AD_____

Award Number: DAMD17-99-1-9041

TITLE: Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men

PRINCIPAL INVESTIGATOR: Alexis E. Te, M.D.

CONTRACTING ORGANIZATION: Columbia University in the City of New York
New York, New York 10032

REPORT DATE: August 1999

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE

Form Approved
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1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	August 1999	Final (15 Jan 99 – 14 Jul 99)

4. TITLE AND SUBTITLE
Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men

5. FUNDING NUMBERS
DAMD17-99-1-9041

6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Columbia University in the City of New York
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

There are significant racial differences in unscreened populations in both prostate cancer incidence and mortality rates. However, to date there are no widely available prostate cancer strategies that can be applied to ethnically diverse men. Some have suggested that this is due to inherent biological differences in prostate cancer growth between African American and Caucasian American males. This concept is supported by increased levels of serum prostate specific antigen in African American males versus Caucasian American males. We have reported that the portion of the prostate that is more commonly associated with benign prostate hyperplasia, the transition zone, is more prominent in African American versus Caucasian American males. Given that this area, the transition zone, produces PSA, it is very conceivable that differences in PSA may reflect a different incidence of benign prostate growth in African American versus Caucasian American than to differences in prostate cancer. This training grant helped support the concept development by the PI, Alexis E. Te, of a study to determine if a new prostate cancer detection strategy, PSAT (the ratio of serum PSA to the volume of transition zone of the prostate) is different among African American males, Caucasian American males and males of other ethnicity's.

14. SUBJECT TERMS
Prostate Cancer

15. NUMBER OF PAGES
163

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

FOREWORD

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____ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

__✓__ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

____ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

8/12/99

PI - Signature Date

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Introduction

There are significant racial differences in unscreened populations in both prostate cancer incidence and mortality rates. However, to date there are no widely available prostate cancer strategies that can be applied to ethnically diverse men. Some have suggested that this is due to inherent biological differences in prostate cancer growth between African American and Caucasian American males. This concept is supported by increased levels of serum prostate specific antigen (PSA) levels in African American males versus Caucasian American males. We have recently reported that the portion of the prostate that is more commonly associated with benign prostate hyperplasia (BPH), the transition zone is more prominent in African American versus Caucasian American males. Given that this area, the transition zone, produces PSA, it is very conceivable that differences in PSA may reflect a different incidence of benign prostate growth in African American versus Caucasian American than to differences in prostate cancer. This training grant helped support the concept development of a study by Alexis E. Te, the principle investigator, to determine if a new prostate cancer detection strategy, PSAT (the ratio of serum PSA to the volume of transition zone of the prostate as measured by transrectal ultrasound) is different among African American males, Caucasian American males and males of other ethnicity's. Briefly, the grant specifically supported the concept development of a recently submitted new investigator DOD grant and the infrastructure for the initial preparations to collect data prospectively for the concept development.

Training Grant Report Body

The training grant has been productive in supporting and accomplishing many of the task described in the approved statement of work for this training grant (see appendices, no. 1) and has culminated in a submitted New Investigator Grant submission to the USAMRMC for the FY 99 Prostate Cancer Research Program (See appendices, no.2). Additionally, the grant has help support the database and computer infrastructure development for the concept development of this grant submission. Data presented in the submitted new investigator grant consisted of data either already published and/or collected prior to the initiation of current training fiscal period of support. Data prospectively collected and partially supported by this grant was initiated in late June of 1999 under current IRB approval. The prospective data collection is currently ongoing and is unpublished.

Details of the work performed for each task under the approved statement of work and comments to them are explained in the following descriptions:

The original training grant support period requested was for 10/1/98 to 3/31/99. It was on this timetable that the submitted new investigator grant was developed. For the projected goal of submitting an New Investigator grant supported by this training grant, the time table for completions of the various tasks of the statement of work were made while awaiting the approval and funding of the current training grant fiscal period of support. In compliance with Federal Law 45 CFR 46 for the protection of human rights, data collected as supported under this grant was collected using the IRB developed under the support of this training grant. This data collection was initiated in late June of 1999 and is currently ongoing. It is the intent of the PI to analyze the data collected in preparation for an abstract to be submitted to the Annual National American Urological Association Meeting in the year 2000 in October 1999.

The statement of work with regards to Task 1- Project Startup and Parameter Development and Task 2- Develop final plan for performing ultrasound imaging and measurements of PSA were completed in order to submit the New Investigator Grant. Regular meetings (weekly to biweekly) with Dr. Steven Kaplan, the established PI attained the goals of Task 1 and 2. During this period, consultations with Dr. Emilia Bagiella refined the recruitment strategies and statistical requirements of the project. She is listed as a co-PI in the submitted New Investigator Grant. To expand recruitment, commitment from Dr. Edward Ikeguchi and Dr. John Franklin were also obtained. IRB approval was also attained and was a requirement for the funding of this training grant. The protocol for the IRB became incorporated into the submitted New Investigator Grant. These works in progress for the accomplishment of these task are demonstrated by Appendices, no. 3-4, and were constructive in the development of the submitted New Investigator grant.

The clinical data for the concept development consists of two parts. First, data collected for the submitted New Investigator Grant consisted of data from previous

publications and from data collected from Asian patients screened during prostate awareness month in 1998. The collection of this data was not supported by this grant since it was collected prior to the fiscal period supported by the training grant. The clinical aspects of Task 3,4,5 as supported by the grant are currently works in progress and it is estimated that a majority of these patients will be recruited in the fall. Purchase of computer equipment and software development were completed during the mid fiscal period of the training grant and provided the infrastructure to the collection of prospective data. The interim analysis of this data will take place in the fall of 1999. Aleta Ashley, the research nurse, has been involved in the clinical aspects of this data collection. Personnel receiving pay under the research-training grant include the PI, Alexis E Te, MD, the Established PI, Steven A. Kaplan, MD, and Aleta Ashley, RN.

During the fiscal period of the training grant, the PI attended the 1999 annual American Urological Association Meeting in Dallas, Texas. The training grant supported the attendance of this meeting. (See appendices, No.5)

In summary, the training grant has been instrumental in supporting this concept development that is still awaiting full funding by the USAMRMC. The various task of the approved statement of work have been either completed or initiated with the support of the training grant. The training grant has been useful in offsetting the cost of the project development and supporting the development of not only the New Investigator grant submission and his career development, but also the initiation of data collection of this prospective study.

Key Research Accomplishments

-Review of literature for concept development
-Development of background for concept development
-Formulation of protocol for concept development
-Review of retrospective data and analysis for preliminary data on PSAT in ethnicity's.
-Analysis of preliminary data on Asian American's PSAT data completed
-Organization of ultrasound protocols, recruitment strategies and statistical requirement.
-Submission and approval of IRB protocol and consent for concept development
-Submission of formal grants proposal to USAMRMC for funding of new investigator grant.
-Development of computer and database infrastructure for proposed project.
-Attended 1999 American Urological Association National Meeting
-Initiation of clinical protocol for prospective study

Reportable Outcomes

1. New Investigator grant submission to the USAMRMC for the FY 99 Prostate Cancer Research Program (See appendices, No.1)
2. Attendance and CME accreditation for 1999 American Urologic Association Conference (See appendices, No. 5)
3. Abstract to year 2000 AUA meeting pending

Conclusions

The training grant has been instrumental in supporting the training of this PI in accomplishing the goal of developing the concept of investigating "Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men". It has resulted in the submission of a formal grant request for full funding by the USAMRMC. Many of the approved statement of work have been either completed or initiated with the support of this training grant and it has allowed the initiation of data collection for this concept development. The PI is grateful for the support by the USAMRMC by this grant to pursue this research concept and to further his career development in prostate cancer research.

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Appendices

1. Copy of original training grant proposal
2. Copy of submitted New Investigator grant proposal for the FY99 Prostate Cancer Research Program.
3. Copy of appendices 4,5,6,7 submitted to USAMRMC Human subject Research Review Board
4. Copy of approved IRB protocol and consent
5. Copy of CME accreditation for attending 1999 American Urological Association Meeting in Dallas, Texas.
6. Copy of PI's curriculum vitae

Appendices 1

PROPOSAL COVER BOOKLET

MARKING INSTRUCTIONS

CORRECT MARK ● INCORRECT MARKS ✓ X ● •

- Use a No. 2 pencil or equivalent.
- Type or print in block letters in the 'non-bubble' areas. (Ink is acceptable.)
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- Do not fold or tear this form.

1. Proposal Log Number (Leave blank.)

2. BAA Identifier and Proposal Category

MPFT-98

3. Proposal Category Code (Enter the Proposal Category Code from the list provided in the Proposal Cover Booklet Instructions. Must agree with Proposal Category listed in question #2.)

4. Organization Code (Leave blank.)

5. Organization Name and Grants/Contracts Office Address

Organization Name: Columbia University

Street Address: 630 West 168th St.

Grants & Contracts Health Science Div.

City: New York State: NY

Country: USA Zip Code: 10032

6. Type of Organization (Enter the Type of Organization from the list provided in the Proposal Cover Booklet Instructions.)

G

7. Principal Investigator

Last Name	First Name	MI
TE	ALEXIS	E

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8. Title

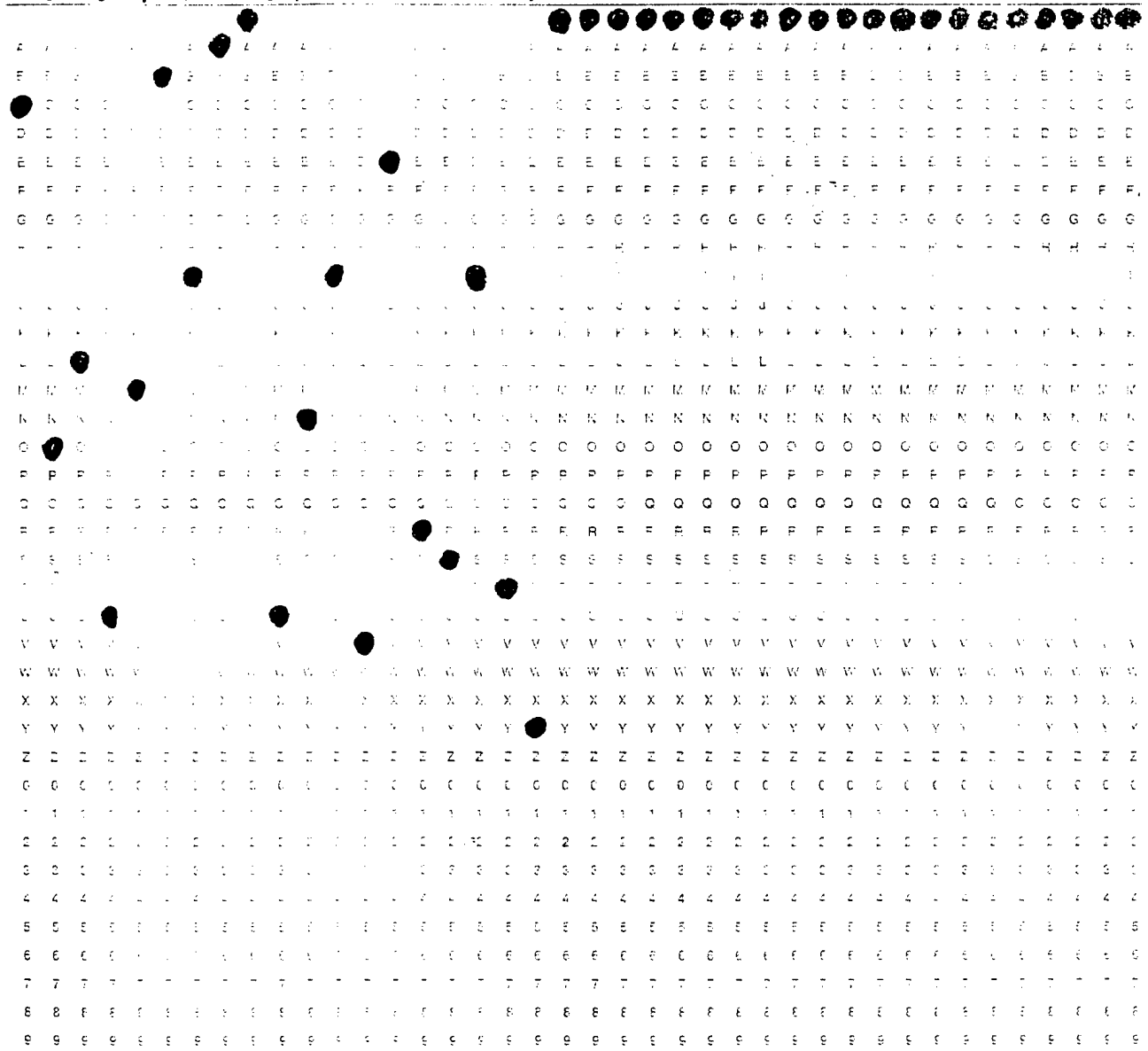
9. Degree(s) of Principal Investigator(s) (Select all that apply.)

Dr
Mr
Ms
M.D.
Ph.D.
J.D.
D.N.Sc.
R.N.
Other Graduate Level Degree (Specify)

0–17. Principal Investigator's Mailing Address. This is the primary address used to contact you. (Do not use a P.O. Box unless unavoidable.)

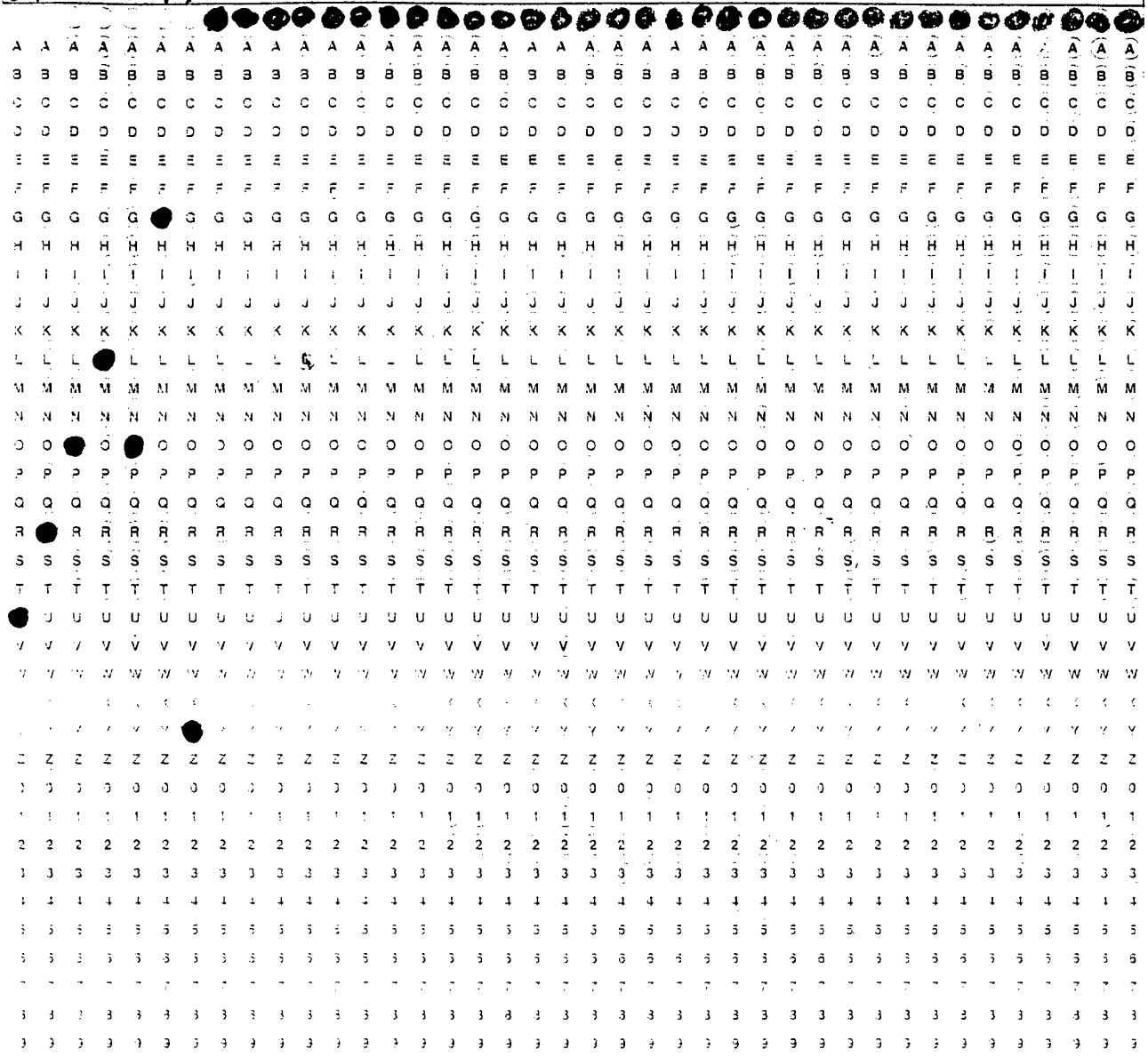
10. PI Address–Organization Name (If none, leave blank. Use spaces as appropriate.)

COLUMBIA UNIVERSITY



11. PI Address–Department Name (If none, leave blank. Use spaces as appropriate.)

UROLOGY



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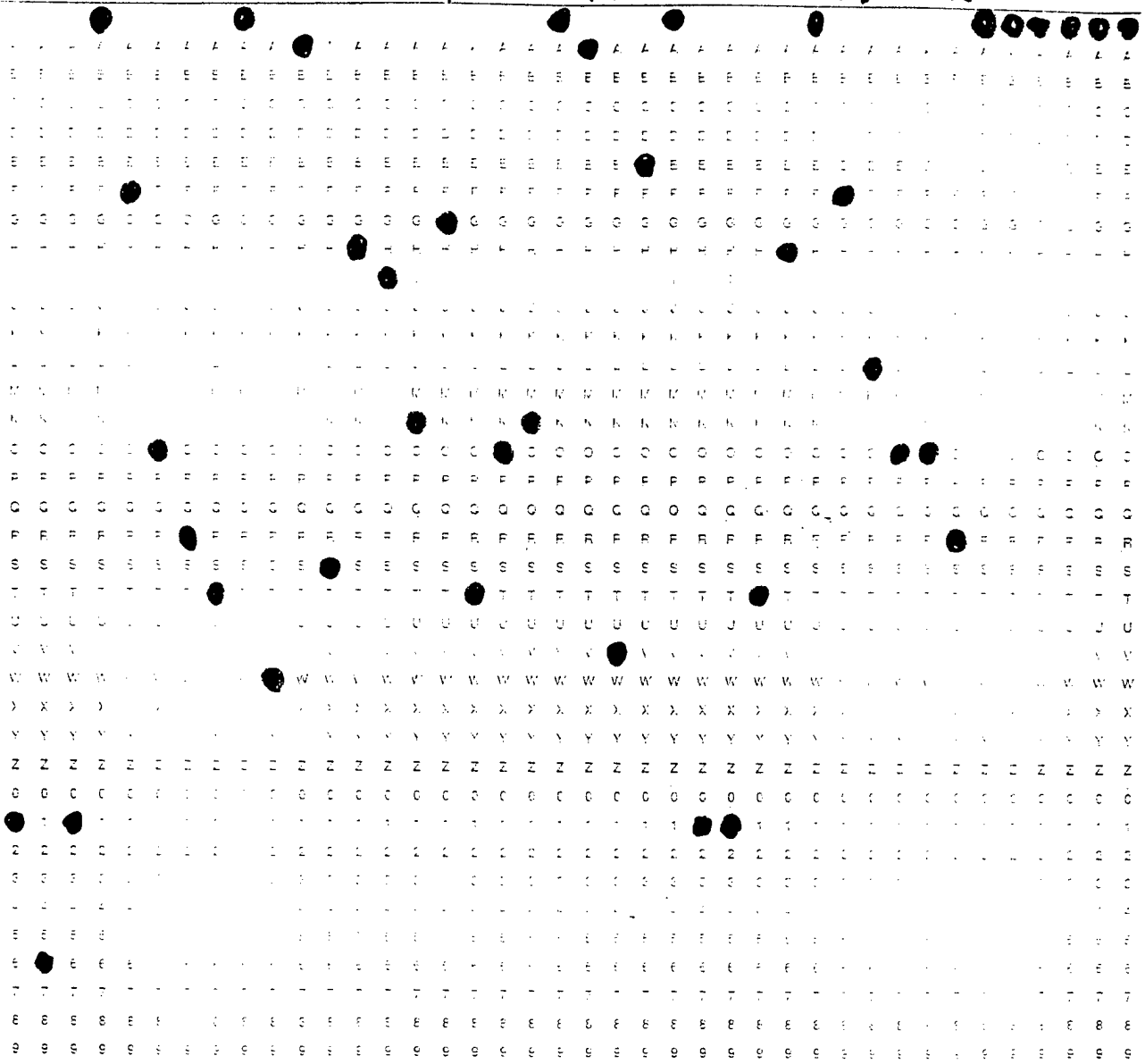
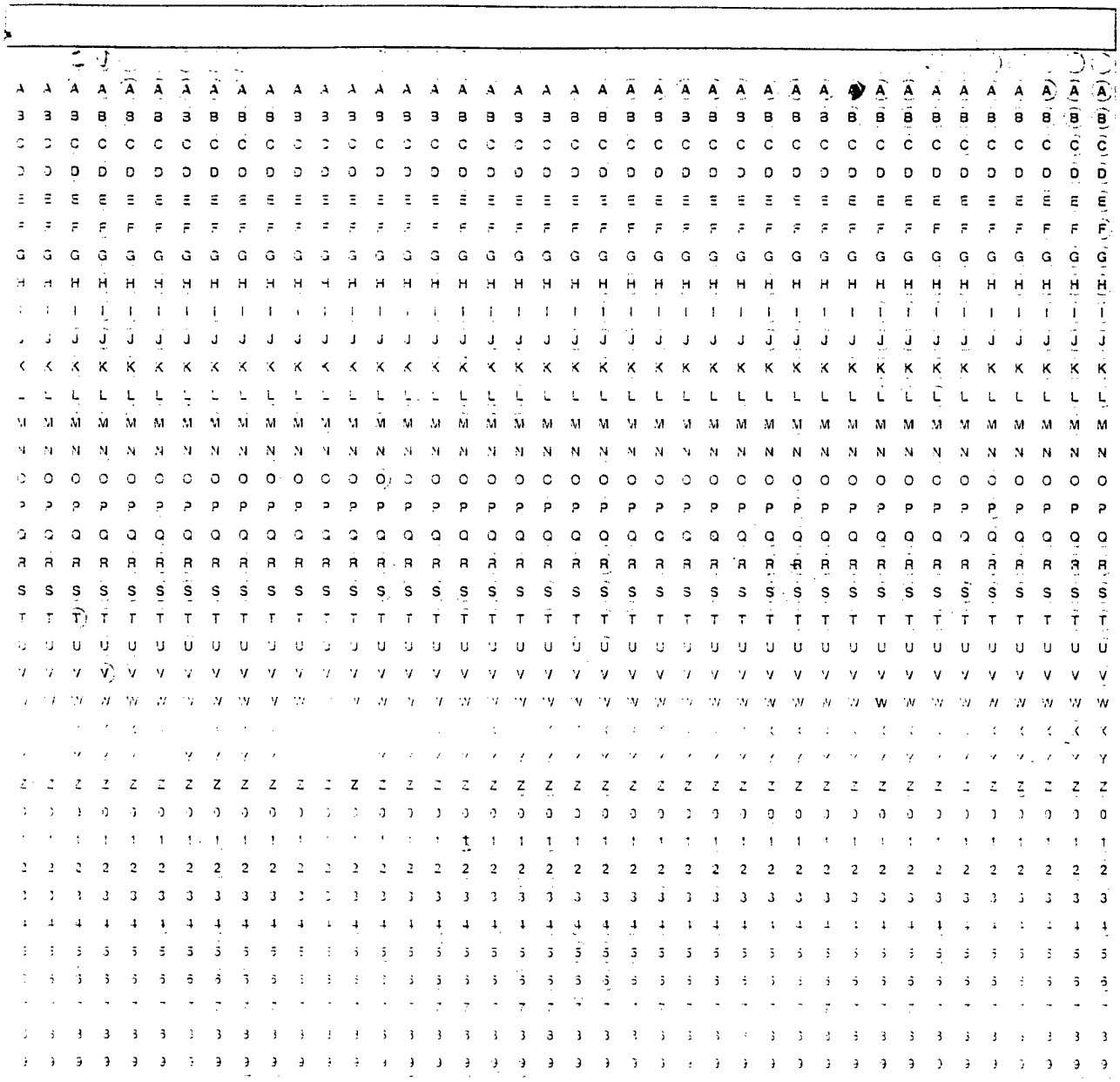
12. PI Address–Street Address Line 1

161 FORT WASHINGTON AVE 11th FLOOR



13. PI Address–Street Address Line 2 (If no Line 2, leave blank.)



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14. PI Address

NEW YORK

15. PI Address

State

NY

16. PI Address

Country

US

17. PI Address–Zip Code (Non-U.S. codes write in below.)

10032-

International Postal Code

18. Principal Investigator's Phone Number (U.S. and Canada only. If you have an International Phone Number, please write in the number, starting with country code, below.)

Area Code

212-305-0136

International Phone Number

19. Principal Investigator's Fax Number (U.S. and Canada only. If you have an international Fax Number, please write in the number, starting with country code, below.)

Area Code: 212 - 305 - 0139

International Fax Number

20. Principal Investigator's E-Mail Address (If available.)

aet1@columbia.edu

21. Principal Investigator Demographics (Optional.)

Gender: ● Male ○ Female

Ethnicity: (Select one.)
- ○ American Indian or Alaska Native
- ● Asian
- ○ Black or African American
- ○ Hispanic or Latino
- ○ Native Hawaiian or Other Pacific Islander
- ○ White
- ○ Other (Specify.):

22. Key Personnel Demographics (Optional, select all that apply.)

Gender: ○ Male ○ Female

Ethnicity:
- ○ American Indian or Alaska Native
- ○ Asian
- ○ Black or African American
- ○ Hispanic or Latino
- ○ Native Hawaiian or Other Pacific Islander
- ○ White
- ○ Other (Specify.):

23. Proposal Title (This may be up to 160 characters long.)

Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men

24. Total Funding Requested from the Government (Direct and Indirect Costs) for the Entire Proposed Period of Research (Whole U.S. dollar figures ONLY. Enter number flush with right-hand margin.)

$ 56858

25. Military/Civilian Collaboration (Mark the appropriate statement. If your proposal DOES represent a Military/Civilian Collaboration, fill in the full name of the Collaborating Organization.)

The proposed work DOES represent a Military/Civilian Collaboration. (Complete the following)

Collaborating Organization: _____

Collaborating Organization Address: _____

_____

The proposed work DOES NOT represent a Military/Civilian Collaboration

26. Human Subjects

In the proposed work, will Human Subjects be used? Yes No

If yes, which Human Subjects will be used? (Select all that apply.)

Minorities	National Guard	Outpatient
Military, Active Duty	Foreign	Other (Specify.): _____
Military, Reserve	Inpatient	

27. Human Anatomical Substances

In the proposed work, will Human Anatomical Substances be used? Yes No

If yes, which Human Anatomical Substance(s) will be used? (Select all that apply.)

Blood	Established Cell Lines	Tissue
Cells	Primary Cell Lines	Urine
DNA	Saliva	Other (Specify.): _____

Can the Human Anatomical Substance(s) indicated above be traced to a specific donor? Yes No

28. Clinical Trials

Does the proposed work include Clinical Trials? Yes No

If yes, select the type of Clinical Trial(s) proposed (Select all that apply.)

Investigational Drugs	Approved Drugs
Investigational Devices	New Indications for Approved Drugs

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29. Demographics of Human Test Subjects/Study Population of Interest

Does your research specifically target any particular segment of the population?

- Yes
- No
- Not applicable

If yes, please answer the following questions:

A. Gender of the Human Test Subjects/Study Population

Does your research *specifically target* any of the following categories?

- Male
- Female
- No target

B. Ethnicity of the Human Test Subjects/Study Population

Does your research *specifically target* any of the following ethnic/racial categories?

- American Indian
- Alaska Native
- Asian
- Black or African American
- Hispanic or Latino
- Native Hawaiian or Other Pacific Islander
- White
- Other (Specify.): _____
- No target

C. Age of the Human Test Subjects/Study Population

Does your research *specifically target* any of the following age ranges?

- Minor (under 18 years of age)
- 18–30 years of age
- 31–50 years of age
- 51–70 years of age
- Over 70 years of age
- No target

D. General Income of the Human Test Subjects/Study Population

Does your research *specifically target* any of the following categories?

- Low income (less than $30,000/year)
- Middle income ($31,000–$45,000/year)
- Upper income (greater than $45,000/year)
- No target

E. General Demographic Target or Focus

Does your research *specifically target* any of the following categories?

- Underserved population(s)
- Understudied population(s)
- No target

30. Animal Subjects

In the proposed work, will Animal Subjects be used? Yes No

In the proposed work, will Animal Subjects be used by a subcontractor? Yes No

If yes to either of the above questions, which Animal Subjects will be used? (Select all that apply.)

Amphibians — Fish — Hamsters — Rodents
Birds — Horses — Sheep — Swine
Cats — Non-human Primates — Swine
Dogs — Rabbits — Other (Specify)

31. Safety Provisions (Select all that apply.)

Biohazards — Investigational Drugs
Genetically Modified Agents — Radioactive Materials
Human Fetal Tissue — Recombinant DNA
Hazardous Chemicals — Other (Specify)

32. Mentor Name (Must be included for all Traineeship proposals.)

Last Name	First Name	MI
KAPLAN	STEVEN	A

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33. Research Classification (Enter the Classification Code from the list provided in the Proposal Cover Booklet Instructions.)

34–38. Research Area (Enter the codes from the list provided in the Proposal Cover Booklet Instructions.)

34. Research Area Level 1	35. Research Area Level 2	36. Research Area Level 3	37. Research Area Level 4	38. Research Area Level 5
100				

39. Have you submitted another proposal in a different Proposal Category? (Do not include Proposals submitted to other programs or for previous years.) Yes No

If yes, please enter the Proposal Category Code from the list provided for question #3 in the Proposal Cover Booklet Instructions.

40. Administrative Representative Authorized to Conduct Negotiations. (Signature MANDATORY.)

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Signature: Richard J. Sohn Date: 7/7/98

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E-Mail Address: osc1@columbia.edu

Signature: Olga S. Carr Date: 7/7/98

41. Institution's Official Proposal Control Number (If none, leave blank.)

42. Principal Investigator (Must match PI listed in question 7. Signature MANDATORY.)

Name: ALEXIS E. TE, M.D.

Department: Department of Urology

Signature: Date: 7/7/98

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Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men

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Proposed Start Date: 10/1/98- 3/31/99

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Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men

Alexis E. Te, M.D.
Research Area = Cell biology with Biomarkers

Key Words: PSA, transition zone density, prostate volume, Black Americans, Asian Americans

Research Concept

There are significant racial differences in unscreened populations in both prostate cancer incidence and mortality rates.(9,10,11,23) Furthermore, serum prostate specific antigen (PSA) is higher in Black American than in White males which are then higher than Asian males.(5,18) Prostate cancer detection strategies such as PSA age adjusted reference ranges and PSA density, the ratio of PSA to total prostate volume (PSAD), have had significant shortcomings when applied to ethnically diverse populations.(3,5,13,15,19,22) In an attempt to optimize the clinical utility of PSAD, various investigators have attempted to utilize the PSA density of the transition zone (TZ) of the prostate as a more effective marker for cancer of the prostate.(1,2,4,17,20,24) We have recently reported that the transition zone volume in age matched patients with benign prostatic hyperplasia is significantly higher in Black Americans than in Whites. (8) Therefore, differences in PSA between Black Americans, Whites and even Asian males may reflect differences in PSA production by the transition zone and not to inherent biological susceptibility of prostate cancer for Black males versus White males versus Asians. Therefore, the goal of this concept development proposal is evaluate whether there is ethnic variation in PSA density of the transition zone (PSAT) and whether differences in serum PSA can be explained by PSAT variation. (6,7) More importantly, we will assess whether PSAT is a better refinement of currently available cancer detection strategies especially in specific ethnic populations.

The proposal seeks to addresses these two issues in an innovative way. First, the analysis of a new PSA reference point prospectively in a screening population will help us to determine if we can enhance sensitivity and specificity of PSA. The potential ability to increase detection without increasing prostate biopsies has enormous medical and economic implications. (16,21) Furthermore, the potential of application in ethnically diverse groups enhances the utility of this PSA reference point. To date, there is no PSA reference point which adequately addresses these issues across a wide spectrum of patients. This study will further enhance the only area where we have had any broad impact on prostate cancer, that is screening and detection. Thus, not only will health and economic concerns be addressed, but this study will have important social implications if PSAT can be applied across a wide spectrum of patients.

The basis for this study relies on the premise that differences in PSA between black, white and Asian males reflect differences in PSA production by the transition zone. This reflects differences in histologic evidence and/or volume of BPH and not to inherent biological susceptibility based on racial differences.

To prove this we must demonstrate that differences in PSA and PSAD among black versus white versus Asian males reflect variations in transition zone volume. Black males have more "BPH" volume manifesting in higher PSA values. Therefore, utilization of current modifications of PSA, i.e. PSAD may not be the most accurate marker for patients at increased risk for prostate cancer. Utilization of PSAT will correct for any measured differences in either PSA or PSAD among ethnically diverse men. We hypothesize that PSAT for black and white males should be the same.

Therefore, PSAT cutoffs for detecting prostate cancer should be similar among black , white and Asian males. Unlike PSAD, which may require different values for blacks and whites, PSAT, which corrects for PSA differences secondary to BPH as reflected by TZ volume, should be the same. Thus, PSAT will be a better predictor of prostate cancer than currently available PSA screening modalities. These include PSA, PSA age specific reference ranges or PSAD. Sensitivity manifested by detection of prostate cancer and specificity manifested by elimination of negative biopsies would then be enhanced compared to currently available screening techniques.

