



Early
Detection
Research
Network



Patient Advocate Webinar

September 22, 2011 4 pm EASTERN



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Welcome

EDRN and Collaborative Group Projects

Q & A

Sudhir Srivastava, PhD, M.P.H.

Joshua LaBaer, M.D., Ph.D.

Group

EDRN Patient Advocates

Carole Siegel (GI)

Merel Grey Nissenberg (Lung, Prostate)

Elda Railey (Breast, GYN)

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Welcome




Sudhir Srivastava, PhD, MPH

National Cancer Institute Program Director

Chief, Cancer Biomarkers Research Group

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How can we save more lives?

- Most cancers are diagnosed when they are 1 - 4 cm in size
- By this time many have already metastasized
- To save more lives we need effective methods for:
 - Risk assessment
 - Early detection
 - Therapy

Mission

The National Cancer Institute's Early Detection Research Network's mission is to implement biomarker research through strategic and systematic, evidence-based discovery, development and validation of biomarkers for cancer risk assessment, early detection, diagnosis and prognosis of cancer.

How Does EDRN Relate to NCI's Mission?

- EDRN is now a driving force behind inter-governmental, inter-institutional and public-private collaboration-building for the rapid advancement of biomarkers and early detection science and its translation to clinical applications.
- This approach is fundamental to meeting NCI's goals of eliminating the suffering and death due to cancer.

Investigator-Driven Consortium

Discovery

Assay Development

Validation

Biomarker Reference Laboratories

Biomarker Developmental Laboratories

Clinical Validation Centers

Network Consulting Team, Chair: Larry Norton, M.D.

Steering Committee, Chair: Ian Thompson, Co-Chair: Joshua Labaer

Data Management and Coordinating Center, Director: Ziding Feng, Ph.D.

Discovery to Validation – the Model

BDL Biomarker Discovery
Samples of Convenience
Case Control
Verify using blinded specimens from collaborators

If promising, BDL works with BRL

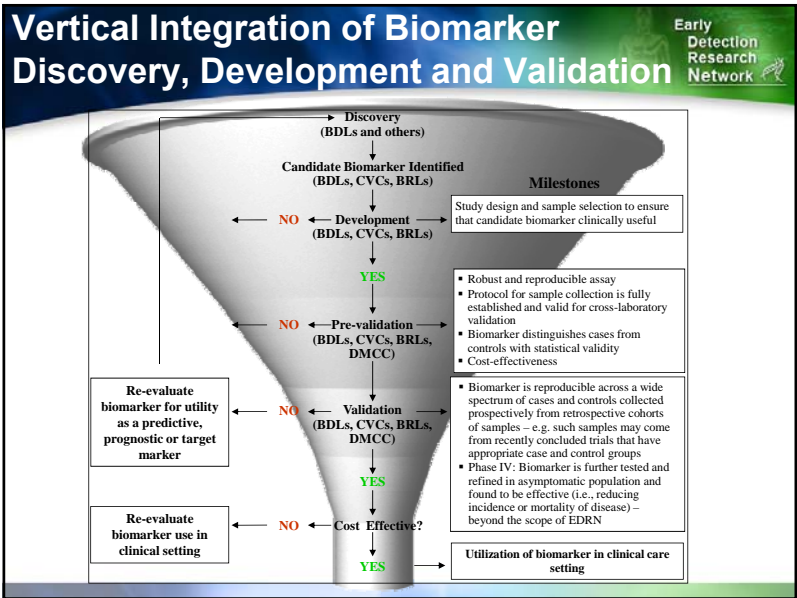
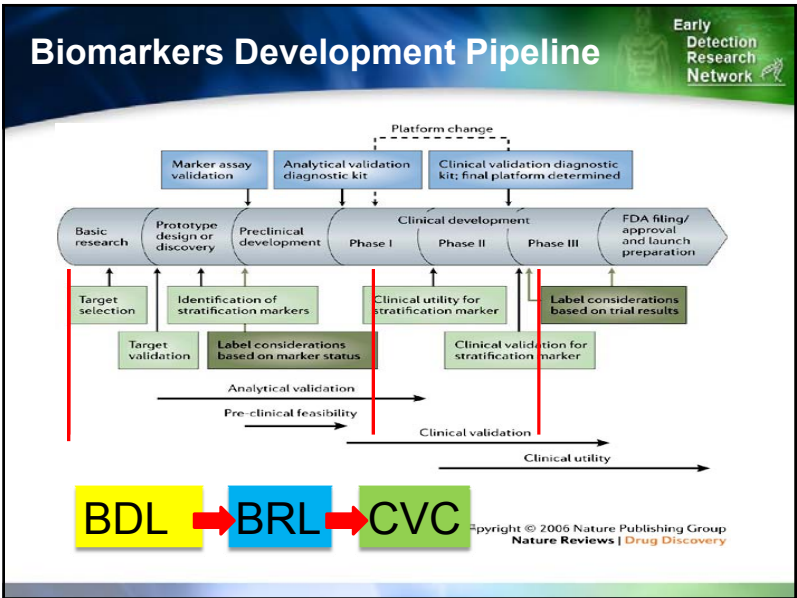
BRL Assay Refinement
Reproduce Results
Samples of Convenience
Verify using new blinded specimens

