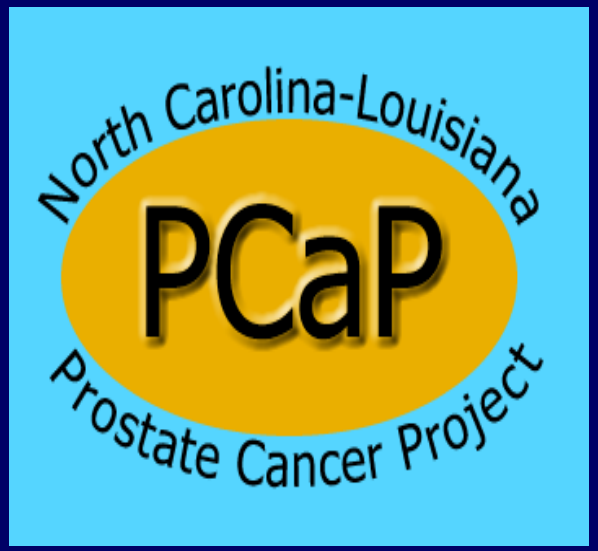
Racial Differences in Prostate Cancer: Influence of Health Care Interaction and Host and Tumor Biology



Prostate Cancer in Caucasian vs African Americans - 2002

- Frequency of incidental prostate cancer the same
- In men < 65, CaP mortality rate is 3.1 times higher in African than Caucasian Americans
- In men > 65, CaP mortality rate is 2.3 times higher in African than Caucasian Americans

Reasons for Racial Disparity - 2002

Compared to Caucasian Americans, African Americans:

- Have more aggressive CaP
- Choose inferior treatments for CaP
- More often present with incurable CaP due to limited access to health care and/or decreased participation in early detection programs

Racial Differences in Health Care System Interaction

- African and Caucasian Americans desire clarity from their physicians but are often confused by the information received. Both lack of substance and poor sequence of information presented generate feelings of mistrust toward physicians.
- Among many characteristics studied (health-related attitudes, beliefs and experiences), African and Caucasian Americans differed in only one- religiosity.
- African Americans treatment decisions were influenced more by personal experiences; Caucasian Americans relied more on data and information.

Collins TC, Med Care, 2002

Barriers to Patient-Physician Communication

- race concordance improves satisfaction
- religious faith vs. medical care
- delay in care until symptoms severe
- fear of impotence and dependence
- mistrust of healthcare system

Mishel, Cancer, 2002

Benefits of Education/Outreach Intervention

- decreased rates and duration of incontinence and impotence
- improved CaP knowledge
- improved communication with physicians
- reduced depression, fatigue, anxiety, and confusion

Mishel, Cancer, 2002

Preliminary Data - 2002

Prostate cancer may be more common and aggressive in African Americans because higher levels of Androgen Receptor and SHBG in African Americans enhance the effect of racially similar levels of tissue androgens but clinical evidence for racial differences in prostate cancer behavior, once diagnosed, remains lacking.

Gaston, J Urol 2003;170:990-993; Mohler, J Urol 2004;171:2277-2280; Mohler, Racial Differences in Prostate Cancer Mortality. In Prostate Cancer: Biology, Genetics, and New Therapeutics, Second Edition. Eds. Simons JW, Chung WK, Isaacs WB. Humana Press Inc, 2007 (in press).

PCaP Goal

To demonstrate whether public health resources should be focused upon altering critical patient-health care system interaction or altering patient or tumor biology to reduce CaP mortality, in general, and CaP mortality in African Americans, specifically

Hypothesis

The mortality rate from prostate cancer is more than two-fold higher in African Americans compared to Caucasian Americans due to racial differences in:

1) interaction with the health care system;

2) diet and biology of the host; and/or

3) characteristics of the tumor.

Hypothesis Testing

Reasons for the disparity in prostate cancer outcome by race will be tested on 3 levels:

Level 1)

Racial differences in **interaction with the health care system** will be evaluated by examining early detection behavior; socioeconomic status; attitudes, beliefs and knowledge; health care access; patient-physician communication; patient decision-making; alternative treatment use and treatment choices.

Hypothesis Testing

Level 2)

Racial differences in **host biology** may affect CaP aggressiveness due to genetic, environmental or gene-environmental interactions. Racial differences will be sought in diet with an emphasis upon antioxidant and fat consumption; serum androgens; exposure to carcinogens; expression of CaP susceptibility genes such as androgen metabolism pathway, detoxification, DNA repair and hereditary CaP genes; and serum protein profiles associated with the aggressive CaP phenotype.

Hypothesis Testing

Level 3)

Racial differences in **tumor characteristics** will be examined in tumor extent (clinical stage and serum PSA, a tumor volume surrogate), tumor differentiation (Gleason grade) and tumor growth rate (apoptosis and cellular proliferation); expression of androgen receptor, androgen receptor co-activators and androgen-regulated genes; and stem-like cells.

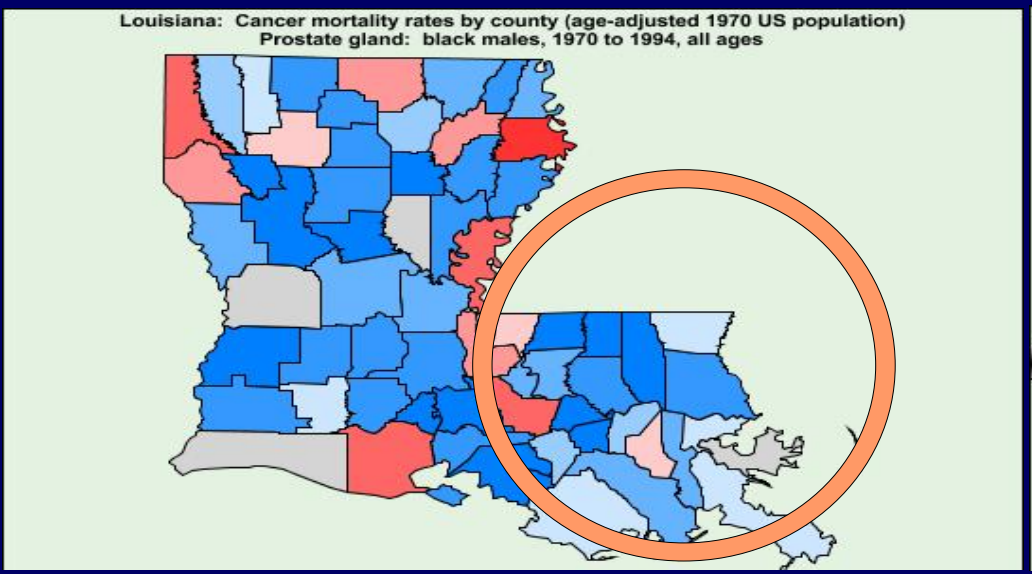
Research Subjects

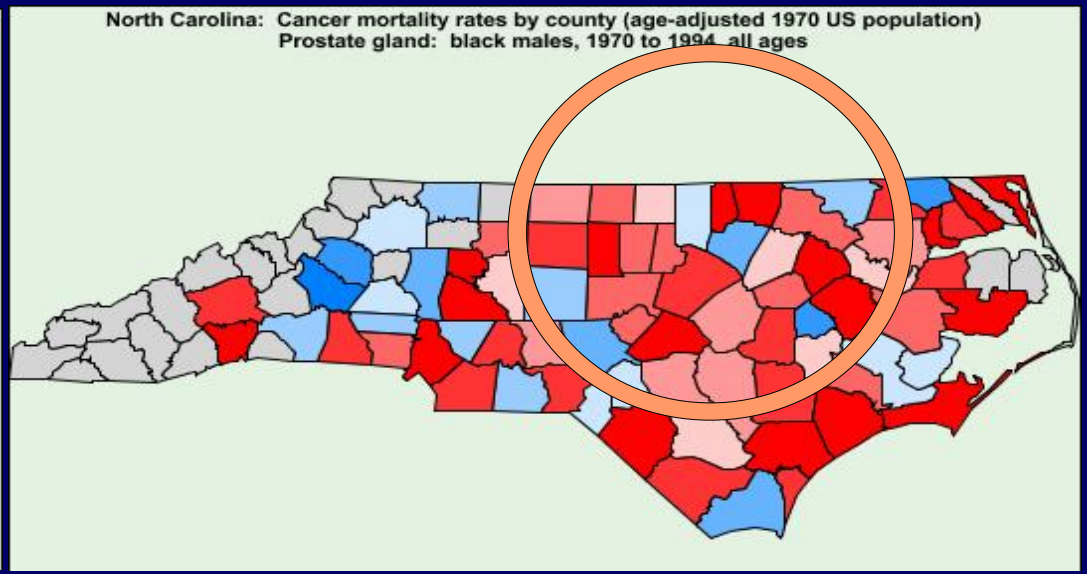
2000 men with newly-diagnosed CaP identified using Rapid Case Ascertainment (RCA)

- 1000 from LA (500 African Americans, 500 Caucasian Americans)
  - 32 Parishes
  - Among African Americans, one of the LOWEST CaP mortality rates in the US[1]
- 1000 from NC (500 African Americans, 500 Caucasian Americans)
  - 42 Counties
  - Among African Americans, one of the HIGHEST CaP mortality rates in the US[1]
  - Similar mortality rates in LA and NC among Caucasians[1]