To develop this concept, Serum PSA and transrectal ultrasound measurements of the prostate will be done in a cohort of Black, White and Asian men over the age of 40. Volumetric determination of both the

entire prostate and transition zone volume of the prostate will be done and both PSAD and PSAT calculated. The objective is to determine whether ethnic variation in PSAD and PSAT exist. To check if determine if PSAT cutoffs for biopsy indications are different among Black, White and Asian men, patients with positive biopsies for prostate cancer will be evaluated to determine whether there are racial differences in PSAT threshold for biopsies among these males. To assess whether PSAT is a better refinement of currently available prostate cancer detection strategies. PSA, age specific PSA reference ranges, PSAD and PSAT will be assessed to determine which produces greatest sensitivity and specificity and whether any ethnic variation exists among PSAT as a cancer detection strategy.

This study is a cross-sectional investigation of differences in prostate morphology as defined by serum PSA and prostate volume an ethnically diverse sample of men. The sample population consists of men aged 40 and above referred for or self-seeking evaluation of their prostate, elevated serum PSA or abnormal findings on digital rectal examination. Subjects will be recruited from the CPMC Squier Urological Clinic, the Prostate Center and from a Chinatown Community Clinic in Brooklyn. For concept development, we intend to study a preliminary group of approximately 36 men for the study, equally divided between White, Asian and Black American male continuously over the limited training study period to determine what differences exists. Consultation for statistical evaluation and adequacy for concept development will be assessed during the training period. Protocol and contract for appropriate recruitment procedures with recruitment sites will be develop and initialized. Software development for data collection, storage and management will be reviewed and formalized along will necessary baseline demographic information. IRB approval for the formalized concept development proposal protocol will be obtained. Finally, a formal grant application will be finalized at the end of the concept development training period.

Collaborative Experience and Arrangement of PI and Established Investigator

The Principle Investigator (PI) and Established Investigator has had extensive collaborative experiences as both a basic science and clinical investigator of various urological and prostate disease processes. The PI has had fellowship training under the guidance of the established investigator and is currently a co-investigator investigator in a current NIH project. With the Established Investigator as director of the Columbia Presbyterian Medical Center Prostate Center and through integration with the Cancer Center, more than 750 patients have entered clinical trials designed to evaluate both benign and malignant disease of the process over the past 6 years. In addition to two NIH awards, the Established Investigator has received more than 16 grants to evaluate various pathologic processes within the prostate. As it relates to this project, the PI and Established Investigator have worked together on various related projects and are well experience in ultrasound measurement technology and technique. The collaborative and supportive relationship is reflected in the numerous publications the PI has co-authored with the Established Investigator. This close supportive/ collaborative relationship translates to a twice weekly interactions that supports collaborative research at many levels. Current support and collaboration includes the preliminary data preparation and consulting for this project which has no funding. The PI has access and use of the facilities described in the addenda.

With regards to the present concept development, two studies have been published by the Established Investigator and the PI regarding the use of transition zone measurements in the prostate.(7,8) (See Addendum A). The latest addresses the use of transition zone volumes in ethically diverse males.(8) These data clearly indicate that African American males have a significantly higher transition zone volume than either Hispanics or Caucasian males. The PSA of the three groups was 3.2, 2.9, and 2.8, respectively. (See Tables 1 and 2)

Table 1: Prostate volume, transition zone volume and TZ index in various ethnic groups (BPH Group)

Parameter	Black American (n = 26)	Hispanic (n = 23)	White (n = 24)
Age (years)	60.1 ± 9.4	62.7 ± 6.5	60.5 ± 4.5
Prostate Volume (ml)	37.5 ± 11.5	38.9 ± 9.8	35.6 ± 13.8
Transition zone volume (ml)	**20.7 ± 9.6**	**15.2 ± 7.5**	**14.8 ± 5.2**
Transition zone index	**0.49**	**0.39**	**0.41**

Bold represents statistical significance of Black American versus Hispanic or White men

Table 2: Correlation of Prostate Volumes and Ethnic Group

	Black – American	Hispanic	White
Prostate volume	0.20	0.14	0.17
Transition zone volume	**0.39**	0.24	0.21
Transition zone index	**0.37**	0.19	0.24

P < 0.01

These data provide compelling evidence that PSA differences in Black America males may reflect volumetric differences in the benign portion of the prostate. Therefore, a PSA reference marker, i.e. PSA density of the transition zone, which corrects for volume differences of the transition zone, would have significantly greater impact in a screening population of ethnically diverse men.

Career Development

The explicit value of this training grant is to enhance the PI's ability to prepare and successfully complete for formal grant application as a primary investigator. The PI has a long record of collaborative research in the area of prostate diseases as a co-investigator. The training grant will allow the PI the time and resource necessary to develop as an independent primary prostate cancer investigator and continue successfully in his current academic pursuits as an investigator in prostate diseases.

Applicant's (PI) Research Background, Current Program of Research and Future Goals.

The PI is currently an Assistant Professor of Urology in the Department of Urology at Columbia University College of Physicians and Surgeons. He graduated from Yale University with a Bachelor of Science in Molecular Biophysics and Biochemistry and has research experience in the area of Molecular Biological Research with in College and in medical school at Cornell University Medical College. During residency training at Columbia Presbyterian Medical Center, he continued his academic interest performing basic bench research and publishing articles, both clinical and basic science as reflected in his resume on various urological problems. He continued his academic career by completing a formal Neurourology and Urodynamics Fellowships with an emphasis on voiding dysfunctions, prostate diseases and treatments, incontinence and female urology. He continues today as a academic faculty member collaborating with the Established Investigator on numerous projects on prostate diseases. Finally, he is a director of the Incontinence Care Center at CPMC and Maimonides Medical Center. Current goals are to continue on the academic tenure tract career and further develop the research interest in urological disease processes such as the numerous prostate diseases including prostate cancer.

Acronym and Symbol Definition

TRUS: transrectal ultrasound of the prostate
PSA: serum prostate specific antigen
PSAD: PSA density (ratio of serum PSA and total prostate volume
PSAT: PSA density of the transition zone
BPH: benign prostatic hyperplasia
CPMC: Columbia Presbyterian Medical Center
PI: Primary Investigator
EI: Established Investigator

Alexis E. Te, MD

Statement of Work

Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men

Task 1: Project Startup and Parameter Development (Month 1)

a. Meet with collaborating established investigator
b. Consult with biostatician for statistical analysis of data to be collected
c. Review database parameters and development of software to collect data.
d. Formulate and review plan to efficiently answer study proposal

Task 2: Develop final plan for performing ultrasound imaging and measurement of PSA (Months 2-3)

a. Recruitment strategies for patient screening to be developed
b. Computer software between two investigative sites to be coordinated
c. Institutional Review Board approval to be obtained

Task 3: Subject recruitment and data collection of preliminary analysis(Months 4-5)

a. Patients screened for eligibility
b. Informed consent obtained
c. All sociodemographic information obtained
d. Serum PSA measured
e. Transrectal biopsy performed on patients with abnormal digital rectal examination or serum PSA outside PSA age – specific reference range.
f. Data collected for sociodemographic factors, serum PSA, PSA density, PSA density of the transition zone

Task 4: Preliminary Data Analysis (Months 6)

a. Statistical analyses of data to be performed
b. Adjustments in protocol to be done, if necessary

Task 5: Final analysis and grant writing (Months 6)

a. Analysis of all transrectal ultrasound measurements will be performed
b. Statistical analysis and correlation to PSA and PSA density of the transition zone will be done
c. Consolidate information, prepare final report, and summarize the efforts accomplished

2.b. DETAILED COST ESTIMATE

Applicants should complete this form for the entire period of proposed funding.

DETAILED BUDGET FOR BUDGET PERIOD	FROM 10-1-98	THROUGH 3-31-98

PERSONNEL		MONTHLY BASE SALARY	NUMBER OF MONTHS	PERCENT OF EFFORT ON PROJECT	DOLLAR AMOUNT REQUESTED (OMIT CENTS)		
NAME	ROLE ON PROJECT				SALARY REQUESTED	FRINGE BENEFITS	TOTALS
ALEXIS E. TE	Applicant	3,333	6	25%	5,000	1,420	6,420
STEVEN A. KAPLAN	Collaborating investigator	3,750	6	20%	4,500	1,278	5,778
ALETA ASHLEY	NURSE	3,333	6	75%	14,999	3,651	18,650
PERSONNEL SUBTOTAL (A)							$30,848

CONSULTANT COSTS			
MAJOR EQUIPMENT COSTS (ITEMIZE)			
MATERIALS, SUPPLIES, AND CONSUMABLES COSTS (ITEMIZE BY CATEGORY)			
TRAVEL COSTS			$2,500
OTHER EXPENSES (ITEMIZE BY CATEGORY)			
OTHER DIRECT COST SUBTOTAL (B)			$2,500
SUBCONTRACT COSTS	DIRECT COST		
	INDIRECT COST		
SUBCONTRACT COSTS TOTAL (C)			$ 0
DIRECT (PERSONNEL, OTHER DIRECT, AND SUBCONTRACT) COSTS (A+B+C)=(D)			$33,348
INDIRECT COSTS TOTAL (E)			$23,510
TOTAL COSTS (D+E)			$56,858

*** Itemize all budget categories on *Justification* page which follows.**

BUDGET JUSTIFICATION

Salary support is requested for:

Dr. Te as the Applicant for the Training Grant. He is an Assistant Professor of Urology at Columbia University. He is a prostate disease specialist at the Prostate Center, the director of the Incontinence Care Center at both Columbia Presbyterian Medical Center and Maimonides Medical Center. He will have responsibility in screening and recruiting patients, and performing transrectal ultrasound guided biopsies. He will be the primary investigator in the development of the proposed concept development in training. The salary and effort presented on the budget page is based on the Columbia University institutional base salary of $41,936.

Dr. Kaplan as the Established Investigator and Mentor of this training grant concept development project who will guide in the development and training of the PI. In addition, he will assist in the modifications and amendments made to the protocol. He will also assist in the clinical aspects of development as necessary. The salary and effort presented on the budget page is based on the Columbia University institutional base salary of $41,936.

Based on our previous experience with recruitment and follow-up of patients in studies of prostate diseases, which require ultrasound, one nurse will be required for this study. Aletta Ashley will devote 100% of her time to seeing patients during the initial evaluation and coordinating patient visits. She will perform managing, collecting, coordinating and processing all data and follow-up visits as well. **As part of Cost Sharing, the Department of Urology will pay 25% of the nurses's salary and only 75% will be charged to the grant proposal.**

Secretarial and clerical functions will be provided by the Department of Urology as part of Cost Sharing at no additional cost to the grant.

The budget is based on a 4% increase in salary per annum. The fringe benefits for the PI and the Established Investigator is 28.4% (Columbia University employees); the fringe benefits for the nurse is 24.34% (Columbia-Presbyterian Medical Center employee).

Travel expenses are related to 1 national meeting per year for the PI for concept development and consultation.

Cost Sharing: As stated above, both the University and Department of Urology have committed resources at no additional expense to the grant proposal. These include 25% of the research nurse salary, and, funding salary support for secretarial and clerical assistance as well as laboratory support.

ADDENDUM A

References

1. Bazinet M, et al: Prospective evaluation of prostate specific antigen density and systematic biopsies for early detection for early detection of prostatic carcinoma. Urology, 43: 44, 1994.
2. Benson, MC, et al: Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. J.Urol, 147:815, 1992.
3. Catalona WJ, et al: Measurement of prostate specific antigen in serum as a screening test for prostate cancer. NEJM, 324: 1156, 1991.
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5. Henderson RJ, et al: Prostate specific antigen (PSA) and PSA density: racial differences in men without prostate cancer. J Natl Can Inst, 89: 134, 1997.
6. Kalish J, et al: Serum PSA adjusted for volume of transition zone (PSAT) is more accurate than PSA adjusted fot total gland volume (PSAD) in detecting adenocarcinoma of the prostate. Urology, 43: 601, 1994.
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12. Moul JD, et al: Three dimensional (3D) computerized tumor volume determination in radical prostatectomy specimens from black and white patients. J Urol, part 2, 155:509A, 1996.
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23. Wingo, PA, et al: Cancer statistics for African – Americans, 1996. CA 46:113, 1996.
24. Zlotta AR et al: Prostate specific antigen density of the transition zone: a new effective parameter of prostate cancer detection. J Urol, 157:1315, 1997.

ADDENDUM B

2.c. BIOGRAPHICAL SKETCH

Applicants should include this form as Addendum B in the submitted proposal.

Provide the following information for the applicant and collaborating investigator listed on the detailed cost estimate

NAME	POSITION TITLE
Alexis E. Te, MD	PRINCIPLE INVESTIGATOR AND APPLICANT

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include post-doctoral training.)

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY
Yale University	B.S.	1980-1984	Molecular Biophysics & Biochemistry
Cornell University Medical College	M.D.	1984-1988	Medicine
Columbia University	Resident	1988-1990	Surgery
Columbia Univeristy	Resident	1990-1994	Urology
Columbia University	Fellowship	1994-1995	Neurourology & Urodynamics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past 3 years and to representative earlier publications pertinent to this application. If the list of publications in the last 3 years exceeds 2 pages, select the most pertinent publications. PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

Attending in Surgery — 7/94-Present
Department of Urology — West Havestraw, NY
Helen Haves Hospital

Clinical Assistant in Urology — 7/94-6/95
J. Bentley Squier Urologic Clinic — New York, NY
College of Physicians and Surgeons of Columbia University
Columbia Presbyterian Medical Center

Director of the Incontinence Care Center — 11/96- Present
Neurourology and Urodynamics Laboratory — Brooklyn, New York
Assistant Attending in Surgery
Division of Urology
Maimonides Medical Center

Assistant Professor of Urology — 7/95- Present
Assistant Attending in Urology — New York, NY
Co-Director of Incontinence Care Center
J. Bentley Squier Urologic Clinic
College of Physicians and Surgeons of Columbia University
Columbia Presbyterian Medical Center

Publication

Peer Review Publications-

1. Te AE, Colombel M, Koo HP, Kaplan SA, Buttyan R, Olsson CA, Shabsigh R. Castration-Induced Apoptosis in the Rat Penis. Surgical Forum 1992; 48: 724-725.

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9. Santarosa RP, Raymond J, Colombel M, Te AE, Koo HP, Olsson CA, Buttvan R & Shabsigh R: Effects of castration on the rat penis. J Urol. In Press.

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16. Kaplan SA, Santarosa RP, Te AE: Transurethral electrovaporization of the prostate: one year experience. Urology 48(6):876-81, 1996.

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18. Kaplan SA, Te AE, Ikeguchi E, Santarosa RP: Safety and efficacy of alpha blockers in the treatment of men over the age of 80 with benign prostatic hyperplasia. Urology, in press.

Non-Peer Review Publications-

1. Kaplan SA, Te AE: Uroflowmetry & Urodynamics.Urologic Clinics of North America 1995; 22: 309-20.

2. Te AE , Kaplan SA: Transurethral Electrovaporization of the Prostate (TVP): A electrosurgical advancement of the standard TURP. Current Surgical Techniques in Urology 1995; 8:1-9.

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Philadephia, J. B. Lippincott Co., 6: 659-668. 1992.

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ADDENDUM B

2.c. BIOGRAPHICAL SKETCH

Applicants should include this form as Addendum B in the submitted proposal.

Provide the following information for the applicant and collaborating investigator listed on the detailed cost estimate

NAME	POSITION TITLE
Steven A. Kaplan, MD	ESTABLISHED INVESTIGATOR

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include post-doctoral training.)

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY
CUNY-Brooklyn College	B.S.	1974-1978	Biochemistry
Mount Sinai School of Medicine	M.D.	1978-1982	Medicine
Mount Sinai Hospital	Resident	1982-1984	Surgery
Columbia University	Resident	1984-1988	Urology

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past 3 years and to representative earlier publications pertinent to this application. If the list of publications in the last 3 years exceeds 2 pages, select the most pertinent publications. PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

1988 - 1990 American Foundation of Urology Scholar
Department of Urology
College of Physicians & Surgeons
Columbia University

1988-1990 Clinical Instructor, Department of Urology
College of Physicians & Surgeons
Columbia University

1990-1995 Assistant Professor, Department of Urology
College of Physicians & Surgeons
Columbia University

1996- 1997 Herbert Irving Associate Professor, Department of Urology
College of Physicians & Surgeons
Columbia University

1996- Present Vice-Chairman, Department of Urology
College of Physicians & Surgeons
Columbia University

1990- Present Director, Prostate Center
J. Bentley Squier Urological Clinic
Columbia Presbyterian Medical Center

1993- Present Director, Neurourology & Urodynamics
J. Bentley Squier Urological Clinic
Columbia Presbyterian Medical Center

1997- Present Professor, Department of Urology
College of Physicians & Surgeons
Columbia University

Relevant Publications (of 142 publications)

Kaplan SA, Shanzer H, Racelli D, et al: Orthotopic, segmental small bowel transplantation in the rat. Mount Sinai Journal of Medicine, 53: 112-116, 1986.

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Te AE, Buttvan R, Koo HP, Olsson CA, Kaplan SA : Nerve growth factors in diabetic cystopathy Neurourol & Urodynam 11:4:303-304. 1992.
Chancellor MB, Kaplan SA, Blaivas JG: The cholinergic and purinergic componenets of detrusor contractility in a whole rabbit bladder model. J Urol,148:906-909, 1992
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Addendum C
Facilities and Equipment

The *Prostate Center* at Columbia-Presbyterian Medical Center was established in 1990. It is dedicated to investigating all alternative treatments in the management of BPH and prostate cancer is well suited and equipped to enroll a suitable number of patients for this clinical trial. Both the Department of Urology and Columbia-Presbyterian Medical Center have demonstrated a willingness to provide space, personnel and technical assistance for this center. A new facility was recently completed in January of 1996 and currently houses the Prostate Center. It has have over 4,000 square feet dedicated to patient research, prostate ultrasound and urodynamics.

Currently, at the Prostate Center, over 750 patients have been enrolled in 17 investigative protocols including medical (5-alpha reductase inhibitors [finasteride, epristeride], alpha blockers [terazosin, doxazosin, tamsulosin] and aromatase inhibitors [atamstane]); transurethral hyperthermia, prostatic stents, electrovaporization and lasers. Our involvement has ranged from designing protocols to investigator status. The E.I. and the applicant have had extensive experience in the field and have worked in many collaborative efforts including the BPH feasibility trial.

The *Prostate Center* consists of 4 fully equipped examination rooms (800 square feet), each having a uroflowmeter and Bladder Scan device. There are 6 office areas (1,500 square feet) and storage space for patient records and storage of medication. In addition, many of the clinical trials have involved either measuring prostate size or obtaining tissue and we have on site facility access to a transrectal ultrasound machine (B&K 8551) as well as MRI technology.

The staff of the *Prostate Center* includes the E.I. who is Director, a staff urologist (Applicant and Co-Investigator) and a yearly Fellow in Neurourology. The other dedicated personnel include a Nurse Coordinator who is responsible for patient care, data collection and supervising a staff nurse and full time data manager. There is a great deal of experience in participating and formulating multi-center clinical trials. We have participated either currently or in the past in 19 multicenter clinical trials involving treatment of prostate disease and two NIH funded trials. The staff is adept at prompt scheduling of patients both in the recruitment and follow-up phases of the study; timely and meticulous entry of data in both source documents and by remote data entry where applicable (within 24 hours of seeing patients) and in handling and shipping tissue and serum specimens on the day that they are obtained.

The Squier Urological Clinic at the Allen Pavilion serves as the major health facility of North Manhattan and serves a large population of ethnically diverse patients. There are 5 office areas and a large area for patient accrual. It is connected by network computer link to the data base at the Prostate Center. This allows for timely and efficient data entry.

A network of IBM compatible computers connected to a central server are maintained in the Prostate Center by the P.I. for word processing, database collection and processing, and statistical analysis. (Total of 29 GB)

P.I. has 400 square foot office. Each Co-Investigator has 200 square foot office. The study nurse and secretary have a 400 square foot office.

The Prostate Ultrasound Facility at Columbia Presbyterian Medical Center has 250 square foot for equipment and patient evaluation. Currently, a B&K ultrasound unit with biopsy guide is available. There is dedicated dressing space and a bathroom.

ADDENDUM D

MPFT SUPPORT DOCUMENTATION

Department of Urology
College of Physicians and Surgeons
of Columbia University

Steven A. Kaplan, M.D., F.A.C.S.
Professor and Vice Chairman of Urology
Director, Neuro-Urology and The Prostate Center

Squier Urological Clinic
The Presbyterian Hospital
in the City of New York

Tel: (212) 305-0140
(212) 305-0146
Fax: (212) 305-0139

July 7, 1998

Commander
US Army Medical Research and Material Command
Att: MCMR-PLF (PCRP-MPFT-98)
1076 Patchel Street Building 1076
Fort Detrick, MD 21702

To Whom It May Concern:

This is a letter of support for Dr. Alexis E. Te's training grant application for the 1998 MPFT grant. I have known Dr. Te since 1988, as a resident, fellow and now as an associate on our academic staff. I have worked with Dr. Te for many years and have co-authored many publications and abstracts with him. As my fellow in Neurourology and Urodynamics, he has been instrumental and valuable in the development and success of several academic and clinical projects including many studies on prostate treatments and prostate disease processes. This is evident from his resume.

As a fellow, he gained expertise not only in Neurourology and Urodynamics, but also in new technologies for BPH therapies, incontinence and female urology. He is now a member of our faculty , a co-investigator and collaborator with me on several projects. I fully support his MPFT application in every manner necessary as his established investigator on the grant. He is a reliable and proven junior researcher and a responsible faculty member that I continue to count on. As member of our attending staff and faculty at Columbia Presbyterian Medical Center and Columbia University, I fully support and am committed to his training and development as a career academician.

I have been actively involved in the fomulation of the training grant research concept. The topic PSAD of the Transition Zone in Ethnically Diverse Men is a project that has involved Dr. Te's collaboration as evident our publications. We propose to explore the rôle of PSA Density of the Transition Zone (PSAT) in the screening evaluation for prostate cancer in an ethnically diverse population of men. Our preliminary data suggest that PSAT may be a better refinement of currently available cancer detection strategies especially in specific ethnic population. This work would also lend to a better understanding of prostate morphology in different ethnic populations.

I enthusiastically support Dr. Te's application for this training grant to further his academic career development and to serve as his established investigator in this proposal.

Sincerely,

Steven A. Kaplan, M.D
Professor and Vice Chairman
Dept of Urology

Department of Urology
College of Physicians and Surgeons
of Columbia University

Carl A. Olsson, M.D.
John K. Lattimer Professor and Chairman

Squier Urological Clinic
The Presbyterian Hospital
in the City of New York

Tel: (212) 305-0100
Fax: (212) 305-0106

July 7, 1998

Commander
US Army Medical Research and Material Command
Att: MCMR-PLF (PCRP-MPFT-98)
1076 Patchel Street Building 1076
Fort Detrick, MD 21702

To Whom It May Concern:

The Department of Urology at the College of Physician and Surgeons of Columbia University is totally dedicated to the career plans of Dr. Alexis E. Te.
Dr. Te is an Assistant Professor in our faculty. He will be relieved of clinical and administrative responsibilities in order for him to pursue his academic career development in the proposed research plan.

Dr. Te is an Asian American physician who has contributed much of his time, both clinical and community related, in the Asian American community. He has been active in minority related concerns and has been honored with awards from the Philippine Chinese American Medical Association and the Philippine Chinese American Association for his achievements. He has an established relationship with Dr. Steven A. Kaplan and will continue mentorship with him as his established investigator in the proposal. Dr. Kaplan is also a member of our faculty, and a Professor and Vice Chairman of the Department of Urology at Columbia.

They propose to evaluate the role of PSA Density of the Transition Zone (PSAT) in the screening evaluation for prostate cancer in an ethnically diverse population of men. Their preliminary data suggest that PSAT may be a better refinement of currently available cancer detection strategies especially in specific ethnic population. This work would also lend to a better understanding of prostate morphology in different ethnic populations.

I enthusiastically support Dr. Te's application for this training grant to further his academic career development.

Sincerely,

Carl A. Olsson, MD
Professor and Chairman
Dept. of Urology

2.d. STATEMENT OF ELIGIBILITY

Applicants should include this form as Addendum E in the submitted proposal.

Applicant's Name: Alexis E. Te, MD

Title of the Proposal: Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men

Applicant's Organization Name: Columbia University

Applicant's Organization Location: New York, NY

Signature of Applicant: _____ **Date:** 7/7/98

STATEMENT OF ELIGIBILITY

For the purpose of the Department of Defense Congressionally Directed Medical Research Prostate Cancer Research Program's Minority Population Focused Training (MPFT) Award category as outlined in this Announcement, the applicant fulfills all of the following criteria:

- has their own independent research facilities;

AND

- holds a position of *at least* Assistant Professor or equivalent;

I, CARL A. OLSSON, MD, of Columbia University
(printed name of the Department Chair, Dean, or equivalent official) (printed name of institution)

attest that the above named investigator fulfills the requirements for an MPFT Award.

Signature of Official: _____ **Date:** 7/7/98

Addendum F

EXISTING/ PENDING SUPPORT

TE, ALEXIS E

ACTIVE

5 UO1 DK46418 - 05	4/95-3/01
Per cent effort	20%
Dr. Te is co-investigator	$334,680
NIH/NIDDK	

Progression of BPH on Medical Therapy

The major goal of this project is to determine the feasibility of assessing various parameters on the progression of benign prostatic hyperplasia (BPH) over a 6 year period.

No Overlap

KAPLAN, STEVEN A.

ACTIVE

5 UO1 DK46418 - 05	4/95-3/01
Per cent effort	20%
P.I. is Steven A. Kaplan	$334,680
NIH/NIDDK	

Progression of BPH on Medical Therapy

The major goal of this project is to determine the feasibility of assessing various parameters on the progression of benign prostatic hyperplasia (BPH) over a 6 year period.

No Overlap

Appendices 2

PROPOSAL COVER BOOKLET

MARKING INSTRUCTIONS CORRECT MARK ● INCORRECT MARKS ✓ X ● •

1. Proposal Log Number (Leave blank.)

2. BAA Identifier and Proposal Category

PCRP-99, NI

3. Proposal Category Code (Enter the Proposal Category Code from the list provided in the Proposal Cover Booklet Instructions. Must agree with Proposal Category listed in question #2.)

15

4. Organization Code (Leave blank.)

5. Organization Name and Grants/Contracts Office Address

COLUMBIA UNIVERSITY
HEALTH SCIENCES DIVISION

630 West 168th Street

New York State NY

USA 10032

6. Type of Organization (Enter the Type of Organization from the list provided in the Proposal Cover Booklet Instructions.)

G

7. Principal Investigator

TE ALEXIS E

1

09610

8. Title

9. Degree(s) of Principal Investigator(s) (Select all that apply.)

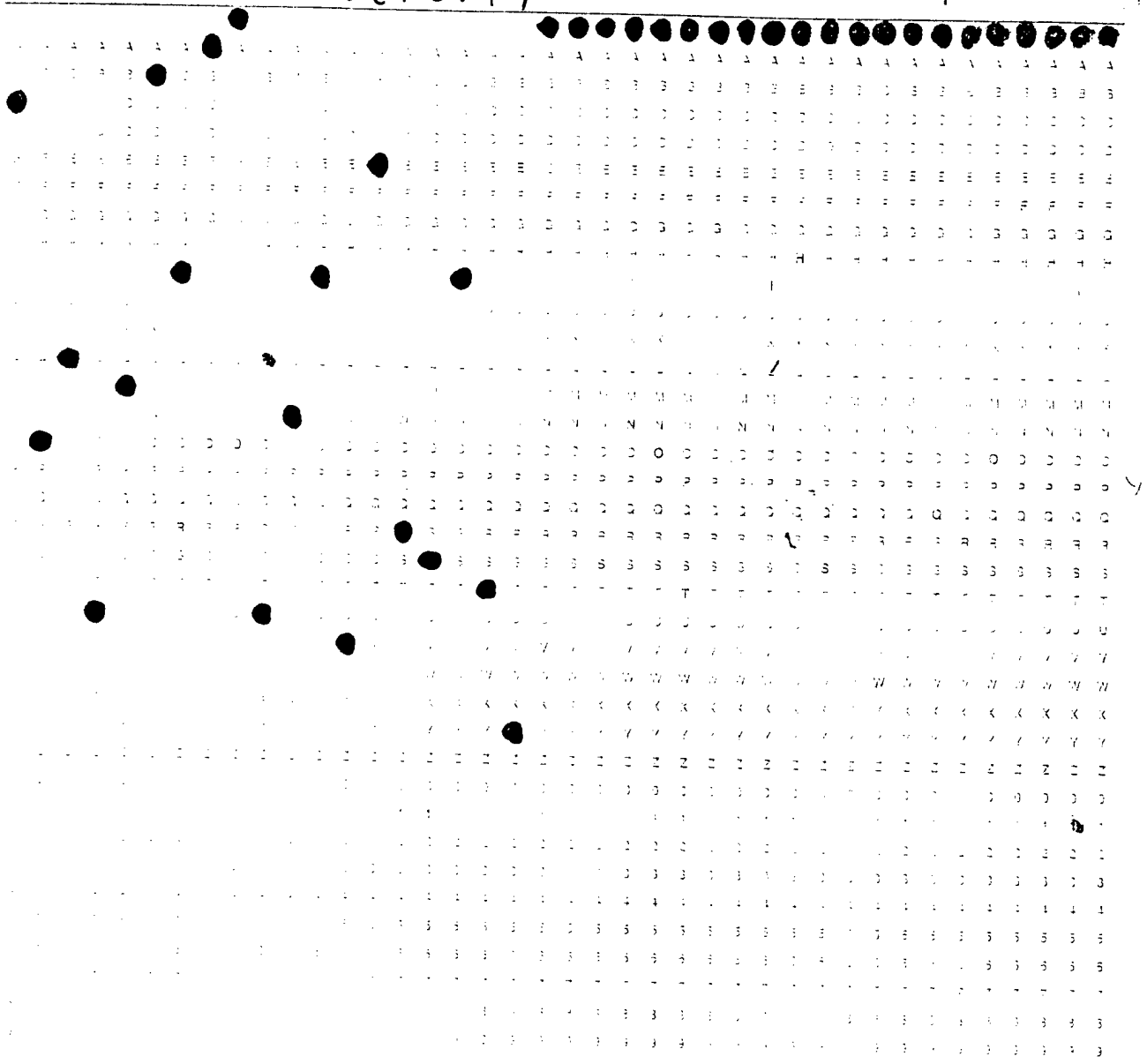
10–17. Principal Investigator's Mailing Address. This is the primary address used to contact you. (Do not use a P.O. Box unless unavoidable.)

10. PI Address–Organization Name (If none, leave blank. Use spaces as appropriate.)

DEPARTMENT OF UROLOGY

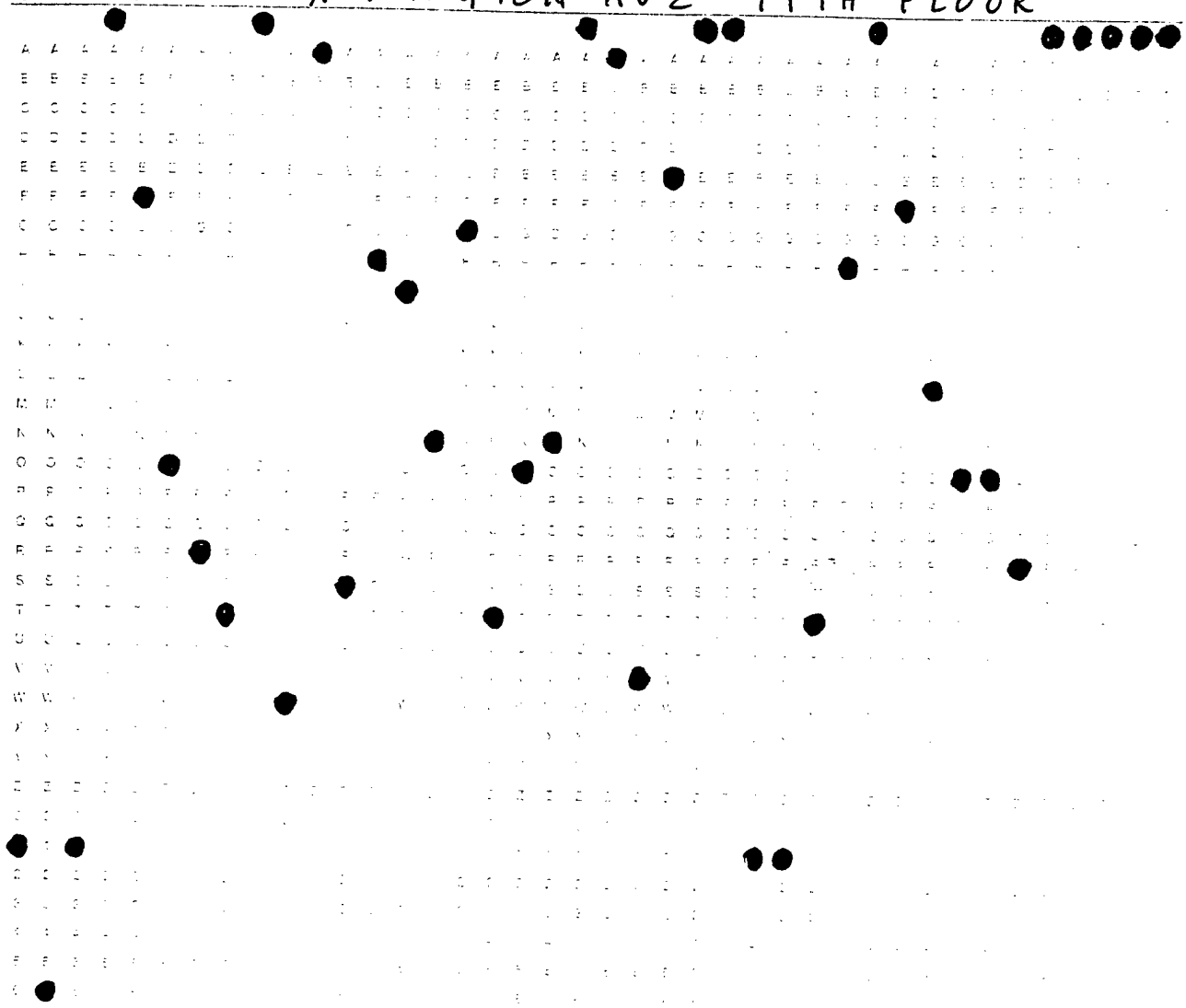
11. PI Address–Department Name (If none, leave blank. Use spaces as appropriate.)

