VASPVT
Valstybinė akreditavimo
sveikatos priežiūros veiklai tarnyba
prie Sveikatos apsaugos ministerijos

Ludwig Boltzmann Institut
Health Technology Assessment

SVEIKATOS TECHNOLOGIJOS VERTINIMAS:
ULTRAGARSINIO SIGNALO ALGORITMINIO ANALIZATORIAUS PROSTATOS AUDINIO DIFERENCIACIJAI – PROSTATE HISTOSCANNING™ – NAUDOJIMAS PROSTATOS VĖŽIO DIAGNOSTIKAI BEI LOKALIZACIJAI

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

2015

Valstybinė akreditavimo sveikatos priežiūros veiklai tarnyba
prie Sveikatos apsaugos ministerijos

Autoriai: Medicinos technologijų skyriaus vyr. specialistės:
Vitalija Keršytė
Kristina Grigaitė

Recenzavo: Liudviko Boltzmano instituto sveikatos technologijų vertinimui direktorė
Dr. Claudia Wild
Medicinos moderniųjų technologijų skyriaus vyr. specialistė
Agnes Kisser

Sveikatos technologijos vertinimas atliktas bendradarbiaujant su
Liudviko Boltzmano institutu sveikatos technologijų vertinimui (LBI–HTA), Austrija

Valstybinė akreditavimo sveikatos priežiūros veiklai tarnyba prie Sveikatos apsaugos ministerijos
Jeruzalės g. 21, LT-08420 Vilnius
Tel. (8 5) 261 5177,
Faks. (8 5) 212 7310,
El. paštas: vaspvt@vaspvt.gov.lt

Sveikatos technologijos vertinimo santrauką galima rasti interneto svetainėje:
http://www.vaspvt.gov.lt/node/486

State Health Care Accreditation Agency
under the Ministry of Health

Authors: Chief specialists of Medical Technology division:
Vitalija Keršytė
Kristina Grigaitė

Reviewers: Director of Ludwig Boltzmann Institute for Health Technology Assessment
Dr. Claudia Wild
Senior researcher in the Department of High Tech Medicine
Agnes Kisser

Health technology assessment was carried out in collaboration with
Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA), Austria

State Health Care Accreditation Agency under the Ministry of Health
Jeruzalės st. 21, LT-08420 Vilnius
Tel. (370 5) 261 5177,
Fax. (370 5) 212 7310,
E. mail: vaspvt@vaspvt.gov.lt

Health technology assessment is available on the website:
http://www.vaspvt.gov.lt/node/486

TABLE OF CONTENTS

ABBREVIATIONS

% – percent;
€ – euro;
2D – two-dimensional;
3D – three-dimensional;
3D-TRUS – 3D-transrectal ultrasound;
CE – Conformité Européene (European Conformity);
cm – centimeter;
cm^3 – cubic centimeters;
DALYs – disability-adjusted life years;
DCE - dynamic contrast-enhanced imaging;
DRE – digital rectal exam;
DWI – diffusion-weighted imaging;
e.g. – for example;
EAU – European Association of Urology;
EPE – extraprostatic extension;
etc. – et cetera;
ICD-10 – International statistical classification of diseases and related health problems 10th revision;
IHME – Institute of Health Metrics and Evaluation;
MA – Massachusetts;
MHz – megahertz;
ml – mililitre;
mpMRI – multiparametric magnetic resonanse imaging;
MRI – magnetic resonance imaging;
n – number;
ng – nanogram;
NPV – negative predictive value;
PCa – prostate cancer;
PHS – prostate HistoScanning™;
PIN – prostatic intraepithelial neoplasia;
PPV – positive predictive value;
PSA – prostate specific antigen;
pts. – patients;
QoL – Quality of Life;
RCT – randomised controlled trial;
RCTs – randomised controlled trials;
RP – radical prostatectomy;
T2WI – T2-weighted;
TNM – Classification of Malignant Tumours;
TRUS – transrectal ultrasound;
TT – true targeting;
TURP – trans-urethral resection of the prostate;
UK – United Kindom;
US – ultrasound;
USA – the United States of America;
vs. – versus.

SANTRAUKA

Tikslinė būklė

Prostatos vėžys, dar vadinamas prostatos karcinoma, vystosi vyrų reprodukcinės sistemos liaukoje – prostatoje. Vis dėlto, natūrali prostatos vėžio eiga nėra visiškai ištirta – liga gali vystytis itin greitai ar lėtai arba visai neprogresuoti; prostatos vėžys dažniausiai prasideda kaip priešvėžinė būklė. (**A0002; A0004**)

Yra daug rizikos veiksnių, susijusių su prostatos vėžio vystymusi (pavyzdžiui, amžius, genetiniai veiksniai, endogeniniai hormonai, medicininės būklės); vis dėlto, manoma, jog rūkymas, nutukimas, ūgis, pasyvus gyvenimo būdas, kalcio kiekis, daržovių trūkumas, rasė, šeimos istorija, oranžinio agento ekspozicija yra agresyvaus prostatos vėžio rizikos šaltiniai. (**A0003; A0006**)

Dėl senstančios gyventojų populiacijos prostatos vėžio įtaka stiprės, net jei susirgimų dažnis išliks pastovus. Taip pat padidės finansinių ir žmogiškųjų išteklių poreikis, tokių kaip gydymo įstaigos bei kvalifikuoti specialistai. (**A0005; A0006**)

Tikslinė populiacija

Prostatos vėžys pagal atvejų skaičių tarp abiejų lyčių yra ketvirtoje vietoje visame pasaulyje arba antroje vietoje tik tarp vyrų. Skaičiuojama, jog 2012 m. pasaulyje buvo diagnozuota 1.1 mln. naujų vėžio atvejų, tai sudaro 15% atvejų iš visų vyrams diagnozuotų vėžių, o 70% atvejų diagnozuota labiau išsivysčiusiose pasaulio šalyse. Negana to, manoma, jog 2030 m. kasmet naujai diagnozuojamų atvejų skaičius pasieks 1.7 mln. ir dėl to įvyks 0.5 mln. mirčių, susijusių su prostatos vėžiu. Lietuvoje prostatos vėžys yra dažniausiai diagnozuojamas vėžys – kasmet nustatoma beveik 3.000 naujų atvejų, miršta apie 500 vyrų. (**A0023**)

Dauguma sergančiųjų – vyrai, sulaukę 50 ir daugiau metų, o su amžiumi rizika didėja. Vidutiniškai, prostatos vėžys diagnozuojamas sulaukus 70–74 m. Rekomenduojama, jog stebėsenos tyrimai (PSA lygis kraujyje) būtų atliekami vyrams tarp 40–70 m. amžiaus, 50–75 m. amžiaus arba tiems, kurie turi padidėjusią riziką susirgti – sulaukusiems 45 m. amžiaus, jei jų tėvai ar broliai sirgo priešinės liaukos vėžiu. (**A0007**)

Remiantis gamintojų pateikta informacija, nuo 2013 m. kovo mėn. tyrimai su PHS technologija buvo atlikti daugiau nei 16.000 pacientų visame pasaulyje. (**A0011**)

Šiuolaikinis prostatos vėžio valdymas

Prostatos vėžio valdymas išlieka kontraversiškas dėl skirtingų rizikos veiksnių gausos, skirtingų gydymo būdų įvairovės bei randomizuotų kontroliuojamų tyrimų (RCT), kuriais būtų palyginti skirtingi gydymo būdai, trūkumo. Vis dėlto, dauguma prostatos navikų pirmiausiai yra aptinkami prostatos specifinio antigeno (PSA) kiekio kraujyje patikros metu ir/ arba digitalinio rektalinio tyrimo (DRE) metu. Vis dėlto, vien PSA tyrimas, kaip ir DRE tyrimas, nėra specifinis testas prostatos vėžio diagnostikai, tačiau šių dviejų tyrimų kombinacija turėtų būti atliekama visiems pacientams, kuriems kliniškai įtariamas prostatos vėžys, arba tiems, kurie pageidauja tolesnio ištyrimo dėl praeityje buvusio prostatos vėžio.

PHS, pateikdamas prostatos vaizdą, turėtų teikti papildomą informaciją geresniam pacientų valdymui. Naudojant Prostate HistoScanning™, kai kuriuos pacientus, kuriems PSA lygis yra nereikšmingai didesnis nei nustatyta norma, galima palikti aktyviam stebėjimui ir taip išvengti biopsijos. (**A0001; A0024; A0025**)

Kompensavimas

Prostate HistoScanning™ yra transrektalinis ultragarsinis HistoScanning™ prietaisas, sukurtas specialiai prostatos audinių diferenciacijai. Nuo 2008 m. HistoScanning™ turi CE ženklinimą pagal Europos direktyvą dėl medicinos prietaisų 93/42/EEC (su pakeitimais 2007/47/EC, 2 priedas); nuo 2009 m. HistoScanning™ yra licencijuotas ir atitinka Health Canada (Kanados sveikatos prietaisų atitikties įvertinimo sistemų politikos) reikalavimus (sertifikato numeris 81234). Beje, Prostate HistoScanning™, naudojamas Europoje, yra skirtas diagnozuoti ir valdyti prostatos vėžį; HistoScanning™ prietaisai krūtims, kiaušidėms ir skydliaukei dar kuriami.

Remiantis platintojo UAB „Interlux“ pateikta informacija, Prostate HistoScanning™ prietaiso kaina (su BK Medical ultragarsiniu prietaisu) Lietuvoje yra 260.000 €. (**A0021**)

Pagrindinės technologijos charakteristikos

Prostate HistoScanning™ (PHS) technologija yra nauja, neinvazinė vaizdinimo priemonė, kuri apdoroja informaciją, gautą 3-D transrektalinio ultragarsinio (3D-TRUS) prietaiso pagalba, o rezultatai atvaizduojami monitoriaus ekrane. Ši technologija buvo sukurta privačios Belgijos įmonės „Advanced Medical Diagnostics“, o prekyboje pasirodė 2008 m. lapkričio mėn. **(B0001)**

Technologijos veikimo principas, paremtas histopatologiniais atgalinės sklaidos signalo vertinimo algoritmais, leidžia aptikti specifinius morfologinius pokyčius audiniuose, diferencijuoti gerybinius ir piktybinius navikus bei charakterizuoti naviko apimtis (dydį). PHS gali padėti priimti klinikinius sprendimus įvairiuose prostatos vėžio valdymo etapuose: pakitusių audinių aptikimas ir diagnozės nustatymas, gydymo planavimas, situacijos stebėjimas po gydymo. Vis dėlto, plačiausiai ši technologija taikoma norint įvertinti tikslią naviko lokalizaciją bei vėžio stadiją (atsižvelgiant į naviko dydį). **(B0002; B0001)**

Nauja PHS technologijos programinės įrangos versija TT (True Targeting) prekyboje pasirodė 2014 m. Patobulinta programinė įranga suteikia galimybę diagnostinės procedūros metu atlikti pritaikomąją biopsiją (angl. *targeted biopsy*) in situ esamuoju laiku ir monitoriuje stebėti visą procesą. Atliekant biopsiją adatos „kelias“ ir audinio mėginio paėmimas yra automatiškai įrašomas, tai užtikrina lengvą ir greitą rezultatų peržiūrą. Ultragarsinės nuotraukos ir kiti duomenys yra įrašomi į laikmeną, todėl procedūros eigą galima peržiūrėti, įvertinti ir ateityje. **(B0002; B0003)**

Ši technologija nesudėtingai integruojama į dabartinę praktiką, kadangi procedūra turėtų būti atliekama ambulatorinėmis sąlygomis, kur diagnozuojama didžioji prostatos vėžio atvejų dalis, arba dienos stacionare (jei reikalinga biopsija). **(B0004)**

Investicijos ir priemonės, reikalingos technologijos naudojimui

Procedūros metu reikalinga įranga susideda iš trijų dalių – ultragarsinio prietaiso, specialaus 3-D transrektalinio daviklio, skleidžiančio ultragarso bangas ir magnetiškai pritvirtinto prie sukimosi laikiklio, bei HistoScanning™ prietaiso su specialia programine įranga. Programinė įranga šiuo metu suderinta naudoti tik su BK Medical (Peabody, MA, JAV) įmonės parduodamais ultragarsiniais prietaisais. Procedūrai atlikti reikalingos ir vienkartinės priemonės: prezervatyvai, medicininis ultragarsinis gelis, specialus gelis su anestetiku. Urologai procedūros metu dėvi vienkartinius chalatus, avalynės apdangalus, kepuraitę, pirštines. Jei procedūros metu atliekama biopsija, reikalingos papildomos priemonės: prie ultragarsinio daviklio pritvirtintas biopsinės adatos nukreipėjas, biopsinė šaudyklė ir biopsinė adata (18 G 25 cm). **(B0009)**

Procedūros eiga ir optimalus rezultatas labai priklauso nuo specialisto įgūdžių. Specialistas, naudojantis PHS technologiją, turėtų gerai išmanyti anatomiją bei būti susipažinęs su transrektalinės ultrasonografijos pagrindais. Apytiksliai apskaičiuota, jog specialistas turi atlikti apie 80 histoskenavimo procedūrų, kad galėtų tinkamai įvertinti rezultatus ir susiformuotų reikiami įgūdžiai. **(B0013)**

Pagrindinės alternatyvių technologijų charakteristikos ir referenciniai standartai

Ultragarsinis prostatos liaukos ir ją supančių struktūrų tyrimas yra naudojamas diagnozuojant prostatos vėžį, gerybinę prostatos hiperplaziją, prostatitą ir kt., stebėjimo ir gydymo procesų metu, įvertinant prostatos dydį bei atliekant biopsijas. Dažniausiai, kai pacientui nustatomas padidėjęs PSA lygis kraujyje bei aptinkami įtartini radiniai digitalinio rektalinio tyrimo metu, rekomenduojama atlikti prostatos biopsijos tyrimą su ultragarsinio prietaiso pagalba. Prostatos biopsijų rūšys klasifikuojamos pagal procedūros atlikimo pobūdį: transrektalinė prostatos biopsija (per tiesiąją žarną), transuretrinė prostatos biopsija (per šlaplę) ir transperinealinė prostatos biopsija (per tarpvietę). **(B0001; B0002)**

Dažniausiai atliekamos transrektalinės biopsijos. Remiantis Europos Urologų Asociacijos (angl. *The European Association of Urology*) parengtomis gairėmis, prostatos vėžio diagnozei patvirtinti rekomenduojama atlikti transrektalinę sistematinę 10–12 mėginių biopsiją, mėginius imant iš kiek įmanoma tolimesnių užpakalinės ir šoninių prostatos zonų. **(B0001)**

Prostatos biopsijos procedūra turi būti atliekama patalpoje, kurioje yra paciento gaivinimo priemonės esant skubiam atvejui (deguonis, gaivinimo vežimėlis, defibriliatorius, specialūs medikamentai, gyvybinių funkcijų stebėjimo aparatūra). Taip pat, biopsijos paprastai atliekamos vietinės nejautros sąlygomis. **(B0004; B0009)**

Vis dėlto, pritaikomosios biopsijos (angl. *targeted biopsy)* įgauna vis daugiau susidomėjimo. Remiantis vaizdinimo technologijų rezultatais, pritaikomųjų biopsijų mėginiai imami tik iš prostatos tikslinių „taškų“. Dauguma pritaikomųjų biopsijų atliekamos vadovaujantis multiparametrinės magnetinio rezonanso tomografijos (mpMRI) tyrimo rezultatais. **(B0003)**

Nors magnetinio rezonanso tomografija atrodo patikimiausia, ultragarso veikimu paremtos technologijos (PHS, elastografija ir kt.) taip pat yra kuriamos ir analizuojamos. **(B0003)**

Pacientų saugumas

Nepageidaujami įvykiai, susiję su PHS technologija, į vertinimą įtrauktuose tyrimuose buvo aprašyti minimaliai. Tik viename tyrime, kuriame pacientams buvo atliktos pritaikomosios biopsijos su TT programine įranga, nurodytos šios komplikacijos: ūminis šlapimo susilaikymas, vidutiniškai sunkus prostatos uždegimas. Gyvybei pavojingų komplikacijų nebuvo. **(C0008)**

Yra žinoma, jog komplikacijos po PHS procedūrų ar pritaikomųjų biopsijų, literatūroje nėra plačiai aprašytos. Logiškai suprantama, jog nepageidaujami įvykiai turėtų būti susiję su paimtų prostatos audinio mėginių skaičiumi. Remiantis literatūros duomenimis, transrektalinės biopsijos, atliekamos TRUS pagalba, susijusios su padidėjusia infekcijos rizika (2–4%), sepsiu (0.1%), daugeliui vyrų būdingas diskomforto jausmas, kraujavimas, tačiau gyvybei pavojingos komplikacijos itin retos. **(C0008)**

Dviejuose tyrimuose buvo nurodyti atsitiktiniai radiniai, aptikti su PHS technologija: prostatos intraepitelinė neoplazija (priešvėžinė būklė) (6.3–12.4%), lėtinis uždegimas (28.1–60.8%), prostatos epitelinių ląstelių proliferacija (2.1%). Įdomu tai, jog viename tyrime naudojant dvi technologijas (PHS ir mpMRI) uždegiminiai prostatos audinio pakitimai buvo identifikuoti kaip

prostatos vėžys. Atlikus radikalią prostatektomiją ir histologiškai ištyrus prostatą paaiškėjo, jog pacientas buvo sveikas. **(C0006)**

Klaidingai teigiamos/ neigiamos reikšmės buvo nurodytos keturiuose tyrimuose ir išskirtos į du pogrupius – „pacientui“ ir „prostatos daliai“. Pogrupyje „pacientui“ klaidingai teigiamos reikšmės (62.5%) buvo nurodytos viename tyrime, o klaidingai neigiamos reikšmės nurodytos visuose tyrimuose. Rezultatai „prostatos daliai“ pogrupyje rodo, jog visuose tyrimuose, lyginant dažnį, klaidingai teigiamų reikšmių yra daugiau nei klaidingai neigiamų. **(C0006)**

Yra moksliškai įrodyta, jog klaidingai teigiami tyrimo rezultatai daro neigiamą įtaką paciento psichologinei būklei, pasireiškia nuolatiniu susirūpinimu ir baime dėl diagnozuotos ligos. Taip pat gali būti susiję su nereikalingu biopsinės procedūros atlikimu ar nereikalingo gydymo taikymu. Dėl klaidingai neigiamų tyrimo rezultatų pacientui gali būti nesuteiktas reikalingas gydymas. **(C0006)**

Informacijos apie PHS technologijos sukeliamas komplikacijas trūksta, todėl kai kurie aspektai nebuvo analizuoti: kaip nepageidaujamų įvykių dažnis priklauso nuo technologijos taikymo dažnio, kaip nepageidaujamų įvykių dažnis ar sudėtingumas priklauso nuo įvairių aplinkybių ar kinta laike, kaip nepageidaujamų įvykių dažnis priklauso nuo technologijos versijos, taip pat, kaip nepageidaujami įvykiai priklauso nuo procedūrą atlikusio specialisto. Informacijos, susijusios su darbuotojų sauga bei poveikiu aplinkai, taip pat nebuvo. **(C0002; C0004; C0007; C0060)**

Testo tikslumas

Prostatos vėžio nustatymo, naudojant Prostate HistoScanning™ technologiją, dažnis grupėje “Technologija, skirta stebėsenai” varijavo nuo 12.3% iki 67.7%. Deja, prostatos vėžio nustatymo dažnis “Technologija, skirta lokalizacijai nustatyti” grupės tyrimuose nebuvo stebėtas. Papildomai referencinių standartų prostatos vėžio nustatymo dažniai buvo nurodyti visuose įtrauktuose tyrimuose, tačiau rezultatai buvo išskirstyti atsižvelgiant į biopsijos tipą – standartinės sistematinės 12 mėginių biopsijos, imamos TRUS pagalba, prostatos vėžio diagnostinis tikslumas buvo 44–78.1%, transperinealinės šabloninės prostatos biopsijos – 54.4%, standartinės sistematinės 10–12 mėginių biopsijos, imamos TRUS pagalba, – 50%, o standartinės sistematinės 14 mėginių biopsijos, imamos TRUS pagalba, – 70.1%. (**D1001; D1002; D1003**)

PHS jautrumas ir specifiškumas nustatant prostatos vėžį “Technologija, skirta stebėsenai” grupėje buvo atitinkamai 22.6–53.3% ir 9–100% “pacientui” bei 48.1–100% ir 5.9–57.5% “prostatos daliai”. Beje, “Technologija, skirta lokalizacijai nustatyti” grupėje PHS jautrumas ir specifiškumas nustatant ≥0.1 ml prostatos vėžį buvo atitinkamai 60% ir 66%; nustatant ≥0.2 ml prostatos vėžį atitinkamai – 63–90% ir 53–72%; o nustatant ≥0.5 ml prostatos vėžį atitinkamai – 37–90% ir 70–71%. (**D1005; D1006; D1007**)

Vis dėlto, viename tyrime lyginant PHS ir mpMRI rezultatus buvo nustatyta, kad jautrumas atitinkamai yra 46.2% ir 52.6%, o specifiškumas atitinkamai 74.1% ir 96.5%. Taip pat, PHS parodė statistiškai reikšmingai ($p<0.0001$) mažesnę PPV vertę nei mpMRI (45.0% vs. 87.2%). Nors bendras vėžio nustatymo dažnis mpMRI ir PHS buvo panašus, tačiau mpMRI identifikavo 19/22 (86.4%) žymių navikų, bet tik 23/62 (37.1%) nežymius navikus; vis dėlto, PHS identifikavo 11/22 (50%) žymių navikų ir 25/62 (40.3%) nežymius navikus. (**D0026; D1001**)

Valdymo pokyčiai

Deja, į tyrimą įtraukti tyrimai nepateikia vieningos nuomonės dėl biopsijos mėginių skaičiaus: vieni siūlo mažinti biopsijos mėginių skaičių PHS neigiamuose sektoriuose ir sutelkti dėmesį į pažeidžiamesnius ar labiau įtarimą keliančius prostatos regionus; vis dėlto, kiti negali

rekomenduoti nusistovėjusių biopsijos mėginių ėmimo standartų keitimo ir biopsijos mėginių mažinimo, remiantis Prostate HistoScanning™ signalu.(**D0021; D0023; D0026**)

Nė viename tyrime nebuvo pateikta informacija apie mirštamumą, sergamumą, gyvenimo kokybę ir pacientų pasitenkinimą procedūra. (**D0020; D0032; D1019; D0029**)

Trūkumai

Turimi duomenys turi tam tikrų trūkumų. Visu pirma, visi duomenys yra iš nekontroliuojamųjų tyrimų; dėl lyginamųjų tyrimų trūkumo negalima daryti jokių apibrėžtų išvadų. Antra, tyrimuose naudojami skirtingi referenciniai standartai; tokie skirtumai dar labiau apsunkina rezultatų palyginimą. Trečia, kai kuriuose tyrimuose pacientų atrankos procesas galėjo būti susijęs su padidėjusia paklaidos, trūkumų rizika; tyrimo kokybė, susijusi su referenciniu standartu, keliuose tyrimuose buvo neaiški.