- [1]Based on rates available at the time of PCaP proposal

Prostate Cancer Mortality: African-American Men 1970 – 1994





61 – 147
45 – 47
16 – 34

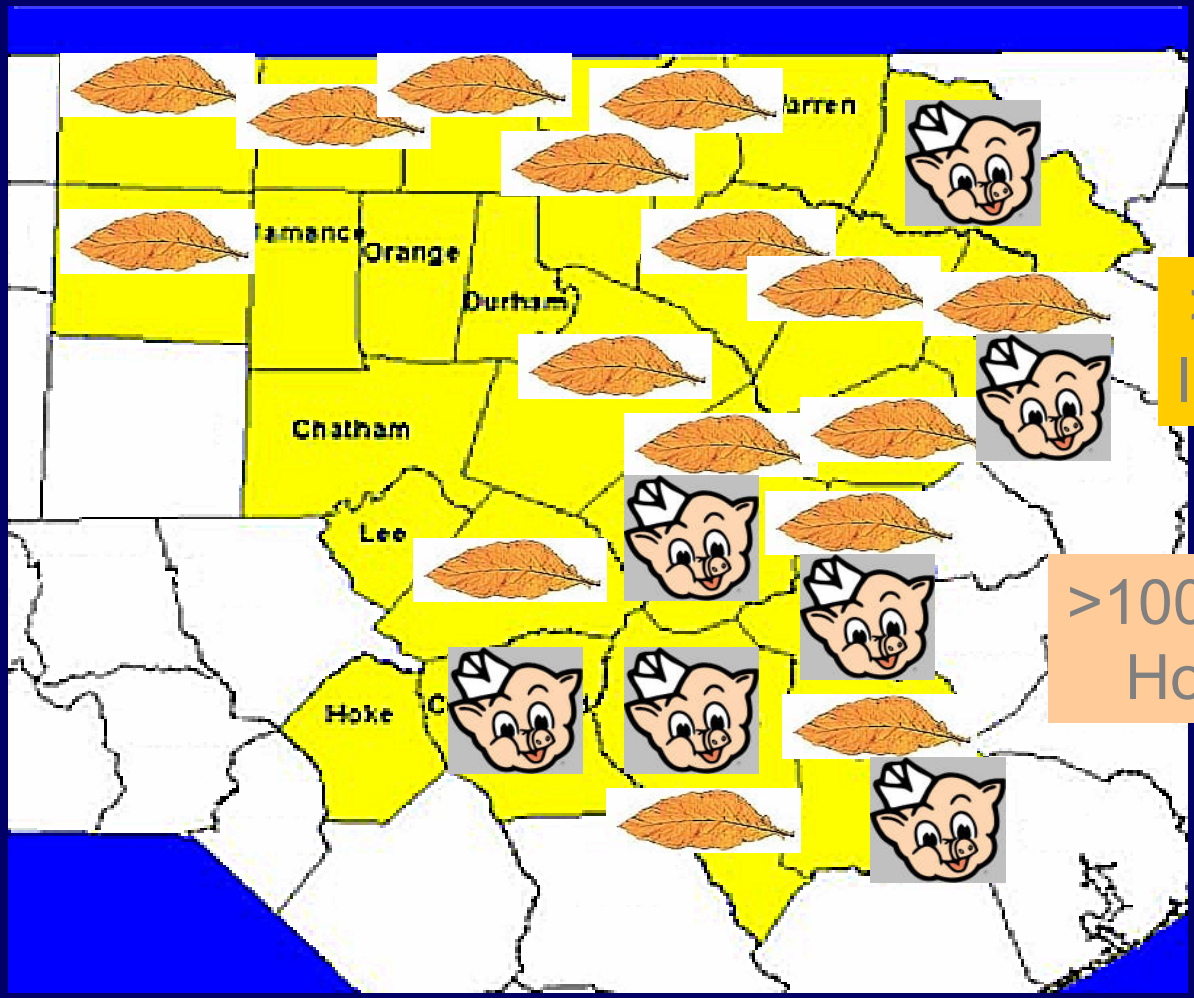
Mortality / 100,000

US: 47 (47 – 48)

LA: 42 (41 – 44)

NC: 55 (54 – 57)