COLUMBIA UNIVERSITY

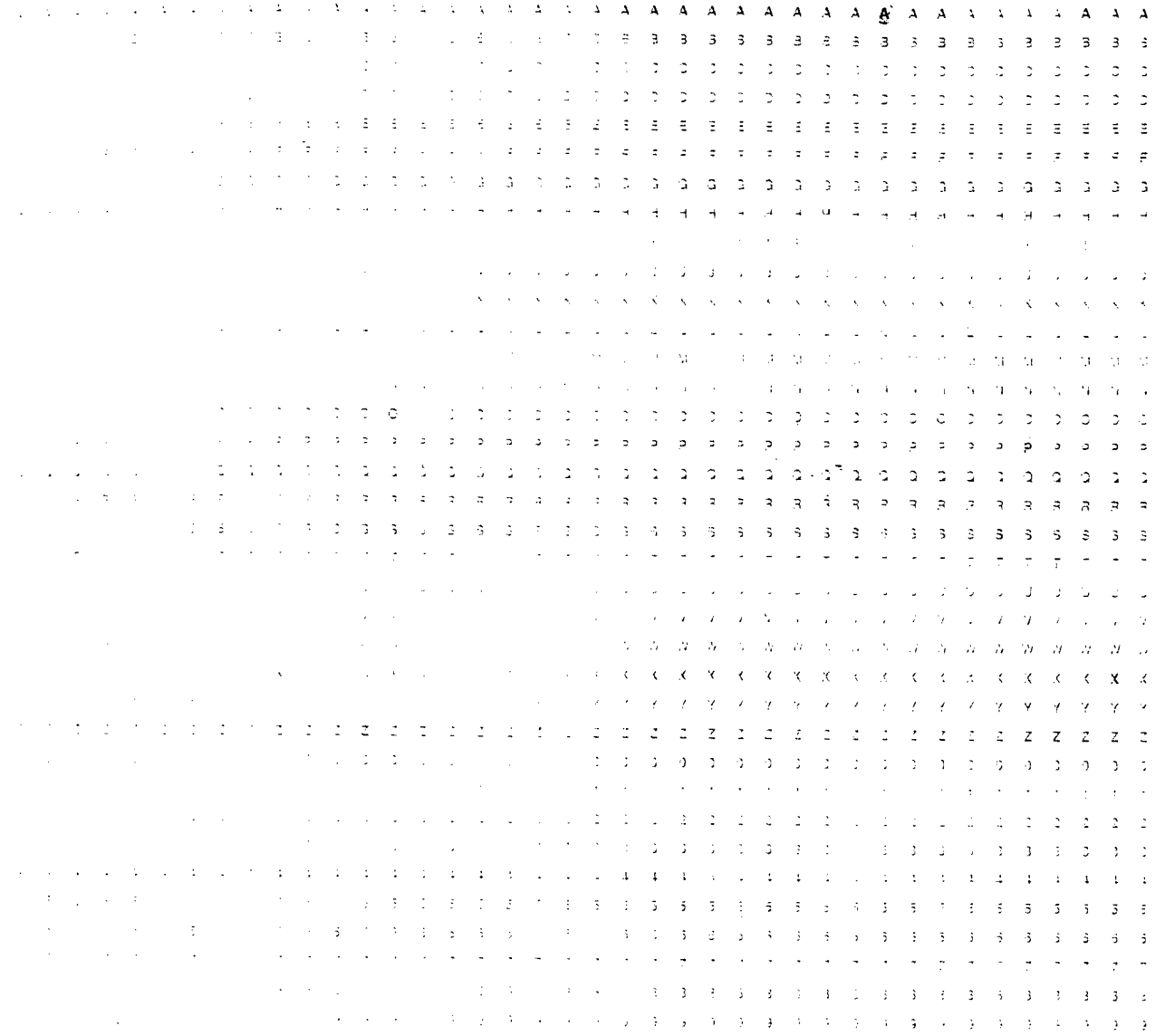


12. PI Address–Street Address Line 1

161 FORT WASHINGTON AVE 11TH FLOOR



13. Pl Address–Street Address Line 2 (If no Line 2, leave blank.)



14. PI Address

NEW YORK

15. PI Address

NY

16. PI Address

US

17. PI Address—Zip Code (Non-U.S. codes write in below.)

10032

18. Principal Investigator's Phone Number (U.S. and Canada only. If you have an International Phone Number, please write in the number, starting with country code, below.)

212-305-0136

19. Principal Investigator's Fax Number (U.S. and Canada only. If you have an International Fax Number, please write in the number, starting with country code, below.)

212-305-0139

20. Principal Investigator's E-Mail Address (If available.)

aet1@columbia.edu

21. Principal Investigator Demographics (Optional.)

Native Hawaiian or Other Pacific Islander

Other (Specify.)

22. Key Personnel Demographics (Optional, select all that apply.)

Native Hawaiian or Other Pacific Islander

23. Proposal Title (This may be up to 160 characters long.)

Prostate Specific Antigen Density of the Transition Zone in ethnically diverse men

24. Total Funding Requested from the Government (Direct and Indirect Costs) for the Entire Proposed Period of Research (Whole U.S. dollar figures ONLY. Enter number flush with right-hand margin.) $ 324846

25. Military/Civilian Collaboration (Mark the appropriate statement. If your proposal DOES represent a Military/Civilian Collaboration, fill in the full name of the Collaborating Organization.)

26. Human Subjects
In the proposed work, will Human Subjects be used?

If yes, which Human Subjects will be used? (Select all that apply.)

27. Human Anatomical Substances
In the proposed work, will Human Anatomical Substances be used?

If yes, which Human Anatomical Substance(s) will be used? (Select all that apply.)

Can the Human Anatomical Substance(s) indicated above be traced to a specific donor?

28. Clinical Trials
Does the proposed work include Clinical Trials?

If yes, select the type of Clinical Trial(s) proposed (Select all that apply.)

29. Demographics of Human Test Subjects/Study Population of Interest

Does your research specifically target any particular segment of the population?

If yes, please answer the following questions:

A. Gender of the Human Test Subjects/Study Population

Does your research *specifically target* any of the following categories?

B. Ethnicity of the Human Test Subjects/Study Population

Does your research *specifically target* any of the following ethnic/racial categories?

Native Hawaiian or Other Pacific Islander

C. Age of the Human Test Subjects/Study Population

Does your research *specifically target* any of the following age ranges?

D. General Income of the Human Test Subjects/Study Population

Does your research *specifically target* any of the following categories?

E. General Demographic Target or Focus

Does your research *specifically target* any of the following categories?

30. Animal Subjects

In the proposed work, will Animal Subjects be used?

In the proposed work, will Animal Subjects be used by a subcontractor?

If yes to either of the above questions, which Animal Subjects will be used? (Select all that apply.)

31. Safety Provisions (Select all that apply.)

32. Mentor Name (Must be included for all Traineeship proposals.)

33. Research Classification (Enter the Classification Code from the list provided in the Proposal Cover Booklet Instructions.)

20

34–38. Research Area (Enter the codes from the list provided in the Proposal Cover Booklet Instructions.)

34. Research Area Level 1	35. Research Area Level 2	36. Research Area Level 3	37. Research Area Level 4	38. Research Area Level 5
4200	4100	4300	6200	1100

39. Have you submitted another proposal in a different Proposal Category? (Do not include Proposals submitted to other programs or for previous years.)

Yes ● No

If yes, please enter the Proposal Category Code from the list provided for question #3 in the Proposal Cover Booklet Instructions.

40. Administrative Representative Authorized to Conduct Negotiations. (Signature MANDATORY.)

Primary Contact

Name: Marilyn Wallace

Department: Office of Grants & Contracts

Telephone Number: (212) 305-4191

Fax Number: (212) 305-3697

E-Mail Address: mw2@columbia.edu

Signature: Marilyn Wallace Date: 3/9/99

Secondary Contact

Name: Marilyn Wallace

Department: Office of Grants & Contracts

Telephone Number: (212) 305-4191

Fax Number: (212) 305-3697

E-Mail Address: mw2@columbia.edu

Signature: Marilyn Wallace 3/9/99

41. Institution's Official Proposal Control Number (If none, leave blank.)

42. Principal Investigator (Must match PI listed in question 7. Signature MANDATORY.)

Name: ALEXIS E. TE, M.D.

Department: Dept of Urology

Signature: [signature] 3/5/99

Peer Review Referral Page:

Title:
Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men

Principle Investigator:
Alexis E. Te, MD

Key Descriptive Technical Terms: Prostate Cancer, PSA, Transition Zone Density, Prostate Volume, African American (AfA), Asian American (AsA), Hispanic American(HA), Caucasian American(CA)

Participants:

Principle Investigator-	Alexis E. Te, MD	Department of Urology
Collaborating Investigators-	Steven A. Kaplan, MD	Department of Urology
	Edward F. Ikeguchi, MD	Department of Urology
	John R. Franklin, MD	Department of Urology
	Emilia Bagiella, MD	Divison of Biostatitics
Nurse Coordinator-	Aleta Ashley, RN	Department of Urology
Institution:	Columbia University, College of Physicians and Surgeons	

Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men

Award Category:

New Investigator

Organization Name and Location:

Department of Urology
Columbia – Presbyterian Medical Center
Atchley Pavilion – 11th floor
161 Fort Washington Avenue
New York, NY 10032

Principal Investigator Information:

Telephone number: (212) 305 – 0136
FAX number: (212) 305 – 0139

Alexis E. Te, MD

Contact Representative

Dr. Richard J. Sohn
Director, Grants and Contracts
Columbia University
Health Sciences Division
630 West 168th Street
New York, NY 10032

Telephone Number: (212) 305-4191

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Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men

Alexis E. Te, MD

Key Words: Prostate Cancer, PSA, Transition Zone Density, Prostate Volume, African American (AfA), Asian American (AsA), Hispanic American(HA), Caucasian American(CA)

Technical Abstract

There are significant racial differences in unscreened populations in both prostate cancer incidence and mortality rates. For example, serum prostate specific antigen (PSA) is higher in African American males than in Caucasian American males. Prostate cancer detection strategies such as PSA age adjusted reference ranges and PSA density, the ratio of PSA to total prostate volume (PSAD), have had significant shortcomings when applied to ethnically diverse populations. In an attempt to optimize the clinical utility of PSAD, various investigators have attempted to utilize the PSA density of the transition zone (TZ) of the prostate as a more effective marker for cancer of the prostate. We have recently reported that the transition zone volume in age matched patients with benign prostatic hyperplasia is significantly higher in African Americans males than in Caucasian American males. Therefore, differences in PSA between African Americans, Caucasian Americans and other ethnicity's may reflect differences in PSA production by the transition zone and not to inherent biological susceptibility of prostate cancer for African American males versus Caucasian American males. Therefore, the goal of this proposal is evaluate whether there is ethnic variation in PSA density of the transition zone (PSAT) and whether differences in serum PSA can be explained by PSAT variation. More importantly, we will assess whether PSAT is a better refinement of currently available cancer detection strategies.

Public Abstract

There are significant racial differences in unscreened populations in both prostate cancer incidence and mortality rates. However, to date there are no widely available prostate cancer strategies that can be applied to ethnically diverse men. Some have suggested that this is due to inherent biological differences in prostate cancer growth between African American and Caucasian American males. This concept is supported by increased levels of serum prostate specific antigen (PSA) levels in African American males versus Caucasian American males. We have recently reported that the portion of the prostate that is more commonly associated with benign prostate hyperplasia (BPH), the transition zone is more prominent in African American versus Caucasian American males. Given that this area, the transition zone, produces PSA, it is very conceivable that differences in PSA may reflect a different incidence of benign prostate growth in African American versus Caucasian American than to differences in prostate cancer. Therefore, the goals of our study is to determine if a new prostate cancer detection strategy, PSAT (the ratio of serum PSA to the volume of transition zone of the prostate as measured by transrectal ultrasound) is different among African American males, Caucasian American males and males of other ethnicity's. More importantly, we will assess whether PSAT is a better refinement of currently available cancer detection strategies.

Statement of Work

Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men

Task 1: Develop final plan for performing ultrasound imaging and measurement of PSA (Months 1 – 3)

a. Recruitment strategies for patient screening to be developed
b. Computer software between two investigative sites to be coordinated

Task 2: Subject recruitment and data collection (Months 3 – 27)

a. Patients screened for eligibility
b. Informed consent obtained
c. All sociodemographic and medical information obtained
d. Serum PSA and other serum chemistries measured
e. Transrectal biopsy performed on patients with abnormal digital rectal examination or serum PSA outside PSA age – specific reference range.
f. Data collected for sociodemographic factors, serum PSA, PSA density, PSA density of the transition zone

Task 3: Final analysis and report writing (Months 24 – 30)

a. Analysis of all transrectal ultrasound measurements will be performed
b. Statistical analysis and correlation to PSA and PSA density of the transition zone will be done
c. Final report and initial abstracts and manuscripts to be prepared

Proposal Relevance and Impact Statement

The diagnosis, staging and treatment of prostate cancer has evolved and dramatically changed over the past decade. Although no revolutionary strides have been made in treatment, the widespread increase in prostate cancer detection strategies has increased awareness and earlier diagnosis and treatment. Despite these strides, there is still a lack of a reliable and reproducible prostate cancer detection paradigm, which can be applied to ethnically diverse populations. This has two important implications. First, on a detection basis the lack of highly sensitive and specific prostate "marker" leads to underdiagnosis in some patients and overdetection with unnecessary biopsy in others. Second, currently available detection strategies such as age – specific PSA reference ranges or PSA density have not been able to be utilized in ethnically diverse patients.

The goals of this study address are to addresses these two issues in an **innovative** way. First, the analysis of a new PSA reference point **prospectively** in a screening population will help us to determine if we can enhance sensitivity and specificity of PSA. The potential ability to increase detection without increasing prostate biopsies has enormous medical and economic implications. Furthermore, **the potential of application in ethnically diverse groups** enhances the utility of this PSA reference point. To date, there is no PSA reference point which adequately addresses these issues across a wide spectrum of patients. This study has significant scientific relevance in that it will further enhance the only area where we have had any broad impact on prostate cancer, that is screening and detection. Moreover, in addition to the health and economic concerns this potentially addresses, this study has important social implications if PSAT can be applied across a wide spectrum of patients.

PROPOSAL BODY

Background and Hypothesis

Prostate specific antigen (PSA) is the most widely utilized serum marker for prostate cancer[1]. However, its role as a screening tool has been impaired because of a lack of disease specificity i.e. benign prostatic hyperplasia (BPH) and prostatitis[2]. There have been a variety of PSA modifications which have been touted as methods to increase sensitivity and specificity including PSA density (the ratio of PSA to total prostate volume), age specific reference ranges for PSA and measurement of free- to- total PSA (percent free PSA)[3].

Our investigative group originally described the use of PSA density (PSAD) to increase the sensitivity of prostate cancer detection in men with intermediate PSA results (4.0 – 10.0 ng/mL). In a population of 533 men, the mean PSAD for prostate cancer was 0.581 while that of BPH was 0.044[4]. Of 34 patients with a PSAD of 0.1 or greater 33 had prostate cancer. Only 2 of the 41 prostate cancer patients and 14 of the BPH patients had a PSAD of 0.05 or less. Predictive value nomograms were created based on the transrectal ultrasound findings in well-characterized populations of men with prostate cancer. However, the use of PSAD has met with conflicting results and dampened its widespread utility. Bazinet et al evaluated 565 consecutive men referred for lower urinary tract symptoms, suspicious digital rectal examination or elevated PSA and concluded that the use of PSAD cutoff of 0.15 could decrease prostate biopsies without compromising detection[5]. This finding was confirmed by Rommel et al who evaluated 2,020 patients in a community setting and found PSAD superior to PSA alone in detecting prostate cancer[6]. In contrast, in a multicenter, prospective study, Catalona et al reported that the use of a PSAD cutoff of 0.15 resulted in more than 50% of prostate cancers not being detected[7]. These differences may be due to variations in "volume" measurements among different investigators, demonstrated variability of PSA density with aging and variable distribution of glandular and stromal components in BPH.

In an attempt to optimize the specificity of PSAD various investigators have attempted to utilize the PSA density of the transition zone (TZ) of the prostate as a more effective marker for cancer of the prostate[8,9]. This is based on the premise that BPH is the result almost exclusively of the TZ. BPH of the peripheral zone is rare and contributes little to overall PSA. Therefore, PSA changes secondary to BPH arise from "volumetric" changes of the TZ. Utilizing serum PSA adjusted for volume of the transition zone (PSAT), Kalish et al compared 21 biopsy – positive patients and 38 biopsy – negative patients. The PSAD difference between these two groups was 0.05 (0.26 versus 0.21). In contrast, for PSAT the difference was 0.79 (1.39 versus 0.60) (($P < 0.001$) [8] . More recently, Zlotta et al retrospectively analyzed 162 patients with a serum PSA of 0.25 to 10.0 ng/mL. Mean PSAD was 0.12 ± 0.07 and 0.22 ± 0.12 ng/mL/cc in patients with BPH and prostate cancer, respectively, while mean PSAT was 0.21 ± 0.13 and 1.02 ± 0.70 ng/mL/cc, respectively ($P < 0.0001$). Utilizing a PSAD cutoff of 0.15 versus a 0.35 cutoff for PSAT, cancer detection rates increased from 10% to 34%. Receiver operating curves demonstrate superior efficacy of PSAT versus PSAD for all PSA values [9] . However, to date there have been no attempts to delineate these potential differences in ethnically diverse men.

There are significant racial differences in unscreened populations in both prostate cancer incidence and mortality rates [10,11, 12]. Wingo et al reported a 30% higher incidence and a 120% higher prostate cancer mortality rate in American black males than white males [13]. Furthermore, blacks tend to present with a more advanced stage than their white counterparts [14]. In addition, based on data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, blacks tend to present with more advanced disease than whites. Of white prostate cancer cases, 33% are diagnosed with localized disease, 16% are diagnosed with regional disease, and 38% are diagnosed with distant disease. The corresponding percentages for black patients are 31, 12 and 45%[15]. Finally, prostate cancer mortality rates for blacks diagnosed with localized, regional, distant and unstaged disease are 1.9, 1.5, 2.4 and 2.0 times those of whites [15].

Racial differences in prostate cancer severity at the time of diagnosis may have two plausible explanations. First, there may be differences in health care utilization for prostate cancer by different racial

groups. This may be either secondary to variable accessibility or because of differences in perceived concern of prostate cancer. Smith et al reported that in a group of 556 black males who answered a 7-question survey of prostate cancer, only 30% answered 3 or more questions correctly[16]. In another study, Price et al surveyed 290 randomly selected black men in Ohio about their knowledge of prostate cancer [17]. Almost 60% did not know that American black men were more likely than white men to develop prostate cancer.

A second potential explanation for racial differences in prostate cancer is that there exists a clear pathophysiologic explanation based on inherent prostate biology. Prostate specific antigen (PSA) is higher in black men and this has been attributed to increased androgen stimulation from higher testosterone levels [18,19]. Sawyer et al reported that in more than 10, 808 men 40 years or older (and 19,482 PSA test results), Black men had a higher range of PSA (for the 95th percentile) in every age group. The largest difference was found in men 70 – 79 years of age[20]. Conversely, prostate cancer has been reported to have a lower prevalence rate in Asian men such as the Japanese. This may be related to the converse of decreased androgen stimulation from lower testosterone levels[18].

More recently, Smith et al. investigated racial differences in operating characteristics of prostate cancer screening tests. In both white and black men, PSA greater than 4.0 ng./mL detected more cancers than rectal examination with a trend for increased sensitivity in black men. However, PSA was associated with fewer false – positives than rectal examination in white but not in black men [21]. In a study of 826 men who underwent one or more prostate biopsies at the VA Medical Center in Shreveport, LA, serum PSA was significantly higher in black men than in white men. In addition, use of a PSA cutoff of 4.0 ng/mL decreased sensitivity of prostate cancer detection in black men by 7.6% and specificity by 14.1%[19]. These data suggest that lower total PSA cutoffs may be a reasonable strategy in black men.

Because of these potential differences, many investigators have advocated utilizing modifications in PSA to more accurately assess black males who are at increased risk for prostate cancer. Presti et al compared ROC curves; predictive values and likelihood ratios were calculated for PSA and PSAD in a group of 297 consecutive white and black patients[22]. The sensitivity and predictive value for a PSA of > 4 ng/mL and PSAD cutoffs of 0.1 and 0.15 were greater in black than in white males. PSAD demonstrated a significant advantage over PSA in all ethnic groups and at all PSA values. More importantly, a PSAD cutoff of 0.1 resulted in a likelihood ratio for a negative test in 95% of black males versus 80% in white males. This was true despite overall PSA, PSAD and prostate volume being the same for both blacks and whites in both the positive and negative biopsy groups. In contrast, Henderson et al reported that despite no differences in calculated overall prostate volume, PSAD was significantly higher in black males[19]. Adballa et al also reported higher PSAD in African American males than in whites or hispanics [23]. To date, there have been no reports of differences in PSAT comparing various ethnic groups.

We explored the role of TZ voluming in our published experience of 61 men with BPH. There was a very significant correlation between TZ volume and TZI (transition zone index: ratio between transition zone and total prostate volume) with urinary symptoms (r = 0.75) and objective urodynamic parameters. (r = 0.43) [24]. In a subsequent study, we examined a group of 104 age matched, ethnically diverse men (36 African American(AfA), 34 Hispanic American(HA), and 34 Caucasian American(CA) and a control group of 55 age and ethnically matched men. All men underwent transrectal ultrasound measurement of prostate volume, TZ volume and PV and TZI [25]. For the control group, PV was 20.9, 18.2 and 19.8 ml, TZ volume was 6.9, 4.9 and 5.4 ml and TZI was 0.33*, 0.27 and 0.25 for African American, Hispanic American and Caucasian American men, respectively. (*P<0.03< AfA vs. HA or CA) In the BPH group, PV was 36.8, 34.2 and 37.2 ml for AfA, HA and CA men, respectively. (P = 0.18). In contrast, TZ (15.8 ml) and TZI (0.43) as significantly higher in AfA men than in either their HA (12.7 ml, 0.37) or CA (13.8 ml, 0.37) counterparts. (P < 0.03). These results suggest that AfA men have significantly more TZ and a higher TZI than their HA or CA counterparts. The PSA of the three groups was 3.2, 2.9, and 2.8, respectively. Additionally, we have further extended the analysis to include data collected on 21 Asian American men. For further comparison (Unpublished Data). The PSA for this group of Asian American men is 1.8 . (See Table 1)

Table 1: Prostate volume, transition zone volume and TZ index in various ethnic groups (BPH Group)

Parameter	AfA (n = 36)	HA (n = 34)	CA (n = 34)	AsA (n = 21)*
Age (years)	62.9 ± 7.6	61.4 ± 6.2	59.8 ± 5.2	58.4 ± 6.6
Prostate Volume (ml)	36.8 ± 12.9	34.2 ± 8.3	37.2 ± 10.1	34.1 ± 10.8
Transition zone volume (ml)	**15.8 ± 7.6**	12.7 ± 8.1	13.8 ± 6.7	12.7 ± 4.7
Transition zone index	**0.43***	0.37	0.37	0.38

(P<0.03)
***Unpublished Data**

These data provide compelling evidence that PSA differences in African American males may reflect volumetric differences in the **benign** portion of the prostate. Therefore, a PSA reference marker, i.e. PSA density of the transition zone, which corrects for volume differences of the transition zone, would have significantly greater sensitivity in a screening population of ethnically diverse men.

This study represents one of the first to report potential inherent physiologic and anatomic differences in BPH among ethnic groups. This observation is further supported by recent data from Moul et al who performed 3 – dimensional tumor and prostate volume in black and white patients undergoing radical prostatectomy. In 145 consecutive men (104 white and 41 black) the surgical PSA density was greater in black men. However, PSA per unit of cancer volume was greater in white men[26]. In other words, blacks had **less PSA per cc cancer** and **more PSA per unit of non-cancer.** This suggests that the "extra" PSA reported in blacks may be secondary to the benign portion of the prostate.

Specific Aims and Hypothesis

The Benign Prostatic Hyperplasia (BPH) size is reflected by transition zone volume. Differences in BPH symptomatology, prostate cancer detection strategies and PSA level between African American(AfA), Asian American(AsA), Hispanic American(HA), and Caucasian American(CA) males may reflect ethnic differences in prostate morphology by transition zone volume. We postulate that differences in histologic evidence and/or volume of BPH is the cause of ethnic difference in PSA levels and not to inherent biological susceptibility of prostate cancer such as that postulated for African American males versus Caucasian American males versus Asian American males.

Therefore, we propose that:

1. *Differences in BPH symptomatology, PSA and PSAD among AfA versus HA versus CA versus AsA males reflect variations in transition zone volume. AfA males have more "BPH" volume manifesting in higher PSA values and possibly worse BPH symptoms. Utilization of current modifications of PSA, i.e. PSAD may, therefore, not be the most accurate marker for patients at increased risk for prostate cancer. Utilization of PSAT will correct for any measured differences in either PSA or PSAD among ethnically diverse men and will also explain possible ethnic variance in BPH symptoms. Consequently, we hypothesize that the difference in PSAT for AfA, AsA, HA and CA males should be small.*
2. *Unlike PSAD, which may require different cutoff values for the various ethnicities, if the PSAT differences are small, the PSAT cutoffs for detecting prostate cancer should be similar among AfA, CA, HA and AsA males. Thus, , a uniform PSAT cutoffs would apply for all ethnicities.*
3. *PSAT will be a better predictor of prostate cancer than currently available PSA screening modalities. These include PSA, PSA age specific reference ranges or PSAD. Sensitivity as manifested by detection of prostate cancer and specificity as manifested by elimination of negative biopsies would be enhanced.*

Technical Objectives

Three specific aims are proposed

Specific Aim #1: Serum PSA and transrectal ultrasound measurements of the prostate will be done in equal cohorts of AfA, CA, HA and AsA men over the age of 40. Baseline levels of TZ and TZI and their correlation with both subjective (symptoms and bothersome scores) and objective (urinary flow rate and post void residual urine volume) indices of BPH will be identified. Volumetric determination of both the entire prostate and transition zone volume of the prostate will be done and both PSAD and PSAT calculated. The objective is to determine whether ethnic variation in prostate morphology as measured by Transition Zone Volume, Transition Zone index, PSAD and PSAT exist and its relationship to BPH.

Specific Aim #2: To determine if PSAT cutoffs are different among AfA, CA, HA and AsA men. Our hypothesis is that any ethnic variability in either PSA or PSAD should be corrected by measurement of PSAT. Patients who undergo routine prostate biopsies according to current clinically accepted criteria for prostate biopsies and who have positive biopsies for prostate cancer will be evaluated to determine whether there are differences in PSAT threshold for biopsies among AfA, CA, HA and AsA males.

Specific Aim #3: To assess whether PSAT is a better refinement of currently available prostate cancer detection strategies. PSA, age specific PSA reference ranges, PSAD and PSAT will be assessed to determine which produces greatest sensitivity and specificity and whether any ethnic variation exists among PSAT as a cancer detection strategy.

Methods:

This study is a cross-sectional investigation of differences in prostate morphology as defined by serum PSA and prostate volume an ethnically diverse sample of men. The sample population consists of men aged 40 and above referred for or self-seeking evaluation of their prostate, elevated serum PSA or abnormal findings on digital rectal examination. Subjects will be recruited from the regional patient populations around the medical center, through its clinic system and physician referral system. An ideal total of approximately 800 men consisting equal cohorts of African American, Hispanic American, Asian American and Caucasian American males will be recruited continuously over the first 24 months of the study period and allow the last 6 months for statistical evaluation. This is a realistic enrollment rate since this study involves no treatment intervention and is relatively non-invasive. The number and racial distribution of men each month that typically visit the Prostate Center and its referral system though the participations of all its coinvestigators will insure the adequacy of enrollment the numbers required and its ethnic distribution. We expect to enroll 200 men of each ethnicity over the study period. This number ensures that power will be at least 80% (based on two-tailed .05 level tests) to detect clinically important differences between different PSAT measurements of AfA, CA, HA and AsA Men. Clinically important differences are assumed to be those that are at least 25% of that measures standard deviation.

Recruitment Procedures

Patients identified as potential subjects by the research assistant will be flagged and brought to the attention of the treating physician. The initial physician recruitment process consists of a history and physical examination, digital rectal examination and a brief explanation of the goals and procedures involved with the study. Prostate examination description will be standardized across all sites and recorded onto a data collection form. Following the physician visit, eligible patients who agree to participate in the study will be referred back to the research assistant on site. At this time, the research assistant will complete the informed consent process and begin recording data onto the data collection form. Subjects will not be paid. Incentives to participate include complete prostate screening evaluation with uroflowmetry, bladder scan for PVR, TRUS (and biopsy where applicable) and serum PSA measurement, cholesterol level and testosterone level. Following informed consent, the research assistant will collect baseline sociodemographic information, serum

PSA, cholesterol, testosterone, uroflowmetry, bladder scan for PVR and will schedule prostatic ultrasonography.

Inclusion and Exclusion Criteria

Inclusion criteria:

1) Males 40 years or older.
2) The patient has the mental capacity of understanding and signing informed consent, and able and willing to participate.

Exclusion criteria:

1) Patients previously treated or diagnosed with prostate cancer.
2) Patients treated for BPH with either finasteride or hormonal agents, i.e. LH – RH analogues, i.e. agents which reduce prostate size and affect serum PSA levels.
3) Patients with previous prostate surgery, including minimally invasive therapeutic alternatives such as thermotherapy.

Data Collection, Storage and Management

All data will be recorded onto standardized data forms. Patient confidentiality will be maintained by storing data in a locked cabinet. The data will be cleaned and managed by a data editor. The data editors' responsibilities will also include data entry and daily data backup. All data will be stored in SPSS (version 7.0).

All data will be transferred or entered daily into a Microsoft Access Database. Data will be stored and mirrored on data secured hard drives on the network. One duplicate backup set of disks will be stored at the Incontinence Care Center in the files of the Principal Investigator. All diskettes will be kept in locked fireproof drawers. Data updates will be printed on a daily basis, and backups involving the central server and diskettes performed on a weekly basis. A codebook will be available for each patient. Data analysis will be performed using SPSS version 7.0. Confidentiality of all research records, data files and subject identifiers will be kept by using locked cabinets and data secured passwords on the network with restricted access.

Sociodemographic Variables

Baseline data will include self-identified race/ethnicity, age at last birthday, years of education and highest degree attained, current or last occupation, income (categorical), address and phone number, and medical insurance carrier. Recruitment location, name of recruiting physician and research assistant, date and time of recruitment and date/time of first interview will also be recorded.

Laboratory Data

All subjects will have a serum BUN, creatinine, testosterone and PSA drawn prior to ultrasonography. Urine studies consist of a urine analysis and urine culture and sensitivities. The purpose of these laboratory studies is to screen for obstructive uropathy, microscopic hematuria, and urinary tract infection. Patients with abnormalities will be evaluated further as necessary. If no significant pathology is detected, these patients remain eligible for the study. Patients with uncomplicated urinary tract infections (UTI) are eligible for study following treatment with appropriate oral antibiotics. Patients with complicated UTI's (i.e., febrile infections, UTI associated with urolithiasis, or pyelonephritis), will be excluded from the study and treated appropriately.

Uroflowmetry

Subjects will be instructed to maintain a full bladder just prior to uroflowmetry. A Dantec 1000 uroflowmeter will be used to measure peak flow rate (Q_{max}), average flow (Q_{avg}), time to peak flow (t_{max}) and voided volume (vol). A minimal voided volume of 150 ml and at least a 2 second interval for peak flow will be required. Uroflowmetry will be performed on-site.

Post Void Residual Volume Determination (PVR)
Immediately following uroflowmetry, PVR volume will be determined non-invasively by the research technician, using the Bard Bladder ScanTM **(model # 2500)** (Bard Pateint Care Division, Murray Hill, NJ). PVR will be performed on-site.

Prostatic Ultrasonography and Transition Zone Voluming
Transrectal ultrasound of the prostate (TRUS) will be performed immediately following uroflowmetry and PVR determination using a portable ultrasound instrument equipped with a longitudinal probe incorporating 7 MHz transducers (To be determined). Imaging will be done in both transaxial and longitudinal views. An experienced examiner, the P.I., Alexis E. Te, MD, who has a large clinical and published experience with transrectal prostate imaging and measurement, will do measurements. Prostatic volume will be calculated using the formula for a prolate ellipsoid (V = width x length x height x 0.52). Width will be measured in the transverse view of the gland and length will be measured in the longitudinal view. Prostatic height will be measured in the longitudinal axis at a right angle to gland length. Maximum diameters will be recorded and used for each of these measurements. Transition zone (TZ) voluming will be similarly performed by prolate ellipsoid calculation. In addition to its reproducibility by a single investigator, there is significant inter-investigator reproducibility in both prostate volume and transition zone volume will be measured in cubic centimeters.

Prostate Biopsy
To date there are various "PSA" criteria for biopsy. Many studies have demonstrated that AfA and CA have different cutoff points. For the purpose of this study the indications for biopsy will be 1) suspicious digital rectal examination 2) abnormal PSA based on age –adjusted. Based on the work of Morgan et al., traditional age – adjusted reference ranges (95% specificity) were found to work well when applied to white men aged 40 years and older[27]*. Yet the first set of age – adjusted reference ranges that group derived for Blacks Americans was determined to have a poor sensitivity: 41% of prostate cancers in this group would have been missed. The following ranges have been recommended and has been applied as clinically accepted criterias for biopsy.*

Age (years)	White	Black American
40 – 49	0 – 2.5	0 – 2.0
50 – 59	0 – 3.5	0 – 4.0
60 – 69	0 – 5.5	0 – 4.5
70 – 79	0 – 6.5	0 – 5.5

Cutoffs for Asian Americans will be similar to Black American since they are unknown. In glands 50 cc or smaller, **6** systematic biopsies (apex, mid and base biopsies done equidistant). To minimize sampling error, **12** systematic biopsies (6 conventional and 6 anteriorly directed) will be performed in prostates > 50cc. In addition, lesion directed biopsies at either abnormalities on digital rectal examination or transrectal ultrasound will be performed. Thus, biopsies will be performed based on the more sensitive but clinically accepted criteria for biopsies. These biopsies would be strongly recommended and performed regardless of the study protocol and are based on accepted clinical criteria's for biopsies. The biopsies are not required for the study.

