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Blacks

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14. ABSTRACT: The purpose of this research was to develop the infrastructure for comparative studies of prostate cancer among blacks who reside in contrasting environmental settings, West Africa, the Caribbean and the United States. This effort addresses six areas: case recruitment, case characterization, tissue collection and storage, integrated database development, targeted laboratory expertise and pilot research. A one-year no-cost extension was granted to submit abstracts, manuscripts, and research proposals. <u>Key Research Accomplishments:</u> 1) established a research infrastructure to support unified measurement of exposure and prostate cancer disease in Chicago, Illinois and Kingston, Jamaica; 2) completed molecular studies in over 40% of subjects enrolled; 3) created a computerized database linking demographical, clinical and pathological characteristics of each case to archived tissue specimens and results of nutritional and genetic measurements. 4) Completed statistical comparisons of i) demographical, clinical and pathological characteristics of cases from Chicago, Kingston and West Africa, ii) levels of antioxidants and fatty acids in serum and prostate tissue in cases diagnosed in Chicago and Jamaica, iii) and performed association studies between variants of genes involved in androgen metabolism and prostate cancer stage within and across cases from Chicago, Jamaica and West Africa; 5) published 2 manuscripts and 6 abstracts.					
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I. INTRODUCTION

The purpose of this research was to develop the infrastructure for comparative studies of prostate cancer among black men who reside in contrasting environmental settings, West Africa, the Caribbean and the United States. This ambitious three-year effort addressed six essential infrastructure areas: case recruitment, case characterization, tissue collection and storage, integrated database development, targeted laboratory expertise and pilot research. The key accomplishments were as follows:

1. Reliable recruitment and data collection strategies in Chicago and Kingston.
2. A centralized data repository in Chicago consisting of demographic and clinico-pathologic history and tissue (serum/plasma, leukocytes, erythrocytes and prostate tissue) for biochemical and molecular studies.
3. Meeting solicitation and recruitment target in Chicago and Kingston.
4. Application of secure web-based technology to permit grading of pathologic tumor by consensus.
5. The foundation to conduct preliminary biologic and molecular comparison of cases in from Chicago and Kingston.
6. Scholarly products that include 2 manuscripts, 6 scientific abstracts, and 5 poster presentations.

Meanwhile, our most important problem was interruptions of enrollment in Jamaica from 9/2000 to 2/2002 (18 months) and in West African since September since 2000 for administrative reasons. The reasons included difficulty establishing reliable collaborations with investigators in West Africa and protocol review process issues in Jamaica. Despite these problems, the project made good progress in several areas. Before describing our progress in the required format, I will summarize the amendments made to our original Statement of Work (Table 1), specify the number of subjects enrolled under each protocol by site (Table 2) and present of timeline summary of work completed.

TABLE I. Statement of Work - Original and Amendments

	<u>ORIGINAL</u>	<u>AMENDMENTS</u>
Statement of Work	Task 1. Provide reliable recruitment of incident cases in region. a) Create consortia of urologist and pathologists in each region: SW Nigeria (incl. Ibadan and Lagos), Jamaica and Chicago, IL. b) Develop incident case recruitment strategies appropriate for each research site, with the goal of <i>soliciting participation</i> of 75% of newly diagnosed cases per site (25-50/region) per year. Task 2. Characterize each case using a common protocol. a) Convene pathologists for a review of the Gleason grading system and group reading of representative slide of cases diagnosed in each region. b) Determine histologic grades ('Gleason sums') of cases subsequently enrolled by consensus via the Internet, using whole slide images created by Bacus Laboratory Inc. and posted on an access-restricted website. c) Identify and monitor adherence to a common set of tumor and lymph node staging procedures. d) Collect baseline demographic, clinical and pathologic data via medical records review and by patient interviews where needed. Task 3. Create a centralized repository for serum, plasma, leukocytes and prostate tissue for biochemical and molecular studies. a) Collect plasma, serum, and leukocytes on each case at the time of diagnosis, as well as fresh normal prostate tissue at the time of surgery from those undergoing radical prostatectomy b) Bank all specimens in Chicago (Department of Preventive Medicine, Loyola University) using an existing barcode driven specimen identification and storage system.	Task 1: a) Per reasons cited in the previous two annual progress reports, attempt to transfer research operations in West Africa from the University of Ibadan in Nigeria to Korle Bu Teaching Hospital of the University of Ghana in Accra, Ghana. Dr. Samuel Gopee, a urologist, will serve as the regional investigator for the study; a pathologist at Korle Bu will be named at a later date. Meanwhile, extend recruitment of eligible African-American men to Prairie Medical, a busy private urology practice on Chicago's predominantly African-American Southside affiliated with Mercy Hospital. b) Since initial recruitment in Chicago and Jamaica tended to exceed expectations, increase the total number of cases to be recruited in each region will be increase from 60 to 120 per year. Task 2: b) Per reasons cited in the previous report, replace Dr. Eva Wojcik with an outside pathologist who will serve as the pathology consultant for the project. Along with his/her colleague in Jamaica and Ghana, this new pathologist will be responsible for making histopathologic determinations on cases enrolled in Chicago area [Loyola University Medical Center/Edward Hines VA and Mercy Hospital] and to participate in the protocol to monitor inter-observer agreement. Level of agreement between pathologists will be monitored using a 25% random sample from each site to be circulated to each pathologist. Determining Gleason sums on all cases by consensus between pathologists will no longer be attempted. Task 3: a) Collect height and weight at baseline, and follow-up data on symptoms, response to treatment, recurrence/progression, vital status and causes of death using a structured questionnaire. b) Process and store all patient specimens in a -70° C freezer Edward Hines, Jr. VA, in Building 1, Room C208.

TABLE I. Statement of Work - - Original and Amendments (Continued)

	ORIGINAL	AMENDED																																						
Statement of Work	Task 4. Link case demographic, clinical and pathologic characteristics to corresponding tissue samples using a computerized database. a) Establish a single computerized registry of demographic, clinic and pathologic data for cases recruited in each region. b) Combine tissue and registry data into a single electronic record, linking case registry information to corresponding tissue samples using their unique barcode identification number. Task 5. Pilot Studies: Conduct comparative studies of genes, nutrition and histopathologic markers of prognosis. a) Compare androgen receptor gene CAG repeat sequence lengths and the distribution of CYP3A4 receptor gene variants among 50 cases vs. 50 age-matched controls in each region, and how they relate to stage at presentation within and between groups. b) In 20 of these men undergoing radical prostatectomy in each region, measure prostatic levels of carotenoids, tocopherols, retinol and fatty acids. Compare mean levels, and explore how they relate to markers and whether they modify a relation between androgen and CYP3A4 receptor gene variants and markers of progression, raising the possibility of gene-nutrient interactions.	Task 4. No changes requested. Task 5. Restructure Pilot Studies as Follows: <table><tr><th>Study Purpose</th><th>Design</th><th>Endpt.</th><th>Feature or Risk Factor</th><th>Within Sites</th><th>Across Sites</th></tr><tr><td>I. Descriptive</td><td>Frequency Distribution</td><td></td><td>Clinico-pathology, Genes, Nutrition, Metabolism</td><td>Yes</td><td>Yes</td></tr><tr><td rowspan="3">II. Analytic</td><td rowspan="2">Cross-sectional</td><td>Inter-mediate Endpoint</td><td>Genes, Nutrition, Metabolism</td><td>Yes</td><td>Yes</td></tr><tr><td>Clinical outcome</td><td>Genes, Nutrition, Metabolism</td><td>Yes</td><td>Yes</td></tr><tr><td>Prospective cohort</td><td>Clinical outcome</td><td>Genes, Nutrition, Metabolism</td><td>Yes</td><td>Yes</td></tr><tr><td rowspan="2">B. Disease Etiology</td><td colspan="2">Traditional case-control studies</td><td>Disease present</td><td>Yes</td><td>Yes</td></tr><tr><td colspan="2"></td><td>Inter-mediate Endpoint</td><td>TBD</td><td>TBD</td></tr></table>	Study Purpose	Design	Endpt.	Feature or Risk Factor	Within Sites	Across Sites	I. Descriptive	Frequency Distribution		Clinico-pathology, Genes, Nutrition, Metabolism	Yes	Yes	II. Analytic	Cross-sectional	Inter-mediate Endpoint	Genes, Nutrition, Metabolism	Yes	Yes	Clinical outcome	Genes, Nutrition, Metabolism	Yes	Yes	Prospective cohort	Clinical outcome	Genes, Nutrition, Metabolism	Yes	Yes	B. Disease Etiology	Traditional case-control studies		Disease present	Yes	Yes			Inter-mediate Endpoint	TBD	TBD
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B. Disease Etiology	Traditional case-control studies		Disease present	Yes	Yes																																			
			Inter-mediate Endpoint	TBD	TBD																																			