If assay reproducible and has sufficient sensitivity and specificity, BDL works with CVC & DMCC to conduct a validation trial.

CVC & DMCC Biomarker Validation
Case Control
BRL performs assays
Verify using blinded specimens from collaborators

If successful,

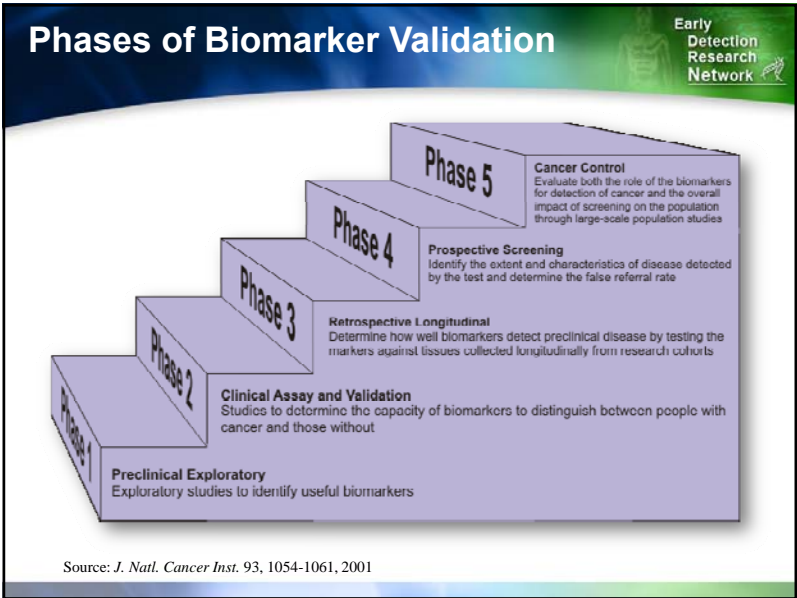
Longitudinal biomarker validation trial



EDRN and Biomarker Discovery

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- Good quality specimens with clinical annotations are being used;
- Clinical questions are well defined;
- Multiple technology platforms being used simultaneously for biomarker discovery;
- EDRN's Reference Sets are used to verify discovered biomarker for intended clinical use;
- A numbers of systems-related approaches are being used to identify potential biomarkers;
- Unsubstantiated, unproven biomarkers are quickly removed from the biomarker pipeline.



Food for Thought

“It costs \$1 billion, Hartwell said, to funnel a single cancer medication through the regulatory pipeline. For a fraction of that, he said, new diagnostics to spot cancers in their earliest stages ultimately could save more lives. “

EDRN Collaborations

- Research collaborations take place within an environment of teamwork across different disciplines and laboratories focused on achieving common goals, such as:
 - Developing and testing promising biomarkers and technologies to obtain preliminary information to guide further testing;
 - Evaluating promising, analytically proven biomarkers and technologies, such as measures of accuracy, sensitivity, specificity and, when possible, potential predictors of outcomes or surrogate endpoints for clinical trials;
 - Analyzing biomarkers and their expression patterns to serve as background for large, definitive validation studies;
 - Collaborating with academic and industrial leaders to develop high-throughput, sensitive assay methods;
 - Conducting early phases of clinical and epidemiological biomarker studies; and
 - Encouraging collaboration and dissemination of information to ensure progress and avoid fragmentation of effort.

