate	RADICAL PROSTATECTOMY: ADENOCARCINOMA, GLEASON SCORE 4+5, WITH BIL...
54	10318	Tissue	Prostate	Normal tissue	Disease type AND/OR category not ass...	NORMAL PROSTATE, FROM PROSTATECTOMY FOR ADENOCARCINOMA.
55	10319	Tissue	Prostate	Adenocarcinoma	Primary malignant neoplasm of prostate	RADICAL PROSTATECTOMY: ADENOCARCINOMA, GLEASON SCORE 5+3, EXTENDI...
56	10320	Tissue	Prostate	Adenocarcinoma	Primary malignant neoplasm of prostate	RADICAL PROSTATECTOMY: ADENOCARCINOMA, GLEASON SCORE 3+5=8, LIMITE...
57	10322	Tissue	Prostate	Adenocarcinoma	Primary malignant neoplasm of prostate	RADICAL PROSTATECTOMY: ADENOCARCINOMA, GLEASON SCORE 4+4=8, INVOL...
58	10324	Tissue	Prostate	Adenocarcinoma	Primary malignant neoplasm of prostate	RADICAL PROSTATECTOMY: ADENOCARCINOMA, GLEASON SCORE 3+4=7, INVOL...
59	10327	Tissue	Prostate	Adenocarcinoma	Primary malignant neoplasm of prostate	RADICAL PROSTATECTOMY: ADENOCARCINOMA, GLEASON SCORE 3+2=5, LIMITE...

Sample Object Details 1

Sample ID	324985
Sample Type	Tissue
Sample Site	Prostate
Disease of Tissue	Primary malignant neoplasm of prostate
General Pathologic Category	MALIGNANT
Species	H.sapiens
General Sample Description	RADICAL PROSTATECTOMY: ADENOCARCINOMA, GLEASON SCORE 4+5, WITH BILATERAL INVOLVEMENT OF SEMINAL VESICLES; REGIONAL NODES NEGATIVE.

Sample Experiment Donor

Samples: 213 (Selected: 1)

Sample Profile 2

Display: Result Samples Compare With: None Sort By: Count

#	Pathology/Morphology	Count	Count %
1	Adenocarcinoma	96	45.07
2	Normal tissue	65	30.52
3	Nodular hyperplasia	44	20.66
4	Epithelial dysplasia	3	1.41
5	Adenocarcinoma in situ	2	0.94
6	Chronic inflammation	1	0.47
7	Malignant lymphoma	1	0.47
8	Rhabdomyosarcoma	1	0.47

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Prostate Cancer | Sample Set Selection

Sample Object Details 1



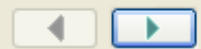
Sample ID	324985		
Sample Type	Tissue		
Sample Site	Prostate		
Disease of Tissue	Primary malignant neoplasm of prostate		
General Pathologic Category	MALIGNANT		
Species	H.sapiens		
General Sample Description	RADICAL PROSTATECTOMY: ADENOCARCINOMA, GLEASON SCORE 4+5, WITH BILATERAL INVOLVEMENT OF SEMINAL VESICLES; REGIONAL NODES NEGATIVE.		
Event	Event Order	Timepoint of Event	Type of Event
	1	0 mo	Sample
	SAMPLE AT DIAGNOSIS		
Pathology/Morphology	Diagnosis	Qualifier	
	Adenocarcinoma		
Pathology Review	Pathology Review		
	ADENOCARCINOMA.		
Donor ID	Donor ID	Species	Gender
	124985	H.sapiens	MALE
Sample Set	Sample Set ID	Sample Set Name	
	179	Prostate, Adenocarcinoma, Primary	
	404	Prostate, Adenocarcinoma, Primary, Age 60 and Over	
	407	Prostate, Adenocarcinoma, Primary; Elevated PSA	
Extracted RNA (genomics sample)	Genomics ID	Comments	
	10317		
Sample Relationship	Sample ID	Sample Type	Relationship
	324986	Tissue	Normal/Malignant
Autopsy Tissue?	Autopsy Tissue?		
	NO		

Sample Experiment Donor

Samples: 213 (Selected: 1)

Prostate Cancer | Sample Set Selection

Sample Object Details 1



Donor ID	124985		
Species	H.sapiens		
Gender	MALE		
Race/Ethnicity	Race/Ethnicity WHITE		
Death	AGE	Death Cause	
	72 yr	PROSTATE CANCER	
Events	Event Order	Timepoint of Event	Type of Event
	1	0 mo	Sample
	2	1 mo	Medical update
	3	36 mo	Medical update
	4	48 mo	Medical update
	5	72 mo	Medical update
	6	84 mo	Medical update
	7	96 mo	Last medical update
Donor's Samples	Sample ID	Sample Type	
	324985	Tissue	
	324986	Tissue	

Prostate Cancer | Sample Set Selection

Sample Object Details 1

Height	Unknown		
Medical History Status	NO ADDITIONAL HISTORY REPORTED		
Medication History Status	UNKNOWN		
Family History Status	UNKNOWN		
Donor Other Diseases	Disease	Donor Age at Diagnosis	Medical Status
	Primary malignant neoplasm of prostate	64 yr	NEW
			T3BN0M0

Surgical History	Surgery for Sample?	Surgical Procedure
	YES	RADICAL PROSTATECTOMY

