



THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN UROLOGICAL ASSOCIATION

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DARE TO CHALLENGE

the approach to initial therapy for patients with **BRCAm mCRPC**

Not an actual patient.

LYNPARZA: the FIRST PARPi approved in combination with abiraterone plus prednisone or prednisolone (abi/pred) as initial therapy for BRCAm mCRPC¹⁻⁴

INDICATION

LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated in combination with abiraterone and prednisone or prednisolone (abi/pred) for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCAm*) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

PROpel: A phase 3 trial

PROpel examined the efficacy of LYNPARZA + abi/pred vs placebo + abi/pred (active comparator) upon mCRPC diagnosis^{1,5}

- PROpel was a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial
- ITT population (N=796): mCRPC with or without HRR mutations
 - **FDA approval of LYNPARZA + abi/pred was based on an exploratory *BRCAm* subgroup (n=85)**
- Patients were randomized 1:1 to receive either LYNPARZA (300 mg BID) + abiraterone (1000 mg QD) with prednisone or prednisolone (5 mg BID) (n=399) or placebo + abiraterone (1000 mg QD) with prednisone or prednisolone (5 mg BID) (n=397). LYNPARZA was continued until objective radiological disease progression determined by investigator or unacceptable toxicity. All patients received a GnRH analog or had prior bilateral orchiectomy
- Patients were stratified by metastatic site and whether they received prior docetaxel at mHSPC stage. *BRCAm* status was not a stratification factor. Prior abiraterone was not allowed

Trial endpoints:

- Primary endpoint (ITT): rPFS by investigator assessment*
- Additional efficacy outcome measure (ITT): Overall survival
- Safety and tolerability
- **Exploratory *BRCAm* subgroup analyses**
 - Investigator-assessed rPFS* and OS in patients with *BRCAm* mCRPC (n=85)
 - Sensitivity analysis of rPFS by BICR

BRCAm status was assessed after randomization and before primary analysis by both NGS-based tumor tissue and ctDNA tests. *BRCAm* classification criteria in line with the FDA-approved assays were used to determine the deleterious and suspected deleterious somatic or germline mutation status of patients.

*Radiological progression-free survival (rPFS) assessed by investigator per RECIST v1.1 (soft tissue) and PCWG3 (bone) criteria.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

There are no contraindications for LYNPARZA.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML):

Occurred in approximately 1.5% of patients exposed to LYNPARZA monotherapy, and the majority of events had a fatal outcome. The median duration of therapy in patients who developed MDS/AML was 2 years (range: <6 months to >10 years). All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy.

Do not start LYNPARZA until patients have recovered from hematological toxicity caused by previous chemotherapy (≤Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt LYNPARZA and monitor blood count weekly until recovery.

If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.

Pneumonitis: Occurred in 0.8% of patients exposed to LYNPARZA monotherapy, and some cases were fatal. If patients present with new or worsening respiratory symptoms such as dyspnea, cough, and fever, or a radiological abnormality occurs, interrupt LYNPARZA treatment and initiate prompt investigation. Discontinue LYNPARZA if pneumonitis is confirmed and treat patient appropriately.

Venous Thromboembolism (VTE): Including severe or fatal pulmonary embolism (PE) occurred in patients treated with LYNPARZA. In the combined data of two randomized, placebo-controlled clinical studies

(PROfound and PROpel) in patients with metastatic castration-resistant prostate cancer (N=1180), VTE occurred in 8% of patients who received LYNPARZA, including pulmonary embolism in 6%. In the control arms, VTE occurred in 2.5%, including pulmonary embolism in 1.5%. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism, and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. Verify pregnancy status in females of reproductive potential prior to initiating treatment.

Females

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months following the last dose.

Males

Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of LYNPARZA and to not donate sperm during this time.

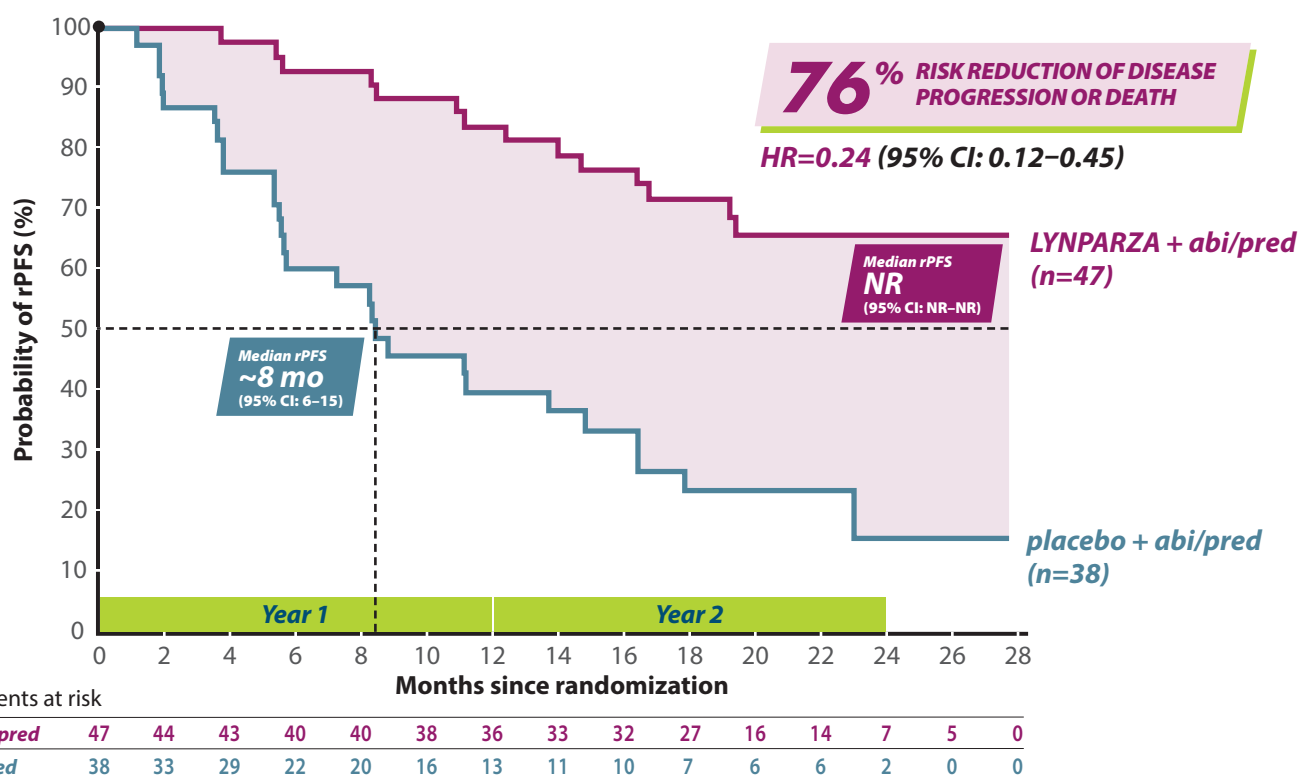
ADVERSE REACTIONS—Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

Most common adverse reactions (Grades 1-4) in ≥10% of patients who received LYNPARZA/abiraterone with a difference of ≥5% compared to placebo for **PROpel** were: anemia (48%), fatigue (including asthenia) (38%), nausea (30%), diarrhea (19%), decreased appetite (16%), lymphopenia (14%), dizziness (14%), and abdominal pain (13%).

Most common laboratory abnormalities (Grades 1-4) in ≥20% of patients who received LYNPARZA/abiraterone for **PROpel** were: decrease in hemoglobin (97%), decrease in lymphocytes (70%), decrease in platelets (23%), and decrease in absolute neutrophil count (23%).

FDA approval of LYNPARZA + abi/pred was based on an exploratory BRCAm subgroup
LYNPARZA + abi/pred demonstrated improvement in rPFS vs placebo + abi/pred in patients with BRCAm mCRPC^{1,5}

rPFS BY INVESTIGATOR ASSESSMENT IN EXPLORATORY BRCAm SUBGROUP



BRCAm subgroup (n=85)

rPFS events, n (%): 14/47 (30) with LYNPARZA + abi/pred and 28/38 (74) with placebo + abi/pred

• Results from the BICR assessment were consistent with the investigator-assessed rPFS results

OS analysis: 70% reduction in risk of death (HR=0.30 [95% CI: 0.15-0.59]) for LYNPARZA + abi/pred vs placebo + abi/pred. OS events, n (%): 13/47 (28) and 25/38 (66), respectively

BRCAm status was not a stratification factor in PROpel, and analysis was not controlled for Type 1 error

ITT population (n=796)

Statistically significant improvement in rPFS* was observed for LYNPARZA + abi/pred compared with placebo + abi/pred. OS for LYNPARZA + abi/pred compared to placebo + abi/pred did not reach statistical significance in the ITT population

Patients without an identified BRCAm (n=711)

Results from exploratory analyses in this subgroup (rPFS: HR=0.77 [95% CI: 0.63-0.96] and OS: HR=0.92 [95% CI: 0.74-1.14]) indicated that the improvement in the ITT population was primarily attributed to the results seen in the BRCAm subgroup

IMPORTANT SAFETY INFORMATION (Cont'd)

DRUG INTERACTIONS

Anticancer Agents: Clinical studies of LYNPARZA with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

CYP3A Inhibitors: Avoid coadministration of strong or moderate CYP3A inhibitors when using LYNPARZA. If a strong or moderate CYP3A inhibitor must be coadministered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.

