Exosome Biomarker Clinical Impact on Timing and Decision to Have a Prostate Biopsy

Jason Alter PhD[1], Sonia Kumar PhD[1], Johan Skog PhD[1], Vinita Verma MPH[1], Yiyuan Yao MS[1], Christian J Ray PhD[1], Brian Haynes PhD[1], Laurence Belkoff DO[2], Ronald Tutrone MD[3], David J. Cahn, MD[4*], Paul Dato, MD[5], Jason Hafron, MD[6], Zachariah Taylor, DO[7], Scott Serpico, DO[8], Lan Huynh, BS[8], Emily T. Ayre, MS[3], Claire E. Biesecker, BS[3] , Katayune Golshan, BFA[5]

1 Exosome Diagnostics, Inc., Waltham, MA 2 MidLantic Urology, Bala Cynwyd, PA 3 United Urology Group, Towson, MD 4 Colorado Clinical Research, Lakewood, CO 5 Genesis Healthcare, San Diego, CA 6 Michigan Institute of Urology, West Bloomfield, MI 7 Main Line Health, Department of Urology. Radnor Township, PA 8 Philadelphia College of Osteopathic Medicine, Philadelphia, PA

* Corresponding/Presenting Author

Introduction

Biomarkers and mpMRI are risk assessment approaches that each have advantages and limitations, and combining biomarkers with mpMRI to provide complementary, layered risk assessment is gaining momentum. The ExoDx™ Prostate (ExoDx) test is a urine-based exosome gene expression assay that does not require a digital rectal exam (DRE) to make informed prostate biopsy decisions. ExoDx does not include any clinical/standard-of-care features and is a standalone test that provides a risk stratification/ assessment score to discriminate between no cancer/low-grade prostate cancer(Gleason Grade Group 1 [GG1]), and high-grade prostate cancer (HGPC [≥GG2]).[1-4] Here, we retrospectively evaluated patient outcomes after ExoDx biomarker was utilized alone and an approach in which mpMRI was added to the biopsy process in a real-world clinical setting.

Methods

A retrospective analysis of original ExoDx usage and subsequent patient follow up included 1,922 data records with 1,365 having data out to at least 4 years (Sub cohort A). Inclusion criteria were men with an ExoDx test prior to 2019 as follow-up to an elevated PSA (2-10 ng/mL). Men must have had at least one PSA measurement /year post-ExoDx testing. Prostate biopsy was not required for participation; however, if a biopsy was performed then the date of biopsy, positive core(s), Gleason grade, and primary tumor stage were recorded. Demographic and health outcomes data were collected for all men (Table 1). All prostate mpMRI results with date and result were captured as well as any prostate cancer (PC) treatment. Cohorts (Figure 1) were defined as:

- Sub cohort A: stratified by ExoDx score using a pre-determined threshold of ≤15.6 (low-risk) and >15.6 (high-risk) resulting in 415 (30.4%) low-risk and 950 (69.6%) high-risk ExoDx scores, respectively (N=1,365).
- Sub cohort B: Men with ExoDx but no mpMRI within one year of their ExoDx results (N=947).
- Sub cohort C: Men with ExoDx and an mpMRI within one year (N=418).
- Sub cohort D: Men with ExoDx and a prostate biopsy within one year (N=334).
- Sub cohort E: Men with ExoDx, mpMRI, and biopsy results within one year (N=142).

Cox proportional hazards models were constructed to estimate the hazard ratios to provide quantitative assessment of the association between ExoDx test result and biopsy event. A Nelson-Aalen estimator was used to show the changes of hazard rate in ExoDx positive and negative groups given the hazard rate for having a biopsy is not constant over time. We also assessed the association of the ExoDx test and mpMRI results with decision to biopsy within one year. In Sub cohorts D and E, we calculated biomarker outcome metrics (sensitivity, specificity, negative predicative value [NPV] and positive predictive value [PPV]). For Sub cohort C, we assessed the sequence of the ExoDx test and mpMRI with the resulting biopsy rates and HGPC observed in clinical practice. Continuous variables include the number of patients, mean, or median (interquartile range [IQR]) by cohort. Categorical variables were summarized using absolute and relative frequencies, n (%). Statistical analysis was performed utilizing R version 4.1.2 (R Core Team, Vienna, Austria, 2018) and Python version 3.11.1 (Python Software Foundation, Wilmington, DE).

