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# Discrepancies in volume: impact of Artemis segmented magnetic resonance imaging, ultrasound, and ExactVu measurements on prostate specific antigen density and National Comprehensive Cancer Network risk stratification

Maximilian J. Rabil[1], Lindsey T. Webb[1], Gabriela M. Diaz[1], Soum D. Lokeshwar[1], Ankur U. Choksi[1], Preston C. Sprenkle[1,2]

[1]*Yale University School of Medicine, New Haven, Connecticut, United States of America*
[2]*Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut, United States of America*

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Corresponding author
Maximilian J. Rabil
Yale University School of Medicine, Yale Urology, 789 Howard Avenue, FMP 300, New Haven, Connecticut 06519, USA
maximilian.rabil@yale.edu

**Introduction** The combination of magnetic resonance imaging (MRI) and ultrasound (US) allows for better lesion targeting and diagnostic probability compared to random prostate biopsies. The Artemis Fusion Biopsy system and ExactVu micro-US technology capitalize on this advantage and provide higher-resolution imaging of the prostate during biopsy. Their accuracy in measuring prostate volume and resulting implications on prostate specific antigen (PSA) density and risk stratification, however, has not been evaluated. We hypothesized that PSA densities as measured by these modalities will demonstrate clinically insignificant differences compared to standard measurement.

**Material and methods** We retrospectively reviewed all prostate fusion biopsy cases performed at our health system with Artemis or ExactVu systems from April 2021 to July 2023 and compared the PSA density calculated from the volume obtained with these systems to standard measurement with ellipsoid calculation from MRI. Change in National Comprehensive Cancer Network (NCCN) prostate cancer risk stratification was analyzed for each system.

**Results** Artemis MRI segmentation (0.179 ng/ml, p = 0.04) and US (0.181 ng/ml, p = 0.067) underestimated and ExactVu micro-US (0.247 ng/ml, p <0.001) overestimated PSA density. Risk stratification changed in 1.2% of Artemis MRI segmentation cases, 1.6% of Artemis US cases, and 1.2% of ExactVu micro-US cases.

**Conclusions** Despite differences in PSA density, choice of fusion biopsy system has minimal clinical impact on risk stratification and any of these studied systems may be used without fear of misrepresenting a patient's disease state.

Key Words: prostate biopsy ‹› prostate cancer ‹› prostate cancer risk stratification ‹› prostate MRI ‹› prostate ultrasound ‹› PSA density

## INTRODUCTION

Fusion of multi-parametric magnetic resonance imaging (mpMRI) and ultrasound (US) allows for better lesion targeting and diagnostic probability of clinically significant prostate cancer compared to template prostate biopsies using US alone [1]. Numerous fusion systems are currently FDA approved, and, in addition to their utility in targeting prostatic lesions, aid in clinical decision making through prostate volume measurement.

The Artemis™ (Eigen, Grass Valley, CA, USA) fusion system provides two prostate volume measurements: standard US manual measurement and

proprietary segmentation software which permits fine tuning of the volume measurement to the gland's morphology on MRI using 3D reconstruction [2]. Once automated segmentation is complete, the reading radiologist contours the measurement to obtain a prostate volume.

The ExactVu™ (Exact Imaging, Inc, Markham, ON, CA) micro-ultrasound system provides high spatial resolution images for volume measurement and cancer detection, which can be further leveraged through fusion [3, 4]. Using an ellipsoid or bullet-shaped measurement paradigm to calculate prostate volume from an mpMRI has been shown to provide significantly different results in PSA density, making it imperative providers understand the modality used to measure prostate volume and hence the resulting PSA density [5].

Accuracy of MRI fusion and micro-US in measuring prostate volume and the resultant implications for PSA density-based decision making, however, have not been evaluated. We hypothesized that PSA density as calculated by volume measurements using either Artemis MRI segmentation, Artemis US, or ExactVu micro-ultrasound will demonstrate clinically insignificant differences compared to MRI ellipsoid calculation.

## MATERIAL AND METHODS

We retrospectively reviewed all cases of prostate fusion biopsy performed with either Artemis™ or ExactVu™ at our academic health system from April 2021 to July 2023. Patients without a pre-biopsy MRI were excluded.

