Repeat Prostate Biopsy Practice Patterns in a Statewide Quality Improvement Collaborative

Frank N. Burks,* Jonathan C. Hu, Dinesh Telang, Alice Liu, Scott Hawken, Zack Montgomery, Susan Linsell, James E. Montie, David C. Miller† and Khurshid R. Ghani† for the Michigan Urological Surgery Improvement Collaborative

From the Departments of Urology, Oakland University William Beaumont School of Medicine, Royal Oak and University of Michigan (AL, SH, ZM, SL, JEM, DCM, KRG), Ann Arbor, Michigan

Abbreviations and Acronyms

ASAP = atypical small acinar proliferation

BCBSM = Blue Cross Blue Shield of Michigan

DRE = digital rectal examination

HGPIN = high grade prostatic intraepithelial neoplasia

MF-HGPIN = multifocal HGPIN

MRI = magnetic resonance imaging

MUSIC = Michigan Urological Surgery Improvement Collaborative

NCCN® = National Comprehensive Cancer Network®

PCa = prostate cancer

PSA = prostate specific antigen

Purpose: We examined rebiopsies in MUSIC (Michigan Urological Surgery Improvement Collaborative) to understand adherence to guidelines recommending repeat prostate biopsy in patients with multifocal high grade prostatic intraepithelial neoplasia or atypical small acinar proliferation.

Materials and Methods: We analyzed data on men undergoing repeat biopsy, practice patterns and cancer detection rates. Multivariate regression modeling was used to calculate the proportion of patients undergoing rebiopsy. We used claims data to validate the treatment classification in MUSIC. To understand reasons for not performing rebiopsy we reviewed records of a sample of patients with atypical small acinar proliferation.

Results: We identified 5,375 men with a negative biopsy, of whom 411 (7.6%) underwent repeat biopsy. In 718 men with high grade prostatic intraepithelial neoplasia, 350 with atypical small acinar proliferation and 587 with high grade prostatic intraepithelial neoplasia and atypical small acinar proliferation or atypical small acinar proliferation alone at initial biopsy the rebiopsy rate was 20.7%, 42.5% and 55.6%, respectively. The adjusted proportion of patients with rebiopsy in each practice ranged from 0% to 17.2% ($p < 0.001$). The overall cancer detection rate at rebiopsy was 39.3%. It was highest after atypical small acinar proliferation (adjusted probability 0.39, 95% CI 0.30–0.48), and after high grade prostatic intraepithelial neoplasia and atypical small acinar proliferation (adjusted probability 0.50, 95% CI 0.35–0.65). The greatest Gleason 7 or greatest detection rate of 41.1% was found in patients with high grade prostatic intraepithelial neoplasia and atypical small acinar proliferation. Chart review revealed that 45.5% of patients with atypical small acinar proliferation underwent prostate specific antigen testing instead of rebiopsy while 36% failed to undergo rebiopsy despite a recommendation.

Accepted for publication February 23, 2017.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

Supported by Blue Cross Blue Shield of Michigan (Michigan Urological Surgery Improvement Collaborative).

* Correspondence: William Beaumont Hospital, 3636 West 13 Mile Rd., Royal Oak, Michigan telephone: (248-551-5000; FAX: 248-336-3180; e-mail: fburks@urologist.org).

† Financial interest and/or other financial relationship with Blue Cross Blue Shield of Michigan.

See http://musicurology.com/ for participating urologists and practices.

0022-5347/17/1982-0322/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2017.02.3338
Vol. 198, 322-328, August 2017
Printed in U.S.A.

Conclusions: Rebiopsy rates vary in Michigan practices with relatively low use in men with high grade prostatic intraepithelial neoplasia and atypical small acinar proliferation or atypical small acinar proliferation alone. Quality improvement strategies should target patients with atypical small acinar proliferation and high grade prostatic intraepithelial neoplasia as they have the highest likelihood of cancer detection.