CYP3A Inducers: Avoid coadministration of strong or moderate CYP3A inducers when using LYNPARZA.

USE IN SPECIFIC POPULATIONS

Lactation: No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infant, advise a lactating woman not to breastfeed during treatment with LYNPARZA and for 1 month after receiving the final dose.

Pediatric Use: The safety and efficacy of LYNPARZA have not been established in pediatric patients.

Hepatic Impairment: No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

Renal Impairment: No dosage modification is recommended in patients with mild renal impairment (CLcr 51-80 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the dose of LYNPARZA to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

Please see accompanying Brief Summary of Prescribing Information on the following pages.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

Choose LYNPARZA + abi/pred as initial therapy for BRCAm mCRPC to help give your patients more time without disease progression

References: 1. LYNPARZA® (olaparib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023. 2. Rubraca® (rucaparib) [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2022. 3. Talzenna® (talazoparib) [prescribing information]. New York, NY: Pfizer Inc.; 2021. 4. Zejula® (niraparib) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2023. 5. Clarke NW, Armstrong AJ, Thierry-Vuillemin A, et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. *NEJM Evid*. Published online June 3, 2022. doi:10.1056/EVIDoa2200043

abi/pred=abiraterone plus prednisone or prednisolone; BICR=blinded independent central review; BID=twice daily; BRCAm=BRCA-mutated or BRCA mutation; CI=confidence interval; ctDNA=circulating tumor DNA; GnRH=gonadotropin-releasing hormone; HR=hazard ratio; HRR=homologous recombination repair; ITT=intent-to-treat; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; NGS=next-generation sequencing; NR=not reached; OS=overall survival; PARPi=poly (ADP-ribose) polymerase inhibitor; PCWG3=Prostate Cancer Working Group 3; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; rPFS=radiological progression-free survival.



LYNPARZAphcp.com to explore additional data from the PROpel trial



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LYNPARZA® (olaparib) tablets, for oral use

Initial U.S. Approval: 2014

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see *Dosage and Administration (2.1) in the full Prescribing Information*].

Treatment of BRCA-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated (BRCAm) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see *Dosage and Administration (2.1) in the full Prescribing Information*].

DOSAGE AND ADMINISTRATION

Patient Selection

Information on FDA-approved tests for the detection of genetic mutations is available at <http://www.fda.gov/companiondiagnostics>.

Select patients for treatment with Lynparza based on the presence of deleterious or suspected deleterious HRR gene mutations, including BRCA mutations, or genomic instability based on the indication, biomarker, and sample type (Table 1).

Table 1 Biomarker Testing for Patient Selection*

Indication	Biomarker	Sample type		
		Tumor	Blood	Plasma (ctDNA)
Germline or somatic HRR gene-mutated metastatic castration-resistant prostate cancer	ATMm, BRCA1m, BRCA2m, BARD1m, BRIP1m, CDK12m, CHEK1m, CHEK2m, FANCLm, PALB2m, RAD51Bm, RAD51Cm, RAD51Dm, RAD54Lm	X		
	gBRCA1m, gBRCA2m		X	
	ATMm, BRCA1m, BRCA2m			X
BRCA-mutated metastatic castration-resistant prostate cancer in combination with abiraterone and prednisone or prednisolone	BRCA1m, BRCA2m	X	X	X

* Where testing fails or tissue sample is unavailable/insufficient, or when germline testing is negative, consider using an alternative test, if available.

Recommended Dosage

The recommended dosage of Lynparza is 300 mg taken orally twice daily, with or without food.

If a patient misses a dose of Lynparza, instruct patient to take their next dose at its scheduled time. Instruct patients to swallow tablets whole. Do not chew, crush, dissolve, or divide tablet.

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Continue treatment until disease progression or unacceptable toxicity for:

- HRR gene-mutated metastatic castration-resistant prostate cancer

BRCA-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

Continue treatment until disease progression or unacceptable toxicity.

When used with Lynparza, the recommended dose of abiraterone is 1000 mg taken orally once daily. Abiraterone should be given in combination with prednisone or prednisolone 5 mg orally twice daily. Refer to the Prescribing Information for abiraterone for dosing information.

Patients with mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

Dosage Modifications for Adverse Reactions

To manage adverse reactions, consider interruption of treatment or dose reduction. The recommended dose reduction is 250 mg taken twice daily.

If a further dose reduction is required, then reduce to 200 mg taken twice daily.

Dosage Modifications for Concomitant Use with Strong or Moderate CYP3A Inhibitors

Avoid concomitant use of strong or moderate CYP3A inhibitors with Lynparza. If concomitant use cannot be avoided, reduce Lynparza dosage to:

- 100 mg twice daily when used concomitantly with a strong CYP3A inhibitor.
- 150 mg twice daily when used concomitantly with a moderate CYP3A inhibitor.

After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the Lynparza dose taken prior to initiating the CYP3A inhibitor [see *Drug Interactions (7.2) and Clinical Pharmacology (12.3) in the full Prescribing Information*].

Dosage Modifications for Renal Impairment

Moderate Renal Impairment

In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the Lynparza dosage to 200 mg orally twice daily [see *Use in Specific Populations (8.6) and Clinical Pharmacology (12.3) in the full Prescribing Information*].

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic syndrome (MDS)/Acute Myeloid Leukemia (AML) has occurred in patients treated with Lynparza and some cases were fatal.

In clinical studies enrolling 2901 patients with various cancers who received Lynparza as a single agent [see *Adverse Reactions (6.1) in the full Prescribing Information*], the cumulative incidence of MDS/AML was approximately 1.5% (43/2901). Of these, 51% (22/43) had a fatal outcome. The median duration of therapy with Lynparza in patients who developed MDS/AML was 2 years (range: < 6 months to > 10 years). All of these patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy.

Do not start Lynparza until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt Lynparza and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Lynparza.

Pneumonitis

In clinical studies enrolling 2901 patients with various cancers who received Lynparza as a single agent [see *Adverse Reactions (6.1) in the full Prescribing Information*], the incidence of pneumonitis, including fatal cases, was 0.8% (24/2901). If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or a radiological abnormality occurs, interrupt Lynparza treatment and promptly assess the source of the symptoms. If pneumonitis is confirmed, discontinue Lynparza treatment and treat the patient appropriately.

Venous Thromboembolism

Venous thromboembolism (VTE), including severe or fatal pulmonary embolism (PE), occurred in patients treated with Lynparza [see *Adverse Reactions (6.1) in the full Prescribing Information*].

In the combined data of two randomized, placebo-controlled clinical studies (PROfound and PROpel) in patients with metastatic castration-resistant prostate cancer (N=1180), VTE occurred in 8% of patients who received Lynparza, including pulmonary embolism in 6%. In the control arms, VTE occurred in 2.5% including pulmonary embolism in 1.5%.

Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

Embryo-Fetal Toxicity

Lynparza can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. In an animal reproduction study, administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily. Advise pregnant women of the potential hazard to a fetus and the potential risk for loss of the pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Lynparza. Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza [see *Use in Specific Populations (8.1, 8.3) in the full Prescribing Information*].

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia [see *Warnings and Precautions (5.1) in the full Prescribing Information*]
- Pneumonitis [see *Warnings and Precautions (5.2) in the full Prescribing Information*]
- Venous Thromboembolism [see *Warnings and Precautions (5.3) in the full Prescribing Information*]

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Unless otherwise specified, the data described in the WARNINGS AND PRECAUTIONS reflect exposure to Lynparza as a single agent in 2901 patients; 2135 patients with exposure to 300 mg twice daily tablet dose including five controlled, randomized, trials (SOLO-1, SOLO-2, OlympiAD, POLO, and PROfound) and to 400 mg twice daily capsule dose in 766 patients in other trials that were pooled to conduct safety analyses. In addition to the 2901 patients, certain subsections in the WARNINGS AND PRECAUTIONS include adverse reactions observed with exposure to Lynparza with abiraterone (n=398) in PROpel. All patients with metastatic castration resistant prostate cancer received concomitant ADT or previous bilateral orchiectomy.

In the pooled safety population, 56% of patients were exposed for 6 months or longer and 28% were exposed for greater than one year in the Lynparza group.

In this pooled safety population, the most common adverse reactions in ≥10% of patients were nausea (60%), fatigue (55%), anemia (36%), vomiting (32%), diarrhea (24%), decreased appetite (22%), headache (16%), dysgeusia (15%), cough (15%), neutropenia (14%), dyspnea (14%), dizziness (12%), dyspepsia (12%), leukopenia (11%), and thrombocytopenia (10%).

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

PROfound

The safety of Lynparza as monotherapy was evaluated in patients with mCRPC and HRR gene mutations who have progressed following prior treatment with enzalutamide or abiraterone in PROfound [see *Clinical Studies (14.7) in the full Prescribing Information*]. This study was a randomized, open-label, multi-center study in which 386 patients received either Lynparza tablets 300 mg orally twice daily (n=256) or investigator's choice of enzalutamide or abiraterone acetate (n=130) until disease progression or unacceptable toxicity. Among patients receiving Lynparza, 62% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Fatal adverse reactions occurred in 4% of patients treated with Lynparza. These included pneumonia (1.2%), cardiopulmonary failure (0.4%), aspiration pneumonia (0.4%), intestinal diverticulum (0.4%), septic shock (0.4%), Budd-Chiari Syndrome (0.4%), sudden death (0.4%), and acute cardiac failure (0.4%).