Figure 1: Consort Flow Diagram

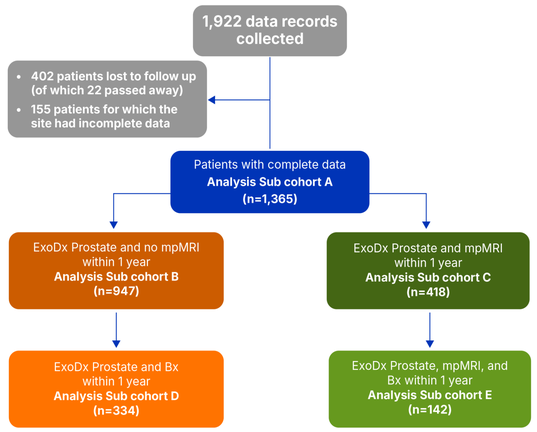

Figure 1. Study Consort Diagram. Records were collected from men with an ExoDx Prostate result prior to 2019 (N=1,922). Of these men, men with complete data regardless of time frame (Sub cohort A) (N=1,365). Men without mpMRI within 1 year of their ExoDx results (Sub cohort B) (N=947). Men without an mpMRI within 1 year (Sub cohort C) (N=418). Men with ExoDx and a prostate biopsy within 1 year (Sub cohort D) (N=334). Men with ExoDx, mpMRI, and biopsy results within one year (Sub cohort E) (N=142).

Table 1

	Sub cohort A (n=1,365)	ExoDx ≤15.6 (n=415)	ExoDx >15.6 (n=950)
Age, years median (IQR)	71 (65-76)	69 (64-74)	72 (66-77)
PSA, median (IQR)	5.2 (3.9-7.3)	5.3 (4.0-7.4)	5.2 (3.9-7.2)
ExoDx Prostate result, median (IQR)	22.2 (13.7-36.4)	10.4 (7.6-13.0)	29.4 (21.5-42.3)
Ethnicity, n (%)			
Caucasian	1,124 (82.3)	365 (88.0)	759 (79.9)
Asian	53 (3.9)	16 (3.9)	37 (3.9)
Black	123 (9.0)	12 (2.9)	111 (11.7)
Hispanic	20 (1.5)	4 (1.0)	16 (1.7)
Native Hawaiian or Other Pacific Islander	2 (0.1)	1 (0.2)	1 (0.1)
Other	43 (3.2)	17 (4.1)	26 (2.7)
Family History, n (%)			
Yes	360 (26.4)	103(24.8)	257(27.1)
No	908 (66.5)	283 (68.2)	625 (65.8)
N/A	97 (7.1)	29 (7.0)	68 (7.2)
ISUP Biopsy GG, n (%)			
Benign	283 (20.7)	59 (14.2)	224 (23.6)
GG1	115 (8.4)	7 (1.7)	108 (11.4)
GG2	59 (4.3)	4 (1.0)	55 (5.8)
GG3	37 (2.7)	2 (0.5)	35 (3.7)
GG4	30 (2.2)	0 (0)	30 (3.2)
GG5	16 (1.2)	2 (0.5)	14 (1.5)
No Biopsy	825 (60.4)	341 (82.2)	484 (50.9)

Table 1. Demographics of Sub cohort A (N=1,365).