TABLE II. Protocols and Subject Recruitment:

	<u>ORIGINAL PROTOCOL</u>		<u>AMENDED PROTOCOL</u>			
Sites w/ Local IRB Approval	*Loyola University of Chicago (LUMC) (Approval date: 10/99)		*Loyola University of Chicago (LUMC) (Approval date: 1/02)			
	*Mercy Hospital (Approval date: 10/01)		*Mercy Hospital (Approval date: 10/02)			
	*The University of the West Indies, Jamaica (Approval date: ~2/2001)		*Korle Bu Hospital, University of Ghana, Accra, Ghana (Approval date: 10/02)			
	*University of Ibadan, Nigeria (Approval date: Per report of regional PI; actual date not known.)		*The University of the West Indies, Jamaica (Enrollment ended as scheduled but before the amended protocol was approved; hence, all of the participants in Jamaica were enrolled under the original protocol.)			
Sites w/ DOD/PCRP Approval	*Loyola University of Chicago (LUMC) (Approval date: 10/00)		*Loyola University of Chicago (LUMC) (Approval date: Fall, 2002)			
	*The University of the West Indies, Kingston, Jamaica (Approval date: 3/2002)					
Dates of data collection by site under original and amended protocols (Eligibility retro-active up to 12 months prior to being contacted and asked to enroll.)	Chicago Area		Chicago Area		Kingston, Jamaica	
	LUMC		LUMC		UWI	
	Apr 10, 2000-Dec 31, 2002 (Eligibility retroactive to 1/1/00)		Jan 1, 2003 - Feb 28, 2003		-	
	May 22, 2000-Sep 1, 2000 (Eligibility retro-active to 1/1/00) Mar 20, 2002-Mar 27, 2003 (Eligibility retro-active to 3/1/01) Months of recruitment = 9 + 12 + 13 = 34		-		-	
No. Enrolled	94	61 + 40 + 105 = 206	24	10	0	0

ADMINISTRATIVE TASKS

TIMELINE:

May-October 2001:	Project planning with Dr. Gepi-Attee of the University of Accra, Ghana <u>Original protocol</u> approved by Mercy Hospital IRB.
October 23 – November 1:	Ghana site visit; feasibility of implementing <i>amended protocol</i> directly assessed with Dr. Gepi-Attee. Dr. Richard Kwasi Gyasi is mentioned as the likely pathologist on the project.
December 17, 2001:	<i>Amended protocol</i> submitted to LUMC IRB for approval.
January 16, 2002:	<i>Amended protocol</i> fully approved by LUMC IRB.

March, 2002:	Implementation of <u>original protocol</u> at the University of the West Indies, Kingston, Jamaica approved by DOD; recruitment resumes at the University of the West Indies shortly thereafter.
April 9, 2002:	<i>Amended protocol</i> and revised budget requests submitted to DOD for detailed review and approval.
April 30, 2002:	Annual Progress Report submitted (Year 2).
May 13-15, 2002:	Memorandum of Record for the approval of the <i>amended protocol</i> at each clinical site (Loyola, Ghana and Mercy Hospital) issued to PI by Mercy Swatson. (See appendix.)
May 16, 2002:	<i>Amended protocol</i> submitted to Noguchi Institute IRB in Accra.
July 14, 2002:	<i>Amended protocol</i> receives conditional approval by the Noguchi Institute.
September 5, 2002:	Response to the Noguchi Institute review of <i>amended protocol</i> submitted.
September 17, 2002:	Responses to Memorandum of Record for <i>amended protocol</i> submitted
September 20, 2002:	Additional administrative requests for <i>amended protocol</i> received.
October, 2002:	<i>Amended protocol</i> fully approved at Mercy Hospital.
October 24, 2002:	<i>Amended protocol</i> fully approved by Noguchi.
October 30, 2002:	Response to these requests sent to Robin Dillner.
Fall, 2002:	<i>Amended protocol</i> at LUMC approved by DOD
December 18, 2002:	Reply from Robin Dillner with a few additional requests for research sites in Ghana and in Jamaica.
December/January 2003:	12-month no-cost extension for the project requested and granted.
March 27, 2003:	Recruitment in Jamaica ends.

DATA COLLECTION, BIOCHEMICAL & MOLECULAR STUDIES,
DATA ANALYSIS

<i>TIMELINE:</i>	<i>CASE REGISTRY: Sociodemographical, clinical and pathological data</i>	<i>BIOCHEMICAL & MOLECULAR STUDIES:</i>
March 2002:	Hand Audit Checks: Each form reviewed for completeness and coherence. (PI)	Plasma and prostate tissue samples sent to Tuft Univ. for antioxidant and fatty acid measurements.
April 2002:	1) Verification and missing data collection (research assistance /project coordinator) 2) 2 nd Round Hand Audit Checks (PI)	Extracted DNA samples sent to Howard Univ. for genotyping of candidate prostate cancer genes (variants of 5- alpha reductase, androgen receptor microsatellite and selected cytochrome P450 proteins).
May 2002:	Case registry form data entered using the double-keyed method. (RA/PC/PI)	1) Genotyping completed. 2) Raw data reviewed and questionable results re-assayed. (PI/Molecular geneticist)
June 2002:	Data cleaning and analysis (PI)	1) Genotyping results certified. 2) Nutrient assays completed.
July 2002:		1) Genetic data entered, cleaned and association studies performed. (PI) 2) Raw nutrient data reviewed. (PI)
August 2002:		1) Nutrient results certified. 2) Comparative studies performed on prostate tissue.
September 2002:		Database integrating demographic, clinical, pathological, nutritional and genetic data created. (PI)

RESULTS DISSEMINATION ACTIVITIES

TIMELINE:

September 2002:	5 Scientific abstracts written (3 by PI, 2 by Jamaican collaborators) and circulated to current and future collaborators (including Drs. Terry Mason and John Cudecki of Mercy Hospital) for comments and revisions. (PI)
October 2002:	1 abstract submitted to the American Urological Association (AUA). (PI)
November 2002:	1) 2 abstracts submitted to the American Association for Cancer Research (AACR). (PI) 2) Jamaican case series paper revised and resubmitted to the <i>West Indian Medical Journal</i> . (Jamaica)
December 2002:	1) 2 abstracts submitted to the American Society of Clinical Oncology (ASCO). (Jamaica) 2) Consensus grading paper extensively revised and resubmitted to the journal <i>The Prostate</i> . (PI)
January 2003:	AACR abstracts accepted for poster presentations.
March 2003:	ASCO abstracts accepted (1 poster, 1 publication only).
April 2003:	Consensus paper accepted by the journal <i>The Prostate</i> .
June 2003	Poster presented at ASCO's annual meeting in Chicago (Jamaica/PI)
July 2003	Posters (2) presented at the AACR's annual meeting in Washington, DC (originally scheduled for Toronto in April, but cancelled due to the SARS epidemic). (PI)

II. BODY

Approved Statement of Work

Task 1. “Provide reliable recruitment of incident cases in region.”

