

Original Article

Molecular genetic testing does not improve the detection of fluoroquinolone resistance before transrectal prostate biopsy

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ABSTRACT

Background: Fluoroquinolone-resistant (FQR) *Escherichia coli* (*E. coli*) causes transrectal prostate biopsy infections. We seek to further identify fluoroquinolones resistance by the incorporation of genetic profiling to influence antibiotic selection for transrectal prostate biopsy and whether the addition of this genetic testing could improve the prediction of FQR detection at the time of biopsy.

Materials and methods: In this prospective observational cohort study, rectal swabs were collected within 30 days of an upcoming prostate biopsy. These swabs were sent for phenotypic and genotypic assessment to predict FQR on the day of the biopsy. Phenotype: Specimens were inoculated onto Mac-Conkey agar containing ciprofloxacin using standard culture techniques to determine FQR status. Genotype: We compared cultures to polymerase chain reaction (PCR) sequence typing (*E.coli*- ST131/H30/ST69) and bacterial plasmids (*gyrA*, *qnrQ*, and *qnrS*). The presence of FQR on this testing was compared to the second rectal swab collected just before biopsy (2 hours after ciprofloxacin prophylaxis), which served as the gold standard for FQR.

Results: Overall, the FQR rate was 23.6%. The bacterial plasmids (*qnr*) were present in 54.1% of samples, and multidrug-resistant *E. coli* ST131 was present in 12.5% of samples. In comparison, phenotypic assessment using rectal culture had a better prediction for the presence of FQR as compared to genotypic testing [area under the curve (AUC) = 0.85 in phenotype arm vs. AUC = 0.45 in genotype arm].

Conclusion: We detected a high prevalence of FQR genes in the rectum, but the addition of PCR-based genotyping did not improve the prediction of culture-based FQR at the time of biopsy.

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1. Introduction

Transrectal ultrasound-guided prostate needle biopsy (TPB) remains the most common technique to diagnose prostate cancer.^{1,2} Traditionally, TPB has a low infection risk when performed using recommended fluoroquinolone prophylaxis,³ however, rates of post-TPB infection have steeply risen over the last decade to over 10% in some series.⁴ Previous studies have linked infections to colonization status of fluoroquinolone-resistant (FQR) *Escherichia*

coli (*E. coli*) identified in asymptomatic individuals prompting alternate prophylaxis regimens.^{5–7}

One way to combat the FQR organism is to perform a rectal swab cultured on fluoroquinolone-infused media before the prostate biopsy, termed “targeted prophylaxis.”⁸ Targeted prophylaxis provides an organism and resistance profile guide to antibiotic decision-making and prevents overuse.⁹ A significant limitation was that laboratories around the country might not perform the specific rectal swab surveillance screening culture (Cx Screen) due to low utilization and cost outside high-volume centers.¹⁰ Lack of availability has led to investigating using other approaches to select antibiotics and alternate sterilization techniques.^{11,12}

One alternate approach is to use next-generation sequencing to identify quinolone resistance (PCR Screen). Our group identified a

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Abbreviations

AUC	area under receiver operating characteristic curve
AST	antibiotic susceptibility testing
DNA	deoxyribonucleic acid
<i>E. coli</i>	<i>Escherichia coli</i>
FQR	fluoroquinolone resistance
PCR	polymerase chain reaction
PSA	prostate-specific antigen
TPB	transrectal ultrasound-guided prostate needle biopsy

strain of *E. coli* (sequence type 131) as a causal source in more than 70% of the infections that occur post-TPB.^{13,14} Plasmids are another mechanism bacteria used to share genetic information to survive antibiotic exposures but have not been thoroughly evaluated.¹⁵ The plasmids *qnr* topoisomerase subunit Q and subunit S (*qnr* plasmids) and DNA gyrase subunit A (*gyrA*) have been associated with FQR. Herein, we test rectal swabs using standard FQR rectal screening culture techniques and compared next-generation sequencing approaches to predict FQR at the time of TPB. The objective was to identify (1) the prevalence of FQR and FQR-associated genotypes in rectal swabs and (2) whether the addition of this genotype testing could improve the prediction of FQR detection at the time of biopsy.