Results

A Nelson-Aalen fit analysis found that the hazard ratios for having a biopsy with ExoDx test positive and ExoDx test negative patients became equivalent at 300+/-90 days (Figure 2). This means that the decision to biopsy is influenced by the ExoDx test result within the first year. In Sub cohort C, a low but significant positive correlation was observed between the ExoDx test and mpMRI results (Figure 3) with both methods providing orthogonal and correlated information with a polyserial correlation coefficient of 0.18 (p<0.001). The AUC value for ExoDx test and mpMRI combined (0.83) was significantly greater than the ExoDx test alone (0.70, p=0.003) (Figure 4). Outcome metrics for Sub cohort D and Sub cohort E are shown in Table 2 with similar rates of biopsy at 334/947 (35.3%) and 142/418 (34.0%), p=0.64, respectively and HGPC at 83/334 (24.9%) and 41/142 (28.9%), p=0.55, respectively between the cohorts. In Sub cohort E, PI-RADS were evenly distributed with 33.1% (n=47) having PI-RADS 1 or 2, 29.6% (n=42) with PI-RADS 3, and 37.3% (n=53) with PI-RADS 4 or 5. In a subset with PI-RADS 1-3, a low-risk ExoDx score resulted in a 13.5% (12/89) biopsy rate as opposed to 86.5% (77/89) for high-risk ExoDx test scores. The NPV for the combined use of ExoDx test and mpMRI was 100.0% regardless of the PI-RADS result or a GG ≥2 or ≥3 and PPV of 33.6% for ≥GG2 (Table 2). We also examined the clinical timeline in men who had both an ExoDx test and mpMRI within the decision time frame of one year (Sub cohort C, n=418). Most men in Sub cohort C had the ExoDx test before mpMRI (n=289, 69.1%) compared to the reverse (n=129, 30.9%).

Regardless of order, men in Sub cohort E with low-risk ExoDx scores had fewer biopsies and observed no HGPC while men with high-risk ExoDx scores had significantly more biopsies and found >30% HGPC (Table 2). In men who had a low-risk ExoDx Prostate score before mpMRI, mpMRI was deferred for over a year with the median number of days to mpMRI recorded as 467 days vs. 58 days, in low- and high-risk ExoDx groups, respectively (p<0.001, Figure 5).

Figure 2

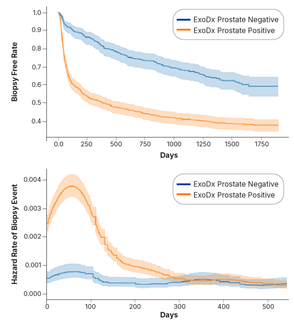

Figure 2: ExoDx Prostate impacts decision to biopsy within the first year. A) Cox proportional hazard test shows the ratio of biopsy between ExoDx Prostate low- and high-risk groups regardless of time to biopsy (n=1,365) is 2.19 and there is a significant difference in biopsy free time between two groups (p<0.001) indicating that men with low-risk ExoDx scores continue to have fewer biopsies at 5 years. B) Nelson-Aalen fit of the rate of biopsy event shows that the rate is equivalent between high- and low-risk ExoDx Prostate groups at ~300±90 days. In clinical practice, ExoDx Prostate has an impact on the decision to biopsy within the first year.

Figure 3

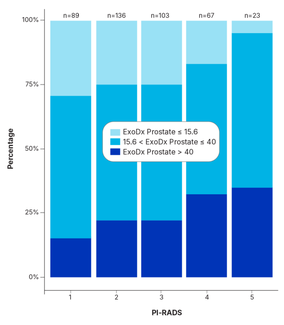

Figure 3: ExoDx Prostate and mpMRI imaging results are positively correlated. Men who had both an ExoDx Prostate and mpMRI result within 1 year (n=418) show that the methods provide orthogonal but overlapping information (p<0.001).