PICO lentelė	
Populiacija	Vyrai, vyresni nei 50 m. amžiaus, kuriems: • įtariamas piktybinis prostatos navikas (PCa) (stebėsena); • diagnozuotas piktybinis prostatos navikas (lokalizacija). MeSH: *Prostatic Neoplasms (C04.588.945.440.770, C12.294.260.750, C12.294.565.625, C12.758.409.750).*
Intervencija	Ultragarsinio signalo algoritminis analizatorius prostatos audinio diferenciacijai – Prostate HistoScanning™ (PHS).
Alternatyvos	• biopsijos, atliekamos transrektalinio ultragarso pagalba (TRUS); • vaizdinimo technologijos. *MeSH terms: Ultrasonography [E01.370.350.850]; Ultrasonography, Interventional [E01.370.350.850.855]; Image-Guided Biopsy (E01.370.225.500.384.100.370, E01.370.225.998.054.370, E01.370.388.100.370, E04.074.370, E05.200.500.384.100.370, E05.200.998.054.370, E05.242.384.100.370)).*
Rezultatai	
Efektyvumas	1) Diagnostinis tikslumas (specifiškumas, jautrumas); 2) Terapinis poveikis (invazinės intervencijos išvengimas arba iniciavimas); 3) Ligai specifinis mirštamumas; 4) Ligai specifinis sergamumas; 5) Gyvenimo kokybė.
Saugumas	1) Nepageidaujami įvykiai; 2) Klaidingai neigiami/ Klaidingai teigiami radiniai; 3) Atsitiktiniai radiniai.
PICO klausimai: 1) Ar ultragarsinio signalo algoritminis analizatorius prostatos audinio diferenciacijai vyrams, vyresniems nei 50 m. amžiaus, yra efektyvesnis ir saugesnis diagnozuojant piktybinį prostatos naviką negu alternatyvūs diagnostiniai metodai, atsižvelgiant į diagnostinį tikslumą, terapinį poveikį, ligai specifinį mirštamumą ir sergamumą, gyvenimo kokybę, nepageidaujamus įvykius ir atsitiktinius radinius? 2) Ar ultragarsinio signalo algoritminis analizatorius prostatos audinio diferenciacijai vyrams, vyresniems nei 50 m. amžiaus, yra efektyvesnis ir saugesnis įvertinant naviko lokalizaciją ir tūrį negu alternatyvūs diagnostiniai metodai, atsižvelgiant į diagnostinį tikslumą, terapinį poveikį, ligai specifinį mirštamumą ir sergamumą, gyvenimo kokybę, nepageidaujamus įvykius ir atsitiktinius radinius?	

IŠVADOS

1. Skirtingos prostatos audinio vaizdinimo technologijos versijos yra naudojamos skirtingai: (1) naudojant Prostate HistoScanning™ technologiją, rezultatai monitoriaus ekrane yra peržiūrimi po procedūros (ne esamuoju laiku), o jei nusprendžiama atlikti prostatos biopsiją, tai daroma vadovaujantis vaizdu, matomu monitoriaus ekrane; (2) Prostate HistoScanning™ technologijos TT versija yra papildyta specialia programine įranga, kuri leidžia apžiūrėti prostatą monitoriaus ekrane, procedūros metu (esamuoju laiku), o, jei reikia, galima atlikti ir biopsiją – biopsinės adatos kelias ir įtartini „taškai“ stebimi monitoriaus ekrane, kol vyksta procedūra.

2. Nepageidaujami įvykiai susiję su Prostate HistoScanning™ technologijos naudojimu nėra gerai ir tiksliai įvardinti. Vis dėlto, jie panašūs į nepageidaujamus įvykius, kurie būdingi tikslinių biopsijų (angl. *targeted biopsy*) procedūroms: diskomforto jausmas, kraujavimas, infekcija. Gyvybei pavojingos komplikacijos yra labai retos.

3. Prostate HistoScanning™ technologijos naudojimas nėra patikimas, nes susijęs su aukštu klaidingai teigiamų rezultatų dažniu: analizuojant pacientus – 0–62.5%; analizuojant skirtingas prostatos liaukos dalis – 14.6–74.2%. Tai reiškia, kad ši technologija rodo paciento prostatoje esančius vėžinius pakitimus, nors iš tikrųjų (patikrinus kitais metodais) tai nepasitvirtina. Tokie atvejai daro didelę neigiamą įtaką paciento psichologinei būklei (nerimas, stresas, baimė, nežinomybė) ir sveikatos sistemos biudžetui, nes padidina nepagrįstas išlaidas, atliekant pacientui papildomus tyrimus ir procedūras, kai realaus pagrindo (prostatos vėžio) nėra.

4. Prostate HistoScanning™ technologija stebėsenai: prostatos vėžio aptikimo dažnis svyravo nuo 12.3% iki 67.7%. Palyginimui, atliekant standartinę sistematinę 12 mėginių biopsiją, atliekamą transrektalinio ultragarso pagalba, vėžio aptikimo dažnis yra nuo 44% iki 78.1%. Prostate HistoScanning™ technologija nepagerina prostatos vėžio aptikimo dažnio ir nėra geresnis diagnostinis įrankis – biopsijos mėginių skaičius negali būti sumažintas remiantis Prostate HistoScanning™ technologijos nurodytais įtartinais „taškais“, juolab, kad dabar biopsijos atliekamos pagal nustatytus standartus.

5. Prostate HistoScanning™ technologija lokalizacijai nustatyti: Prostate HistoScanning™ technologijos ir multiparametrinio magnetinio rezonanso tomografijos tyrimo tikslumo rodikliai, nustatant prostatos vėžį, parodė atitinkamai 46.2% ir 52.6% jautrumą bei 74.1% ir 96.5% specifiškumą. Nors abiejų technologijų bendras prostatos vėžio nustatymo dažnis buvo panašus, tačiau su Prostate HistoScanning™ technologija nebuvo nustatyti didesni ir žymesni navikai negu multiparametrinio magnetinio rezonanso tomografijos tyrimo metu. Vis dėlto, magnetinio rezonanso tomografijos tyrimas yra brangus ir ne visada prieinamas.

6. Trūksta patikimų ir metodologiškai tikslių Prostate HistoScanning™ technologiją nagrinėjančių klinikinių tyrimų. Vertinime naudotų diagnostinio tikslumo tyrimų kokybė buvo įvertinta specialiu „QUADAS-2“ klausimynu – 4 tyrimų (iš 11) pacientų atrankos aspektas buvo įvertintas kaip turintis aukštą neatsitiktinių klaidų riziką, o 3 tyrimų kokybė referencinio standarto aspektu, atsižvelgiant į neatsitiktinių klaidų riziką, buvo įvertinta kaip “neaiški” dėl nepakankamai detalizuotų duomenų.

REKOMENDACIJOS

1. Tam, kad šiuo metu turimi rezultatai iš atliktų diagnostinį tikslumą vertinančių tyrimų būtų patvirtinti, reikalingi kruopščiai suplanuoti prospektyviniai tyrimai su aiškiai apibrėžtais planuojamais tikslais ir referenciniais standartiniais metodais. Iki tol, kol tokio aukšto lygio duomenys taps prieinami, Prostate HistoScanning™ naudojimas turėtų apsiriboti moksliniais klinikiniais tyrimais.

2. Nerekomenduojama Prostate HistoScanning™ technologijos taikyti klinikinėje praktikoje ir tokių tyrimų kompensuoti iš Privalomojo sveikatos draudimo fondo (PSDF) biudžeto dėl žemo technologijos patikimumo lygio ir galimų nepagrįstų sveikatos sistemos išlaidų. Pacientai, kurie vis tik pageidautų šio tyrimo, turėtų būti išsamiai informuojami apie technologiją ir tyrimo išlaidas padengti patys, o konkrečiais atvejais svarstyti galimybę gautus klinikinius rezultatus įtraukti į mokslinius tyrimus.

SVEIKATOS TECHNOLOGIJOS VERTINIMO METODIKA

Vertinimas atliktas remiantis tarptautinio Europos sveikatos technologijų vertinimo tinklo „EUnetHTA“ parengta sveikatos technologijų vertinimo metodika. „HistoScanning™“ diagnostinės technologijos vertinimo analizė atlikta remiantis mokslinės literatūros šaltiniais, esančiais:

- The Cochrane Library duomenų bazėje;
- PubMed (Medline) duomenų bazėje;
- CRD duomenų bazėje;
- Gamintojų internetiniuose puslapiuose, kurių ieškota rankiniu būdu viešai prieinamoje erdvėje (internete).

2015-ųjų metų rugsėjo – spalio mėn. vykdyta sisteminė literatūros paieška nebuvo tikslinama jokiais duomenų filtrais. Sisteminės literatūros paieškos strategija pateikta 2 priede.

Straipsniai, susiję su „Saugumo“ ir „Klinikinio efektyvumo“ skyriais, buvo atrinkti VASPVT (Valstybinė akreditavimo sveikatos priežiūros veiklai tarnyba prie Sveikatos apsaugos ministerijos, Lietuva) Medicinos technologijų skyriaus specialistų ir recenzuoti Liudviko Boltzmano instituto sveikatos technologijų vertinimui (Ludwig Boltzmann Institute-Health Technology Assessment, Austrija) specialistų. Papildomi moksliniai straipsniai buvo įtraukti arba atmesti vadovaujantis PICO lentele, kuri pateikta santraukoje.

Atsakant į „Klinikinio efektyvumo“ ir „Saugumo“ skyrių klausimus, nebuvo rasta sveikatos technologijų vertinimų ar randomizuotų kontroliuojamų tyrimų; buvo remtasi rastomis sisteminėmis literatūros apžvalgomis bei prospektyviniais ir retrospektyviniais nekontroliuojamais tyrimais. Atsakant į „Sveikatos problema ir dabartinis technologijos naudojimas“ bei „Techninės charakteristikos“ skyrių klausimus, į vertinimą įtrauktiems tyrimams jokie apribojimai netaikyti.

Pritrūkus informacijos prieš tai minėtuose literatūros šaltinių tipuose ir negalint atsakyti į kai kuriuos „Sveikatos problema ir dabartinis technologijos naudojimas“ bei „Techninės charakteristikos“ skyrių klausimus, rankiniu būdu (internete) buvo vykdomos papildomos paieškos specifiniuose literatūros šaltiniuose (medicininių rekomendacijų duomenų bazėse, gamintojų internetiniuose puslapiuose ir kt.).

Vertinime naudojamų technologijos diagnostinį tikslumą vertinančių tyrimų kokybė buvo įvertinta specialiu „QUADAS-2“ klausimynu (žr. Priedas 5). Vertinime naudojamų sisteminių literatūros apžvalgų kokybė buvo patikrinta specialiu, sisteminėms literatūros apžvalgoms skirtu, „AMSTAR“ kontrolės klausimynu (žr. Priedas 5).

Atrinktų tyrimų bei juose analizuojamų populiacijų pagrindinės charakteristikos ir rezultatai, susiję su klinikiniu efektyvumu bei saugumu, pateikti lentelėse (žr. Priedas 4).

Rezultatai

Įtrauktų tyrimų charakteristika

Technologijos klinikinio efektyvumo ir saugumo įvertinimui buvo atrinkti 9 prospektyviniai nelyginamieji tyrimai [36,39,40,44,51,86,87,90,91], 1 retrospektyvinis nelyginamasis tyrimas [54] ir 1 prospektyvinis lyginamasis tyrimas [78]. Iš viso, į šį vertinimą buvo įtraukti 9 straipsniai, tačiau viename straipsnyje [93] buvo aprašyti rezultatai iš trijų nepriklausomų tyrimų [86,87,90].

Visuose atrinktuose tyrimuose dalyvavo 553 vyrai (intervalas nuo 24 iki 98). Tyrimai buvo išskirti į dvi grupes, priklausomai nuo iškelto tyrimo klausimo – 6 nelyginamieji tyrimai [36,39,40,51,86,87], įtraukti į “Technologija, skirta stebėsenai” grupę, kuriuose dalyvavo 293 vyrai (intervalas nuo 24 iki 97); 1 lyginamasis tyrimas [78] ir 4 nelyginamieji tyrimai [44,54,90,91],

įtraukti į "Technologija, skirta lokalizacijai nustatyti" grupę, kuriuose dalyvavo 260 vyrų (intervalas nuo 24 iki 98).

Į vertinimą įtrauktuose tyrimuose buvo naudojama skirtinga HistoScanning™ technologijos programinė įranga: 4 tyrimuose [44,86,87,90] naudota 2.1 versija, 2 tyrimuose [40,91] naudota 2.3 versija, kituose 2 tyrimuose [39,51] naudota TT (True Targeting) versija, likę trys tyrimai [36,54,78] duomenų apie programinę įrangą nepateikė.

Interesų konfliktas nurodytas visuose nelyginamuosiuose tyrimuose, tačiau nenurodytas 1 lyginamajame tyrime [78]; 5 tyrimuose [36,39,40,51,91] nebuvo jokio interesų konflikto, kituose 5 tyrimuose [44,54,86,87,90] dalis autorių gavo užmokestį iš įmonių, atstovaujančių gamintojams, taip pat projektų, kiti autoriai patys buvo gamintojų atstovai. Tyrimų finansavimo šaltinis nurodytas 2 tyrimuose [44,78]; finansinę paramą teikė gamintojai [44] ir labdaros fondas [78].

Pacientų charakteristika

Visi pacientai, įtraukti į "Technologija, skirta stebėsenai" grupę (6 iš 11 tyrimų), buvo vyrai, kuriems įtariamas piktybinis prostatos navikas: 3 tyrimuose [51,86,87] nurodyta pacientų amžiaus mediana – nuo 65 iki 68 m. (intervalas 47–79 m.), kituose 3 tyrimuose [36,39,40] nurodytas amžiaus vidurkis – nuo 63.7 iki 66.2 m. (intervalas 40–82 m.). Svarbiausi įtraukimo į tyrimus kriterijai: pakilęs PSA lygis ir/ arba įtartini radiniai atliekant digitalinį rektalinį tyrimą [36,40,51,86,87]; anksčiau atliktos biopsijos, kurių rezultatai buvo neigiami [36,40]; pacientai, kuriems reikalinga prostatos biopsija [39]. Pacientų neįtraukimo į tyrimus kriterijus nurodytas tik 1 tyrime [40] – tai pacientai, kuriems po atliktų procedūrų ir manipuliacijų su prostatos liauka, yra praėjęs trumpesnis nei 3 mėn. laikotarpis. PSA lygis nurodytas visuose tyrimuose – PSA lygio mediana varijuoja nuo 6.3 iki 9.25 ng/ml (intervalas 0.2–54.0) [51,86,87], o PSA lygio vidurkis – nuo 8.0 iki 16.06 ng/ml (intervalas 1.02–36.2) [36,39,40]. Tyrimuose taikytas referencinis standartas labai skirtingas – standartinė sistematinė 12 mėginių biopsija, imama transrektalinio ultragarso pagalba arba standartinė sistematinė 10–12 mėginių biopsija, imama transrektalinio ultragarso pagalba taikyta 4 tyrimuose [36,39,51,86]; transperinealinė šabloninė prostatos biopsija [87] ir sistematinė 14 mėginių biopsija, imama transrektalinio ultragarso pagalba [40] taikyta kituose 2 tyrimuose.

Visi pacientai, įtraukti į "Technologija, skirta lokalizacijai nustatyti" grupę (5 iš 11 tyrimų), buvo vyrai, kuriems diagnozuotas piktybinis prostatos navikas: 1 tyrime [91] nurodyta pacientų amžiaus mediana – 63 m. (intervalas nenurodytas), kituose 4 tyrimuose [44,54,78,90] nurodytas amžiaus vidurkis – nuo 61 iki 67 m. (intervalas 48–77 m.). Vėžio stadijos, remiantis tarptautine piktybinių navikų TNM klasifikacija (angl. *The TNM Classification of Malignant Tumours (TNM)*), nurodytos 2 tyrimuose [54,91]. Dauguma pacientų priklausė T1c grupei (n=117). Svarbiausias įtraukimo į tyrimus kriterijus – pacientai, kuriems paskirta radikalios prostatektomijos (RP) operacija, po histologiškai patvirtintos prostatos vėžio diagnozės [44,54,78,90,91]. Pacientų neįtraukimo į tyrimus kriterijai – neišsamūs klinikiniai duomenys, prastos kokybės duomenys (artefaktai), procedūros protokolo pažeidimai, pacientas atsisakė RP operacijos – nurodyti 3 tyrimuose [44,78,91]; 2 tyrimuose [54,90] neįtraukimo kriterijai nenurodyti. PSA lygis nurodytas visuose išskyrus 1 tyrimą [44]: PSA lygio mediana – 6.4 ng/ml (intervalas nenurodytas) [91], PSA lygio vidurkis varijuoja nuo 5.75 iki 9.9 ng/ml (intervalas 1.3–33.8) [54,78,90]. Referencinis standartas visuose tyrimuose buvo tas pats – radikali prostatektomija.

Kokybės vertinimas

Diagnostinio tikslumo tyrimų kokybei įvertinti buvo naudotas "QUADAS-2" klausimynas. Šį klausimyną sudaro 4 aspektai: pacientų atranka, technologija, referencinis standartas, tyrimo eiga

ir laikas. Atskirai kiekvienas aspektas yra įvertinamas atsižvelgiant į neatsitiktinių klaidų riziką, taip pat pirmieji trys aspektai vertinami taikymo problemos atžvilgiu.