2. Methods

2.1. Study design

The study uses a prospective observational cohort to investigate culture technique (phenotype, Cx Screen) versus PCR-based genetic profiling (genotype, PCR Screen) before a transrectal ultrasound-guided prostate biopsy (schema Fig. 1). A rectal swab was performed on men before an upcoming prostate biopsy procedure as the standard of care to conduct “targeted prophylaxis” within 30 days of the TPB. The Culturette had two cotton swabs per sample. One was sent to the microbiology laboratory for culturing (Cx Screen), and the second was stored in a 15 mL conical tube with 5 mL of phosphate-buffered saline (PBS) (Thermo Fischer Scientific, Waltham, MA, USA). The conical tubes that contained rectal swabs were sent to MicroGenDX for 16s rRNA and PCR analysis (PCR Screen). We further obtained a second rectal swab immediately before the biopsy but 2 hours after a dose of prophylactic

ciprofloxacin 500 mg. This second rectal swab served as a gold standard for the determination of FQR (FQR Bx). Rectal swabs have been determined equivalent to stool culture and are easier to obtain in the office, which improves protocol compliance.¹⁶ We chose MicroGenDX because if the molecular genetic approach worked, they would have the scalability to apply the technique to a large number of users.

2.2. Population

IRB approval was obtained to use rectal swabs stored in our genitourinary biorepository (HSC20050234H). Men presented to the South Texas Veterans Health Care System Audie Murphy Division hospital to evaluate a “for cause” biopsy, usually consisting of elevated PSA or abnormal prostate examination. After shared decision-making, the patient and physician determined the indication for a biopsy. The patient would first undergo rectal swab collection to screen for colonization of FQR *E. coli* as the standard of care. Physicians chose antibiotic prophylaxis that included ciprofloxacin as a base and targeted augmented prophylaxis for all patients with FQR. We used a genitourinary biorepository for the rectal swabs for research with approval to access the specimens with associated demographics. As per the standard of care, patients took ciprofloxacin 500 mg orally on the morning of the biopsy. A second rectal swab was taken at the biopsy procedure before the prostate biopsy and sent for culture.

2.3. Rectal culture (Cx Screen)

The Liquid Stuart Medium swab and transport system (Copan Diagnostics, Murrieta, CA, USA) were obtained at the time of standard digital rectal examination of the prostate and sent to microbiology. The microbiology laboratory inoculated swabs onto MacConkey agar containing 10 µg/mL of ciprofloxacin (Hardy Diagnostics, Santa Maria, CA, USA).¹³ As a control, the sample was also inoculated onto regular MacConkey agar to ensure that enteric bacteria were on the swab. If, after 24-hour incubation, there was no growth on the ciprofloxacin-infused MacConkey agar and there was growth of normal flora on the other agars, the rectal flora was assumed to be ciprofloxacin-susceptible; conversely, any gram-negative (GN) rods growing on the ciprofloxacin-infused MacConkey agar were presumed to be ciprofloxacin resistant.

We analyzed a representative of each distinct colony morphology using the Vitek 2 analyzer (BioMerieux, Durham, NC, USA) for identification by GN cards and sensitivity testing by Antibiotic Susceptibility Testing (AST) cards using Clinical and Laboratory Standards Institute Interpretative Criteria.¹⁴