Statistical Analysis Overview
200 men in each ethnic group is a number that ensures that power will be at least 80% (based on two-tailed .05 level tests) to detect clinically important differences between different PSAT measurements of AfA, CA, HA and AsA Men. Clinically important differences are assumed to be those that are at least 25% of that measures standard deviation.
Graphical and numerical summaries will be used to describe the association between prostate morphology and both subjective and objective indices of disease. TZ and TZI will provide continuous measures of prostate morphology. The AUA symptom score (AUA), SPI, and BII will be used as subjective measures of disease indices, while measures of flow (Qmax, Qavg, tmax) and PVR will be used as objective measures.

Scatterplots of TZ and TZI with each measure of disease (both subjective and objective) provides a graphical description of the relationship between prostate morphology and disease severity. For relationships that are approximately linear, Pearson's correlation coefficient will be used as a numerical summary. If the relationships are clearly nonlinear, we will attempt to transform one or both variables to linearize the relationship and compute Pearson's correlation between the transformed variables and compute Spearman's correlation coefficient (the correlation based on the ranked values of each variable) will be computed. Interval estimates of each correlation be given as approximate 95% confidence intervals.

TZI will be further assessed as a dichotomous variable (>=0.50 versus <0.50). The cutpoint of 0.50 was observed in a previous study to effectively discriminate subjects with severe symptoms. The mean difference between these "low" and "high" TZI groups with respect to each index will be estimated by approximate 95% confidence intervals.

Racial variation in baseline indices of disease, TZ, and the continuous measure of TZI will be assessed based on analysis of variance models, with ethnic group as the independent variable. Approximate 95% confidence intervals (based on Tukey's method of maintaining an overall 5% error rate for each measure assessed) will be used to quantify the description of racial variation for these measures. Logistic regression analysis will be used to estimate racial differences for the dichotomous version of TZI. This model will include two indicator (dummy) variables for the three ethnic groups as independent variables.

Differences between the associations of the disease will indices and the continuous measures of prostate morphology (TZ and TZI) will be based on a series ordinary least squares regression models. These models will have either TZ or TZI as the dependent variable, with a single disease index, indicator variables for race, and index by indicator interactions as independent variables. Corresponding logistic regression models will be used to when TZI is dichotomized. The interaction terms in these models are informative about racial differences in the associations. Similarly, logistic regression models will be used to determine the extent to which the prognostic strength of TZI differs by race.

Data will be also analyzed for 3 groups: 1) the entire group, 2) those with normal digital rectal examination and 3) those with a normal DRE and a PSA of between 4 and 10 ng/mL. Mean and median PSA, PSAD and **PSAT** will be compared between both positive and negative biopsy groups and between Black Americans and whites with the Mann – Whitney U test. Sensitivity, specificity, positive predictive value and negative predictive value with 95% confidence intervals will be calculated for PSA, PSAD and **PSAT** for cancer detection. Receiver operating characteristic curves will be calculated to illustrate the sensitivity and specificity of PSA, PSAD and **PSAT.** Analysis of the different areas of the curve will be calculated with the McNemar test. Finally, **PSAT cutoffs** for biopsy will be evaluated to determine optimal sensitivity and specificity for cancer detection in all patients.

Acronym and Symbol Definition

TRUS: transrectal ultrasound of the prostate
PSA: serum prostate specific antigen
PSAD: PSA density (ratio of serum PSA and total prostate volume
PSAT: PSA density of the transition zone
BPH: benign prostatic hyperplasia
AfA: African American
AsA: Asian American
HA: Hispanic American
CA: Caucasian American

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2.c. BIOGRAPHICAL SKETCH

Applicants should include this form as Addendum B in the submitted proposal.

Provide the following information for the applicant and collaborating investigator listed on the detailed cost estimate

NAME	POSITION TITLE
Alexis E. Te, MD	PRINCIPLE INVESTIGATOR

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include post-doctoral training.)

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY
Yale University	B.S.	1980-1984	Molecular Biophysics & Biochemistry
Cornell University Medical College	M.D.	1984-1988	Medicine
Columbia University	Resident	1988-1990	Surgery
Columbia Univeristy	Resident	1990-1994	Urology
Columbia University	Fellowship	1994-1995	Neurourology & Urodynamics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past 3 years and to representative earlier publications pertinent to this application. If the list of publications in the last 3 years exceeds 2 pages, select the most pertinent publications. PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

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Publication

Peer Review Publications-

1. Te AE, Colombel M, Koo HP, Kaplan SA, Buttyan R, Olsson CA, Shabsigh R. Castration-Induced Apoptosis in the Rat Penis. Surgical Forum 1992; 48: 724-725.
2. Te AE, Koo HP, Kaplan SA, Buttyan R, Olsson CA, Shabsigh R. Neurotrophic Factors in the Diabetic Rat Penis. Surgical Forum 1993: 49: 758-760.
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11. Kaplan SA, Olsson CA & Te AE: The American Urological Association symptom score in the evaluation of men with lower urinary tract symptom: At 2 years of followup, does it work?. J Urol. 155:1971-1974, 1996.
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18. Kaplan SA, Te AE, Ikeguchi E, Santarosa RP: Safety and efficacy of alpha blockers in the treatment of men over the age of 80 with benign prostatic hyperplasia. Br J Urol 1997 Dec;80(6):875-9
19. Kaplan, SA, Reis, RB, Staiman, VB, Te, AE: Is the ratio of transition zone to total prostate volume higher in African-American men than in their Caucasian or Hispanic Counterparts?. Br J Urol 1998, 82: 804-807

Non-Peer Review Publications-

1. Kaplan SA, Te AE: Uroflowmetry & Urodynamics.Urologic Clinics of North America 1995; 22: 309-20.
2. Te AE , Kaplan SA: Transurethral Electrovaporization of the Prostate (TVP): A electrosurgical advancement of the standard TURP. Current Surgical Techniques in Urology 1995; 8:1-9.
3. Te AE , Reis R, Kaplan SA: Transurethral Electrovaporization of the Prostate (TVP): A novel modification of the standard TURP. Contemporary Urology 1995; 7:74-83.
4. Te AE, Kaplan SA: Electrovaporization of the Prostate. Current Opinion in Urology 1996; 6: 2-9.

5. Santarosa RP, Te AE, Kaplan SA: Minimally Invasive Procedures for Benign Prostatic Hyperplasia. Mediguide to Urology 1996; 9:1-6
6. Te AE, Kaplan SA: Transurethral electrovaporization of the Prostate. Mayo Clinic Proceedings Symposium 1998; July Issue, In Press.
7. Te AE and Kaplan SA: Transurethral electrovaporization of the prostate: the year in review. Current Opinion in Urology 1997.

Book Chapters

1. Kaplan SA, Te AE: Bladder Dysfunction in Diabetes, In: Paulson, ed. Problems in Urology; Neurourology and its Role in Urologic Diseases: Part I. Philadephia, J. B. Lippincott Co., 6: 659-668. 1992.
2. Te AE , Kaplan SA: Pharmaceutical Treatment of BPH and its effect on indications for prostate surgery. In: Surgical Technology International III: Endourology. San Francisco. Universal Medical Press, Inc.1994.
3. Te AE, Kaplan SA: Urodynamics and BPH. In: Kirby RS, McConnell JD, Fitzpatrick JM, Roehrborn CG, Boyle P, eds. Textbook of Benign Prostatic Hyperplasia. Oxford. Isis Medical Media, LTD., 187-198. 1996.
4. Te AE, Kaplan SA: Prostatic Endoprosthetics. In: Kirby RS, McConnell JD, Fitzpatrick JM, Roehrborn CG, Boyle P, eds. Textbook of Benign Prostatic Hyperplasia. Oxford. Isis Medical Media, LTD. 453-462.1996.
5. Te AE, Kaplan SA: Electrovaporization Principles. In: Narayan P, ed. Benign Prostatic Hyperplasia. London, Churchill Livingstone, In Press.
6. Te AE, Kaplan SA: Electrovaporization of the Prostate: Advance Application of Electrosurgical Principles to the Treatment of Benign Prostatic Hyperplasia. In: Kirby RS, O'Leary MP, ed. Recent Advances in Urology 7. London, Churchill Livingston, In Press.
7. Te AE, Kaplan SA: Complication of Minimally Invasive Surgery for BPH. In: Taneja SS, Smith RB, Ehrlich RM, ed. Comlication of Urologic Surgery, 3rd ed. Philadelphia, W. B. Saunders, In Press.
8. Santarosa RP, Te AE, Kaplan SA: Transurethral resection, incision and ablation of the prostate. Glenn's Urologic Surgery, 5th edition. Ed. Graham SD. In press.

2.c. BIOGRAPHICAL SKETCH

Applicants should include this form as Addendum B in the submitted proposal.

Provide the following information for the applicant and collaborating investigator listed on the detailed cost estimate

NAME	POSITION TITLE
Steven A. Kaplan, MD	Collaborating Investigator

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include post-doctoral training.)

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY
CUNY-Brooklyn College	B.S.	1974-1978	Biochemisty
Mount Sinai School of Medicine	M.D.	1978-1982	Medicine
Mount Sinai Hospital	Resident	1982-1984	Surgery
Columbia University	Resident	1984-1988	Urology

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past 3 years and to representative earlier publications pertinent to this application. If the list of publications in the last 3 years exceeds 2 pages, select the most pertinent publications. PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

1988 - 1990	American Foundation of Urology Scholar Department of Urology College of Physicians & Surgeons Columbia University
1988-1990	Clinical Instructor, Department of Urology College of Physicians & Surgeons Columbia University
1990-1995	Assistant Professor, Department of Urology College of Physicians & Surgeons Columbia University
1996- 1997	Herbert Irving Associate Professor, Department of Urology College of Physicians & Surgeons Columbia University
1996- Present	Vice-Chairman, Department of Urology College of Physicians & Surgeons Columbia University
1990- Present	Director, Prostate Center J. Bentley Squier Urological Clinic Columbia Presbyterian Medical Center
1993- Present	Director, Neurourology & Urodynamics J. Bentley Squier Urological Clinic Columbia Presbyterian Medical Center
1997- Present	Given Foundation Professor, Department of Urology College of Physicians & Surgeons Columbia University

Relevant Publications (of 142 publications)

Kaplan SA, Shanzer H, Racelli D, et al: Orthotopic, segmental small bowel transplantation in the rat. Mount Sinai Journal of Medicine, 53: 112-116, 1986.

Benson MC, Kaplan SA, Olsson CA: Prostate cancer in men under the age of 45. Journal of Urology, 137:888 - 890, 1987.

Kaplan SA, Sawczuk IS, Olsson CA: Contemporary cystectomy versus preoperative radiotherapy and cystectomy for invasive bladder cancer. Urology 38: 67 - 71, 1988.

Kaplan SA, Brown WC, Blaivas JG: Parameters of detrusor contractility: Effects of hysteresis and bladder volume in an in-vitro whole rabbit model. Surgical Forum 40: 665-666, 1989.

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Chancellor MB, Blaivas JG, Kaplan SA, Axelrod S: Bladder outlet obstruction versus impaired detrusor contractility: the role of uroflow. J. Urol, 145:810 - 814, 1991

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Koo HP, Buttyan R, Olsson CA and Kaplan SA, : Genetic repsonse of the rat bladder during the onset of streptozotocin induced diabetic cystopathy. Surgical Forum, 42:36 - 41, 1991.

Kaplan SA, Shabsigh R, Soldo KA and Olsson CA: Prostatic and Periprostatic Interstitial Temperature Measurments During Transrectal Hyperthermia. J Urol, 147:1562 - 1565, 1992.

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Roehrborn C, Oesterling JE, Auerbach S, Kaplan SA, and the HYCAT Study Group: Effectiveness and safety of terazosin versus placebo in the treatment of men with symptomatic benign prostatic hyperplasia in the HYCAT study. Urology 47 (2): 159-68, 1996.
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Reis RB and Kaplan SA : Significant correlation of the AUA symptom score and a novel urodynamic parameter: detrusor contraction duration. J Urol. 156:1668 - 1672, 1996.
Santarosa RP and Kaplan SA: Stress urinary incontinence in women. Brazilian J Urol 13:329 - 337, 1996.
Kaplan SA and Kaplan NM: Alpha blockade as a monotherapy for both hypertension and BPH. Urol 48 (4): 541-50, 1996.
McKiernan J, Kaplan SA, Santarosa RP and Sawczuk IS: Transurethral electrovaporization of bladder tumors. Urol 48 (2):207-10, 1996.
Kaplan SA, Santarosa RP and Te AE: Transurethral electrovaporization of the prostate: one year experience. Urol 48 (6):876-81., 1996.
Kaplan SA, Te AE, Ikeguchi E, Santarosa RP: Safety and efficacy of alpha blockers in the treatment of men over the age of 80 with benign prostatic hyperplasia. Br J Urol 1997 Dec;80(6):875-9
Kaplan SA, Pressler LB and Te AE: The incidence of hypertension in men with benign prostatic hyperplasia: analysis by race. J. Urol., in press.
Kaplan SA, , Reis B, Staiman VB Te AE: Is the ratio of transition zone volume to total prostate volume higher in African-American men than in their Caucasian or Hispanic counterparts. British J Urology 82:804-807, 1998.

2.c. BIOGRAPHICAL SKETCH

Applicants should include this form as Addendum B in the submitted proposal.

Provide the following information for the applicant and collaborating investigator listed on the detailed cost estimate

NAME	POSITION TITLE
John Roland Franklin, M.D.	Assistant Professor of Urology

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include post-doctoral training.)

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY
Queens College, Queens N.Y.	B.A./M.A.	1984	Chemistry
Columbia University of Physicians & Surgeons, N.Y., NY	M.D.	1988	
UCLA School of Public Health, CA	Degree Exp	1996-97	Epidemiol
Columbia School of Public Health, NY	1999	1997-Present	ogy

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past 3 years and to representative earlier publications pertinent to this application. If the list of publications in the last 3 years exceeds 2 pages, select the most pertinent publications. PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

1988 - 1989	Intern, Nassau County Medical Center, NY
1989 - 1990	Urology Research, Columbia University, NY
1990 - 1994	Urology Residency, Columbia Presbyterian Medical Center, NY
1994 - 1995	Clinical Urolgic Oncology Fellow, UCLA School of Medicine, CA
1995 - 1996	Research Urologic Oncology Fellow, UCLA School of Medicine, CA
1996 - 1997	Staff Urologist, West L.A. VAMC, CA
1996 - 1997	Assistant Clinical Professor, UCLA School of Medicine, C.A.
1996 - 1997	Co-Chairman, Prostate Cancer Center of Excellence, West L.A. VAMC, CA
1997 - 1998	Assistant Professor of Urology, Albert Einstein College of Medicine, Bronx, NY
March 1998 - Present	Professor of Urology, Columbia University
March 1998 - Present	Assistant Attending, Presbyterian Hospital

PROFESSIONAL ACTIVITIES AND HONORS: UCLA's Department of Epidemiology, School of Public Health Traineeship Award - 1996, National Institute of Health, Tumor Immunology Training Grant - June 1995, American Foundation for Urologic Disease, Inc., National Kidney Foundation Joint Resident Fellowships - 1992, First Prize Essay Contest Winner - The Society of Basic Urologic Research - 1992, Salk Scholar Award - 1984, American Urologic Association, National Medical Association, Columbia University College of Physician and Surgeons Alumni, Peer Reviewer, The Journal of Urology.

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

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1. Franklin JR, Olsson CA, and Sawczuk IS. Safety of Urologic Surgical Interventions in the Elderly. Geriatric Nephrol. and Urol. 2: 105 (1992).
2. Franklin J, and Benson M. New Techniques in Management and Treatment of Superficial Bladder Cancer. In DE Neal (ed.), Tumours in Urology. Springer-Verlag London Berlin Heidelberg New York, pp 65-78 (1994).
3. Belldegrun A, Franklin JR, Figlin R: Prognostic factors in renal cell carcinoma. J Urol. 154:1274 (1995).
4. Franklin JR, deKernion JB: Kidney tumors - what's new? Current Opinions in Urology 5 (5):225 (1995).
5. Franklin JR, Raz S, deKernion JB: Female neobladder construction utilizing the UCLA 1 (ileocolic) pouch. In Olsson CA (ed), Surgical Techniques in Urology. 8 (5) (1995).
6. Franklin JR, and deKernion JB. Surgical Approaches To Renal Cell Carcinoma. in MS Ernstoff et al. (ed), Urologic Cancer. W.W. Norton & Company, N.Y., London (1996).
7. Franklin JR, Figlin R, Belldegrun AS: Renal cell carcinoma: Basic biology and clinical behavior. Seminars in Urologic Oncology 14 (4):208 (1996).
8. Franklin JR, Figlin R, Rauch J, Gitlitz B, Dorey F, deKernion JB, and Belldegrun AS: The role of cytoreductive surgery in the management of metastatic renal cell carcinoma. Seminars in Urologic Oncology 14 (4):230 (1996).
9. Franklin JR, and Belldegrun AS: Tumor immunity. In Oesterling J, and Richie J (eds), Urologic Oncology. Philadelphia PA, Saunders, pp 34-52, 1997.
10. Patel A, Dorey F, Franklin J, and deKernion J: Recurrence patterns after radical retropubic prostatectomy: Clinical utility of PSA doubling times and log slope PSA (prostate specific antigen). J Urol., 158: 1441-1445, 1997.
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12. Figlin R, Gitlitz B, Franklin J, Dorey F, Moldawer N, Rausch J, deKernion J, and Belldegrun A: Interleukin-2-based immunotherapy for the treatment of metastatic renal cell carcinoma: an analysis of 203 consecutively treated patients. Cancer J Scientific Amer., 3(suppl 1): 92-97, 1997.
13. Belldegrun AS, Franklin JR, O'Donnell MA, Gomella LG, Klein E, Neir R, Nseyo UO, Ratliff TL, Richards W, and Kellihan M: Superficial Bladder Cancer: The role of Interferon alpha therapy. J Urol. 159: 1793-1801, 1998.

SELECTED ABSTRACTS PUBLISHED AT PROFESSIONAL MEETINGS:

1. Franklin JR, and Bittman R, Ph.D. Synthesis of the alkyl ether phospholipid, racglycerol-3-phosphorylcholine 1-dodecyl ether 2-eicosyl ether and 1-eicosyl ether 2-dodecyl ether. 17th marm Abstract Booklet (ACS, April 1983) p. 208.
2. Franklin JR, Olsson CA, and Buttyan R. Expression of homeobox genes in the rat ventral prostate gland. J Urol 147: 318A (1992)

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

3. Franklin JR, Olsson CA, and Buttyan R. Homeobox gene expression in the mammalian prostate gland. Pan African Urological Surgeons Association (Inaugural international conference). Harare, Zimbabwe, May 1992.
4. deKernion J, and Franklin J: Improved preservation of continence after radical prostatectomy or cystectomy. Pan African Urological Surgeons' Association (2nd Biennial Conference) Sept 4-8, 1995.
5. Sokoloff M, Tso C-L, Randhir K, Franklin J, deKernion J, Pang S, Belldegrun A: Super-sensitive and quantitative polymerase chain reaction (PCR): An innovative technique for staging and monitoring prostate cancer. J Urol 153:294A, 1995.
6. Franklin J, Hoh C, Gitlitz B, Phelps M, Figlin R, and Belldegrun A: Positron emissiontomography (PET) scan for imaging of advanced renal cell carcinoma (RCC). Proceeding of the American Urologic Association. J Urol., 155(suppl): 581A, 1996.
7. Franklin J, Dorey F, Gitlitz B, deKernion J, Figlin R, and Belldegrun A: Cytoreductive nephrectomy in 63 consecutive patients who received adoptive immunotherapy for advanced renal cell carcinoma. Proceeding of the American Urologic Association. J Urol., 155(suppl): 500A, 1996.
8. Dorey F, Franklin J, deKernion J, and Smith R: Use of multiple PSA values for predicting clinical disease recurrence after radical retropubic prostatectomy (RRP). Proceeding of the American Urologic Association. J Urol., 155(suppl): 487A, 1996.
9. Franklin J, Pang S, Sawyer C, Kaboo R, Tso C-L, deKernion J, and Belldegrun A: Prostate specific gene therapy using a novel PSA promoter: In vivo studies. Proceeding of the American Urologic Association. J Urol., 155(suppl): 437A, 1996.
10. Sokoloff M, Tso C-L, Franklin J, Nelson S, Dorey F, deKernion J, and Belldegrun A: Quantitative polymerase chain reaction [PCR] does not improve prostate cancer [PC] staging: A clinical-pathologic-molecular analysis of 121 patients. Proceeding of the American Urologic Association. J Urol., 155(suppl): 417A, 1996.
11. Belldegrun A, Franklin J, Dorey F, Rauch J, deKernion J, and Figlin R: Long termsurvival of 181 patients with metastatic renal cell carcinoma (mRCC) treated with IL-2 based immunotherapy with/without tumor infiltrating lymphocytes. Proceeding of the American Urologic Association. J Urol., 155(suppl): 385A, 1996.
12. Franklin J, Marks L, Dorey F, Shery ED, and deKernion J: Serum PSA levels following TURP in men with BPH: Long-term characterization. Proceeding of the American Urologic Association. J Urol., 155(suppl): 378A, 1996.
13. Franklin J, Pang S, Dannul J, Sawyer C, Kaboo R, Tso C-L, and Belldegrun A: Cloning of an upstream regulatory region augments prostate specific antigen (PSA) promoter activity: In vivo studies. (Abstract) accepted AUA, April, 1997.
14. Franklin JR, Pang S, Dannul J. Sawyer C, Kaboo R, Tso C-L, and Belldegrun A: An Upstream regulatory region augments prostate specific antigen (PSA) promoter activity: In vivo studies. National Medical Association. August 2-7, 1997.

2.c. BIOGRAPHICAL SKETCH

Applicants should include this form as Addendum B in the submitted proposal.

Provide the following information for the applicant and collaborating investigator listed on the detailed cost estimate

NAME	POSITION TITLE
Edward F. Ikeguchi, MD	Collaborating Investigator

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include post-doctoral training.)

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY
Fordham University	B.S.	1984-1988	Chemistry
Colombia University, College of Physicians and Surgeons	M.D.	1988-1992	Medicine
Columbia University, P & S	Resident	1992-1994	Surgery
Columbia Univeristy, P & S	Resident	1994-1998	Urology
Columbia University, P& S	Fellowship	1998-1999	Neurourology & Urodynamics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past 3 years and to representative earlier publications pertinent to this application. If the list of publications in the last 3 years exceeds 2 pages, select the most pertinent publications. PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

Attending in Surgery
Department of Urology
Helen Hayes Hospital
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Clinical Assistant in Urology
J. Bentley Squier Urologic Clinic
College of Physicians and Surgeons of Columbia University
Columbia Presbyterian Medical Center
7/98-6/99
New York, NY

Assistant Professor of Urology
Assistant Attending in Urology
J. Bentley Squier Urologic Clinic
College of Physicians and Surgeons of Columbia University
Columbia Presbyterian Medical Center
7/99- To Start On this Date
New York, NY

Publication

Journal Articles:

Stifelman, M.D., IKEGUCHI, E.F., and Hensle, T.W.: Ureteral Tissue Expansion for Bladder Augmentation: A Long Term Prospective Controlled Trial. Journal of Urology, in press.

IKEGUCHI, E.F., Stifelman, M.D., Hensle, T.W.: Ureteral Tissue Expansion for Bladder Augmentation. Journal of Urology, 159(5): 1665-1668, 1998.

Kaplan, S.A., Te, A.E., IKEGUCHI, E., Santarosa, R.P.: The treatment of benign prostatic hyperplasia with alpha blockers in men over the age of 80 years. Br J Urol, Dec;80(6):875-9, 1997

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Fisch, H., IKEGUCHI, E.F., Goluboff, E.T.: Worldwide Variations in Sperm Counts. Urology, 48(6):909-11, 1996.

Katz, A.E., De Vries, G.M., Olsson, C.A., Benson, M.C., Swanton, P., IKEGUCHI, E.F., Buttyan, R.: Molecular Staging of Genitourinary Malignancies. Urology, 47 (6): 948-58, 1996.

Kaplan, S.A., IKEGUCHI, E.F., Santarosa, R.P., Meade D'Alisera, P., Hendricks, J., Te, A.E., Miller, M.I.: Etiology of Voiding Dysfunction in Men Less Than 50 Years of Age. Urology, 47(6): 836-9, 1996.

Whang, M., O'Toole, K., Bixon, R., Brunetti, J., IKEGUCHI, E., Olsson, C.A., Benson, M.C.: The Incidence of Multifocal Renal Cell Carcinoma In Patients Who are Candidates for Partial Nephrectomy. Journal of Urology, 154 (3): 968-971, 1995.

Book Chapters:

Edward F. IKEGUCHI, Alexis E. Te, James Choi, Steven A. Kaplan: Bladder Outlet Obstruction in Males. In: Appell, R.A., ed. Voiding Dysfunction: Diagnosis and Treatment. Totowa, New Jersey: The Humana Press, Inc. 1999.

IKEGUCHI, E.F. and Hensle, T.W.: The Pediatric Varicocele. In: King, L.R.,ed. Urologic Surgery of Infants and Children. Philadelphia: W.B. Saunders Company, 1998.

Abstracts & Presentations:

Stifelman, M.D., IKEGUCHI, E.F., and Hensle, T.W.: Ureteral Tissue Expansion for Bladder Augmentation: A Long Term Prospective Controlled Trial. Presented at the American Academy of Pediatrics Annual Meeting, New Orleans, LA, 1997.

Stifelman, M.D., IKEGUCHI, E.F., and Hensle, T.W.: Ureteral Tissue Expansion for Bladder Augmentation vs. Enteric augmentation: A Long Term Prospective Controlled Trial. American Urologic Association Annual Meeting, San Diego, CA, 1998.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Emilia Bagiella	Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Universita' degli studi 'La Sapienza', Rome, Italy	Laurea	1980-1985	Statistics
Columbia University, New York, NY	M.S.	1991-1193	Biostatistics
Columbia University, New York, NY	Ph.D.	1993-1997	Biostatistics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Academic Honors and Awards
The John Van Ryzin Memorial award, 1997
Columbia University Alumni Association Academic Award, 1996
Columbia University Alumni Association Academic Award, 1993
Graduation with Academic Honors, 1985

Professional Experience

1985 - 1991 Biostatistic Section Director, Department of Informatics, Sigma-Tau Pharmaceutics, Rome, Italy.
1988 - 1991 Biostatistic Consultant, Department of Neurosurgery, Catholic University, Rome, Italy.
1991 - 1995 Graduate Research Assistant, Department of Psychiatry, Columbia University, New York.
1992 - 1993 Teaching Assistant, Department of Biostatistics, Columbia University, New York.
1992 - 1996 Biostatistician, Stroke and Aging research project, Columbia University, New York.
1995 - 1997 Instructor, Department of Biostatistics, Columbia University, New York.
1996 - Biostatistician, H. Irving Comprehensive Cancer Center, Columbia University, New York.
1996 - Biostatistician, Department of Psychiatry, Columbia University, New York.
1997 - Assistant Professor, Department of Biostatistics, Columbia University, New York.

Publications

Bagiella, E., Sloan R.P, Heitjan D.F. Random effects models in Psychophysiology. Psychophysiology, In Press.

Sloan, R.P, Bagiella E., Powel T. Religion, spirituality and medicine: Empirical findings and ethical issues. The Lancet, In Press.

Saidi J.A., Chang D.T., Goluboff E.T., Bagiella E., Olsen G., Fisch H. Declining U.S. sperm counts? A critical review. J Urol, In Press.

Rubin M.A., Buyyounouski M., Bagiella E., Sharir S., Neugut A., Benson M., de la Taille A., Katz A.E., Olsson C.A.,Ennis R.D. Microvessel Density in Prostate Cancer: Lack of Correlation with Tumor Grade, Pathologic Stage, and Clinical Outcome. Urology, In Press.

Moroney J.T., Bagiella E., Paik M.C., Sacco R.L., Desmond D.W. (1998). Risk Factors for Early Recurrence After Ischemic Stroke : The Role of Stroke Syndrome and Subtype. Stroke, 29, 2118-2124.

Rubin M.A., de La Taille A., Bagiella E., Olsson C.A., O'Toole K.M. (1998). Cribriform carcinoma of the prostate and cribriform prostatic intraepithelial neoplasia: incidence and clinical implications. Am J Surg Pathol, 2(7),840-848.

Balentine J.R., Gaeta T.J., Kessler D., Bagiella E., Lee T. (1998). Effect of 50 millimiters of 50% dextrose in water administration on the blood sugar of euglycemic volunteers. Acad Emerg Med, 5(7)}, 691-694.

Desmond DW, Bagiella E, Moroney JT, Stern Y. The effect of patient attrition on estimates of the frequency of dementia following stroke. Archives of Neurology, in press.

Goluboff ET, Saidi JA, Mazer S, Bagiella E, Heitjan DF, Benson MC, and Olsson CA. Urinary continence after radical prostatectomy: the columbia experience. The Journal of Urology. In press.

Desmond DW, Moroney JT, Bagiella E, Sano M, Stern Y. Dementia as a predictor of adverse outcomes following stroke: An evaluation of diagnostic methods. Stroke 1998;29, 69-74.

Moroney J.T., Bagiella E, Desmond D.W, Paik M.C, Stern Y, Tatemichi T.K. Cerebral hypoxia and ischemia in the pathogenesis of dementia after stroke. Annals of the New York Academy of Sciences 1997;826,433-438.

Muskin PR, Kunkel ES, Worley LL, McCarty TA, Bagiella E, Wallack J, Milne J, McCartney JR, Santulli RB, Stewart F, Frankel B, Margo G, Goldman A, Rieder RO, Tasman A. The multisite field trial of the consultation-liaison psychiatry assessment instrument. General Hospital Psychiatry 1997 , 19(1),16-23

Moroney J.T., Bagiella E, Desmond D.W., Hachinski V.C, Molsa P.K, Gustafson L, Brun A, Fischer P, Erkinjuntti T,Rosen W, Paik M.C., Tatemichi T.K. Meta-analysis of the Hachinski ischemic score in pathologically verified dementias. Neurology 1997;49:1096-1105.

Moroney J.T., Bagiella E, Hachinski V.C, Molsa P.K, Gustafson L, Brun A,Fischer P, Erkinjuntti T, Rosen W, Tatemichi T.K, Desmond D.W. Misclassification of dementia subtype using the Hachinski ischemic score (HIS): Results of a meta-analysis of patients with pathologically verified dementias. Annals of the New York Academy of Sciences 1997;826:490-494.

Moroney, J.T., Bagiella, E., Tatemichi, T.K., Paik, M., Stern, Y., Desmond, D.W. Dementia after stroke increases the risk of long term stroke recurrence. Neurology,1997,48(5), 1317-25 .

Sloan R.P., Demeersman, R.E., Shapiro P.A., Bagiella E., Kuhl J.P, Zion, A.S., Paik M., and Myers M.M. Cardiac autonomic control is inversely related to blood pressure variability responses to psychological challenge. Am. J. Physiol,1997, 272(5 Pt 2), H2227-32.

Moroney, J.T., Bagiella, E., Desmond, D.W., Paik, M., Stern, Y., Tatemichi, T.K. Risk factors for incident dementia after stroke. Role of hypoxic and ischemic disorders. Stroke, 1996, 27, 1283-9.

Sloan R.P., Shapiro P.A., Bagiella E., Bigger J.T. Jr, Sing E. Lo, Gorman J.M. Relationship between circulating catecholamines and low frequency heart period variability as indices of cardiac sympathetic activity during mental stress.Psychosomatic Medicine, 1996, 58, 25-31.

Shapiro P.A., Sloan R.P., Bagiella E., Bigger J.T. Jr., Gorman J.M.. Heart rate reactivity and heart period variability throughout the first year after heart transplantation. Psychophysiology, 1996, 33, 54-62.Sloan R.P..

Shapiro P.A., Bagiella E., Gorman J.M., Bigger J.T. Jr. Temporal stability of heart period variability at aseline and in response to psychological challenge. Psychophysiology. 1995, 33, 54-62.

Sloan R.P., Shapiro P.A., Bagiella E., Fishkin P.E., Gorman J.M, Myers M.M. Consistency of heart rate and sympathovagal reactivity across different autonomic contexts. Psychophysiology, 1994, 32, 452-459.

Sloan R.P., Shapiro P.A., Bagiella E., Steinman R.C., Bigger J.T. Jr..Brief interval HPV by different analytic methods correlates highly with 24-hours analyses in Normals. Biol. Psychol., 1994, 38, 133-142

Sloan R.P., Shapiro P.A., Bagiella E., Paik M., Boni S.M., Bigger J.T. Jr, Steinman R.C., Gorman J.M. Effect of mental stress throughout the day on cardiac autonomic control. Biol. Psychol., 1994, 37, 89-99

Sloan R.P., Shapiro P.A., Bagiella E., Steinman R.C., Gorman J.M., Bigger J.T. Jr. Cardiac autonomic control and hostility in healthy subjects. Am. J. of Cardiol., 1994, 74, 298-300

Shapiro P.A., Sloan R.P., Bigger J.T. Jr., Bagiella E., Gorman J.M.. Cardiac denervation and cardiovascular reactivity to psychological stress. American Journal of Psychiatry, 1994, 151, 1140-1147

Tatemichi T.K., Desmond D.W., Stern Y., Paik M., Sano M., Bagiella E.. Cognitive impairment after stroke: frequency, patterns, and relationship to functional abilities. J. of Neurology, Neurosurgery and Psychiatry, 1994, 57(2), 202-207

Tatemichi T.K., Paik M., Bagiella E., Desmond D.W., Stern Y., Sano M., Hauser W.A., Mayeux R. Risk of dementia after stroke in a hospitalized cohort: results of a longitudinal study. Neurology, 1994, 44(10), 1885-91

Tatemichi T.K., Paik M., Bagiella E., Desmond D.W., Pirro M., Hanzawa L.K. Dementia after stroke is a predictor of long-term survival. Stroke, 1994, 25(10), 1915-9.

