Development of a clinical implementation plan (CarePath) for a novel urine exosome gene expression assay as part of a two-cohort, adaptive decision impact utility trial

MP46-05

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Introduction:

The ability to discriminate indolent from clinically significant prostate cancer (PCa) in the initial biopsy setting remains an important health issue. In Phase 1 of a prospective decision impact trial we conducted a 503 patient second independent validation study (Cohort 1) and assessed performance of the ExoDx *Prostate(IntelliScore)* (EPI) urine exosome test **(Figure 1)** for discriminating Grade group (GG) ≥ 2 from GG1 PCa and benign disease on initial biopsy. We then convened an expert panel to review these results and developed a clinical implementation EPI guidance document (i.e. CarePath) for a second patient cohort (Cohort 2) **(Figure 2)** where EPI results are provided during the initial biopsy decision process [1].

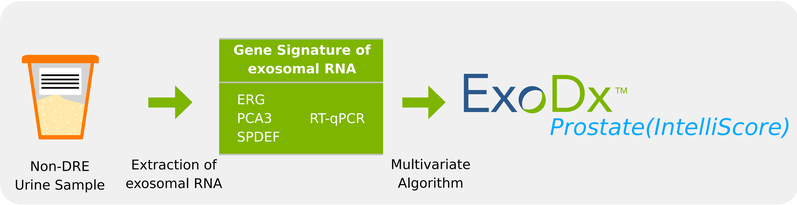

Figure 1: Schematic overview of the ExoDx™ *Prostate(IntelliScore)* (EPI) assay.

Methods:

A panel of clinicians and risk modeling experts compared the area under the receiver operating characteristic curve (AUC), negative predictive value (NPV), sensitivity, and specificity of cohort 1 EPI outcomes (N=503) with previous validation results (N=519) for both the validated and alternative EPI cut-points of 15.6 and 20. The group compared EPI cut-point performances in a derived pooled cohort (N=1022: Cohort 1 N=503 + previous validation N=519).

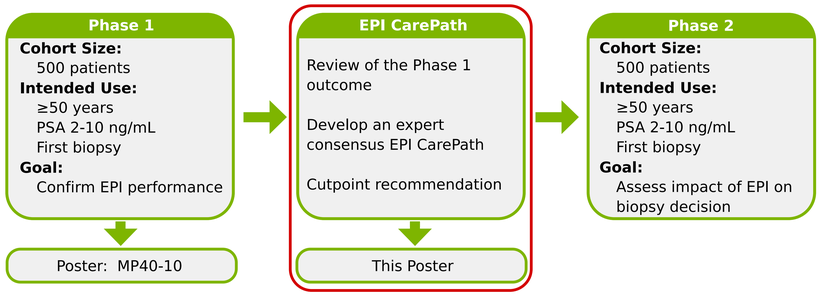

Figure 2: Schematic overview of the adaptive, prospective clincial trial design. After completion of phase 1, a panel of clinicians and risk modeling experts convened at a Consensus Conference to review the performance of the EPI test and compare with previous validation study results using both the validated and alternative cut-points of 15.6 and 20, respectively.

Results:

Expert consensus confirmed comparable performances for discriminating GG2 PCa or greater from benign and GG1 PCa disease in Cohort 1 (EPI AUC 0.70) **(Figure 3A)**, with the original validation cohort (EPI AUC 0.71) and in the pooled cohort (EPI AUC 0.70) **(Figure 3B)**. Using the previously validated cut-point of 15.6 (or alternative 20) would avoid 26% (or 40%) of unnecessary prostate biopsies and 20% (or 31%) of total biopsies, with an NPV of 89% for both cut-points, and missing only 7% (or 11%) of ≥GG3, respectively. Results were also comparable for the pooled cohort.

Phase 1

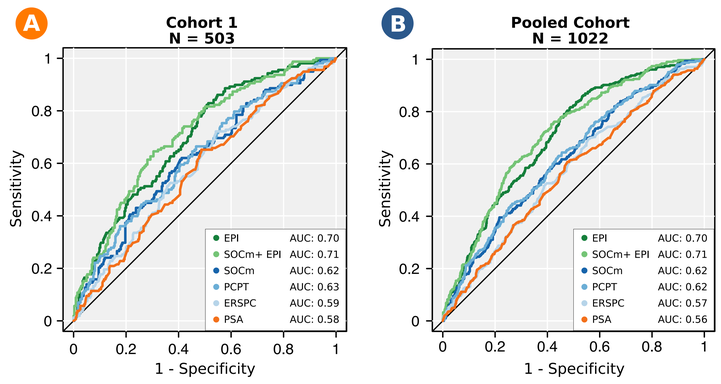

Table 1: Demographics & Performance

	A Cohort 1		B Pooled Cohort	
Cohort Size	503		1022	
Age (Median)	64 years		63 years	
PSA (Median)	5.4 ng/mL		5.3 ng/mL	
African American	14.1%		15.5%	
Familyhistory - Yes	14.3%		18.5%	
EPI Cutpoint	Validated (15.6)	Alternative (20)	Validated (15.6)	Alternative (20)
Prevalence HGPCa	31.4%	31.4%	29.9%	29.9%
Biopsies Avoided	20.1%	30.8%	23.4%	33.8%
Sensitivity	93.0%	89.2%	92.5%	88.2%
Specificity	26.1%	40.0%	30.2%	43.2%
NPV	89.1%	89.0%	90.4%	89.6%

Figure 3: After completion of Phase 1 the results were reviewed in combination with previously developed validation data, separately and in a pooled analysis of all N=1022 subjects.

References:

[1] McKiernan J, Donovan MJ, Margolis A, Partin A, Carter B, Brown G, Torkler P, Noerholm M, Skog J, Shore N, Andriole G, Etzioni R, Thompson I, Carroll P (2018) 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 PSA 2-10 ng/mL at initial biopsy. *European Urology*, Manuscript submitted

Consensus CarePath Meeting

Objectves:

- Comprehensive review of the Phase 1 outcome
- Develop clinical implementation CarePath for EPI test
- Assess patient eligibility and cohort demographics
- Determine if primary endpoint was achieved
- Confirm intended use population
- Recommend cut-point for EPI test
- Finalize CarePath document for Phase 2

Attendees:

James M. McKiernan
Columbia University Medical Center
Michael J. Donovan
Icahn School of Medicine at Mt. Sinai
Eric J. Margolis
Urology Center of Englewood
Alan W. Partin
Johns Hopkins Hospital
H Ballentine Carter
Johns Hopkins Hospital
Gordon A. Brown
Delaware Valley Urology
Neal Shore
Atlantic Urology Clinics
Gerald L. Andriole
Washingtion University, St. Louis
Ruth Etzioni
Fred Hutchinson Cancer Research Center
Ian Thompson
UT Health Science Center
Peter Carroll
University of California

CarePath

ExoDx™ *Prostate(IntelliScore)*

The Consensus CarePath Meeting Attendees agreed:

- The EPI test is to be utilized at the original validated cut-point of 15.6
- Patients with an EPI score <15.6 are considered low risk for having HGPCa (≥GG2)
- Patients with an EPI score ≥15.6 are considered high risk for having HGPCa (≥GG2)
- EPI is designed to be used in conjunction with standard of care prognostic information

Phase 2

Phase 2 / Decision Impact Cohort:

- Provide EPI CarePath Document to Principal Investigators participating in Phase 2
- Assess impact of EPI results on biopsy decision process
- Determine health economics of EPI in biopsy decision process
- Assess physician and patient satisfaction

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