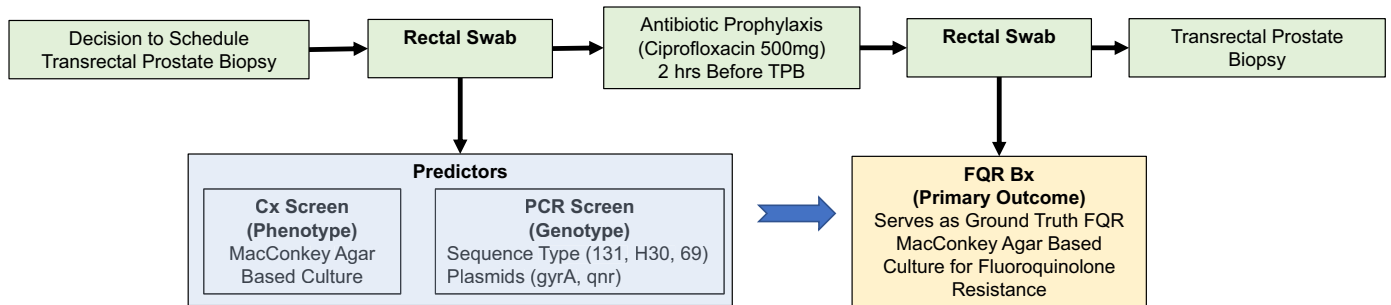


Fig. 1. Study schema. We demonstrate the study schema wherein we enrolled men at the time of biopsy decision. It is the standard in our clinic to send a rectal swab for culture on MacConkey agar infused with ciprofloxacin. At this time, we used two rectal culture swabs (one for culture and one for PCR testing) as predictors (blue box). At the time of prostate biopsy, usually after the patient’s first dose of 500 mg ciprofloxacin, a second rectal culture was obtained, noted as the primary outcome (yellow box). The primary outcome is the ground truth that would indicate the presence of fluoroquinolone-resistant bacteria in the rectum at the time of the prostate biopsy. Cx, culture; FQR, fluoroquinolone resistance; PCR, polymerase chain reaction; TPB, transrectal ultrasound guided prostate needle biopsy.

2.4. PCR at biopsy scheduling (PCR Screen)

We collected rectal swabs using standard Cultiurettes placed in a 15 mL conical tube without PBS solution. The tubes were de-identified and sent to MicroGenDx (Lubbock, TX, USA), a CAP-accredited and CLIA-licensed clinical diagnostic laboratory, for analysis. We used custom primers and targeted sequencing with MicroGenDX to perform rapid PCR specifically focused on quinolone resistance for this study. We used targeted sequences to capture the presence of *qnr* topoisomerase subunit Q and subunit S (*qnr* plasmids) and DNA gyrase subunit A (*gyrA*). Other targeted primers were used to capture Sequence Type 131 (ST131), H30 and ST69 — all shown to have a preponderance of fluoroquinolone resistance. Each target bacterial or fungi DNA, whose concentration was measured to obtain an initial concentration (ng/μL), was diluted to get a six- to eight-fold serial dilution series and run on the quantitative PCR (qPCR) panel assay on the Roche LightCycler 480 II instrument.

2.5. Statistical analysis

The primary outcome of each test's operational characteristic is FQR. All patients undergo targeted prophylaxis as the standard of care to prevent infection; therefore, all subjects positive for FQR organisms received an additional antibiotic. Because of this caveat, a postbiopsy infection was not the primary outcome. Our goal was to predict FQR at the time of the prostate biopsy, as it is a significant risk factor for infection if augmented antibiotics are not prescribed. The culture at the time of the biopsy represents the bacteria in the rectum at the biopsy time. Of note, usually, the biopsy occurs at least 2 hours after the first dose of oral fluoroquinolone. We calculated sensitivity, specificity, negative predictive value, positive predictive value, and an area under receiver operating characteristics curve (AUC). We compared demographics with Student *t* test or Chi-square test, depending on the variable. Statistical analysis was performed using SPSS v21 software (IBM, New York, NY, USA).

3. Results

3.1. Demographics and clinical outcomes

We display the consort diagram in Fig. 2. Table 1 shows demographics from our cohort. More than 50% of our patients were non-Caucasian. Among the 72 patients analyzed at the end of the study, the prevalence of FQR was 23.6% (17/72). We used a targeted antibiotic approach for FQR patients as a standard of care; therefore, patients had augmented prophylaxis (ciprofloxacin 500 mg 2 hours before biopsy plus IM antibiotic) before the prostate biopsy. The technique has been modified based on previous targeted prophylaxis studies that have shown a ciprofloxacin base coverage for prophylaxis would prevent ciprofloxacin-sensitive infections instead of only using the bacterial resistance profile in a single antibiotic agent approach.⁸ The most common antibiotic to augment ciprofloxacin was ceftriaxone ($n = 15$, 20.8%). Infection was defined as any person requiring secondary antibiotics after the procedure. Four patients received secondary antibiotics for post-biopsy infections (Table 3).