North Carolina Study Area



>4,000,000 lbs.Tobacco

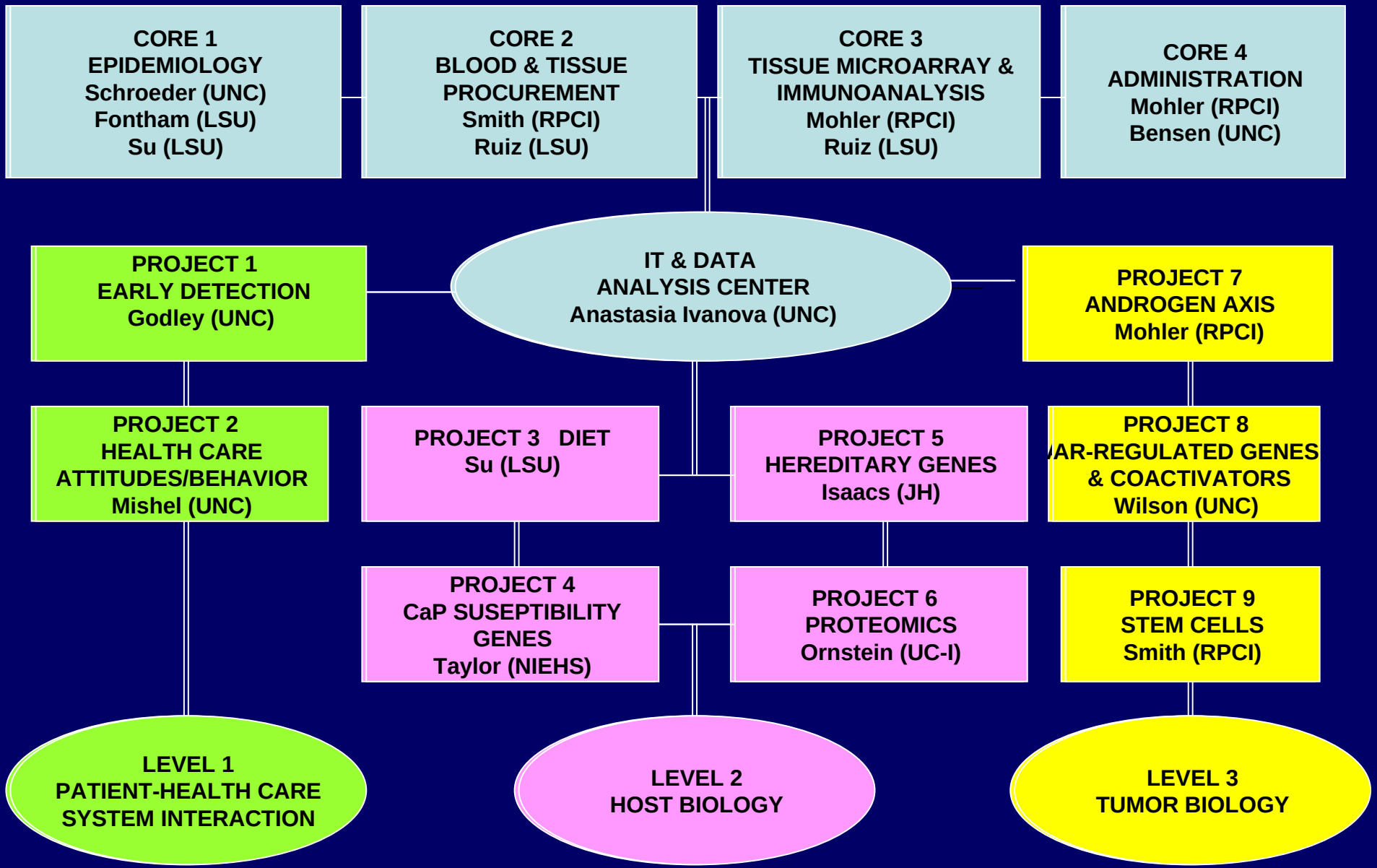
>100,000 Hogs

Louisiana Study Area

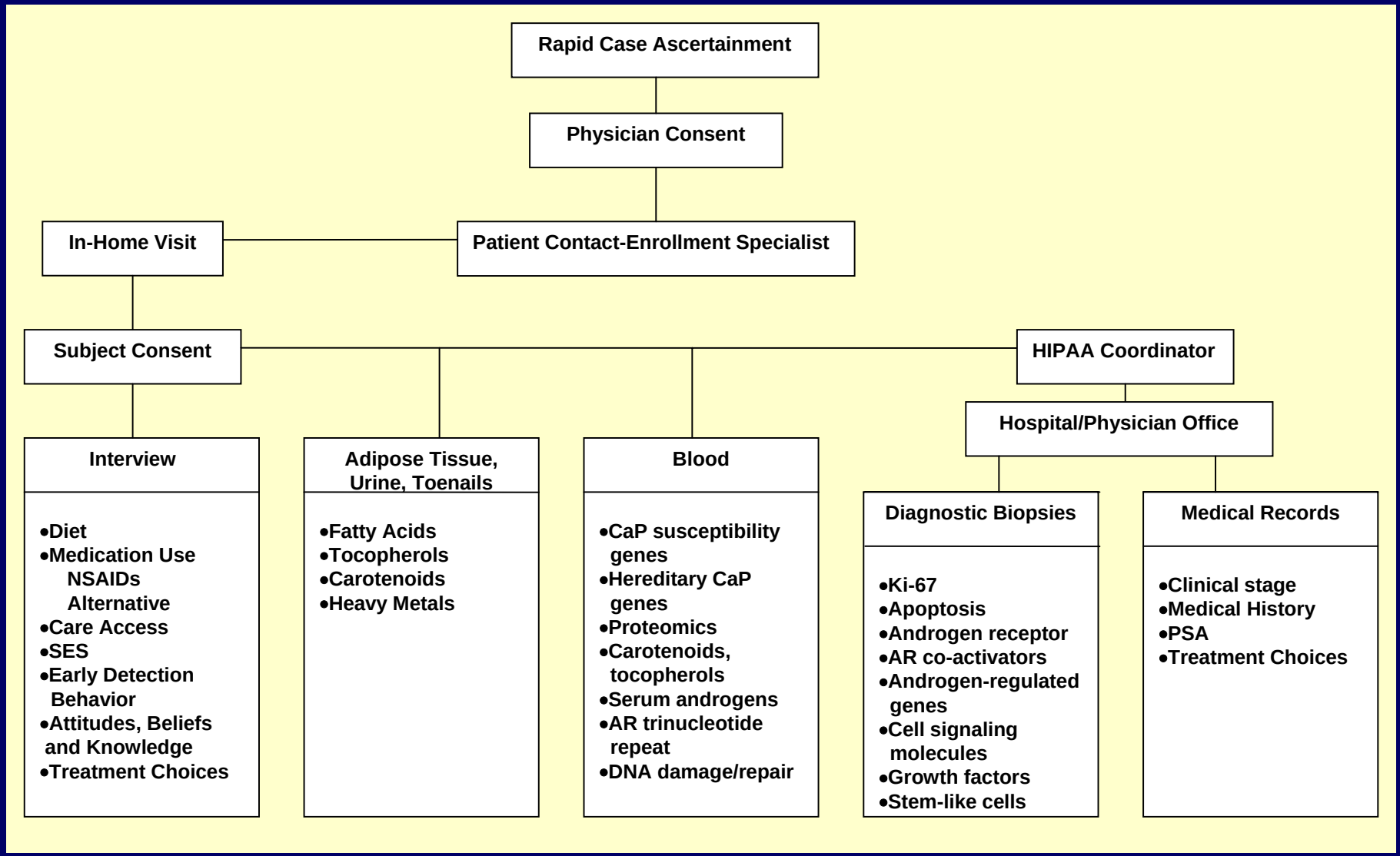
Participating Institutions

- Roswell Park Cancer Institute
- University of North Carolina
- Louisiana State University
- Natl. Inst. Environ. Health Sciences
- George Mason University
- University of South Carolina
- Harvard Medical School
- Boston University
- Johns Hopkins Medical Center
- Wake Forest University
- University of California-Irvine
- Duke University

PCaP Organization



PCaP Research Data Collection



Prostate Cancer Aggressiveness

- Tumor Extent (medical records and pathology review)
  - TNM stage
  - PSA (surrogate for tumor volume)
  - # and % Biopsies + CaP
- Tumor Differentiation (path report and pathology review)
  - Gleason grade (1-5) and sum (2-10)
- Tumor Growth Rate
  - Cellular proliferation (% Ki-67 +)
  - Apoptosis (programmed cell death) (% ACINUS +)

Prostate Cancer Aggressiveness: Clinical Classification

- **Low Aggressive**
  Gleason sum < 7 and
  clinical stage ≤ T2 and
  PSA < 10
- **High Aggressive**
  Clinical stage ≥ T3 and Gleason grade ≥ 7 or
  Gleason sum ≥ 8 or
  PSA > 20
- **Intermediate Aggressive**
  All others
- Originally expected 20% low, 20% high, and 60% intermediate

PCaP End Products

- A repository for future use:
  - Clinical data
  - Epidemiological data
  - Biological specimens
  - Tissue Microarrays
- Coordinated characterization of racial differences in two geographical areas to maximize the chance of identifying factors that are important in CaP outcome

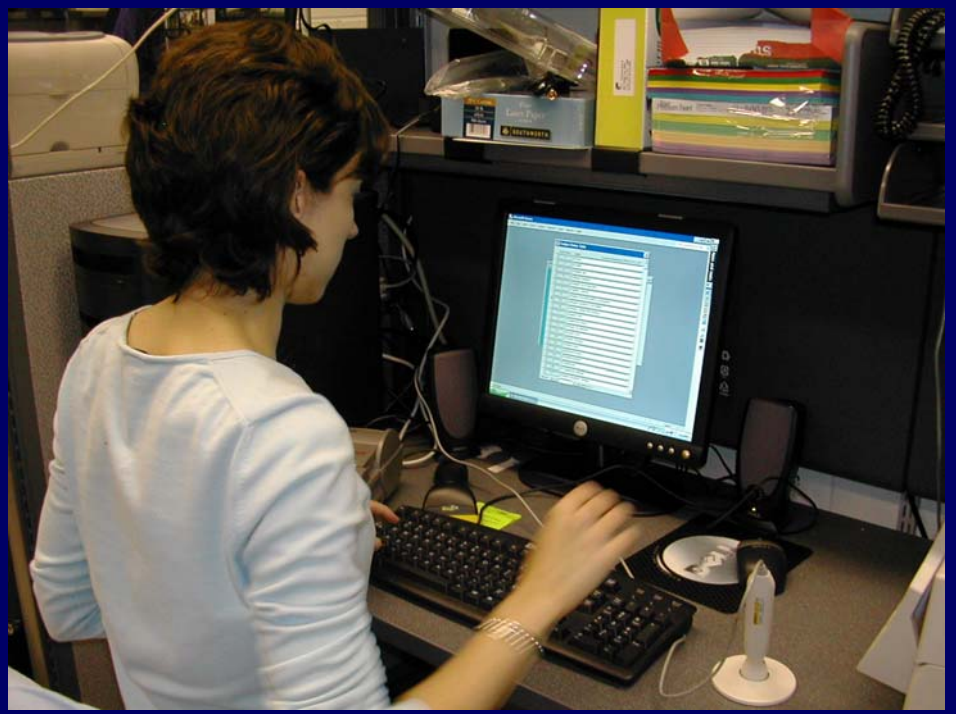
Core 1: Epidemiology

- Established Internet – II videoconferencing link between UNC and LSU
- PCaP participants spent 3 days reviewing every aspect of the PCaP study protocol
- Decisions made and action items generated
- Responsibilities assigned for start-up tasks

Nurse Training and Certification

Patient, Specimen and Data Tracking Systems

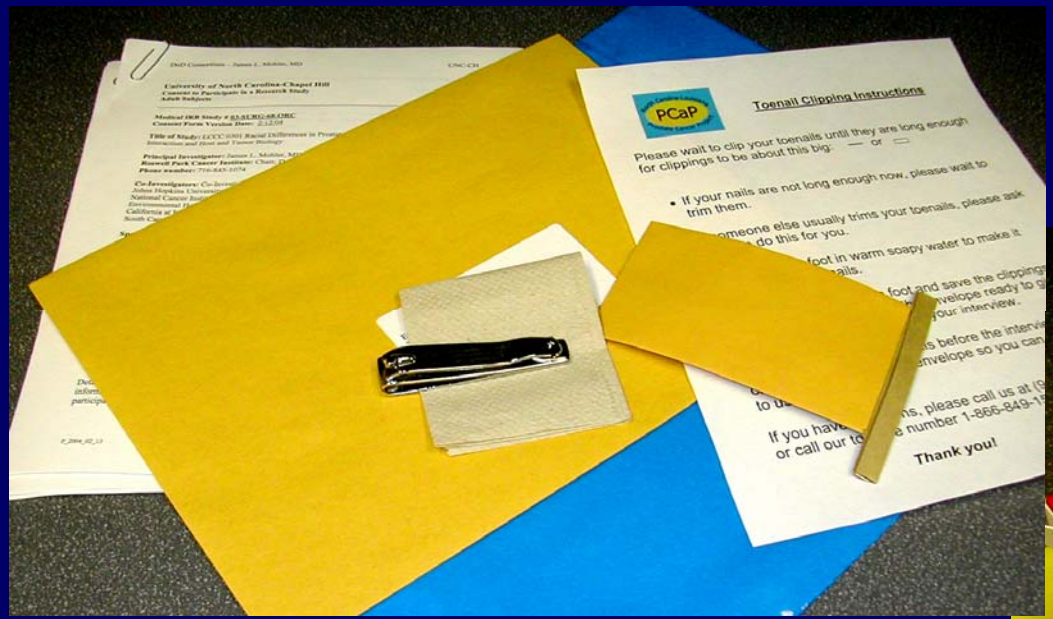
- Hardware and Software Developed
  - Joint effort of PCaP and several UNC School of Public Health Studies
  - Cores 1, 2 and 3 and PCaP database integrated
  - Specimens at RPCI, UNC and LSU linked