Key Words: prostatic neoplasms, prostatic intraepithelial neoplasia, biopsy, quality improvement, diagnosis

TRANSRECTAL prostate biopsy remains the standard for diagnosing PCa.[1] Yet 50% to 70% of patients have negative results after initial biopsy and cannot be confidently excluded from not harboring cancer because of sampling error.[2] Therefore, it is not uncommon for some of these patients to undergo repeat biopsy during followup. While initial biopsy is often performed in response to elevated PSA or abnormal DRE, factors that drive repeat prostate biopsy include rising PSA or pathological findings concerning for an increased risk of PCa.[3] Particularly patients with ASAP or MF-HGPIN at initial biopsy are at greater risk for subsequent PCa.[4,5]

Current NCCN guidelines recommend that men diagnosed with ASAP or MF-HGPIN following prostate biopsy should undergo rebiopsy within 6 months.[6] In a recent study of repeat biopsy practice at a single academic institution HGPIN and ASAP were indications for rebiopsy in only 15% and 6% of patients, respectively.[7] Most studies of repeat biopsy practice have been limited to single institution series.[8] Little is known on a population level about how urologists adhere to guidelines for repeat biopsy.

In this context we sought to understand the use of repeat biopsy among patients in the diverse practices comprising MUSIC. Identifying factors associated with a risk of cancer at repeat biopsy may better inform clinicians and improve the quality of care for patients after a negative initial biopsy.

METHODS

Michigan Urological Surgery Improvement Collaborative

Established in 2011, MUSIC is a statewide, physician led quality improvement consortium funded by BCBSM. The collaborative represents approximately 85% of urologists in Michigan and follows all patients newly diagnosed with PCa in 43 participating practices. Patient data are entered prospectively from the time of prostate biopsy by trained data abstractors into the MUSIC clinical registry, which currently includes more than 30,000 patients, including more than 16,000 with PCa. Participating practices represent a broad spectrum of academic and community practices. Each site obtains regulatory exemption from local institutional review boards to participate in MUSIC and its quality improvement focused goals.

Study Population

In this analysis we included all men who underwent an initial prostate biopsy at 36 MUSIC practices from March 2012, which was the start date of the registry, through August 2015. Clinical data (eg age, race, PSA, prostate size, family history of PCa and digital rectal examination findings) and pathological data were collected on all patients with at least 7 months of followup. Followup PSA and whether rebiopsy was performed were recorded for patients with a negative biopsy.

Primary Outcome

In patients with a first biopsy that was negative we examined the use of repeat biopsy according to patient characteristics across MUSIC practices. We identified all patients in whom pathology findings revealed MF-HGPIN and ASAP or ASAP alone. In this subgroup we examined the frequency of repeat biopsy across practices and cancer detection outcomes.

Statistical Analysis

We assessed the characteristics of patients undergoing repeat prostate biopsy using descriptive summary statistics. Variables coded as unknown were treated as missing data. We used the chi-square and Fisher exact tests to compare the performance of repeat biopsy according to relevant patient and pathology characteristics, and across MUSIC practices.

We then fit a multivariate regression model with practices included as a fixed effect to account for potentially correlated data in each practice. Patient age, PSA, prostate size, family history of PCa and DRE findings were included as additional covariates. We used fixed effects because we included all practices in MUSIC rather than selecting a subset of them. From this model we calculated the adjusted proportion of patients who underwent repeat biopsy in each practice. We also assessed the number of patients with MF-HGPIN and/or ASAP at initial biopsy who underwent repeat biopsy across MUSIC practices. To ensure statistical reliability we excluded practices with fewer than 10 patients who had these pathological conditions. Finally, a separate logistic regression model was performed to calculate the probability of cancer in patients with MF-HGPIN and ASAP or ASAP alone.

Data Validation

We also used claims data from BCBSM to externally validate the repeat biopsies assigned in the MUSIC registry. Among men in the MUSIC registry with BCBSM as the primary payer we obtained all claims data on the 129 with BCBSM insurance in the cohort of

patients with ASAP and/or HGPIN at initial biopsy. We used specific CPT and ICD-9 codes, including 55700 (prostate biopsy; needle or punch, single or multiple, any approach) and 55706 (prostate biopsy; prostate, needle, transperineal, stereotactic template guided saturation sampling, including imaging guidance). We applied Cohen κ statistics to examine the level of agreement between claims based classification of repeat biopsy and biopsy assignment in the MUSIC registry. Finally, to better understand factors contributing to nonguideline based care the MUSIC database coordinator reviewed the charts of a random sample of 22 patients with ASAP across different practices who did not undergo rebiopsy.