Figure 4

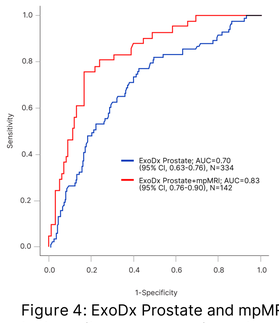

Figure 4: ExoDx Prostate and mpMRI test results appear complementary. ExoDx Prostate and mpMRI test results capture overlapping, but not identical risk information, resulting in potentially improved outcomes when both methods are used. Use of both ExoDx Prostate and mpMRI (Sub cohort E) to guide biopsy decision-making resulted in a higher AUC of 0.83 compared to the AUC of 0.70 of ExoDx alone (Sub cohort D) (p=0.003). For Sub cohort E, the decision to biopsy was influenced by both tests, therefore Sub cohort D was used for ExoDx test AUC. The ExoDx AUC for Sub cohorts D and E were confirmed not to be statistically different. The AUC of mpMRI alone could not be evaluated since all men in Sub cohort E also received an ExoDx Prostate result.

Figure 5

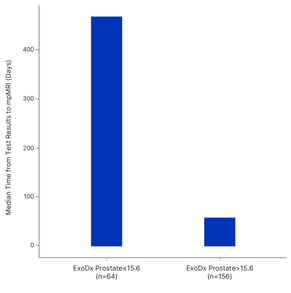

Figure 5: Time to mpMRI after ExoDx Prostate result. Men who had an ExoDx Prostate score followed by a mpMRI (n=220). 29.1% percent were ExoDx low-risk and 70.9% were ExoDx high-risk. Men with ExoDx low-risk results had significantly longer times to receive a mpMRI (p<0.001).

Note: All study results are outcomes based, and should not be confused with performance metrics, which are determined in the validation studies.

Table 2

Sub cohort D	Bx Rate (%)	≤GG1 Incidence	≥GG2 Incidence
ExoDx ≤15.6, n=319	48 (15.0%)	42/48 (87.5%)	6/48 (12.5%)
ExoDx >15.6, n=628	286 (45.5%)	209/286 (73.1%)	77/286 (26.9%)
All ExoDx, n=947	334 (35.3%)	251/334 (75.1%)	83/334 (24.9%)
Sensitivity: 92.8%	Specificity: 16.7%	NPV: 87.5%	PPV: 26.9%
Sub cohort E	**Bx Rate (%)**	**≤GG1 Incidence**	**≥GG2 Incidence**
ExoDx ≤15.6, n=96	18 (18.8%)	18/18 (100.0%)	0/18 (0.0%)
ExoDx >15.6, n=322	124 (38.5%)	83/124 (66.9%)	41/124 (33.1%)
All ExoDx, n=418	142 (34.0%)	101/142 (71.1%)	41/142 (28.9%)
Sensitivity: 100.0%	Specificity: 18.2%	NPV: 100.0%	PPV: 33.6%

Table 2. Men with an ExoDx score, biopsy and mpMRI (Sub cohort E) within 1 year or without an mpMRI (Sub cohort D). Similar rates of Bx (334/947 (35.3%) and 142/418 (34.0%), p=0.64, respectively) and HGPC (83/334 (24.9%) and 41/142 (28.9%), p=0.55, respectively) were detected between the cohorts despite the addition of mpMRI in the clinical decision process in Sub cohort E.

