A Statewide Intervention to Reduce Hospitalizations after Prostate Biopsy

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Purpose: Recent data suggest that increasing rates of hospitalization after prostate biopsy are mainly due to infections from fluoroquinolone-resistant bacteria. We report the initial results of a statewide quality improvement intervention aimed at reducing infection related hospitalizations after transrectal prostate biopsy.

Materials and Methods: From March 2012 through May 2014 data on patient demographics, comorbidities, prophylactic antibiotics and post-biopsy complications were prospectively entered into an electronic registry by trained abstractors in 30 practices participating in the MUSIC. During this period each practice implemented one or both of the interventions aimed at addressing fluoroquinolone resistance, namely 1) use of rectal swab culture directed antibiotics or 2) augmented antibiotic prophylaxis with a second agent in addition to standard fluoroquinolone therapy. We identified all patients with an infection related hospitalization within 30 days after biopsy and validated these events with claims data for a subset of patients. We then compared the frequency of infection related hospitalizations before (5,028 biopsies) and after (4,087 biopsies) implementation of the quality improvement intervention.

Results: Overall the proportion of patients with infection related hospitalizations after prostate biopsy decreased by 53% from before to after implementation of the quality improvement intervention (1.19% before vs 0.56% after, p=0.002). Among post-implementation biopsies the rates of hospitalization were similar for patients receiving culture directed (0.47%) vs augmented (0.57%) prophylaxis. At a practice level the relative change in hospitalization rates varied from a 7.4% decrease to a 3.0% increase. Fourteen practices had no post-implementation hospitalizations.

Conclusions: A statewide intervention aimed at addressing fluoroquinolone resistance reduced post-prostate biopsy infection related hospitalizations in Michigan by 53%.

Key Words: prostate, biopsy, infection, anti-bacterial agents, quality improvement

Abbreviations and Acronyms

IRH = infection related hospitalization

MUSIC = Michigan Urological Surgery Improvement Collaborative

PSA = prostate specific antigen

QI = quality improvement

TRUS-Bx = transrectal ultrasound guided prostate biopsy

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THERE is widespread concern about increasing rates of serious infections and hospitalizations after TRUS-Bx procedures.[1–4] Most available data suggest that the root cause of this trend is the increasing prevalence of

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fluoroquinolone-resistant bacteria, with recent reports estimating that 11% to 24% of the U.S. population harbors such organisms.[5–10] We previously examined this issue among 17 practices participating in the MUSIC. Across this diverse group of academic and community practices we found that 1% of patients are hospitalized after TRUS-Bx and that most of these events involve serious infections with fluoroquinolone-resistant bacteria.[11]

Given the significant human and financial costs associated with these hospitalizations, urologists in the MUSIC implemented a quality improvement initiative aimed at reducing their occurrence by addressing fluoroquinolone resistance as a risk factor for severe post-biopsy infections. To do this, MUSIC practices implemented one or both of the established prophylactic strategies of 1) provision of culture directed antibiotics based on results from a pre-biopsy rectal swab or 2) use of augmented antibiotics (ie along with standard fluoroquinolone therapy) to broaden coverage in the event a patient harbored fluoroquinolone-resistant organisms. Prior single institution reports suggest that both methods can achieve significant reductions in post-biopsy infections.[8,12–14] However, the feasibility and effectiveness of these approaches have not been evaluated across multiple diverse practice settings. In this context we now report rates of post-biopsy IRHs before and after the implementation of this statewide intervention in the Michigan Urological Surgery Improvement Collaborative.

METHODS

Study Population

Since its inception in March 2012 participating practices have joined MUSIC in a staggered fashion. Upon entry into the collaborative, each practice initiates prospective data collection for all men undergoing TRUS-Bx. For each patient standardized clinical and demographic information, biopsy history, comorbidities, prophylactic antibiotics and post-biopsy complications (including hospitalizations related to the biopsy) are entered into an online registry by trained data abstractors from each practice. Details of the quality assurance mechanisms for data in the MUSIC registry are provided elsewhere.[11,15] All practices participating in MUSIC obtained approval from their local institutional review boards. Because the focus of MUSIC is quality improvement, collaborative participation was deemed exempt from institutional review board oversight in all cases.