Serious adverse reactions occurred in 36% of patients receiving Lynparza. The most frequent serious adverse reactions (≥2%) were anemia (9%), pneumonia (4%), pulmonary embolism (2%), fatigue/asthenia (2%), and urinary tract infection (2%).

Dose interruptions due to an adverse reaction of any grade occurred in 45% of patients receiving Lynparza; dose reductions due to an adverse reaction occurred in 22% of Lynparza patients. The most frequent adverse reactions leading to dose interruption of Lynparza were anemia (25%) and thrombocytopenia (6%) and the most frequent adverse reaction leading to reduction of Lynparza was anemia (16%). Discontinuation due to adverse reactions occurred in 18% of Lynparza. The adverse reaction that most frequently led to discontinuation of Lynparza was anemia (7%).

Tables 16 and 17 summarize the adverse reactions and laboratory abnormalities, respectively, in patients in PROfound.

Table 16 Adverse Reactions* Reported in ≥10% of Patients in PROfound

Adverse Reactions	Lynparza tablets n=256		Enzalutamide or abiraterone n=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Blood and lymphatic disorders				
Anemia [†]	46	21	15	5
Thrombocytopenia [‡]	12	4	3	0
Gastrointestinal disorders				
Nausea	41	1	19	0
Diarrhea	21	1	7	0
Vomiting	18	2	12	1
General disorders and administration site conditions				
Fatigue (including asthenia)	41	3	32	5
Metabolism and nutrition disorders				
Decreased appetite	30	1	18	1
Respiratory, thoracic, and mediastinal disorders				
Cough	11	0	2	0
Dyspnea	10	2	3	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

[†] Includes anemia and hemoglobin decreased.

[‡] Includes platelet count decreased and thrombocytopenia.

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza were neutropenia (9%), VTE (7%), dizziness (7%), dysgeusia (7%), dyspepsia (7%), headache (6%), pneumonia (5%), stomatitis (5%), rash (4%), blood creatinine increase (4%), pneumonitis (2%), upper abdominal pain (2%), and hypersensitivity (1%).

Table 17 Laboratory Abnormalities Reported in ≥25% of Patients in PROfound

Laboratory Parameter*	Lynparza tablets n= 256		Enzalutamide or abiraterone n=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	98	13	73	4
Decrease in lymphocytes	62	23	34	13
Decrease in leukocytes	53	4	21	0
Decrease in absolute neutrophil count	34	3	9	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

[†] This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

Treatment of BRCA-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

PROpel

The safety of Lynparza in combination with abiraterone and prednisone or prednisolone for the treatment of patients in the first-line mCRPC setting was investigated in PROpel [see *Clinical Studies (14.8) in the full Prescribing Information*]. Patients were randomized to receive either Lynparza tablets 300 mg orally twice daily plus abiraterone tablets 1000 mg once daily (Lynparza/abiraterone) (n=398), or placebo plus abiraterone 1000 mg once daily (placebo/abiraterone) (n=396) until disease progression or unacceptable toxicity. Patients in both arms also received either prednisone or prednisolone 5 mg twice daily.

Fatal adverse reactions occurred in 6% of patients, including COVID-19 (3%) and pneumonias (0.5%).

Serious adverse reactions occurred in 39% of patients. Serious adverse reactions reported in > 2% of patients included anemia (6%), COVID-19 (6%), pneumonia (4.5%), pulmonary embolism (3.5%), and urinary tract infection (3%).

Permanent discontinuation of Lynparza due to adverse reactions occurred in 16% of patients treated in the Lynparza with abiraterone arm. The most common adverse reactions which resulted in permanent discontinuation of Lynparza were anemia (4.3%) and pneumonia (1.5%).

Dosage interruption of Lynparza due to adverse reactions occurred in 48% of patients treated in the Lynparza with abiraterone arm. The most common (>2%) adverse reactions requiring dosage interruption of Lynparza were anemia (16%), COVID-19 (6%) fatigue (3.5%), nausea (2.8%), pulmonary embolism (2.3%), and diarrhea (2.3%).

Dose reduction of Lynparza due to adverse reactions occurred in 21% of patients treated in the Lynparza with abiraterone arm. The most common (>2%) adverse reactions requiring dosage reductions of Lynparza were anemia (11%) and fatigue (2.5%).

The most common adverse reactions (≥10%) in patients who received Lynparza/abiraterone were anemia (48%), fatigue (38%), nausea (30%), diarrhea (19%), decreased appetite (16%), lymphopenia (14%), abdominal pain (13%), and dizziness (14%).

Tables 18 and 19 summarize adverse reactions and laboratory abnormalities in PROpel, respectively.

Table 18 Adverse Reactions (≥10%) in Patients Who Received Lynparza (with a Difference of ≥5% Compared to Placebo) in PROpel

Adverse Reactions*	Lynparza/abiraterone n=398		Placebo/abiraterone n=396	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Blood and Lymphatic Disorders				
Anemia†	48	16	18	3.3
Lymphopenia‡	14	5	6	1.8
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	38	2.3	30	1.5
Gastrointestinal Disorders				
Nausea	30	0.3	14	0.3
Diarrhea	19	1	10	0.3
Abdominal pain ^α	13	0	7	0.5
Metabolism and nutrition disorders				
Decreased appetite	16	1	7	0
Nervous System Disorders				
Dizziness ^β	14	0.3	7	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

† Includes anemia, anemia macrocytic, and red blood cell count decreased

‡ Includes lymphocyte count decreased and lymphopenia

^α Includes abdominal discomfort, abdominal pain, abdominal pain upper, and abdominal pain lower

^β Includes dizziness and vertigo.

Clinically relevant adverse reactions that occurred in <10% for patients receiving Lynparza plus abiraterone were headache (9%), VTE (8%), rash (7%), dysgeusia (6%), acute kidney injury (3%), and stomatitis (2.5%).

Table 19 Selected Laboratory Abnormalities Reported in ≥20% of Patients in PROpel

Laboratory Parameter	Lynparza/abiraterone n=398†		Placebo/abiraterone n=396†	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	97	12	81	1.3
Decrease in lymphocytes	70	23	49	11
Decrease in platelets	23	1.2	20	0.3
Decrease in absolute neutrophil count	23	5	6	0

† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Lynparza. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity including angioedema.

Skin and subcutaneous tissue disorders: Erythema nodosum, rash, dermatitis.

DRUG INTERACTIONS

Use with Anticancer Agents

Clinical studies of Lynparza with other myelosuppressive anticancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

Effect of Other Drugs on Lynparza

Strong and Moderate CYP3A Inhibitors

Coadministration of CYP3A inhibitors can increase olaparib concentrations, which may increase the risk for adverse reactions [see *Clinical Pharmacology (12.3) in the full Prescribing Information*]. Avoid coadministration of strong or moderate CYP3A inhibitors. If the strong or moderate inhibitor must be coadministered, reduce the dose of Lynparza [see *Dosage and Administration (2.4) in the full Prescribing Information*].

Strong and Moderate CYP3A Inducers

Concomitant use with a strong or moderate CYP3A inducer decreased olaparib exposure, which may reduce Lynparza efficacy [see *Clinical Pharmacology (12.3) in the full Prescribing Information*]. Avoid coadministration of strong or moderate CYP3A inducers.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action [see *Clinical Pharmacology (12.1) in the full Prescribing Information*], Lynparza can cause fetal harm when administered to a pregnant woman. There are no available data on Lynparza use in pregnant women to inform the drug-associated risk. In an animal reproduction study, the administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity

and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily (see *Data*). Advise pregnant women of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. The estimated background risk in the U.S. general population of major birth defects is 2-4%; and the risk for spontaneous abortion is approximately 15-20% in clinically recognized pregnancies.

Data

Animal Data

In a fertility and early embryonic development study in female rats, olaparib was administered orally for 14 days before mating through to Day 6 of pregnancy, which resulted in increased post-implantation loss at a dose level of 15 mg/kg/day (with maternal systemic exposures approximately 7% of the human exposure (AUC_{0-24h}) at the recommended dose).

In an embryo-fetal development study, pregnant rats received oral doses of 0.05 and 0.5 mg/kg/day olaparib during the period of organogenesis. A dose of 0.5 mg/kg/day (with maternal systemic exposures approximately 0.18% of human exposure (AUC_{0-24h}) at the recommended dose) caused embryo-fetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification center; fused or absent neural arches, ribs, and sternbrae), skull (fused exoccipital), and diaphragm (hernia). Additional abnormalities or variants included incomplete or absent ossification (vertebrae/sternbrae, ribs, limbs) and other findings in the vertebrae/sternbrae, pelvic girdle, lung, thymus, liver, ureter, and umbilical artery. Some findings noted above in the eyes, ribs, and ureter were observed at a dose of 0.05 mg/kg/day olaparib at lower incidence.

Lactation

Risk Summary

No data are available regarding the presence of olaparib in human milk, or on its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infants from Lynparza, advise a lactating woman not to breastfeed during treatment with Lynparza and for one month after receiving the last dose.

Females and Males of Reproductive Potential

Lynparza can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1) in the full Prescribing Information*].

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating treatment with Lynparza.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for 6 months following the last dose.

Males

Based on findings in genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Lynparza [see *Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1) in the full Prescribing Information*].

Pediatric Use

Safety and effectiveness of Lynparza have not been established in pediatric patients.