Prostate volumes as measured by Artemis MRI segmentation, Artemis US measurement, and ExactVu micro-US measurement were used to calculate PSA density. These were compared to PSA density calculated from standard MRI ellipsoid measurement as the gold standard using a paired t-test with statistical significance set at $p < 0.05$ in Microsoft Excel (Microsoft Corporation, Redmond, WA).

Change in National Comprehensive Cancer Network (NCCN) risk stratification on the basis of the PSA density criterion for very low risk prostate cancer (PSA density <0.15 ng/ml/g) was analyzed for all comparisons to assess the clinical impact of the discrepancies in measured volume.

## RESULTS

In total, prostate volumes were available for 172 patients with Artemis MRI 3D segmentation, 189 with Artemis US 3D segmentation, and 340 with ExactVu micro-US prostate measurement and ellipsoid volume calculation. 3D-segmented prostate volumes of both Artemis system MRI and US are generally larger than the ellipsoid calculation – resulting in lower average PSA density. The converse was true for the ExactVu micro-ultrasound resulting in, on average, an overestimation of PSA density. Mean PSA density differed significantly from MRI ellipsoid-based calculation when volume was measured with Artemis MRI with segmentation and ExactVu micro-US but did not reach significance for Artemis US (Table 1).

NCCN risk stratification changed in 2/172 (1.2%) Artemis 3D-MRI cases (1 risk progression, 1 regres-

**Table 1.** *PSA density as calculated by different modalities*

| Artemis MRI segmentation vs ellipsoid MRI | | | | | | | |
|---|---|---|---|---|---|---|---|
| n = 172 | Artemis MRI [ng/ml] | Ellipsoid MRI [ng/ml] | p-value | Mean difference (abs. value) | % Error | Changes to NCCN risk stratification (N) | |
| Mean | 0.179 | 0.196 | 0.04 | 0.044 | 18.15 | Stage progression | 1 |
| Variance | 0.032 | 0.046 | – | – | – | Stage regression | 1 |
| Artemis US vs ellipsoid MRI | | | | | | | |
| n = 189 | Artemis US [ng/ml] | Ellipsoid MRI [ng/ml] | p-value | Mean difference (abs. value) | % Error | Changes to NCCN risk stratification (N) | |
| Mean | 0.181 | 0.193 | 0.067 | 0.046 | 21.44 | Stage progression | 1 |
| Variance | 0.027 | 0.037 | – | – | – | Stage regression | 2 |
| ExactVu US vs ellipsoid MRI | | | | | | | |
| n = 340 | ExactVu US [ng/ml] | Ellipsoid MRI [ng/ml] | p-value | Mean difference (abs. value) | % Error | Changes to NCCN risk stratification (N) | |
| Mean | 0.247 | 0.180 | <0.001 | 0.079 | 24.69 | Stage progression | 4 |
| Variance | 0.083 | 0.032 | – | – | – | Stage regression | 0 |

MRI – magnetic resonance imaging; NCCN – National Comprehensive Cancer Network; US – ultrasound

sion); 3/189 (1.6%) Artemis US cases (1 risk progression, 2 regression); and 4/340 (1.2%) ExactVu cases (all risk progression).

## DISCUSSION

Although our modalities for measuring prostate volume provide statistically significant differences in PSA density, these discrepancies do not result in clinically significant differences in NCCN risk stratification, allowing clinical decision making to proceed confidently. Stated differently, while prostate volumes as measured with different modalities may vary, this study suggests that direct comparisons of risk assessment can be made with PSA density measurements from any of the studied imaging systems without compromising accuracy and clinical relevance.

A study from over a decade ago investigated variation in PSA density measurement between trans-rectal-US, trans-abdominal US, computed tomography (CT) scans finding only CT produced statistically significant differences in PSA density [6], but the dearth of literature comparing the imaging advancements in the interim decade persists.

To our knowledge, this is the first study to investigate variation in PSA density and its impact on prostate cancer risk stratification, and we hope that our findings inform others' practice and encourage discourse and further investigation.