Intervention

With iterative input from colleagues in infectious disease and microbiology we developed clinical pathways for culture directed and augmented antibiotic prophylaxis based on the published literature in this area (supplementary figure 1, http://jurology.com/).[8,13,14,16–18] After discussing options among the clinical champions at our collaborative-wide meetings, each MUSIC practice made its own decision about which pathway(s) to adopt. The Coordinating Center was informed about the practice choice and date of implementation (supplementary figure 2, http://jurology.com/).

Among the 30 MUSIC practices collecting data during the interval for this analysis (March 2012 through May 2014), 3 sites had initiated augmented antibiotic prophylaxis before development of this specific intervention, and 3 practices joined MUSIC and started collecting data after we initiated the intervention. Accordingly, 24 practices had data for biopsies performed before and after implementation of the quality improvement intervention.

Primary Outcome

Using methods described previously our primary outcome was the occurrence of an IRH within 30 days of TRUS-Bx.[11] Once a hospitalization was identified we also collected detailed clinical information about this event, including admission, diagnosis and any available culture data from the hospital stay. We defined IRH as those admissions with fever, sepsis, urinary tract infection or acute prostatitis as the primary diagnosis.

To validate this outcome measure we also obtained medical claims data for a sample of men (228) in the MUSIC registry with BCBSM (Blue Cross Blue Shield of Michigan) as primary payer. We identified all patients with claims for a hospitalization within 30 days of the date of TRUS-Bx, reviewed the admitting diagnoses and compared these events with data in the registry. From the claims data we identified 5 hospitalizations (2.2%) within 30 days after TRUS-Bx. We noted perfect (100%) concordance between the claims data and the MUSIC registry. The 2 hospitalizations with diagnoses attributable to the TRUS-Bx (urinary tract infection, fever) were also identified in the MUSIC registry. Conversely the 3 hospital admissions with diagnoses unrelated to TRUS-Bx (malignancy of sigmoid colon, pathological intertrochanteric fracture, prostate cancer surgery) were not included in the registry as biopsy related hospitalizations.

Statistical Analyses

For analytic purposes we classified all biopsies according to whether they were performed before or after implementation of the QI intervention. Biopsies performed in the post-implementation period were further categorized as culture directed or augmented based on the strategy used in each case. For patients with more than 1 biopsy during the study period (367) we only included the first biopsy in this analysis.

We used chi-squared and Wilcoxon rank sum tests to compare demographic and clinical characteristics for patients in the pre-implementation and post-implementation cohorts. We then compared collaborative-wide and practice specific rates of IRHs for biopsies performed in the pre-implementation vs post-implementation period, using Fisher's exact test where appropriate. Because MUSIC collects the specific antibiotics administered for each biopsy, we performed an intent to treat analysis (in which each patient's biopsy was defined as pre- or post- based on its relationship to the date of implementation in each

practice) and a "per pathway analysis" (in which each patient's biopsy was defined as pre- or post- based on the actual antibiotics administered). We also fit a multivariate logistic regression model to estimate rates of IRH before and after implementation of the QI intervention across the entire collaborative, adjusting for patient characteristics including age and history of prior TRUS-Bx. Because the number of hospitalizations was small for most sites, we did not fit similar models for comparisons of the culture directed vs augmented pathways and for the practice level analyses. Finally, we compared results of culture data available from hospitalizations occurring before or after implementation of the QI intervention. All statistical testing was performed using SAS® 9.0 or Stata® 13.1 at the 5% significance level.

RESULTS

[T1] Table 1 presents a comparison of patient characteristics for biopsies performed before vs after implementation of the quality improvement intervention. The pre-implementation and post-implementation cohorts comprised 5,028 and 4,087 men, respectively. Patient age was similar between the 2 cohorts. A higher proportion of men in the post-implementation cohort had at least 1 prior transrectal biopsy (21.6% vs 16.6%, p <0.01). The observed differences in race and insurance status between these 2 groups represent changes in both variables collected and in definitions for a specific variable since the inception of data collection in the MUSIC.

For the intent to treat analysis we used the complete pre-implementation and post-implementation cohorts (table 2). Before implementation of the QI [T2] intervention the IRH rate was 1.19% (60 of 5,028) (fig. 1, *A*). After implementation IRHs decreased to [F1] 0.56% (23 of 4,087), representing a 53% relative reduction in the frequency of these events across the state of Michigan (p=0.002). After adjusting for relevant patient characteristics the likelihood of post-biopsy IRH was 49% lower after implementation (OR 0.51, 95% CI 0.31–0.85). The corresponding model predicted probability of hospitalizations is presented in figure 1, *B*.