RESULTS

During the study period 11,511 men underwent an initial prostate biopsy and were entered in the MUSIC registry. This initial biopsy was negative for PCa in 5,375 men, of whom 411 (7.6%) underwent repeat biopsy at a median of 236 days (range 8 to 1,360) during followup. The table lists the demographic characteristics of these men. Overall median age was 63 years. Of the patients 85.2% were white and 77.5% reported a negative family history of PCa. Median PSA was 4.89 ng/ml and 78.7% of patients had a negative DRE.

Men undergoing repeat biopsy demonstrated no significant difference in age, DRE findings or prostate size compared to men who did not undergo another biopsy (see table). Men undergoing rebiopsy had significantly higher PSA and PSA velocity, and a family history of PCa. They were more likely to have MF-HGPIN (20.4% vs 4.4%) and ASAP (38.2% vs 3.9%). Figure 1 shows the likelihood of a repeat prostate biopsy across 36 MUSIC practices after adjusting for age, PSA, prostate size, family history of PCa and DRE findings. The incidence ranged from 0% to 17.2% across the practices ($p < 0.001$).

In 718 patients HGPIN was detected at initial biopsy, including 1 core in 418 of 5,375 and multiple cores in 300 of 5,375. ASAP was detected in 350 patients (6.5%) at initial prostate biopsy while 587 (10.9%) had MF-HGPIN and ASAP or ASAP alone at initial biopsy.

Figure 2 shows unadjusted rates of rebiopsy (range 0% to 61.5%) in patients with MF-HGPIN and ASAP or ASAP alone at initial biopsy across 17 MUSIC practices. Repeat biopsy rates were highest at 55.6% when patients had MF-HGPIN

Descriptive statistics of men in MUSIC practices who underwent repeat biopsy after initial negative biopsy from March 2012 to August 2015

	Initial Neg Biopsy		No Repeat Biopsy		Repeat Biopsy		p Value*
No. pts (%)	5,375	(100)	4,964	(92.4)	411	(7.6)	
Median age (IQR)	63.0	(57.4—68.3)	63.1	(57.4—68.4)	62.8	(57.2—67.8)	—
No. age (%):							0.28
Less than 55	871	(16.2)	799	(16.1)	72	(17.5)	
55—Less than 69	3,307	(61.5)	3,047	(61.4)	260	(63.3)	
69 or Greater	1,196	(22.3)	1,117	(22.5)	79	(19.2)	
No. cc gland vol (%):							
Less than 30	998	(19.3)	914	(19.1)	84	(21.0)	0.0847
30—60 or Less	2,741	(53.0)	2,517	(52.7)	224	(56.0)	
Greater than 60	1,436	(27.7)	1,344	(28.1)	92	(23.0)	
No. race (%):							0.27
White	4,016	(85.2)	3,707	(85.4)	309	(82.8)	
Black	490	(10.4)	441	(10.2)	49	(13.1)	
Asian	61	(1.3)	58	(1.3)	3	(0.8)	
Other	148	(3.1)	136	(3.1)	12	(3.2)	
No. family history (%):							0.0071
Neg	3,872	(77.5)	3,586	(77.9)	286	(72.0)	
Pos	1,127	(22.5)	1,016	(22.1)	111	(28.0)	
Median ng/ml PSA (IQR)	4.89	(3.58—6.51)	4.84	(3.5—6.5)	5.70	(4.1—8.47)	0.2624
No. ng/ml PSA (%):							<0.0001
Less than 4	1,614	(30.4)	1,515	(30.9)	99	(24.1)	
4—10	3,245	(61.1)	2,996	(61.2)	249	(60.6)	
Greater than 10	449	(8.5)	386	(7.9)	63	(15.3)	
No. ng/ml/yr PSA velocity (%):							
0.75 or Less	1,146	(75.3)	1,040	(81.9)	106	(42.1)	<0.0001
Greater than 0.75	376	(24.7)	230	(18.1)	146	(57.9)	
No. DRE (%):							0.1053
Pos	1,051	(21.3)	981	(21.6)	70	(18.0)	
Neg	3,890	(78.7)	3,572	(78.5)	318	(82.0)	
Median No. biopsy cores (range)	12	(0—35)	12	(0—35)	12	(0—28)	—
No. cores multifocal HGPIN (%):							<0.0001
1	418	(7.8)	342	(6.9)	76	(18.5)	
2 or Greater	300	(5.6)	216	(4.4)	84	(20.4)	
No. ASAP (%)	350	(6.5)	193	(3.9)	157	(38.2)	<0.0001

* Based only on known data.