EXISTING/ PENDING SUPPORT

TE, ALEXIS E.

ACTIVE

5 UO1 DK46418 - 05 — 4/95-3/01

Per cent effort — 20%
Dr. Te is co-investigator — $334,680
NIH/NIDDK
Progression of BPH on Medical Therapy

The major goal of this project is to determine the feasibility of assessing various parameters on the progression of benign prostatic hyperplasia (BPH) over a 6 year period.

No Overlap

DAMD17-99-1-9041 — 01/99-07/99

Per cent effort — 25%
Dr. Te is PI — $49,516
DOD
Prostate specific antigen density of the transition zone in ethnically diverse men

This is a minority focused training grant that is funding the support necessary for the preliminary work to prepare this current grant application. Funding will be completed when this project is initiated.

No Overlap

IKEGUCHI, EDWARD F.

None

FRANKLIN, JOHN R.

PENDING

DAMD	Pending
Per cent effort	25%
Dr. Franklin is PI	$50,000
DOD	

Race/ Ethnic Based Genetic Variation In Human Genes: Defining the Genetic Evidence For Disparity Of Prostate Cancer Risk And Mortality Between different Populations.

No Overlap

KAPLAN, STEVEN A.

ACTIVE

5 UO1 DK46418 - 05	4/95-3/01
Per cent effort	20%
P.I. is Steven A. Kaplan	$334,680
NIH/NIDDK	

Progression of BPH on Medical Therapy

The major goal of this project is to determine the feasibility of assessing various parameters on the progression of benign prostatic hyperplasia (BPH) over a 6 year period.

No Overlap

DAMD17-99-1-9041	01/99-07/99
Per cent effort	20%
Dr. Kaplan is Established Investigator/ Mentor	$49,516
DOD	

Prostate specific antigen density of the transition zone in ethnically diverse men

This is a minority focused training grant that is funding the support necessary for the preliminary work to prepare this current grant application. Funding will be completed when this project is initiated.

No Overlap

PENDING

DK 98-018 — Pending
Per cent effort — 15%
Dr. Kaplan is PI
NIH
Ischemia and Angiogenesis in Urologic Diseases

No Overlap

OTHER SUPPORT

Emilia Bagiella

ACTIVE:

R01 MH43977 (Sloan, RP) 5/1/96-4/30/00 15% effort
NIMH $1,124,448
Cardiac denervation and Psychological Reactivity

R01 HL61287 (Sloan, RP) 4/1/98-3/31/01 10% effort
NHLBI $894,586
Psychophysiologic stress, exercise and autonomic control

P30-CA13696 (Antman, K) 50% effort
NCI
Cancer Center Support Grant

PENDING

01/01/00-12/31/03 (Sloan, RP) 20% effort
NMIH
Hostility reduction and autonomic control of the heart.

1999-2001 (Hauser, AW) 20% effort
NIH
Clinical trial pilot grant to study treatment of cysticercosis.

Facilities and Equipment

The *Prostate Center* at Columbia-Presbyterian Medical Center was established in 1990. It is dedicated to investigating all alternative treatments in the management of BPH and prostate cancer is well suited and equipped to enroll a suitable number of patients for this clinical trial. Both the Department of Urology and Columbia-Presbyterian Medical Center have demonstrated a willingness to provide space, personnel and technical assistance for this center. A new facility was recently completed in January of 1996 and currently houses the Prostate Center. It has have over 4,000 square feet dedicated to patient research, prostate ultrasound and urodynamics.

Currently, at the Prostate Center, over 750 patients have been enrolled in 17 investigative protocols including medical (5-alpha reductase inhibitors [finasteride, epristeride], alpha blockers [terazosin, doxazosin, tamsulosin] and aromatase inhibitors [atamstane]); transurethral hyperthermia, prostatic stents, electrovaporization and lasers. Our involvement has ranged from designing protocols to investigator status. The P.I. and his co-investigators have had extensive experience in the field and have worked in many collaborative efforts including the BPH feasibility trial.

The *Prostate Center* consists of 4 fully equipped examination rooms (800 square feet), each having a uroflowmeter and Bladder Scan device. There are 6 office areas (1,500 square feet) and storage space for patient records and storage of medication. In addition, many of the clinical trials have involved either measuring prostate size or obtaining tissue and we have on site facility access to a transrectal ultrasound machine (B&K 8551) as well as MRI technology.

The staff of the *Prostate Center* includes the P.I. who is senior staff urologist, the Director (Co-Investigator), another staff urologist (Co-Investigator) and a yearly Fellow in Neurourology. The other dedicated personnel include a Nurse Coordinator who is responsible for patient care, data collection and supervising a staff nurse and full time data manager. There is a great deal of experience in participating and formulating multi-center clinical trials. The Center has participated either currently or in the past in 19 multicenter clinical trials involving treatment of prostate disease and two NIH funded trials. The staff is adept at prompt scheduling of patients both in the recruitment and follow-up phases of the study; timely and meticulous entry of data in both source documents and by remote data entry where applicable (within 24 hours of seeing patients) and in handling and shipping tissue and serum specimens on the day that they are obtained.

The Squier Urological Clinic at the Allen Pavilion serves as the major health facility of North Manhattan and serves a large population of ethnically diverse patients. There are 5 office areas and a large area for patient accrual. It is connected by network computer link to the data base at the Prostate Center. This allows for timely and efficient data entry.

A network of IBM compatible computers connected to a central server are maintained in the Prostate Center by the P.I. for word processing, database collection and processing, and statistical analysis. (Total of 29 GB)

P.I. has 400 square foot office. Each Co-Investigator has 200 square foot office. The study nurse and secretary have a 400 square foot office.

The Prostate Ultrasound Facility at Columbia Presbyterian Medical Center has 250 square foot for equipment and patient evaluation. Currently, a B&K ultrasound unit with biopsy guide is available. There is dedicated dressing space and a bathroom.

STATEMENT OF ELIGIBILITY

Applicant's Name: Alexis E. Te, MD

Title of Proposal: Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men

Applicant's Organization Name: Columbia University

Applicants's Organization Location: 630 West 168th Street, NY, NY 10032

Signature of Applicant:

STATEMENT OF ELIGIBILITY

For the purpose of the Department of Defense Congressionally Directed Meidcal Research Program's Prostate Cancer Research Program New Investigator Award category as outlined in the Announcement, the applicant fulfills all of the following criteria:

- Holds a position of Assistant Professor or equivalent;

AND

- Has access to appropriate research facilities;

I, Carl A. Olsson, MD, of the Columbia University
(printed name of Department Chair)

attest that the above-named investigator fulfills the requirements for a New Investigator Award.

Signature of Official Date: 3-5-99

Department of Urology
College of Physicians and Surgeons
of Columbia University

STEVEN A. KAPLAN, M.D., F.A.C.S.

Given Foundation Professor of Urology
Vice Chairman and Administrator
Department of Urology

Squier Urological Clinic
The Presbyterian Hospital
in the City of New York

Tel: (212) 305-0140
(212) 305-0146
Fax: (212) 305-0139
Email: sk46@columbia.edu

March 4, 1999

Commander
US Army Medical Research and Material Command
Att: MCMR-PLF (PCRP-MPFT-98)
1076 Patchel Street Building 1076
Fort Detrick, MD 21702

To Whom It May Concern:

This is a letter of support for Dr. Alexis E. Te's new investigator grant concerning " Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men". As Vice Chairman and Administrator of the Department of Urology as well as Director of the Prostate Center, I fully support his project. As outlined in the grant, the department and the prostate center will provide all necessary support to carry out the project.

I have known Dr. Te since 1988, as a resident, fellow and now as an associate on our academic staff. I have worked with Dr. Te for many years and have co-authored many publications and abstracts with him. As my fellow in Neurourology and Urodynamics, he has been instrumental and valuable in the development and success of several academic and clinical projects including many studies on prostate treatments and prostate disease processes.

I have been actively involved in the formulation of this research concept as Dr. Te's established investigator in the minority focused training grant sponsored by the DOD on this topic. The topic PSAD of the Transition Zone in Ethnically Diverse Men is a project that has involved Dr. Te's collaboration as evident from our publications. We propose to explore the role of PSA Density of the Transition Zone (PSAT) in the screening evaluation for prostate cancer in an ethnically diverse population of men. Our preliminary data suggest that PSAT may be a better refinement of currently available cancer detection strategies especially in specific ethnic population. This work would also lend to a better understanding of prostate morphology in different ethnic populations.

I enthusiastically support Dr. Te's application for this training grant to further his academic career development and to serve as his established investigator in this proposal.

Sincerely,

Steven A. Kaplan, M.D
Professor and Vice Chairman
Dept of Urology

Department of Urology
College of Physicians and Surgeons
of Columbia University

Carl A. Olsson, M.D.
John K. Lattimer Professor and Chairman

Squier Urological Clinic
The Presbyterian Hospital
in the City of New York

Tel: (212) 305-0100
Fax: (212) 305-0106

March 4, 1999

Commander
US Army Medical Research and Material Command
Att: MCMR-PLF (PCRP-MPFT-98)
1076 Patchel Street Building 1076
Fort Detrick, MD 21702

To Whom It May Concern:

The Department of Urology at the College of Physician and Surgeons of Columbia University is totally dedicated to the career plans of Dr. Alexis E. Te. Dr. Te is an Assistant Professor in our faculty. As part of the department's commitment to the proposed project, Dr. Te will be relieved of clinical and administrative responsibilities in order for him to pursue his academic career development in the proposed research plan. Additionally, as outlined in the grant, the department will provide the appropriate support to carry out the project.

Dr. Te is an Asian American physician who has contributed much of his time, both clinical and community related, in the Asian American community. He has been active in minority related concerns and has been honored with awards from the Philippine Chinese American Medical Association and the Philippine Chinese American Association for his achievements. He has an established relationship with Dr. Steven A. Kaplan who will continue as collaborating investigator in the proposal. Dr. Kaplan is also a member of our faculty, and a Professor and Vice Chairman of the Department of Urology at Columbia.

They propose to evaluate the role of PSA Density of the Transition Zone (PSAT) in the screening evaluation for prostate cancer in an ethnically diverse population of men. Their preliminary data suggest that PSAT may be a better refinement of currently available cancer detection strategies especially in specific ethnic population. This work would also lend to a better understanding of prostate morphology in different ethnic populations.

I enthusiastically support Dr. Te's application for this new investigator grant to further his academic career development.

Sincerely,

Carl A. Olsson, MD
Professor and Chairman
Dept. of Urology

2.c. Detailed Cost Estimate

Principal Investigator (last,first,middle): Te, Alexis E.

Detailed Budget for Initial Budget Period					**From**		**Through**
					9/1/99		8/31/00
					Dollar Amount Requested		
Personnel					(omit cents)		
Name	**Role on Project**	**Type Appt. (Months)**	**Annual Base Salary**	**% Effort on Project**	**Salary Requested**	**Fringe Benefits**	**Totals**
Alexis E. Te, MD	**Principal Investigator**	12	$40,000	20%	$8,000	$2,088	$10,088
Steven A. Kaplan, MD	Co-Investigator	12	$45,000	5%	$2,250	$588	$2,838
Edward Ikeguchi, MD	Co-Investigator	12	$45,000	5%	$2,250	$588	$2,838
John R. Franklin, MD	Co-Investigator	12	$45,000	5%	$2,250	$588	$2,838
Aleta Ashley, RN	Nurse Coordinator	12	$50,000	50%	$25,000	$6,085	$31,085
Emelia Bagiella, PhD	Co-Investigator	12	$62,000	5%	$3,100	$809	$3,909
Subtotals >>>>>>>>>>>>>>>>>>					$42,850	$10,746	$53,596
Consultant Costs (Itemize on Justification Page - 3)							
Major Equipment Costs (Itemize on Justification Page - 3)							
Materials, Supplies, and Consumables Costs (Itemize by Category on Justification Page - 3)							
Travel Costs (Itemize on Justification Page - 3)							$1,200
Research-Related Patient Costs (Itemize on Justification Page - 3)							$41,606
Other Expenses (Itemize by Category on Justification Page - 3)							
Subtotal Other Direct Costs for Initial Budget Period (Subtotal B) >>>>>>>>>>>>>>>>>>							$42,806
Consortium Costs	Direct Cost (Itemize on Justification Page - 3)						
	Indirect Cost (Itemize on Justification Page - 3)						
Total Personnel & Other Direct Costs For Initial Budget Period							$96,402
Total Indirect Costs For Initial Budget Period							$38,631
Total Costs For Initial Budget Period							$135,033

Principal Investigator (last,first,middle): Te, Alexis E.

Budget for Entire Proposed Period Of Support						
Budget Category Totals*	Initial Budget Period	Additional Years of Support Requested				Total
	(From Form Page 1)	2nd	3rd	4th	5th	
Personnel	$42,850	$44,564	$23,173			$110,587
Fringe Benefits	$10,746	$11,176	$5,812			$27,734
Consultant Costs	$0					$0
Major Equipment	$0					$0
Materials, Supplies, and Consumables	$0					$0
Travel Costs	$1,200	$1,200	$1,000			$3,400
Research-Related Patient Costs	$41,606	$41,606	$0			$83,212
Other Expenses	$0					$0
Subtotal Direct Costs	$42,806	$42,806	$1,000	$0	$0	$86,612
Direct Consortium Costs	$0					$0
Indirect Consortium Costs	$0					$0
Total Direct Costs	$96,402	$98,546	$29,985	$0	$0	$224,933
Total Indirect Costs	$38,631	$40,143	$21,139			$99,913
Total Direct Costs for Entire Proposed Period of Support						$224,933
Total Indirect Costs for Entire Proposed Period of Support						$99,913
Total Costs for Entire Proposed Period of Support**						$324,846

* Itemize all budget categories for additional years on *Justification* page which follows.

** This amount should agree with that entered on the cover sheet booklet, item #24.

BUDGET JUSTIFICATION

Salary support is requested for:

Dr. Te as the Principal Investigator and supervisor of this project will participate in the evaluation of patients. He is a prostate disease specialist and a senior staff physician in the Prostate Center as well as the Director of the Incontinence Care Center at Columbia Presbyterian Medical Center and Maimonides Medical Center. He will have responsibility in screening and recruiting patients, and performing transrectal ultrasound guided biopsies. In addition, he will be responsible for modifications and amendments made to the protocol. He will also perform all transition zone measurements. The salary and effort presented on the budget page is based on the Columbia University institutional base salary of $40,000.

Dr. Kaplan, Ikeguchi and Franklin will serve as Co-Investigators. Dr. Kaplan is a Professor of Urology at Columbia University and Director of the Prostate Center. Dr. Franklin is an Assistant Professor of Urology at Columbia University and the primary urologic oncologist at the Squier Urology Clinic at the Allen Pavilion. Dr. Ikeguchi is a currently a fellow in Neurourology and Urodynamics and will be Assistant Professor of Urology at the initiation of funding of this project. He is also a Staff Physician at the Prostate Center. These physicians with the principle investigator will have responsibility in screening and recruiting patients, and performing transrectal ultrasound guided biopsies. The salary and effort presented on the budget page is based on the Columbia University institutional base salary of $45,000.

Dr. Emilia Bagiella will serve as the biostatistician for the study and perform the analysis of the data. She will also review modifications and amendments to the protocol. The salary and effort presented on the budget page is based on the Columbia University institutional base salary of $62,000.

Based on our previous experience with recruitment and follow-up of patients in studies of prostate diseases, which require ultrasound, one nurse coordinator will be required for this study. Aleta Ashley will devote 100% of her time to seeing patients during the initial evaluation and coordinating patient visits. She will perform managing, collecting, coordinating and processing all data and follow-up visits as well. **As part of Cost Sharing, the Department of Urology will pay 50% of Ms. Ashley's salary and only 50% will be charged to the grant proposal.**

Secretarial and clerical functions will be provided by the Department of Urology as part of Cost Sharing at no additional cost to the grant.

The budget is based on a 4% increase in salary per annum. The fringe benefits for the P.I. and Co-PI is 26.1% (Columbia University employees); the fringe benefits for the nurse is 24.34% (Columbia-Presbyterian Medical Center employee).

Travel expenses are related to 1 national meeting per year for the P.I.

Outpatient costs are related to the patient visits and tests required during the protocol. We assume that 50% of the patients will be recruited during the first budget period. (N= 400) Therefore, 50% of patient costs will be distributed evenly between the first and second budget period. We also assume based on our data as well as published series that 15% of patients (n = 60) will undergo concomitant prostate biopsy.

For the first year, 400 patients will be recruited. Parameters of evaluation include serum PSA and transrectal ultrasound measurement (TRUS) of the prostate. The charge for a serum PSA and associated blood test is $30 for a total of $12,000. For the TRUS, there is a facility charge for each ultrasound study. (This is related to charges for the facility use of the ultrasound and related supplies and rent). **As part of cost sharing, the Department of Urology will forego the normal facility fee of $678 and charge a fee of $50/patient for a total of $20,000. In addition, there will be no physician-related fees for the TRUS.** In addition, patients will not be billed for expenses related to additional charges for the study. Finally, there will be no charge for equipment, disposables and needle biopsy guides. We anticipate that 15% of patients will require biopsy. Therefore, 60 patients will have biopsy and tissue sent for pathological examination. The pathologist fee is $161 or a total of $9660.

Year 1

TRUS facility fee: 30,000
PSA measurement: 12,000
Pathologist fee: 9,660

Therefore, in the first year, total outpatient costs related to the study for the first 400 patients will be = **$41,660**

In year #2, the recruitment for the remaining 400 patients for a total of 800 will be completed. Therefore, in the second year, total outpatient costs related to the study for the next 400 patients will be = **$41,606**

In year #3, there are no patient related costs in the final 6-month budget period.

The rate of 70.50% MTDC is being used for the purpose of this application.

Cost Sharing: As stated above, both the University and Department of Urology have committed resources at no additional expense to the grant proposal. These include 50% of the research nurse salary, and, funding salary support for secretarial and clerical assistance.

Furthermore, the Department has reduced the facility fee for transrectal ultrasound from $671 to $50 per patient. Moreover, all supplies and disposables will be paid through the Department of Urology and not charged to the grant.

0022-5347/95/1545-1764$03.00/0
THE JOURNAL OF UROLOGY

Vol. 154, 1764–1769, November 1995
Printed in U.S.A.

TRANSITION ZONE INDEX AS A METHOD OF ASSESSING BENIGN PROSTATIC HYPERPLASIA: CORRELATION WITH SYMPTOMS, URINE FLOW AND DETRUSOR PRESSURE

STEVEN A. KAPLAN, ALEXIS E. TE, LEE B. PRESSLER AND CARL A. OLSSON

From the Department of Urology, College of Physicians and Surgeons, Columbia University, New York, New York

ABSTRACT

Purpose: Prostate volume has been poorly correlated to various parameters used to assess benign prostatic hyperplasia (BPH), including symptoms, peak urine flow and detrusor pressure at peak urine flow. The purpose of this study was 2-fold: 1) to determine if transrectal ultrasound measurement of the transition zone of the prostate served as a better proxy for determining prostate size and correlated better with American Urological Association symptom score, peak urine flow and detrusor pressure, and 2) if the parameter transition zone index (the ratio between transition zone volume and prostate volume) was useful in evaluating clinical prostatism.

Materials and Methods: We prospectively evaluated 61 men with symptomatic BPH (age 64.6 ± 9.7 years) according to symptoms, peak urine flow, pressure/flow analysis, transrectal ultrasound volume of the entire prostate and the transition zone, and calculation of the transition zone index.

Results: Age correlated with symptoms ($r = 0.31$, $p = 0.01$) and peak urine flow correlated negatively with symptoms and age ($p = 0.002$). Age also correlated with prostate volume ($r = 0.54$ and $p = 0.03$) and transition zone ($r = 0.31$, $p = 0.05$). There was a weak correlation between prostate volume and symptoms, peak urine flow and detrusor pressure at peak urine flow; a stronger correlation between transition zone and symptoms ($r = 0.48$, $p = 0.03$), and peak urine flow ($r = -0.34$, $p = 0.05$), and a significant correlation ($p = 0.001$) between transition zone index and symptoms ($r = 0.75$), peak urine flow ($r = -0.71$) and detrusor pressure at peak urine flow ($r = 0.43$). A transition zone index of greater than 0.50 was a useful cutoff point and highly significant ($p = 0.002$) for delineating patients with more severe abnormalities of symptoms, peak urine flow and detrusor pressure at peak urine flow.

Conclusions: Transition zone index is a parameter that correlates significantly with evaluated parameters of BPH and may serve as a useful proxy for evaluating worsening obstruction. Studies are underway to determine if transition zone index can be used prospectively to predict and correlate response with therapies designed to ablate prostatic tissue medically or surgically.

KEY WORDS: prostate, prostatic hypertrophy

Evaluation of prostatic size in men with benign prostatic hyperplasia (BPH) is done primarily to ascertain if a transurethral or open procedure is required and to avoid potential complications of prolonged resection.[1] Digital rectal examination, urethrocystoscopy and retrograde urethrography may provide erroneous results in assessing prostatic size,[2,3] which is particularly true when the prostate is large.[4] The advantages of transabdominal and transrectal ultrasound in more accurately assessing prostatic size have been well described.[4-6]

Others have reported conflicting results when describing the correlation between prostatic size and parameters of the evaluation of prostatism, such as symptoms, urine flow and detrusor pressure.[7-11] Jensen et al noted that the estimation of prostatic weight by simultaneous digital rectal examination and cystoscopy correlated with resected weight and symptoms.[12] However, prostatic size did not correlate with symptoms and, more importantly, it did not correlate with the outcome of resection.

This lack of correlation may partially be due to measuring the wrong part of the prostate. As described by McNeal, BPH is secondary to hyperplasia of the transition zone with a minor contribution from hyperplasia of the central zone and periurethral glands.[13] Greene et al reported that sonographic measurement of the transition zone correlated with aging and clinical evidence of BPH.[14] However, in that study parameters for evaluating BPH, that is symptoms, urine flow and urodynamics, were not reported. In addition, the relationship of the transition zone relative to whole prostate volume was not delineated.

Recently Kalish et al reported the potential benefit in assessing men with intermediate elevation of prostate specific antigen (PSA) using an adjusted measurement of transition zone volume versus total gland volume.[15] They recognized and attempted to correct for BPH contribution to PSA level by determining the volume of the transition zone by transrectal ultrasound. Tewari et al reported the use of transition zone volume and transition zone to total prostate volume in evaluating responders versus nonresponders to finasteride therapy.[16] However, they did not document a correlation between transition zone volume, and baseline symptoms and urine flow. Thus, we were stimulated to evaluate the potential role of measuring transition zone volume as a more sensitive prostate size marker for BPH and to evaluate if this marker correlates with American Urological Association (AUA) symptom score, urine flow and detrusor pressure. Furthermore, we determined the relationship between the transition zone and total gland volume, expressed as transition zone index, and its potential to predict prospectively and correlate response with therapies designed to ab-

MATERIALS AND METHODS

Patients. A total of 61 patients with symptomatic prostatism was enrolled into this prospective study. Patients were being evaluated for various therapeutic intervention trials, including medications and minimally invasive alternative therapy for BPH. Parameters of evaluation included AUA symptom score, peak urine flow and synchronous video pressure/flow analysis. Patients with a known neurogenic bladder, cancer of the prostate, or a history of prostate surgery or therapy for symptomatic BPH were excluded. Two sets of control subjects were used in this study: men younger than 35 years without BPH or voiding symptoms (control A) and age matched men without BPH based on digital rectal examination and AUA symptom score (control B).

Transrectal ultrasound of the prostate. A Bruel & Kjaer model 1846 ultrasound instrument equipped with a model 1850 radial probe and a model 8537 longitudinal probe incorporating 7 MHz. transducers was used to perform transrectal ultrasound. Imaging was done in transaxial and longitudinal views.

Prostate and transition zone volume determination. Measurements were done by a single examiner. Prostatic volume was calculated using the formula for a prolate ellipsoid (V = width × length × height × 0.52). Width was measured in the transverse view of the gland, while length was measured in the longitudinal view (fig. 1). Prostatic height was measured in the longitudinal axis at a right angle to gland length to prevent the "salami effect" previously described by Kalish et al.[15] Maximum diameters were used for each measurement. The determination of transition zone volume was similarly performed by prolate ellipsoid calculation (fig. 2). Transition zone index was calculated according to the formula, transition zone index = transition zone volume/total gland volume.

Urodynamic evaluation. Synchronous video pressure studies and fluoroscopic voiding cystourethrography were performed. A 10F triple lumen catheter was introduced into the bladder transurethrally. One lumen was used for bladder filling with meglumine diatrozoate at room temperature and at medium fill at a rate of 100 ml. per minute. An opening 1 cm. proximal to the catheter tip was used to record intravesical pressure through the second lumen. Intra-abdominal pressures were recorded via a rectal tube held in place by a water filled balloon. Intravesical and rectal pressures were simultaneously transduced on the Lifetech Janus System. Peak urine flow was measured during a urine flow study without urethral instrumentation using a Dantec 1000 flowmeter. The single examiner who performed prostate volume measurements was blinded to symptom scores and urodynamic findings.

Statistical analysis. The Student 2-sample t test was used to compare transition zone volume and index to patient symptoms, peak flow rate and detrusor pressure. Unadjusted p values were calculated. Relationships among these characteristics were measured using Pearson's correlation coefficient.

RESULTS

Mean age of the 61 patients in the study was 64.6 ± 9.7 years. Baseline clinical characteristics are shown in table 1. Mean AUA symptom score and peak urine flow were 16.7 ± 3.4 and 9.2 ± 2.7 ml. per second, respectively.

Control subjects. There were 10 control A subjects (mean age 27 ± 4.3 years) and 15 control B subjects (mean age 62.4 ± 8.7 years). For the control A group mean prostate and transition zone volumes were 18.3 ± 3.4 ml.^{3} and 5.4 ± 1.7 ml.^{3}, respectively. No patient had a transition zone index of greater than 0.2. For the control B patients mean prostate and transition zone volumes were 42.7 ± 9.8 ml.^{3} and 12 ± 7.7 ml.^{3}, respectively. Mean transition zone index was 0.17 and no patient had a transition zone index of greater than 0.25. Mean AUA symptom score for this group was 1.4 (table 2).

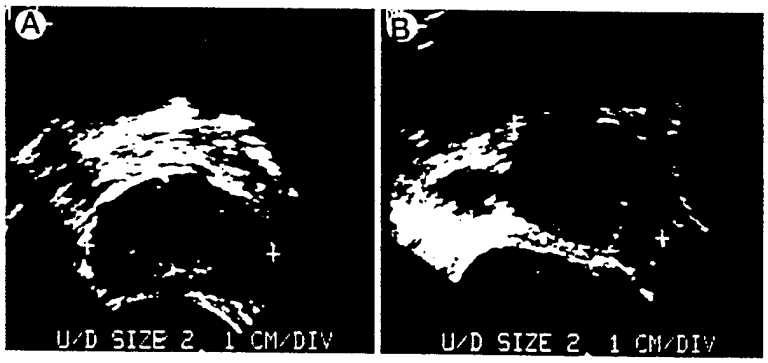

FIG. 1. Transrectal ultrasound. *A*, maximal width of whole prostate gland in transverse view. *B*, maximal length of whole prostate gland in longitudinal view.

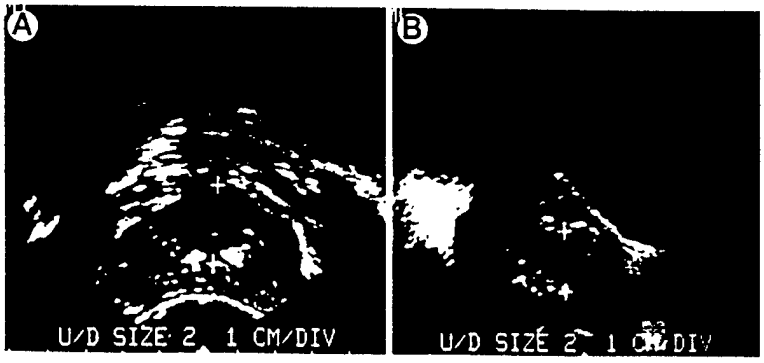

FIG. 2. Transrectal ultrasound. *A*, height of transition zone in transverse view (2.0 cm.). *B*, "salami effect" height of transition zone in longitudinal view (1.6 cm.)

TABLE 1. *Baseline clinical characteristics of 61 patients with BPH*

Characteristic	Mean (range)
Pt. age (yrs.)	64.6 (53–79)
Prostate vol. ($ml.^3$)	49.1 (23–126)
Transition zone vol. ($ml.^3$)	23.3 (4–63)
Transition zone index	0.47 (0.14–0.7)
AUA symptom score	16.7 (8–31)
Peak urine flow (ml./sec.)	9.2 (4.5–14.6)
Detrusor pressure at peak urine flow (cm. water)	62.1 (37–125)

TABLE 2. *Prostate and transition zone volumes, and transition zone index in control groups*

	Control A	Control B
Pt. age (yrs.)	27 ± 4.3	62.4 ± 8.7
Prostate vol. ($ml.^3$)	18.3 ± 3.4	42.7 ± 9.8
Transition zone vol. ($ml.^3$)	5.4 ± 1.7	12.0 ± 7.7
Transition zone index	0.14	0.17

Correlation between age and BPH parameters. A positive correlation (r = 0.31) was noted between patient age and symptom score (p = 0.01). In contrast, there was a significant negative correlation between peak urine flow, and AUA symptom score (r = −0.47) and age (r = −0.41, p = 0.002). There was little correlation among symptoms, peak urine flow and detrusor pressure at peak urine flow (r = 0.07, p = 0.17).

Correlation between age and volume parameters. When evaluating the relationship between patient age and various prostate volume parameters, we noted a positive correlation between age and total prostate volume (r = 0.54, p = 0.03), and a weaker positive correlation between age and transition zone volume (r = 0.31, p = 0.05). The dependent variable transition zone index similarly increased with increasing age (r = 0.46, p = 0.03). Transition zone volume strongly correlated to increasing prostate volume (r = 0.89, p = 0.01, fig. 3).

Correlation between prostate volume and BPH parameters. The relationship between prostate volume, transition zone volume and transition zone index with AUA symptom score, peak urine flow and detrusor pressure at peak urine flow is listed in table 3. There was a weak correlation between prostate volume and AUA symptom score (r = 0.17), peak urine flow (r = −0.20) and detrusor pressure at peak urine flow (r = 0.13, fig. 4). None was statistically significant. However, transition zone or BPH volume had a significantly stronger correlation with AUA symptom score (r = 0.48), peak urine flow (r = −0.34, p = 0.03) and detrusor pressure at peak urine flow (r = 0.20, fig. 5). The strongest and most

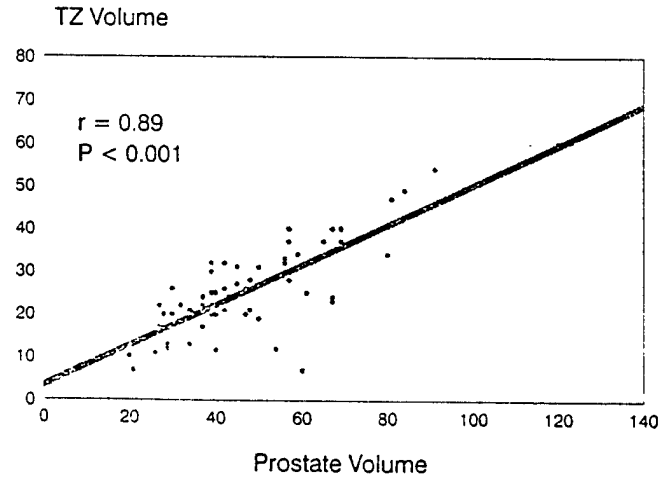

FIG. 3. Scattergram comparing total prostate gland to transition zone (*TZ*) volume with correlation (r = 0.89, p = 0.001, solid line).

TABLE 3. *Correlation of prostate volumes and BPH parameters*

	Total Vol.	Transition Zone	Transition Zone Index*
AUA symptom score	0.17	0.48†	0.75
Peak urine flow	−0.20	−0.35‡	−0.71
Detrusor pressure at peak urine flow	0.13	0.20	0.43

* p = 0.001.
† p = 0.03.
‡ p = 0.05.

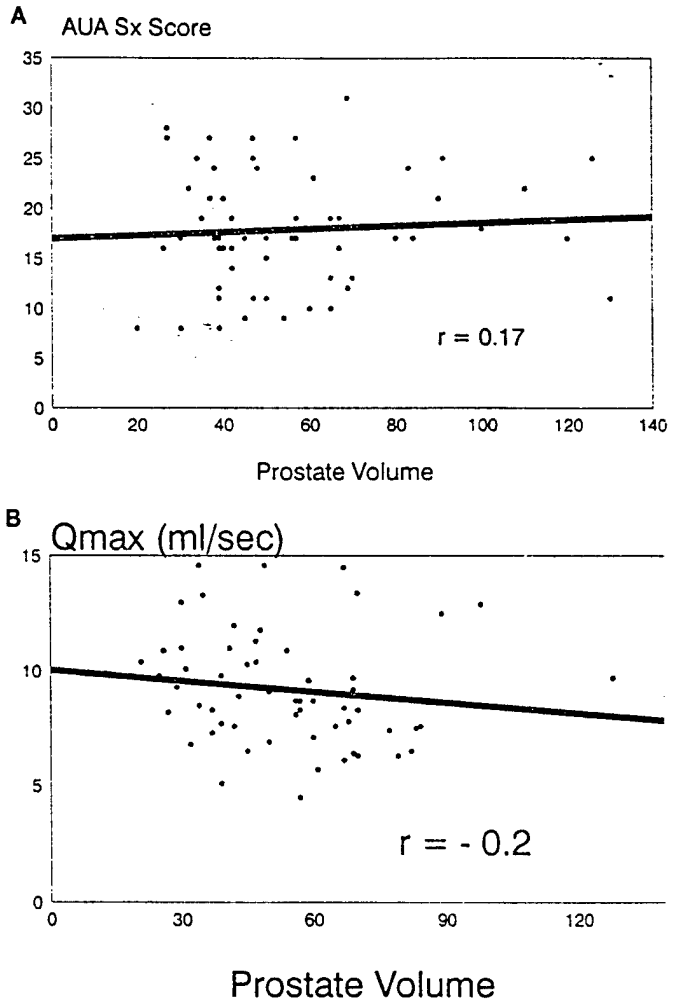

FIG. 4. *A*, scattergram comparing AUA symptom (*Sx*) score to total prostate gland volume with poor correlation (r = 0.17, solid line). *B*, correlation between prostate volume and peak urine flow (*Qmax*, r = −0.20).

significant correlation was between transition zone index and the BPH parameters of AUA symptom score (r = 0.75), peak urine flow (r = −0.71) and detrusor pressure at peak urine flow (r = 0.43, p = 0.001, fig. 6).