Table 2 presents the distribution of antibiotic prophylaxis strategies among the pre- and post-implementation cohorts, and informs our per-pathway analysis. In the pre-implementation cohort 3,458 men (68.8%) received monotherapy (ie a single prophylactic antibiotic) and 1,183 (23.5%) actually received more than 1 antibiotic (ie augmented therapy) even before implementation of the QI intervention. For the post-implementation cohort most patients received augmented antibiotic prophylaxis (3,604, 88.7%), while 215 (5.3%) received a culture directed single antibiotic. A small number

Table 1. *Patient characteristics*

	Pre-Implementation		Post-Implementation		p Value
No. unique pts (%)	5,028	(100)	4,087	(100)	
Median age (range)	64	(35–99)	64	(28–93)	0.5
No. race (%):*					<0.0005
African-American	609	(15.2)	416	(10.8)	
Caucasian	3,227	(80.8)	3,286	(85.6)	
Other	160	(4.0)	137	(3.6)	
No. insurance category (%):†					<0.0005
Private	2,490	(49.8)	2,311	(57.1)	
Public	1,999	(40.0)	1,613	(39.8)	
Uninsured/self-pay	44	(0.9)	31	(0.8)	
Other	468	(9.3)	94	(2.3)	
No. PSA (ng/ml) at biopsy (%):‡					0.007
Less than 4	1,138	(22.9)	819	(20.2)	
4–10	3,067	(61.7)	2,606	(64.2)	
Greater than 10	765	(15.4)	634	(15.6)	
Median ng/ml PSA at biopsy (range)	5.39	(0.06–6,873.4)	5.56	(0.08–3,966)	0.007
No. abnormal digital rectal examination (%)§	1,093	(23.3)	901	(23.3)	0.95
No. cc prostate vol (%):‖					0.02
Less than 30	1,169	(23.8)	827	(21.5)	
30–60	2,576	(52.5)	2,047	(53.2)	
Greater than 60	1,164	(23.7)	972	(25.3)	
No. previous biopsy (1+)(%)¶	828	(16.6)	868	(21.6)	<0.0005
No. received pre-biopsy enema (%)**	3,082	(73.7)	2,409	(62.4)	<0.0005
No. prescribed AUA Best Practice compliant antibiotics (%)††	4,607	(99.3)	3,994	(99.6)	0.088

* Missing or unknown values for 1,032 (pre-intervention group) and 248 (post-intervention group).
† Missing or unknown values for 27 (pre-intervention group) and 38 (post-intervention group).
‡ Missing or unknown values for 58 (pre-intervention group) and 28 (post-intervention group).
§ Missing or unknown values for 342 (pre-intervention group) and 214 (post-intervention group).
‖ Missing or unknown values for 119 (pre-intervention group) and 241 (post-intervention group).
¶ Missing or unknown values for 35 (pre-intervention group) and 59 (post-intervention group).
** Missing or unknown values for 845 (pre-intervention group) and 226 (post-intervention group).
†† Missing or unknown values for 387 (pre-intervention group) and 75 (post-intervention group).

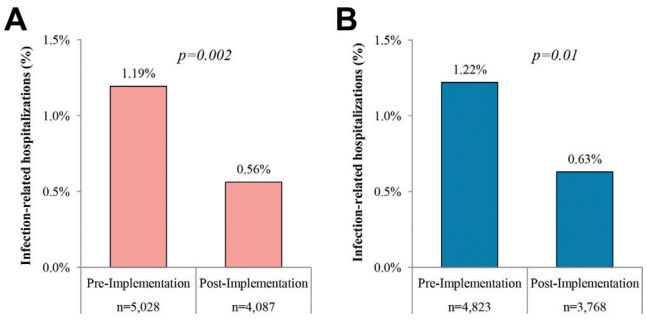

Figure 1. Unadjusted (*A*) and risk adjusted (*B*) rate of infection related hospitalizations before and after implementation of QI intervention (adjusted for age, history of prior biopsy, prostate size and PSA). Patients were excluded from model if covariate values were missing.