Geriatric Use

Of the 2901 patients with advanced solid tumors who received Lynparza as a single agent, 680 (23%) patients were aged ≥65 years, and this included 206 (7%) patients who were aged ≥75 years. Thirteen (0.4%) patients were aged ≥85 years.

Of the 535 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with bevacizumab (PAOLA-1), 204 (38%) patients were aged ≥65 years, and this included 31 (6%) patients who were aged ≥75 years.

Of the 398 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with abiraterone and prednisone or prednisolone (PROpel), 268 (67%) patients were aged ≥65 years, and this included 95 (24%) patients who were aged ≥75 years.

No overall differences in the safety or effectiveness of Lynparza were observed between these patients and younger patients.

Renal Impairment

No dosage modification is recommended in patients with mild renal impairment (CL_{Cr} 51 to 80 mL/min estimated by Cockcroft-Gault). Reduce Lynparza dosage to 200 mg twice daily in patients with moderate renal impairment (CL_{Cr} 31 to 50 mL/min) [see *Dosage and Administration (2.5) in the full Prescribing Information*]. There are no data in patients with severe renal impairment or end-stage disease (CL_{Cr} ≤30 mL/min) [see *Clinical Pharmacology (12.3) in the full Prescribing Information*].

Hepatic Impairment

No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C) [see *Clinical Pharmacology (12.3) in the full Prescribing Information*].

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AUA-2024^{MAY 3-6} San Antonio

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AUANews

December 2023, Volume 28 | Issue 12

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PROSTATE CANCER

Grade Group 1 Should Be Followed as a Neoplasm, Not a Cancer

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For millennia, cancer was defined clinically—usually late in its course—and was understood by physicians, patients, and the public to be a lethal diagnosis associated, more than anything, with spread preceding death. For fewer than 200 years we have defined cancer based on histopathologic rather than clinical findings, but still, historically, only after a symptomatic tumor was identified. Only recently have screening and biopsy allowed pathologists access to small samples of tissue years or decades before a neoplasm would be clinically apparent—if ever. At the same time, our understanding of carcinogenesis, progression, and prognosis has progressed far beyond hematoxylin-and-eosin staining, but diagnostic standards and nomenclature have not kept pace.

In the case of prostate cancer, diagnostic tools now clinically available for patients with negative biopsy and rising PSA are based on changes in methylation in histologically normal tissue; more recently, spatial transcriptomic studies have demonstrated that molecular changes accumulate progressively before anything is apparent to pathologists, and in fact the changes separating “cancer” from “normal” are fewer than those between different adjacent areas of visually normal but preneoplastic tissue.¹ The loss of the prostate glandular basal cell layer—the hallmark of a diagnosis of carcinoma—should be understood in contemporary parlance as a hallmark of neoplasm, not malignancy.

Prostate cancer biology reflects a continuum from normal to premalignant molecular changes to Grade Group (GG) 1 to higher grade adenocarcinoma with progressive capacity to spread. We should recognize that drawing the cancer line between the second and third state has always been arbitrary from a

biological and clinical standpoint, and there is no particular reason the line could not move 1 step to the right. Doing so would dramatically improve the quality of care for men at risk of prostate cancer.

GG1 in the prostate is so exceptionally prevalent on autopsy studies (50% of Black men by their 70s and White men by their 80s)² it might be considered a normal feature of aging. Modern imaging and liquid biomarkers as secondary tests for those with elevated PSA explicitly dichotomize the anticipated biopsy outcome as GG ≥ 2 vs negative or GG1. In using these tests we are implicitly advising patients that if only GG1 is present, neither we nor they want know about it—and in the era of such testing, low-grade disease has fallen from half of new diagnoses to fewer than 20%.³ GG1 is rapidly devolving to an inadvertent finding whose diagnosis is entirely incidental to efforts to identify clinically meaningful cancer (ie, many but not all cancers GG2 and higher). So when we accidentally diagnose GG1, should we really be assigning these patients cancer labels? When we do, particularly for a universally indolent entity, the harm to a patient seems exponentially greater than the benefit.

Broad agreement across guidelines now supports active surveillance as preferred management for GG1. Even in the era of image guidance, prostate biopsy can undersample a cancer, and a subset of GG1 tumors will progress to higher grade disease over the years. Therefore, were GG1 called something other than cancer, surveillance should change minimally, if at all. Confirmatory biopsy, follow-up PSAs, imaging tests, and biopsies would remain essential. The only key clinical change would be that rates of immediate radical treatment for GG1 should drop far below the current 40%.³ That is not to say the treatment rate should be even close to zero; cases of strong family history of early lethal disease, for example, might justify preemptive treatment of GG1. After all, by

“Concerns have been raised that absent a cancer diagnosis, men would not be conscientious about surveillance protocols, but these are theoretical, not empirical.”

analogy, thousands of women annually undergo prophylactic mastectomy and oophorectomy based on genetic risk alone.⁴

Concerns have been raised that absent a cancer diagnosis, men would not be conscientious about surveillance protocols, but these are theoretical, not empirical. Patients with colon polyps undergo endoscopic surveillance at increased frequency, and many nonneoplastic conditions indicate surveillance even with invasive procedures. In any case, PIVOT and ProtecT would suggest that for low-risk disease, surveillance even at reduced intensity relative to current US guidelines would not result in many missed opportunities for needed cure of progressive disease. To be clear, the number of men who would die of prostate cancer specifically because they did not take a GG1 diagnosis seriously, and who would have been more compliant given a cancer diagnosis, is doubtless above zero—but probably not by very much. How many men must experience needless psychological suffering, financial distress (loss of life insurance, increase in premiums), and adverse effects of avoidable treatment in pursuit of these few?

Besides, a change in nomenclature would very likely save many thousands of lives annually in the US alone. Many men who die from clinically significant, high-grade, “real” prostate cancer missed a win-

dow of opportunity to be screened, detected early, and cured. PSA is an incredibly useful test when used early—yet well under half of men get a baseline test before 60. The hostility to prostate cancer screening from the USPSTF (US Preventive Services Task Force) and other primary care thought leaders over the past 15 years is multifactorial in origin but substantially reflects the impact of overdiagnosis and overtreatment on the public health.

Improvements in overtreatment rates were cited directly in the USPSTF revision of their recommendation from a “D” to a “C” in 2018,⁵ but we clearly have a long way to go. If we substantively address overtreatment as well as upstream overdiagnosis, the ratio of benefits to harms would likely improve to the point of being unquestionable. If primary care providers make PSA screening recommendations and decisions knowing their patients are at a greatly reduced risk of overdiagnosis, lives ultimately saved through a nomenclature change would outnumber those lost by orders of magnitude.

GG1 is not normal—but neither is it cancer. It is a premalignant finding indicating close surveillance but rarely immediate treatment. In 2023, its definition and label should reflect this contemporary understanding of its place on the biological continuum. ■

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PROSTATE CANCER

Reclassifying Gleason 6 Cancer Is a Flawed Solution for Overtreatment

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There continues to be a vigorous debate about the merits of reclassifying Gleason Grade Group 1 (GG1) as something other than cancer. The rationale for such a change is based on the perception that GG1 never causes harm and that there is significant overtreatment. The sentiment behind the proposed change in designation is sound; if we knew a patient had GG1 cancer and the patient had no risk of progression, there would be no reason to monitor and treat. Unfortunately, in 2023 we know that many patients with biopsy-proven GG1 harbor higher-grade elements, that there is a risk of progression to higher-grade disease, and that there likely would be unintended consequences of changing nomenclature that would hamper care.

First, a high percentage of patients with GG1 have grade reclassification on repeat biopsy. The key point is that even men with very low-risk disease, close to 15%, will have higher grade on subsequent

biopsy.¹ As a result, a change to a noncancer designation would likely result in no alteration in the need for active surveillance since all patients with low risk need to be monitored to ensure no clinical progression. Why change the designation if there is no change in care?

Second, the grade of the tumor as GG1 is not the sole factor that should be considered in treatment decisions. Tumor volume, clinical stage, imaging, genetic background, and genomic testing can all impact on decision to treat.²⁻⁵ For example, PIRADS (Prostate Imaging Reporting and Data System) 4 and 5 are associated with upgrading and therefore have been integrated into decision-making. Should a patient with a PIRADS 5 GG1 tumor on biopsy be told they don't have cancer? Should a patient with BRCA2 germline mutations not be treated? Patients should be risk stratified using more than just Gleason score.

Third, removing the label of cancer in men with GG1 cancer on biopsy will make it challenging to ensure close follow-up. While patients with optimal insurance will likely not be affected by a change

in terminology, those with policies that are less robust may fall into a trap where follow-up is curtailed when GG1 is renamed noncancer, resulting in financial toxicity. This is particularly an issue in underserved communities. Currently, patients already fail to follow up for active surveillance. Analysis of SEER (Surveillance, Epidemiology, and End Results) data demonstrated that close to 40% of all men and 60% of Black men with low-risk prostate cancer failed to follow surveillance strategies.⁶ It is logical and expected that renaming GG1 as not cancer will lead to less compliance with follow-up.

Fourth, there is concern that defining GG1 as noncancer could paradoxically lead to more treatment. Pathologists may be wary of a noncancer diagnosis if the patient is not going to be managed closely. Consciously or unconsciously, borderline cases could be upgraded. The result is more treatment in men who could be safely followed.