Trys tyrimai [51,86,87] (iš 6 tyrimų), įtraukti į "Technologija, skirta stebėsenai" grupę, buvo įvertinti kaip turintys žemą neatsitiktinių klaidų riziką visais 4 aspektais. Kitų trijų tyrimų [36,39,40] kokybė, referencinio standarto aspektu, atsižvelgiant į neatsitiktinių klaidų riziką, buvo įvertinta kaip "neaiški" dėl nepakankamai detalizuotų duomenų. Tik viename tyrime [36], vienas aspektas (pacientų atrankos) buvo įvertintas kaip turintis aukštą neatsitiktinių klaidų riziką. Rizika, susijusi su galimomis taikymo problemomis, buvo įvertinta kaip "žema".

Du tyrimai [54,91] (iš 5 tyrimų), įtraukti į "Technologija, skirta lokalizacijai nustatyti" grupę, buvo įvertinti kaip turintys žemą neatsitiktinių klaidų riziką visais 4 aspektais. Trijuose tyrimuose [44,78,91] pacientų atrankos aspektas įvertintas kaip turintis aukštą neatsitiktinių klaidų riziką; viename tyrime [44] referencinio standarto aspektas įvertintas kaip turintis aukštą neatsitiktinių klaidų riziką; dar viename tyrime [91] tyrimo eigos ir laiko aspektas įvertintas kaip turintis aukštą neatsitiktinių klaidų riziką. Rizika, susijusi su galimomis taikymo problemomis, buvo įvertinta kaip "žema" visuose tyrimuose.

Detalesnę informaciją apie kokybės vertinimą galima rasti 5 priede.

Rezultatai

Visi rezultatai, išskyrus nepageidaujamus įvykius ir atsitiktinius radinius, abiejose grupėse – "Technologija, skirta stebėsenai" ir "Technologija, skirta lokalizacijai nustatyti" – buvo išskirti į pogrupius "pacientui" ir "prostatos daliai".

Keturiuose tyrimuose [36,51,86,87] iš šešių "Technologija, skirta stebėsenai" grupės buvo nurodyti jautrumas, specifiškumas, prognostinės teigiamos/ neigiamos testo vertės (PPV/ NPV); viename tyrime [51] minėtieji rodikliai buvo išskirti atsižvelgiant į slenkstines vertes (>0ml, >0.2ml, >0.5ml). Jautrumas [36,86,87] "pacientui" varijavo nuo 22.6% iki 53.3%, o "prostatos daliai" – nuo 48.1% iki 100%. Specifiškumas atitinkamai varijavo nuo 0% iki 100% ir nuo 5.9% iki 57.5%. PPV ir NPV intervalai "pacientui" buvo atitinkamai 20–100% ir 28.6–56.3%, o "prostatos daliai" atitinkamai 26–51.4% ir 78.1–100%. Vis dėlto, atsižvegiant į skirtingas PHS signalo slenkstines vertes (>0 ml, >0.2 ml, >0.5 ml), jautrumas, specifiškumas, PPV ir NPV "prostatos daliai" [51] atitinkamai buvo: 20.7%, 78.2%, 17.4%, 81.6%, ir 20.7%, 82%, 20.3%, 82.3%, ir 12.1%, 94.6%, 33.3%, 82.6%. Be to, prostatos vėžio nustatymo dažnis "pacientui" ir/ arba "prostatos daliai" buvo nurodytas visuose tyrimuose, įtrauktuose į "Technologija, skirta stebėsenai" grupę ir varijavo nuo 12.6% iki 67.7%; beje, referencinio standarto prostatos vėžio nustatymo dažnis kinta priklausomai nuo biopsijos tipo.

Jautrumas, specifiškumas, PPV ir NPV vertės buvo nurodytos visuose penkiuose "Technologija, skirta lokalizacijai nustatyti" grupės tyrimuose, tačiau keturiuose [44,54,90,91] šios vertės nurodytos atsižvelgiant į slenkstines vertes (≥1ml, <0.2ml, ≥0.2ml, ≥0.5ml). Kai PHS signalo slenkstinė vertė yra ≥0.1ml [91], jautrumas ir specifiškumas "pacientui" yra 60% ir 66%; kai signalo slenkstinė vertė yra <0.2ml [54] atitinkamai 48% ir 84%. Beje, kai PHS signalo slenkstinė vertė yra ≥0.2ml [44,90] jautrumas ir specifiškumas "prostatos daliai" varijuoja atitinkamai tarp 63–90% ir 53–72%; o kai PHS signalo slenkstinė vertė yra ≥0.5ml [44,90] atitinkamai 37–90% ir 70–71%. PPV ir NPV intervalai "pacientui" [54] atitinkamai buvo 34% ir 91%; "prostatos daliai" šios vertės pateiktos atsižvelgiant į PHS signalo slenkstines vertes (≥0.2ml, ≥0.5ml) [44]: PPV buvo 83–84%, o NPV – 82–80%. Papildomai, vienas tyrimas [91] palygino PHS aptikto naviko tūrį (1.38 cm^3, intervalas 0.1–9.3) ir histologiškai aptikto naviko tūrį (2.24 cm^3, intervalas 0.22–11.7). Beje, vienas tyrimas [78] palygino PHS ir mpMRI rezultatus: atitinkamai jautrumas 46.2% ir 52.6%, specifiškumas 74.1% ir 96.5%, PPV – 45% ir 87.2%, NPV – 75% ir 81.6%. Taip pat PHS parodė reikšmingai mažesnį diagnostinio tikslumo lygį negu mpMRI (65.3% vs. 82.7%).

Nepageidaujami įvykiai ir atsitiktiniai radiniai “Technologija, skirta stebėsenai” grupėje buvo nurodyti 3 tyrimuose [36,39,40] (n=172), tačiau “Technologija, skirta lokalizacijai nustatyti” grupėje ši informacija nebuvo pateikta. Klaidingai teigiamos/ neigiamos reikšmės buvo nurodytos 4 tyrimuose [36,40,86,87] (iš 6 tyrimų) “Technologija, skirta stebėsenai” grupėje.

Nė viename tyrime nebuvo informacijos apie gyvenimo kokybę, paciento užtikrintumą, dėl tyrimo rezultatų (pacientas jaučiasi saugus, kai tyrimo rezultatai rodo, jog jis neserga vėžiu) ir ligai specifinį mirštamumą/ ligai specifinį sergamumą. Taip pat, informacija apie terapinį poveikį ir pacientų būklės valdymą tyrimuose nebuvo pateikta dėl stebėjimo laiko nebuvimo.

SUMMARY OF THE HISTOSCANNING™ TECHNOLOGY FOR PROSTATE CANCER

Target condition

Prostate cancer, also known as carcinoma of the prostate, is the development of cancer in the prostate, a gland in the male reproductive system. However, natural course of 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. (**A0002; A0004**)

There are many risk factors which have been implicated in the development of PCa (e.g. age, genetic conditions, endogenous hormones, medical conditions); however, smoking, obesity, tall height, lack of exercise and a sedentary lifestyle, high calcium intake, African-American race, family history, Agent Orange exposure and lack of vegetables in diet, are linked to be a risk factors for aggressive PCa. (**A0003; A0006**)

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. (**A0005; A0006**)

Target population

PCa is the fourth most common cancer worldwide in both sexes combined and the second most common cancer in men. An estimated 1.1 million men worldwide were newly diagnosed with PCa in 2012, accounting for 15% of all cancers diagnosed in men, with almost 70% of the cases occurring in more developed regions. Furthermore, the number of new PCa cases diagnosed annually is predicted to increase to 1.7 million worldwide by 2030, possibly leading to around 0.5 million deaths yearly due to this disease. PCa is the most common cancer in Lithuanian men, nearly 3.000 men are newly diagnosed with PCa and about 500 deaths occur from this disease annually. (**A0023**)

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. However, 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. (**A0007**)

Until 2013 March over 1.500 patients have been enrolled in clinical studies on PHS and more than 16.000 patients have benefited already from it in clinical practice, according to the information from manufacturers. (**A0011**)

Current management of the condition

The management of prostate cancer remains controversial because of its variable natural history, the diversity of available treatments and the lack of randomised controlled trials (RCTs) comparing the different treatment approaches. However, mostly PCa is first found during screening with a prostate specific antigen (PSA) blood test and/ or a digital rectal exam (DRE). However, PSA alone is not a specific test for PCa, as well as 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 PCa.

PHS is expected to provide an 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. (**A0001; A0024; A0025**)

Regulatory status

Prostate HistoScanning™ (PHS) is the commercially available transrectal ultrasound-based product of HistoScanning™, specifically conceived to detect suspicious areas in the prostate. HistoScanning™ is licensed by Health Canada (certificate number is 81234) since 2009 and CE marked under the European Medical Device Directive 93/42/EEC (as amended by 2007/47/EC Annex II) since 2008. However, Prostate HistoScanning™, available in Europe, supports the diagnosis and management of PCa; HistoScanning™ products for breast, ovaries, and thyroid are in development.

According to the distributor „Interlux“ the price of the PHS device (with BK Medical ultrasound scanner) in Lithuania is 260.000 €. (**A0021**)

Features of the technology

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. **(B0001)**

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. However, the evaluation of prostate gland so far is mainly focused on tumor localization and staging in patients with PCa. **(B0002; B0001)**

The new biopsy software tool prostate HistoScanning™ TT, or True Targeting, was introduced in 2014. Prostate HistoScanning™ TT uses an additional specialized software that allows to perform the target biopsy with PHS in situ and provides real-time guidance. During the biopsy procedure, the needle is automatically recorded at the time the core is taken, allowing the results to be quickly and easily reviewed. The data and ultrasound images are stored for later retrieval and review. **(B0002; B0003)**

Prostate HistoScanning™ can be easily integrated in the existing clinical pathway; procedure can be performed in outpatient settings where most PCa are diagnosed or in day treatment unit (if biopsy is planned). **(B0004)**

Investments and tools required to use the technology

Procedure with Histoscanning™ requires specific equipment – ultrasound scanner, 3D-ultrasound probe magnetically attached to a rotation holder and PHS workstation with special software. The PHS workstation is currently approved for use only with BK Medical (Peabody, MA, USA) ultrasound scanners. Some disposable items for procedure are needed as well: condoms, ultrasound gel, endorectal lidocaine gel. Urologist has to wear special disposable gown, footwear, cap and gloves. Some additional equipment is required to perform the target biopsy: biopsy needle guide, biopsy gun and biopsy needle 18 G 25 cm. **(B0009)**

PHS is an operator-dependent ultrasound-based technology, so for optimal results data acquisition is the key point of the analysis. Therefore, the examiner needs to be familiar with

transrectal ultrasonography and the appropriate anatomy. It is estimated that approximately 80 cases of PHS need to be worked on in order to overcome the learning curve and improve results. **(B0013)**

Features of the comparator and the reference standard

Ultrasound examination of the prostate and surrounding structures is used in the diagnosis of PCa, benign prostatic hyperplasia, prostatitis, etc.; for the monitoring and treatment of PCa, abscesses, and benign prostatic hyperplasia; to estimate the size of the prostate and to guide the needle biopsies. 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. **(B0001; B0002)**

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. **(B0001)**

Prostate biopsies should be performed in a setting that is designated for the procedure and where resuscitation equipment is readily available (oxygen, arrest trolley, defibrillator, emergency drug pack and monitoring equipment). Also, these procedures should normally be performed under local anaesthesia. **(B0004; B0009)**

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.) **(B0003)**

Although MRI may ultimately show the most promise diagnostically, ultrasound-based technologies, such as PHS, elastography and etc. are emerging and being investigated as well. **(B0003)**

Patient 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. **(C0008)**

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. **(C0008)**

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. **(C0006)**

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. **(C0006)**

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. **(C0002; C0004; C0007; C0060)**

Test accuracy

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%. (**D1001; D1002; D1003**)

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. (**D1005; D1006; D1007**).

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. (**D0026; D1001**)

Change in management

Unfortunately, studies represented contraversial 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. (**D0021; D0023; D0026**)

However, none of the studies provided information about mortality, morbidity, quality of life and patient satisfaction. (**D0020; D0032; D1019; D0029**)

Limitations

The available evidence has some limitations. First, all evidence is from uncontrolled case series; no definite conclusion can be drawn due to lack of comparative studies. Second, different

reference standarts is used among the studies; no proper comparison can be made. Third, the patient selection had high risk of bias is some studies; the quality of reference standard aspect in some studies was uncertain as well.

Scope

PICO for Prostate HistoScanning™	
Population	Men over 50 years old with: • suspected malignant neoplasm of prostate (for screening); • diagnosed malignant neoplasm of prostate (for staging). MeSH: Prostatic Neoplasms **(**C04.588.945.440.770, C12.294.260.750, C12.294.565.625, C12.758.409.750**).**
Intervencija	Prostate HistoScanning™ (PHS).
Comparison	• Transrectal ultrasound (TRUS) guided biopsies; • Imaging technologies. *MeSH terms: Ultrasonography [E01.370.350.850]; Ultrasonography, Interventional [E01.370.350.850.855]; Image-Guided Biopsy (E01.370.225.500.384.100.370, E01.370.225.998.054.370, E01.370.388.100.370, E04.074.370, E05.200.500.384.100.370, E05.200.998.054.370, E05.242.384.100.370)).*
Outcomes	
Efficacy	6) Diagnostic accuracy (Specificity, Sensitivity) – surrogates 7) Therapeutic impact (patient management: initiation or avoidance of invasive intervention) – surrogates 8) Disease specific-mortality, Disease specific-morbidity – patient relevant endpoints 9) QoL: fear/ worry; appeasement 10) Safeguarding
Safety	4) Adverse events (AE) 5) False negative/ false positive findings 6) Incidental findings
PICO research questions: 1) Is Prostate HistoScanning™ for the diagnosis of malignant neoplasm of prostate more effective and safer concerning diagnostic accuracy, therapeutic impact, quality of life, adverse events and incidental findings than comparative diagnostic procedures? 2) Is Prostate HistoScanning™ for the staging of malignant neoplasm of prostate more effective and safer concerning diagnostic accuracy, therapeutic impact, quality of life, adverse events and incidental findings than comparative diagnostic procedures?	

HEALTH PROBLEM AND CURRENT USE OF THE HISTOSCANNING™ TECHNOLOGY [1]

Target Condition

Prostate cancer (PCa), also known as carcinoma of the prostate, is the development of cancer in the prostate, a gland in the male reproductive system [2]. According to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) prostate cancer is defined as a Malignant neoplasm of prostate with code C61 [3].

Prostate cancer is typically staged according to the American Joint Committee on Cancer's tumor, node, metastasis (TNM) system. Approximately 75–90% of men with PCa have clinically localized PCa which is classified as stages T1 (non-palpable) and T2 (palpable) and is confined within the prostatic capsule. The likelihood of progression to invasive cancer is associated with the presence of more poorly differentiated cells and other histopathologic features [4]. There are many risk factors which have been implicated in the development of PCa (e.g. age, genetic conditions, endogenous hormones, medical conditions) [5]; however, smoking, obesity, tall height, lack of exercise and a sedentary lifestyle, high calcium intake, African-American race, family history, Agent Orange exposure and lack of vegetables in diet, are linked to be a risk factors for aggressive PCa [6].

The natural course of PCa is not fully understood: PCa can grow extremely slowly or fast, while in some patients tumor never progresses [7]. PCa starts out as a pre-cancerous condition (some changes in prostate gland cells). Prostatic cancerous cells develop into malignant tumors or masses, which then overwhelm surrounding tissues by invading their space and taking vital oxygen and nutrients. Cancer cells from these tumors can eventually invade remote organs via the bloodstream and the lymphatic system. Common metastatic locations where PCa cells may eventually be found include pelvic lymph nodes, bones, and rarely lungs, liver [8].

Very early PCa generally does not cause any symptoms; however, advanced PCa can cause frequent urination or a weaker flow of urine, but these symptoms can also be caused by benign prostate conditions [2]. In later stages PCa can cause difficulties urinating, blood in the urine, or pain in the pelvis, back or when urinating, and tiredness due to low levels of red blood cells [9].

Prostate cancer is the fourth most common cancer worldwide in both sexes combined and the second most common cancer in men. Furthermore, the number of new PCa cases diagnosed annually is predicted to increase to 1.7 million worldwide by 2030, possibly leading to around 0.5 million deaths yearly due to this disease [10]. Prostate cancer is the most common cancer in Lithuanian men, nearly 3.000 men are newly diagnosed with PCa and about 500 deaths occur from this disease annually [11]. In 2013 PCa morbidity was 17.266 cases (5.84 cases per 1.000 men) [12] and there were 523 death cases in 2014 [13].

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 [14]. According to the IHME (Institute of Health Metrics and Evaluation) data in 225 countries (in 2013) global prostate cancer DALYs in all ages were 3.788.750 years [15]. The mean direct costs in 2010 per patient for initial treatment annually were 3.698 € in Germany, 3.256 € in Spain, 3.682 € in the UK, 5.226 € in Italy and 5.851 € in France [16]. However, this does not include indirect costs, such as time and productivity lost through cancer-related illnesses, the impact of the physical and mental suffering of both patients and relatives during diagnosis and follow-up or end-of-life costs [17].

Target Population

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 [18]. However, 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 [19,20].

Utilisation of the Histoscanning™ Technology

Prostate HistoScanning™ (PHS) is the commercially available transrectal ultrasound-based product of HistoScanning™, specifically conceived to detect suspicious areas in the prostate. Because of its ability to identify, locate and assess the size of differentiated prostate tissue, this technology may guide clinical decisions throughout entire prostate cancer care [21]. Also, this technology has been tested in clinical trials aimed to distinguish benign from malignant tissue in the breast, ovaries and thyroid, but its widespread clinical use has not been adopted for these tissues; these options are in development [22].

Until 2013 March over 1.500 patients have been enrolled in clinical studies on PHS and more than 16.000 patients have been tested already from it in clinical practice, according to the information from manufacturers [21].

According to the distributor „Interlux“ the price of the PHS device (with BK Medical ultrasound scanner) in Lithuania is 260.000 €.

Current Management of the Condition

Mostly PCa is first found during screening with a prostate specific antigen (PSA) blood test and/ or a digital rectal exam (DRE). However, PSA alone is not a specific test for PCa (many false positive results), as well as 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 PCa [23,24]. The decision whether or not to have a prostate biopsy should be made in the light of DRE findings, prostate size, ethnicity, age, comorbidities, family history, patient values and history of previous biopsy, as well as on the PSA level [24]. A prostate biopsy should be carried out using transrectal ultrasound (TRUS) and multiparametric magnetic resonanse imaging (mpMRI) should be considered for men with a negative TRUS 10–12 core biopsy to determine whether another biopsy is needed [14]. In case that multiparametric MRI is negative, another biopsy should not be offered [14].

The management of PCa remains controversial because of its variable natural history, the diversity of available treatments and the lack of randomised controlled trials (RCTs) comparing the different treatment approaches [25]. PHS is claimed to provide an additional and meaningful information for better management of PCa patients by providing visual reassurance for decision making [26]. 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 [27].

For the long time for the treatment of PCa standard options like passive treatment (watchful waiting, active surveillance), surgical treatment (radical prostatectomy, transurethral resection of the prostate), radiotherapy (external-beam radiation therapy, brachytherapy) and hormone therapy or chemotherapy was applied [9,14,28].

PCa treatment could have a significant impact in man’s life and cause physical problems such as erectile dysfunction and urinary incontinence, bowel changes, fatigue, pain, hot flashes, body image changes, distant metastasis, lower back pain, weight loss, haematuria, anemia, inability to walk and force lifestyle changes [29]. Failures to address physical and psychosocial problems can result in suffering for both – the patient and their family, and potentially affect the course of the disease [30].

Regulatory Status

HistoScanning™ is a trademark of Advanced Medical Diagnostics s.a. (Waterloo, Belgium); R-Action Distribution (R-Action SAS, Meudon, France) has exclusive worldwide distribution rights for the HistoScanning™ technology that it supports through its internal sales organisation and a distributor network [31,32].

HistoScanning™ is licensed by Health Canada (certificate number is 81234) since 2009 and CE marked under the European Medical Device Directive 93/42/EEC (as amended by 2007/47/EC Annex II) since 2008 [33]. However, Prostate HistoScanning™, available in Europe, supports the diagnosis and management of PCa; HistoScanning™ products for breast, ovaries, and thyroid are in development [26,34].

Discussion

Prostate cancer, also known as carcinoma of the prostate, is the development of cancer in the prostate, a gland in the male reproductive system [2]. PCa often has no early symptoms, but most patients with PCa are diagnosed at an early stage and many diagnoses are made in asymptomatic men [35]. The management of PCa remains controversial because of its variable natural history [25].