Category	Area	Panel	Property	Value, reported as String	Qualitative Assessment		
Diagnostics	Chemistry	Chemistry	Albumin	4.6 g/dl	Normal		
			BUN	13 mg/dl	Normal		
			Ca	7.4 mg/dl	Low		
			Cholesterol	197 mg/dl	Normal		
			Cl	109 mEq/L	Normal		
			Creatinine	1.4 mg/dl	Normal		
			Glucose	126 mg/dl	High		
			K	4.4 mEq/L	Normal		
			Na	145 mEq/L	Normal		
			PO4	1.6 mg/dl	Low		
			Serum PSA	17.7 ng/ml	High		
			Hematology	Hematology	% Eosinophils	5.7 %	High
					% Lymphocytes	17.4 %	Low
					% Monocytes	7.3 %	Normal
% Neutrophils	72.6 %	High					
Hb	15.5 g/dl	Normal					
Hct	43.6 %	Normal					
Platelet count			206 x10 ⁹ /L	Normal			
RBC/blood			4.74 x10 ¹² /L	Normal			
WBC			5.6 x10 ⁹ /L	Normal			

Samples: 213 (Selected: 1)

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Analysis and Visualization Methodologies

- Comparative Analysis: Differential Expression
- Contrast Analysis: Selective Pattern Matching
- Absolute Analysis: E-Northern Visualization

Comparative Analysis

- Expression Criteria:

- Fold Change ≥ 5.0
- p-value ≤ 0.05

- Results:

- 28 Changing Genes

Comparative Analysis Tool 1

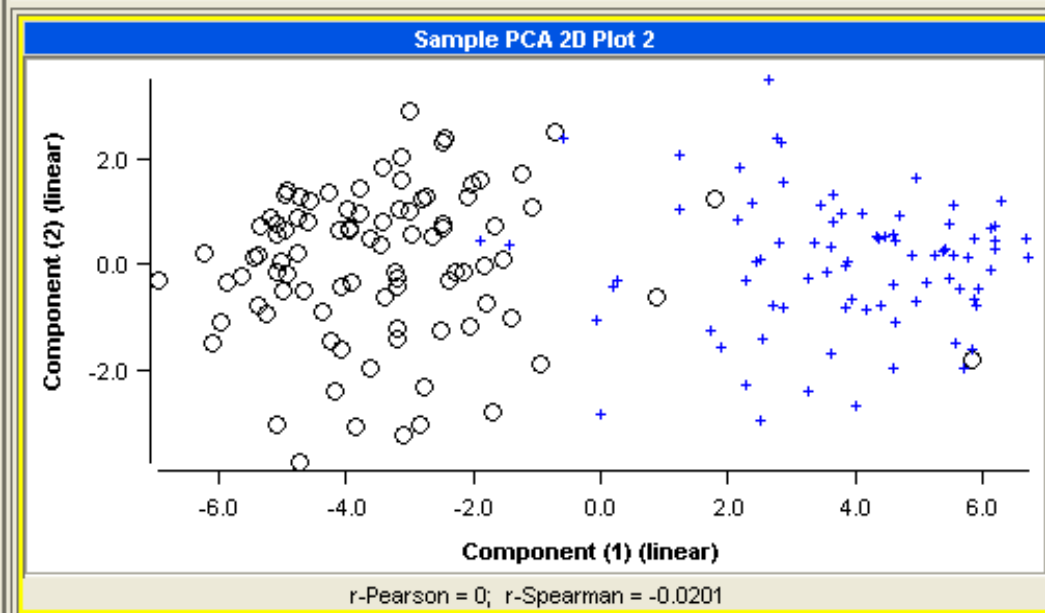
File Viewer View Data Windows Help

Tool Parameters Analysis Filter Gene Query Filter Gene Sorter Sample Sorter Sample Exclusions Gene Exclusions View

X=7 Y=3

Gene Table 1

#	Sequence Clusters: Cluster Title	Known Genes: Gene Symbol	t-Test p-Value (Prostate, Normal vs. Prostate, Adenocarcinoma)	FC Signed Magnitude (Prostate, Normal vs. Prostate, Adenocarcinoma)	FC Signed Magnitude (/public/SampleSets/ASCENTA/Human/Disease/Normal/Normal/Prostate/Prostate, Normal vs. Prostate, Benign Nodular Hyperplasia)	t-Test p-Value (/public/SampleSets/ASCENTA/Human/Case/Normal/Normal/Prostate/Prostate Normal vs. Prostate, Benign Nodular Hyperplasia)
1	Alpha-methylacyl-CoA racemase	AMACR	6.6695E-33	10.62	-1.14	0.40
2	Alpha-methylacyl-CoA racemase	AMACR	3.2271E-32	8.53	-1.06	0.60
3	Alpha-methylacyl-CoA racemase	AMACR	4.2314E-30	8.52	-1.13	0.31
4	Hepsin (transmembrane protease, se...	HPN	3.2326E-26	5.08	-1.08	0.54
5	Transcribed locus		7.9979E-25	5.32	1.08	0.58
6	PDZ and LIM domain 5	PDLIM5	1.3589E-21	6.04	-1.25	0.21
7	Distal-less homeobox 1	DLX1	3.5151E-21	8.18	-1.29	0.22
8	Cytochrome P450, family 3, subfamily...	CYP3A5	6.6245E-20	-6.49	-1.12	0.51
9	Solute carrier family 2 (facilitated gluc...	SLC2A5	1.1243E-19	-6.59	-1.11	0.60
10	Prostate cancer antigen 3	PCA3	1.4915E-19	7.73	-1.18	0.39



Sample Profile 1

Display: Result Samples Compare With: None Sort By: Value Groups: 3 (Selected: 1)

#	Pathology/Morphology	Count	Count %
1	Adenocarcinoma	82	47.40
2	Nodular hyperplasia	34	19.65
3	Normal tissue	57	32.95

Contrast Analysis: Identifying genes by pattern matching

Contrast Analysis Tool : contrast

File Viewer View Data Windows Help

Tool Parameters Analysis Filter Gene Query Filter Gene Sorter Sample Sorter Sample Exclusions Gene Exclusions Viewer 1 Viewer 2 Viewer 3

Chipset
Species: H.sapiens
Chips: HG-U133

Workspace Browser
Show Sample Sets: All sample sets
Show Gene Sets: All gene sets