- a. Create consortia of urologist and pathologists in each region: southwest Nigeria, the island of Jamaica and Chicago, IL.
- b. Develop incident case recruitment strategies appropriate for each research site, with the goal of *soliciting participation* of 75% of newly diagnosed cases per site (25-50 cases per region) per year.
- c. To help meet enrollment target for the Chicago area, extend recruitment of eligible African-American men to a Mercy Hospital-affiliated private practice

We were able to establish productive and reliable recruitment strategies at our research sites in Chicago and Jamaica, but were not able to establish recruitment in Ghana.

Task 2. “Characterize each case using a common protocol.”

- a. Convene pathologists for a review of the Gleason grading system and group reading of representative slide of cases diagnosed in each region.
- b. Level of agreement between pathologist will be monitored using a 25% random sample from each site to be circulated to each pathologist..
- c. Identify and monitor adherence to a common set of tumor and lymph node staging procedures.

Tasks 2a through 2c were accomplished between Chicago and Jamaica.

Task 3. “Create a centralized repository for serum, plasma, leukocytes, and prostate tissue for biochemical and molecular analyses”

- a. Collect plasma, serum, and leukocytes on each case as well as fresh normal prostate tissue from patients undergoing radical prostatectomy.
- b. Collect height and weight at baseline, and follow-up data on symptoms, response to treatment, recurrence/progression, vital status, and causes of death using a structured questionnaire.
- c. Process and store all patient specimens in a -70⁰ freezer at Edward Hines, Jr. VA in Bldg 1, RM. C208

Task 3a thru 3c have been accomplished.

Task 4. “Link case demographic, clinical, and pathologic characteristics to corresponding tissue samples using a computerized database.”

This task has been accomplished.

Task 5. Pilot Studies: Conduct comparative studies of genes, nutrition, and histopathologic markers of prognosis.

This task has been accomplished. Results of pilot studies have been published in abstract form and/or presented in poster presentations at national meetings. The products are cited in the bibliography.

III. KEY RESEARCH ACCOMPLISHMENTS

- The purpose of this research was to develop the infrastructure for comparative studies of prostate cancer in blacks who reside in contrasting environmental settings. The key accomplishments are as follows:
- An epidemiological research infrastructure (specifically, accessible populations, clinical resources, and data collection methods) to support unified measurement of exposures and prostate cancer in Chicago, IL and Kingston, Jamaica.
- Biochemical and genetic studies in approximately 40% of subjects enrolled.
- A clean electronic database that integrates demographical, clinical, and pathologic tumor characteristics of each case to corresponding archived tissue specimens.
- Statistical analysis of a) case demographical, clinical, and pathologic characteristics between Chicago, Kingston, and West Africa; b) levels of antioxidants and fatty acids in serum and prostate tissue in cases from Chicago and Kingston; c) association of studies of variants of genes involved in androgen metabolism with clinical stage of prostate cancer within and across sites (Chicago, Kingston, and West Africa).
- Two manuscripts, 6 abstracts, and 5 posted presentations.

IV. REPORTABLE OUTCOMES

A. Manuscripts

1. **Freeman VL**, Coard KCM, Wojcik E, Durazo-Arvizu R. Use of the Gleason system in international comparisons of prostatic adenocarcinomas in blacks. *Prostate* 2004; 58(2):169-173
2. Coard KCM, **Freeman VL**. Gleason grading of prostate cancer: level of concordance between pathologists at the University Hospital of the West Indies. *Am J Clin Pathol* 2004 122:373-376.

B. Abstracts

1. **Freeman, VL**, Coard, K, Ogunbiyi, O, Wojcik, EM. Gleason scoring system: high level of agreement between pathologists from three countries. Proceedings of the United States and Canadian Academy of Pathology. *Lab Invest* Volume 81, pg. 108A, #624, January 2001
2. Wojcik, EM, Coard, K, **Freeman, VL**. Prostate cancer in African Americans and Jamaicans. Proceedings of the United States and Canadian Academy of Pathology. *Lab Invest* Volume 81, pg. 128A, #743, January 2001
3. **Freeman VL**, Kittles RA, Adebamowo A, Bennett F, Tullock T, Aiken W, Coard KCM, Pantan B, Cudecki JJ, Mason T, Flanigan RC, Sylvester N. Steroid 5-alpha reductase type II V89L substitution and risk of advanced prostate cancer in black men from Nigeria, Jamaica and Chicago. *Proceedings of the American Association for Cancer Research*, Volume 44, 2nd ed., #3613, July 2003.
4. **Freeman VL**, Kittles RA, Bennett F, Aiken W, Tullock T, Coard KCM, Pantan B, Adebamowo A, Mason T, Cudecki JJ, Flanigan RC, Sylvester N. Steroid 5-alpha reductase type II V89L variant frequencies and androgen receptor CAG microsatellite lengths among black men with prostate cancer from Nigeria, Jamaica and Chicago, Illinois. *Proceedings of the American Association for Cancer Research*, Volume 44, 2nd ed., pg 717, #3614, July 2003.
5. Bennett FI, **Freeman VL**, Coard K, Aiken W, Tulloch T, Forrester T, Pantan B, Flanigan R. Fatty acid composition of prostatic tissue from blacks in Jamaica and Chicago. *Proceedings of the American Society of Clinical Oncology*, Volume 22, #1658, May 2003
6. Aiken W, Tulloch T, **Freeman V**, Bennett F, Coard K, Pantan B, Kittles R, Mason T, Flanigan R. Differences in Patient Characteristics in Black Men with Prostate Cancer from Jamaica and Chicago. *Proceedings of the American Society of Clinical Oncology*, Volume 22, #1764, May 2003.

C. Presentations

1. 90th Annual Meeting of the United States and Canadian Academy of Pathology (USCAP), Atlanta GA, USA. "Gleason scoring system: high level of agreement between pathologists from three countries." March 5, 2001.
2. 90th Annual meeting of the United States and Canadian Academy of Pathology (USCAP), Atlanta, GA USA. "Prostate cancer in African Americans and Jamaicans."

3. American Association for Cancer Research (AACR), 94th Annual Meeting, Toronto, Canada: “Steroid 5-Alpha Reductase Type II V89L Variant Frequencies and Androgen Receptor CAG Microsatellite Lengths Among Black Men With Prostate Cancer From Nigeria, Jamaica and Chicago, Illinois.” April 7, 2003. (Rescheduled for July 12, 2003, Washington, DC.)
4. American Association for Cancer Research (AACR), 94th Annual Meeting, Toronto, Canada: “Steroid 5-Alpha Reductase Type II V89L Substitution and Risk of Advanced Prostate Cancer in Black Men from Nigeria, Jamaica and Chicago.” April 7, 2003. (Rescheduled for July 12, 2003, Washington, DC.)
5. 2003 Annual Meeting of the American Society of Preventive Oncology (ASCO), Chicago, IL. “Fatty Acid Composition of Prostatic Tissue from Blacks in Jamaica and Chicago.” June 1, 2003.

D. Tissue Repository

We obtained the following biospecimens from N subjects: leukocytes (n=303), plasma/serum (n=262), fresh normal prostate tissue (n=44).

List of Paid Personnel

Chicago:

Vincent L. Freeman, MD, MPH – PI
Christopher Dorgan, BA – Project Coordinator

Jamaica: (through subcontract with the University of the West Indies)

Barbara Panton, RN – Site Project Coordinator

V. CONCLUSIONS:

We were able to establish the feasibility of developing the infrastructure needed for comparative studies of prostate cancer in blacks in the Chicago and in Kingston, Jamaica. The assumption that these sites differ in lifestyle exposures is probably correct. Our data also suggest that lycopene plays an etiopathogenic role in prostate cancer and that inheriting a variant of the gene encoding 5-alpha-reductase associated with lower enzymatic activity may lower the risk of advanced-stage prostate cancer.