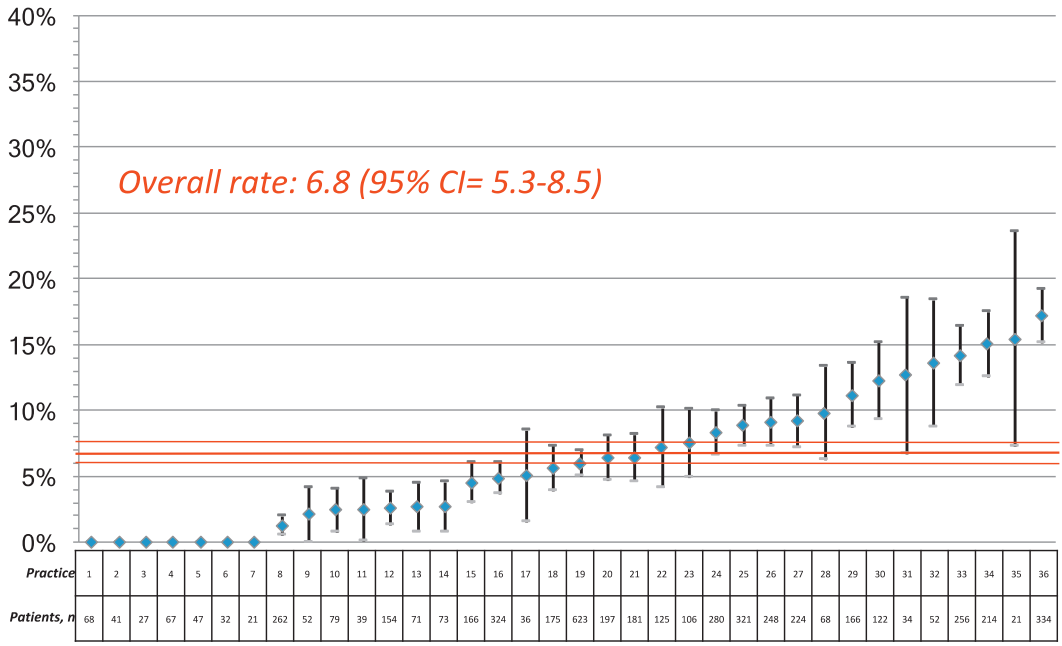

Figure 1. Predicted probability of undergoing repeat prostate biopsy stratified by MUSIC practices and adjusting for age, PSA, prostate size, family history and DRE findings.

plus ASAP followed by ASAP at 42.5%. The lowest rate of 20.7% was found in men with MF-HGPIN.

Figure 3 shows repeat biopsy and cancer detection rates in men with MF-HGPIN and/or ASAP. The overall cancer detection rate at rebiopsy was 39.3%. The detection rate was 30.6%, 40.2% and 48.6% in men with MF-HGPIN, ASAP and MF-HGPIN plus ASAP, respectively. Detection of Gleason 7 or greater cancer was highest in patients with MF-HGPIN plus ASAP (41.1%) compared to those with ASAP only (22.5%) or MF-HGPIN only (20%). On multivariate analysis the adjusted probability of MF-HGPIN on repeat biopsy was 0.18 (95% CI 0.13–0.25). It was 0.39 (95% CI 0.30–0.48) for ASAP and 0.50 (95% CI 0.35–0.65) for MF-HGPIN plus ASAP.