- GS 3
- JM27 alias
- normal normal prostate
- normal prostate
- prostate genes
- BPH no cancer
- 2678-1 neonatal prostate epithel.
- adenocarcinoma GS 5 (13)
- adenocarcinoma GS 5-9 (81)

Contrasts
 up in cancer
 down in cancer
 up in BPH
 down in BPH
 progressive up

Add Define Gene Edit Remove

Data Transform
 None Symmetric Log Unlog for Display
 Log with Floor Floor Floor value:

Present Marginal Absent
 Unknown No Value

Upper Percentile: 75
Lower Percentile: 25

COMPUTE

Add Pattern

Pattern Name (optional): "Up in Cancer"
Pattern

Balanced Pattern :

normal normal prostate (1)
 BPH no cancer (2)
 GS 5 (3)
 GS 6 (4)
 GS 7 (5)
 GS 8 (6)
 GS 9 (7)

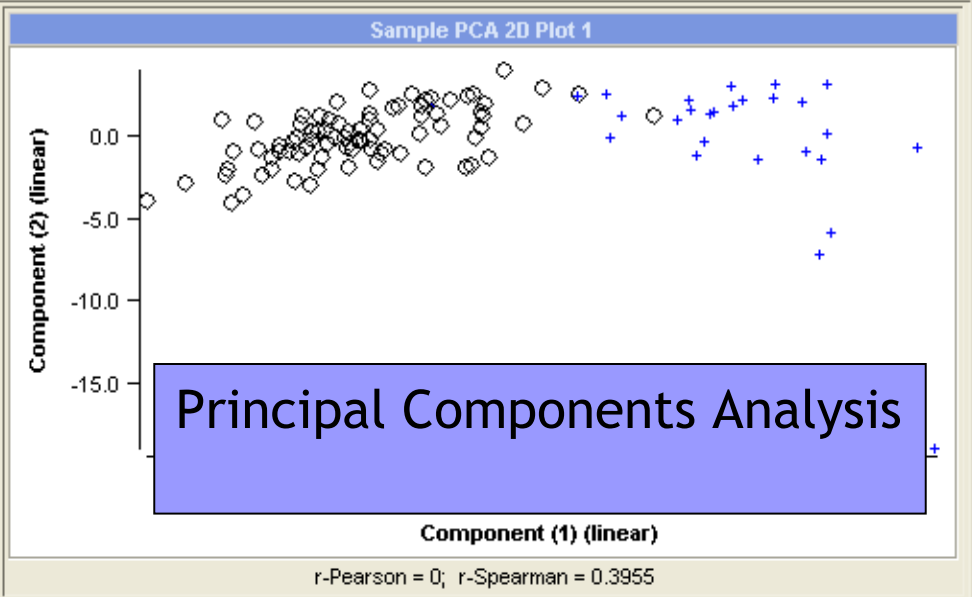
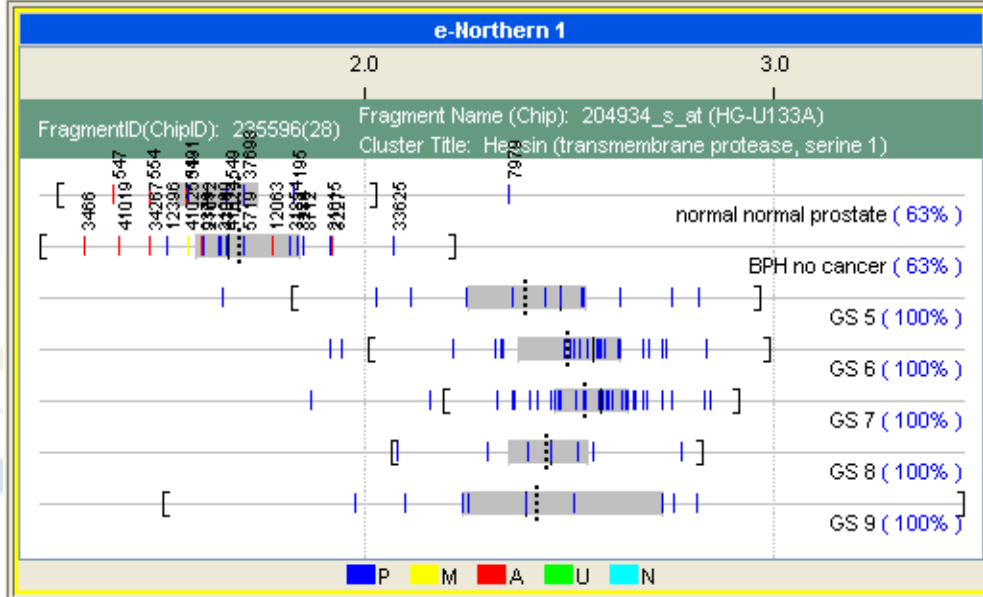
Add Select All Clear Close Help

Result Example: Hepsin

Gene Table 1					
#	Known Genes: Gene Name	Known Genes: Gene Symbol	Max t-Score	F-Score	Pattern of Max t-Score
1	hepsin (transmembrane protease, serine 1)	HPN	13.12	38.77	up in cancer
2	golgi phosphoprotein 2	GOLPH2	12.78	38.37	up in cancer
3	tumor-associated calcium signal transducer 1	TACSTD1	11.87	34.05	up in cancer
4	clusterin (complement lysis inhibitor, SP-40,40, s...	CLU	12.86	33.47	down in cancer
5	single minded homolog 2 (Drosophila)	SIM2	12.55	32.09	up in cancer
6	E...	EFEMP2	11.90	31.45	down in cancer
7	A...	ABCC4	10.41	28.03	up in cancer
8	snail homolog 2 (Drosophila)	SNAI2	10.78	27.42	down in cancer
9	alpha-methylacyl-CoA racemase	AMACR	10.78	24.64	up in cancer