UNC-LSU Tracking System Training Session

Rapid Case Ascertainment

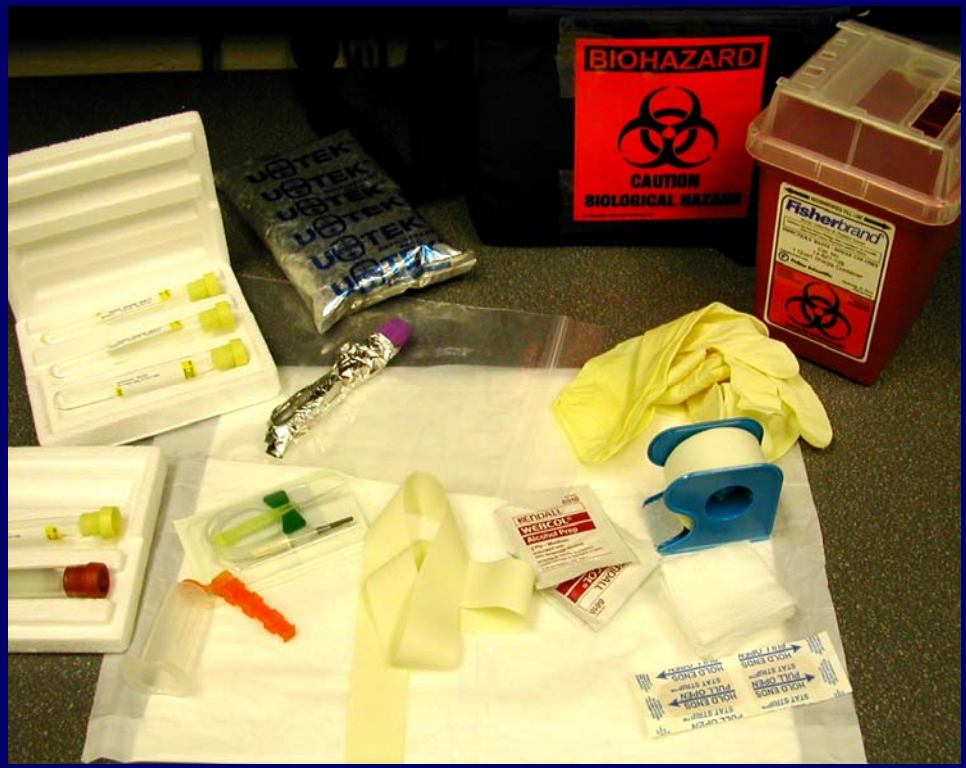
Pre-interview Communication



PCaP Questionnaires

- Uniform administration
  - NC vs LA
  - AA vs CA
  - Nurses
- Converted PCaP Questionnaires to Scannable Forms

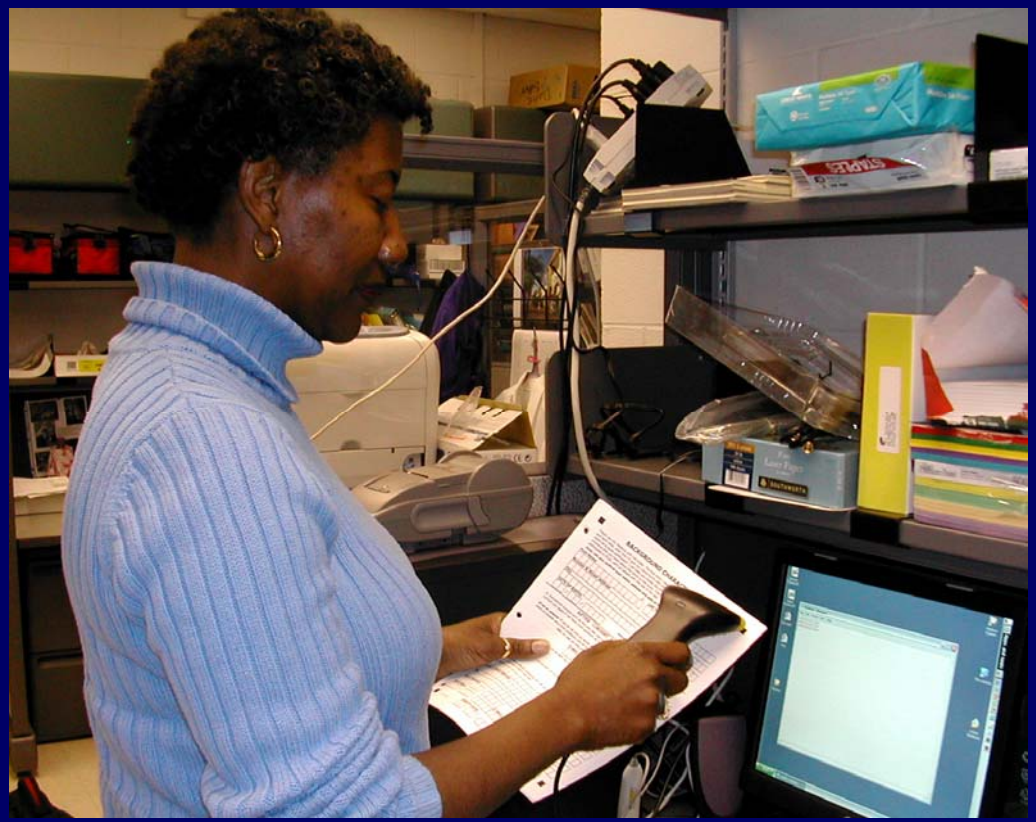
Specimen Collection Kits



Pre-Labeled Forms

On-demand printing with bar-coded study ID

- Specimen collection forms and labels
- Consent forms
- Questionnaires
- Post-interview data form
  - Timing, problems, etc.
- Staff codes
- Date and time



Specimen Handling and Transport

Core 2: Blood and Tissue Procurement

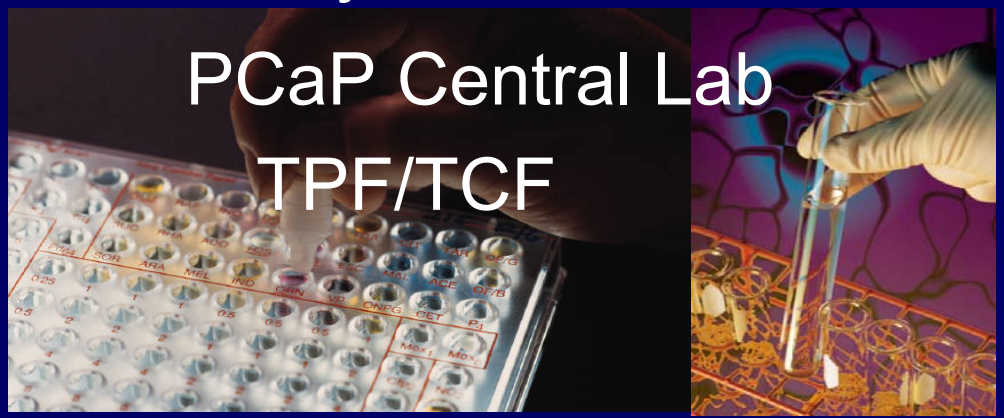
- Samples from research subjects collected at the in-home visit and buccal swabs of those without DNA
- Specimens in biorepository include:
  - Plasma
  - Serum
  - RBCs
  - Immortalized WBCs
  - DNA
  - Urine
  - Adipose tissue
  - Toenails

PCaP Pilot
Transport of Biologic Specimens

Projects

Daily/Batch

Field Office



Core 3: Tissue Microarray and ImmunoAnalysis

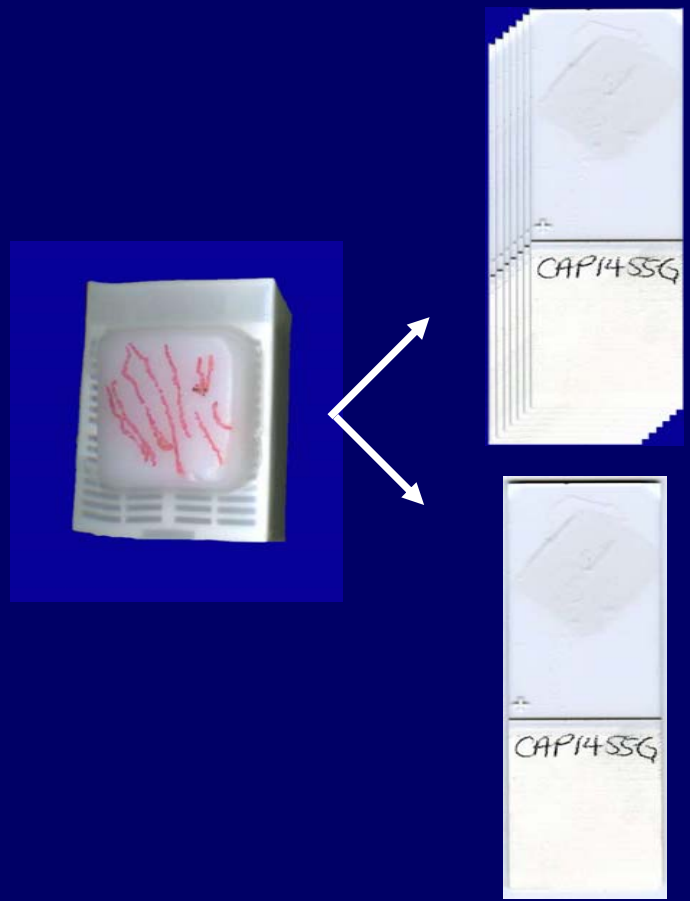
Tissue MicroArrays (TMAs) could not be constructed using paraffin blocks of community-acquired diagnostic prostate biopsies

Singh S, Mehedent DC, Ford OH, Maygarden SJ, Ruiz B, Mohler JL. Feasibility of constructing tissue microarrays from diagnostic prostate biopsies. Prostate 2007;67:1011-18.