This report is respectfully submitted by

Vincent L. Freeman, MD, MPH
Principal Investigator
Division of Epidemiology and Biostatistics
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APPENDICIES

Manuscripts

1. Freeman VL, Coard KCM, Wojcik E, Durazo-Arvizu R. Use of the Gleason system in international comparisons of prostatic adenocarcinomas in blacks. *Prostate* 2004; 58(2):169-173
2. Coard KCM, Freeman VL. Gleason grading of prostate cancer: level of concordance between pathologists at the University Hospital of the West Indies. *Am J Clin Pathol* 2004 122:373-376.

Use of the Gleason System in International Comparisons of Prostatic Adenocarcinomas in Blacks

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BACKGROUND. Comparisons of prostate cancer in blacks living in different countries can shed light on factors responsible for high rates of the disease among blacks in America. Since the prognostic value of the Gleason grading system is well established, we assessed agreement between pathologists in countries where black populations of the African Diaspora reside.

METHODS. Three genitourinary pathologists at hospitals in Nigeria, Jamaica, and the US independently assessed sextant biopsies from 12 patients. Gleason sum and percentage involvement were recorded, and a percent-weighted average calculated. Agreement under different groupings was evaluated using the kappa statistic generalized to three raters.

RESULTS. Agreement was significant for individual sums ($\kappa=0.3317$, $P=0.0173$), sums grouped as well (2–4), moderately (5–6), and poorly differentiated (7–10) ($\kappa=0.2437$, $P<0.0001$) and other groupings. Agreement between at least two raters was 91.7–100%; complete agreement was 41.7–66.7%.

CONCLUSIONS. The Gleason system is feasible and practical for international studies of prostate cancer among blacks from contrasting environments. *Prostate* 58: 169–173, 2004.

Published 2003 Wiley-Liss, Inc.[†]

KEY WORDS: prostatic neoplasm; African Americans; prognosis

INTRODUCTION

Comparative studies of prostate cancer disease among blacks who reside in contrasting environmental settings can shed light on the environmental and inheritable factors responsible for the high rates of the disease among blacks in the US [1]. However, conducting such studies are complex, with standardized assessment of disease severity and prognosis posing particularly difficult challenges. Correlation between prostate cancer's diverse architectural and cytologic appearances and its wide-ranging biologic behavior is widely recognized [2–5]. Several different grading systems that group these appearances into prognostically relevant grades of prostate cancer have been proposed [6–10]. However, the architecturally based

Gleason system is the one in most general use worldwide [10]. Its value for clinical prediction has been established in a greater number of patient-years follow-up than for any other system, criteria for assigning grade are clearly defined and relatively reproducible

Grant sponsor: The US Department of Defense; Grant number: DAMD17-00-1-0029 and the Department of Veterans Affairs (RCD 97-317).

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[10–14]. Indeed, the World Health Organization recommends that histologic grading using the Gleason system be used routinely in the prognostic evaluation of prostatic adenocarcinomas [15].

Therefore, the Gleason system should play an integral role in the prognostic stratification of prostatic adenocarcinomas in international comparisons of the disease. However, assigning Gleason sums (GSs) is susceptible to inter-individual variation, even between pathologists from the same institution. To examine the feasibility of using the Gleason system in this context, we assessed the level of agreement in the assignment of GSs between pathologists practicing in three countries where black populations of the African Diaspora reside.

MATERIALS AND METHODS

Twelve slides of sextant biopsies positive for prostate cancer were randomly selected from archives at our institution. Three pathologists, one each from Kingston, Jamaica, Ibadan, Nigeria, and the Chicago metropolitan area, were asked to participate. Three criteria for selection were used: (1) genito-urinary pathology was their subspecialty, (2) their practice was based primarily at an academic institution, (3) and they reviewed the majority of prostate tissue specimens collected at their institution. Slides of the 12 US cases were circulated to the pathologists for independent histologic evaluation. Each was blinded to the question under study, and there was no advance didactical preparation. GS and percentage involvement of each positive core were recorded using a uniform scoring form, a percent-weighted average GS was calculated for each subject for each pathologist and sums rounded to the nearest integer. The Kruskal–Wallis statistic was used to compare mean sums, and agreement under three pre-determined groupings was evaluated using the kappa (κ) statistic generalized to three raters as described by Fleiss [16] (see Appendix).

RESULTS

Table I compares the variability of GSs assigned by each pathologist to the 12 cases. Although sums assigned by pathologist #3 demonstrated the greatest variation, mean sums between pathologists were not

statistically different from one another ($P = 0.411$). Excluding a ‘negative’ biopsy result from pathologist 3 moved the mean sum (SD) to 6.35 (1.18) ($P = 0.684$).

Figures 1–3 show the GSs assigned to each case by each pathologist under various groupings. ‘Complete agreement’ was defined as all three pathologists assigning the case to the same category. For individual sums (Fig. 1), complete agreement was observed in 5 of 12 cases (41.6%), and agreement between at least two pathologists was seen in 11 of 12 cases (91.7%) ($\kappa = 0.3317$, $P = 0.0087$). Figure 2 shows pathologists’ assignments when sums were grouped as well (GS 2–4), moderately (5–6), and poorly (7–10) differentiated. Complete agreement occurred in 8 of 12 cases (66.7%), and agreement between at least two pathologists was again observed in 11 of 12 cases ($\kappa = 0.2437$, $P < 0.0001$). When sums were grouped as well to moderately differentiated (2–6), GS = 7 and poorly differentiated (8–10) (Fig. 3), agreement between at least two pathologist occurred in 100% of cases, but complete agreement was observed in only half ($\kappa = 0.2761$, $P = 0.0336$).

DISCUSSION

International variation in prostate cancer mortality suggests a causative role for environmental factors. Among black populations, available data seemed to support a gradient of risk with relatively low rates in Africa, intermediate rates in the Caribbean, and the highest rates in America [17]. However, recent reports of comparable disease rates in these regions appear to dispute these historically accepted ranking and suggest a possible role for inheritable or shared lifestyle factors [18–20]. International comparisons of prostate cancer disease in these populations can play an important role in helping to disentangle the contributions of the environment and genetics to prostate cancer disease in general. Therefore, having robust and reproducible markers of prognosis with which to make such epidemiologic comparisons would be essential. Our results suggest that use of the Gleason system is not only feasible but is practical for this purpose. The level of agreement between the three pathologists based on various measures was generally high. However, the finding of full concordance in only 6 of the 12 cases when sums were grouped as <7, 7, and >7 suggests a need for approaches that help better distinguish

TABLE I. Descriptive Statistics

Pathologist	1	2	3	<i>P</i> -value
Gleason sum range ^a	6–7.23	6–8	0–8.11	
Mean Gleason score (SD)	6.38 (0.14)	6.67 (0.18)	5.82 (0.62)	0.411

^aGleason score (GS) calculated as the %-of-core-weighted mean GS.