PCA Summary 1	
Principal Component	% Variability
Component (1)	58.79
Component (2)	3.42
Component (3)	2.56
Component (4)	2.46
Component (5)	1.83
Component (6)	1.79
Component (7)	1.66
Component (8)	1.46
Component (9)	1.27
Component (10)	1.15

List of 205 Genes



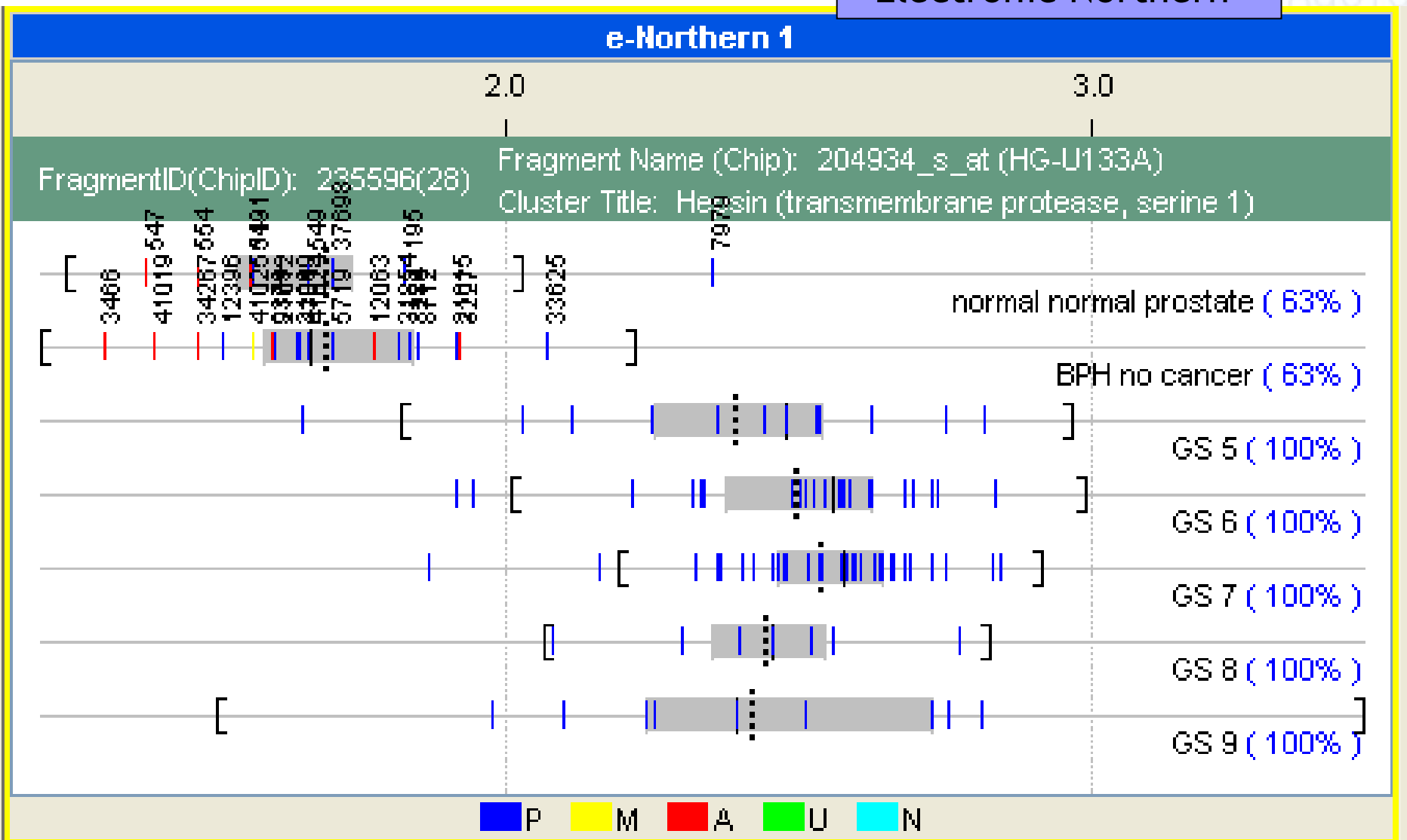
Principal Components Analysis

Genes: 205 (Selected: 1) Samples: 111 (Selected: 27) Normalization: Affymetrix (MAS 5.0) Data Transform: Symmetric Log

Absolute Analysis - E-Northern for Hepsin

“Electronic Northern”

e-Northern 1



Genes: 205 (Selected: 1) Samples: 111 (Selected: 27) Normalization: Affymetrix (MAS 5.0) Data Transf

J Urol. 2004 Jan;171(1):187-91.

[Related Articles, Links](#)



Hepsin is highly over expressed in and a new candidate for a prognostic indicator in prostate cancer.

Stephan C, Yousef GM, Scorilas A, Jung K, Jung M, Kristiansen G, Hauptmann S, Kishi T, Nakamura T, Loening SA, Diamandis EP.

Department of U

PURPOSE: Other
tissue compared
real-time polyme
MATERIALS A
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(Roche Diagnost
normalize data. R