Core 3: Diagnostic Biopsies

Based on pathology report from laboratory and medical record:

- If cancer present, cut seven 5 micron sections per block
- If cancer not present, cut 1 section per block



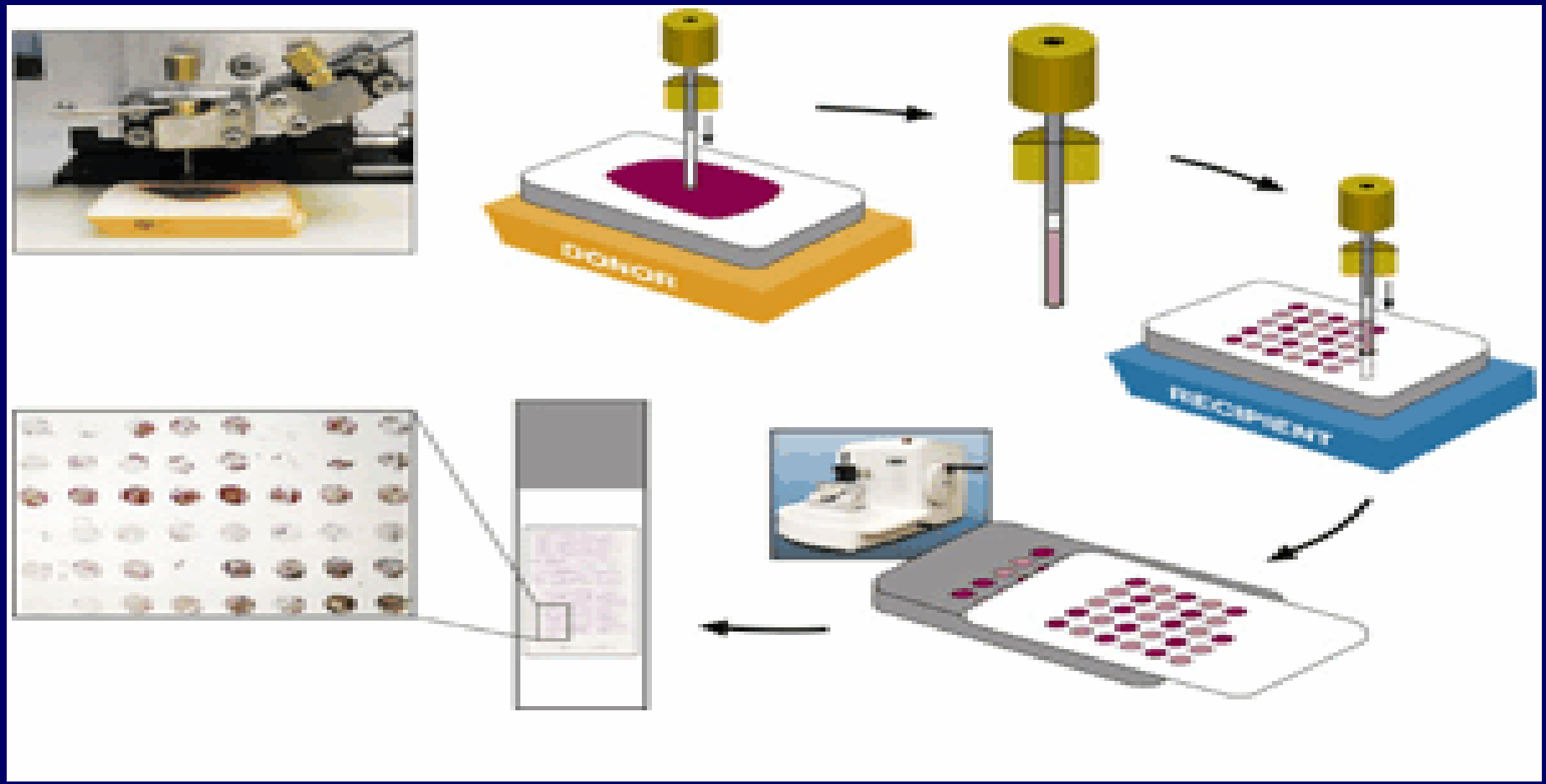
Core 3: Diagnostic Biopsies

- H&Es reviewed by Dr. Maygarden
- All cancer encircled and Gleason scored
- All sections digitally recorded
- % cancer determined from digital image of each slide

PCaP TMAs

0.6 mm core TMA block contains

600 RRP specimens



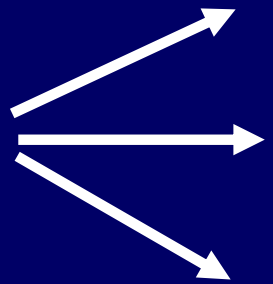
Core 3: Radical Prostatectomy TMA

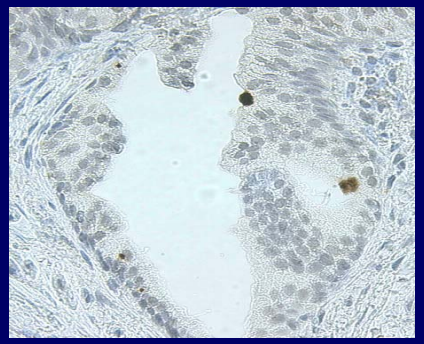
Specimen tracking system for one quadrant of a TMA

ml	ml	ml	98-17737A	98-17737A	98-17737A	98-17737A	98-17737A	98-17737A	ml
ml	98-17737B	98-17737B	98-17737B	98-17737B	98-17737B	98-17737C	98-17737C	98-17737C	ml
ml	95-55-1	95-55-1	95-55-1	95-55-1	95-55-1	95-55-1	95-55-1	95-55-1	ml
ml	95-55-1	95-55-1	95-55-1	95-55-1	98-9298-a	98-9298-a	98-9298-a	98-9298-a	ml
ml	98-9298-a	98-9298-a	98-9298-a	98-9298-a	98-9298-a	98-9298-a	98-9298-a	98-9298-a	ml
ml	00-8737-b	00-8737-b	00-8779-a	00-8779-a	00-8779-a	00-8779-a	00-8779-a	00-8779-a	ml
ml	00-8779-a	00-8779-a	00-8779-a	00-8779-a	99-18080-c1	99-18080-c1	99-18080-c1	99-18080-c1	ml
ml	99-18080-a1	99-18080-a1	99-18080-a1	99-18080-a1	99-18080-a1	99-18080-a1	99-18080-a1	99-18080-a1	ml
ml	99-6853-5	99-6853-5	99-6853-5	99-6853-5	99-6853-6	99-6853-6	99-6853-6	99-6853-6	ml
ml	99-6853-4	99-6853-4	00-4307-b1	00-4307-b1	00-4307-b1	00-4307-b1	00-4307-e1	00-4307-e1	ml
ml	00-4307-f1	00-4307-f1	00-4307-f1	00-4307-f1	96-570-1	96-570-1	96-570-2	96-570-2	ml
ml	96-570-4	96-570-4	96-570-5	96-570-5	96-570-5	96-570-5	98-11755-2	98-11755-2	ml
ml	00-5866-a	00-5866-a	00-5866-a	95-3554-1	95-3554-1	ml	ml	ml	ml

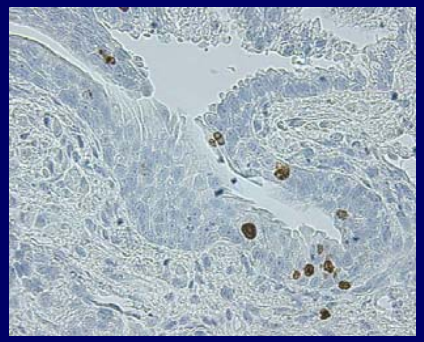
width of array is 12mm ml=mouse lung

Core 3: TMA Immunostaining

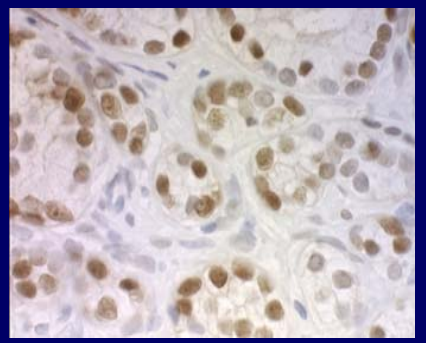




acinus (apoptosis)