In summary, there is strong rationale for retaining the cancer designation for GG1 prostate cancer. The arguments for renaming GG1

prostate cancer primarily revolved around protecting the patient from overtreatment. This argument is weakened over time with greater acceptance of active surveillance. While there is widespread agreement that some prostate cancer is of no threat to the patient, the underlying clinical challenge is how to identify those patients and how to minimize treatment. Simply relabeling GG1 as a benign condition is not going to address this conundrum. ■

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PROSTATE CANCER

Removing the Cancer Label From Gleason 6 (Grade Group 1) Would Improve Public Health

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PSA screening has undoubtedly contributed to a dramatic decrease in age-adjusted prostate cancer mortality,¹ but has also ushered in a dual pandemic: (1) millions of men who have been unnecessarily diagnosed and treated for a "cancer" never destined to cause symptoms or shorten their lifespan, and (2) not enough men undergoing

screening. We can do better; we must do better.

Active surveillance (AS) is an important step in the right direction. Although data supporting AS have been available for more than 15 years, 40% of US men still undergo immediate treatment for low-risk prostate cancer.² In some countries it's < 10%, while in others it's > 90%. Despite all international guidelines recommending AS as the preferred man-

agement for low-risk disease—all with Grade Group (GG) 1—there remains an extraordinarily large group of men undergoing unnecessary treatment.

Cancer is a loaded term and frequently alters self-image and mental health. Even among men with GG1 on AS, there are increased levels of anxiety,³ suicide,⁴ financial toxicity,⁵ difficulties obtaining life insurance,⁶ and the semiregular testing including biopsies.

I frequently tell men I wish I could undiagnose their GG1.

Nearly every prostate cancer specialist acknowledges the goal of screening is to identify those with GG2 or higher. There has been notable progress through biomarkers and MRI, all proven and appropriately marketed to diagnose fewer men with GG1, despite 30% to 50% of all men over the age of 50 having

REMOVING THE CANCER LABEL FROM GLEASON 6 (GRADE GROUP 1) WOULD IMPROVE PUBLIC HEALTH

→ Continued from page 8

it.⁷ GG1 is a natural part of aging. It is natural but inappropriate to continue calling it a cancer. There is a rich body of literature in the social sciences evaluating the human behavioral tendency to stick to pre-existing beliefs and reject fresh ideas that contradict them, despite adequate evidence (eg, the Semmelweis reflex, a form of cognitive bias).⁸

Until someone shows me otherwise, I am not aware of anyone with a metastasis or death from GG1 (using ISUP [International Society of Urological Pathology] 2014 standards) without higher-grade cancers simultaneously present. Among 14,000 men undergoing prostatectomy, none had GG1 with lymph node metastases,⁹ and among 12,000 men with only GG1 at prostatectomy, there were basically no deaths from prostate cancer,^{10,11} despite all 26,000 of these men having GG1 for many years or even decades prior to surgery. In the Merriam-Webster Dictionary, cancer is defined as “a malignant tumor of potentially unlimited growth that expands locally by invasion and systemically by metastasis.” Pure GG1 literally cannot metastasize. So why are we calling it cancer?

We call it cancer due to the long-standing, entrenched, and understandable reliance on microscopy. Cancer was defined 2500 years ago by Hippocrates based on palpable, symptomatic, or metastatic disease. The microscope was invented 400 years ago, and localized prostate cancer diagnosis relies on it. With near certainty, future generations will scoff at our current definition, a microscopic lack of basal cells being the sine qua non. For example, Gleason 2 through 5 were cancers for decades until a stain for basal cells was developed and then—poof—no longer considered cancer. Patients only care about microscopic findings if it might eventually impact their quality or quantity of life.

A nomenclature downgrading, eliminating the term carcinoma or cancer, has been successfully accomplished many times before: in prostate, bladder (PUNLMP [papillary urothelial neoplasm of low malignant potential]), kidney (clear cell papillary), thyroid (NIFTP [non-invasive follicular thyroid neoplasm with papillary-like nuclear feature]),

and cervical (SIL [squamous intraepithelial lesion]) cancers. For the exact same reason, it should be done for GG1: improvement of public health.

In prostate, it has been discussed by many highly experienced groups,¹² has corollaries in other cancers,¹³ and has been long-standing (since at least 2006),¹⁴⁻¹⁷ although is now gathering far more traction and conversation.¹⁸ In a recent survey of 1300 physicians involved in prostate cancer care, 39% responded a name change was a “good idea,” 30% “uncertain,” and 31% “disagree.” Rates of agreement were even higher among clinicians (vs pathologists) and those who are younger, fellowship-trained in oncology, and with busier prostate cancer practices.¹⁹ Anecdotally, I’ve had countless physicians share their strong support for a name change though are “not ready yet to say it publicly.” Similarly, discrete choice experiments among prostate cancer patients, their partners, and healthy men all showed a strong preference for a name change.²⁰ Notably, 4 prominent genitourinary pathologists recently advocated for a name change: “driven by the primary goal of reducing harm for patients.”^{21,22}

The counterarguments are predictable and easily contested. The most common is the concern for unsampled higher-grade cancers. I’m not aware of another solid organ cancer where it is routine to treat based on what might’ve been missed on biopsy (or isn’t present at all). Additionally, all notable long-term AS series (containing many patients with unsampled higher-grade cancers) accrued for long periods of time with sextant biopsies, no MRI, or early restaging biopsies, and were prior to ISUP 2014 grading changes restricting the definition of GG1 (therefore, included many men which by modern standards had GG2).²³⁻²⁵ Yet they uniformly have superb results for GG1, as low as 0.1% risk of 15-year cancer-specific mortality. Whether it be screening or AS: PSA, PSA density, biomarkers, and MRI findings should be used to risk-stratify likelihood of GG2 or higher and, if needed, consider another biopsy. If a name change ultimately occurs, this strategy would continue.

A second point is the molecular or genetic overlap between some GG1 and higher-grade can-

cers. This is true, though unmentioned is a similar overlap between noncancerous lesions (high-grade prostatic intraepithelial neoplasia) and higher-grade cancers (copy number alterations and ERG fusions), and I don’t hear anyone calling for them to be upgraded to a cancer.²³⁻²⁵

A third concern is compliance, which I share. However, clinics are filled with millions of men with high PSAs and negative biopsies or high-grade prostatic intraepithelial neoplasia/atypical small acinar proliferation. A considerable number have unsampled high-grade prostate cancer, and I’ve never heard a urologist express concern about their compliance. For those undergoing screening or AS, we recommend follow-up, explain why, and they ultimately decide whether to. Is that any different if GG1 underwent a name change? Is it different than those with a precancerous colon polyp or a lung nodule requiring follow-up?

The rationale for a name change is robust, evidence based, has strong and growing multidisciplinary support, and most importantly would have a major net benefit on public health. Ironically, some of the loudest voices opposed to a name change also predicted AS would lead to widespread unnecessary deaths. A symposium earlier this year, with representation from all relevant specialties, patients, the CDC, the National Cancer Institute, and breast and thyroid cancer experts, purposely included a variety of perspectives and brainstormed a path forward. There are ongoing efforts in education, modeling, policy, basic science, and trial development to further the discussion for what I believe will ultimately happen and be a momentous advance in the quality of prostate cancer care. ■

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PROSTATE CANCER

Editorial Comment

William J. Catalona, MD

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The 2019 modification of the International Society of Urologic Pathology prostate cancer grading system is well established for diagnosing and managing patients.¹ Recently, to avoid the “cancer label” and address the “overtreatment crisis” (which is diminishing),^{2,3} some authors are calling for removing the cancer label from Gleason grade group (GG) 1.^{4,5}

Is it appropriate for urologists to direct pathologists who review prostate cancer specimens to change the well-established pathology cancer label of GG1 disease, regardless of other risk-assessment parameters? This would be a major step, affecting all men who currently would be offered active surveillance (AS) by telling them they do not have a cancer to surveil, as well as those who, under today’s guidelines, fall under the higher-risk GG2 category.

To justify this proposed change, they cite the precedents for low-grade bladder and thyroid cancer. These tumors are inappropriate examples, for with these tumors, the lesion has been excised and more aggressive histology ruled out.⁶ They also question the relevance of treating any patients initially diagnosed with low-risk prostate cancer because the PIVOT⁷ and ProtecT⁸ trials found no significant difference in 10- to 15-year mortality rates between patients managed with “active monitoring” vs those managed with radical treatment. In the ProtecT trial, half the patients randomized to monitoring received treatment within 10 years, and not all randomized to radical treatment were treated promptly.

A discrete choice experiment reported that patients, their partners, and healthy individuals all preferred to have a “noncancer” label applied to GG1, which increased their choice of adopting AS.^{2,9} However, discrete choice experiments have limitations: participants are presented with oversimplified, hypothetical decisions; they may not be completely aware of their

true preferences; they may be overwhelmed by the number of possible scenarios presented; and the choices offered may not cover their entire range of preferences. Moreover, the study populations may be nonrepresentative, rendering the results not applicable to real-world situations or across different populations.⁹ Most importantly, participants in these experiments may be unduly influenced by how the options are presented to them.