In light of our findings, the question remains whether current a prostate-specific antigen density (PSAd) thresholds, established in the era of earlier imaging, remain accurate with the myriad new imaging systems used for fusion prostate biopsy which offer new techniques to measure prostate volume. A PSAd threshold to distinguish clinically significant and insignificant prostate cancer of 0.10 ng/ml/cc was first established in 1994 on retrospective review of prostate volumes calculated with direct measurement of prostatectomy pathology specimens and TRUS ellipsoid measurement [7].

The practice patterns of prostate cancer and the tools we use have naturally changed significantly in the intervening 30 years. The need for re-evaluation of PSAd thresholds with new imaging techniques is well established: the currently used 0.15 ng/ml/cc was deemed too high and not sensitive enough when prostate volume was measured by a spherical formula for dimensions measured by US [8].

As mpMRI became more prevalently used in prostate cancer care in the late 2000s and early 2010s, the improved visualization offered made measurement by the ellipsoid formula and early semi-automated segmentation programs more precise, bringing a threshold of 0.15 ng/ml/cc to favor especially when combined with Prostate Imaging-Reporting and Data System (PI-RADS) scores to make clinical decisions [9, 10].

With quality of MRI improved and more robust segmentation schemes developed, Pellegrino et al. [11] suggests, instead, a PSAd threshold of 0.20 ng/ml/cc for patients with a negative MRI to undergo prostate biopsy as the current threshold of 0.15 ng/ml/cc is too non-specific except in the case of low quality MRI imaging. If this higher threshold was used in our analysis, all Artemis 3D-MRI and US risk changes two of the four ExactVue risk discrepancies would no longer have occurred.

In contrast, increasing the PSAd threshold is not fully supported by the literature base; despite the more accurate contouring of segmentation software, PSAd cannot be relied on in isolation of other patient factors. Use of PSAd alone to make decisions on whether or not to biopsy risks missing clinically significant cancer, with 15% of clinically significant cancers would be missed in patients with PI-RADS score of 3 and PSAd below 0.15 ng/ml/cc [12].

Finally, if there is one situation where new methods of prostate volume measurement differ most from the ellipsoid formula and thus PSAd would be most affected, it would be in cases of abnormal prostate anatomy such as post-transurethral resection of the prostate [13].

Altogether, further investigation is needed to decide if PSAd thresholds need to be changed as the landscape of peri-biopsy prostate imaging evolves. To aid in this, clear documentation of prostate volume methods should be included in studies of PSAd and its uses in dictating clinical decisions. With our findings and the existing literature base in mind, it is the authors' assertion that PSAd thresholds likely should be reconsidered given the diversity of methods used across practices, the greater granularity provided by modern imaging systems and their accompanying software-based enhancement and measurement capabilities, and the rich store of other risk-stratifying data points (PI-RADS score, genomic classifiers, etc.) for which PSAd can serve as an adjunct.

This study is limited by its single-institution retrospective design, inclusion of only two of the many available fusion biopsy imaging systems, inability to make direct comparisons between imaging modalities as measurement by one fusion system was mutually exclusive of measurement with the other, and the small role PSA density plays in NCCN risk stratification as it only separates very low risk and low risk disease. Nevertheless, the distinction

between very low risk and low risk prostate cancer in the context of the broader clinical picture may still dictate a patient's decision and a Urologist's recommendation.
Future studies validating these findings outside of our health system and including other fusion biopsy imaging systems in comparisons would broaden the implications of these findings and be valuable in supporting that confidence in decision-making.

## CONCLUSIONS

The measured volumes across the studied fusion biopsy systems differ considerably, but PSA density values as calculated by Artemis MRI segmentation, Artemis US, or ExactVu micro-ultrasound do not demonstrate significant differences in NCCN risk stratification when compared to measurement by MRI ellipsoid calculation. They can therefore be safely used to make clinical decisions without fear of misrepresenting the patient's medical condition.

### CONFLICTS OF INTEREST
The authors declare no conflict of interest.

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### ETHICS APPROVAL STATEMENT
The ethical approval was not required.

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