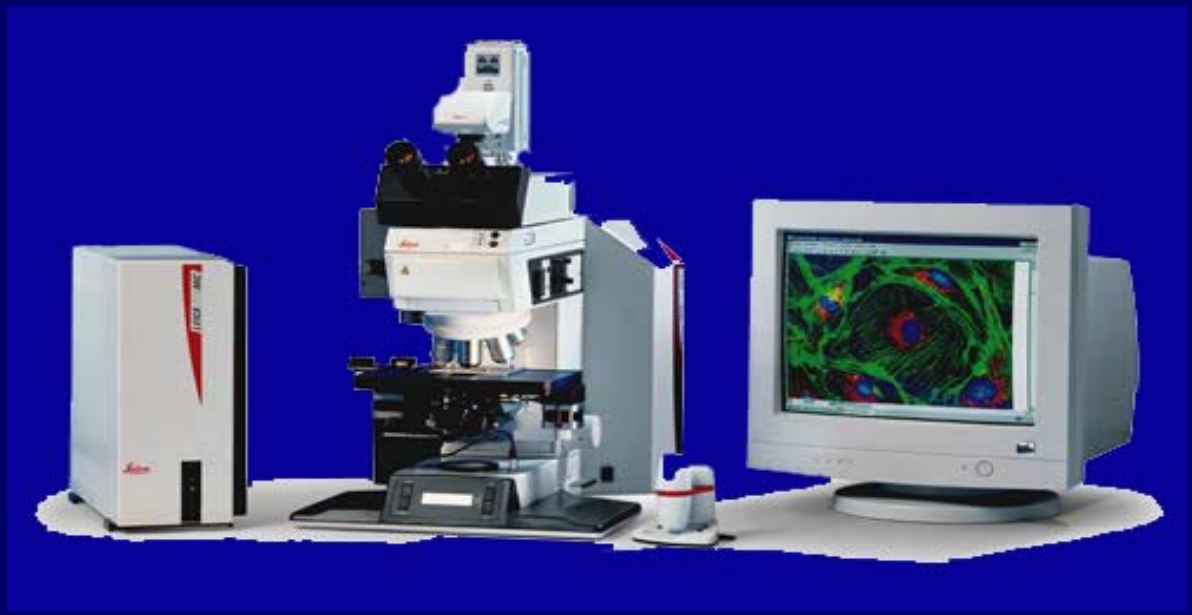
Ki-67 (proliferation)



androgen receptor

Core 3: Digital Color Quantitative Image Analysis

- Images acquired from regions of cancer circled by Core 3 pathologist for each immunostain
- Nuclei segmented
- % nuclei positive (apoptosis or proliferation)
- MOD for each positive nucleus (androgen receptor)



As of August 2007, Core 3 has received diagnostic biopsy blocks from 513 men (1707 blocks) and radical prostatectomy blocks from 251 men (2998 blocks). Core 3 has transferred QIA information for growth rate calculation on diagnostic biopsies from 250 men and constructed TMAs from radical prostatectomy specimens from 200 men.

Example of data derived from one research subject's diagnostic prostate biopsies

						Apoptosis marker ACINUS				Proliferation marker KI-67		
PCaP #	Location from prostate	Gleason primary grade	Gleason secondary grade	Number of biopsies per slide	Image #	total number of cells per FOV	total number of positive cells per FOV	random visual for total number of cells	Image #	total number of cells per FOV	total number of positive cells per FOV	random visual for total number of cells
						Total Cells	Visual Positive	Visual Total		Total Cells	Visual Positive	Visual Total
2676	right apex	3	4	3	2676 3-11m.	224	0		26763-10m.	186	2	
2676	right apex	3	4	3	2676 3-12m.	286	0		26763-1.	292	2	
2676	right apex	3	4	3	2676 3-13m.	276	1		26763-2.	149	1	
2676	right apex	3	4	3	2676 3-1m.	84	0		26763-3.	370	3	
2676	right apex	3	4	3	2676 3-2m.	217	0		26763-4m.	76	0	
2676	right apex	3	4	3	2676 3-3m.	382	0		26763-5m.	261	5	
2676	right apex	3	4	3	2676 3-4m.	184	0		26763-6m.	179	4	177
2676	right apex	3	4	3	2676 3-5m.	151	0	125	26763-8m.	236	0	
2676	right apex	3	4	3	2676 3-6m.	259	0		26763-9m.	177	1	
2676	right apex	3	4	3	2676 3-7m.	179	9		999	no	no	
2676	right apex	3	4	3	2676 3-8m.	180	0		999	no	no	
2676	right apex	3	4	3	2676 3-9m.	319	0		999	no	no	
2676	left middle	3	3	3	2676 5-10m.	104	1		26765-10.	218	3	
2676	left middle	3	3	3	2676 5-11m.	244	0		26765-11.	190	6	
2676	left middle	3	3	3	2676 5-12m.	179	0		26765-12.	54	1	36
2676	left middle	3	3	3	2676 5-1m.	195	0		26765-13.	268	5	
2676	left middle	3	3	3	2676 5-2m.	141	3	114	26765-1.	280	4	
2676	left middle	3	3	3	2676 5-3m.	273	1		26765-2.	235	10	
2676	left middle	3	3	3	2676 5-4m.	281	0		26765-3.	233	10	
2676	left middle	3	3	3	2676 5-5m.	152	0		26765-4.	235	7	
2676	left middle	3	3	3	2676 5-7m.	59	0		26765-5.	235	6	
2676	left middle	3	3	3	999	no	no		26765-6.	190	5	
2676	left middle	3	3	3	999	no	no		26765-7.	283	5	
2676	left middle	3	3	3	999	no	no		26765-8.	224	6	
2676	left middle	3	3	3	999	no	no		26765-9.	212	4	
2676	left apex	3	3	2	2676 6-10m.	77	2		26766-9.	139	4	
2676	left apex	3	3	2	2676 6-5m.	70	0		26766-1.	110	0	
2676	left apex	3	3	2	2676 6-6m.	217	0		26766-2.	180	7	165
2676	left apex	3	3	2	2676 6-7m.	179	1	147	26766-3.	221	1	
2676	left apex	3	3	2	2676 6-8m.	217	0		26766-4.	196	1	
2676	left apex	3	3	2	2676 6-9m.	86	0		26766-5.	237	2	
2676	left apex	3	3	2	999	no	no		26766-6.	122	1	
2676	left apex	3	3	2	999	no	no		26766-7.	195	1	
2676	left apex	3	3	2	999	no	no		26766-8.	224	9	

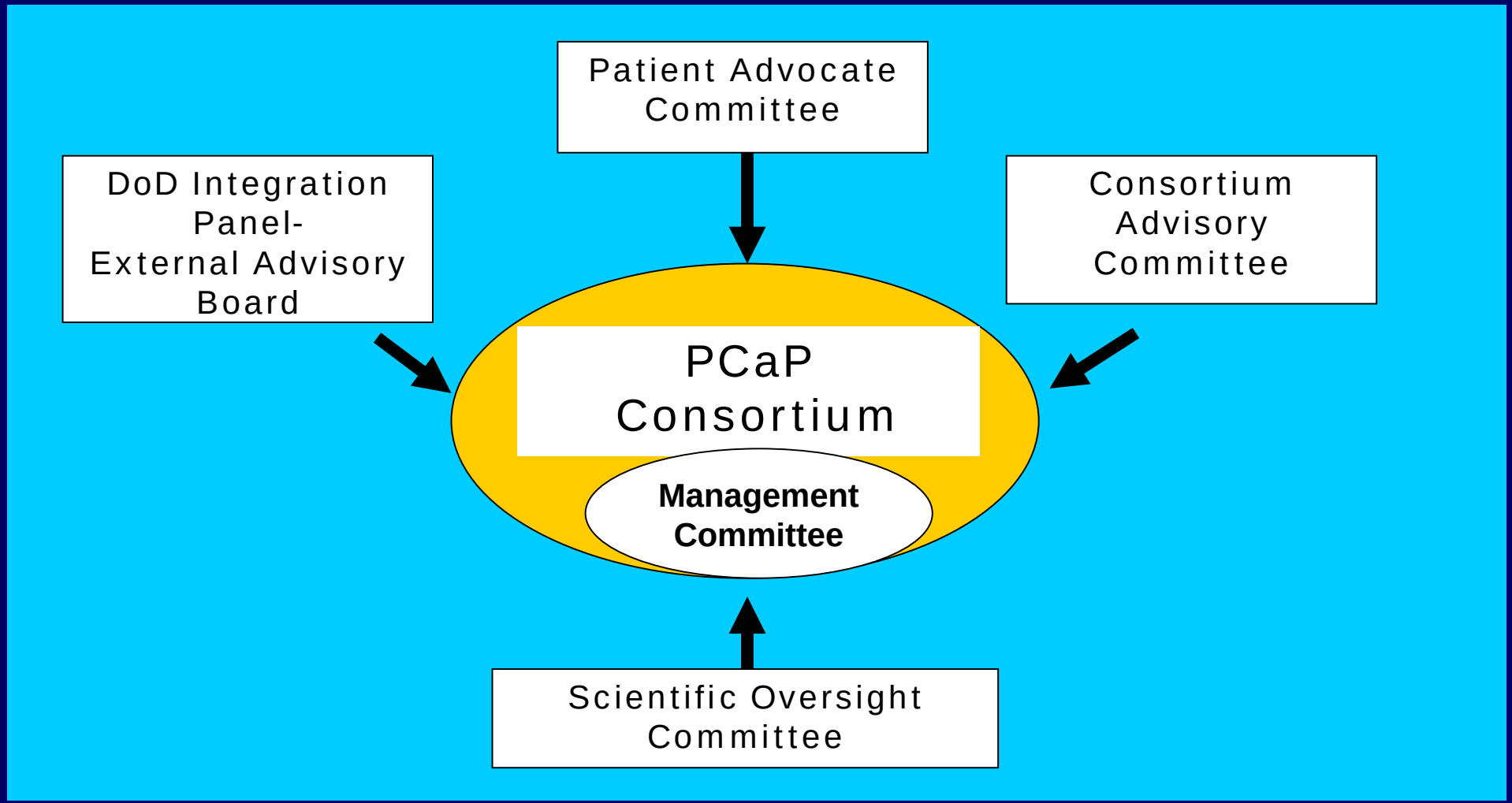
Pilot Study of Assigned Clinical Aggressiveness vs Calculated Growth Rate