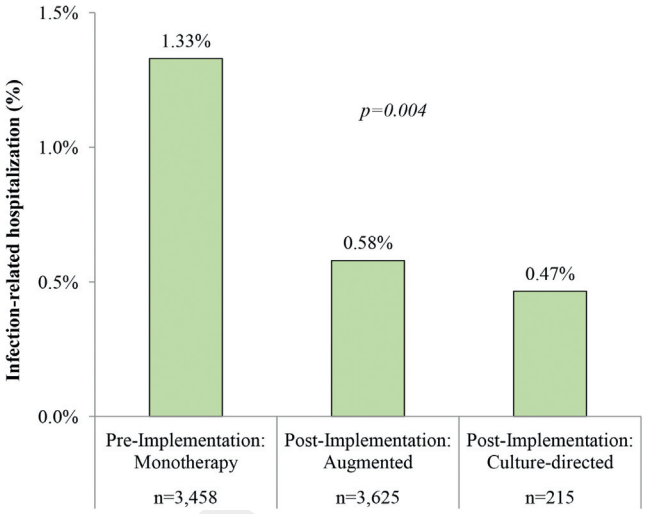

Figure 2. Unadjusted infection related hospitalizations after prostate biopsy by MUSIC pathway.

of patients (238, 5.8%) in the post-implementation cohort received a single antibiotic without a prior culture. Figure 2 presents results from per pathway analysis and illustrates the reduction in hospitalization after implementation of the QI intervention. Rates of IRH were similar for post-implementation biopsies performed with culture directed vs augmented prophylaxis. The hospitalization rate for the 238 patients in the post-implementation group who received a single, nonculture directed antibiotic was 0.42%. This was a heterogeneous group of patients with regard to the antibiotics provided, and included oral and parenteral agents.

Among 24 practices with biopsies performed before and after implementation of one or both pathways 16 (66.7%) sites had lower rates of IRH after implementation (fig. 3). Collectively these 24 practices reduced the frequency of post-biopsy IRHs by 60% (1.19% vs 0.48%, p=0.001). Of the 24 practices 14 had no IRHs after intervention. Culture data were obtained for 75 of the 83 IRHs, including 55 of 60 (91.7%) from the pre-implementation period and 20 of 23 (87.0%) from the post-implementation period (table 3). The cultures were positive for Escherichia coli in 92.7% (51 of 55) and 90% (18 of 20) of the pre-implementation and post-implementation cases, respectively. Fluoroquinolone-resistant organisms were identified in 78.2% vs 63.2% of pre-implementation vs post-implementation cultures (p=0.20). Among the 12 post-implementation cases

Table 2. *Patterns of prophylactic antibiotic use before and after implementation of QI initiative*

	No. Pre-Implementation (%)	No. Post-Implementation (%)
Totals	5,028 (100)	4,087 (100)
Monotherapy	3,458 (68.8)	238 (5.8)
Combination/ augmented	1,184 (23.5)	3,625 (88.7)
Culture directed	0 (0)	215 (5.3)
Unknown	386 (7.7)	9 (0.2)

hospitalized with fluoroquinolone-resistant organisms, 1 received culture directed prophylactic antibiotics (intramuscular gentamicin monotherapy) while the remaining 11 patients received augmented prophylaxis (see supplementary table, http://jurology.com/). Data regarding gentamicin-resistant bacteria were available for 53 and 19 of the pre-implementation and post-implementation admissions, respectively. Gentamicin resistance was identified in 8 patients (15.1%) in the pre-implementation cohort and 1 (5.3%) in the post-implementation cohort (p=0.27).

DISCUSSION

After implementation of clinical pathways for addressing fluoroquinolone resistance as a risk factor for serious infections, the rate of post-biopsy IRHs decreased by 53% across diverse practices participating in the Michigan Urological Surgery Improvement Collaborative. Fourteen participating practices had no IRHs in the post-implementation period. In terms of specific pathways the rates of hospitalization were similar for patients who received culture directed vs augmented antibiotic prophylaxis.