Table 3

PI-RADS 1 & 2	Bx Rate (%)	≤GG1 Incidence	≥GG2 Incidence
ExoDx ≤15.6, n=60	4 (6.7%)	4/4 (100.0%)	0/4 (0.0%)
ExoDx >15.6, n=165	43 (26.1%)	36/43 (83.7%)	7/43 (16.3%)
All ExoDx, n=225	47 (20.9%)	40/47 (85.1%)	7/47 (14.9%)
Sensitivity: 100.0%	Specificity: 10.0%	NPV: 100.0%	PPV: 16.3%
		Bx within 1yr, ≤GG2	Bx within 1yr, ≥GG3
ExoDx ≤15.6, n=60		4/4 (100.0%)	0/4 (0.0%)
ExoDx >15.6, n=165		39/43 (90.7%)	4/43 (9.3%)
Sensitivity: 100.0%	Specificity: 9.3%	NPV: 100.0%	PPV: 9.3%
PI-RADS 3	**Bx Rate (%)**	**≤GG1 Incidence**	**≥GG2 Incidence**
ExoDx ≤15.6, n=24	8 (33.3%)	8/8 (100.0%)	0/8 (0.0%)
ExoDx >15.6, n=79	34 (43.0%)	26/34 (76.5%)	8/34 (23.5%)
All ExoDx, n=103	42 (40.8%)	34/42 (81.0%)	8/42 (19.0%)
Sensitivity: 100.0%	Specificity: 23.5%	NPV: 100.0%	PPV: 23.5%
		≤GG2 Incidence	≥GG3 Incidence
ExoDx ≤15.6, n=24		8/8 (100.0%)	0/8 (0.0%)
ExoDx >15.6, n=79		32/34 (94.1%)	2/34 (5.9%)
Sensitivity: 100.0%	Specificity: 20.0%	NPV: 100.0%	PPV: 5.9%
PI-RADS 4 & 5	**Bx Rate (%)**	**≤GG1 Incidence**	**≥GG2 Incidence**
ExoDx ≤15.6, n=12	6 (50.0%)	6/6 (100.0%)	0/6 (0.0%)
ExoDx >15.6, n=78	47 (60.3%)	21/47 (44.7%)	26/47 (55.3%)
All ExoDx, n=90	53 (58.9%)	27/53 (50.9%)	26/53 (49.1%)
Sensitivity: 100.0%	Specificity: 22.2%	NPV: 100.0%	PPV: 55.3%
		≤GG2 Incidence	≥GG3 Incidence
ExoDx ≤15.6, n=12		6/6 (100.0%)	0/6 (0.0%)
ExoDx >15.6, n=78		29/47 (61.7%)	18/47 (38.3%)
Sensitivity: 100.0%	Specificity: 17.1%	NPV: 100.0%	PPV: 38.3%

Table 3: Men with a mpMRI result and biopsy within 1 year stratified by PI-RADS Score. All metrics were for Bx within 1 year of the ExoDx result. Of the 142 patients in Sub cohort E, PI-RADS were evenly distributed (PI-RADS 1/2 n=47, 33.1%, PI-RADS 3 n=42, 29.6% and PI-RADS 4/5 n=53, 37.3%). While biopsy rates vary, the NPV for the combined use of ExoDx and mpMRI was 100.0% regardless of the PI-RADS result or a GG cut point of ≥2 or ≥3.

Conclusion

This study captured real-world clinical practice of the ExoDx Prostate (ExoDx) biomarker test and mpMRI and supports a growing consensus that biomarkers in combination with mpMRI provide complementary clinical value. The results presented here align with the recently updated AUA guidelines on the use of biomarkers and mpMRI for initial prostate biopsy.

Literature Cited

1. McKiernan J, et al. A novel urine exosome gene expression assay to predict high-grade prostate cancer at initial biopsy. JAMA Oncology. (2016);2(7):1-8
2. McKiernan J, et al. A prospective adaptive utility trial to validate performance of a novel urine exosome gene expression assay to predict high-grade prostate cancer in patients with prostate-specific antigen 2–10 ng/mL at initial biopsy. Eur Urol (2018); 74:731-738
3. Margolis E, et al. Predicting high-grade prostate cancer at initial biopsy: clinical performance of the ExoDx (EPI) Prostate Intelliscore test in three independent prospective studies. Prostate Cancer and Prostatic Diseases (2021); https://doi.org/10.1038/s41391-021-00456-8
4. Tutrone R, et al. Clinical utility of the exosome based ExoDx Prostate(IntelliScore) EPI test in men presenting for initial Biopsy with a PSA 2–10 ng/mL. Prostate Cancer and Prostatic Diseases (2020);23:607–614.