3.2. Bacterial phenotypic assessment

Our definition of the phenotype was the bacteria's demonstration of fluoroquinolone resistance on culture (Cx Screen). The culture technique used fluoroquinolone-infused MacConkey agar from a rectal swab obtained at the time of prostate biopsy consent. Cx Screen performed before the prostate biopsy had the highest

sensitivity of 88% [95% confidence interval (CI) 77%–95%] and specificity of 95% (90%–97%) (Table 2) to predict (FQR Bx), which is FQR on the day of the biopsy after exposure to a fluoroquinolone. The best predictor of FQR on the biopsy day was to perform a rectal swab culture (Cx Screen) on ciprofloxacin-infused MacConkey agar (AUC = 0.85, Table 2). Using the standard of culture, we only identified *E. coli* as the primary organism in positive call cases.

3.3. Genotypic assessment

The definition of genotype was predicting fluoroquinolone resistance behavior based on genetic sequencing (PCR Screen). During previous work, we discovered that ST131 *E. coli* is a significant cause of FQR infections after prostate biopsy and that the H30 subclone was of particular concern¹³. Sequence type is inherent to the chromosome of a particular *E. coli* strain and tends to be FQR. We noted nine patients (12.5%) colonized with ST131 *E. coli*, and none were H30 subclones. Plasmid *qnr* genes were positive in 54.1% (39/72) of our study population. Plasmid *qnr* genes were detected in 55% (30/55) in FQR negative samples and 53% (9/17) in FQR positive samples ($P = 0.9$). None of the patients had DNA *gyrA* plasmid detected in their rectal swabs.

Using receiver operating characteristic analysis to assess the predictive ability of genotype assessment for FQR, the testing sequence type ST131, overall, resulted in good specificity at 87% (95% CI 76%–95%) but inferior sensitivity of only 12% (95% CI 2%–36%) for FQR prediction. The AUC shows no benefit for ST131 testing alone to predict FQR at the time of biopsy with an AUC of 0.49. Adding the detection of plasmid *qnr* genes at this point of care also did not improve the prediction of FQR on the rectal culture at the time of biopsy (AUC = 0.45). The PCR Screen as a combination of sequence typing, *qnr* genes, and *gyrA* detection using PCR again showed no benefit (AUC = 0.45) in predicting FQR Bx.

4. Discussion

We determined that the Cx Screen (phenotypic) approach was superior to a molecular genetic-based approach (PCR Screen) for identifying and predicting FQR organisms' presence at the time of transrectal prostate needle biopsy. Based on our findings, Cx Screen using a rectal swab with selective culture media for phenotypic FQR identification is the best approach to perform targeted prophylaxis before transrectal prostate biopsy. In clinical practice, we use fluoroquinolone as base prophylaxis and then use an augmented antibiotic based on the culture results.^{5,9,15,16} In our cohort that used this targeted prophylaxis approach, we did not have any infections caused by FQR organisms.

The prevalence of FQR was 23.6% (17/72, similar to previously described cohorts),¹⁷ and ST131 *E. coli* was 12.5% (9/72). ST131 is a common culprit in FQR organisms; the majority of ST131 was found in the group negative for FQR.^{13,14} It is unknown if this organism could be driving non-FQR infection rates. Concerningly, in a study performed on healthy adult women with 8.8%, ST131 persisted for long periods, indicating that those with a previous infection from ST131 could still harbor the bacteria.¹⁸ Although ST131 bacteria may be multidrug-resistant, they are more likely persistent colonizers and do not necessarily cause infection by their presence. A surprising finding was that we detected *qnr* plasmids in 54.2% of men ($n = 39/72$). Other studies have shown a prevalence of *qnr* plasmids below 30%, usually in bacteria isolate^{19,20} Our study is one of the largest studies to investigate the prevalence of *qnr* plasmids in the rectum. The gene may be present but not activated or functional, making this finding very concerning regarding the unexpectedly high prevalence. Interestingly, the more common gene linked to FQR is the *gryA* plasmid gene, but this gene was not found in any