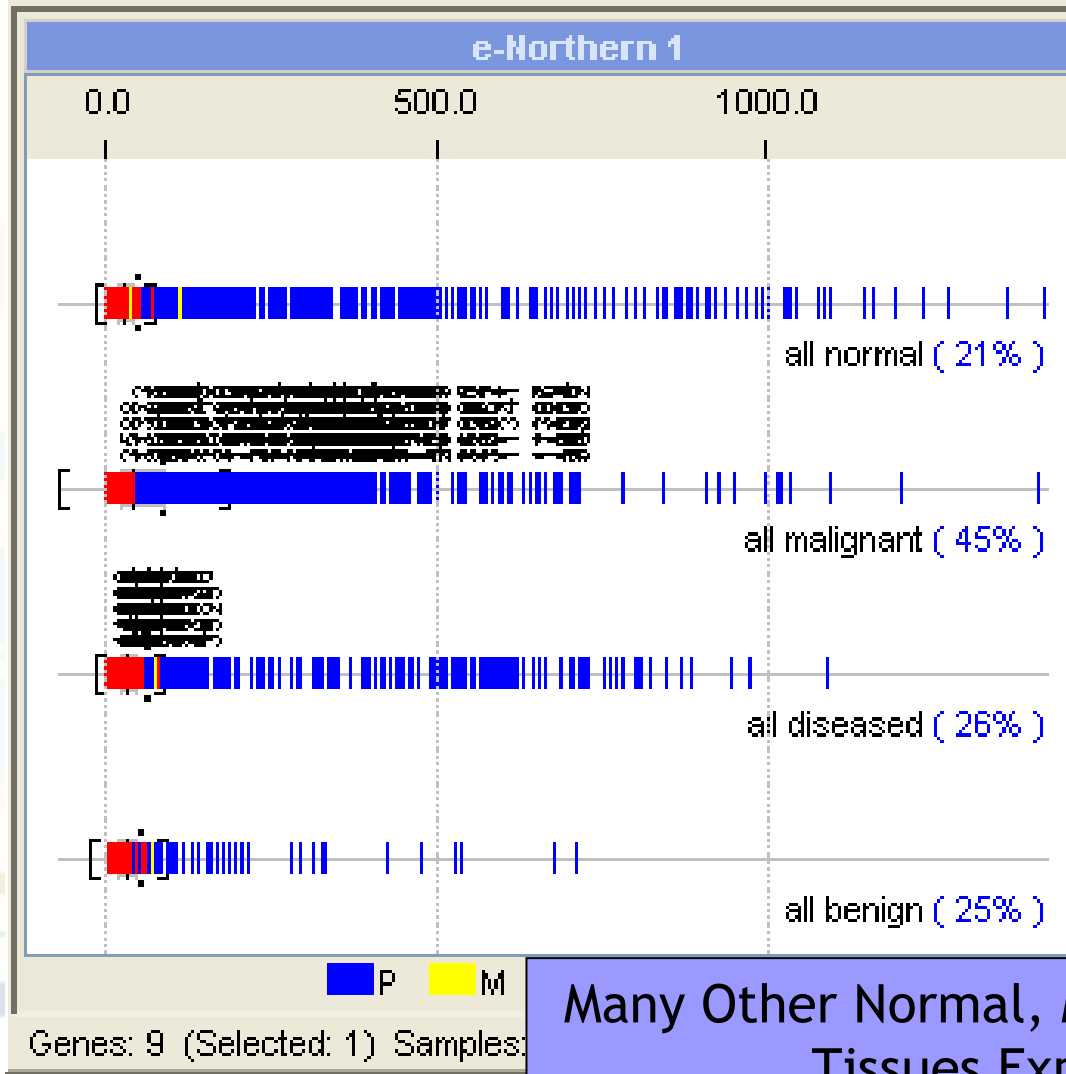
“...This report of the quantitative analysis of hepsin expression ... shows strong and significant over expression in prostate cancer tissue.

“ Hepsin expression may be a new prognostic marker that could be used for assessing prostate cancer aggressiveness.”

RESULTS: Hepsin over expression in cancerous compared with noncancerous tissue was found in 81 of the 90 patient samples (90%, $p < 0.001$). In 48 patients (53%) hepsin over expression was more than 10-fold in cancerous tissue. The ratio of cancerous-to-noncancerous hepsin expression was significantly higher in the 39 patients with grade 3 tumors compared with the 51 with grade 2 tumors (median 15.5 vs 9.6, $p = 0.031$). For the prognosis a cutoff at the 75th percentile provided a significant difference between patients at lower risk (pT2, G2 and Gleason score less than 7) and higher risk (pT3/4, G3 and Gleason score 7 or greater) for relapse. CONCLUSIONS: This report of the quantitative analysis of hepsin expression, which is the first to our knowledge, shows strong and significant over expression in prostate cancer tissue. Hepsin expression may be a new prognostic marker that could be used for assessing prostate cancer aggressiveness.

prostate cancer
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cohort of samples.
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I on a LightCycler
e) was used to
in 81 of the 90

How Specific is Hepsin to Prostate Cancer?