In contrast, a randomized online survey was administered to 718 men without prostate cancer, presenting them with a hypothetical scenario in which they were newly diagnosed with low-grade prostate cancer and comparing the labels of “Gleason 6 out of 10,” “grade group 1 out of 5,” or “IDLE” (ie, not cancer). Notably, IDLE was not associated with differences in anxiety or preference for active surveillance and was not a preferred disease label term compared with traditional Gleason score nomenclature.¹⁰

The proportion of men diagnosed with GG1 cancer has decreased with the use of MRI-guided biopsies.^{10,11} Nevertheless, MRI scans are imperfect, as not all clinically significant cancers are visible on MRI.^{11,12} Tumor grade and volume reclassification have been reported in up to 30% to 50% of GG1 tumors.^{13,14,15} Even if the national rate of initial GG1 diagnoses were to decrease to 10%, it would amount to telling 30,000 GG1 patients per year in the US alone that they do not have prostate cancer.

A multifocal, heterogeneous disease, prostate cancers do not all carry the same risk; some progress at different rates.^{16,17,18} Patients legitimately worry because they know that true knowledge about the biological potential of their tumor is lacking. Biopsy cores containing GG1 cancer may harbor genomic features associated with tumor grade progression and clinically aggressive behavior, or the biopsy procedure may have failed to sample more aggressive disease elsewhere in the prostate.^{19,20}

Studies claiming GG1 cancers can

never metastasize come from radical prostatectomy series in which the early resection of the entire prostate gland cured most patients.²¹ Long-term follow-up is required to assess the clinical significance of low-grade prostate cancers.²² To accurately assess the biology of GG1 disease, outcomes with more than 20-year follow-up of patients never receiving treatment would be required—an impracticable study that is unlikely ever to be undertaken.⁶

In the PIVOT⁷ and ProtecT⁸ trials, with 10 to 15 years of follow-up, twice as many patients in the monitoring groups developed metastases. In ProtecT, 51% who developed metastases and 46% who died of prostate cancer were diagnosed at baseline with GG1 disease; the deaths occurred largely 12 to 25 years after treatment. The US SEER (Surveillance, Epidemiology, and End Results) data with 20 years of follow-up revealed that more patients diagnosed with GG1 disease died of prostate cancer than those diagnosed with GG2 or higher tumors.²³ In Sweden, the long-term prostate cancer mortality rate for GG1 patients managed with AS was 13%.²⁴

While metastatic behavior is not the only criterion for malignancy, GG1 meets all the morphologic criteria seen in higher-grade prostate cancers: the basal cell layer is absent, and there is stromal and perineural invasion that correlates with the risk of grade reclassification. Extracapsular tumor extension and seminal vesicle invasion can occur with GG1 tumors.⁶

Genomic instability drives prostate cancer, activating oncogenes and inactivating tumor suppressors. GG1 cancers can contain high genomic risk variants not found in normal prostate tissues.^{19,20} High-risk genomic variants in GG1 tumors are identical to those seen with higher-grade tumors, and GG2 tumors may arise clonally from GG1 tumors.^{19,20} The cancers containing high-risk variants have more adverse pathology and more frequent recurrences after treatment.^{25,26} The greater the amount of GG1 cancer found in the diagnostic

biopsy specimens, the more likely there are adverse genomic markers and the tumor will exhibit aggressive behavior.^{26,27} Recent epigenetic evidence shows that GG1 tumor are true cancers and are clearly separate from benign prostate tissue.²⁸

Numerous unintended consequences would follow the declassification of GG1. Surveillance protocols currently recommended for GG1 cancer would be used only for patients with GG2 disease that is currently called low-intermediate-risk disease. GG2 disease is associated with a 3- to 4-fold higher risk of cancer progression than for GG1, for which the surveillance protocols should be more intensive.^{29,30} The compliance rates with AS biopsies—already poor for GG1 disease—would be worse if GG1 were not called cancer.³¹ Poorer compliance rates correlate with worse outcomes, and underserved populations have lower compliance rates³²; hence, racial disparities would increase. High-volume GG1 would never trigger treatment, and pathologists incorrectly grading GG1 and GG2 tumors would result in some patients not receiving proper counseling for AS and others receiving unnecessary treatment.

Additional prediction tools are available to help overcome biopsy undersampling and genomic risk issues. PSA isoform measurements help assess the clinical significance of prostate cancer and the risk of dying from it.^{33,34} Testing germline DNA for monogenic and polygenic variants more likely to be associated with aggressiveness is now available,³⁵ and somatic genomic testing of urine and biopsy specimens is gaining increased use.¹⁷ New artificial intelligence-enhanced pathology and imaging methods promise to reduce interreader variability and provide more accurate risk assessments.^{36,37}

The practical way forward is to continue to acknowledge overtreatment, develop evidence-based guidelines to increase the appropriate adoption and quality of AS, use these guidelines to educate patients and physicians, apply implementation

EDITORIAL COMMENT

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science procedures to induce physicians to do the right thing, and integrate new risk parameters with the established ones.

The medical community should insist that any changes in GG classification be based on firm scientific evidence, which is now lacking. The slow initial uptake of AS in the US is not sufficient reason to change the biological definition of cancer. The current International Society of Urologic Pathology grading system classifies GG1 tumors as “1 on a scale of 1 to 5” rather than “6 on a scale of 2 to 10.” Under this classification system, patients feel more comfortable choosing AS for the lowest GG1 group.³⁸

The responsibility for proposed changes in the designation GG1 as cancer rests on urologists, radiation oncologists, medical oncologists, and pathologists; however, the ultimate authority to decide should remain in the purview of pathologists. Only 15% of pathologists support declassification.² The arguments for renaming GG1 cancer are weakening, and there is strong support for retaining the cancer designation.³⁹ ■

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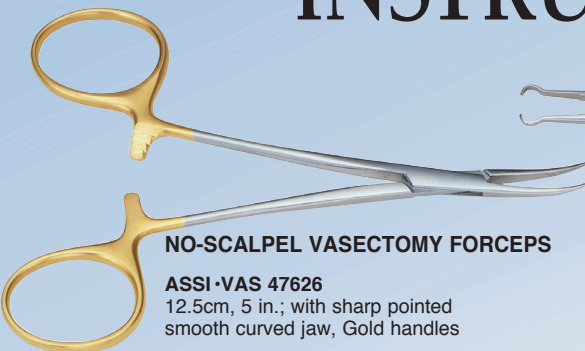
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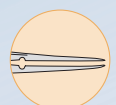
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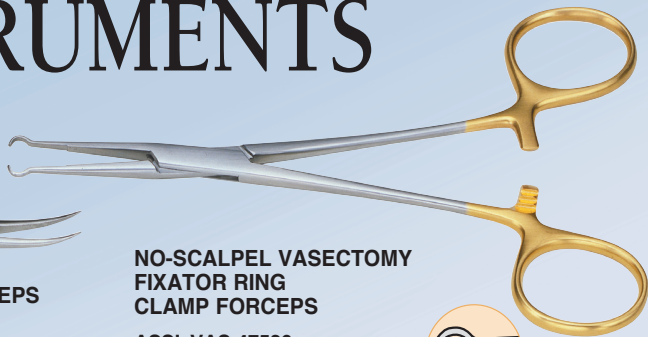
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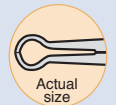
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12.5cm, 5 in.; with sharp pointed smooth curved jaw, Gold handles



ASSI-VAS 47726
12.5cm, 5 in.; **very delicate curved**, smooth pointed jaw, Gold handles

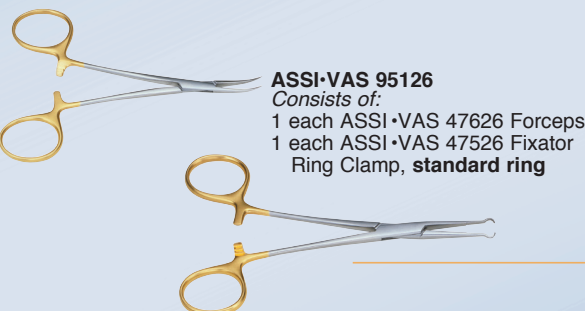


NO-SCALPEL VASECTOMY FIXATOR RING CLAMP FORCEPS
ASSI-VAS 47526
14cm, 5.5 in.; with blunt tips, **standard ring**, Gold handles

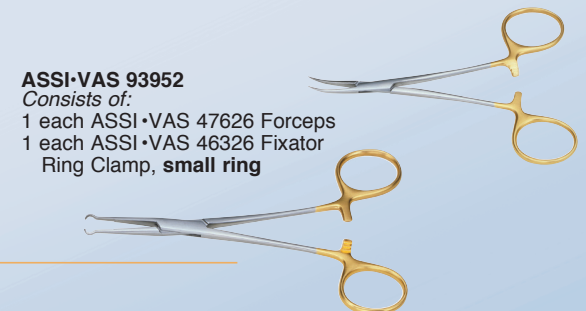


ASSI-VAS 46326
14cm, 5.5 in.; with blunt tips, **small ring**, Gold handles

NO-SCALPEL VASECTOMY INSTRUMENT SETS

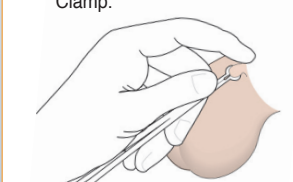


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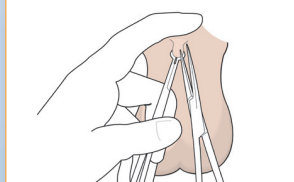


ASSI-VAS 93952
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1 each ASSI-VAS 46326 Fixator Ring Clamp, **small ring**

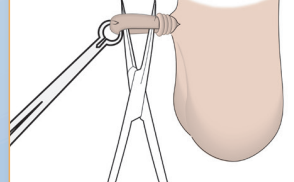
1 Fixation of the vas under the scrotal skin using the extracutaneous vas fixation clamp, ASSI® No-Scalpel Vasectomy Fixator Ring Clamp.