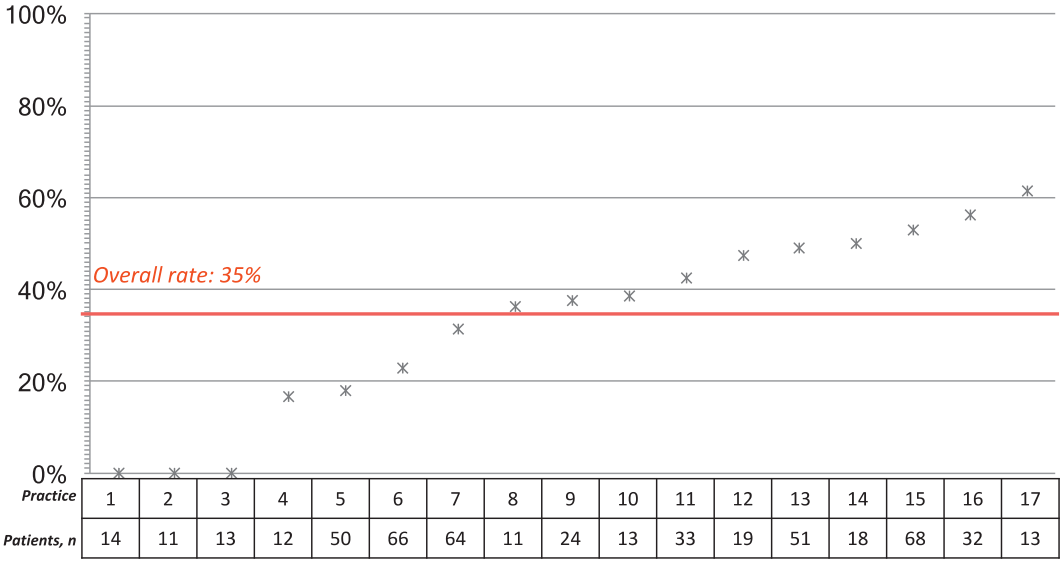

Figure 2. Unadjusted rates of repeat biopsy in patients with ASAP and/or MF-HGPIN at initial prostate biopsy in MUSIC practices with at least 10 patients in whom these pathology reports were assessed.

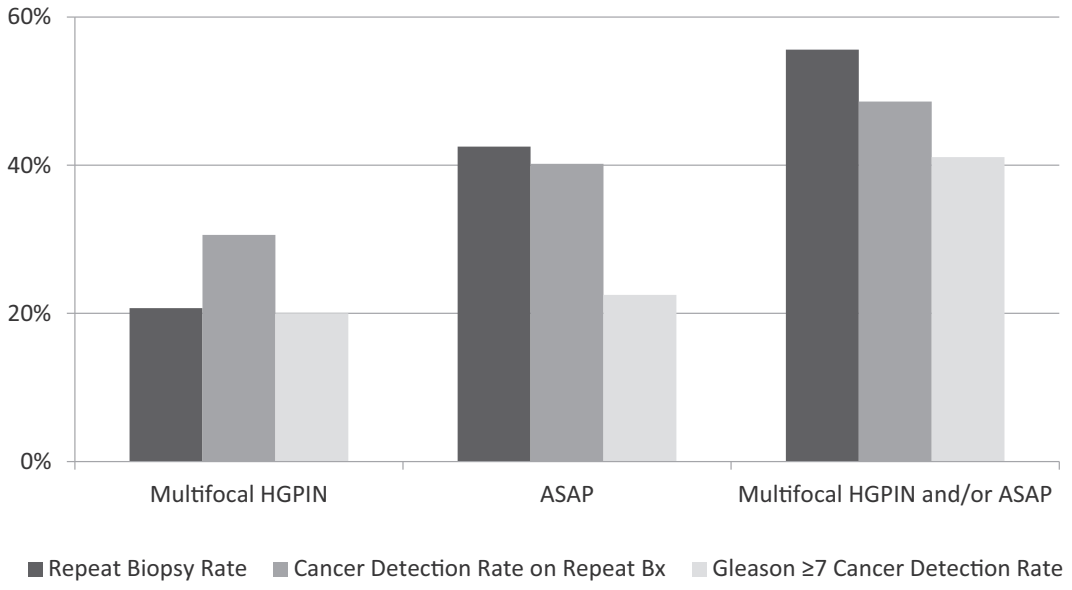

Figure 3. Rates of cancer detection and Gleason 7 or greater cancer in patients with MF-HGPIN plus ASAP or ASAP alone who underwent repeat biopsy.