What is a Biomarker?


What is a Biomarker?

Biological event which takes place between “health” exposure and the subsequent development of a disease

Well State → Biomarker → Disease

Doctors use them to understand how a patient is doing or to make predictions

Example of a Biomarker



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Why Biomarkers for Cancer?

Risk Assessment
Early Detection

Prognosis
Therapeutic Prediction
Therapeutic Monitoring

“Prevention”

“Treatment”

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What Do We Use Biomarkers for?

- Monitor disease (esp. chronic illnesses)
 - Cancer
 - Diabetes
 - Autoimmune
- Monitor therapeutic intervention
 - Surrogate marker for response in clinical trials
- Drug development
 - Predict toxicity
 - Predict efficacy
- Screening tool to diagnose disease
 - Chronic diseases: Early detection of cancer
 - Acute diagnosis: Myocardial Infarctions/Infections
 - Used as either a primary or secondary screening test
- Screening tool to diagnose infectious disease
 - Predict vaccine targets
- Personalized medicine
 - Clarify molecular diagnosis
 - Predict best possible individualized clinical management

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Discovery Strategy Using High Throughput Technologies

Genomics Platforms (genes)
Proteomics Platforms (proteins)

Gene Product
-Methylated Gene
-Mutated Gene
-Polymorphism

↓

Gene Technology Assay

Specific target/protein product isolated, identified
Make antibody
Create immunoassay

↓

Immunoassay based Biomarkers

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What Do You Want in an “Ideal” Biomarker?

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- High positive and negative predictive values (excellent ROC characteristics)
- Easy to sample (preferably urine, serum)
- Cheap to assay
- Easy to quality control (Automated, rapid throughput technology)
- Algorithmic usage

Key Concepts to Understanding Biomarkers

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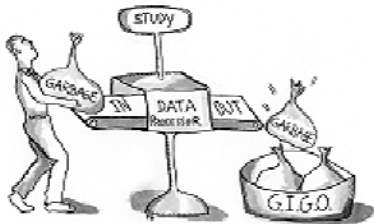
Sample Handling

Analytics

Validation

Handling a Sample

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GARBAGE IN — GARBAGE OUT

Key Concepts to Understanding Biomarkers

Early Detection Research Network

Sample Handling

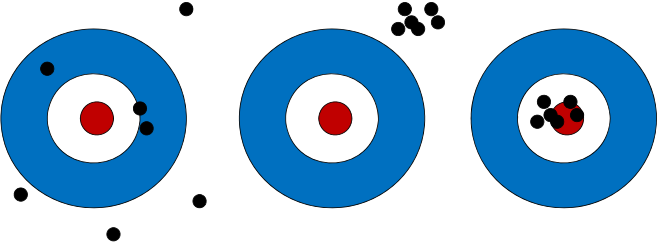
Analytics

Validation

Components of the Assay

- Sensitivity
- Precision and Accuracy
- Selectivity
- Throughput
- Dynamic range
- Stability
- Cost

Precision and Accuracy



Statistics for Advocates

And now for a little bit of basic statistics...

But don't be frightened, this will be easy and I will do it all for you...

Besides it is really important and has real life implications.

Statistics for Advocates

		Disease	
		Present	Absent
Test	Positive	a	b
	Negative	c	d

$a+b+c+d$ = all the people in the study or population

Statistics for Advocates

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		Disease	
		Present	Absent
Test	Positive	a	b
	Negative	c	d

a = true positives = test correctly calls the disease

Statistics for Advocates

Early Detection Research Network

		Disease	
		Present	Absent
Test	Positive	a	b
	Negative	c	d

d = true negatives = test correctly calls the disease absent

Statistics for Advocates

Early Detection Research Network

		Disease	
		Present	Absent
Test	Positive	a	False Positive
	Negative	c	d

b = false positives = test calls the disease when it is absent

Statistics for Advocates

Early Detection Research Network

		Disease	
		Present	Absent
Test	Positive	a	False Positive
	Negative	c	d

Consequences of False Positives:

- Emotional angst
- Expensive and unnecessary additional testing
- Falsely reduces success rate of a treatment regimen