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EDITORIAL COMMENT

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SPECIALTY SOCIETIES

A New National Effort to Address Prostate Cancer Outcomes Disparities in Black Men

Brian A. Stone, MD, FACS

ConDUC, Atlanta, Georgia
 Jasper Urology & Clinical Diversity Solutions,
 Alabama

In a culminating educational event for Prostate Cancer Awareness Month, the Consortium on Disparities of Urologic Conditions (ConDUC) hosted its third annual African American Prostate Cancer Symposium at Clark Atlanta University, one of the HBCUs (historically Black colleges and universities), September 29 to 30, 2023. ConDUC is a not-for-profit organization whose mission is to develop strategies to improve disparate outcomes in underserved populations with urologic diseases, the current focus being prostate cancer. The initiative is led by a team of prominent Black urologists and is assisted by a multidisciplinary team of scientists that include radiation oncologists, basic and clinical researchers, health care outcomes specialists, and health care and patient advocacy experts. In addition, ConDUC has received input from the pharmaceutical and biotech industry leaders. ConDUC, in partnership with ArborMetrix (a data science company), developed the Scientific Consortium on Prostate Cancer Education (SCOPE) Registry. The registry will capture clinical,

pathologic, genomic, and serum biomarker data as well as social determinants impacting health in men with prostate cancer over time.

The catalyst for the creation of ConDUC and the SCOPE Registry was the frustration with a lack of data-driven treatment algorithms applicable to Black prostate cancer patients stemming from poor accrual of Black men into pivotal studies in prostate cancer. While SEER (Surveillance, Epidemiology, and End Results) prostate cancer survival

“ConDUC is a not-for-profit organization whose mission is to develop strategies to improve disparate outcomes in underserved populations with urologic diseases, the current focus being prostate cancer.”

data have shown modest survival improvement in older Black prostate cancer patients over the past few decades, the mortality rate in Black men has remained proportionally almost 2.5 times that of White prostate cancer patients. The executive director, Walter Rayford, MD, PhD, MBA, and the ConDUC team members decided to tackle the unresolved issue of the absence of adequate data on prostate cancer in Black men themselves. In the years since the ConDUC concept was created, ConDUC has recruited a strong executive team, an external advisory board, and an extremely talented scientific committee to achieve its goals.

The theme of this year’s conference was “Collaborative Partnerships to Improve Outcomes.” It is no secret that Black American males have a significantly higher incidence and mortality rate from prostate cancer. The SCOPE Registry trial is currently onboarding sites and enrolling patients to significantly accelerate and increase data collection among Black prostate cancer patients. The goal of SCOPE is to become the largest data bank of Black prostate cancer patients in the nation. The focus of the symposium was fostering collaboration between like-minded entities that share the same goals as the ConDUC team.

ConDUC has received the endorsement of the AUA, American Cancer Society, and the National Cancer Institute’s Urologic Oncology Branch. ConDUC has an established relationship with the Center for Cancer Research and Therapeutic Development at Clark Atlanta University, which serves as the administrative office for ConDUC. ConDUC is excited about this partnership with an HBCU as it highlights the cultural significance of the project.

The symposium chairs, Ashanda Esdaille, MD (Emory University), and Simpa Salami, MD, MPH (University of Michigan), formulated a 2-day program in collaboration with the ConDUC executive team, in partnership with Clark Atlanta University. The Saturday morning program was highlighted by the session, “Disparities in Prostate Cancer: State of the Science,” and included the following presentations: “Clinical Research Perspectives” by Isla Garraway, MD, PhD (associate professor of urology, University of California Los Angeles), and “Basic and Translational Research Perspectives” by Olorunsean Ogunwobi, PhD (chair of biochemistry and molecular biology, Michigan State

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A NEW NATIONAL EFFORT TO ADDRESS PROSTATE CANCER

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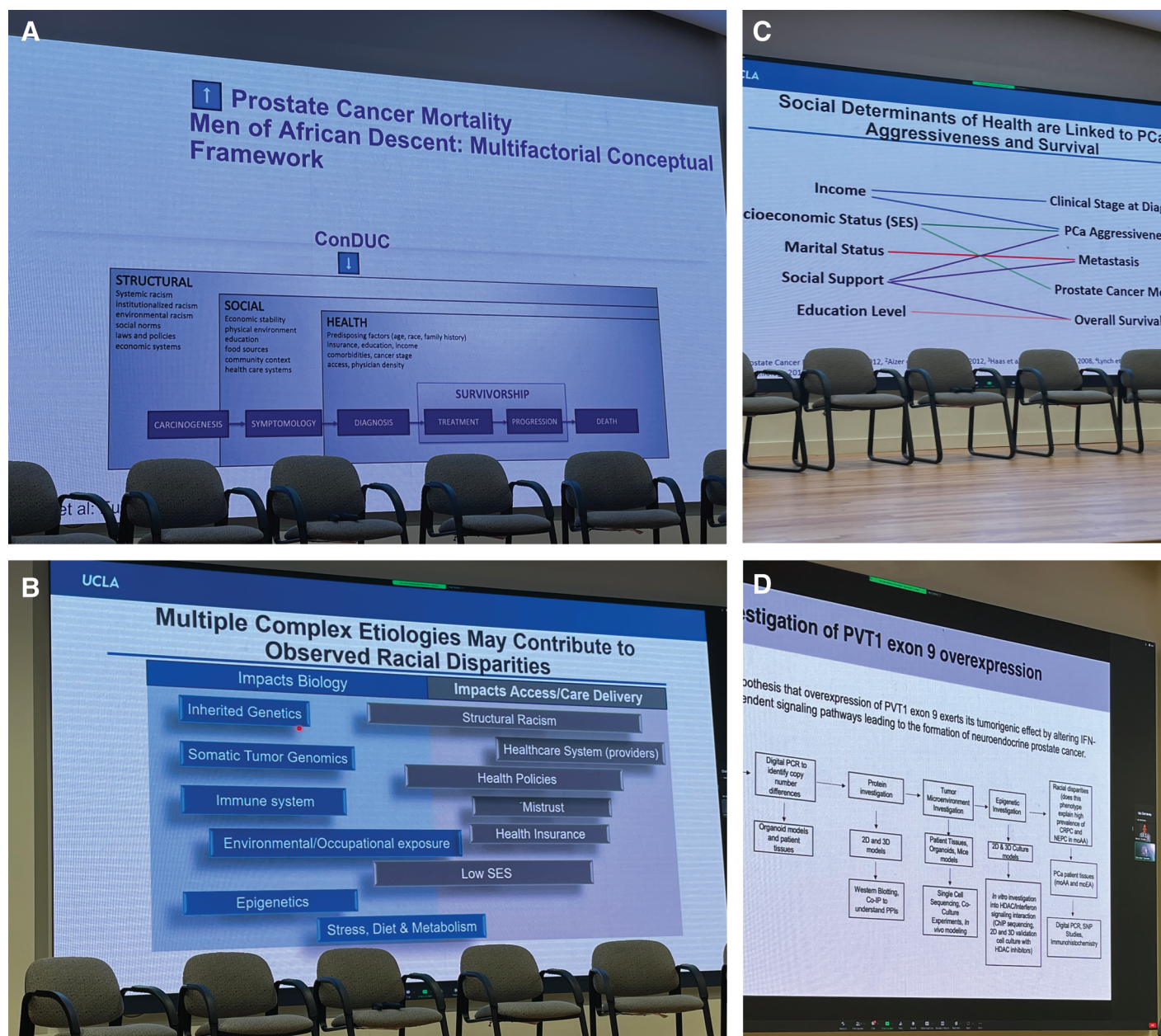


Figure 1. A to C, Slides 3 to 5 are from the symposium session, “Disparities in Prostate Cancer: State of the Science,” by Isla Garraway, MD, PhD, associate professor of urology at the University of California Los Angeles. Her talk, titled “The Clinical Research Perspective,” addressed the unknown impacts of the social determinants of health on prostate cancer mortality and how ConDUC (the Consortium on Disparities of Urologic Conditions) and the SCOPE (Scientific Consortium on Prostate Cancer Education) Registry can truly help contribute to identifying and understanding these unknowns. D, From the same session in the presentation, “The Basic and Translational Research Perspective,” presented by Olorunseun Seun Ogunwobi, PhD, chair, department of biochemistry and molecular biology, and professor, Michigan State University. He was discussing their hypothesis that the overexpression of the PVT1 exon 9 exerts its tumorigenic effect altering IFN-dependent and -independent pathways leading to the formation of highly aggressive neuroendocrine prostate cancer.

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University). The keynote address was titled, “The MUSIC Roadmap to Improve Outcomes in Prostate Cancer” by Kevin Ginsburg, MD, MS (assistant professor, Wayne State University). The luncheon speaker was Thomas Farrington, President, and Founder of the Prostate Health Education Network, who related his personal journey as a prostate cancer survivor and the importance of patient advocacy and what the Prostate Health Education Network has accomplished toward patient education and clinical trial enrollment.