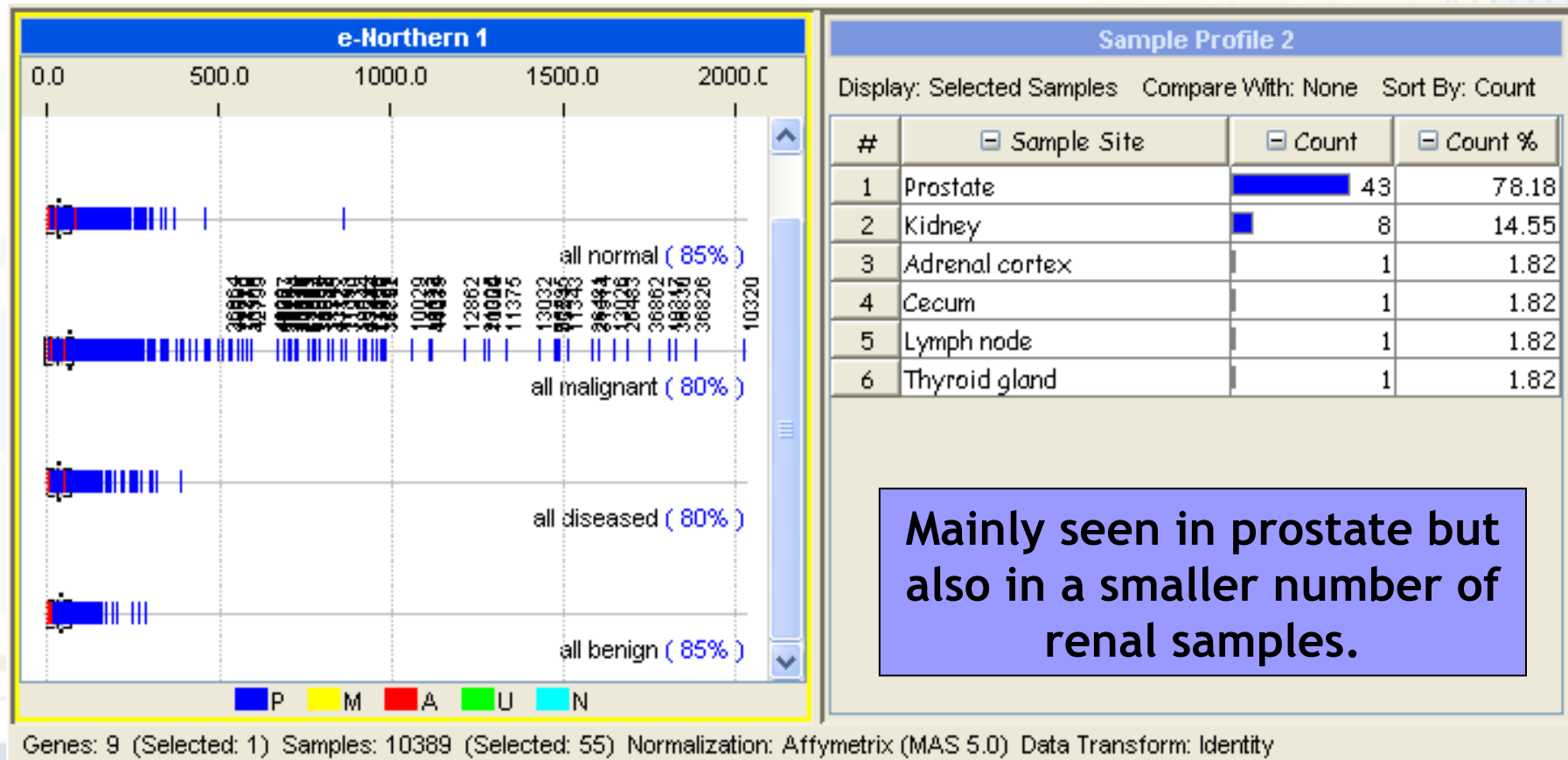
Many Other Normal, Malignant and Diseased Tissues Express Hepsin.

Sample Profile 2

Display: Selected Samples Compare With: None Sort By: Count

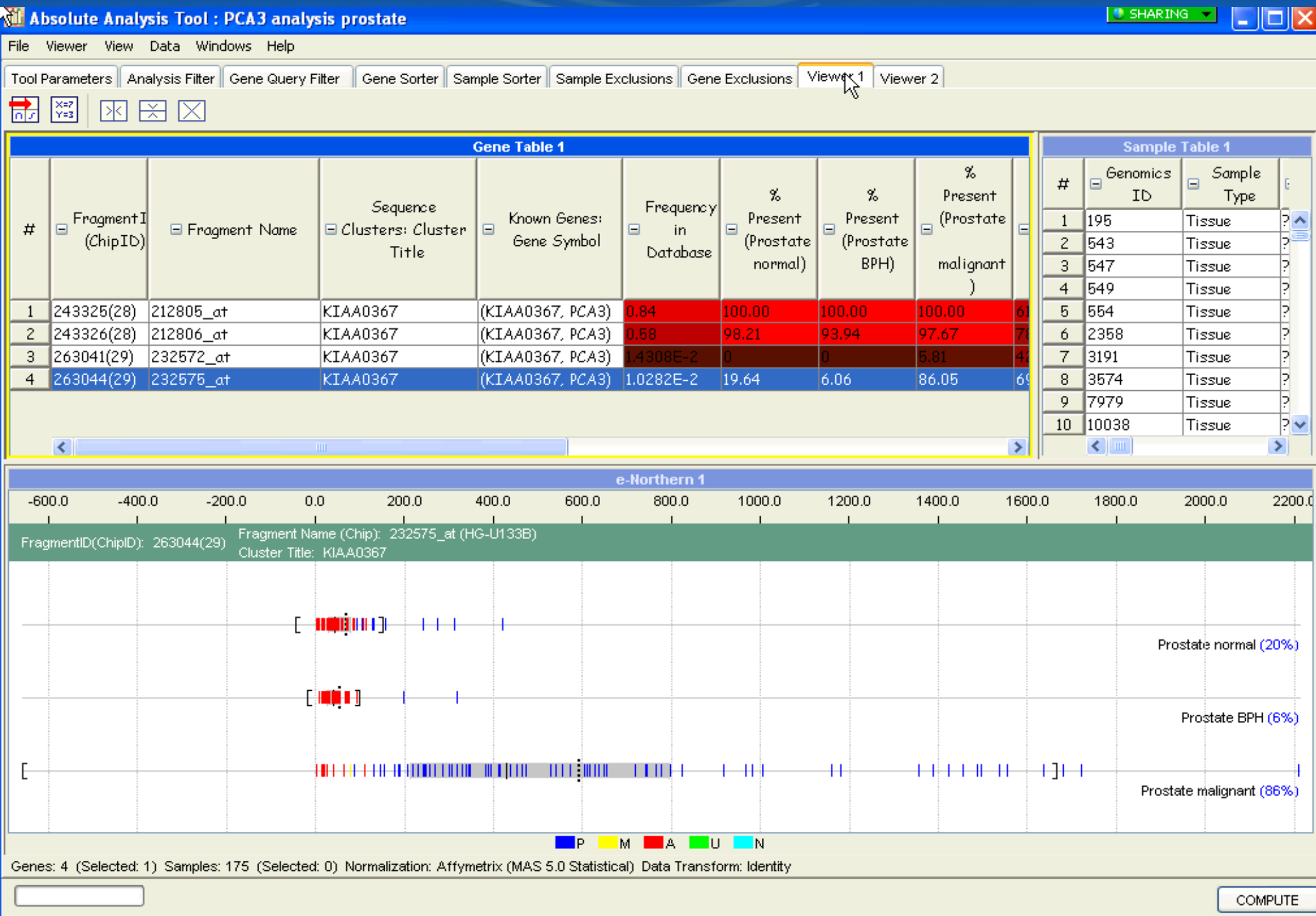
#	Sample Site	Count	Count %
1	Prostate	136	100.00