Prostate HistoScanning™ is a relatively new ultrasound-based diagnostic method with results in the detection of PCa [36,37]. PHS can detect specific changes in the morphology of the tissue by extracting and quantifying statistical features from back-scattered ultrasonographic data, which might further allow differentiation between benign and malignant tissue [38]. HistoScanning™ technology is CE marked under the European Medical Device Directive (93/42/EEC) and licensed by Health Canada (certificate number is 81234) since 2009; however, it is currently not yet available for commercial use in the USA [31].

DESCRIPTION AND TECHNICAL CHARACTERISTICS OF THE HISTOSCANNING™ TECHNOLOGY [2]

Features of the HistoScanning™ technology

HistoScanning™ is a novel non-invasive imaging modality that analyzes the data acquired from 3D-*transrectal ultrasound (3D*-TRUS) using computer aided application [21,39,40]. HistoScanning™ was developed by privately held Belgium company Advanced Medical Diagnostics (Waterloo, Belgium) and commercially launched in November 2008 [41,42,43].

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 [38,44]. PHS may guide clinical decisions throughout entire prostate cancer care: detection and diagnosis, treatment planning, treatment guidance and post-treatment monitoring. However, the evaluation of prostate gland so far is mainly focused on tumor localization and staging in patients with PCa [21,45].

PHS procedure requires a specific system equipped with a 3D-ultrasound probe and software to analyze the raw data [45]. Data acquisition is first carried out by holding the probe holder in a steady position, with the patient on his side or in the lithotomy position [46]. During acquisition the holder rotates so that the attached probe (operating at 9 MHz) scans the prostate with a sagittal view from right to left by 179°, scanning 1 frame per 0.2°; ultrasound produces a continuous stream of echoes emanating from the tissue‘s underlying microscopic features, known as ultrasound backscatter [40,47]. All these frames are joined together to create a 3D image of the prostate. HistoScanning™ analysis requires the operator first to define the contour of the prostate, along with the apex and base points, and left and right lateral edges of the prostate using a semi-automated tool. During a manual modification, the operator may erase areas on the PHS analysis, which are not of interest, e.g., the urethra [37]. PHS applies three characterisation algorithms that are embedded within the machine software data. These algorithms have been developed and best fitted to detect the changes in the raw ultrasound signals that are caused by alterations in tissue properties induced by cancerous cells and their surrounding stroma within the prostate. Once applied to regions of interest within the prostate the algorithms give a prediction as to the presence or absence of cancer [46,47,48].

The information about „suspicious“ areas is displayed as a coloured (red) overlay in the 3D model of the prostate [40]. It is possible that part of the combined volume may contain lower quality data, e.g., due to shadows cast by calcifications. In this event, a second algorithm is applied that identifies the low quality data and displays it as purple overlays. The minimum volume of tissue that is individually characterized is 0.04 ml [46,47].

PHS is not a real-time imaging because the data acquisition and processing usually take a few minutes, and the results are viewed on the screen afterward. Data processing usually takes more time with the large prostates [46].

Prostate HistoScanning™ can be easily integrated in the existing clinical pathway; procedure can be performed in outpatient settings where most PCa are diagnosed or in day treatment unit (if biopsy is planned) [21,49,50]. Therefore, the actual steps in using PHS are threefold [43,51]:

- motorized transrectal ultrasound generates a complete scan of the prostate;
- the physician defines the region of interest within the PHS embedded software;
- the computerized PHS analyses provide color-coded areas suspicious for PCa, as well as the corresponding tumor volume in non-real-time fashion.

The new biopsy software tool prostate **HistoScanning™ TT**, or True Targeting, was introduced in 2014 [52]. It uses the results of PHS analysis to target suspicious tissues for biopsy. The software calculates and displays the optimal needle-track through the tissue to the biopsy target and computes the required position of the ultrasound probe, fitted with needle guide, to follow the track. In addition, 2D sagittal and transverse digital overlays of the prostate boundary are calculated so that the sample core intersects with the selected target. During the biopsy procedure, the digital overlays of the prostate boundary are displayed together with the real-time grey-scale ultrasound images. This allows the operator to position the probe so that the shape and size of the prostate is aligned with the digital overlays that were calculated during biopsy planning.

In addition, PHS TT software provides feedback to the operator on how to rotate (roll), tilt (pitch), and translate (depth of penetration) the probe using the sagittal and transverse image views. During the biopsy procedure, the needle is automatically recorded at the time the core is taken, allowing the results to be quickly and easily reviewed. The data and ultrasound images are stored for later retrieval and review [47,53].

What is the claimed benefit of the Prostate HistoScanning™ technology in relation to the comparators [36,39,43,47,54,55,56,57]**?**

- visualizes cancerous lesions and provides anatomic pictures useful for surgery planning (e. g., nerve-sparing radical prostatectomy);
- as a consequence of the visualization, side-specific prediction is possible;
- shows a potential role in selecting patients in whom prostate biopsies are necessary;
- helps to reduce local tissue trauma, patient discomfort, and the surgical effort through the smaller number of targeted biopsies required;
- procedure is accessible – can be performed by urologist himself, at any time he chooses;
- procedure is patient-friendly – it lasts for a short time and does not require anesthesia;
- procedure is accurate – compared to a traditional B-mode image, a raw ultrasound frame used in PHS analysis contains approximately 30 times more data;
- the lacking ability to perform a biopsy at real-time is not a problem anymore; Prostate HistoScanning™ TT uses an additional specialized software that allows to perform the target biopsy with PHS in situ and provides real-time guidance.

Features of the comparator and the reference standard

Comparator of PHS for screening

Transrectal ultrasound. In the United States, the first of several reports of the use of transrectal ultrasound for evaluation of the prostate was published in 1973 by William King, under the guidance of William H. Boyce [58]. The development in understanding of prostate anatomy and the introduction of PSA into clinical practice were complimentary factors in the rapid uptake of high-frequency TRUS into standard urological practice in the 1980s [59].

Since then, ultrasound examination of the prostate and surrounding structures is used in the diagnosis of PCa, benign prostatic hyperplasia, prostatitis, prostatic abscesses, congenital anomalies, male infertility; for the monitoring and treatment of PCa, abscesses, and benign prostatic hyperplasia; to estimate the size of the prostate and to guide the needle biopsies. It is most commonly performed in the out-patient setting and is both affordable and accessible [46,60,61,62].

The procedure begins when lidocaine is infiltrated into the periprostatic area. The patient is positioned in lithotomy, in knee-elbow position or in either the right or left lateral decubitus position (lying on left side). This allows for easier insertion of the rectal probe containing multiple acoustic

transducers that send pulses of sound into the tissues to be examined [58,63,64]. Whenever a sound wave encounters a boundary between different tissues, part of the sound wave is reflected back to the probe and is detected as an echo. The time it takes for this echo to travel back to the probe is measured and used to calculate the depth of the tissue interface causing the echo. Larger echoes result from greater differences between the density of two types of tissue. The distance and intensity of each echo are used to generate a two-dimensional image. The prostate should be imaged in its entirety in at least 2 orthogonal planes, sagittal and axial or longitudinal and coronal, from the apex to the base of the gland. An estimated volume is determined from measurements in 3 orthogonal planes (volume = length*height*width *0.52) [58,60].

The frequencies used for ultrasonographic imaging fall in the range of 1–18 MHz. Generally, a 5.0- to 9.0-MHz transducer is used for prostate ultrasonography, with most institutions employing between a 6.0- to 7.5-MHz transducer; this can produce images in both sagittal and axial planes. Both side-fire and end-fire transducers may be used. The procedure usually takes about 15–30 minutes [58,60,61,64].

Although gray-scale TRUS does not detect PCa with adequate reliability and, therefore, cannot replace systematic biopsies, it is the current standard method for guiding prostate biopsies. New sonographic modalities such as sonoelastography, color Doppler, power Doppler, imaging contrast-enhanced ultrasound or computerised ultrasound are being investigated. However, there is not currently enough evidence for their routine use [45,59,63,65,66].

Reference standard of PHS for screening

Biopsies. All doctors know that the reference standard in cancer diagnosis and cancer characterization is histology, and therefore no doctor will consider that an imaging technique is equivalent to the Standard [38]. In the case of elevated PSA or abnormal digital rectal examination PCa diagnosis is usually established by biopsy. Age, potential comorbidity and therapeutic consequences should also be considered and discussed beforehand [45,65]. Traditional prostate biopsies can be classified based on the approaches adopted in the procedure. There are 3 types namely [67,68]:

- **Transrectal** – **biopsy** performed using a probe passed through anus into the rectum;
- **Transurethral** – **biopsy** performed using a probe passed through the urethra;
- **Transperineal** – **biopsy** done through the skin in front of the anus.

A transrectal approach is used for most prostate biopsies, although some urologists prefer a perineal approach. Therefore, the ultrasound-guided biopsy is the standard of care and **transrectal ultrasound-guided biopsy** is now the standard diagnostic technique in patients with suspected PCa [58,65]. Furthermore, although the theoretical risk of infection is greater with a transrectal biopsy when compared to a transrectal ultrasound-guided transperineal biopsy, a recent meta-analysis demonstrated no difference in the diagnostic accuracy or complication rate between the two approaches [58].

TRUS-guided biopsy is a technique used by radiologists/ urologists for obtaining prostate tissue cores. An ultrasound probe is inserted into the rectum to aid needle guidance, enabling accurate biopsies to be taken. The needle removes a cylinder of tissue, usually about 1/2-inch long and 1/16-inch across [69,70]. The systematic sextant biopsy has been the standard procedure used for many years [71]. However, the 12-core biopsy scheme (sextant template plus laterally directed sampling from each sextant template) has become the most widely accepted method in recent years, with some authors adding a core from the extreme apex on each side based on the observation that this is the most common site where cancer is missed during initial biopsy [72]. 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 [65].

Prostate biopsies should be performed in a setting that is designated for the procedure and where resuscitation equipment is readily available (oxygen, arrest trolley, defibrillator, emergency drug pack and monitoring equipment). Also, these procedures should normally be performed under local anaesthesia [59,65,73]. The majority of patients tolerate the procedure with low levels of discomfort and experience minimal side effects including haematuria, haematospermia, blood in the stools, and dysuria [59].

Targeted biopsies guided by imaging are gaining interest as a diagnostic procedure for PCa detection. Most of the procedures are based on multiparametric MRI [74].

Cognitive MRI-guided biopsy. Prostate biopsies can also be performed utilizing information from MR imaging (MRI), which provides more detailed images of the prostate than is possible with ultrasound. MR imaging is being investigated and used for detection and localization of PCa in patients in whom the presence of PCa is suspected despite a negative result at TRUS–guided biopsy [75]. Cognitive fusion refers to the operator viewing lesions on MRI, allowing to attempt biopsy of the visualized location from memory using real-time US [64]. Disadvantages: the images are not real time and a certain amount of educated guessing goes into the procedure; increased cost of procedure; lack of availability [76].

MRI-US fusion biopsy. MRI coregistration with ultrasound, commonly referred to as MRI-US fusion, has been an area of increasing research and is a potential replacement for systematic biopsy [64]. MRI-US fusion allows MRI data to be used to obtain biopsies under ultrasound guidance.

The MRI of the prostate, which is performed beforehand and stored in the device, is fused with real-time ultrasound using the detection software to pinpoint specific areas, allowing the target(s), previously delineated by a radiologist, to be brought into the aiming mechanism of the ultrasound machine. The fusion results in creation of a 3D reconstruction of the prostate, and on the reconstructed model, the aiming and tracking of biopsy sites occurs [77]. The disadvantage of this method is that it is indirect, involves use of an additional device and requires specialized operator training [77].

Although MRI may ultimately show the most promise diagnostically, ultrasound-based technologies, such as PHS, elastography and etc. are emerging and being investigated as well [58,74].

Comparator of PHS for staging

mpMRI technology. Multiparametric magnetic resonance imaging of the prostate has been shown to improve the specificity and accuracy of PCa detection and localization over T2-weighted (T2WI) MRI alone, through the use of functional sequences assessing qualitative tissue characteristics; mpMRI includes high-resolution T2WI and at least two functional MRI techniques (diffusion-weighted imaging (DWI) and dynamic contrast-enhanced imaging (DCE)) [78,79]. In addition to improving accuracy for detection and localization, mpMRI has shown promise in disease risk stratification, and it has recently been employed in the guidance of prostate biopsy, risk assessment; therefore, it provides a more accurate therapeutic option to the patient [78,79].

Reference standard of PHS for staging

Radical prostatectomy (RP) whole-mount step sectioned histology. The goal of RP is complete surgical removal of the entire prostate and its investing fascia, as well as the seminal vesicles [80]. One of the main issues for pathologists is the identification in RP specimens of those prognostic factors that could predict accurately patient outcomes [81]. RP specimens may be processed as either whole-mount or standard sections [82]. Whole-mount sectioning includes specimen weighing, measuring, fixation in buffered formalin for at least 24 hours, and inking, along with separate removal of the apex and the base [65]. The prostate gland is sectioned contiguously in 3–5 mm sections from base to apex in planes roughly perpendicular to the rectal wall and urethra. All

sections are mounted on glass slides and frequently require the use of slides larger than those typically employed in routine histopathology. Tumor maps are duplicated for each slide and show the great advantage of displaying the architecture of the prostate, critical features including locations of extraprostatic extension (EPE), positive margins and tumor foci; further, it is easier to compare the pathological findings with those obtained from DRE, TRUS and prostate biopsies [82,83]. However, for routine sectioning, the advantages of whole mounts do not outweigh their disadvantages [65].

Investments and tools required to use the HistoScanning™ technology

Procedure with Histoscanning™ requires specific equipment – ultrasound scanner, 3D-ultrasound probe magnetically attached to a rotation holder and PHS workstation with special software. The PHS workstation is currently approved for use only with BK Medical (Peabody, MA, USA) ultrasound scanners. Some disposable items for procedure are needed as well: condoms, ultrasound gel, endorectal lidocaine gel. Urologist has to wear special disposable gown, footwear, cap and gloves.

Some additional equipment is required to perform the target biopsy: biopsy needle guide, biopsy gun and biopsy needle 18 G 25 cm [45,46,49,84].

Training and information needed to use the HistoScanning™ technology

PHS is an operator-dependent ultrasound-based technology, so for optimal results data acquisition is the key point of the analysis. Therefore, the examiner needs to be familiar with transrectal ultrasonography and the appropriate anatomy. At least Level 1 competency should be obtained by anyone performing unsupervised diagnostic imaging. Practical training for Level 1 should involve at least one ultrasound list per week over a period of 3–6 months, with approximately 5–10 examinations performed by the trainee (under supervision) per session. A minimum of 250 examinations should be undertaken. Practical training for Level 2 competency should involve at least one year of experience at Level 1 with a minimum of one session per week and a further 600 examinations should have been undertaken. To acquire Level 3 competency practitioners have to spend a significant part of their time undertaking ultrasound examinations, teaching, research and development. Only in this level practitioners can perform specialised ultrasound examinations or advanced ultrasound-guided invasive procedures [46,85].

After this, it is estimated that approximately 80 cases of PHS need to be worked on in order to overcome the learning curve and improve results [46].

Discussion

Prostate cancer is a worldwide major health issue and one of the most significant pathologies in the field of urology [35]. Despite recent advances in PCa detection and treatment, PCa continues to be one of the leading causes of cancer-related mortality in men. Thus, accurate diagnosis and appropriate treatment are crucial [45].

The primary rationale for screening with PSA testing is to identify high-grade, localized prostate cancer at earlier, asymptomatic stages, in order to enhance the chances of a cure [4]. However, PSA alone is not a specific test for prostate cancer; DRE is also not a very sensitive and reproducible investigation and has a low positive predictive value (PPV), but DRE in combination with PSA test should be done in patients with clinical suspicion of PCa [23,24].

Nevertheless, TRUS imaging and systematic TRUS-guided biopsies are gold standard procedures for diagnostics and detection of PCa. However, the power to identify – and in particular

to exclude – cancer reliably is limited due to low PCa specificity of grey scale ultrasound patterns [40]. Another imaging method for detecting PCa is MRI; although MRI may ultimately show the most promise diagnostically, ultrasound-based technology would be much less expensive and easier to use in real-time [50,58]. This is why interest in using reliable imaging for diagnosis, guiding biopsies or clinical staging still remains a diagnostic challenge and is increasing [37,78].

Prostate HistoScanning™ is a novel non-invasive imaging modality that analyzes the data acquired from 3D-transrectal ultrasound using computer aided application [21,39]. Also, the new biopsy software tool prostate HistoScanning™ TT, or True Targeting, was introduced in 2014; now even the lacking ability to perform a biopsy at real-time is not a problem, because this new software allows to perform it [52].

SAFETY [3]

PHS for SCREENING

Adverse events related to the Prostate HistoScanning™ technology were reported very poorly. Only one case serie (of 6) [39] reported some adverse events such as acute retention of urine (5/43 pts., 11.6%), which required short term urethral catheterization and alpha blockers; mild prostatitis (3/43 pts., 7%), which was treated with antibiotics. Mild prostatitis was diagnosed to the 3 patients out of 5 who had acute retention of urine. 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 [39].

Two case series (of 6) [36,40] 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%). However, in one study [36] it is unclear if all incidental findings were detected by PHS instead of some findings detected by standard systematic 12-core TRUS guided biopsy. Moreover, these findings were confirmed only after histopathological examination and it means that PHS cannot differentiate between cancerous tissue and incidental findings accurately; incidental findings might cause higher rates of false positive results.

False positive/ negative findings were reported in 4 case series (of 6) [36,40,86,87]. Also, these findings were distributed according to subgroups – 'per patient' and 'per section'. Two case series (n=81) [86,87] reported 0% false positive findings and one case serie (n=32) [36] reported 62.5% of false positive findings in 'per patient' subgroup. In the same case series (n=113) [36], false negative findings varied from 15.6% to 42.1% in 'per patient' subgroup.

False positive findings were reported in four case series (n=210) [36,40,86,87] and varied from 14.6% to 74.2% in 'per section' subgroup. However, one study (n=97) [40,86,87] reported only false positive findings and only in 'per section' subgroup. False negative findings were reported in three case series (n=113) [36,86,87] and varied from 0% to 12.3% in 'per section' subgroup. Two case series [86,87] were using 2.1 software version of PHS during procedures, one study [40] used 2.3 software version of PHS and one study [36] did not report this data.

Results show that in 'per patient' subgroup only one study [36] reported false positive findings (62.5%) and false negative findings were reported in all studies [36,86,87]. However, results in 'per section' subgroup show higher rates in false positive findings in all studies [36,40,86,87] when compared with false negative findings. Moreover, it is of note that one case serie [36] identified HistoScanning™ signal suspicious for PCa to be true positive, even in cases with exclusive prostatic intraepithelial neoplasia (PIN).

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 [88,89].

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.

PHS for STAGING

Adverse events and incidental findings related to the Prostate HistoScanning™ technology were not reported in four case series [44,54,90,91]. Yet, one study [78] 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 not reported in the studies.

Discussion

The contemporary methods for detection of prostate cancer have been largely unchanged since the inception of transrectal ultrasound guidance [78]. Men with elevated PSA levels or abnormal digital rectal examination results are subjected to a systematic sampling of the prostate under transrectal ultrasound guidance, typically in 10 to 12 locations. Although this method of sampling has been derived to maximize the cancer detection rate, it remains a process that is 'blind' to the location of the tumors [50]. The risk of sampling errors can result in both – the underdetection of potentially lethal PCa, or, in some cases, in misclassification of higher risk cancer as low risk [78]. Also, it involves the risk of complications and false negative results. Reliable imaging tools might decrease the need for repeat biopsies and reduce the high rate of reclassification within active surveillance programs. Additionally, such a tool might help to reduce unnecessary biopsies and subsequently related complications as well as costs [78,92].

Prostate HistoScanning™ represents a modern imaging tool for tissue characterization which could be a valuable tool in the hands of experienced TRUS examiner [37,43,92]. However, it is difficult to evaluate safety aspect because adverse events following PHS and targeted biopsies are not specifically reported in literature [39]. Nevertheless, 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 [39,48].