Eight of the 129 men in the validation sample had claims data to indicate rebiopsy but this was not recorded in the MUSIC registry. In the 2 data sources 43 men had a rebiopsy record while 78 had no biopsy recorded in either data source. We observed excellent concordance in the procedural assignment from the 2 data sources ($\kappa = 0.87$).

Figure 4 shows the reasons for not undergoing rebiopsy in 22 patients with ASAP at initial biopsy. Of the patients 45.5% were advised to monitor PSA and immediate rebiopsy was not recommended while 36.4% were advised to undergo immediate repeat biopsy but did not proceed.

DISCUSSION

We found that the incidence of repeat biopsy varies across practices in Michigan with an overall rebiopsy rate of 7.6%. High PSA velocity and pathology findings such as MF-HGPIN or ASAP were the most significant factors that drove repeat biopsy. Our analysis also showed that repeat biopsies are

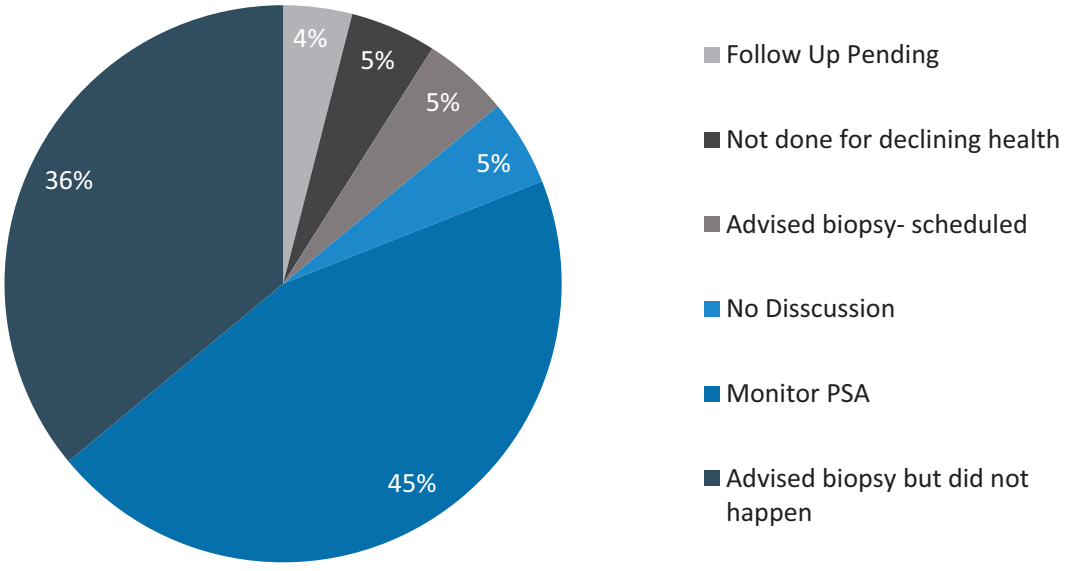

Figure 4. Reasons why patients did not undergo repeat biopsy after initial biopsy revealed ASAP pathology

performed infrequently in patients with MF-HGPIN and/or ASAP, who represent the cohort in which guidelines indicate immediate rebiopsy within 6 months.[6] Only 35% of these patients in our series underwent repeat biopsy. The cancer detection rate was highest in patients with MF-HGPIN plus ASAP who underwent rebiopsy. These men also had double the rate of Gleason 7 or greater cancer compared to men with only ASAP or only MF-HGPIN.

Many investigators have examined repeat biopsy patterns in clinical practice. Abraham et al evaluated the contemporary patterns of repeat prostate biopsy at a single academic institution and found that drivers of repeat biopsy included increasing PSA and pathology findings such as HGPIN or ASAP.[7] They also found that successive rounds of repeat biopsy showed a decreasing rate of PCa diagnosis. In our study similar factors influencing repeat biopsy were seen.

