HEALTH TECHNOLOGY ASSESSMENT:
ULTRASOUND-BASED APPLICATION FOR DIFFERENTIATION OF PROSTATE TISSUE – PROSTATE HISTOSCANNING™ – USE FOR DIAGNOSTICS AND LOCALISATION OF PROSTATE CANCER

SUMMARY

Methods and description of the evidences used. The assessment was made on the basis of health technology assessment methodology prepared by International European Health Technology Assessment Network ‘EUnetHTA’. The rapid assessment was based primarily on a basic systematic literature search in the following sources: • Cochrane Library database; • PubMed (Medline); • CRD database; • Hand searches including articles from the manufacturers.

The systematic literature search was conducted in September-October in 2015 without any limitations. Relevant articles for the ‘Safety’ and ‘Clinical effectiveness’ domains were selected by the VASPVT (State Health Care Accreditation Agency under the Ministry of Health, Lithuania) and checked by the LBI-HTA (Ludwig Boltzmann Institute-Health Technology Assessment, Austria). References were included or excluded according to the PICO scheme.

The quality of diagnostic accuracy studies was assessed by QUADAS-2 checklist. For assessing the quality of SRs, the AMSTAR checklist for systematic reviews was used.

Substantiation for Health Technology Assessment. Natural course of prostate cancer (PCa) is not fully understood: PCa can grow extremely slowly or fast, while in some patients tumor never progress; PCa often starts out as a pre-cancerous condition. The main risk factors in the development of prostate cancer are race (ethnicity), family history and age. Prostate cancer mainly affects men over 50 and the risk increases with age. The average age for men to be diagnosed with prostate cancer is between 70 and 74 years. The impact of prostate cancer in an aging population is expected to increase, even if the incidence rate were to remain constant. There will also be an increased need for financial and human resources such as treatment facilities and trained specialists. Prostate cancer is the most common cancer in Lithuanian men, nearly 3,000 men are newly diagnosed with prostate cancer and about 500 deaths occur from this disease annually.

Recommendation for PSA screening generally encourage the test in men between the ages of 40 to 70 years or 50 to 75 years and in men with an increased risk of PCa – men from 45 years old if their father or brothers were diagnosed with PCa. However, PSA alone is not a specific test for PCa, as well as digital rectal exam (DRE), but DRE in combination with PSA test should be done in patients with clinical suspicion of PCa or in those who wish further investigation for the presence of PCas.

PHS is claimed to provide additional and meaningful information for better management of PCa patients by providing visual reassurance for decision making. For some patients with only a slightly elevated PSA level, it seems to be possible to keep the situation under active surveillance using PHS and avoid the need for biopsy.

Prostate HistoScanning™ (PHS). HistoScanning™ is a novel non-invasive imaging modality that analyzes the data acquired from 3D-transrectal ultrasound (3D-TRUS) using computer aided application. HistoScanning™ was developed by privately held Belgium company Advanced Medical Diagnostics (Waterloo, Belgium) and commercially launched in November 2008.

This technology can detect specific changes in the tissue morphology by extracting and quantifying statistical features from backscattered ultrasonographic data, which might further allow
differentiation between benign and malignant tissue and characterization of the disease volume. PHS may guide clinical decisions throughout entire prostate cancer care: detection and diagnosis, treatment planning, treatment guidance and post-treatment monitoring.

The new biopsy software tool prostate HistoScanning™ TT, or True Targeting, was introduced in 2014. Prostate HistoScanning™ TT uses additional specialized software that allows to perform the target biopsy with PHS in situ and provides real-time guidance. The PHS workstation is currently approved for use only with BK Medical (Peabody, MA, USA) ultrasound scanners.

**Features of the comparator and the reference standard.** In the case of elevated PSA or abnormal digital rectal examination PCa diagnosis is usually established by biopsy. Traditional prostate biopsies can be classified based on the approaches adopted in the procedure: trasrectal, tranurethral, transperineal.

A transrectal approach is used for most prostate biopsies. According to European Association of Urology (EAU) guidelines on PCa initial recommended biopsy is TRUS-guided systemic 10- to 12-core biopsy, with a sample site as far posterior and lateral into the peripheral zone. Targeted biopsies guided by imaging are gaining interest as a diagnostic procedure for PCa detection. Most of the procedures are based on multiparametric MRI (e. g., cognitive MRI-guided biopsy, MRI-US fusion biopsy.)

**Safety.** Adverse events related to the Prostate HistoScanning™ technology were reported very poorly. Only one case serie reported some adverse events such as acute retention of urine and mild prostatitis. Procedure was performed with a new software version of PHS – TT, which allows to perform the target biopsy and provides real-time guidance. No major complication was observed.

It is known that adverse events following PHS and targeted biopsies are not specifically reported in literature. Logically, the complications should be proportional to the number of biopsy cores taken. According to literature, TRUS biopsies carry risk of infection (2–4%) and rising levels of life-threatening sepsis (0.1%) as they traverse the contaminated rectal mucosa; most men experience discomfort and bleeding, but major complications are very rare.

Two case series reported some incidental findings detected by PHS: prostatic intraepithelial neoplasia (precancerous condition) (6.3–12.4%), chronic inflammation (28.1–60.8%), atypical small acinar proliferation (2.1%). Moreover, one study reported that incidental finding such as inflammatory changes of prostate tissue were recognized as PCa on both exams – PHS and mpMRI. However, radical prostatectomy specimen analysis showed that patient did not have PCa at all.