Our results are consistent with existing literature demonstrating the effectiveness of culture directed and augmented prophylaxis in single-institution settings. Two separate analyses from large academic medical centers reported no post-biopsy admissions after implementation of culture directed prophylaxis based on a rectal swab.[8,12] In terms of augmented prophylaxis, Adibi et al reported reduced hospitalization rates at their institution after adding gentamicin to standard fluoroquinolone

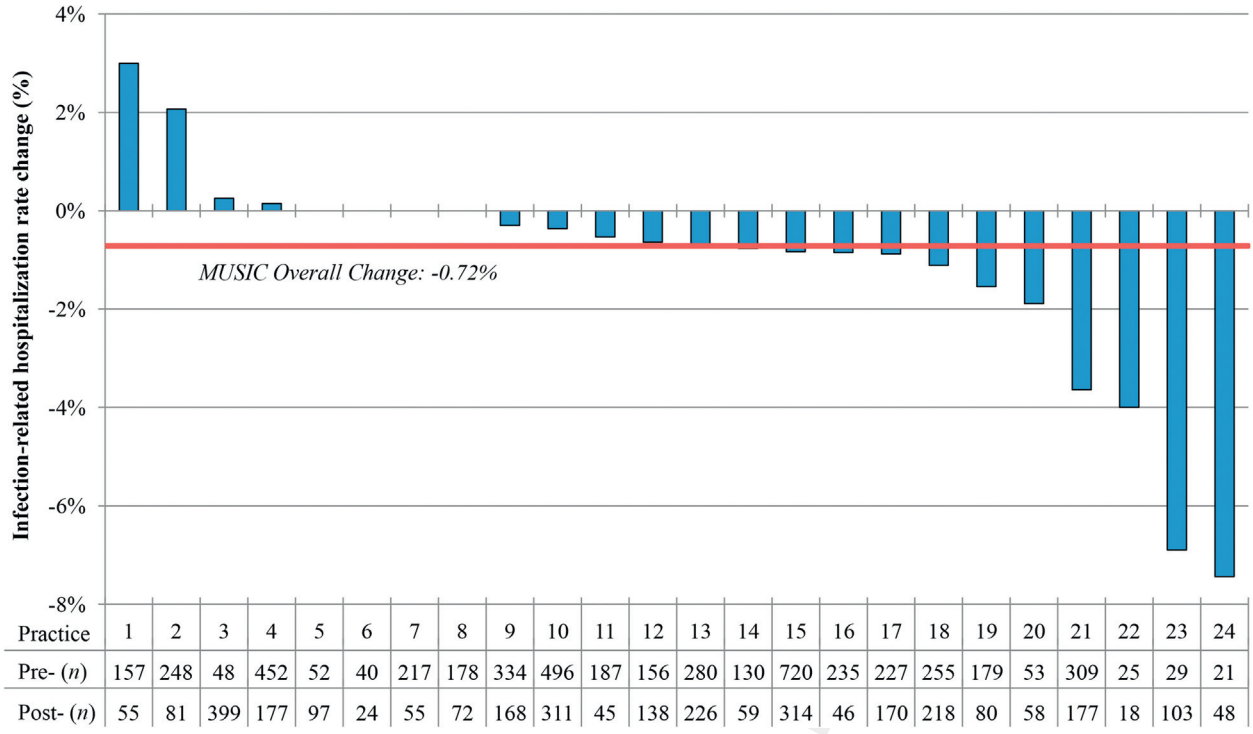

Figure 3. Change in infection related hospitalization rate across MUSIC practices from before to after implementation of QI intervention to address fluoroquinolone resistance. Six practices with augmented antibiotic pathway at start of data collection were excluded from analysis.

prophylaxis.[18] Others have achieved similar reductions by adding alternative agents including piperacillin/tazobactam and amikacin.[13,14] Our results extend this prior work by demonstrating the feasibility and effectiveness of these interventions on a much larger scale.

Nonetheless our findings should be considered in the context of several limitations. The absence of a control group limits our ability to establish causality between implementation of the QI intervention and reductions in post-biopsy hospitalizations. In particular, the absence of a control group renders our findings susceptible to bias due to the Hawthorne effect, whereby the process of measurement alone leads to improved outcomes. Likewise, the finding of similar rates of hospitalization in the post-implementation period among the small number of patients who received only a single antibiotic agent (without a rectal swab culture) raises the possibility that factors other than our intervention (eg patient selection, biopsy technique or increased attention to receipt and timing of monotherapy after intervention) may be contributing to the observed reduction in hospitalizations. While we readily acknowledge these issues it is also true that a control group is generally not feasible in the setting of a quality improvement collaborative. In addition, there were no systematic attempts to change patient selection, biopsy technique or other relevant factors in MUSIC practices during this period. Finally, even if the Hawthorne effect impacted our results, the net benefit for patients in Michigan is unchanged.