Gann et al examined clinical data as a predictor of subsequent PCa detection and found that age, abnormal DRE, pathology findings (ASAP or MF-HGPIN) and changes in PSA were associated with an increased risk of PCa detection.[3] Prostatitis on biopsy, the number of negative biopsies and gland volume greater than 35 cc were inversely associated with PCa detection.

Previous studies have demonstrated an increased incidence of subsequent cancer diagnosis in patients with MF-HGPIN and ASAP.[9] However, our data indicate that repeat biopsy is infrequently performed in such men. In a recent study by Dorin et al the rate of clinically significant PCa in patients with ASAP was 51%.[10] Similar to our findings, they also noted that only half of patients with ASAP underwent repeat biopsy.

Contrary to NCCN guidelines, which recommend repeat biopsy in all patients with MF-HGPIN plus ASAP or ASAP alone at initial biopsy,[6] we found that not all patients in MUSIC underwent repeat biopsy. The qualitative analysis of patients with ASAP revealed that approximately 50% were advised to not undergo rebiopsy and instead monitor PSA. While this is in opposition to that proposed by NCCN, whether this represents reasonable clinical care is open to debate. It may be argued that an aggressive rebiopsy strategy should be reserved only for patients with MF-HGPIN plus ASAP, in whom the likelihood of detecting higher grade cancer is greatest, as we have found. The risks of routine rebiopsy, including sepsis, hematuria, urinary retention and pain, must be balanced against the over detection of low risk prostate cancer.

Despite the strength of prospective data collection in our project[11] some limitations warrant discussion. Because prior MUSIC work has demonstrated variation in cancer detection rates among practices,[12] it is possible that there may be variation in the reporting of ASAP or MF-HGPIN. The rate of cancer detection in MUSIC is higher than in prior biopsy cohorts,[12] which may be a result of less PSA screening and a shift toward biopsy in patients at higher risk for cancer. Other factors, such as multiparametric MRI or genomic tests/biomarkers, may influence the rebiopsy and cancer detection rates, and these variables were not measured in the MUSIC registry during this period. Due to the unknown effect of these confounding factors the reported cancer detection rates at rebiopsy may be different than if all men had undergone routine repeat biopsy.

We also acknowledge that during our study period PSA screening guidelines changed in the United States. This may have affected overall biopsy and rebiopsy practice patterns with possibly less emphasis on aggressively diagnosing all prostate cancers.

Further, some cases of repeat biopsy may have been missed despite data entry by trained abstractors at practices and periodic auditing. For these reasons we validated claims to determine the reliability of our data collection. The excellent concordance that we found suggests that the accuracy of our registry is sufficiently high.

Also, while rebiopsy in men with MF-HGPIN plus ASAP or ASAP alone is the current NCCN recommendation,[6] the use of multiparametric MRI and biomarkers to detect PCa is an emerging tool that MUSIC is currently studying.[13,14] MRI-fusion biopsy and biomarkers may help better risk stratify patients for repeat biopsy beyond the standard histology for repeat biopsy.

Our study highlights significant opportunity for quality improvement in adherence to NCCN guidelines for repeat biopsy[6] in Michigan. The decision to rebiopsy a patient depends on available clinical data, guidelines and clinical judgement. Barocas et al examined a collaboration of urologists and their compliance with guideline care for postoperative intravesical chemotherapy.[15] The study demonstrated the concept of judicious use with regard to the implementation of treatment guidelines and certainly this concept applies to our findings.

Knowledge of real world clinical practices can be a key factor when gauging the practicality of clinical guidelines. Based on our findings we now recommend in MUSIC immediate repeat biopsy in patients with ASAP only. We have set a target rebiopsy rate of 70% for these patients vs the 100% set by NCCN.[6]

CONCLUSIONS

We found that high PSA velocity and pathology results such as MF-HGPIN and ASAP are the strongest indications for repeat biopsy. We also found

that patients with ASAP have the highest detection rate of clinically significant cancer. The most common reasons for absent rebiopsy was the physician decision to monitor PSA or the patient refusal to proceed to biopsy despite being requested to do so. While these data suggest poor compliance with current NCCN guidelines,[6] it may be argued that an aggressive rebiopsy strategy should be reserved only for men with MF-HGPIN plus ASAP, in whom the likelihood of detecting higher grade cancer is the greatest.