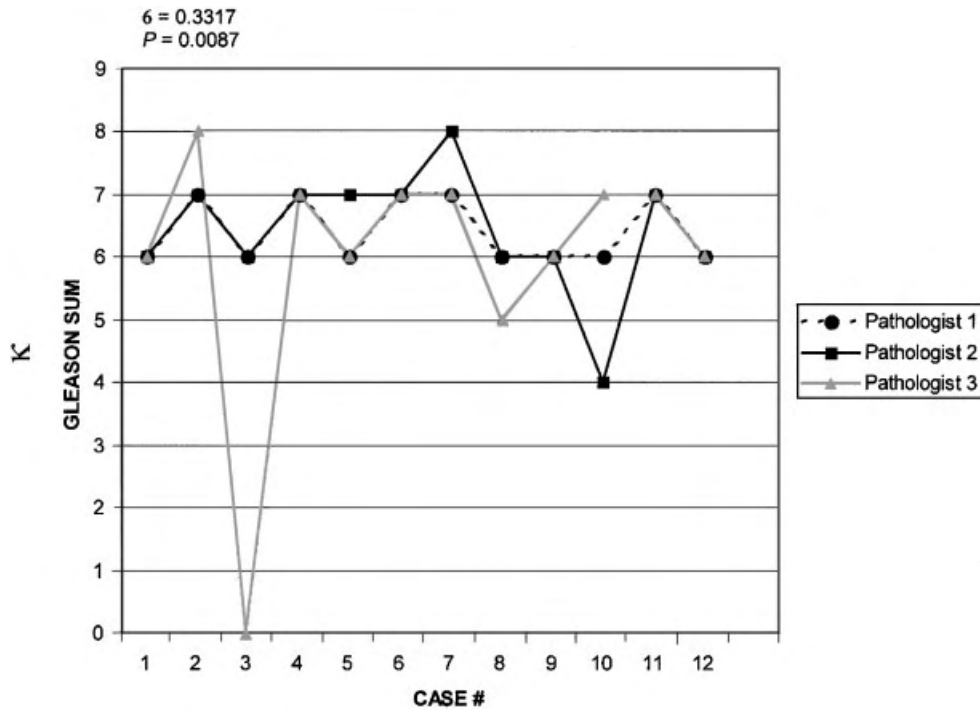


Fig. 1. Gleason sum (GS) assignments for each case. GS = 0 for biopsies (N = 1) interpreted as negative by a pathologist. Kappa (κ) = $(P_0 - P_E) / (1 - P_E)$, where P_0 and P_E are the observed and expected proportion of agreement, respectively.

between GSs of 6 and 7. The Internet and web-based strategies hold considerable promise in this regard [21].

The strengths of this study included blinding pathologists to the question under study, lack of advanced

didactical preparation on their part, and independent assessment. Although slides were selected at random, a potentially important limitation was the narrow spectrum of sums evaluated. While it may have reflected the

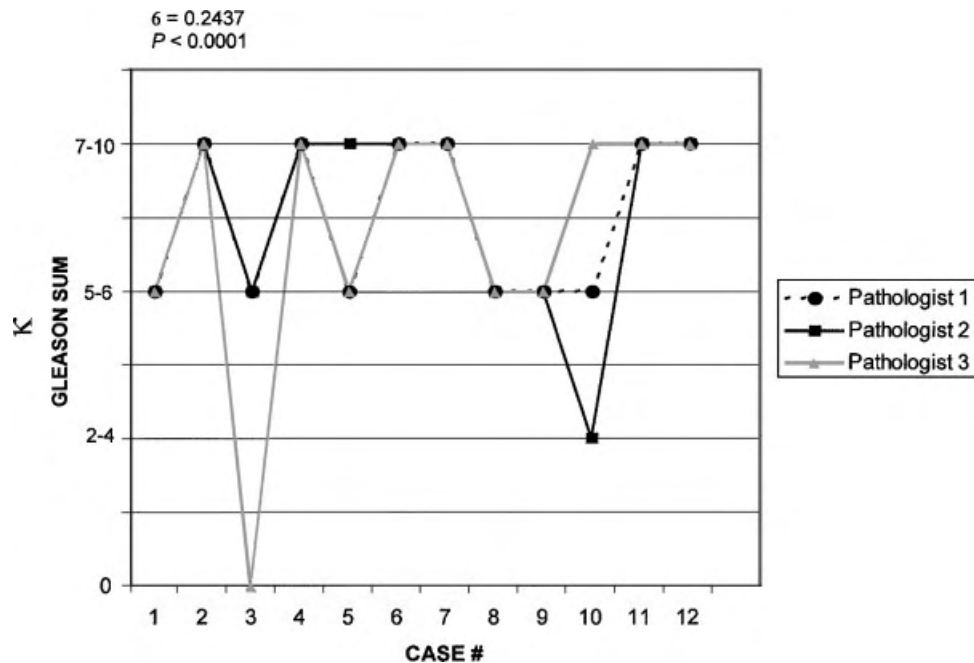


Fig. 2. GS assignments for each case with sums grouped into 2–4, 5–6, and 7–10, corresponding to well, moderated, and poorly differentiated, respectively. GS = 0 for biopsies (N = 1) interpreted as negative by a pathologist. Kappa (κ) = $(P_0 - P_E) / (1 - P_E)$, where P_0 and P_E is the observed and expected proportion of agreement, respectively.

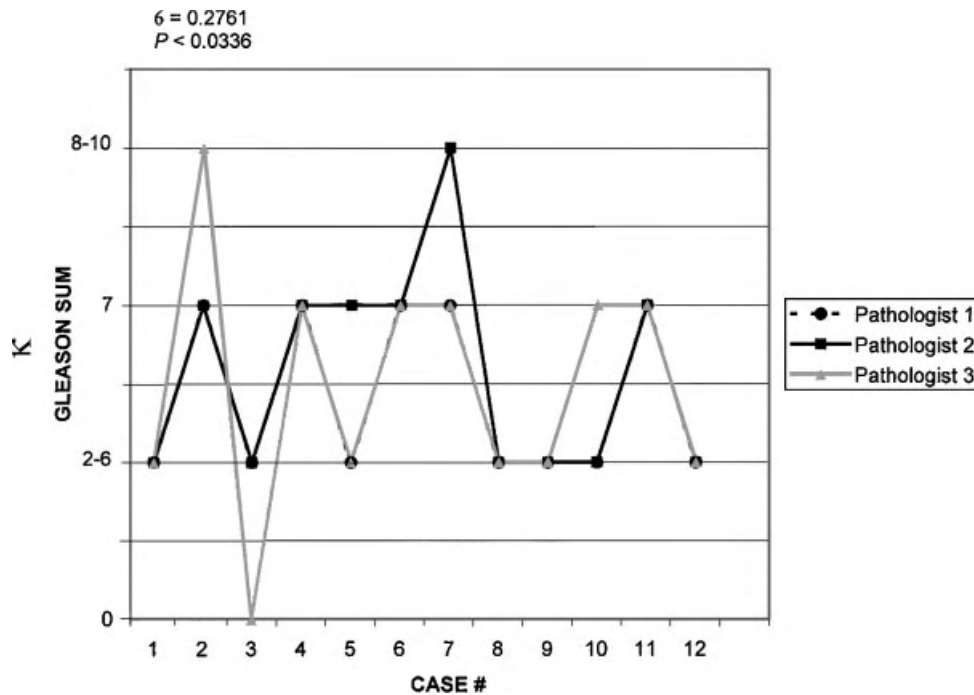


Fig. 3. GS assignments for each case with GS = 7 considered separately. GS = 0 for biopsies (N = 1) interpreted as negative by a pathologist. Kappa (6) = $P_0 - P_E / 1 - P_E$, where P_0 and P_E is the observed and expected proportion of agreement, respectively.

average distribution of histopathologic findings, not all possible sums or combinations were evaluated. This could have enhanced performance, thus overestimating agreement.

CONCLUSIONS

The Gleason system for the routine prognostic evaluation of prostate cancer appears to be both feasible and practical for international comparative studies of the disease in black populations of the African Diaspora. Strategies that help distinguish between sums of 6 and 7 could greatly enhance the validity of the Gleason system for standardized disease assessment under this study design.

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APPENDIX

Calculation of Kappa Statistic: The use of kappa and weighted kappa is usually restricted to the case where both the number of raters is two and where the same two raters rate each subject. The method used to calculate kappa in this setting was based on that described by Fleiss [15]. This method considers the case

of more than two raters and the case where the raters judging one subject are not necessarily the same as those judging another.