Increasing transition zone index was significantly associated with a progressively worsening AUA symptom score, peak urine flow and detrusor pressure at peak urine flow. Table 4 lists the mean AUA symptom score, peak urine flow and detrusor pressure at peak urine flow at different transition zone index levels. Using a transition zone index cutoff point of 0.5 (the index was less in 50% of patients) there was a highly significant difference in AUA symptom score, peak urine flow and detrusor pressure at peak urine flow (p = 0.001) to lower transition zone index cutoff points. A transition zone index of greater than 0.50 did not increase the likelihood of diagnosis in a patient with worse BPH parameters.

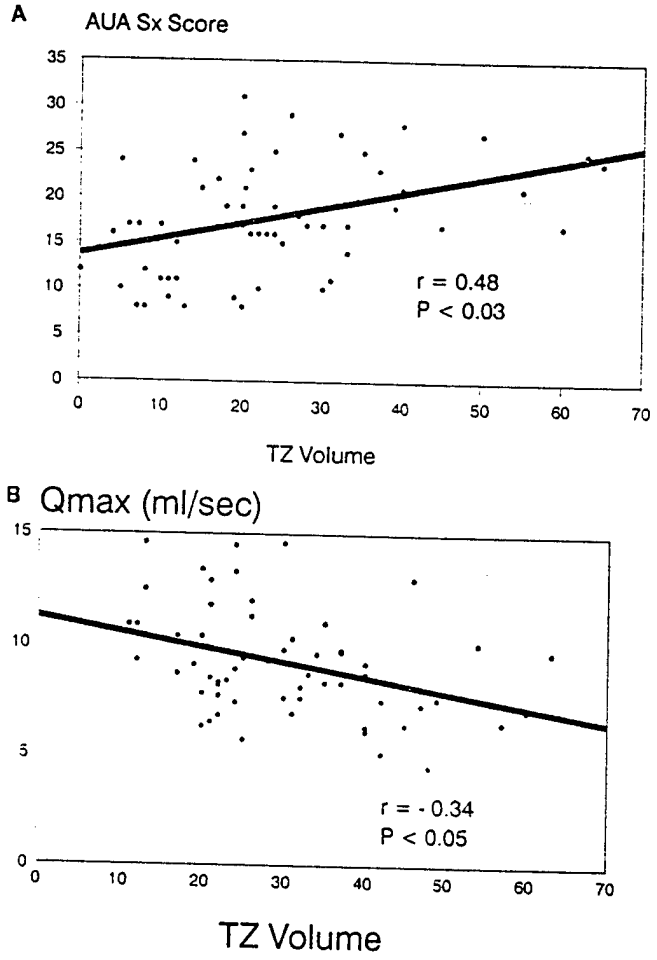

FIG. 5. *A*, scattergram comparing AUA symptom (*Sx*) score to transition zone (*TZ*) volume with correlation (r = 0.48, p <0.03, solid line). *B*, increasing correlation of transition zone volume to peak urine flow (r = −0.35).

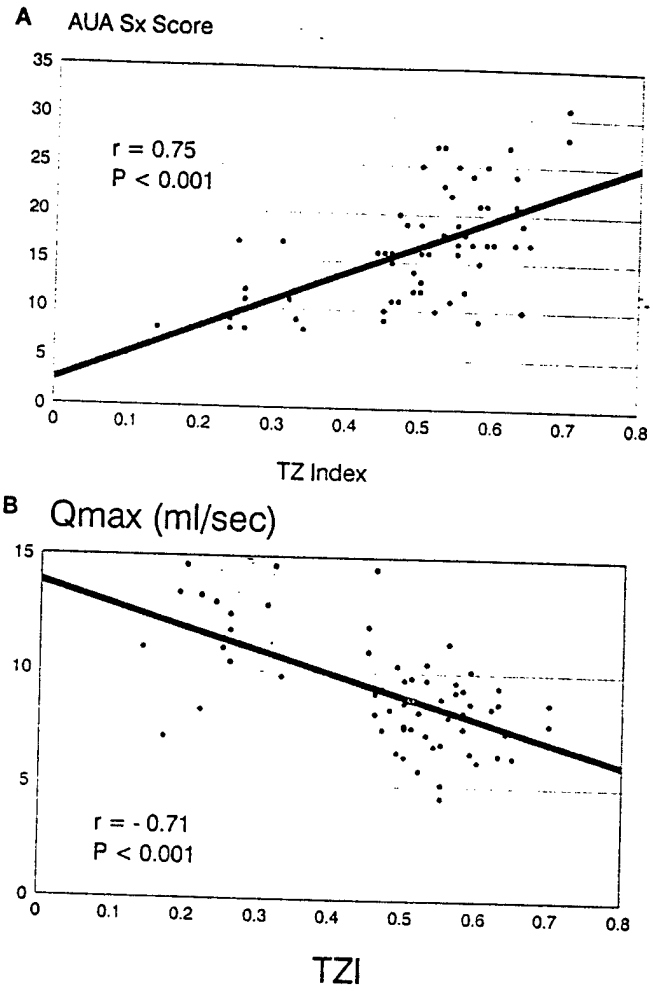

FIG. 6. *A*, scattergram comparing AUA symptom (*Sx*) score to transition zone (*TZ*) index with correlation (r = 0.75, p <0.001, solid line). *B*, strong correlation between transition zone index (*TZI*) and peak urine flow (*Qmax*, r = −0.71).

DISCUSSION

The correlation between various BPH parameters and prostate size has been debated in the literature during the last 2 decades. This debate is due to various methods of assessing prostate size, including digital rectal examination, transabdominal ultrasound and cystoscopy.[3,4,17] In addition, the use of different symptom scores and various urodynamic parameters, including peak flow rate, post-void residual and urethral resistance, have contributed to this lack of consensus. Castro et al[9] and Anderson and Nordling[10] reported that estimated weight at cystoscopy correlated with the magnitude of urodynamic obstruction as manifested by flow rate, opening bladder pressure and minimal urethral resistance. In addition, there was little correlation between symptoms and flow rate. In contrast, Turner-Warwick noted little correlation between digital rectal examination assessment of prostatic size and degree of obstruction.[18] Jensen et al described the potential use of prostatic weight as measured by bladder neck-verumontanum distance.[12] Not surprisingly, they observed a significant correlation to resected weight. In contrast, symptoms and urodynamic findings did not correlate with prostatic size. More importantly, prostatic weight did not predict patients with poor postoperative results. However, these studies were based on the premise that prostate size was determined by measuring the whole gland.

The description of the zonal anatomy of the prostate by McNeal contributed to our understanding that there was a BPH portion, which was predominantly limited to the transition zone.[13] Various sonographers have described features of the transition zone of the prostate.[5,6] Rifkin et al described features of BPH ranging from diffuse echogenic inhomogeneity to clear focal lesions.[19] Lee et al described BPH as diffuse transition zone enlargement.[20] Using these sonographic parameters to delineate the transition zone of the prostate Greene et al noted that patients with BPH had a transition zone volume of 24.81 ± 14.4 ml.^{3} in contrast to a transition zone volume of 6.14 ± 3.2 ml.^{3} in those without

TABLE 4. *BPH parameters according to transition zone index level*

Transition Zone Index Cutoff Point	No. Pts.	Mean AUA Symptom Score	Mean Peak Urine Flow (ml./sec.)	Mean Detrusor Pressure at Peak Urine Flow (cm./water)
0.3	11/50	10.3/16.4	12.7/9.7	48.4/53.6
0.4	14/47	11.7/17.8	11.3/8.9	51.0/57.4
0.5	30/31	13.7/19.6	10.4/8.0	52.4/69.5
0.6	53/8	14.1/19.8	10.0/7.5	57.4/70.4

Values at less than/greater than transition zone index cutoff point.

clinical BPH.[14] This finding compares to the mean transition zone volume of 23.3 ml.[3] in symptomatic men with BPH and age matched men without BPH of 12 ml.[3] in our series. Clearly the phenomenon of transition zone volume and its relation to total prostate volume is more readily apparent in patients with clinical BPH. In the series by Greene et al a statistically significant increase in transition zone volume with increasing age was reported,[14] which is consistent with our findings and those of others who have reported increasing prostate weights with age.[21] However, Greene et al did not delineate the diagnosis of BPH, that is symptoms and urodynamic parameters, and no attempts were made to correlate transition zone volume with these parameters.

The potential impact of volumetrically distinguishing the BPH portion of the prostate was recently reported by Kalish et al.[15] Ultrasonographic volume determination of the whole prostate and transition zone increased the sensitivity of PSA in detecting prostate cancer in the peripheral or nonBPH portion of the prostate. Using this premise we were stimulated to investigate if volumetric separation of the nonBPH portion of the prostate from transition zone volume would improve the correlation with symptoms, urine flow and urodynamics. Is transition zone volume a better proxy for BPH size?

The results of our study demonstrate that AUA symptom score, peak urine flow and detrusor pressure at peak urine flow correlate significantly better with transition zone volume than total prostate volume alone. Intuitively these results are consistent with the hypothesis that the symptoms and urodynamic abnormalities associated with BPH are caused by mechanical or static compression of the prostate. Therefore, progressively increasing mechanical obstruction by the BPH or transition zone portion of the prostate would result in worsening symptoms and more restricted flow rates. However, as noted previously, small prostates with relatively small transition zone volumes may also result in severely symptomatic patients with markedly impaired flow rates and high voiding pressures.

This observation led us to examine the relationship of the BPH portion of the prostate relative to total prostate volume. This ratio, which we have termed the transition zone index, resulted in the strongest and most significant correlation with the BPH parameters of AUA symptom score ($r = 0.75$), peak urine flow ($r = -0.71$) and detrusor pressure at peak urine flow ($r = 0.43$). It is conceivable that each patient may have a critical volume of transition zone relative to the prostate, which results in bladder outlet obstruction. This factor would help to explain why patients with a small prostate and high transition zone index may have more symptoms and significant obstruction than those with a large prostate and lower transition zone index. In our series a transition zone index of greater than 0.5 resulted in significantly higher symptoms, lower flow rates and higher voiding pressures. It is also noteworthy that a transition zone index cutoff point of 0.5 divided this patient group equally.

The potential therapeutic impact of the transition zone index was not examined in this study. It would be a reasonable conclusion that patients with a higher transition zone index would respond better to therapies designed to reduce transition zone volume medically or surgically. For example, Tempany et al reported that androgen deprivation with finasteride resulted in preferential and significant reduction of periurethral tissue versus peripheral zones.[22] Gormley et al reported that the efficacy of finasteride, as determined by AUA symptom score and peak urine flow, was similar in patients with smaller and larger prostates, as measured by transrectal ultrasound or magnetic resonance imaging.[23] However, in that study total prostate volume was measured. It is plausible that reduction in transition zone index or transition zone volume would have been a more accurate predictor of success than total prostate volume. In fact, this concept was recently tested by Tewari et al, who used transition zone volume and the ratio of transition zone volume to total prostate volume as parameters to evaluate the response to finasteride.[16] They reported that responders had a greater reduction in transition zone volume and there was significant correlation among transition zone volume, transition zone ratio and improvement in flow rate. In addition, the pretreatment transition zone ratio was useful in predicting the patients who would respond to finasteride, particularly when it was greater than 0.51. However, there was no correlation of transition zone volume or transition zone ratio to improvement in symptoms.

CONCLUSIONS

Transition zone volume is a more useful, significant proxy of BPH size than total prostate volume. Furthermore, there is compelling evidence that the transition zone index, a new parameter that correlates significantly with evaluated parameters of BPH, may be the best proxy for BPH size and evaluation of worsening obstruction. The potential role of transition zone index in prospectively predicting the patients who will respond best to therapies designed to ablate transition zone tissue medically or surgically remains to be determined.

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British Journal of Urology (1998), 82, 804–807

Is the ratio of transition zone to total prostate volume higher in African-American men than in their Caucasian or Hispanic counterparts?

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Objective To determine if the transition zone index (TZI, the ratio between transition zone volume, TZV, and total prostate volume, as estimated by transrectal ultrasonography, TRUS) differs among African-American (AA), Hispanic and Caucasian men.

Patients and methods The study group consisted of 104 age-matched men (36 AA, 34 Hispanic and 34 Caucasian) with lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH). A control group of 55 age-matched men, equally distributed among the three ethnic groups, but with no BPH (based on a digital rectal examination) were also evaluated. All men completed the International Prostate Symptom Score (IPSS) and a measurement of peak urinary flow rate (Q_{max}), prostate volume and TZV (by TRUS) and the TZI calculated.

Results In the control group, the mean prostate volume was 20.9, 18.2 and 19.8 mL, the TZV 6.9, 4.9, and 5.4 mL and the TZI 0.33, 0.27 and 0.25 for AA, Hispanic and Caucasian men, respectively. The TZI was significantly higher in AA than in either Hispanic or Caucasian men ($P<0.03$). Although there were no differences in prostate volume among the three ethnic groups with BPH, the mean (SD) TZV and TZI were significantly higher in AA men than in either their Hispanic or Caucasian counterparts, at 15.8 (7.6) mL and 0.43, 12.7 (8.1) mL and 0.37, and 13.8 (6.7) mL and 0.37, respectively. For all groups, age correlated with the IPSS ($r=0.22$, $P<0.04$); the mean (SD) IPSS was 14.3 (5.7), 10.2 (2.9) and 10.6 (4.9) for AA, Hispanic and Caucasian men, respectively. There was no correlation between the IPSS and either prostate volume or TZV, but there was a strong correlation with the TZI ($r=0.29$, $P<0.01$), regardless of race.

Conclusions These results suggest that AA men have a greater TZV and a higher TZI than their Caucasian or Hispanic counterparts, regardless of the presence of lower urinary tract symptoms. Studies are underway to determine if these differences are clinically significant and correlate with either subjective and/or objective parameters of BPH.

Keywords Benign prostatic hyperplasia, transition zone volume, transition zone index, race

Introduction

BPH is the most common affliction of men over the age of 50 years [1]; with the advent of approved medications and alternative therapies, more than 3 million men with symptoms of BPH will be treated in 1996. Although LUTS are the most common reason why patients seek treatment, unfortunately, there is poor correlation between subjective indices such as symptoms and objective variables such as urinary flow rates and residual urine. In addition, there is no widely accepted objective index that allows the prediction of either progression of disease or response to therapy. Therefore, the ability to ascertain who needs therapy and to predict who will have progression of disease without therapy is severely hampered.

The transition zone index (TZI), i.e. the ratio between transition zone volume (TZV) (or BPH) and total prostate volume has been described as a reproducible measurable variable of BPH size [2]. The TZI has been reported to correlate significantly with both subjective indices such as symptoms and objective diagnostic variables such as uroflow and bladder function. If reproducible in a large diverse cohort of men, this index may allow the severity and progression of disease to be assessed in both the treated and untreated state.

Thus the aim of the present study was to investigate differences in prostate morphology (by TZV and TZI) in an ethnically diverse sample of men with BPH. The potential effect of this study is to establish the significance of TZI as an objective marker for the severity of BPH in a large group of ethnically diverse men.

Accepted for publication 12 August 1998

Patients and methods

The study was a cross-sectional investigation of differences in prostate morphology and symptoms in an ethnically diverse sample of men with BPH. The sample population consisted of 104 consecutive, age-matched men 50 years or older. Patients were referred for or had sought evaluation and treatment for LUTS. Patients identified as having BPH ('prostatism', 'prostate trouble', difficulty voiding', etc.) were referred for potential entry into the study. These patients then completed the IPSS. Patients then had a blood sample taken for serum PSA measurement and underwent a DRE. Finally, all patients entered into the study had their peak urinary flow rate (Q_{max}) measured (minimum volume 125 mL).

Inclusion criteria were that patients were at least 50 years old, seeking treatment for symptomatic prostatism and an IPSS of >0. The rationale for this is that the TZI of all categorical groups of patients (i.e. mild, moderate and severe symptoms) will provide an important insight into the relationship between 'BPH' size and various levels of symptoms. Excluded were men previously treated for BPH, with a history of prostate or bladder cancer, pelvic irradiation, urethral stricture, or prior surgery for bladder outlet obstruction, and patients with a known primary neurological condition such as multiple sclerosis or spinal cord injury, which may affect bladder function. Patients with either an abnormal DRE and/or an elevated PSA level were similarly excluded. The rationale for these exclusion criteria was to select patients who were most likely have BPH as the aetiology of their voiding symptoms. The control group consisted of 55 age- and racially matched men without BPH (based on TRUS and symptoms).

TRUS of the prostate was performed using a Bruel & Kjaer model 1846 ultrasound instrument equipped with a model 1850 radial probe and a model 8537 longitudinal probe incorporating 7 MHz transducers (B&K Medical Systems, Marlborough, MA, USA). Images were obtained in both transaxial and longitudinal views and the measurements made by one investigator (S.A.K.).

The prostatic volume was calculated using the formula for a prolate ellipsoid (V = width × length × height × 0.52), using the technique reported previously [2]. Briefly, width was measured in the transverse view of the gland and length (prostate base to apex) in the longitudinal view. Prostatic height was measured in the longitudinal axis at a right-angle to gland length, to prevent distortion by refraction, as described by Kalish *et al.* [3]. Maximum diameters were recorded and used for each of these measurements; for the transverse view, this was usually at the mid-portion of the prostate gland and for the longitudinal view, at the midline. The TZV was measured similarly using the prolate ellipsoid calculation [2,3]. The TZI was a continuous variable (range 0–1) and calculated as the TZV/total gland volume.

Student's two-sample *t*-test was used to compare the TZV and TZI with patient's symptoms and Q_{max}; unadjusted *P* values were calculated. Relationships among these characteristics were measured using Pearson's correlation coefficient.

Results

The mean (SD) PSA level in the control group was 2.3 (0.9) ng/mL; the indications for evaluation were erectile dysfunction ($n=35$), haematuria ($n=14$) and flank pain ($n=6$). The age, prostate volume, TZV and TZI for the control group are shown in Table 1. When categorized by ethnic group, the TZI was significantly higher in AA men than in either of the other groups ($P<0.03$); no patient had a TZI of >0.35 (range 0.08–0.32, Table 1).

In the BPH group the mean (SD) PSA level was 2.7 (1.1) ng/mL; the prostate volume, TZV and TZI for the whole group and categorized by ethnic group are shown in Table 1. Although there were no differences in prostate volume in the three ethnic groups, the TZV and TZI were significantly higher in AA men than in either of the other two groups ($P<0.04$ and $P<0.01$, respectively).

For all groups, age correlated with the IPSS ($r=0.22$, $P<0.04$); Q_{max} correlated negatively with both the IPSS and age ($r=-0.24$, $P<0.03$). The mean (SD) IPSS was 14.3 (5.7), 10.2 (2.9) and 10.6 (4.9) for AA, Hispanic and Caucasian men, respectively. There was no correlation between race and Q_{max} ($r=0.12$, $P=0.14$). However, the TZI correlated with the IPSS ($r=0.29$, $P<0.01$), regardless of race.

Discussion

The symptom complex associated with histological evidence of BPH has been commonly referred to as prostatism or LUTS. However, the underlying pathophysiology for this symptom complex is multifactorial and often poorly defined in individual patients. To date, there has been no measurable anatomical variable that correlates well with subjective, e.g. symptoms, or objective variables, e.g. urodynamic evidence of bladder outlet obstruction [4].

Prostate size is known not to correlate with either symptoms or urodynamic evidence of obstruction. However, this may be because part of the prostate not involved with BPH is also measured [5–7]. The overall aim of the present study was to further evaluate volumetric variables, the TZV and TZI. Kaplan *et al.* first described the latter as a variable of BPH size [2]; the TZI

Table 1 Baseline characteristics, prostate volume, transition zone volume and TZI in various ethnic groups with and without BPH

	Number of patients	*Mean (SD) Age*	*Volume (mL) Prostate*	*TZ*	*TZ index*	Q_{max} *(mL/s)*
Baseline						
Control (no BPH)	55	62.6 (4.1)	19.6 (7.8)	5.9 (2.8)	0.28	14.6 (3.7)
With BPH	104	61.5 (5.8)	36.8 (7.9)	18.9 (7.9)	0.41	10.4 (4.7)
Control						
African-American	18	64.4 (5.6)	20.9 (8.4)	6.9 (2.2)	0.33*	
Hispanic	20	61.9 (3.8)	18.2 (7.2)	4.9 (3.5)	0.27	
Caucasian	17	62.7 (4.1)	19.8 (8.1)	5.4 (1.9)	0.25	
With BPH						
African-American	36	62.9 (7.6)	36.8 (12.9)	15.8 (7.6)	0.43*	
Hispanic	34	61.4 (6.2)	34.2 (8.3)	12.7 (8.1)	0.37	
Caucasian	34	59.8 (5.2)	37.2 (10.1)	13.8 (6.7)	0.37	

*$P < 0.03$, AA versus either Hispanic or Caucasian.

was found to be highly correlated with both symptoms and objective diagnostic variables, e.g. uroflow and bladder function. In the present pilot study, the TZI correlated with symptoms regardless of prostate size, TZV or race. Therefore, the TZI may provide a useful baseline index of disease severity, regardless of prostate volume. Moreover, if these data were reproduced in a larger sample, TZI could be used to predict progression of disease and/or response to medical therapy for BPH.

Racial differences in the severity of BPH may have two plausible explanations. First, there may be differences in the use of healthcare for BPH by different racial groups, either secondary to variable accessibility or because of differences in perceived bother of symptoms. Second, there may be a clear pathophysiological explanation for the increased incidence of symptomatic BPH in various ethnic groups based on prostate morphology. The data presented here, albeit in a small population sample, suggests that there may be ethnic diversity in BPH size compared with total prostate volume. The TZI was larger in AA men, both in the control and BPH group. This finding represents possible early evidence of physiological differences between the BPH of racially diverse groups, i.e. AA men may have more prominent growth of their transition zone relative to their total prostate; notably, in this group the patients were more symptomatic.

Perhaps a better indicator or proxy of disease, i.e. the TZI, may help illuminate the perplexing finding that AA men who seek treatment seem to have more severe disease. An examination of the relationship between disease status based on prostate morphology (based on TZV, TZI and prostate volume) and symptom levels may at least answer the question of whether AA men delay treatment because of better symptom tolerance. Is there different progression of disease among different ethnic groups with the same level of disease at baseline? It would therefore be advantageous to examine these issues of racial differences in BPH with symptomatic, objective and morphological variables, particularly in a large cohort of ethnically diverse men with good racial sample subpopulations.

In summary, the underlying pathophysiology of BPH and LUTS is complex, multifactorial and more importantly, poorly defined in individual patients and in large ethnically diverse populations of patients. To date, there are no single unifying measurable symptomatic, objective and morphological variables that correlate well with other measures of BPH such as symptom scores, urinary flow rates and urodynamic evidence of bladder outlet obstruction.

The TZI has the potential to be functionally relevant and important to the urologist and patients in the management of LUTS. The data presented here suggest that the TZI may be a better predictor of prostate disease than other previously reported variables. More importantly, there may be some inherent differences of these factors in various ethnic groups. Obviously, further study in much larger groups of patients will determine if the TZI is a useful variable for assessing LUTS and whether there are inherent differences in prostate morphology, as manifested by volume, among different ethnic groups.

References

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Appendices 3

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Commander
U.S. Army Medical Research and Material Command
Building 524 (PCRP-MPFTA)
Fort Detrick, MD 21702-0524

November 12, 1998

Dear Commander,

Thank you for the good news about your selection for funding of my DOD PCRP MPFTA entitled " Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men". As stated in your letter, I have enclosed appendix 4-7 as per your RCQ instruction. Please note Appendix 6 was not included because no animal research is to be performed. Therefore, the 5 copies of the following are enclosed:

Appendix 4	Certificate of Environmental Compliance
Appendix 5	DOD/ USA MRMC Clinical Research Protocol
	IRB Protocol, Lay Summary and Consent
Appendix 6	Not Applicable
Appendix 7	Safety Program Plan
	Affirmation of Safety Statement

If you have any questions, please feel free to call.

Sincerely,

Alexis E. Te, MD

APPENDIX 4

Certificate of Environmental Compliance

The offeror currently ✓ IS ___ IS NOT (check appropriate category) in compliance with applicable national, state, and local environmental laws and regulations. (If not in compliance, attach details and evidence of approved mitigation measures.)

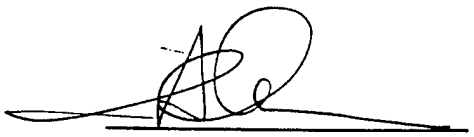
The offeror has examined the activities encompassed within the proposed action entitled "Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men P.I. ALEXIS E. TEJ"
(enter title and/or Solicitation number, and Principal Investigator's name), for compliance with environmental laws and regulations. The offeror states that the conduct of the proposed action:

1. WILL NOT violate any applicable national, state, or local environmental law or regulation, and

2. WILL NOT have a significant impact on the environment.

The offeror agrees that if the work required under the proposed action at any time results in a significant impact on the environment or a violation of any applicable environmental law or regulation, the offeror will immediately take appropriate action, to include notifying and/or coordinating with the appropriate regulatory agencies as required by law and notifying the Contracting Officer.

EA Christman
Name of Official Responsible for Environmental Compliance


Signature

Director EH&S
Title

11/12/98
Date

Columbia Univ. HSD
Name of Organization

Appendix 5

DOD/USAMRMC Research Protocol

1. Project Title:
Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men

2. Phase:
N/A

3. Principal Investigator:
Alexis E. Te, MD

4. Location of Study:
Department of Urology, Columbia University, College of Physician and Surgeons
161 Fort Washington Ave, 11th Floor
New York, NY 10032

5. Start and Finish Date:
10/01/98-10/30/00

6. Objectives:

Specific Aims and Hypothesis

The Benign Prostatic Hyperplasia (BPH) size is reflected by transition zone volume. Differences in BPH symptomatology, prostate cancer detection strategies and PSA level between black, white and possibly Asian males reflect ethnic differences in prostate morphology by transition zone volume. We postulate that differences in histologic evidence and/or volume of BPH is the cause of ethnic difference in PSA levels and not to inherent biological susceptibility of prostate cancer for black males versus white males versus Asian males. Therefore, we propose that:

1) *Differences in BPH symptomatology, PSA and PSAD among African American versus white versus asian males reflect variations in transition zone volume. Black males have more "BPH" volume manifesting in higher PSA values and possibly worse BPH symptoms. Utilization of current modifications of PSA, i.e. PSAD may, therefore, not be the most accurate marker for patients at increased risk for prostate cancer. Utilization of PSAT will correct for any measured differences in either PSA or PSAD among ethnically diverse men and will also explained possible ethnic variance in BPH symptoms. Consequently, we hypothesize that PSAT for black, white and Asian males should be the same.*
2) *PSAT cutoffs for detecting prostate cancer should be similar among black and white males. Unlike PSAD, which may require different values for blacks and whites, PSAT, which corrects for PSA differences secondary to BPH as reflected by TZ volume, should be the same.*
3) *PSAT will be a better predictor of prostate cancer than currently available PSA screening modalities. These include PSA, PSA age specific reference ranges or PSAD. Sensitivity as manifested by detection of prostate cancer and specificity as manifested by elimination of negative biopsies would be enhanced compared.*

Technical Objectives

Three specific aims are proposed

Specific Aim #1: Serum PSA and transrectal ultrasound measurements of the prostate will be done in a cohort of black, white and Asian men over the age of 40. Baseline levels of TZ and TZI and their correlation with both subjective (symptoms and bothersome scores) and objective (urinary flow rate and post void residual urine volume) indices of BPH will be identified. Volumetric determination of both the entire prostate and transition zone volume of the prostate will be done and both PSAD and PSAT calculated. The objective is to determine whether ethnic variation in prostate morphology as measured by Transition Zone Volume, Transition Zone index, PSAD and PSAT exist and its relationship to BPH.

Specific Aim #2: To determine if PSAT cutoffs are different among Black, White and Asian men. Our hypothesis is that any ethnic variability in either PSA or PSAD should be corrected by measurement of PSAT. Patients with positive biopsies for prostate cancer will be evaluated to determine whether there are differences in PSAT threshold for biopsies among black, white and asian males.

Specific Aim #3: To assess whether PSAT is a better refinement of currently available prostate cancer detection strategies. PSA, age specific PSA reference ranges, PSAD and PSAT will be assessed to determine which produces greatest sensitivity and specificity and whether any ethnic variation exists among PSAT as a cancer detection strategy.

7. Study Population:

All men over the age of 40 years desiring routine prostate evaluations including Whites, African Americans, Hispanic Americans and Asians Americans during course of routine clinical evaluations/ screening for prostate diseases.

Inclusion criteria:

1) Patients at least 40 years of age seeking treatment of symptomatic prostatism. The rationale for this is that this is a current clinically accepted criterias for routine evaluations of men to evaluate/ screen men for BPH and prostate cancer that includes the lower screening criterias for African American men.
2) Patients with any AUA Symptom Score. The rationale for this is that TZI of all categorical groups of patients (i.e., mild, moderate, and severe symptoms) will lend important insight into the relationship between "BPH' size, various levels of symptoms and PSA levels.
3) The patient has the mental capacity of understanding and signing informed consent, and able and willing to participate.

Exclusion criteria:

1) Patients previously treated for BPH, Prostatitis and Prostate cancer due to therapies potentially affecting prostate size..
2) Patients with a history of prostate or bladder cancer, pelvic irradiation, urethral stricture, or prior surgery for bladder or prostate disorders.
3) Patients with a known primary neurologic condition such as multiple sclerosis or spinal cord injury, which may affect bladder function.
4) Patients with an active urinary tract disease (e.g., acute prostatitis, complicated urinary tract infection, bladder stones) or has undergone cystoscopy or biopsy of the prostate within 2 weeks prior to first screening.
5) Patients with an imminent need for surgery will also be excluded (e.g., refractory gross hematuria or urinary retention).

The rationale is to exclude patients that may have any pathophysiology that would affects prostate size in acutely or in a chemical or surgical manner.

8. Protocol Design:

Method of investigation:

This study is a cross-sectional investigation of differences in prostate morphology as defined by serum PSA and prostate volume an ethnically diverse sample of men. The sample population consists of men aged 40 and above referred for or self-seeking evaluation of their prostate, elevated serum PSA or abnormal findings on digital rectal examination. Subjects will be recruited from the regional patient populations around the medical center, through its clinic system and physician referral system. An ideal total of approximately 600 men for the study of White, Black American and Asian males continuously over the first 24 months of the study period and allow the last 6 months for statistical evaluation. This is a realistic enrollment rate since this study involves no treatment intervention and is relatively non-invasive. This number ensures that power will be at least 80% (based on two-tailed .05 level tests) to detect clinically important differences between different PSAT measurements of Black Americans, Whites and Asians. Clinically important differences are assumed to be those that are at least 25% of that measures standard deviation.

Recruitment Procedures

Patients identified as potential subjects by the research assistant will be flagged and brought to the attention of the treating physician. The initial physician recruitment process consists of a history and physical examination, digital rectal examination and a brief explanation of the goals and procedures involved with the study. Prostate examination description will be standardized across all sites and recorded onto a data collection form. Following the physician visit, eligible patients who agree to participate in the study will be referred back to the research assistant on site. At this time, the research assistant will complete the informed consent process and begin recording data onto the data collection form. Subjects will not be paid. Incentives to participate include complete prostate screening evaluation with uroflowmetry, bladder scan for PVR, TRUS (and biopsy where applicable) and serum PSA measurement, cholesterol level and testosterone level. Following informed consent, the research assistant will collect baseline sociodemographic information, serum PSA, cholesterol, testosterone, uroflowmetry, bladder scan for PVR and will schedule prostatic ultrasonography.

Inclusion and Exclusion Criteria

Inclusion criteria:

1) Males 40 years or older.
2) The patient has the mental capacity of understanding and signing informed consent, and able and willing to participate.

Exclusion criteria:

1) Patients previously treated or diagnosed with prostate cancer.
2) Patients treated for BPH with either finasteride or hormonal agents, i.e. LH – RH analogues, i.e. agents which reduce prostate size and affect serum PSA levels.
3) Patients with previous prostate surgery, including minimally invasive therapeutic alternatives such as thermotherapy.

Data Collection, Storage and Management

All data will be recorded onto standardized data forms. Patient confidentiality will be maintained by storing data in a locked cabinet. The data will be cleaned and managed by a data editor. The data editors' responsibilities will also include data entry and daily data backup. All data will be stored in SPSS (version 7.0).

All data will be transferred or entered daily into a Microsoft Access Database. Data will be stored and mirrored on data secured hard drives on the network. One duplicate backup set of disks will be stored at the Incontinence Care Center in the files of the Principal Investigator. All diskettes will be kept in locked fireproof drawers. Data updates

will be printed on a daily basis, and backups involving the central server and diskettes performed on a weekly basis. A codebook will be available for each patient. Data analysis will be performed using SPSS version 7.0. Confidentiality of all research records, data files and subject identifiers will be kept by using locked cabinets and data secured passwords on the network with restricted access.