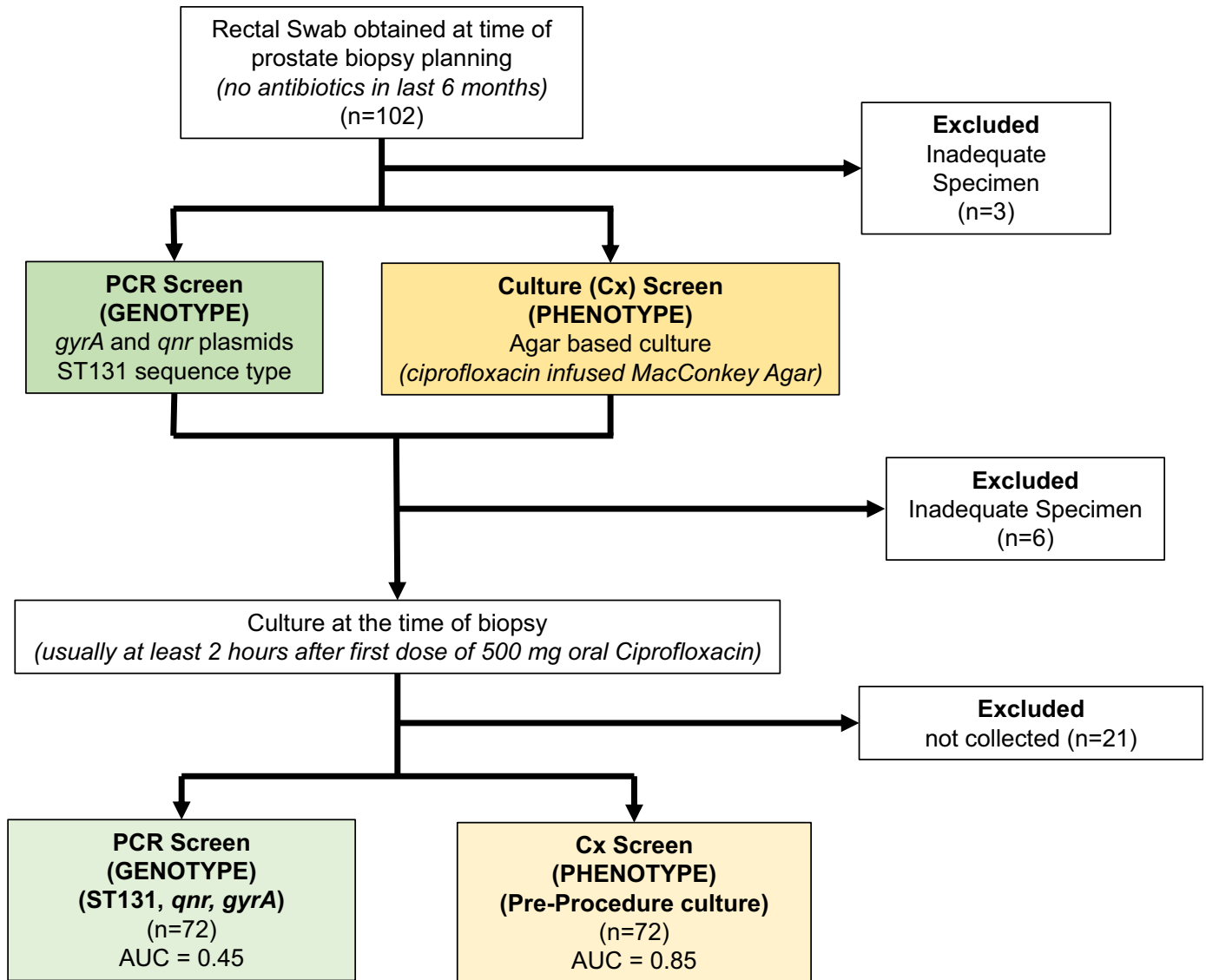


Fig. 2. Consort diagram. The consort diagram shows the enrollment of men before transrectal prostate biopsy. The outcome was the ability to predict fluoroquinolone resistance at the time of prostate biopsy. We distinguish PCR and culture-based screening methods by the AUC values. AUC, area under the receiver-operator curve; Cx, culture; PCR, polymerase chain reaction.

subjects. Overall, using next-generation sequencing in a genomic-based antibiotic strategy would result in a significant overuse of antibiotics, potentially perpetuating the problem of antibiotic resistance.

The MUSIC (Michigan Urological Surgery Improvement Collaborative) showed that urologists choose to give additional broad-spectrum antibiotics rather than culture-based targeted prophylaxis approach.²¹ Given our population of 23% of men with FQR *E. coli* on rectal culture, we potentially could be prescribing 77% of men with additional antibiotics unnecessarily if we took the “augment all” approach. Adding augmented antibiotics to all patients undergoing a prostate biopsy is not a sustainable long-term infection prevention strategy. Based on the complexities of initiating a targeted prophylaxis program, we attempted to use a genomic approach to predict FQR that would be easier for urologists to implement. A PCR-based analysis that does not rely on more labor-intensive approaches of traditional cultural techniques could have been more convenient. Unfortunately, in our initial attempt at real-time PCR, we missed about 30% of FQR bacteria at the time of

prostate biopsy.²² Therefore, this study was to determine if adding *qnr* plasmids to known sequence types would improve the predictive ability of FQR. Our results are that *qnr* plasmids are prevalent but do not improve the prediction of FQR.