Let N = the total number of subjects (cases), n = number of raters (pathologists) per subject, k = number of categories (grades), n_{ij} = number of raters who assigned the i th subject to the j th category, and p_j = the proportion of all assignments made to the j th category ($= \sum n_{ij} / Nn$). The level of agreement among ' n ' pathologist for the i th subject can then be indexed by the proportion of agreeing pairs out of all the $n(n-1)$ possible pairs of assignments. This proportion is:

$$P_i = \frac{1}{n(n-1)} \sum_{j=1}^k n_{ij}(n_{ij} - 1) = \frac{1}{n(n-1)} (\sum_{j=1}^k n_{ij}^2 - n)$$

The overall extent of agreement is then measured by the mean of P_i 's:

$$\begin{aligned} \bar{P} &= \frac{1}{Nn(n-1)} \sum_{i=1}^N \sum_{j=1}^k n_{ij}(n_{ij} - 1) \\ &= \frac{1}{Nn(n-1)} (\sum_{i=1}^N \sum_{j=1}^k n_{ij}^2 - Nn) \end{aligned}$$

Let the mean of the P_i 's = 0.60. This result is interpreted as follows: let a case be selected at random and graded by a randomly selected pathologist. If the case were to also be graded by a randomly selected pathologist, the second pathologist would agree with the first

for 60% of the time. However, some degree of agreement would be expected solely on the basis of chance. In fact, if the pathologists made their assignments purely at random, one would expect the mean proportion of agreement to be:

$$P_{J \text{ expected}} = \Sigma P_j^2 = 0.3765$$

The quantity $1 - P_{\text{expected}}$ measures the degree of agreement attainable over and above what would be expected by chance. Kappa (κ) is the degree of agreement actually attained in excess of chance is calculated as follows:

$$\kappa = \frac{P - P_{\text{expected}}}{1 - P_{\text{expected}}}$$

which is a normalized measure of overall agreement corrected for the amount expected by chance. Since this normalized estimate of κ follows a normal distribution, we can test the following null hypothesis to evaluate whether the normalized estimate of agreement between the pathologists is significant:

$$H_0 : \frac{\kappa}{(\text{Standard error})} < 1.96,$$

This is equivalent to the hypothesis of "no agreement." The standard error of κ ($SE(\kappa)$) is equal to the square-root of the variance of κ ($Var(\kappa)^{1/2}$). The variance of κ under the hypothesis of "no agreement" beyond chance is approximately equal to:

$$Var(\kappa) = \frac{2}{Nn(n-1)} \times \frac{[\Sigma P_j^2 - (2n-3)(\Sigma P_j^2)^2 + 2(n-2)(\Sigma P_j^3)]}{(1 - \Sigma P_j^2)^2}$$

If $\kappa/(SE) > 1.96$, then the agreement between pathologists is significantly greater than you would expect by chance alone.

REFERENCES

1. Kittles RA, Chen W, Panguluri RK, Ahaghotu C, Jackson A, Adebamowo CA, Giffin R, Williams T, Ukoli F, Adams-Campbell L, Kwagyan J, Isaacs W, Freeman V, Dunston GM. CYP3A4-V and prostate cancer in African Americans: Causal or confounding association because of population stratification. *Hum Genet* 2002;110:553-560.
2. Galle MPW, Ten Kate JW, Mulder GH. Histologic grading of prostatic carcinoma in prostatectomy specimens. *Br J Urol* 1990;65:368-375.
3. Schroeder FH, Bloom JH, Hop WC, Mostofi FK. Grading of prostatic carcinoma: I. An analysis of the prognostic significance of single characteristics. *Prostate* 1985;6:81-100.
4. Grahack JT, Assimos DG. The prognostic significance of tumor grade and stage in patients with carcinoma of the prostate. *Prostate* 1983;4:13-433.
5. Gleason DF. Histologic grading of and clinical staging of prostatic carcinoma. In: Tannenbaum M, editor. *Urologic pathology: The prostate*. Lea and Febiger, Philadelphia 1977. pp 171-197.
6. Utz DC, Farrow GM. Pathologic differentiation and prognosis in and prognosis in prostatic carcinoma. *JAMA* 1969;209:1701.
7. Mostofi FK. Grading of prostatic carcinoma. *Cancer Chemother Rep (Part I)* 1975;59:111-117.
8. Harada M, Mostofi FK, Corle DK, Byar DP, Trump BF. Preliminary studies of prognosis in cancer of the prostate. *Cancer Treat Rep* 1977;61:223-225.
9. Brawn P, Ayala AG, Von Eschenbach AC, Hussey DH, Johnson DE. Histologic grading study of prostate adenocarcinoma: The development of a new system and comparison with other methods—a preliminary study. *Cancer* 1982;49:525-532.
10. Gleason DF, Mellinger GT, The Veterans Administration Cooperative Urologic Research Group. Prediction of prognosis for prostatic adenocarcinoma and combined histologic grading and clinical staging. *J Urol* 1974;111:58-64.
11. Sogani P, Israel A, Lieberman P, Lesser ML, Whitmore WF Jr. Gleason grading of prostate cancer: A predictor of survival. *Urology* 1985;25:223-227.
12. Nemoto R, Uchida K, Harada M, Koiso K, Abe R, Kato T. Experience with Gleason histopathologic grading of prostate cancer in Japan. *Urology* 1987;30:436-440.
13. Gardner WA, Coffey D, Karr JP, Chiarodo A, Epstein J, McNeal JE, Miller G. A uniform histopathologic grading system for prostate cancer. *Hum Pathol* 1988;19:119-120.
14. Murphy GP, Whitmore WF. A report of the workshops on the current status of the histologic grading of prostate cancer. *Cancer* 1979;44:1490-1494.
15. Bostick DG, Foster CS. Predictive factors in prostate cancer: Current concepts from the 1999 College of American Pathologists Conference on Solid Tumors Prognostic Factors and the 1999 World Health Organization Second International Consultation on Prostate Cancer. *Semin Urol Oncol* 1999;17:222-272.
16. Fleiss JL. Measuring nominal scale agreement among many raters. *Psych Bull* 1971;76:378-382.
17. Muir CS, Nectoux J, Staszewski J. The epidemiology of prostatic cancer. Geographical distribution and time-trends. *Acta Oncol* 1991;30:133-140.
18. Osegebe DN. Prostate cancer in Nigerians: Facts and nonfacts. *J Urol* 1997;157:1340-1343.
19. Glover FE, Coffey DS, Douglas LL, Cadogan M, Russell H, Tulloch T, Baker TD, Wan RL, Walsh PC. The epidemiology of prostate cancer in Jamaica. *J Urol* 1998;159:1984-1987.
20. Bunker CH, Patrick AL, Konety BR, Dhir R, Brufsky AM, Vivas CA, Becich MJ, Trump DL, Kuller LH. High prevalence of screening-detected prostate cancer among Afro-Caribbeans: The Tobago Prostate Cancer Survey. *Cancer Epidemiol Biomarkers Prev* 2002;11:726-729.
21. Kronz JD, Silberman MA, Allsbrook WC, Baskacky SI, Burks RT, Cina SJ, Mills SE, Ross JS, Sakr WA, Tomaszewski JE, True LD, Ulbright TM, Weinstein MW, Yantiss RK, Young RH, Epstein JI. Pathology resident's use of a Web-based tutorial to improve Gleason grading of prostate carcinoma on needle biopsies. *Hum Pathol* 2000;31:1044-1050.