Statistics for Advocates

Early Detection Research Network

		Disease	
		Present	Absent
Test	Positive	a	b
	Negative	False Negative	d

c = false negatives = test misses the disease when it is present

Statistics for Advocates

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		Disease	
		Present	Absent
Test	Positive	a	b
	Negative	False Negative	d

Consequences of False Negatives:

- Missed diagnosis
- Missed opportunity for intervention
- Most common cause for malpractice lawsuits

The Probability of Disease

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		Disease	
		Present	Absent
Test	Positive	a	b
	Negative	c	d

$\frac{a+c}{a+b+c+d}$

Probability of disease = $a+c/(a+b+c+d)$ = prevalence

Key Terms for Tests

Early Detection Research Network

		Disease	
		Present	Absent
Test	Positive	a	b
	Negative	c	d

$\frac{a}{a+c}$

Sensitivity = $a/(a+c)$ = finding disease when it exists

Specificity = $d/(b+d)$ = ruling out disease when it is absent

PPV = $a/(a+b)$ = predictive value of a positive test

NPV = $d/(c+d)$ = predictive value of a negative test

Key Terms for Tests

Early Detection Research Network

		Disease	
		Present	Absent
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Key Terms for Tests

Early Detection Research Network

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Why Do We Care About these Numbers?

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Patient Group	Cases/100,000
All men	35
Men \geq 75 y.o.	500
Clinically suspicious nodule detected	50,000

Watson, R.A., Tang, D.B., NEJM (1980) 303:497-499

Using Tests in a Low Risk Group

Clinical nodule
(50,000/100,000)

		Disease		
		Present	Absent	
Test	Positive	35,000	5,000	88%
	Negative	15,000	45,000	

Sensitivity = $a/(a+c) = 70\%$
Specificity = $d/(b+d) = 90\%$
PPV = $a/(a+b)$ = predictive value of a positive test for men with a clinical evidence of a nodule

Using Tests in a Low Risk Group

All men
(35/100,000)

		Disease		
		Present	Absent	
Test	Positive	25	9,997	0.2%
	Negative	10	89,969	

Sensitivity = $a/(a+c) = 70\%$
Specificity = $d/(b+d) = 90\%$
PPV = $a/(a+b)$ = predictive value of a positive test For all men

Key Concepts to Understanding Biomarkers

Sample Handling

Analytics

Validation

Picking Winners and Losers

Industry

Academics

Literature

Biomarker Discovery Convenience Set Data

Entry to Reference Set

Reference Set Characterization and Refinement

Entry to Cross Sectional Validation

Cross Sectional Validation

Longitudinal Study

Statistically Derived Panels of Biomarkers

Lab: High throughput CLIA Q/A, Q/C

Setting Criteria for Biomarker Performance
Endpoints: Colon Adenocarcinoma Detection

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Types of Markers

Population Screen

- Identifies individual who needs more further workup
- End result = Colonoscopy

Diagnostic Marker

- Rules in/out the presence of cancer
- End result = Surgery

Successes

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- Identified more than 1000 biomarkers
- More than 200 prioritized biomarkers are ready for verification and validation studies
- Six validation studies completed
 - MSA for bladder cancer
 - DCP and AFP-alpha 3 for liver cancer
 - ProPSA, PCA3 and MS proteomic assay for prostate cancer
 - Circulating protein markers for ovarian cancer
- Ten valuable clinical specimen reference sets available for rapid and inexpensive testing of future biomarkers

Successes

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- More than 25 patent and licenses
- More than 15 collaborations with biotech and diagnostic companies
- More than 700 collaborative papers generated
- 5 clinical trials have moved forward to test biomarkers for the early detection of liver, bladder, lung, mesothelioma, and prostate cancer

Lung

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The strategic goals to address current clinical needs are:

- determine if a **test for early detection of lung cancer** be developed that achieves a performance above the overriding risk factor that smoking presents
- determine whether biomarkers can be developed for use in conjunction with CT imaging in order to identify **which patients with an indeterminate nodule of ≤ 3 cm should receive further work-up** for diagnosis of lung cancer
- and determine whether a test can be devised to **improve the negative predictive value** and better classify true positives to enhance the performance **of imaging techniques** in samples from the National Lung Cancer Screening Trial (NLST).