The ability of PHS to image and analyse anterior tissue in large prostate glands, or those with extensive calcification is another issue. It became apparent that attempts to compress larger prostates with ultrasonography probe leads to distortion of the gland which creates false red PHS signals within the gland. The PHS system is not accurate in prostate volumes greater than 50 grams [39,93]. High rate of false positive findings is the major drawback of PHS and was documented in the vast majority of biopsy-related studies, as well as in the studies focusing on prediction of disease stage at radical prostatectomy [43,93]. Many factors may be responsible for this discrepancy. Macek et al. showed that the overall performance of PHS was affected by rectal distance, bladder fullness, index cancer volume, total cancer volume and the sector location [39].

Sivaraman et al. observed that PHS detects any altered echo texture within prostate. Also, PHS performance was affected by prior TURP/ biopsy which appears to produce false positive signals as well and hence reduce the accuracy of target biopsies. The microarchitectural disturbances can be produced by prostatitis, prostate biopsy, prior prostate surgery and PCa. Attempts should be made to improve the ability of PHS to effectively differentiate cancer from other textural alterations [39].

Taken together, it is highly debatable whether PHS might improve the detection of PCa. Consequently, existing guidelines either question its value, or do not mention HistoScanning™ at all [43].

It is more important than ever to look for ways to detect and locate the cancer before subjecting patients to more or less invasive procedures (e.g., radical prostatectomy) [56]. Multiparametric magnetic resonance imaging is the most evaluated conventional imaging modality in this respect. However, it is time consuming and expensive; its accessibility to patients is limited and even if a patient is exposed to mpMRI, the image interpretation is frequently not conclusive. As such, having additional TRUS imaging-based information could conceivably be of value because of lower costs, better accesibility, quick and easy performance [22,49,58].

CLINICAL EFFECTIVENESS [4]

PHS for SCREENING

Test accuracy

PCa detection rate of Prostate HistoScanning™ was reported in all studies and varied from 12.3% to 67.7% in ‚per patient' subgroup, except one study [36] where results of PCa detection rate were not reported. Also, one study [40] reported both PHS approaches in ‚per patient' subgroup – transperineal and transrectal; however, no significant differences were found between these approaches for prostatic biopsy – 64.5% and 67.7%, respectively. However, PCa detection rates in ‚per section' group were reported only in one case serie [40] (248 cores) in different approaches: transperineal PHS reported 13% detection rate of PCa, transrectal PHS – 11%, and TRUS – 5%.

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 [36,39,86] was 44–78.1%, by transperineal template prostate biopsy [87] – 54.4%, by standard systematic 10- to 12-core TRUS-guided biopsy [51] – 50% and by systematic 14-core TRUS-guided biopsy [40] – 70.1%.

All in all, the results of two studies [39,86] may be comparable because of the same index (transretal PHS) and reference standard (standard systematic 12-core TRUS-guided biopsy) tests. PCa detection rates of index and reference standard tests were 33.3% and 62.5% in one study [86] (n=24, median age – 68 yrs., median PSA level – 9.25 ng/ml), and 26% and 44% in other study [39] (n=42, mean age – 63.7 yrs., mean PSA level – 16.06 ng/ml), respectively. However, PHS TT was used in the latter study [39] and the threshold value of ≥0.2 ml was set; for a comparison, PHS software 2.1 version was used in other study [86] and any threshold value was determined.

PHS performance for detection of PCa was reported in 4 studies (of 6) and had sensitivity of 22.6–53.3%, and specificity of 9–100% in 'per patient' subgroup [36,86,87].

However, sensitivity and specificity of PHS were 48.1–100% and 5.9–57.5% in 'per section' subgroup [36,86,87], respectively. Moreover, one study [51] reported sensitivity and specificity in 'per section' subgroup (319 octants were analysed of 320) according to the threshold values (>0 ml, >0.2 ml, >0.5 ml): 20.7%, 20.7%, 12.1% and 78.2%, 82.0%, 94.6%, respectively.

After all, the results of two studies [36,86] seem to be comparable because of the same index (transretal PHS) and reference standard (standard systematic 12-core TRUS-guided biopsy) tests; however, differences between populations of these studies are very substantial – one study [86] reported that all patients were suspected with PCa because of an elevated PSA level or abnormal DRE, and another study [36] reported that in 8 patients this was a first biopsy due to elevated PSA level or suspicious DRE, in 14 patients with previous negative biopsies this was a repeat biopsy due to elevated PSA level, and 10 patients had a previous diagnosis of prostate adenocarcinoma.

Positive and negative predictive values (PPV/ NPV) were reported in three studies [36,86,87]. PPV and NPV varied from 20% to 100% and from 28.6% to 56.3% in 'per patient' subgroup, respectively. The lowest values of PPV and NPV were in diversed population (8 patients with first biopsy, 14 – repeated biopsy, 10 – diagnosed PCa) [36] – 20% and 28.6%, respectively.

Also, PPV/ NPV were reported in 'per section' subgroup – 26–51.4% and 78.1–100%, respectively; however, the results cannot be compared due to a different type of biopsies and number of biopsy cores taken (varies between 144 and 342 cores).

However, none of the studies in "PHS for screening" group provided information about mortality, morbidity, quality of life (QoL), patient satisfaction and changes of decisions in PCa management.

PHS for STAGING

Test accuracy

Sensitivity and specificity were reported in all 4 studies; however, results were distributed according to subgroups ('per patient' [54,91] and 'per section' [44,90]) and threshold values (≥0.1 ml [91], ≥0.2 ml [44,54,90], and ≥0.5 ml [44,54,90]).

PHS performance for detection of PCa lesions ≥0.1 ml [91] had sensitivity of 60%, and specificity of 66%. However, sensitivity and specificity of PHS for detecting tumor foci ≥0.2 ml in volume were 63–90% and 53–72% in 'per section' subgroup [44,54,90], respectively. PHS showed sensitivity of 37–90% and specificity of 70–71% for the localization of lesions ≥0.5 ml. Furthermore, sensitivity and specificity of PHS volume <0.2ml for performing a nerve sparing radical prostatectomy [54] were 48% and 84%, respectively.

However, one study [78] 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 [78].

PPV/ NPV were reported in two studines [44,54]: in 'per patient' subgroup were reported in one study [54]: 34% and 91%, respectively; in 'per section' subgroup these values were reported according to the PHS signal volume cutoffs (≥0.2 ml, ≥0.5 ml) [44]: PPV were 83–84% and NPV were 82–80%, respectively. PPV and NPV are influenced by the prevalence of disease in the population that is being tested. In that case, wide range of PPV might be due to inclusion of the patients – the study with PPV of 83–84% [44] included only selected and eligible for the analysis patients, and study with PPV of 34% [54] included all consecutive patients.

Change in management

One study [91] compared tumor volume by PHS (1.38 cm^3, range 0.1–9.3) and by histology (2.24 cm^3, range 0.22–11.7). However, another study [54] showed that preoperative imaging method that can accurately predict the probability of a negative surgical margin: PHS analysis (with 93% probability of having a negative surgical margin in the frozen section) could predict whether a nerve sparing procedure may be securely performed.

However, none of the studies in "PHS for staging" group provided information about mortality, morbidity, QoL and patient satisfaction.

Discussion

12-core TRUS-guided biopsy is the current standard diagnostic technique in patients with suspected PCa [58]. However, detection rates are low: only in 67.8% of patients, PCa was detected histologically on samples obtained with repeat *ex-vivo* biopsies, using the same mapping postoperatively [94]. For a comparison, PHS PCa detection rate varied from 12.3% to 67.7%. Due to the low risk of bias, the results are robust.

Unfortunately, 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 [40,51]. However, even PHS detection rates 'per section' are superior to standard biopsy in the end this makes no difference for the patient.

The most ensured method to compare results of PHS from patients who were scheduled for a RP may be the whole-mount pathology. Even though whole-mounts of sections from RP specimens appear not to be superior to sections from standard blocks in detecting adverse pathological features, their use has the great advantage of displaying the architecture of the prostate and the identification and location of tumour nodules more clearly, with particular reference to the index tumour; further, it is easier to compare the pathological findings with those obtained from DRE, TRUS, and prostate biopsies [82].

Encouraging results have been reported by studies using multiparametric MRI for the detection of PCa in expert centers [95]. In the assessment included results suggest that mpMRI may be more accurate both in identifying individual PCa lesions and in localizing those lesions to a specific region of the prostate. Cancers missed by mpMRI were more often of lower grade and smaller than cancers missed by PHS [78]. However, issues of costs, availability of MRI and reproducibility of these results outside of expert centers inhibit widespread adoption for now [95].

Finally, HistoScanning™ has one thing in common with most of the other innovative imaging methods, such as multiparametric MRI, elastography, computerized TRUS or contrast-enhanced ultrasound: data are sparse, and multicentric studies to show the real impact of these methods on the patients are missing [96].

Future studies will need to address the following research questions: (1) In men at risk of PCa, could PHS be used as triage test before a prostate biopsy, to reduce the number of biopsies taken? (2) Could PHS replace the role of MRI in local staging of the prostate in men considering radical therapy? (3) Could PHS be used to target focal or regional therapy for men with prostate cancer? (4) Could PHS be used as a monitoring instrument for men on active surveillance [97]?

Currently, there is a nice pool of competing US based modalities – Prostate HistoScanning™, color Doppler US, power Doppler US, contrast-enhanced US, real-time elastography and shearwave elastography. Moreover, there are several technologies available that allow fusion of MR and real-time US image. Of course, we should not forget MRI with functional modifications such as dynamic contrast enhancement, diffusion weighted MRI, MR spectroscopy as parts of a multiparametric MRI. A comparison of various imaging modalities is difficult, however, because of the great variability of used primary end points (sensitivity, accuracy, positive/negative predictive values, etc.) and also the intended use (PCa detection vs. image guidance) [91].

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.

6. There is a lack of studies which could provide sufficient data and low risk of bias in patient selection and reference standard domains. The quality of diagnostic accuracy studies was assessed by QUADAS-2 checklist – 4 studies (of 11) had high risk of bias in patient selection domain and in other 3 studies risk of bias in reference standard domain was assessed as unclear because of insufficient data.

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. Prostate HistoScanning™ is not recommended in routine practice and cannot be reimbursed from Compulsory Health Insurance Fund budget considering the results of safety and clinical effectiveness. However, this technology currently is available in Lithuania if patient or health care institution pays for the procedure; data from such diagnostic procedures should be included in clinical trials.

REFERENCES

1. HTA Core Model Application for Diagnostic Technologies (2.1). Available from: http://meka.thl.fi/htacore/model/AE-tables-diagnostics-2.1.pdf
2. National Cancer Institute. Prostate Cancer. Overview. Available from: http://www.cancer.gov/types/prostate
3. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). WHO version, 2015. Available from: http://apps.who.int/classifications/icd10/browse/2015/en#/C61
4. Chou R, Dana T, Bougatsos C, Fu R, Blazina I, Gleitsmann K, Rugge JB. Treatments for Localized Prostate Cancer: Systematic Review to Update the 2002 U.S. Preventive Services Task Force Recommendation. 2011 Oct. Available from: http://www.ncbi.nlm.nih.gov/books/NBK82315/
5. Cancer reasearch UK. Prostate cancer risk factors. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/riskfactors/prostate-cancer-risk-factors
6. Prostate cancer foundation (PCF). Prostate Cancer Risk Factors. Available from: http://www.pcf.org/site/c.leJRIROrEpH/b.5802027/k.D271/Prostate_Cancer_Risk_Factors.htm
7. The Boston Group U. Urology Care Foundation - Urology A-Z - Prostate Cancer: Causes, Natural History, & Diagnosis. Available from: http://www.urologyhealth.org/urology/index.cfm?article=103
8. Rosenberg MT, Froehner M, Albala D, Miner MM. The biological and natural history of prostate cancer. International Journal of Clinical Practice. 2010 Dec; 64(13):1746-1753. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1742-1241.2010.02541.x/full
9. National Cancer Institute. Prostate Cancer Treatment for health professionals (PDQ®). Available from: http://www.cancer.gov/types/prostate/hp/prostate-treatment-pdq#link/stoc_h2_0
10. Globocan fact sheets: prostate cancer. Estimated Incidence, Mortality and Prevalence Worldwide in 2012. Available from: http://globocan.iarc.fr/old/FactSheets/cancers/prostate-new.asp
11. Kišonas J, Burneckis A, Ivanauskas A, Mickevičius R, Vėželis A. First experience of salvage HDR brachytherapy after prostate cancer radiotherapy. Journal of Acta medica Lituanica. 2014; 21(4):195-199. Available from: http://www.lmaleidykla.lt/ojs/index.php/actamedicalituanica/article/view/3049
12. Institute of Hygiene. Health Information Centre. Lithuanian population health and health care activities in 2013. Available from: http://sic.hi.lt/
13. Institute of Hygiene. Health Information Centre. Causes of death 2013. Available from: http://sic.hi.lt/
14. NICE. National Collaborating Centre for Cancer. Prostate Cancer: diagnosis and treatment. Clinical guidelines. 2014 Jan. Available from: https://www.nice.org.uk/guidance/cg175/resources/cg175-prostate-cancer-full-guideline3
15. Institute for Health Metrics and Evaluation (IHME). GBD Database. IHME, University of Washington. 2014. Available from: http://ghdx.healthdata.org/global-burden-disease-study-2013-gbd-2013-data-downloads
16. Sanyal C, Aprikian AG, Chevalier S, Cury FL, Dragomir A. Direct cost for initial management of prostate cancer: a systematic review. Journal of Current Oncology. 2013 Dec; 20(6):e522-e531. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3851348/
17. National end of life care programme. Deaths from urological cancers in England, 2001-2010. National End of Life Care Intelligence Network. 2012. Available from: http://www.endoflifecare-intelligence.org.uk/resources/publications/deaths_from_urological_cancers

18. Prostate Cancer UK. Prostate information: Are you at risk. 2015 Jan. Available from: http://prostatecanceruk.org/prostate-information/are-you-at-risk
19. Mayo clinic. Diseases and Conditions: Prostate cancer. Prostate cancer screening: Should you get a PSA test? 2015 Oct. Available from: http://www.mayoclinic.org/diseases-conditions/prostate-cancer/in-depth/prostate-cancer/art-20048087
20. LR sveikatos apsaugos ministro 2014 m. liepos 16 d. įsakymas Nr.V-814 „Dėl Nacionalinės vėžio profilaktikos ir kontrolės 2014–2025 metų programos patvirtinimo“. Available from: https://www.e-tar.lt/rs/legalact/051d0e500ce211e4adf3c8c5d7681e73/transcript
21. Advanced Medical Diagnostics. Clinical studies summary. Prostate HistoScanning™. A tissue characterisation technology supporting prostate cancer, 2013 Mar. Available from: http://medical-bg.info/resources/20130326184522_MK2U0399M-EN_Clinical-Studies-Summary_Prostate-HistoScanning_15-03-2013_e.pdf
22. Faure Walker NA, Nir D, Simmons L, Agrawal A, Chung C, Leminski A, Rashid T, Shamsuddin A, Winkler M. Using imaging biomarkers to improve the planning of radical prostatectomies. Urologic Oncology: Seminars and Original Investigations, 2015 Jan; 33(1).
23. American Cancer Society. Prostate Cancer. How is prostate cancer diagnosed? Available from: http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-diagnosis
24. Horwich A, Parker C, de Reijke T, Kataja V. Prostate Cancer: ESMO Clinical Practice Guidelines. Annals of Oncology. 2013; 24(6):vi106-vi114. Available from: http://www.esmo.org/Guidelines/Genitourinary-Cancers/Prostate-Cancer
25. Silberstein JL, Pal KS, Lewis B, Sartor O. Current clinical challenges in prostate cancer. Translation andrology and urology. 2013 Sep; 2(3). Available from: http://www.amepc.org/tau/article/view/2755/3626
26. Advanced Medical Diagnostics. AMD announces new HistoScanning™ research. 2011, Mar. Available from: http://www.businesswire.com/news/home/20110315006685/en/AMD-Announces-HistoScanning-TM-Research
27. MHL for advenced medical treatments. Advanced treatments for Prostate Cancer. Available from: http://findbesttreatment.com/prostate_cancer.html#Histoscanning
28. NHS. Treating prostate cancer. Available from: http://www.nhs.uk/Conditions/Cancer-of-the-prostate/Pages/Treatment.aspx
29. Watts S, Leydon G, Birch B, Prescott P, Lai L, Eardley S, Lewith G. Depression and anxiety in prostate cancer: a systematic review and meta-analysis of prevalence rates. BMJ open. 2014 Mar; 4(3). Available from: http://bmjopen.bmj.com/content/4/3/e003901.full
30. Howell D, Olsen K. Distress – the 6th vital sign. Journal of Current Oncology. 2011; 18(5):208-210. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3185896/pdf/conc-18-208.pdf
31. Advanced Medical Diagnostics. Prostate HistoScanning™. Certificates and compliance with international standards. 2015. Available from: http://new.histoscanning.webfactional.com/prostate-histoscanningtm-tt/certificates-and-compliance-with-international-sta/
32. R-Action Distribution. HistoScanning TT. Prostate Cancer Diagnostics. Available from: http://www.radistribution.com/index.php/products-videos/histoscanning-tt-prostate-cancer-diagnostics
33. CE Certificate. Production Quality Assurance. No. 2179339CE01. Available from: https://matrixreq.com/news/20150920/2179339CE01.pdf
34. Certificate. CE marking of conformity. Medical devices. No. 2115828CE01. Available from: http://new.histoscanning.webfactional.com/media/files/2115828CE01.pdf
35. Xiong T, Turner RM, Wei Y, Neal DE, Lyratzopoulos G, Higgins JPT. Comparative efficacy and safety of treatments for localised prostate cancer: an application of network meta-analysis. BMJ Open. 2014 Apr; 4(5). Available from: http://bmjopen.bmj.com/content/4/5/e004285.abstract

36. Nunez-Mora C, Garcia-Mediero JM, Patino P Orellana C, Garrido A, Rojo A, Rendón D. Utility of Histoscanning™ prior to prostate biopsy for the diagnosis of prostate adenocarcinoma. Actas Urológicas Españolas (English Edition), 2013 Jun; 37(6):342-346.
37. Schiffmann J, Fischer J, Tennstedt P, Beyer B, Böhm K, Michl U, Graefen M, Solomon G. Comparison of prostate cancer volume measured by HistoScanning™ and final histopathological results. World Journal of Urology, 2014 Aug; 32(4):939-944.
38. Aigner F, Frauscher F. Computer-aided Ultrasonography (Histoscanning): a Novel Technology for Locating and Characterizing Prostate Cancer. BJU International, 2009 Jan; 103(1):115-116.
39. Sivaraman A, Sanchez-Salas R, Barret E, Macek P, Validire P, Galiano M, Rozet F, Cathelineau X. Prostate histoscanning true targeting guided prostate biopsy: initial clinical experience. World Journal of Urology, 2014 Dec; 1-5.
40. Hamann MF, Hamann C, Trettel A, Jünemann KP, Naumann CM. Computer-aided transrectal ultrasound: does prostate HistoScanning™ improve detection performance of prostate cancer in repeat biopsies? BMC Urology. 2015 Jul 30;15:76.
41. Analogic. BK Medical and AMD Collaborate to Feature Prostate HistoScanning and Premium Ultrasound Solutions in Combined Booth at EAU, 2011 Mar. Available from: http://globenewswire.com/news-release/2011/03/18/442615/216618/en/BK-Medical-and-AMD-Collaborate-to-Feature-Prostate-HistoScanning-and-Premium-Ultrasound-Solutions-in-Combined-Booth-at-EAU.html
42. Advanced Medical Diagnostics. HistoScanning TT. Mission and Vision, 2014 May. Available from: http://new.histoscanning.webfactional.com/company/mission-and-vision/
43. Schiffmann J, Manka L, Boehm K, Leyh-Bannurah SR, Karakiewicz PI, Graefen M, Hammerer P, Salomon G. Controversial evidence for the use of HistoScanning™ in the detection of prostate cancer. World Journal of Urology, 2015 Apr 10.
44. Simmons LA, Autier P, Zát'ura F, Braeckman J, Peltier A, Romic I, Stenzl A, Treurnicht K, Walker T, Nir D, Moore CM, Emberton M. Detection, localisation and characterisation of prostate cancer by prostate HistoScanning™. BJU International, 2012 Jul; 110(1):28-35.
45. Pummer K, Rieken M, Augustin H, Gutchi T, Shariat SF. Innovations in diagnostic imaging of localized prostate cancer. World Journal of Urology, 2014 Aug; 32(4):881-890.
46. Barret E, Durand M. Technical Aspects of Focal Therapy in Localized Prostate Cancer. Springer-Verlag France, 2015. Available from: https://books.google.lt/books?id=9G5yBgAAQBAJ&pg=PA65&lpg=PA65&dq=position+for+histoscan&source=bl&ots=M7HhiKhEWe&sig=3FYRwglpuY9ycgRT7rhJ8CirOgI&hl=lt&sa=X&ved=0CEoQ6AEwBWoVChMIwsLMw9jnyAIVgrQUCh2ingHs#v=onepage&q=position%20for%20histoscan&f=false
47. Advanced Medical Diagnostics. The Technology. A Complete Ultrasound Solution for Patients at Risk of Prostate Cancer, 2014 May. Available from: http://new.histoscanning.webfactional.com/prostate-histoscanningtm-tt/the-technology/
48. Simmons LA, Ahmed HU, Moore CM, Punwani S, Freeman A, Hu Y, Barratt D, Charman SC, van der Meulen J, Emberton M. The PICTURE study—Prostate Imaging (multi-parametric MRI and Prostate HistoScanning™) Compared to Transperineal Ultrasound guided biopsy for significant prostate cancer Risk Evaluation. Contemporary Clinical Trials, 2014 Jan; 37(1):69-83.
49. Tamošauskienė J. Prostatos vėžio tyrimas dėl vėžio histoskenavimo metodu. Vilniaus universiteto Onkologijos institutas. 2014. Available from: http://www.interlux.lt/uploads/downloads/Prostatos%20tyrimas%20small.pdf
50. Braeckman J, Autier P, Soviany C, Nir R, Nir D, Michielsen D, Treurnicht K, Jarmulowicz M, Bleiberg H, Govindaraju S, Emberton M. The accuracy of transrectal ultrasonography supplemented with computer-aided ultrasonography for detecting small prostate cancers. BJU International, 2008 Dec; 102(11):1560-1565.