Gleason Grading of Prostate Cancer

Level of Concordance Between Pathologists at the University Hospital of the West Indies

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Key Words: Gleason grading; Gleason score; Prostate cancer; Interobserver reproducibility

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Abstract

Our aim was to study the level of interobserver concordance in the Gleason scores of prostate needle biopsy specimens reported at 1 institution. A retrospective review of all prostate needle biopsy specimens in which a diagnosis of adenocarcinoma was made during the year 2000 was conducted. Parameters evaluated included the Gleason score, Gleason grades identified, the percentage of Gleason grades 4 and 5, and the percentage of tumor in the biopsy specimen. Our results demonstrated a 60% overall concordance in consensus Gleason scores, which increased to 80% when considered in groups of a Gleason score of less than 7 vs 7 or more. The greatest discordance seemed to be in distinguishing Gleason score 6 from 7 and was more frequent among biopsy specimens with lower tumor volumes, particularly among those with less than 30% involvement. A small percentage of Gleason grade 4 pattern might predict disagreement as well. Strategies for improving accuracy of Gleason score 7 should be devised, and consensus diagnosis for biopsy specimens that demonstrate a low percentage of tumor volume is recommended.

The Gleason histologic grade of prostate adenocarcinoma is thought to be one of the most powerful predictors of biologic behavior and often has an important role in determining patient treatment. It is well known among pathologists that assessment of this histologic grade is associated with interobserver variation. However, the usefulness of any grading system must depend on reasonable interobserver concordance. With this in mind, we sought to study the level of interobserver agreement in the Gleason scores assigned to prostate needle biopsy specimens and reported at the University Hospital of the West Indies, Kingston, Jamaica.

Materials and Methods

We prospectively obtained all prostate needle biopsy specimens for which a diagnosis of carcinoma was made at the University Hospital of the West Indies during the year 2000. This diagnosis was made by any of 9 staff anatomic pathologists (including one of us [K.C.C.]), who received the biopsy specimens while on surgical pathology sign-out duties according to the service roster. One of us (K.C.C.) then reviewed all biopsy specimens without knowledge of the previous Gleason score. This pathologist, by virtue of participation in an international collaborative project on prostate cancer, has had the added advantage of reviewing a large number of such biopsy specimens. Moreover, the interobserver variation for this pathologist previously was compared with that of pathologists from 3 different countries, with a good level of concordance ($\kappa = 0.3317$; $P = .0173$; and $\kappa = 0.2437$; $P < .0001$, respectively, for individual Gleason sums and various sum groupings).¹

During the histopathologic review, the following factors were evaluated: Gleason score, Gleason grades, percentage of Gleason 4 and 5 pattern, and overall percentage of tumor in the biopsy specimen. Evaluation of concordance of the biopsy score with that of a subsequent radical prostatectomy specimen was not undertaken.

Statistical Analysis

Means and SEs were calculated for selected histopathologic characteristics. Because dichotomizing Gleason scores into those less than 7 and those 7 or more helps distinguish between cancers with relatively favorable and those with unfavorable prognoses, respectively,² disagreement in the assignment of Gleason scores of 6 and 7 can be clinically significant. Therefore, interobserver agreement across these categories was assessed by using the weighted κ statistic, and histopathologic correlates of disagreement were determined by using the 2-sample t test and logistic regression analysis.

Results

During the 1-year period, there were 90 needle biopsy specimens for which a diagnosis of prostate cancer was made. Each was assigned a Gleason score ranging from 6 to 10. There were no cases with Gleason scores less than 6. Following review, all scores also ranged from Gleason 6 to 10, but with a change in the distribution. The frequency distribution of the first and second assessment of Gleason scores is given in **Table 1**. The second opinion concurred with the original in 54 (60%) of the cases overall. Correlation within 1 grade was present in 85 (94%), with the remaining 5 cases within 2 of the original grade.

When scores were grouped in categories of Gleason score less than 7 vs 7 or more, agreement occurred 80% ($n = 19 + 53$) of the time **Table 2**. The κ score (95% confidence interval) equaled 0.5429 (0.3648-0.7210), which denotes good reproducibility.³ Eighteen of 90 cases were discordant,

mostly ($n = 15$) owing to undergrading by the original pathologist relative to the review pathologist **Image 1**.

Table 3 shows correlates of interobserver disagreement as determined by using the 2-sample t test. The percentage of tumor involvement was significantly lower in cases in which pathologists disagreed. The percentage of tumor also predicted disagreement in logistic regression ($P = .0454$). Finally, the amount of Gleason grade 4 pattern tended to be lower among discordant ratings than among concordant ratings.

Discussion

In addition to making the diagnosis of adenocarcinoma on needle biopsy specimens from the prostate gland, an important role of the pathologist is to grade the tumor accurately. This grade is perceived by the urologists, radiotherapists, and oncologists to be indispensable because it is used, along with the clinical stage and the prostate-specific antigen level, not only to predict prognosis but also in planning treatment. Although most specialists who use this information accept implicitly the pathologist's grade, far fewer of them perhaps realize the degree of interobserver variation often present in making such an evaluation.

A number of studies comparing the Gleason score in needle biopsy specimens with that in subsequent radical prostatectomy specimens have been reported, and most show a general tendency toward undergrading.⁴⁻⁶ On the other hand, there have been relatively few studies focusing exclusively on the degree of variability of Gleason grading in needle biopsy specimens only. This information is, perhaps, even more imperative, because the grading of a biopsy specimen is one of the more critical factors used in making important decisions about subsequent management, including the efficacy of a radical prostatectomy. Furthermore, unlike the differences between grades assigned to needle biopsy specimens and those assigned to subsequent prostatectomy specimens that, to some extent, could be

Table 1
Frequency Distribution of Raw Gleason Scores on Biopsy Specimens*

Original Gleason Score	Gleason Score Assigned by Reviewer (K.C.C.)					Total
	6	7	8	9	10	
6	19	12	3	—	—	34
7	2	18	8	—	—	28
8	1	3	9	4	1	18
9	—	—	1	7	1	9
10	—	—	—	—	1	1
Total	22	33	21	11	3	90

* Boldface numbers represent concordance.

Table 2
Concordance Between Gleason Scores of <7 vs ≥7*

Original Score	Revised Score		Total
	<7	≥7	
<7	19	15	34
≥7	3	53	56
Total	22	68	90

* Boldface numbers represent concordance.

attributed to tissue sampling error, among biopsy specimens themselves, differences more likely are due to interobserver variability, perhaps because of varying experience. Such studies comparing the degree of consensus specifically relating to needle biopsy specimens have been reported.⁷⁻⁹ The conclusions from 2 of these studies that independently rated concordance in general and in urologic pathologists was that while the interobserver reproducibility of the Gleason grading among urologic pathologists was judged to be acceptable,⁷ that among general pathologists was considered, at best, only moderate and should be improved.⁸

In the present study, the overall rate of concurrence of 60% between original interpretations and review of the needle biopsy specimens is comparable to that of a similar study.⁹ We demonstrated, however, that disagreement was correlated inversely with the percentage of tumor involvement of the biopsy specimen wherein involvement of less than 30% was noted to be associated with a significantly greater risk of discordance in grading between our pathologists. We believe that, at least in our setting, this observation identifies a subgroup of cases that might benefit from consensus grading amongst staff. A similar observation has been reported to affect the level of accuracy in the grading of radical prostatectomy specimens compared with grading of the original needle biopsy specimen⁴ but has not been reported in the comparison of needle biopsy specimens exclusively.