The afternoon session was titled, “Organizational Programs, Initiatives, and Funding Opportunities to Reduce Disparities in Prostate Cancer.” This session featured a series of short talks on “Faith Based Health Initiatives” by Lydell Lettsome, MD (Bayhealth Medical Center, Delaware), in addition to funding updates from the Prostate Cancer Foundation by Howard Soule, PhD, “The National Cancer Institute” by Peter Pinto, MD (senior investigator, National Cancer Institute Center for Cancer Research), “National Institute on Minority Health and Health Disparities Opportunities” by Vanessa Marshall, PhD, CCRP (NIH), and “The American Cancer Society” by Lorelei Mucci, ScD, MPH (Director of Strategic Partnerships, American Cancer Society, and professor, Harvard School of Public Health). This was a very interactive session with audience engagement.



Figure 2. Dr Arthur “Bud” Burnett (moderator), with Dr Lydell Lettsome and Dr Peter Pinto.



Figure 3. Some of the ConDUC team members (left to right): Simpa Salami, MD; Lydell Lettsome, MD; Walter Rayford, MD, PhD, MBA; Kelly Brown-Morris (Clark Atlanta University); Randy Bradley, PhD; Robert Waterhouse, MD, MBA; and Brian Stone, MD.

A NEW NATIONAL EFFORT TO ADDRESS PROSTATE CANCER

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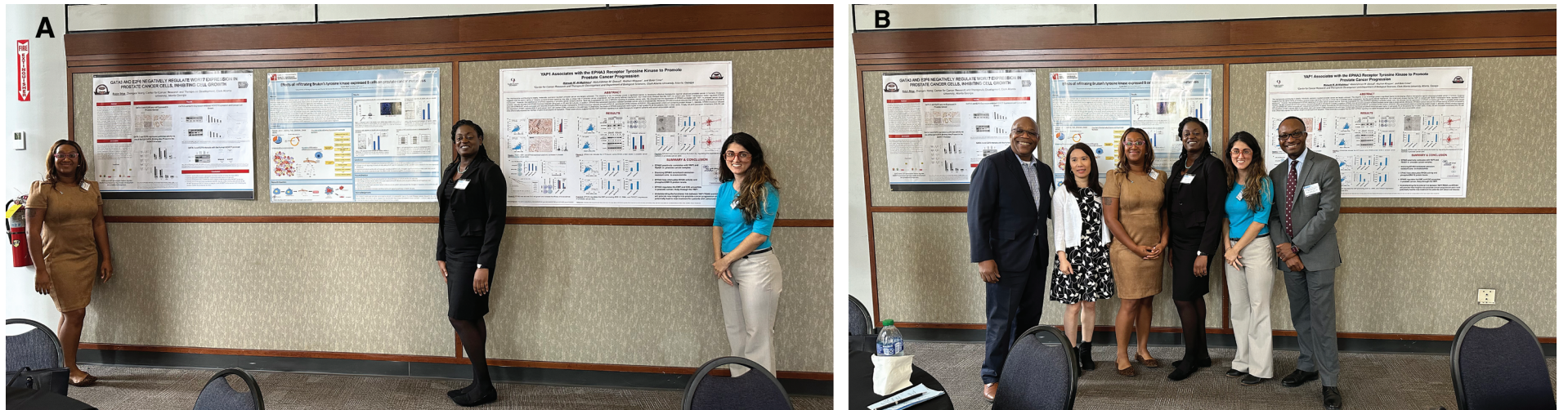


Figure 4. A, Clark Atlanta University graduate students by their poster presentations (left to right): Robin Brice, Crystal Byrd, and Kezhan Khazaw. B, Some of the judges with the graduate students (left to right): Curtis Pettaway, MD (professor of urology, MD Anderson Cancer Center), Geou-Yarh (Stancy) Liou, PhD (associate professor, Center for Cancer Research and Therapeutic Development, Clark Atlanta University), Robin Brice (Clark Atlanta University graduate student), Crystal Byrd (Clark Atlanta University graduate student), Kezhan Khazaw (Clark Atlanta University graduate student), and Simpa Salami, MD (associate professor of urology, University of Michigan).

The highlight of the afternoon was a very enlightening lecture, “Building Diversity in Genomics Research at the Regeneron Genetics Center” by Timothy Thornton, PhD (senior director of statistical genetics and machine learning).

Sunday’s program was also interactive, requiring attendees and

program faculty to break up into the following 2 working groups to discuss how to address disparities in prostate cancer:

Group A—Collaborative Team Research Programs (policy/funding programs, targeted Request for Applications minority investigators) and Group B—Patient

Engagement, Minority Patient Recruitment, and Reducing Barriers to Clinical Trials. These sessions resulted in recommendations and actionable items to help ConDUC and the SCOPE Registry achieve their goals. The conference ended with student presentations of their posters re-

lated to basic research on biologic mechanisms of disparate outcomes in prostate cancer. Three \$1000 awards were presented.

SAVE THE DATE! NOVEMBER 8 to 10, 2024. 4th Annual Prostate Cancer Symposium at Clark Atlanta University. Addressing Prostate Cancer Disparities! ■

HUMANITARIAN

Vanderbilt’s Monroe Carell Jr Children’s Hospital: Healing Across Borders

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In the realm of short-term medical missions, the importance of delivering consistent care cannot be overstated. Achieving clinical success and understanding surgical outcomes rely heavily on maintaining continuity. For over a decade, the Monroe Carell Jr Children’s Hospital at Vanderbilt has extended its compassionate care not only to children at home but also to those in need around the globe.

Since 2005, the Monroe Carell Jr Children’s Hospital has been



Figure 1. The 2022 pediatric urology team from Monroe Carell Jr Children’s Hospital at Vanderbilt poses for a traditional welcome photo in front of the Moore Pediatric Surgery Center in Guatemala City.

a driving force behind 23 1-week pediatric surgical expeditions to Guatemala City, Guatemala. These missions have brought much-needed surgical care to children facing desperate circumstances. Each trip focuses on 1 of 4 pediatric surgical specialties: ophthalmology, orthopedics, otolaryngology, and urology. These surgical missions, conducted twice a year, are possible through collaboration with their partner in Guatemala, the Shalom Foundation.

The Shalom Foundation, a faith-based 501(c)(3) nonprofit organization headquartered in Franklin, Tennessee, has dedicated itself to providing life-changing medical

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VANDERBILT'S MONROE CARELL JR CHILDREN'S HOSPITAL: HEALING ACROSS BORDERS

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“The shared objectives of the Moore Center and the Monroe Carell Jr Children’s Hospital revolve around delivering continuous care through recurring short-term mission trips.”

and surgical care to impoverished children in Guatemala. In a landmark achievement, the foundation, with significant assistance from Vanderbilt, inaugurated the Moore Pediatric Surgery Center in Guatemala City in February 2011 (Figure 1). This innovative facility was developed through the expertise of Vanderbilt’s anesthesia, surgery, nursing, and architecture teams. It stands as a unique beacon in Guatemala, offering world-class pediatric care. Within its walls, visiting surgical teams find a modern facility equipped with full-time pediatricians, nurses, pharmacists, 3 functional operating rooms, sterilization equipment, and essential support staff (Figure 2). Teams of volunteer medical professionals from various US children’s hospitals, including Vanderbilt, converge here to collaborate with local



Figure 2. Dr John Brock and trip organizer, Jenni Logsdon, take a quick photo with a patient prior to surgery.



Figure 3. Members of the 2016 pediatric urology mission team smile for a photo with a young boy prior to surgery in one of 3 state-of-the-art operating rooms at the Moore Center.



Figure 4. The 2019 team gathers for a group photo in the recovery room after a long day of operating.



Figure 5. The 2015 pediatric urology team poses for a photo in the courtyard of the Moore Center on the last day of the mission trip.

medical specialists, offering health, healing, and hope to children and their families. The shared objectives of the Moore Center and the Monroe Carell Jr Children’s Hospital revolve around delivering continuous care through recurring short-term mission trips. An exemplary case is that of a young boy who endured a pelvic fracture and posterior urethral disruption and received surgical care across 3 separate mission trips by the dedicated Vanderbilt team (Figure 3).

Throughout the years, the Monroe Carell Jr Children’s Hospital mission trips have left an indelible mark. Their 23 teams have performed over 1100 surgeries and have evaluated more than 2000 patients in clinics. Each surgical mission brings together 15 to 17 Vanderbilt faculty and staff, offering a distinctive opportunity to serve children in dire need. The mission typically unfolds with a full clinic day at the Moore Center on Sunday, where surgeons and anesthesiologists evaluate over 100 children to identify the most suitable surgical candidates for the week. Subsequently, the week from Mondays through Fridays becomes a continuous stream of full days dedicated to surgery, averaging about 48 cases per mission, depending on the specialty (Figures 4 and 5). Remarkably, the otolaryngology team set a record with an astounding 91 cases in a single mission trip back in September 2019.

However, sometimes on these noble missions, the medical team encounters a patient whose condition necessitates more advanced surgical services than can be provided within Guatemala’s borders. In such cases, arrangements are made to bring the child to Nashville, Tennessee, for surgery. The Monroe Carell Jr Children’s Hospital International Leadership Committee has laid out a well-defined policy for the submission and approval process of potential recipients of international charity care. Typically, 1 to 2 such cases are approved each fiscal year. Since 2008, 20 children hailing from various countries, including China, Iraq, Guatemala, Honduras, Liberia, and Uganda, have been fortunate recipients of international charity care through this compassionate initiative. ■



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