Lung



Project: Blood Test to Detect Solitary Pulmonary Nodules

A lung collaborative team project is being implemented to test some of the most promising lung cancer candidate biomarkers in blood, in the context of CT-detection of solitary pulmonary nodules in the range of 0.5-3 cm in diameter.

Project: Gene Expression Changes in Nasal Cells: May Be Early Diagnostic Biomarker for Lung Cancer

A simple, minimally-invasive technique using cells from the interior of the nose could help clinicians detect lung cancer in its earliest – and most treatable – stages.

Patient Advocate – Merel Grey Nissenberg

Colorectal Cancer Plan



Investigators are working toward the following:

- Conduct rigorous clinical validation of promising biomarkers for the **detection of early stage colorectal cancer and adenomas**;
- Use proteomic, genomic and epigenomic techniques to identify biomarkers that determine **which patients are at high-risk for adenocarcinoma and in need of having a colonoscopy**; and
- Develop and test **novel optical imaging methods** to detect colon cancer using brushings from rectal tissues.

Colorectal Cancer Team Projects



Team Project 1: Adenoma Detection

Colonoscopy reduces incidence and mortality of colorectal cancer primarily through the removal of adenomas. However, as non-colonoscopy-based methods, such as FOBT, detect only about half of the high-risk adenomas (adenomas ≥ 1 cm), **there is a need for biomarkers detectable in stool, blood, or urine** with improved sensitivities for advanced adenomas. This team project will employ a phased approach to the discovery, verification and validation of markers of advanced adenomas in bodily fluids.

Team Project 2: Biomarkers to Predict Adenoma Recurrence

Individuals who have adenomas are at higher risk of forming recurrent adenomas and interval colorectal cancers, and all subjects with adenomas undergo surveillance, but our ability to gauge their risk of subsequent neoplasia is crude and imprecise. This team project will employ a phased approach to the **discovery of biomarkers to predict the risk of adenoma recurrence** and interval cancers.

GI – Colorectal



Preliminary Validation of Biomarkers for the Detection of Colorectal Adenomas

Clinical Use: Screening for early detection – eventually supplant colonoscopy

Training set:

- 50 healthy screening controls
- 50 healthy surveillance controls
- 50 adenomatous polyps
- 50 advanced adenomatous polyps
- 50 early stage cancers
- 50 late stage cancers
- Test set (blinded):
 - 95 healthy normal,
 - 95 adenomatous polyps,
 - 95 advanced adenomatous polyps,
 - 95 early stage cancer, and
 - 95 late stage cancers
- These 475 participants will be sampled once in the un-prepped and non-fasting state. (Brenner)
- Biomarkers should beat occult blood testing sensitivity by 20% with minimum specificity of 70%

GI - Pancreatic



- **Project: Prioritization of Biomarkers for Early Detection of Pancreatic Cancer**
 - Study: EDRN has constructed a **high-quality reference set** (serum and plasma) consisting of well-characterized samples from **early stage pancreatic cancer**. These include autoantibodies to tumor specific glycopeptides; mucin type glycoproteins; glycosylation pattern of specific proteins associated with pancreatic cancer; miRNAs; genomic markers; and SNP's.
- **Project: Development of Biomarkers that Distinguish Benign Pancreatic Cysts from Precancerous Lesions**
 - Study: EDRN is currently in the process of establishing a **second pancreatic cancer reference set for IPMNs** (Intraductal papillary mucinous neoplasm). Top-performing biomarkers in distinguishing pancreatic cancer cases from controls using the pre-validation reference set will be further tested on the IPMN reference set for their ability to distinguish between benign pancreatic cysts from premalignant lesions. Panels of diverse biomarkers will be also tested for improved predictive performance.
- **Project: Spectral Markers for Risk Assessment of Pancreatic Cancer**
 - Study: EDRN investigators will evaluate the possibility of combining the imaging modality partial wave spectroscopy (PWS) with molecular biomarkers, including tissue miRNAs to detect pancreatic cancer.
- **Patient Advocate – Carole Seigel**

Breast GYN Group



- Investigators in the Breast and Gynecological Cancers Collaborative group are working toward the identification and validation of:**
- Biomarkers to further **improve the interpretation of conventional mammography** or other computer-aided technologies;
 - Biomarkers that detect characteristics of benign and malignant breast lesions and **stratify benign disease into high and low risk** for progression;
 - Biomarkers which, in conjunction with mammography, can **distinguish malignant from benign lesions** in order to reduce or eliminate unnecessary biopsies;
 - Biomarkers to **detect highly proliferative early malignant lesions** associated with increased mortality; and
 - Tumor-specific biomarkers that could be used as contrast agents to **improve the performance of existing imaging modalities**.