51. Schiffmann J, Mehring G, Tennstedt P, Manka L, Boehm K, Leyh-Bannurah SR, Karakiewicz PI, Hammerer P, Graefen M, Salomon G. True targeting-derived prostate biopsy: HistoScanning™ remained inadequate despite advanced technical efforts. World Journal of Urology, 2015 Jul 28.
52. European Association of Urology Congress. HistoScanning™ by AMD. Available from: http://eauvienna2011.org/?id=103&X=241312
53. Advanced Medical Diagnostics. Prostate HistoScanning™. Visual Reassurance for Decision Making and True Targeting. Available from: http://www.radistribution.com/images/brochures/HistoScanning-Brochure-Website.pdf
54. Salomon G, Spethmann J, Beckmann A, Autier P, Moore C, Durner L, Sandmann M, Haese A, Schlomm T, Michl U, Heinzer H, Graefen M, Steuber T. Accuracy of HistoScanning™ for the prediction of a negative surgical margin in patients undergoing radical prostatectomy. BJU International, 2013 Jan; 111(1):60-66.
55. De Coninck V, Braeckman J, Michielsen D. Prostate HistoScanning: a screening tool for prostate cancer? International Journal of Urology, 2013 Dec; 20(12):1184-1190.
56. Hamann M F, Hamann C, Schenk E, Al-Najar A, Naumann CM, Jünemann KP. Computer-aided (HistoScanning) biopsies versus conventional transrectal ultrasound-guided prostate biopsies: do targeted biopsy schemes improve the cancer detection rate? Urology, 2013 Feb; 81(2):370-375.
57. Apolikhin O, Sivkov A, Efremov G, Keshishev N, Zhukov O, Koryakin A. Histoscanning-aided template biopsies for patients with previous negative TRUS biopsies, 2013 May. Available from: http://pharmaceuticalintelligence.com/2013/05/05/from-aua2013-histoscanning-aided-template-biopsies-for-patients-with-previous-negative-trus-biopsies/
58. Rosoff JS, Prasad SM, Savage SJ. Ultrasonography in prostate cancer: current roles and potential applications in radiorecurrent disease. World Journal of Urology, 2013 Dec; 31(6):1353-1359.
59. The British Association of Urological Surgeons. Transrectal Ultrasound and Prostatic Biopsy: Guidelines and Recommendations for Training, 2015 Apr. Available from: http://www.baus.org.uk/_userfiles/pages/files/Publications/Transrectal%20Ultrasound%20%20Prostatic%20Biopsy%20FINAL.pdf
60. American College of Radiology and the Society of Radiologists in Ultrasound. Ultrasound Evaluation of the Prostate (and Surrounding Structures), 2015. Available from: http://www.aium.org/resources/guidelines/prostate.pdf
61. Canadian Cancer Society. Transrectal Ultrasound (TRUS). Available from: http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/tests-and-procedures/transrectal-ultrasound-trus/?region=on
62. Schersten T, Baile MA, Asua J, Jonsson E. Prostate cancer screening. Evidence synthesis and update. Statement of Finding. (INAHTA Joint Project). Vitoria-Gasteiz: Dpt. of Health Basque Goverment. Basque Office for Health Technology Assessment, Osteba, 1999.
63. Carroll P, Shinohara K. Transrectal Ultrasound Guided Prostate Biopsy. Available from: http://urology2008-2012.ucsf.edu/patientguides/pdf/uroonc/prostate_biopsy.pdf
64. Sugandh Sh, Chirag D, Zubin Sh. Transrectal Ultrasonography of the Prostate Periprocedural Care. Equipment, 2015 Aug. Available from: http://emedicine.medscape.com/article/457757-periprocedure
65. European Assocciation of Urology. Guidelines on Prostate Cancer, 2015 Mar. Available from: http://uroweb.org/wp-content/uploads/09-Prostate-Cancer_LR.pdf
66. Harvard Medical School+Harvard Health Publications. What is Transrectal Ultrasonography (TRUS)?, 2011 Mar. Available from: http://www.harvardprostateknowledge.org/what-is-transrectal-ultrasonography-trus
67. Prostate Cancer Treatment Guide™. Prostate Cancer Treatment Overview. Available from: http://www.prostate-cancer.com/prostate-cancer-treatment-overview/overview-biopsy.html
68. HealthHype. Prostate Biopsy Procedure, Preparation, Anesthesia. Available from: http://www.healthhype.com/prostate-biopsy-procedure-preparation-anesthesia.html

69. Accute Hospital NHS Trust. Guideline, Procedure and Medicine Administration Protocols for Trans Rectal Ultrasound Guided Biopsy of the Prostate Gland Under Local Anaesthetic by Perioperative Specialist Practitioners, 2015 Jul. Available from: http://www.worcsacute.nhs.uk/EasysiteWeb/getresource.axd?AssetID=11301&type=full&servicetype=Attachment
70. AETNA. Prostate Saturation Biopsy, 2015 Oct. Available from: http://www.aetna.com/cpb/medical/data/600_699/0698.html
71. Centre for Reviews and Dissemination. A Systematic Review of Prostate Cancer Biopsy Schemes, 2005 Aug. Available from: http://webarchive.nationalarchives.gov.uk/20150506150512/http://www.cancerscreening.nhs.uk/prostate/pcbs01-short.pdf
72. Ukimura O, Coleman JA, de la Taille A, Emberton M, Epstein JI, Freedland SJ, Giannarini G, Kibel AS, Montironi R, Ploussard G, Roobol MJ, Scattoni V, Jones JS. Contemporary Role of Systematic Prostate Biopsies: Indications, Techniques, and Implications for Patient Care. European Urology, 2013 Feb; 63(2):214-230. Available from: http://www.europeanurology.com/article/S0302-2838%2812%2901101-3/fulltext/contemporary-role-of-systematic-prostate-biopsies-indications-techniques-and-implications-for-patient-care
73. NHS Cancer Screening Programmes. Undertaking a Transrectal Ultrasound Guided Biopsy of the Prostate, 2006 Dec. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/422654/pcrmp01.pdf
74. van Hove A, Savoie PH, Maurin C, Brunelle S, Gravis G, Salem N, Walz J. Comparison of image-guided targeted biopsies versus systematic randomized biopsies in the detection of prostate cancer: a systematic literature review of well-designed studies. World Journal of Urology, 2014 Aug; 32(4):847-858.
75. Yacoub JH, Verma S, Moulton JS, Eggener S, Oto A. Imaging-guided Prostate Biopsy: Conventional and Emerging Techniques. RadioGraphics, 2012 May-Jun; 32(3). Available from: http://pubs.rsna.org/doi/full/10.1148/rg.323115053
76. Sperling D. MRI is Changing Prostate Biopsy. Sperling Prostate Center, 2015 Mar. Available from: http://sperlingprostatecenter.com/mri-changing-prostate-biopsy/
77. Marks L, Young Sh, Natarajan Sh. MRI-ultrasound fusion for guidance of targeted prostate biopsy. Current Opinion in Urology, 2013 Jan; 23(1):43-50. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3581822/
78. Orczyk C, Rosenkrantz AB, Deng FM, Melamed J, Babb J, Wysock J, Kheterpal E, Huang WC, Stifelman M, Lepor H, Taneja SS. A prospective comparative analysis of the accuracy of HistoScanning and multiparametric magnetic resonance imaging in the localization of prostate cancer among men undergoing radical prostatectomy. Urologic Oncology, 2015 Aug 31.
79. Ghai S, Haider MA. Multiparametric-MRI in diagnosis of prostate cancer. Indian Journal of Urology, 2015 Jul-Sep; 31(3): 194–201. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4495493/
80. Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology. Tenth Edition. Elsevier Sounders, 2012. Available from: https://books.google.lt/books?id=W1aeyJD46kIC&pg=PA2845&lpg=PA2845&dq=radical+prostatectomy+whole+mount+sectioning&source=bl&ots=Ptgb97KkIe&sig=mkXp43LsiGA3-6jbqkQj4hl9fKQ&hl=lt&sa=X&ved=0ahUKEwip8cWj2tDJAhXChSwKHe_XCXAQ6AEISTAG#v=onepage&q=radical%20prostatectomy%20whole%20mount%20sectioning&f=false
81. Kirby R, Montorsi F, Gontero P, Jr Smith JA. Radical Prostatectomy: from open to robotic. Informa healthcare, 2007 Sep. Available from: https://books.google.lt/books?id=IZmhwzwGyuMC&pg=PA249&lpg=PA249&dq=radical+prostatectomy+whole+mount+sectioning&source=bl&ots=ldbp5d80zN&sig=xHdeEp-

HuNrZDIny7SfPEPZ4Oas&hl=lt&sa=X&ved=0ahUKEwiX2_qT3NDJAhXjEXIKHflTBeQQ6AEIVDAI#v=onepage&q=radical%20prostatectomy%20whole%20mount%20sectioning&f=false
82. Montironi R, Beltran AL, Mazzucchelli R, Cheng L, Scarpelli M. Handling of Radical Prostatectomy Specimens: Total Embedding with Large-Format Histology. International Journal of Breast Cancer. 2012; ID 932784. Available from: http://www.hindawi.com/journals/ijbc/2012/932784/
83. Dicker AP, Merrick G, Gomella L, Valicenti RK, Waterman F. Basic and Advanced Techniques in Prostate Brachytherapy. Taylor&Francis, 2005. Available from: https://books.google.lt/books?id=zwrNHNK4UbUC&pg=PA36&lpg=PA36&dq=radical+prostatectomy+whole+mount+sectioning&source=bl&ots=eKEvvjWNgg&sig=_BH8pbV12w3aoFci6ix9lHfJzFI&hl=lt&sa=X&ved=0ahUKEwjxl9e429DJAhXGCiwKHainCnIQ6AEIODAD#v=onepage&q=radical%20prostatectomy%20whole%20mount%20sectioning&f=false
84. UAB Interlux. Submitted Application to the Accreditation Agency 2015–02–24 for the Evaluation of the Health Technologies Related to Medical Devices.
85. The Royal College of Radiologists. Ultrasound Training recommendations for medical and surgical specialists. Second edition. UK, 2012. Available from: https://www.rcr.ac.uk/sites/default/files/publication/BFCR%2812%2917_ultrasound_training.pdf
86. Javed S, Chadwick E, Edwards AA, Beveridge S, Laing R, Bott S, Eden C, Langley S. Does prostate HistoScanning™ play a role in detecting prostate cancer in routine clinical practice? Results from three independent studies. BJU International, 2014 Oct; 114(4):541-548; *Study-1*.
87. Javed S, Chadwick E, Edwards AA, Beveridge S, Laing R, Bott S, Eden C, Langley S. Does prostate HistoScanning™ play a role in detecting prostate cancer in routine clinical practice? Results from three independent studies. BJU International, 2014 Oct; 114(4):541-548; *Study-2*.
88. American Cancer Society. Prostate Cancer early detection. 2015 Jun. Available from: http://www.cancer.org/cancer/prostatecancer/moreinformation/prostatecancerearlydetection/prostate-cancer-early-detection-finding-prostate-cancer-early
89. U.S. Preventive Services Task Force. Final Recommendation Statement: Prostate Cancer: Screening. 2014 Oct. http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening
90. Javed S, Chadwick E, Edwards AA, Beveridge S, Laing R, Bott S, Eden C, Langley S. Does prostate HistoScanning™ play a role in detecting prostate cancer in routine clinical practice? Results from three independent studies. BJU International, 2014 Oct; 114(4):541-548; *Study-3*.
91. Macek P, Barret E, Sanchez-Salas R, Galliano M, Rozet F, Ahallal Y, Gays JM, Durant M, Mascle L, Giedelman C, Lunelli L, Validire P, Nesvadba M, Cathelineau X. Prostate histoscanning in clinically localized biopsy proven prostate cancer: an accuracy study. Journal of Endourology, 2014 Mar; 28(3):371-376.
92. Schiffmann J, Tennstedt P, Fischer J, Tian Z, Beyer B, Boehm K, Gandaglia G, Michl U, Graefen M, Salomon G. Does HistoScanning™ predict positive results in prostate biopsy? A retrospective analysis of 1,188 sextants of the prostate. World Journal of Urology, 2014 Aug; 32(4):925-930.
93. Javed S, Chadwick E, Edwards AA, Beveridge S, Laing R, Bott S, Eden C, Langley S. Does prostate HistoScanning™ play a role in detecting prostate cancer in routine clinical practice? Results from three independent studies. BJU International, 2014 Oct; 114(4):541-548.
94. Serefoglu EC, Altinova S, Ugras NS, Akincioglu E, Asil E, Balbay MD. How reliable is 12-core prostate biopsy procedure in the detection of prostate cancer? Canadian Urological Association Journal. 2013; 7 (5-6): E293-E298. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3668408/
95. Postema A, Idzenga T, Mischi M, Frinking P, Rosette J, Wijkstra H. Ultrasound modalities and quantification: developments of multiparametric ultrasonography, a new modality to detect, localize and target prostatic tumors. Current Opinion in Urology, 2015 May; 25(3):191-197.

96. Salomon G. Editorial Comment from Dr Salomon to Prostate HistoScanning: A screening tool for prostate cancer? International Journal of Urology, 2013 Dec; 20(12):1191-1191.
97. Braeckman J, Autier P, Garbar C, Marichal MP, Soviany C, Nir R, Nir D, Michielsen D, Bleiberg H, Egevad L, Emberton M. Computer-aided ultrasonography (HistoScanning): a novel technology for locating and characterizing prostate cancer. BJU International, 2008 Feb; 101(3):293-298.

APPENDIX 1: 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 without limitations; systematic literature search strategies are introduced further in Appendix 2.

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 described in the summary.

In terms of study design, no HTAs or RCTs were found; only prospective and retrospective case series were selected for answering questions related to the domains 'Safety' and 'Clinical effectiveness'. For the two other domains 'Health problem and current use of the technology' and 'Description and technical characteristics', no restrictions in terms of study design were applied.

In cases where questions within the domains 'Health problem and current use of technology' and 'Description and technical characteristics of technology' could not be answered using the information retrieved from the basic systematic literature search described earlier, additional searches within specific information sources (e.g. databases for clinical guidelines, websites of manufactures etc.) and, if needed, hand searching were performed.

The quality of diagnostic accuracy studies was assessed by QUADAS-2 checklist (see Appendix 5). The tool assesses study quality in four domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and concerns regarding applicability (for the first three domains). Application of the tool results in a judgement of risk of bias for each study categorised as low, high, or unclear. For assessing the quality of SRs, the AMSTAR checklist for systematic reviews was used (see Appendix 5).

Study details, study population, results regarding efficacy/ effectiveness and safety of selected studies were extracted into a data extraction tables (see Appendix 4).

Reporting of results

Study characteristics

Nine prospective non-comparative case-series [36,39,40,44,51,86,87,90,91], one retrospective non-comparative study [54] and one prospective comparative study [78] were included for effectiveness and safety assessment. There were nine articles included in the assessment, however, one article [93] had results from three independent studies [86,87,90].

In all studies a total of 553 (range from 24 to 98) men were included. All studies were grouped into two parts depending on the research question – 6 non-comparative studies [36,39,40,51,86,87] were included in "PHS for screening" group with a total of 293 (range from 24 to

97) men; 1 comparative study [78] and 4 non-comparative studies [44,54,90,91] were included in "PHS for staging" group with a total of 260 (range from 24 to 98) men.

In four case-series [44,86,87,90] 2.1 version of "Prostate HistoScanning™" software was used, in two case-series [40,91] 2.3 version of software was used, in other two case-series [39,51] True Targeting version of "Prostate HistoScanning™" was used and three studies [36,54,78] did not report any version of software that was used.

Conflict of interest was reported in all non-comparative case-series, but was not reported in one comparative study [78]; five studies [36,39,40,51,91] reported no conflict of interest and five studies [44,54,86,87,90] reported that some authors received personal fees from distribution companies, projects and some authors were paid consultants of manufacturers. The source of funding was reported in two case-series [44,78]; financial support was provided by manufacturer [44] and Charitable Trust [78].

Patient characteristics

All patients included in "PHS for screening" group (6 of 11 studies) were men with suspected malignant neoplasm of prostate, with median age from 65 to 68 years (range 47–79) in three studies [51,86,87] and with mean age from 63.7 to 66.2 years (range 40–82) in other three studies [36,39,40]. The most important inclusion criteria were elevated PSA level and/ or abnormal/ suspicious DRE or both [36,40,51,86,87]; previous negative biopsies [36,40]; patients requiring prostate biopsy [39]. Exclusion criteria were reported only in one study [40]; patients with less than 3 months after the previous manipulations of the prostate gland were excluded. PSA level was reported in all studies – median PSA level from 6.3 to 9.25 ng/ml (range 0.2–54.0) [51,86,87] and mean PSA level from 8.0 to 16.06 ng/ml (range 1.02–36.2) [36,39,40]. Reference standard differed among the studies – standard systematic 12-core TRUS-guided biopsy or standard systematic 10- to 12-core TRUS-guided biopsy was used in four case-series [36,39,51,86]; transperineal template prostate biopsy [87] and systematic 14-core TRUS-guided biopsy [40] was used in other two case-series.

All patients included in "PHS for staging" group (5 of 11 studies) were men with diagnosed malignant neoplasm of prostate, with median age of 63 years (range was not reported) [91] and with mean age from 61 to 67 years (range 48–77) in four studies [44,54,78,90]. Cancer staging was reported in two case-series [54,91] and was based on the TNM Classification of Malignant Tumours (TNM). Majority of the patients were in T1c group (n=117). The most important inclusion criteria was histologically confirmed PCa in men scheduled for radical prostatectomy (RP) [44,54,78,90,91]. Exclusion criteria in three studies [44,78,91] were incomplete clinical data, poor quality data (artifacts), pathology protocol violation and declined RP, other two studies [54,90] did not report any exclusion criteria. PSA level was reported in all studies – except one study [44]: median PSA level was 6.4 ng/ml (range was not reported) [91], mean PSA level was from 5.75 to 9.9 ng/ml (range 1.3–33.8) [54,78,90]. Reference standard was the same in all studies – radical prostatectomy.

Quality assessment

The quality of diagnostic accuracy studies was assessed by QUADAS-2 checklist. QUADAS-2 consists of four key domains: patient selection, index test, reference standard, flow and timing. Each domain is assessed in terms of the risk of bias and the first three are also assessed in terms of concerns regarding applicability.

Three studies [51,86,87] (of 6) that were included in "PHS for screening" group had low risk of bias in all domains. In other three studies [36,39,40] risk of bias was assessed as unclear only in reference standard domain because of insufficient data. Only in one case-serie [36] one domain

(patient selection) was assessed as high risk of bias. Concerns regarding applicability were rated as "low".