α -Methylacyl-CoA Racemase (AMACR)

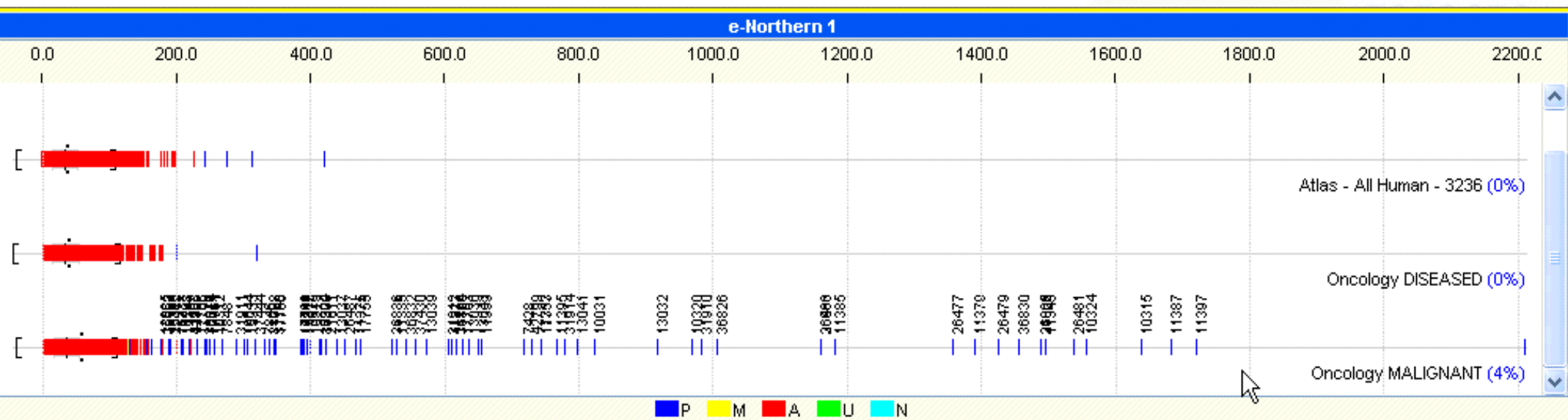


Mainly seen in prostate but also in a smaller number of renal samples.

Absolute Analysis - Across Prostate Sample Sets



Absolute Analysis - Disease and Tissue Specificity



Sample Profile 1

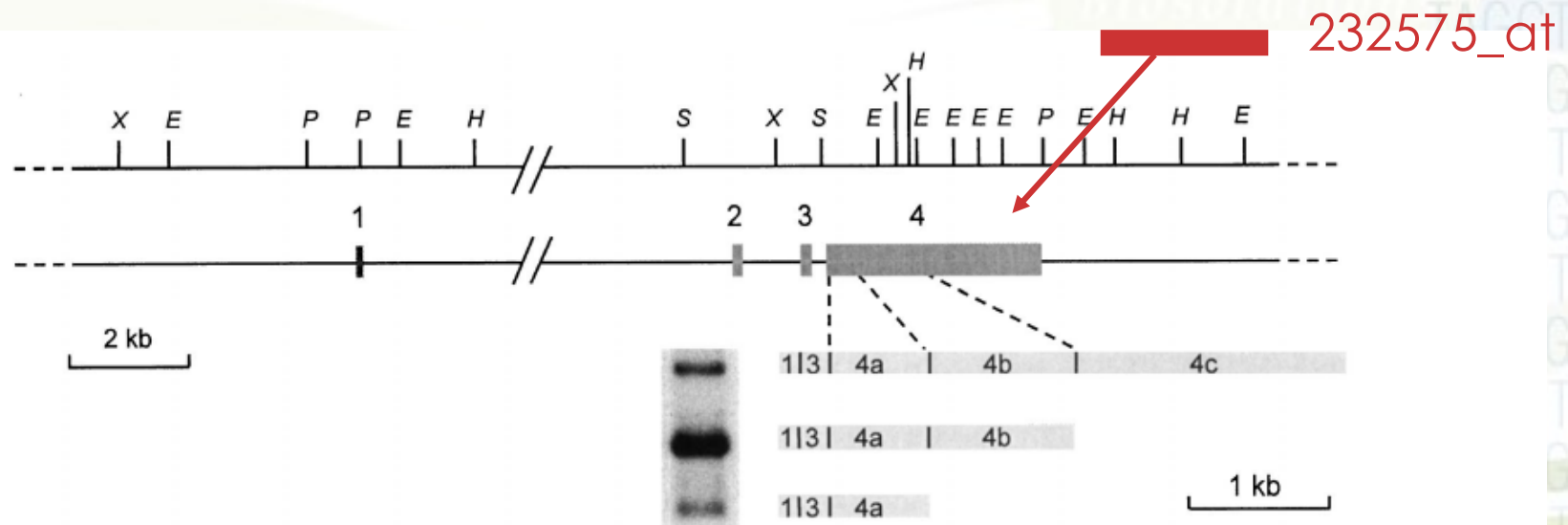
Display: Selected Samples Compare With: None Sort By: Value Groups: 4

#	Sample Site	Count	Count %
1	Lymph node	1	1.32
2	Pancreas	1	1.32
3	Pelvic lymph node	1	1.32
4	Prostate	73	96.05

Genes: 4 (Selected: 1) Samples: 8446 (Selected: 76) Normalization: Affymetrix (MAS 5.0 Statistical) Data Transform: Identity

PCA3 Splice Variants in the Literature

- The PCA3 RNA was described as the most prostate-specific gene and could not be detected in other than prostatic normal and malignant human tissues (*Bussemakers et al., 1999*).