- The data from the first 168 completed subjects were compared to the clinically assigned aggressiveness of either low, intermediate, or high
- The subjects were divided into two groups: those above and below their median according to the growth rates

	Low	Interm.	High
Below median growth rate	44	24	14
Above median growth rate	32	33	21

- Growth rate differs among aggressiveness groups (P = 0.04, one-sided scores test)

Core 4: PCaP Advisory Committees



PCaP Management Committee

Meets monthly after PCaP study-wide monthly meeting using videoconferencing between UNC and LSUHSC

- Administrative
  - Dr. James Mohler
  - Dr. Jeannette Bensen
- Case Accrual
  - Dr. Jane Schroeder
  - Dr. Elizabeth Fontham
  - Dr. Joseph Su
- Community Relations and Clinical Advisors
  - Dr. Paul Godley
  - Dr. James Mohler
- Interview, Biological and Tumor Tissue
  - Dr. Merle Mishel
  - Dr. Gary Smith
  - Dr. James Mohler

Scientific Oversight Committee

- Chair, Dr. H. Shelton Earp, UNC-LCCC Director
- Dr. Candace Johnson, RPCI Assoc. Director for Translational Research
- Dr. Augusto Ochoa, Stanley S. Scott Cancer Center Director
- Overall scientific direction of the Consortium and address any scientific issues that cannot be resolved by the Management Committee

PCaP Advisory Committee

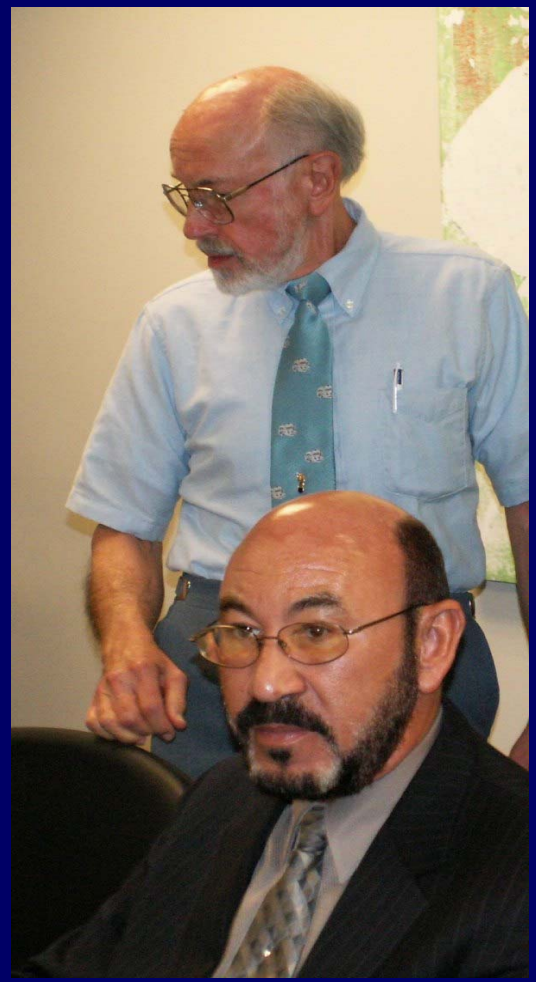
- Drs. Litwin, Giovanucci and French
- Medical monitors
- Provide independent oversight in 3 areas of primary research focus for PCaP:
  - Androgen regulation
  - Nutritional epidemiology
  - Health outcomes research

Patient Advocate Committees

- 8 NC and 3 LA advocates
- Annual meetings
  - Update activities of committee members
  - Update PCaP progress in NC and LA
  - Advise on study accrual and logistics

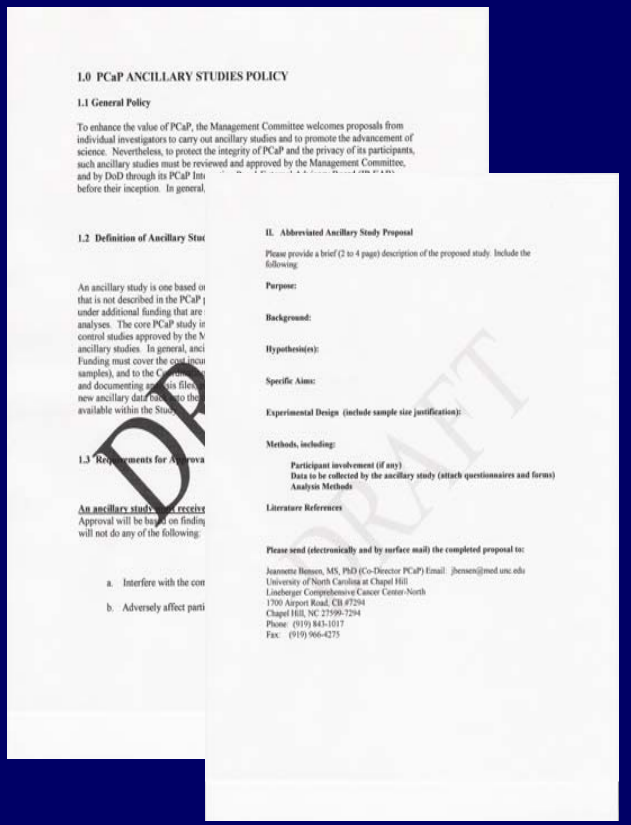
NC Patient Advocate Committee

- Development of recruitment materials, brochure, family letter
- Distribution of brochures to MD offices
- Development of public website
- Liaison among PCaP, advocates and support groups



Core 4: PCaP Administrative Management Policies

- Ancillary Study Submission
  - Letter of Intent
- Data Sharing Agreement
- Abstract & Manuscript Submission
- Authorship Agreement



1.0 PCaP ANCILLARY STUDIES POLICY

1.1 General Policy

To enhance the value of PCaP, the Management Committee welcomes proposals from individual investigators to carry out ancillary studies and to promote the advancement of science. Nevertheless, to protect the integrity of PCaP and the privacy of its participants, such ancillary studies must be reviewed and approved by the Management Committee, and by DoD through its PCaP Int before their inception. In general,

1.2 Definition of Ancillary Stu

An ancillary study is one based o that is not described in the PCaP under additional funding that are analyses. The core PCaP study i control studies approved by the M ancillary studies. In general, anci Funding must cover the cost incu samples), and to the C and documenting an this files new ancillary data back into the available within the Stud

1.3 Requirements for Approva

An ancillary study will receive Approval will be based on findin will not do any of the following:

a. Interfere with the con

b. Adversely affect parti

II. Abbreviated Ancillary Study Proposal

Please provide a brief (2 to 4 page) description of the proposed study. Include the following:

Purpose:

Background:

Hypothesis(es):

Specific Aims:

Experimental Design (include sample size justification):

Methods, including:

Participant involvement (if any)
Data to be collected by the ancillary study (attach questionnaires and forms)
Analysis Methods

Literature References

Please send (electronically and by surface mail) the completed proposal to:

Jeannette Bensen, MS, PhD (Co-Director PCaP) Email: jbensen@med.unc.edu
University of North Carolina at Chapel Hill
Lineberger Comprehensive Cancer Center-North
1700 Airport Road, CB #7294
Chapel Hill, NC 27599-7294
Phone: (919) 843-1017
Fax: (919) 966-4275

HIPAA Impact on PCaP

The **Health Insurance Portability and Accountability Act** (**HIPAA**) enacted by the US Congress in 1996 and **the Privacy Rule** took effect **April 14, 2003**

- Patient advocates prevented from assisting with enrollment
- All PCaP staff must receive HIPAA training
- All subjects must sign HIPAA document
- HIPAA document critical for contact with MDs and pathology labs and access to, and receipt of, clinical data (medical records, tumor blocks)
- Full-time coordinator hired for HIPAA and IRB compliance