False positive/ negative findings were reported in 4 case series. Also, these findings were distributed according to subgroups – ‘per patient’ and ‘per section’. Results show that in ‘per patient’ subgroup only one study reported false positive findings (62.5%) and false negative findings were reported in all studies. However, results in ‘per section’ subgroup show higher rates in false positive findings in all studies when compared with false negative findings. (C0006)

There is adequate evidence that false positive test findings are associated with negative psychological effects, including persistent worry and fear about PCa; this can lead some men to have a prostate biopsy (with small risks of pain, infection, and bleeding) when they do not have cancer and – most important – there is a risk for overdiagnosis coupled with overtreatment. Meanwhile false negative findings could delay the treatment and give some men a false sense of security even though they actually have cancer.

Since data regarding adverse events of PHS is limited, information about harms related to frequency of applying the technology; changes in frequency or severity of harms over time or in different settings; changes of the safety profile of the technology between different generations or approved versions; association of the technology with user-dependent harms – was not analysed and provided. Information considering occupational and environmental safety was not provided as well.

**Clinical effectiveness.** PCa detection rate of transrectal Prostate HistoScanning™ varied from 12.3% to 67.7% in „PHS for screening“ group. However, PCa detection rates in „PHS for staging“ group were not observed. Additionally, PCa detection rates of reference standard were reported in all studies, though results were distributed according to type of the biopsy – PCa detection rate reported by standard systematic 12-core TRUS-guided biopsy was 44–78.1%, by transperineal template prostate biopsy – 54.4%, by standard systematic 10- to 12-core TRUS-guided biopsy – 50% and by systematic 14-core TRUS-guided biopsy – 70.1%.
PHS performance for detection of PCa in „PHS for screening“ group had sensitivity of 22.6–53.3%, and specificity of 9–100% in ‘per patient’ subgroup; sensitivity and specificity of PHS were 48.1–100% and 5.9–57.5% in ‘per section’ subgroup, respectively. However, PHS performance in „PHS for staging“ group for detection of PCa lesions ≥0.1 ml had sensitivity of 60% and specificity of 66%; for detecting tumor foci ≥0.2 ml were 63–90% and 53–72%, respectively; for the localization of lesions ≥0.5 ml were 37–90% and 70–71%, respectively.

However, one study compared accuracy of PHS and mpMRI and results showed sensitivity of 46.2% and 52.6%, specificity of 74.1% and 96.5%, respectively. Also, PHS reported significantly (p<0.0001) lower PPV than mpMRI (45.0% vs. 87.2%). Although the overall cancer detection rate for mpMRI and PHS was similar, mpMRI identified 19/22 (86.4%) high-grade cancers, but only 23/62 (37.1%) low-grade cancers; however, PHS detected 11/22 (50%) high-grade cancers and 25/62 (40.3%) of low grade.

Unfortunately, studies represented controversial suggestions on the number of biopsy cores: one suggested a reduction of biopsies in non-PHS positive sectors and to focus on more vulnerable or suspect regions in the prostate; the other cannot recommend variation of well-established biopsy standards or a reduction in biopsy cores based on HistoScanning™ signals.

However, none of the studies provided information about mortality, morbidity, quality of life and patient satisfaction.

**Investments required to use the technology.** According to the distributor „Interlux“ the price of the PHS device (with BK Medical ultrasound scanner) in Lithuania is 260.000 €, and the costs (direct and indirect) of use per test (condoms, disposable gowns, biopsy needles) – about 20 €, i.e., the same as the standard transrectal prostate biopsy.

**Conclusions:**
1. Different PHS versions could be used in different ways: Prostate HistoScanning™ is not a real-time imaging and results are viewed on the screen afterward; if needed, biopsy is performed under the guidance of PHS image; Prostate HistoScanning™ TT uses an additional specialized software that allows to perform the target biopsy with PHS in situ and provides real-time guidance.
2. Adverse events related to the Prostate HistoScanning™ technology are poorly and not specifically reported. However, they are similar to adverse events related to targeted biopsies, which could be: discomfort, bleeding or infection. Major complications are rare.
3. PHS technology is associated with higher rates in false positive findings: when analysing individual patients (0–62.5%); when analysing different parts of the prostate (14.6–74.2%). False positive findings are associated with negative psychological effects, including persistent worry and fear about PCa, overdiagnosis and overtreatment.
4. PHS for screening: PHS detection rate of prostate cancer in men with suspicious screening results varied from 12.3% to 67.7%. For a comparison, a detection rate of a standard systematic 12-core TRUS-guided biopsy varied from 44% to 78.1%. PHS is not able to improve PCa detection rates and fails to be a better diagnostic tool. In this case, the number of biopsy cores cannot be reduced according to PHS positive sectors and because of well-established biopsy standards.
5. PHS for staging: accuracy of PHS and mpMRI in men with diagnosed prostate cancer showed sensitivity of 46.2% and 52.6%, specificity of 74.1% and 96.5%, respectively. Cancers missed by mpMRI were more often of lower grade and smaller than cancers missed by PHS. However, issues of costs, availability of MRI and reproducibility of these results outside of expert centers inhibit widespread adoption of MRI.

**Recommendations:**
1. The results from diagnostic accuracy studies require confirmation in well designed, prospective trials of sufficient size with appropriate end points and reference standard methods. Until data of this level become available, the use of HistoScanning™ should be restricted to clinical trials.
2. Considering situation in Lithuania (Prostate HistoScanning™ technology is already available), we suggest PHS for patients with suspected prostate cancer and/ or for patients with diagnosed PCa to improve localization and volume of the lesion. However, data from such diagnostic procedures should be included in clinical trials.