Our study has several limitations. First, we did not assess all the known FQR (*ParC*, *ParE*) genes for this study. We also did not study for extended-spectrum beta-lactamases (ESBL)-producing *E. coli*. We were unable to link FQR status to infection because all subjects underwent targeted prophylaxis with directed antibiotic prophylaxis. We did not collect cultures from presumed infections to determine the culprit bacteria. We noted infections in the non-FQR group more so than in the FQR group, largely due to additional antibiotics given in the FQR group. The fact that we can no longer directly attribute most infections to FQR is concerning that there may be another culprit bacteria causing infections not associated with FQR. We did not identify an exhaustive list but used a commercially available service from MicroGenDx, easily available to urologists, which only tested to *qnrs*. Both the *qnr* gene and *gyrA* mutations may be present in species besides *E. coli*, which may add

Table 1
Demographics of the study population.

Demographic	FQR negative N (%) or median (IQR) N = 55	FQR positive N (%) or median (IQR) N = 17	P
Age (y)	65 (59–70)	65 (59–68)	0.9
Race/Ethnicity			0.07
White	26 (47%)	3 (18%)	
African American	12 (23%)	4 (29%)	
Hispanic/Latino	16 (29%)	9 (52%)	
Other	1 (2%)	1 (5%)	
Body mass index (kg/m ²)	29.5 (26.5–34.3)	30.0 (26.7–33.1)	0.8
Diabetes	17 (31%)	5 (30%)	0.9
Family history of prostate cancer	14 (26%)	3 (19%)	0.6
Family history of breast cancer	6 (11%)	0 (0%)	0.2
Abnormal prostate examination	8 (15%)	1 (6%)	0.3
Prostate-specific antigen	6.33 (4.95–7.25)	9.5 (7.7–9.8)	0.03*
Prostate size (mm ³)	37.6 (28.7–53.0)	50.0 (37.7–62.3)	0.08
Postprostate biopsy infections	4 (7.3%)	0 (0%)	0.3
Antibiotics in the last 90 d	10 (18%)	2 (12%)	0.5
Genotypes			
ST131	7 (13%)	2 (12%)	0.9
H30	0 (0%)	0 (0%)	–
ST69	4 (7%)	2 (12%)	0.6
gyrA	0 (0%)	0 (0%)	–
qnrB or qnrS	30 (55%)	9 (53%)	0.9

P < 0.05 is considered to be statistically significant.