ACKNOWLEDGMENTS

Support was provided by the Value Partnerships program at BCBSM.

REFERENCES

1. Boczko J, Messing E and Dogra V: Transrectal sonography in prostate evaluation. Radiol Clin North Am 2006; **44:** 679.
2. Fleshner N, O'Sullivan M and Fair W: Prevalence and predictors of a positive repeat transrectal ultrasound guided needle biopsy of the prostate. J Urol 1997; **158:** 505.
3. Gann P, Fought A, Deaton R et al: Risk factors for prostate cancer detection after a negative biopsy: a novel multivariable longitudinal approach. J Clin Oncol 2010; **28:** 1714.
4. Lee M, Moussa A, Yu C et al: Multifocal high grade prostatic intraepithelial neoplasia is a risk factor for subsequent prostate cancer. J Urol 2010; **184:** 1958.
5. Merrimen J, Jones G, Hussein S et al: A model to predict prostate cancer after atypical findings in initial prostate needle biopsy. J Urol 2011; **185:** 1240.
6. Carroll P, Parsons J, Andriole G et al: NCCN Guidelines Insights: Prostate Cancer Early Detection, Version 2.2016. J Natl Compr Canc Netw 2016; **14:** 509.
7. Abraham N, Mendhiratta N and Taneja S: Patterns of repeat prostate biopsy in contemporary clinical practice. J Urol 2015; **193:** 1178.
8. Leone A, Rotker K, Butler C et al: Atypical small acinar proliferation: repeat biopsy and detection of high grade prostate cancer. Prostate Cancer 2015; **2015:** 1.
9. Terris M: Prostate biopsy strategies: past, present, and future. Urol Clin North Am 2002; **29:** 205.
10. Dorin R, Wiener S, Harris C et al: Prostate atypia: does repeat biopsy detect clinically significant prostate cancer? Prostate 2015; **75:** 673.
11. Montie J, Linsell S and Miller D: Quality of care in urology and the Michigan Urological Surgery Improvement Collaborative. Urol Pract 2014; **1:** 74.
12. Riedinger C, Womble P, Linsell S et al: Variation in prostate cancer detection rates in a statewide quality improvement collaborative. J Urol 2014; **192:** 373.
13. Bjurlin M, Meng X, Le Nobin J et al: Optimization of prostate biopsy: the role of magnetic resonance imaging targeted biopsy in detection, localization and risk assessment. J Urol 2014; **192:** 648.
14. Kim T, Montie J, Peabody J et al: PD42-07: Implementation of methodology to capture data from prostate MRI within a regional quality-improvement collaborative. J Urol 2016; **195:** e989.
15. Barocas D, Liu A, Burks F et al: Practice based collaboration to improve the use of immediate intravesical therapy after resection of nonmuscle invasive bladder cancer. J Urol 2013; **190:** 2011.

EDITORIAL COMMENT

MUSIC is an important health quality initiative in our field. This latest study reveals a surprisingly low 7.8% rate of repeat prostate biopsy in men with multifocal HGPIN or ASAP on initial biopsy, which is recommended under the most recent NCCN guidelines (reference 6 in article). Is this yet another example of suboptimal compliance with guideline or best practice driven care?

Prostate biopsy is not without potential complications. Particularly infectious and multiple factors are likely at play here.[1] The diagnostic goals of prostate needle biopsy have shifted in the last decade with a focus on the detection of clinically relevant tumors. Most prostate cancers diagnosed on repeat biopsy after finding ASAP are low grade and potentially nonlife threatening.[2] Novel tools, including biomarkers and multiparametric MRI, are available that can further risk stratify men regarding the need for repeat biopsy. These data question the relevance of these guidelines in the early detection of contemporary prostate cancer.

Marc Dall'Era
Department of Urology
University of California-Davis
Davis, California

REFERENCES

1. Borghesi M, Ahmed H, Nam R et al: Complications after systematic, random, and image-guided prostate biopsy. Eur Urol 2017; **71:** 353.
2. Leone A, Gershman B, Rotker K et al: Atypical small acinar proliferation (ASAP): is a repeat biopsy necessary ASAP? A multi-institutional review. Prostate Cancer Prostatic Dis 2016; **19:** 68.