Two studies [54,91] (of 5) that were included in "PHS for staging" group had low risk of bias in all domains. Other three studies [44,78,91] had high risk of bias in patient selection domain; one study [43] had high risk of bias in reference standard domain and one study [91] had high risk of bias in flow and timing domain as well. Concerns regarding applicability were rated as "low" in all studies.

More detailed information on the quality assessment can be found in Appendix 5.

Outcomes

All outcomes, except adverse events and incidental findings, in both groups – "PHS for screening" and "PHS for staging" – were distributed into several subgroups: per patient and per section.

Sensitivity, specificity and positive/ negative predictive values were reported in 4 studies in "PHS for screening" group [36,51,86,87,]; only one study [51] reported these outcomes according to the threshold values (>0 ml, >0.2 ml, >0.5 ml). Sensitivity [36,86,87] in 'per patient' subgroup varied from 22.6% to 53.3% and in 'per section' subgroup – from 48.1% to 100%. Specificity varied from 0% to 100% and from 5.9% to 57.5%, respectively. Intervals of PPV and NPV in 'per patient' subgroup were 20–100% and 28.6–56.3%, respectively; values of PPV and NPV in 'per section' were 26–51.4% and 78.1–100%. However, according to different PHS signal volume cutoffs (>0 ml, >0.2 ml, >0.5 ml), the sensitivity, specificity, PPV and NPV for 'per section' subgroup [51] were: 20.7%, 78.2%, 17.4%, 81.6%, and 20.7%, 82%, 20.3%, 82.3%, and 12.1%, 94.6%, 33.3%, 82.6%, respectively. Moreover, PCa detection rates 'per patient' and/ or 'per section' were reported in all "PHS for screening" studies and varied from 12.6% to 67.7%; however, PCa detection rate for the reference standard differs depending on the type of the biopsy.

Sensitivity, specificity and positive/ negative predictive values were reported in all 5 studies in "PHS for staging" group but 4 studies (of 5) [44,54,90,91] reported these values according to the threshold values (≥1 ml, <0.2 ml, ≥0.2 ml, ≥0.5 ml). When PHS signal volume cutoff is ≥0.1 ml [91], the sensitivity and specificity in 'per patient' subgroup are 60% and 66%; when cutoff is <0.2 ml [54] – 48% and 84%, respectively. However, when PHS signal volume cutoff is ≥0.2 ml [90,44] the sensitivity and specificity in 'per section' subgroup vary between 63–90% and 53–72%, respectively; when PHS signal volume cutoff is ≥0.5 ml [44,90] sensitivity and specificity 'per section' varies between 37–90% and 70–71%, respectively. Intervals of PPV and NPV in 'per patient' subgroup were reported in one study [54]: 34% and 91%, respectively; in 'per section' subgroup these values were reported according to the PHS signal volume cutoffs (≥0.2 ml, ≥0.5 ml) [44]: PPV were 83–84% and NPV were 82–80%, respectively. Furthermore, one study [91] compared tumor volume by PHS (1.38 cm^3, range 0.1–9.3) and by histology (2.24 cm^3, range 0.22–11.7). However, one study [78] compared accuracy of PHS and mpMRI and results showed sensitivity of 46.2% and 52.6%, specificity of 74.1% and 96.5%, PPV of 45% and 87.2%, NPV of 75% and 81.6%, respectively. Also, PHS reported significantly lower accuracy level than mpMRI (65.3% vs. 82.7%).

Adverse events and incidental findings in "PHS for screening" group were reported in 3 studies [36,39,40] (n=172). None of the studies in "PHS for staging" group provided information about adverse events or incidental findings. Moreover, false positive/ negative values were reported in 4 (out of 6) studies [36,40,86,87] in "PHS for screening" group.

None of the studies provided information about QoL, safeguarding (feeling secure due to a negative result) and disease specific-mortality/ disease specific-morbidity. Also, there was no information about therapeutic impact (patient management) due to unavailable follow-up period.

APPENDIX 2: DOCUMENTATION OF THE BASIC SEARCH STRATEGIES

Database: PubMed
Search date: 2015-10-15
Results: 36 hits.

	Searches	Results
1.	Prostatic Neoplasms[MeSH Terms]	98397
2.	prostate	147540
3.	(tumor OR cancer OR ?carcinoma* OR neoplasm*)	3549902
4.	(prostate) AND (tumor OR cancer OR ?carcinoma* OR neoplasm*)	118039
5.	histoscan*	42
6.	(prostate AND (tumor OR cancer OR ?carcinoma* OR neoplasm*)) OR Prostatic Neoplasms[MeSH Terms]	133280
7.	prostate AND ((tumor OR cancer OR ?carcinoma* OR neoplasm*) OR Prostatic Neoplasms[MeSH Terms]) AND histoscan*	36

Database: Cochrane Library
Search date: 2015-10-15
Results: 3 hits.

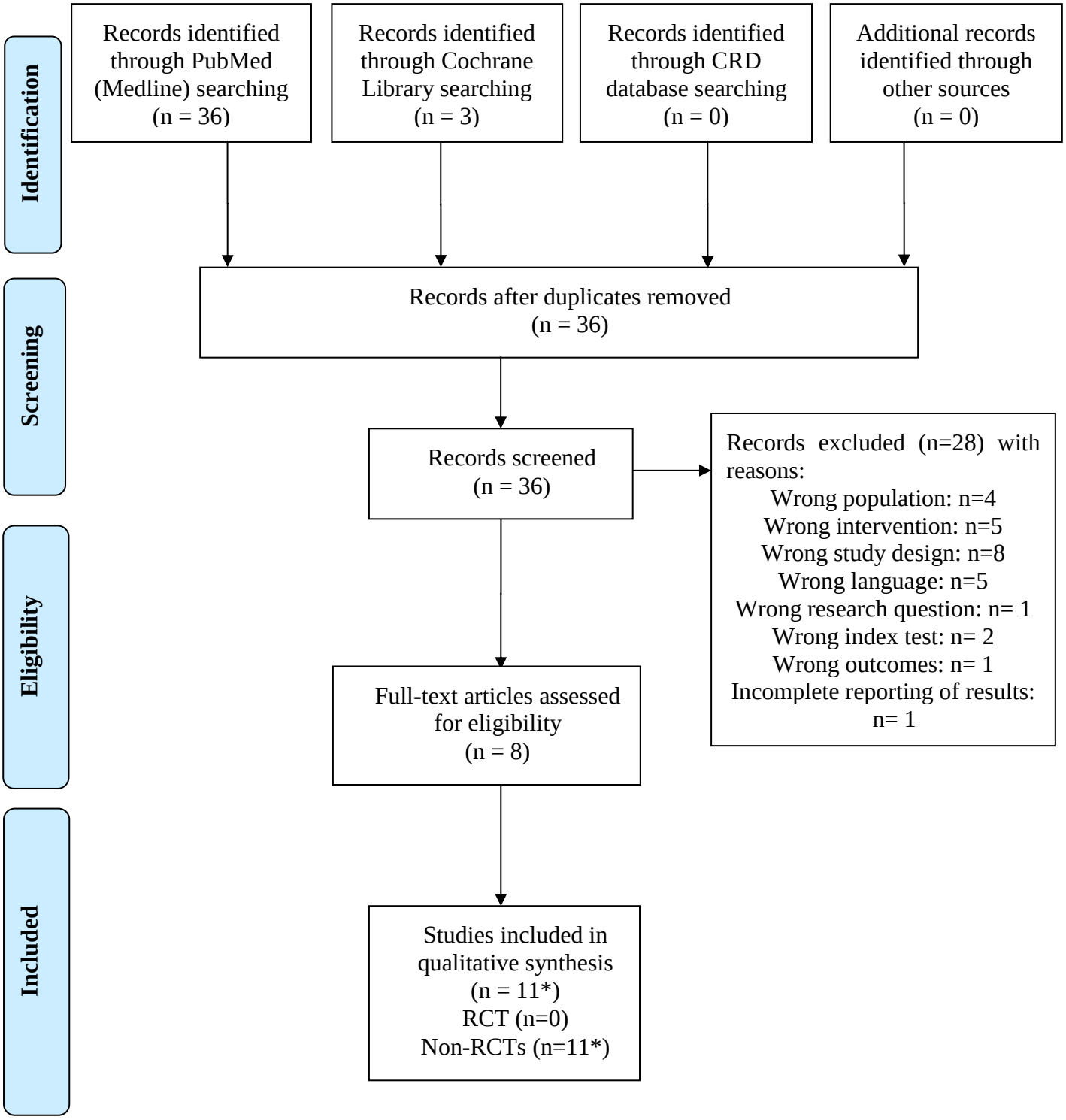
	Searches	Results
1.	MeSH descriptor: [Prostatic Neoplasms] explode all trees	3580
2.	prostate	11589
3.	tumo*r* OR cancer* OR neoplasm* OR ?carcinoma*	110356
4.	#2 AND #3	7908
5.	#1 OR #4	8024
6.	histoscan*	3
7.	#5 AND #6	3

Database: CRD database
Search date: 2015-10-15
Results: 0 hits.

	Searches	Results
1.	MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES	684
2.	(prostate) AND (neoplasm* OR cancer* OR tumo*r* OR ?carcinoma*))	684
3.	(histoscan*)	0
4.	#1 OR #2	684
5.	#3 OR #4	0

Flow charts of study selection

Table 1. Flow chart showing selection of studies.



*One study (Javed S, 2014) was distributed into three studies.

APPENDIX 3: QUESTIONS USED FROM HTA CORE MODEL APPLICATION FOR DIAGNOSTIC TECHNOLOGIES (VERSION 2.1)

Health Problem and Current Use of the HistoScanning™ Technology

Element ID	Research question
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the prostate cancer?
A0004	What is the natural course of the prostate cancer?
A0005	What is the burden of prostate cancer for the patient?
A0006	What are the consequences of the prostate cancer for the society?
A0024	How the prostate cancer is currently diagnosed according to published guidelines and in practice?
A0025	How the prostate cancer is currently managed according to published guidelines and in practice?
A0001	For which health conditions and populations, and for what purposes is the HistoScanning™ technology used?
A0011	How much is the HistoScanning™ technology utilised?
F0001	Is the HistoScanning™ technology a new, innovative mode of care, an add-on to or modification of a standard mode of care or replacement of a standard mode of care?
A0020	For which indications has the HistoScanning™ technology received marketing authorisation or CE marking?
A0021	What is the reimbursement status of the HistoScanning™ technology?

Description and Technical Characteristics of the HistoScanning™ Technology

Element ID	Research question
B0001	What is the HistoScanning™ technology and the comparators?
B0002	What is the claimed benefit of the HistoScanning™ technology in relation to the comparators?
B0003	What is the phase of development and implementation of the HistoScanning™ technology and the comparators?
B0004	Who administers the HistoScanning™ technology and the comparators and in what context and level of care are they provided?
B0009	What equipment and supplies are needed to use the HistoScanning™ technology and the comparators?
B0013	What kind of training and information is needed for the personnel/ carer using the HistoScanning™ technology?

Safety

Element ID	Research question
C0008	How safe is the HistoScanning™ technology in relation to the comparators?
C0002	Are the harms related to dosage or frequency of applying the HistoScanning™ technology?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0006	What are the consequences of false positive, false negative and incidental findings generated by using the technology from the viewpoint of patient safety?
C0007	Are the HistoScanning™ technology and comparator(s) associated with user-dependent harms?
C0060	How does the safety profile of the technology vary between different generations, approved versions or products?

Clinical Effectiveness

Element ID	Research question
D0026	How does the HistoScanning™ technology modify the effectiveness of subsequent interventions?
D0032	How does the test-treatment intervention modify the magnitude and frequency of morbidity?
D0020	Does use of the test lead to improved detection of the condition?
D0021	How does use of the test change physicians' management decisions?
D0023	How does the HistoScanning™ technology modify the need for other technologies and use of resources?
D1001	What is the accuracy of the test against reference standard?
D1002	How does the test compare to other optional tests in terms of accuracy measures?
D1003	What is the reference standard and how likely does it classify the target condition correctly?
D1005	What is the optimal threshold value in this context?
D1006	Does the test reliably rule in or rule out the target condition?
D1007	How does test accuracy vary in different settings?
D1019	Is there evidence that the replacing test is more specific or safer than the old one?
D0029	What are the overall benefits and harms of the HistoScanning™ technology in health outcomes?

APPENDIX 4: DESCRIPTION OF THE EVIDENCE USED

Evidence tables of individual studies included

Table 2. Evidence table for case series study details in „PHS for screening“ group.

Study details			Study population			Index test: PHS targeted biopsies		
Author, years [ref.]	**Country**	**CoI SoF**	**No. of patients**	**Age [range years]**	**Previous tests (PSA [range], previous biopsies)**	**Version of PHS**	**Blinding from reference standard and Analysis**	**Threshold Value(s)**
Javed, 2014 [86]	UK	CoI: 2 authors received personal fees: Oncura/ GE Healthcare, ABSSH, WebBXT; all: The Prostate Project. SoF: NR	24	Med.=68 [56-76]	PSA Med.=9.25ng/ml [0.7-54]. Prev.Bx: None.	2.1	Blinding: Yes Analysis: Operator 1: 10yr. experience in ultrasonography; Operator 2: trained in the use of PHS. PHS images were inspected by both operators. Probe: BK8818.	None
Javed, 2014 [87]	UK	CoI: 2 authors received personal fees: Oncura/ GE Healthcare, ABSSH, WebBXT; all: The Prostate Project. SoF: NR.	57	Med.=65 [48-78]	PSA Med.=9.0ng/ml [4.1-53.9]. Prev.Bx: None.	2.1	Blinding: Yes Analysis: Operator 1: 10yr. experience in ultrasonography; Operator 2: trained in the use of PHS. PHS images were inspected by both operators. Probe: BK8818.	None
Núñez-Mora, 2013[36]	ES	CoI: None SoF: NR	32*	Mean=63.7 [40-82]	PSA Mean=8.0ng/ml [3.5-36.2]. Prev.Bx: 14 pts., type:NR.	NR	Blinding: Yes Analysis: NR	None
Sivaraman, 2014[39]	FR	CoI: None SoF: NR	43	Mean=63.7	PSA Mean=16.06ng/ml Prev.Bx: None.	TT 2.3	Blinding: Yes Analysis: operator subjectively decided number of cores depending on the volume of the abnormal areas. Probe: BK8818. No. of TT-Bx cores: 204.	≥0.2 cm^3
Schiffmann, 2015[51]	DE	CoI: None SoF: NR	40	Med.=65 [47-79]	PSA Med.=6.3ng/ml [0.2-26.0] Prev.Bx: None.	TT	Blinding: Yes Analysis: single examiner trained by PHS manufacturer (AMD). No. of TT-Bx cores: 69.	>0ml >0.2 ml >0.5 ml
Hamann, 2015[40]	DE	CoI: None SoF: NR	97**	Mean=66.2 [44-82]	PSA Mean=10.42ng/ml [1.02-35.00] Prev.Bx: 97 pts., type:NR.	2.3	Blinding: Yes Analysis: 3 targeted cores from each suspicious region (maximum of 3) based on the PHS image were taken: 1) targeted transperineal biopsy (probe: BK8848); 2) targeted transrectal biopsy (probe: BK8818).	None

*8 pts. – first biopsy, 14 pts. – repeated biopsy, 10 pts. diagnosed PCa before; **97 pts. – repeated biopsy.

Legend: ABSSH – American Brachytherapy Summer School Honorarium; AMD – Advanced Medical Diagnostics; CoI – conflict of interest; DE – Germany; ES – Spain; FR – France; yr. – years; Med – median; No. – number; NR – not reported; PCa – prostate cancer; PHS – prostate HistoScanning™; Prev. Bx – previous biopsy; PSA – *prostate-specific antigen;* pts. – patients; ref. – references; SoF – source of funding; UK – United Kingdom.

Table 3. Evidence table for case series study outcomes in „PHS for screening“ group.

	Reference standard: biopsies				Outcomes						
Author, years [ref.]	**Name(s) of the biopsy**	**Blinding from index test and Analysis**	**No. of biopsy cores [range]**		**PCa detection rate**	**Sensitivity**	**Specificity**	**PPV/ NPV**	**False negative/ False positive**	**Adverse events**	**Incidental findings**
Javed, 2014[86]	Standard systematic 12-core TRUS-guided biopsy*	Blinding: Yes Analysis: The pathology from the Bx results was reported by a local dedicated uropathologist.	**per patient**	NR	trPHS: 33.3% (8/24) TRUS: 62.5% (15/24)	53.3%	100%	100%/ 56.3%	FN 7/24(29.2%) FP 0/24(0%)	NR	NR
			per section	144 sextants	NR	100%	5.9%	31%/ 100%	FN 0/144(0%) FP 95/144(66%)		
Javed, 2014[87]	Transperineal template prostate biopsy	Blinding: Yes Analysis: The pathology from the Bx results was reported by a local dedicated uropathologist. Probe: BK8848.	**per patient**	NR	trPHS: 12.3% (7/57) TTB: 54.4% (31/57)	22.6%	100%	100%/ 52%	FN 24/57(42.1%) FP 0/57(0%)	NR	NR
			per section	342 sextants	NR	48.1%	57.5%	26%/ 78.1%	FN 42/342(12.3%) FP 111/342(32.5%)		
Núñez-Mora, 2013[36]	Standard systematic 12-core TRUS-guided biopsy**	Blinding: Unclear Analysis: Transperineal Bx of suspicious areas which may not be accessible by transrectal approaches were subsequently performed, taking 2 samples from each suspicious area.	**per patient**	7.5 [6-9]	trPHS: NR TRUS: 78.1% (25/32)	50%	9%	20%/ 28.6%	FN 5/32(15.6%) FP 20/32(62.5%)	NR	PIN 2/32 (6.3%); Chronic inflammation 9/32 (28.1%).
			per section	239 cores	NR	88%	42.6%	51.4%/ 83.9%	FN 5/239(2.1%) FP 35/239(14.6%)		
Sivaraman, 2014[39]	Standard systematic 12-core TRUS-guided biopsy*	Blinding: Unclear Analysis: NR	**per patient**	NR	trPHS: 26% (11/43) TRUS: 44% (19/43)	NR	NR	NR	NR	Acute retention of urine (grade2) 5/43 (11.6%); Mild	NR

			per section	516 cores	NR	NR	NR	NR	NR	prostatitis 3/43 (7%).	
Schiffmann, 2015[51]	Standard systematic 10- to 12-core TRUS-guided biopsy*	Blinding: Yes Analysis: Bx was taken by 2nd operator. All Bx were assigned according to 8 localizations of the prostate: apex left and right, middle left and right, basis left and right, and median left and right.	**per patient**	NR	trPHS: 20% (8/40) TRUS: 50% (20/40)	NR	NR	NR	NR	NR	NR
			per section	319/320 octants	NR	>0 ml: 20.7% >0.2 ml: 20.7% >0.5 ml: 12.1%	>0 ml: 78.2% >0.2 ml: 82.0% >0.5 ml: 94.6%	>0 ml: 17.4%/ 81.6% >0.2 ml: 20.3%/ 82.3% >0.5 ml: 33.3%/ 82.9%	NR		
Hamann, 2015[40]	Systematic 14-core transrectal TRUS-guided biopsy	Blinding: No Analysis: Bx were performed randomly by 4 senior surgeons with ≥5yr. Bx experience.	**per patient**	NR	tpPHS: 64.5% (20/31) trPHS: 67.7% (21/31) TRUS: 70.1% (22/31)	NR	NR	NR	NR	NR	Atypical small acinar proliferation: PHS-TTBx– 2/97(2.1%), PHS-TRUSBx– 2/97(2.1%); High-grade PIN: PHS-TTBx– 9/97(9.3%), PHS-TRUSBx– 12/97(12.4%); Chronic inflammation: PHS-TTBx– 59/97(60.8%), PHS-TRUSBx– 59/97(60.8%).
			per section	248 cores	tpPHS: 13% trPHS: 11% TRUS: 5%	NR	NR	NR	FP 184/248(74.2%)		

* Expression of "systematic" was added to the name of the biopsy. All standard biopsies are systematic.