FQR, fluoroquinolone resistance; IQR, interquartile range.

Table 2
Comparison of operational characteristics (sensitivity, specificity, NPV, PPV, and AUC) of phenotype assessment (prebiopsy rectal culture) and genotype assessment (*qnr* plasmids, ST131 chromosomal gene and combined) for prediction of fluoroquinolone resistance.

Sample (N)	FQR technique	Type	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)	AUC
72	Prebiopsy rectal culture	Phenotype	76% (50%–93%)	93% (82%–98%)	93% (84%–97%)	76% (55%–90%)	0.85
72	<i>qnr</i> plasmid genes	Genotype	47% (23%–72%)	44% (30%–58%)	73% (61%–82%)	21% (13%–31%)	0.45
72	ST131 chromosomal gene	Genotype	12% (2%–36%)	87% (75%–95%)	76% (72%–79%)	22% (6%–55%)	0.49
72	Combined ST131 and <i>qnr</i>	Genotype	47% (23%–72%)	40% (27%–54%)	71% (58%–81%)	20% (12%–30%)	0.45
72	<i>gyrA</i> Mutations	Genotype	N/A	N/A	N/A	N/A	N/A

AUC, area under the receiver-operator curve; CI, confidence interval; FQR, fluoroquinolone resistance; NPV, negative predictive value; PPV, positive predictive value.

Table 3
Patients who developed postprostate biopsy infections in the study cohort

Patient ID	Study cohort	Age (y)	Comorbidities	History of antibiotic use in previous 90 d	Use of augmented prophylaxis	History of antibiotic use in previous 90 d	Presence of sepsis due to infection	Genotype			Antibiotic administered
								ST131	H30	ST69	
Patient 1	FQR negative	65	None	None	No	None	No	Negative	Negative	Negative	Ceftriaxone
Patient 2	FQR negative	58	None	None	No	None	No	Negative	Negative	Negative	Ceftriaxone + ciprofloxacin
Patient 3	FQR negative	48	None	None	No	None	No	Positive	Negative	Negative	Piperacillin/Tazobactam + Vancomycin
Patient 4	FQR negative	46	None	None	No	None	Yes	Negative	Negative	Negative	Piperacillin/Tazobactam + Vancomycin

FQR, fluoroquinolone resistance.

to the high number detected. Moreover, this additional testing using MicroGenDx kit would further add around \$400 to the financial burden for patients undergoing prostate biopsy. We also were not able to capture a couple of key details that could impact risk, such as recent foreign travel and the number of previous prostate biopsies.²³

5. Conclusion

In conclusion, the genotypic assessment of bacteria did not reflect the bacterial resistance profile for fluoroquinolones in this study. We detected a high prevalence (54.2%) of FQR-associated

plasmids along with a known uropathogenic strain *E. coli* (ST131–12.5%). These results could be very concerning for the future of quinolone antibiotics and encourage alternative strategies to augment antibiotics before prostate biopsy selectively or use transperineal approaches to avoid the rectum.

Ethics approval and consent to participate

IRB approval was obtained for this study (Ref IRB No: HSC20050234H). The study was carried out in accordance with relevant guidelines and regulations as per the Declaration of Helsinki. Participants' informed consent was obtained for the study.

Consent for publication

Not applicable.

Registry and the registration no. of the study/trial

Not applicable.

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Availability of data and materials

The data that support the findings of this study are available from Dr Michael A. Liss (corresponding author), but restrictions apply to the availability of these data, which were used under license for the present study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the corresponding author (Dr Michael A. Liss).

Conflicts of interest

MicroGenDX is funding a clinical trial for antibiotic selection before ureteroscopy (MAL).

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