Hurricane Katrina

LSUHSC

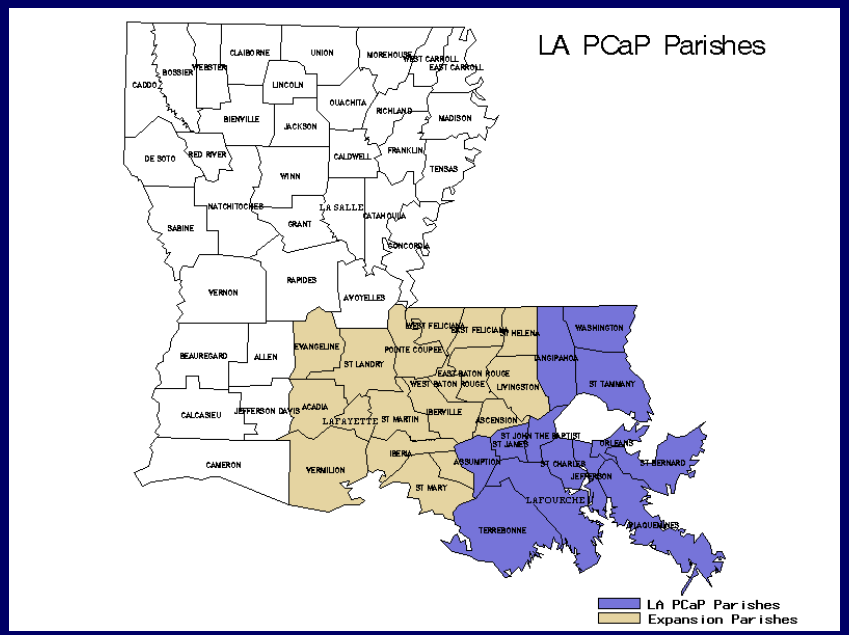
LSUHSC School of Public Health

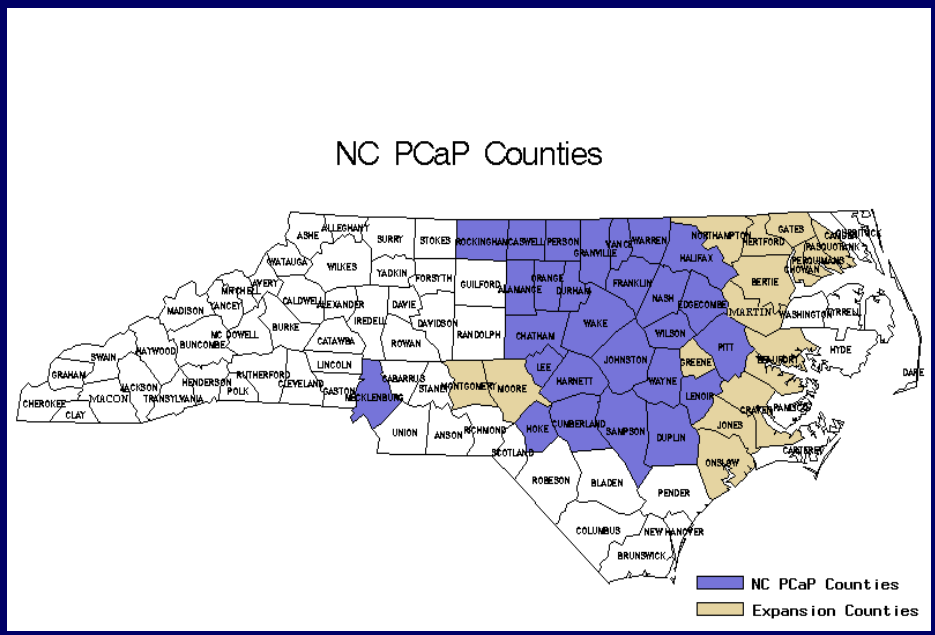
PCaP Response:

- Suspend then start over in LA
- Expand study areas in both states
- Seek additional funding

DoD Response:

- Total support





PCaP Study Participation

- Good RCA reporting among urologists, pathologist & hospitals in study area
- 94% MD consent rate
- 63% study-wide cooperation rate
  - Typical of epidemiological studies enrolling older men
- 94 → 98% Biologics collection rates
- 99.8% Release of medical records
- 97% Consent to future contact

Prostate Cancer Aggressiveness : Clinical Classification

- **Low Aggressive (20% patients)**
  - Gleason sum < 7 and
  - clinical stage ≤ T2 and
  - PSA < 10
- **High Aggressive (20% patients)**
  - Clinical stage ≥ T3 and Gleason grade ≥ 7 or
  - Gleason sum ≥ 8 or
  - PSA > 20
- **Intermediate Aggressive (60% patients)**
  - All others

Clinical Aggressiveness at Diagnosis

Aggressiveness	#Subjects	Percent	Pred.
Low	429	50.2%	20%
Intermediate	268	31.3%	60%
High	158	18.5%	20%
Total	855	100%	

Improved statistical power!

Race, Health Insurance and Radical Prostatectomy: Preliminary Data from PCaP

Jane Schroeder, DVM, PhD, UNC Core 1 Leader, et al.

Symposia Session 43-2

- As expected, RP is less common among:
  - Older (65+) than younger (<65) men
  - Gleason score > 7 than ≤ 7
  - Higher than lower co-morbidity
- Race: Little evidence of association with RP (2 - 4% difference)
- Poverty: Strong predictor of RP (16% less common after adjustment for race, age, grade, stage, co-morbidity)

Completed In-Home Visits

Completed In-Home Visits by State (through August 31, 2007)						
	African American			Caucasian		
	Completed	Goal	% Total	Completed	Goal	% Total
North Carolina	464	500	93%	514	500	103%
Louisiana						
Pre-Katrina*	122	—	—	94	—	—
Post-Katrina	119	500	24%	256	500	51%
Totals*	705			865		

* includes 216 in-home visits pre-Katrina

Total In-Home Visits Completed = 1570 (of 2216 goal)

Department of Defense Funding

- Grant to prepare consortium proposal
  $150,000
- NC-LA Prostate Cancer Project (PCaP)
  $9,913,157
- Cost extension after Hurricane Katrina
  $4,177,369
- Total PCaP funding 2002-2009
  $14,240,526

Future Activities

Pending Grants

- Racial admixture
- Metabonomics
- Follow-up, treatment and survivorship

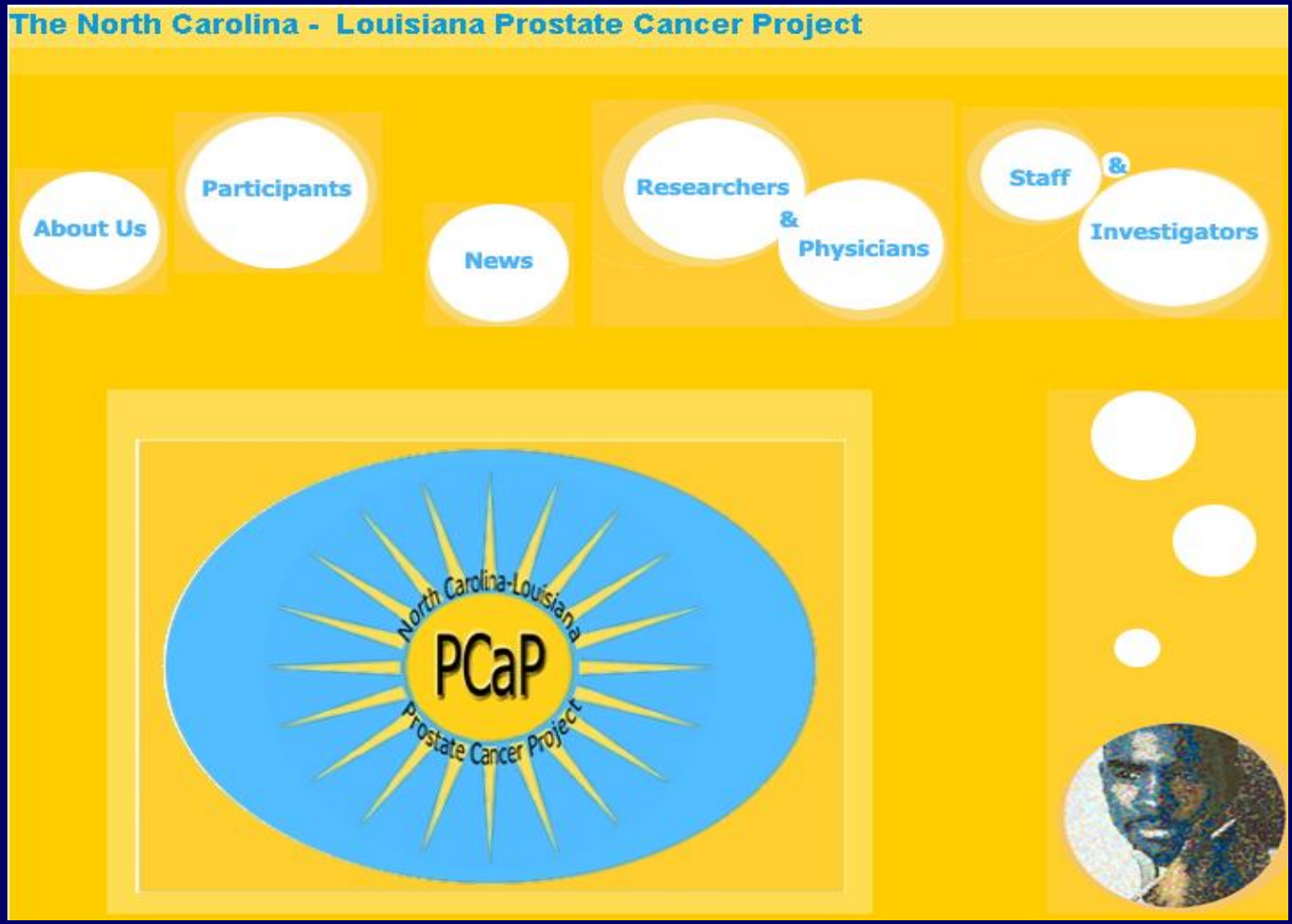
Pending Manuscripts

- Tumor growth rate as a measure of CaP aggressiveness
- Impact of insurance on CaP treatment
- Interaction and communication with health care system

PCaP Description

Schroeder JC, Bensen JT, Su JL, Mishel M, Ivanova A, Smith GJ, Godley PA, Fontham ETH, Mohler JL. The North Carolina – Louisiana Prostate Cancer Project (PCaP): Methods and design of a multidisciplinary population-based cohort study of racial differences in prostate cancer outcomes. Prostate 2006;66:1162-76.

PCaP Website



http://www.ncla-pcap.org/

Acknowledgements

- Department of Defense
- UNC Lineberger Comprehensive Cancer Center
- LSUHSC Stanley F. Scott Cancer Center
- PCaP Cores and Projects
- NC and LA State Tumor Registries
- Advisory Committees
- 12 Participating Institutions
- And, most importantly, the

PCaP Research Subjects