Sociodemographic Variables

Baseline data will include self-identified race/ethnicity, age at last birthday, years of education and highest degree attained, current or last occupation, income (categorical), address and phone number, and medical insurance carrier. Recruitment location, name of recruiting physician and research assistant, date and time of recruitment and date/time of first interview will also be recorded.

Laboratory Data

All subjects will have a serum BUN, creatinine, cholesterol, testosterone and PSA drawn prior to ultrasonography. Urine studies consist of a urine analysis and urine culture and sensitivities. The purpose of these laboratory studies is to screen for obstructive uropathy, microscopic hematuria, and urinary tract infection. Patients with abnormalities will be evaluated further as necessary. If no significant pathology is detected, these patients remain eligible for the study. Patients with uncomplicated urinary tract infections (UTI) are eligible for study following treatment with appropriate oral antibiotics. Patients with complicated UTI's (i.e., febrile infections, UTI associated with urolithiasis, or pyelonephritis), will be excluded from the study and treated appropriately.

Uroflowmetry

Subjects will be instructed to maintain a full bladder just prior to uroflowmetry. A Dantec 1000 uroflowmeter will be used to measure peak flow rate (Q_{max}), average flow (Q_{avg}), time to peak flow (t_{max}) and voided volume (vol). A minimal voided volume of 150 ml and at least a 2 second interval for peak flow will be required. Uroflowmetry will be performed on-site.

Post Void Residual Volume Determination (PVR)

Immediately following uroflowmetry, PVR volume will be determined non-invasively by the research technician. using the Bard Bladder ScanTM **(model # 2500)** (Bard Pateint Care Division, Murray Hill, NJ). PVR will be performed on-site.

Prostatic Ultrasonography and Transition Zone Voluming

Transrectal ultrasound of the prostate (TRUS) will be performed immediately following uroflowmetry and PVR determination using a portable ultrasound instrument equipped with a longitudinal probe incorporating 7 MHz transducers (To be determined). Imaging will be done in both transaxial and longitudinal views. An experienced examiner, the P.I., Alexis E. Te, MD, who has a large clinical and published experience with transrectal prostate imaging and measurement, will do measurements. Prostatic volume will be calculated using the formula for a prolate ellipsoid (V = width x length x height x 0.52). Width will be measured in the transverse view of the gland and length will be measured in the longitudinal view. Prostatic height will be measured in the longitudinal axis at a right angle to gland length. Maximum diameters will be recorded and used for each of these measurements. Transition zone (TZ) voluming will be similarly performed by prolate ellipsoid calculation. In addition to its reproducibility by a single investigator, there is significant inter-investigator reproducibility in both prostate volume and transition zone volume will be measured in cubic centimeters.

Prostate biopsy

To date there are various "PSA" criteria for biopsy. As alluded to above, most studies have demonstrated that Black Americans and Whites have different cutoff points. For the purpose of this study the indications for biopsy will be 1) suspicious digital rectal examination 2) abnormal PSA based on age –adjusted. Based on the work of Morgan et al., traditional age – adjusted reference ranges (95% specificity) were found to work well when applied to white men aged 40 years and older. (24) Yet the first set of age – adjusted reference ranges that group derived for Black Americans was determined to have a poor sensitivity: 41% of prostate cancers in this group would have been missed. Therefore, the following ranges will be utilized.

Age (years)	White	Black American
40 – 49	0 – 2.5	0 – 2.0
50 – 59	0 – 3.5	0 – 4.0
60 – 69	0 – 5.5	0 – 4.5
70 – 79	0 – 6.5	0 – 5.5

Cutoffs for Asian Americans will be similar to Black American since they are unknown. In glands 50 cc or smaller, 6 systematic biopsies (apex, mid and base biopsies done equidistant). To minimize sampling error, 12 systematic biopsies (6 conventional and 6 anteriorly directed) will be performed in prostates > 50cc. In addition, lesion directed biopsies at either abnormalities on digital rectal examination or transrectal ultrasound will be performed.

Statistical Analysis Overview

Graphical and numerical summaries will be used to describe the association between prostate morphology and both subjective and objective indices of disease. TZ and TZI will provide continuous measures of prostate morphology. The AUA symptom score(AUA), SPI, and BII will be used as subjective measures of disease indices, while measures of flow (Qmax, Qavg, tmax) and PVR will be used as objective measures. Scatterplots of TZ and TZI with each measure of disease (both subjective and objective) provides a graphical description of the relationship between prostate morphology and disease severity. For relationships that are approximately linear, Pearson's correlation coefficient will be used as a numerical summary. If the relationships are clearly nonlinear, we will attempt to transform one or both variables to linearize the relationship and compute Pearson's correlation between the transformed variables and compute Spearman's correlation coefficient (the correlation based on the ranked values of each variable) will be computed. Interval estimates of each correlation be given as approximate 95% confidence intervals.

TZI will be further assessed as a dichotomous variable (>=0.50 versus <0.50). The cutpoint of 0.50 was observed in a previous study to effectively discriminate subjects with severe symptoms. The mean difference between these "low" and "high" TZI groups with respect to each index will be estimated by approximate 95% confidence intervals.

Racial variation in baseline indices of disease, TZ, and the continuous measure of TZI will be assessed based on analysis of variance models, with ethnic group as the independent variable. Approximate 95% confidence intervals (based on Tukey's method of maintaining an overall 5% error rate for each measure assessed) will be used to quantify the description of racial variation for these measures. Logistic regression analysis will be used to estimate racial differences for the dichotomous version of TZI. This model will include two indicator (dummy) variables for the three ethnic groups as independent variables.

Differences between the associations of the disease will indices and the continuous measures of prostate morphology (TZ and TZI) will be based on a series ordinary least squares regression models. These models will have either TZ or TZI as the dependent variable, with a single disease index, indicator variables for race, and index by indicator interactions as independent variables. Corresponding logistic regression models will be used to when TZI is dichotomized. The interaction terms in these models are informative about racial differences in the associations. Similarly, logistic regression models will be used to determine the extent to which the prognostic strength of TZI differs by race.

Data will be finally be also analyzed for 3 groups: 1) the entire group, 2) those with normal digital rectal examination and 3) those with a normal DRE and a PSA of between 4 and 10 ng/mL. Mean and median PSA, PSAD and **PSAT** will be compared between both positive and negative biopsy groups and between Black Americans and whites with the Mann – Whitney U test. Sensitivity, specificity, positive predictive value and negative predictive value with 95% confidence intervals will be calculated for PSA, PSAD and **PSAT** for cancer detection. Receiver operating characteristic curves will be calculated to illustrate the sensitivity and specificity of PSA, PSAD and **PSAT.** Analysis of the different areas of the curve will be calculated with the McNemar test. Finally, **PSAT cutoffs** for biopsy will be evaluated to determine optimal sensitivity and specificity for cancer detection in all patients.

9. Risk/ Benefit Assessment:

Risk entailed in this study are no greater than that in standard clinical evaluation specifically involving criteria's for evaluation and the diagnostic procedure itself specifically those of blood drawing, transrectal ultrasound and prostate biopsy. The benefits are detection of prostate diseases and its early treatment.

10. Reporting of Serious and Unexpected Adverse Events:

Serious and unexpected adverse experiences will be immediately reported by telephone to the USAMRMC Deputy Chief of Staff for Regulatory Compliance and Quality as described in HSPD Clause 0001.02 as well as the Institutional Review Board.

11. Description of Drugs or Devices:

No experimental drugs or devices are utilized in this study

12. Disposition of Data:

All data will be stored under lock and key until 6 months after completion of study analysis.

13. Modification of Protocol:

Modifications will be reviewed and approved by both the PI and institutional review board. Additionally, All DOD/ USAMRMC requirements will be in compliance.

14.Role and Responsibility of Study Personnel:

Research Nurse- Aleta Ashley, RN- Assist in the clinical portion of the protocol and data collection management
Principle Investigator- Alexis E. Te, MD- Supervise, collect data and perform diagnostic procedures

15. Signature and Attestation of PI:

I have read the foregoing protocol and agree to conduct the study as outlined herein.

Alexis E. Te, MD

OMB No. 9999-0020
Approved for use through 7/31/94

Protection of Human Subjects
Assurance Identification/Certification/Declaration
(Common Federal Rule)

POLICY: Research activities involving human subjects may not be conducted or supported by the Departments and Agencies adopting the Common Rule (56FR28003, June 18, 1991) unless the activities are exempt from or approved in accordance with the common rule. See Section 101(b) the common rule for exemptions. Institutions submitting applications or proposals for support must submit certification of appropriate Institutional Review Board (IRB) review and approval to the Department or Agency in accordance with the common rule.

Institutions with an assurance of compliance that covers the research to be conducted on file with the Department, Agency, or the Department of Health and Human Services (HHS) should submit certification of IRB review and approval with each application or proposal unless otherwise advised by the Department or Agency. Institutions which do not have such an assurance must submit an assurance and certification of IRB review and approval within 30 days of a written request from the Department or Agency.

1. Request Type	2. Type of Mechanism	3. Application or Proposal Identification No. *(if known)*
[X] ORIGINAL	[XX] GRANT [ ] CONTRACT [ ] FELLOWSHIP	Department of Defense
[ ] FOLLOWUP	[ ] COOPERATIVE AGREEMENT	
[ ] EXEMPTION	[ ] OTHER: _____	

4. Title of Application or Activity	5. Name of Principal Investigator, Program Director, Fellow, or Other
PROSTATE SPECIFIC ANTIGEN DENSITY OF THE TRANSITION ZONE IN ETHNICALLY DIVERSE MEN	Alexis E. Te, M.D.

6. Assurance Status of this Project *(Respond to one of the following)*

[XX] This Assurance, on file with the Department of Health and Human Services, covers this activity:

Assurance identification no. M- 1356 IRB identification no. 01

[ ] This Assurance, on file with *(agency/dept.)* _____, covers this activity.

Assurance identification no. _____ IRB identification no. _____ *(if applicable)*

[ ] No assurance has been filed for this project. This institution declares that it will provide an Assurance and Certification of IRB review and approval upon request.

[ ] *Exemption Status:* Human subjects are involved, but this activity qualifies for exemption under Section 101 (b), paragraph _____.

7. Certification of IRB Review *(Respond to one of the following IF you have an Assurance on file)*

[X] This activity has been reviewed and approved by the IRB in accordance with the common rule and any other governing regulations or subparts on

(date) pending by: [ ] Full IRB Review or [ ] Expedited Review.

[ ] This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by the common rule will be reviewed and approved before they are initiated and that appropriate further certification will be submitted.

8. Comments

The CPMC IRB is currently reviewing this study.

9. The official signing below certifies that the information provided above is correct and that, as required, future reviews will be performed and certification will be provided.	10. Name and Address of Institution
	Columbia University, Health Sciences 630 West 168th St. New York, New York 10032

11. Phone No. *(with area code)*	12. Fax No. *(with area code)*
(212) 305-5883	(212) 305-1316

13. Name of Official	14. Title
Donald S. Kornfeld, M.D.	Chairman, CPMC IRB

15. Signature	16. Date
Donald S. Kornfeld	11/12/98

Authorized for local reproduction

OPTIONAL FORM 310 (9-92)
Sponsored by HHS/PHS/NIH

Columbia Presbyterian Medical Center

LAY SUMMARY

Title: PROSTATE SPECIFIC ANTIGEN (PSA) DENSITY OF THE TRANSITION ZONE IN ETHNICALLY DIVERSE MEN

Principle Investigator: Alexis E. Te, MD **Department of Urology**

Study Purpose

Prostate Cancer is a leading cause of death in men and Benign Prostatic Hyperplasia (BPH) is the most common affliction in men over 40 years old and BPH size is reflected by transition zone volume. PSA is currently utilized to evaluate prostate cancer. Patients often seeking treatment due to frequency and urgency of urination and nighttime voiding as well as those over the age of 40 can undergo prostate evaluations consisting of a thorough examination that includes a measurement of PSA level. Studies concerning these evaluations and normal values for PSA have been in largely single ethnic population of white men. The purpose of this research is to determine whether there are ethnic difference in prostate size especially of the transition zone (the portion of the prostate that directly surrounds the urethra) and its relationship to PSA levels. This study will investigate differences in prostate morphology in an ethnically diverse sample of men with BPH and evaluate if there is a better way to use PSA to screen for prostate cancer.

Design of the Study

The study is a cross-sectional investigation of differences in prostate morphology and PSA in an ethnically diverse sample of men. The study will include men over 4O years old. The initial evaluation will include a history and complete physical examination, including a digital rectal exam. Patients will be invited to participate and a review of the informed consent with physician. Patients will then be invited back on another date to begin recording data such as sociodemographics, blood and urine collection for analysis, a uroflowmetry (special device that patient is asked to urinate into which records flow rate and volume), prostate ultrasound to record the measurements of the prostate size. Each will be asked to complete an AUA Symptoms Score and BPH Impact Index questionnaire to assess severity of their symptoms and effect on their quality of life. The data and diagnostic procedures are all considered clinical acceptable methods of evaluation of men for prostate disorders.

Population

The plan is to accrue approximately 600 men over a 24 month period. The sample of men are age 40 and above, and referred for, or self-seeking for evaluation of their prostate for BPH or Prostate Cancer.

Recruitment Method

Subjects will be recruited from the Columbia-Presbyterian Prostate Center (4 Attendings) and the CPMC Squier Urological Clinic of the Allen Pavilion (3 Attendings). Patients will be referred from these sources and invited to participate.

Study Procedures

The patients data will be recorded over two visits. On visit 1, the patient is evaluated for his prostate condition and symptoms. He will asked to complete the AUA Symptom Score, Symptom Impact Index, along with collection of urine for analysis and culture to rule out active urinary tract infection. A history and complete physical examination including a digital rectal exam will be performed. If the patient agrees to continue in the study he will have blood drawn (approx. 15m/L) for chemistries and prostate specific antigen (PSA). He will be schedule for Visit 2 in which he will be asked to perform a uroflow, a bladder ultrasound for measurement of residual urine and a transrectal ultrasound in order to measure the size of the prostate. The ultrasound is a small tube that is inserted into the rectum and takes pictures of the prostate.

Columbia-Presbyterian Medical Center

Protocol

Title: PROSTATE SPECIFIC ANTIGEN (PSA) DENSITY OF THE TRANSITION ZONE IN ETHNICALLY DIVERSE MEN

Principle Investigator: Alexis E. Te, MD **Department of Urology**

Purpose

The primary goals of the study are:

1) To identify baseline levels of the transition zone and their correlation with both subjective (based on AUA symptom scores, BPH problem and impact index) and objective (based on urinary flow and post void residual urine volume) indices of BPH.

2) To evaluate racial differences in prostate morphology as measured by ultrasound measurements of various portions of the prostate.

3) To evaluate racial differences in subjective and objective indices of BPH, transition zone volume, total prostate volume, transition zone index (transition zone volume/ total prostate volume) and PSA.

4) To evaluate racial differences in PSA density of the transition zone (PSAT) and whether it is a useful screening tool for detecting prostate cancer in a population of ethnically diverse men.

Description of Study Design

The study is a cross-sectional investigation of differences in prostate morphology and PSA in an ethnically diverse sample of men. The sample population consists of men age 40 and above referred for, or self-seeking evaluation for their prostate. Subjects will be recruited from Columbia-Presbyterian Prostate Center, the CPMC Squier Urological Clinic at Allen Pavilion, the Harlem Hospital Center and Urology Clinic.

Subjects will be required to make 2 visits to one of the locations. At Visits 1, the patient is required to undergo a history and complete physical examination including a digital rectal exam

of their prostate. An ultrasound of their prostate to measure the dimensions. Blood (approximately 30 m/L) will be drawn and urine specimen collected for analysis and culture. Subjects will be asked to complete an AUA Symptoms score and BPH Index questionnaires.

At Visit 2, the subjects will be asked to urinate into a special device that records the rate of the urine flow and calculates the volume. A bladder ultrasound is performed to measure any residual urine in the bladder after urination.

Study Questionnaires

The copies of AUA, BPH Problem and Impact Index questionnaires are attached.

Inclusion/Exclusion

Inclusion

1) Men at least 40 years of age seeking evaluation of their prostate.
2) Subjects with any AUA Symptom Score
3) The patients be capable of understanding and signing the informed consent.

Confidentiality

All records and data collected during the course of the study will only be available to the study personnel. Patients will be assigned a number and records will be stored in a locked area and not accessible to other staff members.

Location of the study

The study takes place in the offices at the Prostate Center in Atchley Pavilion, 11th floor despite recruitment from other center locations.

Risks/Benefits

This is not a therapeutic trial and therefore no risk is anticipated. Patients may have transient discomfort from their transrectal ultrasound although this is self-limiting.

Compensation and Cost to Subjects

There is no compensation provided to subjects who participate. There will be no extra charge for office visits, procedures or tests related to the study.

Minors and Research Subjects

Minors are not included in this study.

Columbia Presbyterian Medical Center

Consent to Participate in a Research Study

The purpose of this consent is to provide you with the information you need to consider in deciding whether to participate in this research study.

TITLE: PROSTATE SPECIFIC ANTIGEN (PSA) DENSITY OF THE TRANSITION ZONE IN ETHNICALLY DIVERSE MEN

Purpose

You have been invited to participate in a research study which is designed to see if the shape and size of the prostate, and PSA blood level are different in man of various ethnicity's

You were selected as a possible candidate in the study because you are a man over the age of 40 seeking an evaluation of your prostate. There will be approximately 600 men 40 years and older enrolled in this study. This is a cross-sectional investigation of the differences in prostates and its relationship to prostate diseases in a various racially different men.

Procedures

If you decide to participate in this study and sign the informed consent, the information recorded in your prostate evaluation will be utilized to examine these possible differences. You may be asked in the future to provided us with additional information. At visit 1, you will be asked to complete questionnaires concerning your urinating symptoms and their effect on your life. A urine specimen will be obtained for analysis and culture to determine whether you may be suffering from a urinary tract infection. The physician will take a full medical history and perform a physical examination including a digital rectal examination of your prostate. Blood will be taken (approx. two teaspoons).

At Visit 2, you will be asked to urinate into a special device that measures the flow of the urine and the volume voided. A bladder ultrasound will be performed to estimate the amount of urine left in the bladder after voiding. A transrectal ultrasound (small tube placed into the rectum) will takes pictures of your prostate and allows for accurate measuring of the prostate. Each of these visits will take about 1 hour.

Study Risks

There is a risk that you may develop a bruise from the blood drawing. This usually resolves in a few days. There is slight discomfort associated with the transrectal ultrasound.

Study Benefits

You may or may not benefit personally from this study. Benefits to you may include comprehensive examination of your prostate health.

Cost and Compensation

All the visits, blood work, ultrasound, urine testing are performed as part of your complete prostate evaluation and there is no additional cost for your participation in the study.

Confidentiality

Any information obtained during the study and identified with you and will remain confidential.

Study participation and confidentiality

Your participation in this study is voluntary. If you wish, you may decline to participate by simply telling your doctor. You will still complete the routine prostate evaluation that you seek and any necessary treatment that you may require for your urinary condition. Your decision will not in any way affect your future medical care and treatment. If you decide to participate in this study, and then later decide that you do not wish to continue, you may, at that time, withdraw from this study. Again, your decision will not in any way affect your future medical care and treatment.

Your records will be handled as confidentially as possible. Only Clinical Research personnel will maintain information from your medical records in a locked filing system accessible, This information may include information relative to your medical condition prior to evaluation of the device as well as implant and follow up examinations and procedures Your name will be not be used. Certain data from this study may also be used in medical and scientific publication, but your name will not be disclosed.

Dr. Te will answer all your questions. If you have questions in the future, you may call Dr. Te, Principal Investigator at (212) 305-0136 24 hours a day. He will be available during the study to answer questions related to the study and your rights as a participant. A physician, nurse or technician involved with this study may also be available at (212) 305-0146.

CONSENT TO PARTICIPATE IN THE STUDY

I have discussed this study with my physician to my satisfaction. I understand that my participation is voluntary and that can withdraw from the study at any time without prejudice. I have read the above and agree to enter this research study. Signing this does not waive any of my legal rights.

I have been informed that if I believe that I have sustained injury as a result of participating in a research study, I may contact the Principal Investigator, Dr Te, at (212) 305-0136, or the Institutional Review Board, at (212) 305-5883, so that I can review the matter and identify the medical resources which may be available to me.

I understand that:

a) The Presbyterian Hospital will furnish that emergency medical care determined to be necessary by the medical staff of this hospital.

b) I will be responsible for the cost of such care, either personally or through my medical insurance or other form of medical coverage.

c) No monetary compensation for wages lost as a result of injury will be paid to me by ColumbiaPresbyterian Medical Center, and;

d) I will receive a copy of this consent form.

Signature:_____Date:
Participants

Signature: _____Date:
Physician

The solicitation of subjects into this study has been approved by the Columbia-Presbyterian Medical Center Institutional Review Board.

Alexis E. Te, MD

(212) 305-0136

AUA Symptom Score

NAME:_____

Date:_____

AUA Symptom Score	Not at all	less than 1 time in 5	less than half the time	about half the time	more than half the time	almost always
1) Over the past month or so, how often have you had as sensation of not emptying your bladder completely after urinating?	0	1	2	3	4	5
2) Over the past month or so, how often have you had the urge to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
3) Over the past month or so, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4) Over the past month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5) Over the past month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
6) Over the past month or so, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
7) Over the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5 or more times

AUA Symptom Score = sum of questions 1-7

TOTAL SCORE: _____

Alexis E. Te, MD

(212) 305-0136

Symptom Problem Index and BPH Impact Index

NAME:_____

Date:_____

Symptom Problem Index	No Problem	Very Small Problem	Small Problem	Medium Problem	Big Problem
1. Over the past month, how much has a sensation of not emptying your bladder been a problem for you?	0	1	2	3	4
2. Over the past month, how much has frequent urination during the day been a problem?	0	1	2	3	4
3. Over the past month, how much has getting up at night to urinate been a problem for you?	0	1	2	3	4
4. Over the past month, how much has shopping and starting when you urinate been a problem for you?	0	1	2	3	4
5. Over the past month, how much has a need to urinate with little warning been a problem for you?	0	1	2	3	4
6.Over the past month, how much has impaired size and force of urinary stream been a problem for you?	0	1	2	3	4
7. Over the past month, how much has having to push or strain to begin urination been a problem for you?	0	1	2	3	4

BPH Impact Index	None	A Little	Some	A lot	
1. During the last month, how much physical discomfort did any urinary problems cause you?	0	1	2	3	
2. During the last month, how much did you worry about your health because of any urinary problems?	0	1	2	3	
3. Overall, how bothersome has any trouble with urination been during the last month?	0	1	2	3	
4. During the last month, how much of the time has any urinary problem kept you from doing the kinds of things you would usually do?	None _____ 0	A Little _____ 1	Some of the time _____ 2	Most of the time _____ 3	All of the time _____ 4

10. Claim of Exemption from Review by the Human Subjects Research Review Board

United States Army Research and Materiel Command
Office of the Deputy Chief of Staff for Regulatory Compliance and Quality
Human Subjects Protection Division

PROTOCOL TITLE Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men
PI'S NAME ALEXIS E. TE, M.D.
INSTITUTION COLUMBIA UNIVERSITY

EXEMPT CATEGORY CLAIMED (Please refer to Exempt Categories - Section 4-b.)

1. Will existing or archived data, documents, records, or biological specimens be used? ✓ Yes ___ No

   a. Will any data or biological specimens be collected from subjects? ✓ Yes ___ No

   b. What is the source(s) of existing or archived data/biological specimens? (all that apply)

✓	existing data	publicly available?	___ Yes ✓ No
✓	archived data	publicly available?	___ Yes ✓ No
✓	biological specimens	publicly available?	___ Yes ✓ No

   c. Will the information be recorded in such a manner that subjects cannot be identified, directly or indirectly through links? ✓ Yes ___ No

2. Will data be recorded?

   a. by audiotape? ✓ Yes ___ No

   b. by videotape? ___ Yes ✓ No

3. If survey instruments are used, will sensitive or private topics be explored? ___ Yes ✓ No

4. Will the subjects be identifiable either by name or through demographic data? If yes, describe on a separate sheet how the confidentiality of a subject's identity will be maintained and plans for maintaining or destroying identifying links to subjects after the study is completed. ___ Yes ✓ No

PI'S Signature

Appendix 7
Safety Program Plan

1. Affirmation of Safety

Alexis E, Te, MD affirms that there is an existing safety program that is in accordance with appropriate Federal, State and local regulations, as required by the Occupational Safety and Health Act; that hazards have been identified, eliminated, and/or controlled; and that research may be performed safely under laboratory conditions. Alexis E. Te, MD shall be held responsible and liable for inaccuracies of the information provided, failure to implement an effective safety and occupational heath program, and /or adverse condition that may result from the failure of the recipient to identify hazard information.

Alexis E. Te, MD

Date

2.Research Operation (SOPs)
N/A

3.Facilty Equipment and Description
N/A

4. Hazard Analysis
N/A

5. Radioactive Materials
N/A

6. Recombinant DNA
N/A

Appendices 4

Department of Urology
College of Physicians and Surgeons
of Columbia University

Alexis E. Te, M.D.
Assistant Professor of Urology

Squier Urological Clinic
The Presbyterian Hospital
in the City of New York

Tel: (212) 305-0136
(718) 283-6100
Fax: (212) 305-0139

Colonel Julie K. Zadinsky
Office of the Deputy Chief of Staff for Regulatory Compliance
And Quality Human Subjects Protection Division
C/O Catherine Smith
MCMR-RCQ-HR
Fax (301) 619-7803

December 10, 1998

Dear Colonel Zadinsky,

Enclosed is the modified IRB as per your letter dated 12/7/98. The protocol will not save or use any serum or urine for any other study and does not require HSPD Clause 004.01. All other recommendations have been incorporated as well as those from the Columbia Presbyterian Meidcal Center IRB. Enclosed is the modified consent form. I have also read HSPD clause 013.01 and agree to comply with all HSPD requirements. If you have any questions, please feel Free to contact me.

Sincerely,

Alexis E. Te, MD

FAXED 12-10-98

161 FORT WASHINGTON AVENUE, NEW YORK, NY 10032

Columbia Presbyterian Medical Center

LAY SUMMARY

Title: PROSTATE SPECIFIC ANTIGEN (PSA) DENSITY OF THE TRANSITION ZONE IN ETHNICALLY DIVERSE MEN

Principle Investigator: Alexis E. Te, MD **Department of Urology**

Study Purpose

Prostate Cancer is a leading cause of death in men and Benign Prostatic Hyperplasia (BPH) is the most common affliction in men over 40 years old and BPH size is reflected by transition zone volume. PSA is currently utilized to evaluate prostate cancer. Patients often seeking treatment due to frequency and urgency of urination and nighttime voiding as well as those over the age of 40 can undergo prostate evaluations consisting of a thorough examination that includes a measurement of PSA level. Studies concerning these evaluations and normal values for PSA have been in largely single ethnic population of white men. The purpose of this research is to determine whether there are ethnic difference in prostate size especially of the transition zone (the portion of the prostate that directly surrounds the urethra) and its relationship to PSA levels. This study will investigate differences in prostate morphology in an ethnically diverse sample of men with BPH and evaluate if there is a better way to use PSA to screen for prostate cancer.

Design of the Study

The study is a cross-sectional investigation of differences in prostate morphology and PSA in an ethnically diverse sample of men. The study will include men over 4O years old. The initial evaluation will include a history and complete physical examination, including a digital rectal exam. Patients will be invited to participate and a review of the informed consent with physician. Patients will then be invited back on another date to begin recording data such as sociodemographics, blood and urine collection for analysis, a uroflowmetry (special device that patient is asked to urinate into which records flow rate and volume), prostate ultrasound to record the measurements of the prostate size. Each will be asked to complete an AUA Symptoms Score and BPH Impact Index questionnaire to assess severity of their symptoms and effect on their quality of life. The data and diagnostic procedures are all considered clinical acceptable methods of evaluation of men for prostate disorders.

Population

The plan is to accrue approximately 600 men over a 24 month period. The sample of men are age 40 and above, and referred for, or self-seeking for evaluation of their prostate for BPH or Prostate Cancer.

Recruitment Method

Subjects will be recruited from the Columbia-Presbyterian Prostate Center (4 Attendings) and the CPMC Squier Urological Clinic of the Allen Pavilion (3 Attendings). Patients will be referred from these sources and invited to participate.

Study Procedures

The patients data will be recorded over two visits. On visit 1, the patient is evaluated for his prostate condition and symptoms. He will asked to complete the AUA Symptom Score, Symptom Impact Index, along with collection of urine for analysis and culture to rule out active urinary tract infection. A history and complete physical examination including a digital rectal exam will be performed. If the patient agrees to continue in the study he will have blood drawn (approx. 15m/L) for chemistries and prostate specific antigen (PSA). He will be schedule for Visit 2 in which he will be asked to perform a uroflow, a bladder ultrasound for measurement of residual urine and a transrectal ultrasound in order to measure the size of the prostate. The ultrasound is a small tube that is inserted into the rectum and takes pictures of the prostate.

Columbia-Presbyterian Medical Center

Protocol
Title: PROSTATE SPECIFIC ANTIGEN (PSA) DENSITY OF THE TRANSITION ZONE IN ETHNICALLY DIVERSE MEN
Principle Investigator: Alexis E. Te, MD **Department of Urology**

Purpose

The primary goals of the study are:
1) To identify baseline levels of the transition zone and their correlation with both subjective (based on AUA symptom scores, BPH problem and impact index) and objective (based on urinary flow and post void residual urine volume) indices of BPH.
2) To evaluate racial differences in prostate morphology as measured by ultrasound measurements of various portions of the prostate.
3) To evaluate racial differences in subjective and objective indices of BPH, transition zone volume, total prostate volume, transition zone index (transition zone volume/ total prostate volume) and PSA.
4) To evaluate racial differences in PSA density of the transition zone (PSAT) and whether it is a useful screening tool for detecting prostate cancer in a population of ethnically diverse men.

Description of Study Design

The study is a cross-sectional investigation of differences in prostate morphology and PSA in an ethnically diverse sample of men. The sample population consists of men age 40 and above referred for, or self-seeking evaluation for their prostate. Subjects will be recruited from Columbia-Presbyterian Prostate Center, the CPMC Squier Urological Clinic at Allen Pavilion, the Harlem Hospital Center and Urology Clinic.

Subjects will be required to make 2 visits to one of the locations. At Visits 1, the patient is required to undergo a history and complete physical examination including a digital rectal exam of their prostate. An ultrasound of their prostate to measure the dimensions. Blood (approximately 30 m/L) will be drawn and urine specimen collected for analysis and culture. Subjects will be asked to complete an AUA Symptoms score and BPH Index questionnaires. At Visit 2, the subjects will be asked to urinate into a special device that records the rate of the urine flow and calculates the volume. A bladder ultrasound is performed to measure any residual urine in the bladder after urination.

Study Questionnaires

The copies of AUA, BPH Problem and Impact Index questionnaires are attached.

Inclusion/Exclusion

Inclusion

1) Men at least 40 years of age seeking evaluation of their prostate.
2) Subjects with any AUA Symptom Score
3) The patients be capable of understanding and signing the informed consent.

Confidentiality

All records and data collected during the course of the study will only be available to the study personnel. Patients will be assigned a number and records will be stored in a locked area and not accessible to other staff members.

Location of the study

The study takes place in the offices at the Prostate Center in Atchley Pavilion, 11th floor despite recruitment from other center locations.

Risks/Benefits

This is not a therapeutic trial and therefore no risk is anticipated. Patients may have transient discomfort from their transrectal ultrasound although this is self-limiting.

Compensation and Cost to Subjects

There is no compensation provided to subjects who participate. There will be no extra charge for office visits, procedures or tests related to the study.

Minors and Research Subjects

Minors are not included in this study.

Columbia Presbyterian Medical Center

Consent to Participate in a Research Study

The purpose of this consent is to provide you with the information you need to consider in deciding whether to participate in this research study.

TITLE: PROSTATE SPECIFIC ANTIGEN (PSA) DENSITY OF THE TRANSITION ZONE IN ETHNICALLY DIVERSE MEN

Purpose

You have been invited to participate in a research study which is designed to see if the shape and size of the prostate, and PSA blood level are different in men of various races. You were selected as a possible candidate in the study because you are a man over the age of 40 seeking an evaluation of your prostate. There will be approximately 600 men 40 years and older enrolled in this study. This is a cross-sectional investigation of the differences in prostates and its relationship to prostate diseases in racially different men.

Procedures

If you decide to participate in this study and sign the informed consent, the information recorded in your prostate evaluation will be utilized to examine these possible differences. The main difference in your evaluations is that a transrectal ultrasound will be performed to visualized and measure your prostate size at a subsequent visit. You may be asked in the future to provided us with additional information. At visit 1, you will be asked to complete questionnaires concerning your urinating symptoms and their effect on your life. A urine specimen will be obtained for analysis and culture to determine whether you may be suffering from a urinary tract infection. The physician will take a full medical history and perform a physical examination including a digital rectal examination of your prostate. Blood will be taken (approx. two teaspoons).

At Visit 2, you will be asked to urinate into a special device that measures the flow of the urine and the volume voided. A bladder ultrasound (small probe placed over your abdomen) will be performed to estimate the amount of urine left in the bladder after voiding. A transrectal ultrasound (small tube placed into the rectum) will takes pictures of your prostate and allows for accurate measuring of the prostate. If your doctor determines that you require a biopsy of the prostate for clinical purposes. The result of the biopsy will be included in the data to be analyzed. Each of these visits will take about 1 hour.

Study Risks

There is a risk that you may develop a bruise from the blood drawing. This usually resolves in a few days. There is slight discomfort associated with the transrectal ultrasound.

Study Benefits

You are not expected to benefit personally from this study. It is hoped that the information gathered form this study will help in the diagnosis and treatment of future patients.

Cost and Compensation

All the visits, blood work, ultrasound, urine testing are performed as part of your complete prostate evaluation and there is no additional cost for your participation in the study.