A related concern is that we did not observe a statistically significant reduction in the proportion of admitted patients with cultures identifying fluoroquinolone-resistant bacteria (again suggesting that factors may be at play other than our intervention aimed at addressing fluoroquinolone resistance). While this is a reasonable consideration, the relative reduction in this measure was 19.2% and the absence of statistical significance likely reflects limited power due to the small number of events. Moreover it is possible that the prevalence of fluoroquinolone resistance in our population changed during the project interval (making interpretation of the culture data less definitive) or that the gentamicin administration (route or dose) provided insufficient antimicrobial coverage for all cases.

Table 3. *Culture data for patients with infection related hospitalizations*

	Pre-Implementation	Post-Implementation	p Value
No.	55	20	
Pos culture (%)	96.4	90.0	0.28
E. coli (%)	92.7	90.0	0.70
Fluoroquinolone resistance (%)*	78.2	63.2	0.20

* One patient with culture data in the post-implementation period did not have fluoroquinolone sensitivities available.

Finally, when this project began we did not routinely collect (and so could not adjust for) certain relevant patient characteristics such as recent travel, prior antibiotic use and comorbidity. However, we are now collecting these data using a pre-biopsy checklist across MUSIC practices, which will strengthen future analyses in this area.

These limitations notwithstanding, our findings have significant implications for several stakeholders. For patients in Michigan with, or at risk for, prostate cancer, these data provide a specific metric demonstrating the high level of safety for prostate biopsies performed across the state. For urologists this work provides a pragmatic blueprint for addressing fluoroquinolone resistance in diverse practice settings ranging from rural, solo practices to large urban and/or academic practices. Because rates of hospitalization were similar for patients who received culture directed vs augmented antibiotic prophylaxis, individual practices aiming to reduce serious infections after TRUS-Bx could reasonably select the option best suited to their environment. However, efforts to develop an intervention of similar scale (ie statewide) outside of Michigan may be challenging without funding and resources supplied by BCBSM and the MUSIC practices. Nonetheless, urologists in several other states have already launched regional quality improvement collaboratives. Work being done in Michigan underscores the benefits of this model and could accelerate the funding of such initiatives by private and public payers alike. In fact, the recent Transforming Clinical Practice Initiative from the Centers for Medicare and Medicaid (CMS) Innovation reflects the growing interest that CMS and other payers have in expanding the scope of physician led quality improvement collaboratives.[19]

Moreover while the absolute number of post-biopsy hospitalizations is small, these events are expensive (potentially including admissions to intensive care units), and reducing these admissions can yield significant cost savings for private payers and CMS. Finally, for policymakers, including the U.S. Preventive Services Task Force, these data provide clear evidence of the concerted efforts being made by urologists to reduce the morbidity associated with prostate cancer detection strategies.

Moving forward, our work in this area will capitalize on the rapidly increasing number of patients in the MUSIC registry to better define differences in the clinical and cost-effectiveness of culture directed vs augmented antibiotic prophylaxis. Most MUSIC practices selected the augmented approach because its implementation is more straightforward than rectal swab cultures. However, we do maintain and discuss concerns about the implications of the augmented strategy for accelerating new antibiotic resistance patterns. As such, data suggesting a clear benefit to the rectal swab approach, from a clinical or financial perspective, would likely accelerate wider adoption of this approach in Michigan.

In addition, we are using data from the pre-biopsy checklist to identify specific patient subgroups at highest risk for infection. For this group of patients it may be necessary to further modify the timing, dosing and route (ie intramuscular vs intravenous) of prophylactic antibiotic administration. Finally, we are using site visits to MUSIC practices with the highest vs lowest rates of hospitalization to examine and compare patient flow, procedure setting and personnel, instrument sterilization and/or other biopsy processes (eg formalin rinse) that may influence infection risk. We are optimistic that these continued efforts, coupled with longitudinal monitoring of hospitalization rates in all MUSIC practices, will allow us to sustain this population level improvement in the safety of TRUS-Bx.

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