Breast GYN Group



PROJECTS

- Tissue Biomarkers for Progression of Benign Breast Disease to Invasive Breast Cancer
- Circulating Biomarkers of Triple Negative Breast Cancer
- Circulating Biomarkers of Ovarian Cancer

Patient Advocate Representative

Elda Railey

Prostate



Prostate Cancer - The Plan

- **To accomplish the strategic goals the collaborative group proposed the following plan:**
 - Develop biomarkers, which could **discriminate between indolent and aggressive prostate cancers** based on a variety of "omics" approaches (genomics, epigenomics, proteomics and metabolomics);
 - Develop urine and blood based assays for all promising prostate cancer biomarkers;
 - Conduct **rigorous clinical evaluation of promising biomarkers** for early detection and of aggressive prostate based on recently discovered cancer specific fusion transcripts such as TMPRSS2-ERG, TMPRSS2-ETV1 etc ;
 - Perform a meta-analysis on the performance of all validated promising prostate cancer biomarkers to **select the best markers for earlier detection of clinically significant prostate cancers**;
 - Evaluate reactive cancer stroma markers in tissue and urine samples; and
 - **Combine biomarkers with imaging modalities** for better and earlier detection of aggressive prostate cancer.
- **Patient Advocate – Merel Grey Nissenberg**

Prostate



- **Project 1: Evaluation of Urine PCA3 and TMPRSS2-ERG**
 - Study: The project will determine whether multiplex combination of urinary measurement of TMPRSS2-ERG fusion and PCA3, together with serum PSA and percent-proPSA can improve the early detection of histopathologically aggressive prostate cancer.
- **Project 2: Establishing Community-Based Normal Distributions of Urinary PCA3 and TMPRSS2-ERG**
 - Study: The frequency of detection of post-DRE urinary PCA3 and TMPRSS2-ERG fusion, and percent-free PSA and percent-proPSA in serum of a community-based sample of men undergoing prostate cancer screening will be determined by this project. The goal is to examine whether frequency differs between African-American men as compared to men of other racial backgrounds, and between Hispanic-American men as compared to men of non-Hispanic ethnicity.
- **Project 3: Measuring Multiple Cancer Secreted Proteins**
 - Study: The study will discern aggressive from indolent prostate cancer by measuring multiple proteins secreted by prostate cancer cells that are shed in voided urine.

Prostate



- **Project 4: Tissue Microarrays for Biomarker Validation**
 - Study: Identification and testing of available tissue microarrays (TMAs) is essential for evaluation and validation of diagnostic and prognostic biomarkers.
- **Project 5: Upgrading Gleason Scores on Radical Prostatectomies**
 - Study: This project will determine the clinical parameters associated with upgrading Gleason scores on radical prostatectomies.
- **Project 6: Molecular Sub-Classification of ETS and Non-ETS Rearrangements**
 - Study: This project addresses the molecular sub-classification of ETS and non-ETS rearrangements in prostate cancer.

Prostate




- **Project 7: Prostate Cancer Phenotypes and Clinical Outcomes**
 - Study: This project is focused on prostate cancer phenotypes and clinical outcomes. Two markers can group patients into three survival or disease risk categories. Additional informative sub-grouping will be provided by markers associated with Gleason pattern 4 vs. pattern 3 cells, and CD10+ vs. CD10- cancer cell types. Further reactive stroma markers will be added based on a recently developed classification.
- **Project 8: Vascular Tissue Biomarkers for Molecular Imaging**
 - Study: This project, centers on the identification of cancer related vascular tissue biomarkers for molecular imaging.

Resources and Reading



- EDRN web site <http://edrn.nci.nih.gov/>
- **Research Advocacy Network**
 - Biomarkers in Cancer Tutorial for Advocates www.researchadvocacy.org

Contacts



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