Study participation and confidentiality

Your participation in this study is voluntary. If you wish, you may decline to participate by simply telling your doctor. You will still complete the routine prostate evaluation that you seek and any necessary treatment that you may require for your urinary condition. Your decision will not in any way affect your future medical care and treatment. If you decide to participate in this study, and then later decide that you do not wish to continue, you may, at that time, withdraw from this study. Again, your decision will not in any way affect your future medical care and treatment.

Your records will be handled as confidentially as possible. Only clinical research personnel will maintain information from your medical records in a locked filing system accessible only to the research staff. This information will be not be used. Certain data from this study may also be used in medical and scientific publication, but your name will not be disclosed.

Any information obtained during the study and identified with you and will remain confidential. Additionally, any blood and urine specimen will not be saved and utilized for any other study.

Dr. Te will answer all your questions. If you have questions in the future, you may call Dr. Te, Principal Investigator at (212) 305-0136 at anytime. He will be available during the study to answer questions related to the study and your rights as a participant. A physician, nurse or technician involved with this study may also be available at (212) 305-0146. If you have any questions about your rights as a research subject, you may call the Columbia Presbyterian Medical Center Institutional Review Board at (212) 305-5883.

CONSENT TO PARTICIPATE IN THE STUDY

I have discussed this study with Dr. Te to my satisfaction. I understand that my participation is voluntary and that I can withdraw from the study at any time without prejudice. I have read the above and agree to enter this research study. Signing this does not waive any of my legal rights.

I have been informed that if I believe that I have sustained injury as a result of participating in a research study, I may contact the Principal Investigator, Dr Te, at (212) 305-0136 at anytime, or the Institutional Review Board, at (212) 305-5883, so that I can review the matter and identify the medical resources which may be available to me.

I understand that:

a) The Presbyterian Hospital will furnish that emergency medical care determined to be necessary by the medical staff of this hospital.

b) I will be responsible for the cost of such care, either personally or through my medical insurance or other form of medical coverage.

c) No monetary compensation for wages lost as a result of injury will be paid to me by ColumbiaPresbyterian Medical Center, and;

d) I will receive a copy of this consent form.

Signature:_____Date:_____

Print Name:_____
Participants

Signature: _____Date:_____

Print Name:_____
Physician

Signature:_____Date:_____

Print Name:_____
Witness

The solicitation of subjects into this study has been approved by the Columbia-Presbyterian Medical Center Institutional Review Board.

AUA Symptom Score

NAME:_____

Date:_____

AUA Symptom Score	Not at all	less than 1 time in 5	less than half the time	about half the time	more than half the time	almost always
1) Over the past month or so, how often have you had as sensation of not emptying your bladder completely after urinating?	0	1	2	3	4	5
2) Over the past month or so, how often have you had the urge to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
3) Over the past month or so, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4) Over the past month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5) Over the past month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
6) Over the past month or so, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
7) Over the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5 or more times

AUA Symptom Score = sum of questions 1-7

TOTAL SCORE: _____

Symptom Problem Index and BPH Impact Index

NAME:_____

Date:_____

Symptom Problem Index	No Problem	Very Small Problem	Small Problem	Medium Problem	Big Problem
1. Over the past month, how much has a sensation of not emptying your bladder been a problem for you?	0	1	2	3	4
2. Over the past month, how much has frequent urination during the day been a problem?	0	1	2	3	4
3. Over the past month, how much has getting up at night to urinate been a problem for you?	0	1	2	3	4
4. Over the past month, how much has shopping and starting when you urinate been a problem for you?	0	1	2	3	4
5. Over the past month, how much has a need to urinate with little warning been a problem for you?	0	1	2	3	4
6.Over the past month, how much has impaired size and force of urinary stream been a problem for you?	0	1	2	3	4
7. Over the past month, how much has having to push or strain to begin urination been a problem for you?	0	1	2	3	4

BPH Impact Index	None	A Little	Some	A lot	
1. During the last month, how much physical discomfort did any urinary problems cause you?	0	1	2	3	
2. During the last month, how much did you worry about your health because of any urinary problems?	0	1	2	3	
3. Overall, how bothersome has any trouble with urination been during the last month?	0	1	2	3	
4. During the last month, how much of the time has any urinary problem kept you from doing the kinds of things you would usually do?	None _____ 0	A Little _____ 1	Some of the time _____ 2	Most of the time _____ 3	All of the time _____ 4

COLUMBIA UNIVERSITY
COLLEGE OF PHYSICIANS & SURGEONS

COLUMBIA-PRESBYTERIAN MEDICAL CENTER INSTITUTIONAL REVIEW BOARD
CPMC IRB

December 15, 1998

Alexis Te, MD
Department of Urology
AP 11th Flr.

RE: IRB#: 8783, "PROSTATE SPECIFIC ANTIGEN (PSA) DENSITY OF THE TRANSITION ZONE IN ETHICALLY DIVERSE MEN,"

Dear Dr. Te

Thank you for forwarding the revised consent form to be used with this study. Since the new consent form includes all the revisions requested by the IRB reviewers, the enrollment of subjects into this study is now approved. I am enclosing your **stamped IRB approved consent forms.**

The official date of the IRB approval for the study is the date of the meeting at which it was discussed and recommended for approval (November 24, 1998). The study was approved for twelve months from that date. Therefore, the next renewal application (IRB Form C) will be due in October, 1999.

Any modification of the study procedures or recruitment methods must be submitted for IRB review before being implemented, unless it is necessary for a subject's safety.

As with all IRB protocols, any serious or excepted adverse events must be reported as they occur.

Sincerely,

Donald S. Kornfeld, MD
Chairman, CPMC IRB

DSK/bd

cc: Susanne Wise-Campbell
Mitchell Benson, MD
Carl A Olsson, MD
Randy Weiss

630 West 168th Street P&S 3-460 New York, NY 10032 212-305-5883 Fax 212-305-1316

Columbia-Presbyterian Medical Center
Institutional Review Board

IRB Form A
(Rev 8/97)

Application for Approval of a Research Proposal Involving Human Subjects

Please TYPE ALL INFORMATION and complete both sides

IRB number 8783
New study
5 Year Renewal

Title: Prostate Specific Antigen Density of the Transition Zone in Ethnically Diverse Men

Investigator Information

Principal Investigator *(Must have Columbia rank of Assistant Professor or Associate Research Scientist or above)*:

Name	Department	Signature
Alexis E. Te, M.D.	Urology	

Mailing address	Telephone number	Fax number
AP-11	(212) 305-0136	(212) 305-0139

Name of contact person	Mailing address	Telephone number	Fax number
Alexis E. Te, M.D.	AP-11	7-0136	70139

Co-Investigators:

Name	Mailing address	Telephone number	Department
Name	Mailing address	Telephone number	Department
Name	Mailing address	Telephone number	Department

Departmental Approvals

Chair, Department Committee on Human Investigation — Date 11/11/98

Department Chair or Institute or Center Director — Date 11/11/98

IRB Approval

(Leave this blank. After the study has been reviewed and approved, this will be signed by the Chairman of the IRB)

Chairman, Institutional Review Board — Date 11/24/98

RECEIVED NOV 24 1998

Columbia Presbyterian Medical Center

Consent to Participate in a Research Study

The purpose of this consent is to provide you with the information you need to consider in deciding whether to participate in this research study.

TITLE: PROSTATE SPECIFIC ANTIGEN (PSA) DENSITY OF THE TRANSITION ZONE IN ETHNICALLY DIVERSE MEN

Purpose

You have been invited to participate in a research study which is designed to see if the shape and size of the prostate, and PSA blood level are different in men of various races. You were selected as a possible candidate in the study because you are a man over the age of 40 seeking an evaluation of your prostate. There will be approximately 600 men 40 years and older enrolled in this study. This is a cross-sectional investigation of the differences in prostates and its relationship to prostate diseases in racially different men.

Procedures

If you decide to participate in this study and sign the informed consent, the information recorded in your prostate evaluation will be utilized to examine these possible differences. The main difference in your evaluations is that a transrectal ultrasound will be performed to visualized and measure your prostate size at a subsequent visit. You may be asked in the future to provided us with additional information. At visit 1, you will be asked to complete questionnaires concerning your urinating symptoms and their effect on your life. A urine specimen will be obtained for analysis and culture to determine whether you may be suffering from a urinary tract infection. The physician will take a full medical history and perform a physical examination including a digital rectal examination of your prostate. Blood will be taken (approx. two teaspoons).

At Visit 2, you will be asked to urinate into a special device that measures the flow of the urine and the volume voided. A bladder ultrasound (small probe placed over your abdomen) will be performed to estimate the amount of urine left in the bladder after voiding. A transrectal ultrasound (small tube placed into the rectum) will takes pictures of your prostate and allows for accurate measuring of the prostate. If your doctor determines that you require a biopsy of the prostate for clinical purposes. The result of the biopsy will be included in the data to be analyzed. Each of these visits will take about 1 hour.

Study Risks

There is a risk that you may develop a bruise from the blood drawing. This usually resolves in a few days. There is slight discomfort associated with the transrectal ultrasound.

Study Benefits

You are not expected to benefit personally from this study. It is hoped that the information gathered form this study will help in the diagnosis and treatment of future patients.

Cost and Compensation

All the visits, blood work, ultrasound, urine testing are performed as part of your complete prostate evaluation and there is no additional cost for your participation in the study.

Study participation and confidentiality

Your participation in this study is voluntary. If you wish, you may decline to participate by simply telling your doctor. You will still complete the routine prostate evaluation that you seek and any necessary treatment that you may require for your urinary condition. Your decision will not in any way affect your future medical care and treatment. If you decide to participate in this study, and then later decide that you do not wish to continue, you may, at that time, withdraw from this study. Again, your decision will not in any way affect your future medical care and treatment.

Your records will be handled as confidentially as possible. Only clinical research personnel will maintain information from your medical records in a locked filing system accessible only to the research staff. This information will be not be used. Certain data from this study may also be used in medical and scientific publication, but your name will not be disclosed.

Any information obtained during the study and identified with you and will remain confidential. Additionally, any blood and urine specimen will not be saved and utilized for any other study.

Dr. Te will answer all your questions. If you have questions in the future, you may call Dr. Te, Principal Investigator at (212) 305-0136 at anytime. He will be available during the study to answer questions related to the study and your rights as a participant. A physician, nurse or technician involved with this study may also be available at (212) 305-0146. If you have any questions about your rights as a research subject, you may call the Columbia Presbyterian Medical Center Institutional Review Board at (212) 305-5883.

CONSENT TO PARTICIPATE IN THE STUDY

I have discussed this study with Dr. Te to my satisfaction. I understand that my participation is voluntary and that I can withdraw from the study at any time without prejudice. I have read the above and agree to enter this research study. Signing this does not waive any of my legal rights.

I have been informed that if I believe that I have sustained injury as a result of participating in a research study, I may contact the Principal Investigator, Dr Te, at (212) 305-0136 at anytime, or the Institutional Review Board, at (212) 305-5883, so that I can review the matter and identify the medical resources which may be available to me.

I understand that:

a) The Presbyterian Hospital will furnish that emergency medical care determined to be necessary by the medical staff of this hospital.

b) I will be responsible for the cost of such care, either personally or through my medical insurance or other form of medical coverage.

c) No monetary compensation for wages lost as a result of injury will be paid to me by ColumbiaPresbyterian Medical Center, and;

d) I will receive a copy of this consent form.

Signature:_____Date:_____

Print Name:_____
Participants

Signature: _____Date:_____

Print Name:_____
Physician

Signature:_____Date:_____

Print Name:_____
Witness

The solicitation of subjects into this study has been approved by the Columbia-Presbyterian Medical Center Institutional Review Board.

Appendices 5

AMERICAN UROLOGICAL ASSOCIATION, INC.
OFFICE OF EDUCATION
2425 West Loop South, Suite 333, Houston, Tx. 77027-4207, (713) 622-2700, FAX # (713) 622-2898

Certificate of Completion

Alexis Edwin Te, M.D.
Atchley Pavillion 11th Fl
161 Fort Washington Ave
New York, NY 10032

320528

This is to certify that the above-named physician has completed the following program(s) sponsored or jointly sponsored by the American Urological Association and is accordingly awarded the indicated credit:

Program or Course	Date		CME Credit Category	CME Credit Hours
99 Annual Mtg: General Cat 1 Dallas, TX	5/01/99	5/01/99	1	35.5

Credit
American Urological Association, Inc.® designates this educational activity for a maximum of (or "for up to") [number of hours] hours in category 1 credit towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Accreditation
American Urological Association, Inc.® is accredited by the Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. This CME activity was planned and produced in accordance with the ACCME Essentials.

Joseph N. Corriere, Jr., M.D.
Director of Education

Appendices 6

Curriculum vitae

Alexis Edwin Te, M.D.

Office Address
J. Bentley Squier Urologic Clinic
College of Physicians and Surgeons of Columbia University
Columbia Presbyterian Medical Center
161 Fort Washington Ave, 11th Floor
New York, New York 10032-3784
(212) 305-0136 Office
(212) 305-0139 Office Fax

Brooklyn Office
Professional Building
953 49th Street, 2nd Floor
Brooklyn, NY 11219
(718) 283-6100
D.O.B. 2/15/62
SS# 100-50-0903

Education:

Cornell University Medical College Medical Doctorate	New York, NY May 1988
Yale University Bachelor of Science Major: Molecular Biophysics & Biochemistry Associate Member of Sigma Xi Research Society	New Haven, CT May 1984
Polytechnic Preparatory Country Day School High School Diploma Cum Laude Honor Society	Brooklyn, NY June 1980

Licensure and Qualifications:

New York State Medical Board Certification and License # 180421	1989
DEA Certification # BT 4033825	1994
American Board of Urology Certification # 11868	1998

Work Experience:

Assistant Professor of Urology Assistant Attending in Urology Co-Director of Incontinence Care Center J. Bentley Squier Urologic Clinic College of Physicians and Surgeons of Columbia University Columbia Presbyterian Medical Center	7/95- Present New York, NY
Director of the Incontinence Care Center Neurourology and Urodynamics Laboratory Assistant Attending in Surgery Division of Urology Maimonides Medical Center	11/96- Present Brooklyn, New York
Attending in Surgery Department of Urology Helen Hayes Hospital	7/94-Present West Havestraw, NY
Fellow in Neurourology and Urodynamics Clinical Assistant in Urology J. Bentley Squier Urologic Clinic College of Physicians and Surgeons of Columbia University Columbia Presbyterian Medical Center	7/94-6/95 New York, NY
Urology Chief Resident J. Bentley Squier Urologic Clinic College of Physicians and Surgeons of Columbia University Columbia Presbyterian Medical Center	7/93-6/94 New York, NY
Urology Residency Training Program, PGY 3, 4, 5 & 6 J. Bentley Squier Urologic Clinic College of Physicians and Surgeons of Columbia University Columbia Presbyterian Medical Center	7/90-6/94 New York, NY
General Surgical Residency Training, PGY 1 & 2 General Surgery Department College of Physicians and Surgeons of Columbia University Columbia Presbyterian Medical Center	7/88-6/90 New York, NY

Research Experience:

Columbia University
College of Physicians and Surgeons
Assistant Professor of Urology
Department of Urology
Co-Investigator: Steve Kaplan, MD
1995- Present
New York, NY
Areas of Current Research: BPH, Therapies in BPH, Incontinence,Prostatitis, Neurourology and Urodynamics

Current Active Projects

Principle Investigator

1. The Effects of Doxazosin on Diurnal Blood Pressure Variation in Dipper and Non-Dipper Hypertensives with Lower Urianry Tract Symptoms.

Funding Source: DICE Competitive Award, Pfizer Pharmaceuticals Group

2. Prostate Specific Antigen (PSA) Density of the Transition Zone in Ethnically Diverse Men

Funding Source: Department of Defense Training Grant

3. Clinical efficacy and tolerability/safety of tolterodine prolonged release capsules and tolterodine immediate release tablets vs. placebo. A randomized, double-blind, placebo-controlled, multinational study in patients with symptoms of overactive bladder

Funding Source: Pharmacia UpJohn

Co- Investigator with Dr. Kaplan

1. Microwave Thermotherapy vs. TURP, a randomized comparative study

Funding Source: Urologix, Inc., Minneapolis, MN.

2. Peripheral Sacral Nerve Stimulation for the treatment of Voiding Dysfunctions

Funding Source: Medtronics, Inc., Minneapolis, MN.

3. Medical Therapy of BPH Study (MTOPS)

Funding Source: NIH

Past Research Experience

Columbia University
College of Physicians and Surgeons
Department of Urology
1994-1995
New York, NY
Sponsors: Steven A. Kaplan, M.D. & Carl A. Olsson, M.D.
Topic: Transurethral Electrovaporation of the Prostate

Columbia University
College of Physicians and Surgeons
Department of Urology
1992-1994
New York, NY
Sponsors: Steven A. Kaplan,M.D., Ridwan Shabsigh,M.D.,Ralph Buttyan,Ph.D.& Carl Olsson, M.D.

Topic: Neurotrophic factors in developing and diabetic bladders ,and penis
Castration-Induced Apoptosis in the Rat Penis

Cornell University Medical College — July 1987
Brady Urology Research Laboratory — New York, NY
Sponsor: E. Darracott Vaughan,Jr.,M.D.
Topic: Intraperitoneal infusion of alkaline irrigating solutions used in uric acid stone treatment

University of California, San Francisco — Summer 1985
Department of Biophysics & Biochemistry — San Francisco,CA
Sponsor: Robert Fletterick, Ph.D.
Topic: Isolation of human liver glycogen phosphorylase gene from human genomic cDNA library

Yale University — Academic Year 1983-1984
Department of Molecular Biophysics & Biochemistry — New Haven, CT
Sponsor: W. Dean Rupp, Ph.D.
Topic: The DNA sequence of the uvrB gene in E. Coli.

University of California, San Francisco — Summer 1983
Department of Biophysics & Biochemistry — San Francisco, CA
Sponsor: Robert Fletterick, Ph.D.
Topic: The DNA sequence of human muscle glycogen phosphorylase

Yale University Medical School — Academic year 1982-83
Department of Cardiovascularpathophysiology — New Haven, CT
Sponsor: S. Evans Downing, M.D.
Topic: Biochemical assay to measure heart muscle scars in rabbits

The New York Blood Center — Summer 1982
Department of Cell Biochemistry — New York, NY
Sponsor: Jack Goldstein, Ph.D.
Topic: Protein purification of N- Acetyl-D-Galactosaminodase

The Jackson Laboratory — Summer 1979
Sponsor: David E. Harrison, Ph.D. — Bar Harbor, Maine
Topic:Water solubility changes of collagen in aging mice skin

Peer Review Publications-

1. Te AE, Colombel M, Koo HP, Kaplan SA, Buttyan R, Olsson CA, Shabsigh R. Castration-Induced Apoptosis in the Rat Penis. Surgical Forum 1992; 48: 724-725.

2. Te AE, Koo HP, Kaplan SA, Buttyan R, Olsson CA, Shabsigh R. Neurotrophic Factors in the Diabetic Rat Penis. Surgical Forum 1993: 49: 758-760.

3. Kaplan SA, Te AE & Jacobs BZ. Urodynamic evidence of vesical neck obstruction in men with " chronic n-bacterial " prostatitis and the therapeutic role of the endoscopic incision of the bladder neck. J Urol. 1995; 152:2063-2065.

4. Te AE, Santarosa R, Buttyan R, Greene L, Koo HP, Kaplan SA, Olsson CA & Shabsigh R. Neurotrophic Factors in the Rat Penis. J Urol.1994; 152:2167-2172.

5. Kaplan SA, Te AE. , Blaivas JG: Urodynamic findings in patients with diabetic cystopathy. J Urol. 1995; 153:342-344.

6. Kaplan SA, Te AE. Transurethral Electrovaporization of the Prostate (TVP): A novel method of treating men with benign prostatic hyperplasia. Urology 1995; 45: 566-573.

7. Kaplan SA, Te AE. A comparative study of transurethral resection of the prostate using a modified electrovaporizaing loop and transurethral laser vaporization of the prostate. J. Urol. 1995; 154: 1785-90.

8. Kaplan SA, Te AE, Pressler LB, Olsson CA. Transition zone index (TZI): A novel method of assessing benign prostatic hyperplasia: correlation with symptoms, uroflow and detrusor pressure. J Urol. 1995; 154: 1764-69.

9. Santarosa RP, Raymond J, Colombel M, Te AE, Koo HP, Olsson CA, Buttyan R & Shabsigh R: Effects of castration on the rat penis. J Urol. In Press.

10. Kaplan SA, Bowers DA, Te AE, Olsson CA: Differential diagnosis of prostatism: 12-year retrospective analysis of symptoms, urodynamics and satisfaction with therapy. J Urol. 1996; 155: 1305-1308.

11. Kaplan SA, Olsson CA & Te AE: The American Urological Association symptom score in the evaluation of men with lower urinary tract symptom: At 2 years of followup, does it work?. J Urol. 155:1971-1974, 1996.

12. Kaplan SA, Ikeguchi EF, Santarosa RP, Meade D' Alisera P, Hendriks J, Te AE & Miller MI: Etiology of voiding dysfunction in men less than 50 years of age. Urology. 47: 836-839, 1996.

13. Kaplan SA, Santarosa RP & Te AE: Comparison of fascial and vaginal wall slings in the management of intrinsic sphincter deficiency. Urology. 47: 885-889, 1996.

14. McKiernan JM, Kaplan SA, Santarosa RP, Te AE, Sawczuk IS: Transurethral vaporization of bladder cancer. Urology 48(2): 207-10

15. Te AE, Santarosa R, Kaplan SA.:Electrovaporization of the prostate: electosurgical modification of standard resection in 93 patients with benign hyperplasia. J Endourol 11(1):71-5, 1997.

16. Kaplan SA, Santarosa RP, Te AE: Transurethral electrovaporization of the prostate: one year experience. Urology 48(6):876-81, 1996.

17. Kaplan SA, Santarosa RP, D' Alisera PM, Fay BJ, Ikeguchi EF, Hendricks J, Te, AE: Pseudodyssynergia (contraction of the external sphincter during voiding) misdiagnosed as chronic nonbacterial prostatitis and the role of biofeedback as a therapeutic option. J Urol 157(6):2234-7, 1997

18. Kaplan SA, Reis RB, Cologna A, Suaid HJ, Martins ACP, Kohn IJ, Te AE: Intermittent alpha-blocker therapy in the treatment of men with lower urinary tract symptoms. Urology 52(1):12-16, 1998.

19. Kaplan SA, Te AE, Ikeguchi E, Santarosa RP: Safety and efficacy of alpha blockers in the treatment of men over the age of 80 with benign prostatic hyperplasia. Br J Urol 1997 Dec;80(6):875-9

20. Kaplan, SA, Reis, RB, Staiman, VB, Te, AE: Is the ratio of transition zone to total prostate volume higher in African-American men than in their Caucasian or Hispanic Counterparts?. Br J Urol 1998, 82: 804-807

21. Kaplan SA, Reis RB, Kohn IJ, Ikeguchi EF, Laor E, Te AE, Martins ACP: Safety and efficacy of sildenafil in postmenopausal women with sexual dysfunction. Urology 1999, 53:481-486.

22. Kaplan SA, Reis RB, Kohn IJ, Shabsigh R, Te AE: Combination therapy using oral alpha blockers and intracavernosal injection in men with erectile dysfunction. Urology 1998, 52(5): 739-43.

23. Kaplan SA, Laor E, Fatal M, Te AE: Transurethral resection of the prostate versus transurethral electrovaporization of the prostate: a blinded, prospective comparative study with 1 years followup. J Urology 1998, 159(2):454-8.

24. Reis RB, Te, AE, Cologna AJ, Suaid HJ, Kaplan SA: Interstitial Thermometry in Men Undergoing Electrovaporization of the Prostate. J Endourology 1999, 13 (1): 53-56.

Non-Peer Review Publications-

1. Kaplan SA, Te AE: Uroflowmetry & Urodynamics.Urologic Clinics of North America 1995; 22: 309-20.

2. Te AE , Kaplan SA: Transurethral Electrovaporization of the Prostate (TVP): A electrosurgical advancement of the standard TURP. Current Surgical Techniques in Urology 1995; 8:1-9.

3. Te AE , Reis R, Kaplan SA: Transurethral Electrovaporization of the Prostate (TVP): A novel modification of the standard TURP. Contemporary Urology 1995; 7:74-83.

4. Te AE, Kaplan SA: Electrovaporization of the Prostate. Current Opinion in Urology 1996; 6: 2-9.

5. Santarosa RP, Te AE, Kaplan SA: Minimally Invasive Procedures for Benign Prostatic Hyperplasia. Mediguide to Urology 1996; 9:1-6

6. Te AE, Kaplan SA: Transurethral electrovaporization of the Prostate.Mayo Clin Proc 1998 Jul;73(7):691-5

7. Te AE and Kaplan SA: Transurethral electrovaporization of the prostate: the year in review. Current Opinion in Urology 1997; 7:25-36.

Book Chapters

1. Kaplan SA, Te AE: Bladder Dysfunction in Diabetes, In: Paulson, ed. Problems in Urology; Neurourology and its Role in Urologic Diseases: Part I. Philadephia, J. B. Lippincott Co., 6: 659-668. 1992.

2. Te AE , Kaplan SA: Pharmaceutical Treatment of BPH and its effect on indications for prostate surgery. In: Surgical Technology International III: Endourology. San Francisco. Universal Medical Press, Inc.1994.

3. Te AE, Kaplan SA: Urodynamics and BPH. In: Kirby RS, McConnell JD, Fitzpatrick JM, Roehrborn CG, Boyle P, eds. Textbook of Benign Prostatic Hyperplasia. Oxford. Isis Medical Media, LTD., 187-198. 1996.

4. Te AE, Kaplan SA: Prostatic Endoprosthetics. In: Kirby RS, McConnell JD, Fitzpatrick JM, Roehrborn CG, Boyle P, eds. Textbook of Benign Prostatic Hyperplasia. Oxford. Isis Medical Media, LTD. 453-462.1996.

5. Te AE, Kaplan SA: Electrovaporization Principles. In: Narayan P, ed. Benign Prostatic Hyperplasia. London, Churchill Livingstone, In Press.

6. Te AE, Kaplan SA: Electrovaporization of the Prostate: Advance Application of Electrosurgical Principles to the Treatment of Benign Prostatic Hyperplasia. In: Kirby RS, O'Leary MP, ed. Recent Advances in Urology 7. London, Churchill Livingston, In Press.

7. Te AE, Kaplan SA: Complication of Minimally Invasive Surgery for BPH. In: Taneja SS, Smith RB, Ehrlich RM, ed. Complication of Urologic Surgery, 3rd ed. Philadelphia, W. B. Saunders, In Press.

8. Santarosa RP, Te AE, Kaplan SA: Transurethral resection, incision and ablation of the prostate. Glenn's Urologic Surgery, 5th edition. Ed. Graham SD. 1998.

9. Te AE, Santarosa RP, Kaplan SA: Tranurethral Electrovaporization of the Prostate. In: Resnick MI, Thompson IM, ed. Surgery of the Prostate. London, Churchill Livingston.295-307. 1998.

Abstracts-

1. Te AE, Buttyan R, Koo HP, Greene LA, Kaplan SA, Olsson CA & Shabsigh R: Abundant expression of nerve growth factor (NGF) in the rat penis, a developmental study. J Urol. 147:239A, 1992.

2. Te AE, Buttyan R, Koo HP, Shabsigh R, Olsson CA & Kaplan SA: Nerve growth factor in diabetic cystopathy. J Urol. 147:350A, 1992.

3. Koo HP, Buttyan R, Te AE, Kaplan SA, Olsson CA & Shabsigh R: Neurotrophin expression in diabetic rat penis: a new insight into pathogenesis of erectile dysfunction. J Urol. 147:240A, 1992.

4. Shabsigh R, Buttyan R, Koo HP, Kaplan SA, Olsson CA & Te AE: Expression of neurotrophins: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF) in the rat penis. J Urol. 147:318A, 1992.

5. Brown W, Te AE, Olsson CA & Benson MC: Management of complications of continent urinary diversions. J Urol. 147:390A, 1992.

6. Te AE, Buttyan R, Koo HP, Olsson CA & Kaplan SA: Nerve growth factors in diabetic cystopathy. Neurourology and Urodynamics. 11(4):303, 1992.

7. Te AE, Buttyan R, Koo HP, Shabsigh R, Olsson CA & Kaplan SA: Nerve growth factors in diabetic cytopathy. Diabetes. 41(Sup 1):140A, 1992.

8. Kaplan SA, Te AE & Blaivas JG: Urodynamic findings in patients with diabetes and voiding symptoms: surprising results. International Continence Society. 22nd Ann. Mtg. Abstract 115, 1992.

9. Te AE, Buttyan R, Koo HP, Kaplan SA, Olsson CA & Shabsigh R: Neurotrophic Factors in the diabetic rat penis: an extended study. J Urol. 149:247A, 1993.

10. Santarosa RP, Te AE, Koo HP, Buttyan R, Kaplan SA, Olsson CA & Shabsigh R: Androgen Deprivation and Apoptosis in Rat Erectile Tissue. J Urol. 151:494A, 1994.

11. Te AE, Olsson CA & Kaplan SA: Use of the AUA-BPH treatment guidelines in men with symptomatic benign prostatic hyperplasia (BPH): At one year, is it effective?. J Urol. 151:507A, 1994.

12. Shabsigh R, Te AE, Koo HP, Kaplan SA, Olsson CA & Shabsigh: Localization of nerve growth factor beta (NGF) in the rat penis by in-situ hybridization. Society for Basic Urologic Research Fall Symposium, Rochester, MN, 1991.

13. Te AE, Colombel M, Koo HP, Kaplan SA, Buttyan R, Olsson CA & Shabigh R: Castration- induced apoptosis in the rat penis. ACS Annual Mtg. Chicago Il, 1992.

14. Shabsigh R, Te AE & Fisch H: Cavernous electromyography as an indication of adequate smooth muscle relaxation during duplex ultrasonography. 5th World Meeting on Impotence. Milan, Italy, 1992.

15. Te AE, Buttyan R, Koo HP, Greene L, Kaplan SA, Olsson CA & Shabsigh R: Neurotrophins in the rat penis. 5th World Meeting on Impotence. Milan, Italy, 1992.

16. Santarosa RP, Te AE, Koo HP, Raymond J, Columbel M, Olsson CA, Buttyan R & Shabsigh R: Testoterone sensitivity of the erectile tissue of the rat penis to castration. 7th World Meeting on Impotence. Singapore, ISIR, 1994.

17. Te AE, Kaplan SA, Dann JA. Transurethral electrovaporization of the prostate (TVP): A novel method for treating men with benign prostatic hyperplasia. J Urol. 1995; 153: 436A.

18. Te AE, Santarosa R, Kaplan SA. Transurethral electrovaporization of prostate (TVP): A modification on the standard TURP. J Endourology 1995; 9: S58.

19. Kaplan SA, Santarosa RP, Te AE: Electrovaporization of the prostate for symptomatic benign prostatic hyperplasia: the 1 year experience. J Urol. 1996, 155(5):405A.

20. Reis RB, Cologna AJ, Suaid HJ, Kaplan SA, Te AE: Electrovaporzation of the prostate VAP): a comparison of roller electrode configurations for resecting prostate tissue. J Urol. 1996, 155(5):406A.

21. Laor E, Kaplan SA, Te AE, Tolia BM and Reid RE: Laser vaporization of 'large" prostate glands: long term follow - up. J Urol. 1996, 155(5):706A.

22. Reis RB, Cologna AJ, Suaid HJ, Te AE and Kaplan SA: Interstitial thermometry in men undergoing electrovaporization: is it safe? J Urol. 1996, 155(5):707A.

23. Kaplan SA, Santarosa RP, Te AE: The incidence of hypertension in men with benign prostatic hyperplasia. XIIth European Urology Association, Paris, 1996.

24. Kaplan SA, Laor E, Te AE: Transurethral rsection of the prostate (TURP) versus electrovaporization of the prostate (VAP): a prospective, blinded comparative study of the treatment of benign prostatic hyperplasia (BPH). XXIIth European Urology Association, Paris, 1996.

25. Avillo C, Stifelman M, Te A, Sandler P and Kaplan SA: The urodynamic parameter: detrusor contraction duration (DCD) predicts response to alpha blocker therapy for lower urinary tract symptoms (LUTS). J Urol.1997, 157(4): 136.

26. Te AE, Laor EL, Kaplan SA, Babayan R, Noble M, Mbust W, Bruskewitz R, Whitfield HN: Transurethral resection of the prostate (TURP) versus vaporization of the prostate utilizing a vaporizing loop (TVLOOP): a multicenter, blinded, prospectie comparative study. J Urol.1997, 157(4): 313.

27. Te AE, Laor E, and Kaplan SA: Transurethral resection of the prostate (TURP) versus transurethral electrovaporization of the prostate (TVP): a blinded, prospective comparative study with 1 year follow - up. J Urol.1997, 157(4): 313.

28. Pressler LB, Santarosa RP, Te AE and Kaplan SA: The incidence of hypertension (HTN) in a population of men with benign prostatic hyperplasia (BPH): analysis based on the AUA symptom score and race. J Urol.1997, 157(4): 371.

29. D'Alisera PM, Stifelman M, Kohn I, Te AE, Weiner DM, Kaplan SA: Correlation of lower urinary tract symptom (LUTS) severity by International Prostate Symptom Score (IPSS) and erectile dysfunction (ED) in men over 50 years of age. J Urol. 1998, 159(5): 103.

30. Reis RB, Suaid HJ, Cologna AJ, Te AE, Kaplan SA: Men with lower urinary tract symptoms (LUTS) and inguinal hernias (HERN) have significantly greater bladder outlet obstruction (BOO) than men with LUTS alone. J Urol. 1998, 159(5): 139.

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1. "Doxazosin: Safety and Efficacy in Elderly Men". Pfizer Roundtable. NY, NY 12/5/98
2. "Tranurethral Electrovaporization of the Prostate". Levaquin Speaker Training Course. Phoenix, Arizona 1/14-16/99.
3. "Interstitial Laser Coagulation of Prostate Therapy and Laser Safety Certification". Maimonides Medical Center, Division of Urology Grand Rounds. Brooklyn, NY 1/7/99.