- It has been reported (*Gandini et al., 2003*) that:
 - PCA3 splice variants spanning exons 1-3 can be detected by RT-PCR in a wide variety of normal and malignant human tissues
 - Prostate specific expression was observed only for variants including exon 4

PCA3 in the Literature: A Potential Diagnostic Marker for Prostate Cancer

- 1: [Eur Urol. 2003 Jul;44\(1\):8-15; discussion 15-6.](#)

ELSEVIER
FULL-TEXT ARTICLE

Comment in:

- [Eur Urol. 2004 Aug;46\(2\):271-2.](#)

DD3(PCA3)-based molecular urine analysis for the diagnosis of prostate cancer.

[Hessels D](#), [Klein Gunnewiek JM](#), [van Oort I](#), [Karthaus HF](#), [van Leenders GJ](#), [van Balken B](#), [Kiemenev LA](#), [Witjes JA](#), [Schalken JA](#).

Department of Experimental Urology, Nijmegen Center for Molecular Life Sciences, P.O Box 9101, 6500 HB Nijmegen, The Netherlands.

BACKGROUND: DD3(PCA3) is the most prostate cancer-specific gene described to date. To assess the clinical utility of DD3(PCA3) a time-resolved fluorescence-based, quantitative RT-PCR analysis for DD3(PCA3) was developed. **METHODS:** The diagnostic potential of DD3(PCA3) was determined by quantitative measurement of DD3(PCA3) transcripts in non-malignant and malignant prostate specimens. Moreover, DD3(PCA3) transcripts were determined quantitatively in urine sediments obtained after prostatic massage. A cohort of 108 men, admitted for prostate biopsies based on a PSA of >3ng/ml, was studied. **RESULTS:** Prostate tumors showed a 66-fold up-regulation of DD3(PCA3) (median 158.4.10(5) copies/microg tissue RNA) when compared to benign prostate tissue (median 2.4.10(5) copies/microg tissue RNA). This up-regulation was found in more than 95% of prostate cancer specimens studied. These data revealed that specimens with less than 10% of cancer cells could be accurately discriminated from non-cancer tissues. Hence, detection of a small fraction of prostate cancer cells in a background of normal cells seemed feasible. Therefore, this DD3(PCA3)-based RT-PCR assay was used for the identification of prostate cancer in urine sediments obtained after prostatic massage. From 108 men with a serum PSA value >3ng/ml, 24 men were shown to have prostate cancer upon biopsy. Of these 24 men, 16 were shown to be positive for DD3(PCA3), indicating a sensitivity of the assay of 67%. Furthermore, a negative predictive value of 90% was calculated. **CONCLUSION:** The quantitative RT-PCR assay for DD3(PCA3) described, bears great promise as a tool for molecular urine analysis. It has great potential in reducing the number of unnecessary biopsies. A multi-center study using this DD3(PCA3) assay can provide the basis for the utility of molecular diagnostics in clinical urological practice.

PMID: 12814669 [PubMed - indexed for MEDLINE]

[Related Articles, Links](#)

PCA3 in the News: A Novel Diagnostic Marker

News

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Industry Events

Media

Gen-Probe Acquires From DiagnoCure Exclusive Worldwide Diagnostic Rights To New Prostate Cancer Gene

Companies Form Collaboration to Develop Molecular Test for PCA3^{DD3} That May Offer Advantages Over Traditional PSA Testing

- Agreement Accelerates Gen-Probe's Growth in Oncology -

SAN DIEGO, CA , November 20 -- Gen-Probe (Nasdaq: GPRO) and DiagnoCure (Toronto: CUR) announced today that they have signed a license and collaboration agreement under which they will develop, and Gen-Probe will market, an innovative urine test to detect a new, highly specific genetic marker for prostate cancer.

The diagnostic test will detect a recently described gene called PCA3^{DD3} that has been shown by studies to date to be over-expressed only in malignant prostate tissue. The test may offer advantages over prostate specific antigen (PSA) testing, the current standard for initial prostate cancer screening in conjunction with a digital rectal exam.

Under the terms of the agreement, Gen-Probe will pay DiagnoCure an upfront US \$3 million fee, and future fees and contract development payments of up to US \$7.5 million over the next three years. Gen-Probe will receive exclusive worldwide rights to diagnostic products resulting from the agreement, and will pay DiagnoCure royalties of 8% on cumulative net product sales of up to \$50 million, and royalties of 16% on cumulative net sales above \$50 million.

"The completion of this license agreement represents a major milestone in our planned and communicated strategy," said Pierre Desy, president and CEO of DiagnoCure. "We expect this test to detect the PCA3^{DD3} gene in urine to be the first gene-based, adjunctive screen for this devastating disease. Gen-Probe is the ideal partner to bring this important new test to the market. Their leadership in nucleic acid testing (NAT), their proprietary APTIMA(R) technologies, and their strong desire to become a leader in gene-based testing in oncology are the fundamentals that will realize and optimize all the potential of this marker."

Conclusions: The Power of BioExpress® System

- Identify differentially expressed genes between disease and normal state for many disease indications
- Correlate (or not) expression of chosen gene with relevant clinical parameters from extensive list and/or pathology
- Rapidly confirm expression in wide range of normal tissues
- Access annotation and sequence information for each fragment



Ocimum-Gene Logic

Your Partner for Genomics Outsourcing