In the past, Gleason scores were grouped together in prognostic groups as follows: Scores 2 through 4, 5 through 7, and 8 through 10, which were designated well-, moderately, and poorly differentiated, respectively. More recently, however, it has been recognized that Gleason score 7 tumors represent a worse prognosis than those with which it was previously grouped.^{2,10} This group is, therefore, separately identified under the category moderately to poorly differentiated.¹¹ The differences in disease progression between patients with tumors graded Gleason 5 or 6 and those graded Gleason 7 suggest that the presence of any component of high-grade tumor (Gleason patterns 4 and 5) worsens the prognosis markedly. Some recent data even suggest that the volume of tumor with a high-grade pattern has prognostic

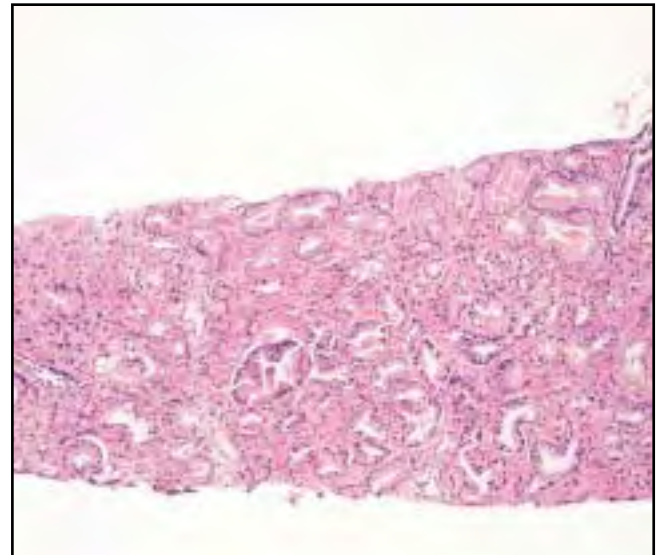


Image 1 Needle biopsy specimen interpreted as Gleason score 6 by original pathologist but 7 by review pathologist. Note the small foci of glandular fusion (pattern 4) to the left and the right center of the photomicrograph, disregarded in the original evaluation of Gleason score (H&E, ×100).

Table 3
Percentage of Tumor Involvement and Percentage of Gleason Grade 4 of Discordant vs Concordant Ratings (Gleason Score, <7 vs ≥7)

	Discordant (n = 18)	Concordant (n = 72)	P
Tumor involvement (%)			
Mean	44.4	62.2	.0405
Median	30.0	70.0	
Gleason grade 4 (%)			
Mean	28.9	44.9	.1132
Median	12.5	50.0	

significance.¹² The implications are, therefore, that disagreement in the assigning of Gleason scores of 6 and 7, particularly that of undergrading, might be clinically significant. The difference in prognosis between these 2 grades is even more relevant than among the higher-grade tumors,² and, likewise, treatment decisions are more likely to be between these 2 grades than among the higher grades.⁸ Thus, in our study, the difference of opinion in the 15 cases of Gleason score 6 tumors that were categorized as Gleason score 7 on review could have had an adverse effect on outcome, if the Gleason scores had the main role in the treatment option selected.

The technical challenges of differentiating a Gleason pattern 3 from 4 are well known, relying in part on the distinction of single and separate glands from poorly formed, fused glands. With crushed tissue, this distinction

could be admittedly difficult. The problem is compounded further because the spectrum of patterns on which the Gleason system of grading is based is a continuum. Some tumors with patterns lying on the interfaces of 2 classic pattern grades often are present, increasing the chances of interobserver variation in interpretation. These same problems accounted for some of the nonconsensus cases in the study reporting grading by urologic pathologists.⁷ Nevertheless, nuances of differentiation can be learned. Recent studies have demonstrated that by using reference images in hard copy¹³ or Web-based¹⁴ formats, the accuracy of Gleason grading among practicing pathologists can be improved easily. The latter is particularly attractive given the widespread availability of the Internet in recent times even to countries, like Jamaica, that traditionally are considered third world. A recent study from Japan also has validated the opinion that improvement in concordance on Gleason grading can be obtained easily by using simple educational resources.⁹

In one of the aforementioned studies, an interesting demographic characteristic associated with more accurate pretutorial Gleason grading was fewer than 5 years in pathology practice.¹⁴ The authors attributed this to the fact that Gleason grading has received greater emphasis during residency training in recent years. It is noteworthy that 7 of 9 pathologists in the present study have been practicing pathologists for more than 10 years. Better pretutorial correlation also was noted when the Gleason system had been learned at a meeting or course as opposed to being self-taught.^{8,14} All but 2 of the pathologists in the present series were self-taught. Notwithstanding this, our overall good correlation supports the opinion of others that the Gleason grading system can, with relative ease, be learned and is reproducible.⁵

A conspicuous observation in this series was that no tumor was assigned a Gleason score of less than 6. This is in contrast with that of many earlier series that identified these lower grade tumors, albeit in small numbers.⁴ While this might be coincidental, this finding supports the recent recommendations by Epstein¹⁵ that a Gleason score of 2 through 4 should not be made on needle biopsy specimens, a view that was, however, criticized by Milette et al.¹⁶

This review of interobserver concordance on the needle biopsy diagnosis of prostate carcinoma in our department reveals reasonably good agreement despite the absence of formal training for most of the pathologists. The greatest discordance seems to be in distinguishing Gleason score 6 from 7, and this is more likely in biopsy specimens with smaller tumor volumes. Strategies for improving accuracy of this grade should be devised, and consensus diagnosis for biopsy specimens with less than 30% tumor volume is recommended.

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References

- Freeman VL, Coard KC, Wojcik E, et al. Use of the Gleason system in international comparisons of prostatic adenocarcinomas in blacks. *Prostate*. 2004;58:169-173.
- Epstein JI, Pizov G, Walsh PC. Correlation of pathologic findings with progression after radical retropubic prostatectomy. *Cancer*. 1993;71:3582-3593.
- Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33:159-174.
- Bostwick DG. Gleason grading of prostatic needle biopsies: correlation with grade in 316 matched prostatectomies. *Am J Surg Pathol*. 1994;18:796-803.
- Steinberg DM, Sauvageot J, Piantadosi S, et al. Correlation of prostate needle biopsy and radical prostatectomy Gleason grade in academic and community settings. *Am J Surg Pathol*. 1997;21:566-576.
- Carlson GD, Calvanese CB, Kahane H, et al. Accuracy of biopsy Gleason scores from a large uropathology laboratory: use of a diagnostic protocol to minimize observer variability. *Urology*. 1998;21:525-529.
- Allsbrook WC Jr, Mangold KA, Johnson MH, et al. Interobserver reproducibility of Gleason grading of prostatic carcinoma: urologic pathologists. *Hum Pathol*. 2001;32:74-80.
- Allsbrook WC Jr, Mangold KA, Johnson MH, et al. Interobserver reproducibility of Gleason grading of prostatic carcinoma: general pathologists. *Hum Pathol*. 2001;32:81-88.
- Mikami Y, Manabe T, Epstein JI, et al. Accuracy of Gleason grading by practicing pathologists and the impact of education on improving agreement. *Hum Pathol*. 2003;34:658-665.
- Tefilli MV, Gheiler EL, Tiguert R, et al. Should Gleason score 7 prostate cancer be considered a unique grade category? *Urology*. 1999;53:372-377.
- Allsbrook WC Jr, Mangold KA, Yang X, et al. The Gleason grading system: an overview. *J Urol Pathol*. 1999;10:141-157.
- Sakr WA, Tefilli MV, Grignon DJ, et al. Gleason score 7 prostate cancer: a heterogeneous entity? correlation with pathologic parameters and disease-free survival. *Urology*. 2000;56:730-734.
- Egevad L. Reproducibility of Gleason grading of prostate cancer can be improved by the use of reference images. *Urology*. 2001;57:291-295.
- Kronz JD, Silberman MA, Allsbrook WC, et al. A Web-based tutorial improves practicing pathologists' Gleason grading of images of prostate carcinoma specimens obtained by needle biopsy. *Cancer*. 2000;89:1818-1823.
- Epstein JI. Gleason score 2-4 adenocarcinoma of the prostate on needle biopsy; a diagnosis that should not be made [editorial]. *Am J Surg Pathol*. 2000;24:477-478.
- Milette F, Lariviere L, Piche J. Gleason grading of prostatic biopsies [letter]. *Am J Surg Pathol*. 2000;24:1443.