** Expression of "bisextant" was changed to "standard systematic 12-core" in order to unify the names of the biopsies.

Legend: Bx – biopsy; FN – false negative; FP – false positive; yr. – years; No. – number; NPV – negative predictive value; NR – not reported; PCa – prostate cancer; PHS – prostate HistoScanning™; PHS-TRUSBx – PHS template targeted transperineal biopsy; PHS-TTBx – PHS targeted transrectal biopsy; PIN – prostatic intraepithelial neoplasia; PPV – positive predictive value; ref. – references; tpPHS – transperineal PHS; trPHS – transrectal PHS; TRUS – transrectal ultrasound.

Table 4. Evidence table for case series study details in „PHS for staging“ group.

Study details			Study population				Index test: PHS		
Author, years [ref.]	**Country**	**CoI SoF**	**No. of patients**	**Age [range years]**	**PSA level (ng/ml)**	**Clinical TNM stage**	**Version of PHS**	**Blinding from ref.stand. and Analysis**	**Threshold Value(s)**
Javed, 2014 [90]	UK	CoI: 2 authors received personal fees: Oncura/ GE Healthcare, ABSSH, WebBXT; all: The Prostate. Project. SoF: NR.	24	Mean=67 [49-77]	Mean=9.9 [2.5-22]	NR	2.1	Blinding: Yes. Analysis: The findings of PHS were compared immediately before the surgery. PHS scans were acquired by dedicated clinicians with extensive experience in TRUS scanning and prostate brachytherapy, who were trained in PHS by the manufacturer.	≥0.2ml ≥0.5ml
Macek, 2014 [91]	FR	CoI: None. SoF: NR.	98	Med.=63	Med.=6.4	T1c=54 (55.1%) T2a=29 (29.6%) T2b=9 (9.2%) T2c=4 (4.1%) T3a=2 (2%)	2.3	Blinding: Yes. Analysis: Ultrasonography was performed by 5 urologists. The prostate volume was created by embedded software with operator interaction. Highlighted lesions were reviewed on the screen and manual adjustment was performed. PHS analysis was performed by one urologist. Probe: BK8818.	≥0.1cm^3
Salomon, 2013 [54]	DE	CoI: 2 authors were paid consultants of AMD. SoF: NR.	80	Mean=64 [48-76]	Mean=6.0 [1.3-33.8]	T1c=63 (79%) T2a=14 (18%) T2b=3 (3%)	NR	Blinding: Yes. Analysis: The analysis of the PHS data took place after surgery. 3 urologists performed the TRUS, 1 urologist performed the PHS analysis. Probe: BK8818.	≥0.2ml ≥0.5ml
Simmons, 2012 [44]	UK	CoI: 5 authors had CoI, others – declared none. SoF: AMD.	27	Mean=63 [56-75]	Mean=NR [2.6-26]	NR	2.1	Blinding: Yes. Analysis: Experience with PHS varied amongst users, most had little to no prior experience. PHS analysis was undertaken centrally at the laboratories of AMD. The initial prostate segmentation was performed by AMD's clinical research assistant. Probe: BK8818.	≥0.2ml ≥0.5ml
Orczyk, 2015 [78]	USA	CoI: NR. SoF: Supported in part by Charitable Trust.	31	Mean=61 [52-70]	Mean=5.75 [3.09-8.41]	NR	NR	Blinding: Yes. Analysis: 2 image acquisition cycles were performed. Images were processed by a single operator blinded to the results of pathology and mpMRI.	NR

Legend: ABSSH – American Brachytherapy Summer School Honorarium; AMD – Advanced Medical Diagnostics; CoI – conflict of interest; DE – Germany; FR – France; yr. – years; Med. – median; mpMRI – multiparametric magnetic resonanse imaging; No. – number; NR – not reported; PCa – prostate cancer; PHS – prostate HistoScanning™; PSA – prostate-specific antigen; ref. – references; SoF – source of funding; TNM – Classification of Malignant Tumours; TRUS – transrectal ultrasound; UK – United Kingdom; USA – the United States of America.

Table 5. Evidence table for case series study outcomes in „PHS for staging“ group.

	Reference standard: radical prostatectomy		No. of sectors		Outcomes						
Author, years [ref.]	**Type of sectioning**	**Blinding from index test and Analysis**			**Tumor volume by PHS**	**Tumor volume by histology**	**Sensitivity**	**Specificity**	**NSM/ PSM**	**PPV/ NPV**	**AE/ Incidental findings**
Javed, 2014 [90]	NR	Blinding: Yes. Analysis: The dedicated uropathologist reporting the whole-mount RP specimens.	**per patient**	6	NR	NR	NR	NR	NR	NR	NR
			per section	144 sextants	NR	NR	≥0.2 ml: 63% ≥0.5 ml: 37%	≥0.2 ml: 53% ≥0.5 ml: 71%	NR	NR	NR
Macek, 2014 [91]	3-4mm	Blinding: Yes. Analysis:All histologically detected lesions were considered. Analysis was done by 1 pathologist.	**per patient**	12	1.38cm^3 [0.1-9.3]	2.24cm^3 [0.22-11.7]	≥0.1cm^3 60%	≥0.1cm^3 66%	NR	NR	NR
			per section	1176 sectors	NR	NR	NR	NR	NR	NR	
Salomon, 2013 [54]	3-5mm	Blinding: Yes. Analysis: 5 ‘high-volume’ surgeons performed the RP. From each of 3-5mm thick slices, two 5mm thick sections were cut and mounted on microscopic glass.	**per patient**	NR	NR	NR	<0.2 ml: 48%	<0.2 ml: 84%	NR	34%/ 91%	NR
			per section	160 sides	NR	NR	NR	NR	NR	NR	
Simmons, 2012 [44]	3-4mm	Blinding: No. Analysis: The RP specimens were all processed centrally by pathologists at Bostwick Laboratories, London, UK.	**per patient**	6	NR	NR	NR	NR	NR	NR	NR
			per section	162 sextants	NR	NR	≥0.2 ml: 90% ≥0.5 ml: 90%	≥0.2 ml: 72% ≥0.5 ml: 70%	NR	≥0.2 ml: 83%/ 82% ≥0.5 ml: 84%/ 80%	
Orczyk, 2015 [78]	NR	Blinding: Yes. Analysis: Step-section histologic evaluation of the RP specimen was performed by a single pathologist, blinded to the results of imaging.	**per patient**	31	NR	NR	NR	NR	NR	NR	1pts. No PCa after RP (mpMRI and HS showed FP)
			per section	248 octants	NR	NR	PHS: 46.2% MRI: 52.6%	PHS: 74.1% MRI: 96.5%	NR	PHS: 45%/ 75% MRI: 87.2%/ 81.6%	

Legend: AE – adverse events; FP – false positive findings; mpMRI – multiparametric magnetic resonanse imaging; No. – number; NPV – negative predictive value; NR – not reported; NSM – negative surgical margins; PHS – prostate HistoScanning™; PPV – positive predictive value; PSM – positive surgical margins; pts. – patients; ref. – references; RP – radical prostatectomy; UK – United Kingdom.

APPENDIX 5: QUALITY ASSESSMENT OF SELECTED STUDIES

Included studies

Case series	
1.	Hamann MF, Hamann C, Trettel A, Jünemann KP, Naumann CM. Computer-aided transrectal ultrasound: does prostate HistoScanning™ improve detection performance of prostate cancer in repeat biopsies? BMC Urology. 2015 Jul 30;15:76.
2.	Javed S, Chadwick E, Edwards AA, Beveridge S, Laing R, Bott S, Eden C, Langley S. Does prostate HistoScanning™ play a role in detecting prostate cancer in routine clinical practice? Results from three independent studies. BJU International, 2014 Oct; 114(4):541-548; *Study-1*.
3.	Javed S, Chadwick E, Edwards AA, Beveridge S, Laing R, Bott S, Eden C, Langley S. Does prostate HistoScanning™ play a role in detecting prostate cancer in routine clinical practice? Results from three independent studies. BJU International, 2014 Oct; 114(4):541-548; *Study-2*.
4.	Javed S, Chadwick E, Edwards AA, Beveridge S, Laing R, Bott S, Eden C, Langley S. Does prostate HistoScanning™ play a role in detecting prostate cancer in routine clinical practice? Results from three independent studies. BJU International, 2014 Oct; 114(4):541-548; *Study-3*.
5.	Macek P, Barret E, Sanchez-Salas R, Galliano M, Rozet F, Ahallal Y, Gays JM, Durant M, Mascle L, Giedelman C, Lunelli L, Validire P, Nesvadba M, Cathelineau X. Prostate histoscanning in clinically localized biopsy proven prostate cancer: an accuracy study. Journal of Endourology, 2014 Mar; 28(3):371-376.
6.	Nunez-Mora C, Garcia-Mediero JM, Patino P Orellana C, Garrido A, Rojo A, Rendón D. Utility of Histoscanning™ prior to prostate biopsy for the diagnosis of prostate adenocarcinoma. Actas Urológicas Españolas (English Edition), 2013 Jun; 37(6):342-346.
7.	Salomon G, Spethmann J, Beckmann A, Autier P, Moore C, Durner L, Sandmann M, Haese A, Schlomm T, Michl U, Heinzer H, Graefen M, Steuber T. Accuracy of HistoScanning™ for the prediction of a negative surgical margin in patients undergoing radical prostatectomy. BJU International, 2013 Jan; 111(1):60-66.
8.	Schiffmann J, Mehring G, Tennstedt P, Manka L, Boehm K, Leyh-Bannurah SR, Karakiewicz PI, Hammerer P, Graefen M, Salomon G. True targeting-derived prostate biopsy: HistoScanning™ remained inadequate despite advanced technical efforts. World Journal of Urology, 2015 Jul 28.
9.	Simmons LA, Autier P, Zát'ura F, Braeckman J, Peltier A, Romic I, Stenzl A, Treurnicht K, Walker T, Nir D, Moore CM, Emberton M. Detection, localisation and characterisation of prostate cancer by prostate HistoScanning™. BJU International, 2012 Jul; 110(1):28-35.
10.	Sivaraman A, Sanchez-Salas R, Barret E, Macek P, Validire P, Galiano M, Rozet F, Cathelineau X. Prostate histoscanning true targeting guided prostate biopsy: initial clinical experience. World Journal of Urology, 2014 Dec; 1-5.
11.	Orczyk C, Rosenkrantz AB, Deng FM, Melamed J, Babb J, Wysock J, Kheterpal E, Huang WC, Stifelman M, Lepor H, Taneja SS. A prospective comparative analysis of the accuracy of HistoScanning and multiparametric magnetic resonance imaging in the localization of prostate cancer among men undergoing radical prostatectomy. Urologic Oncology, 2015 Aug 31.
Systematic Reviews	
12.	Pummer K, Rieken M, Augustin H, Gutchi T, Shariat SF. Innovations in diagnostic imaging

	of localized prostate cancer. World Journal of Urology, 2014 Aug; 32(4):881-890.
13.	van Hove A, Savoie PH, Maurin C, Brunelle S, Gravis G, Salem N, Walz J. Comparison of image-guided targeted biopsies versus systematic randomized biopsies in the detection of prostate cancer: a systematic literature review of well-designed studies. World Journal of Urology, 2014 Aug; 32(4):847-858.
14.	Schiffmann J, Manka L, Boehm K, Leyh-Bannurah SR, Karakiewicz PI, Graefen M, Hammerer P, Salomon G. Controversial evidence for the use of HistoScanning™ in the detection of prostate cancer. World Journal of Urology, 2015 Apr 10.

Excluded studies

Reference		**Exclusion criteria**
1.	Borofsky MS, Ito T, Rosenkrantz AB, Taneja SS. Focal therapy for prostate cancer - where are we in 2011? Therapeutic Advances in Urology, 2011 Aug; 3(4):183-192.	Wrong intervention.
2.	De Coninck V, Braeckman J, Michielsen D. Prostate HistoScanning: a screening tool for prostate cancer? International Journal of Urology, 2013 Dec; 20(12):1184-1190.	Wrong population.
3.	Dinter DJ, Weidner AM, Wenz F, Pelzer AE, Michel MS, Schoenberg SO. Imaging diagnostics of the prostate. Der Urologe. Ausg. A., 2010 Aug; 49(8):963-975.	Wrong language: German.
4.	Glybochko PV, Aliaev Iu G, Amosov AV. Early diagnosis of prostate cancer using histoscanning device. Urologija, 2012 Sept-Oct; (5):70-76.	Wrong language: Russian.
5.	Muller BG, van den Bos W, Pinto PA, de la Rosette JJ. Imaging modalities in focal therapy: patient selection, treatment guidance, and follow-up. Current Opinion in Urology, 2014 May; 24(3):218-224.	Wrong intervention.
6.	Robertson NL, Moore CM, Ambler G, Bott SR, Freeman A, Gambarota G, Jameson C, Mitra AV, Whitcher B, Winkler M, Kirkham A, Allen C, Emberton M. MAPPED study design: a 6 month randomised controlled study to evaluate the effect of dutasteride on prostate cancer volume using magnetic resonance Imaging. Contemporary Clinical Trials, 2013 Jan; 34(1):80-89.	Wrong intervention.
7.	Schiffmann J, Beyer B, Fischer J, Tennstedt P, Boehm K, Michl U, Graefen M, Salomon G. Histoscanning has low sensitivity and specificity for seminal vesicle invasion. Urology, 2014 Nov; 84(5):1168-1171.	Wrong population.
8.	Simmons LA. Editorial comment from Dr Simmons to prostate HistoScanning: a screening tool for prostate cancer? International journal of urology, 2013 Dec; 20(12):1192.	Wrong population.
9.	Taneja SS. Re: Prostate HistoScanning: a screening tool for prostate cancer? The Journal of Urology, 2013 Nov; 190(5):1763.	Wrong population.
10.	Walz J, Loch T, Salomon G, Wijkstra H. Imaging of the prostate. Der Urologe. Ausg. A., 2013 Apr; 52(4):490-496.	Wrong language: German.
11.	Yamamoto H, Nir D, Vyas L, Chang RT, Popert R, Cahill D, Challacombe B, Dasgupta P, Chandra A. A Workflow to Improve the Alignment of Prostate Imaging with Whole-mount Histopathology. Academic radiology, 2014 Aug; 21(8):1009-1019.	Wrong research question.
12.	Zhang YY, Hu B, Chen L. Imaging fusion in the diagnosis of prostate cancer.	Wrong

	Zhonghua Nan Ke Xue, 2015 Jan; 21(1):78-81.	language: Chinese
13.	Hamann MF, Hamann C, Olzem D, Trettel A, Juenemann KP, Naumann CM. Value of perineal HistoScanning™ template-guided prostate biopsy. Der Urologe. 2015 Mar 22.	Wrong language: German
14.	Faure Walker NA, Nir D, Simmons L, Agrawal A, Chung C, Leminski A, Rashid T, Shamsuddin A, Winkler M. Using imaging biomarkers to improve the planning of radical prostatectomies. Urologic Oncology: Seminars and Original Investigations, 2015 Jan; 33(1).	Wrong index test.
15.	Hamann M F, Hamann C, Schenk E, Al-Najar A, Naumann CM, Jünemann KP. Computer-aided (HistoScanning) biopsies versus conventional transrectal ultrasound-guided prostate biopsies: do targeted biopsy schemes improve the cancer detection rate? Urology, 2013 Feb; 81(2):370-375.	Incomplete reporting of results.
16.	Schiffmann J, Tennstedt P, Fischer J, Tian Z, Beyer B, Boehm K, Gandaglia G, Michl U, Graefen M, Salomon G. Does HistoScanning™ predict positive results in prostate biopsy? A retrospective analysis of 1,188 sextants of the prostate. World Journal of Urology, 2014 Aug; 32(4):925-930.	Wrong index test.
17.	Schiffmann J, Fischer J, Tennstedt P, Beyer B, Böhm K, Michl U, Graefen M, Solomon G. Comparison of prostate cancer volume measured by HistoScanning™ and final histopathological results. World Journal of Urology, 2014 Aug; 32(4):939-944.	Wrong outcome.
18.	Aigner F, Frauscher F. Computer-aided Ultrasonography (Histoscanning): a Novel Technology for Locating and Characterizing Prostate Cancer. BJU International, 2009 Jan; 103(1):115-116.	Wrong study design.
19.	Braeckman J, Autier P, Garbar C, Marichal MP, Soviany C, Nir R, Nir D, Michielsen D, Bleiberg H, Egevad L, Emberton M. Computer-aided ultrasonography (HistoScanning): a novel technology for locating and characterizing prostate cancer. BJU International, 2008 Feb; 101(3):293-298.	Wrong study design.
20.	Braeckman J, Autier P, Soviany C, Nir R, Nir D, Michielsen D, Treurnicht K, Jarmulowicz M, Bleiberg H, Govindaraju S, Emberton M.. The accuracy of transrectal ultrasonography supplemented with computer-aided ultrasonography for detecting small prostate cancers. BJU International, 2008 Dec; 102(11):1560-1565.	Wrong study design.
21.	Salomon G. Editorial Comment from Dr Salomon to Prostate HistoScanning: A screening tool for prostate cancer? International Journal of Urology, 2013 Dec; 20(12):1191-1191.	Wrong study design.
22.	Simmons LA, Ahmed HU, Moore CM, Punwani S, Freeman A, Hu Y, Barratt D, Charman SC, van der Meulen J, Emberton M. The PICTURE study– Prostate Imaging (multi-parametric MRI and Prostate HistoScanning™) Compared to Transperineal Ultrasound guided biopsy for significant prostate cancer Risk Evaluation. Contemporary Clinical Trials, 2014 Jan; 37(1):69-83.	Wrong intervention.
23.	Postema A, Idzenga T, Mischi M, Frinking P, Rosette J, Wijkstra H. Ultrasound modalities and quantification: developments of multiparametric ultrasonography, a new modality to detect, localize and target prostatic tumors. Current Opinion in Urology, 2015 May; 25(3):191-197.	Wrong intervention.
24.	Rosoff JS, Prasad SM, Savage SJ. Ultrasonography in prostate cancer: current roles and potential applications in radiorecurrent disease. World Journal of Urology, 2013 Dec; 31(6):1353-1359.	Wrong intervention.

*18-24 numbers go into Background section.

Quality assessment

Table 6. Quality assessment of the selected case-series regarding risk of bias and applicability concerns.

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
PHS FOR SCREENING							
Javed Study-1, 2014 [86]	Low	Low	Low	Low	Low	Low	Low
Javed Study-2, 2014 [87]	Low	Low	Low	Low	Low	Low	Low
Nunez-Mora, 2013 [36]	High	Low	Unclear	Low	Low	Low	Low
Sivaraman, 2014 [39]	Low	Low	Unclear	Low	Low	Low	Low
Schiffmann, 2015 [51]	Low	Low	Low	Low	Low	Low	Low
Hamann, 2015 [40]	Low	Low	Unclear	Low	Low	Low	Low
PHS FOR STAGING							
Javed Study-3, 2014 [90]	Low	Low	Low	Low	Low	Low	Low
Macek, 2014 [91]	High	Low	Low	High	Low	Low	Low
Salomon, 2012 [54]	Low	Low	Low	Low	Low	Low	Low
Simmons, 2012 [44]	High	Low	High	Low	Low	Low	Low
Orczyk, 2015 [78]	High	Low	Low	Low	Low	Low	Low

Table 7. Quality assessment of the selected systematic reviews.

	Pummer, 2014 [45]	van Hove, 2014 [74]	Schiffmann, 2015 [43]
1.Was an 'a priori' design provided?	Yes	Yes	Yes
2.Was there duplicate study selection and data extraction?	NA	NA	NA
3.Was a comprehensive literature search performed?	No	No	No
4.Was a status of publication (i.e. grey literature) used as an inclusion criterion?	No	No	No
5.Was a list of studies (included and excluded) provided?	No	No	No
6.Were the characteristics of the included studies provided?	Yes	Yes	Yes
7.Was the scientific quality of the included studies assessed and documented?	No	No	No
8.Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	No	No
9.Were the methods used to combine the findings of studies appropriate?	No	NA	No
10.Was the likelihood of publication bias assessed?	No	No	No
11.Was the conflict of interest included?	No	No	No

*NA – Not applicable

QUADAS-2 checklist for case series

Phase 1: State the review question:

Patients (setting, intended use of index test, presentation, prior testing):

Phase 2: Draw a flow diagram for the primary study

Phase 3: Risk of bias and applicability judgments

QUADAS-2 is structured so that 4 key domains are each rated in terms of the risk of bias and the concern regarding applicability to the research question (as defined above). Each key domain has a set of signalling questions to help reach the judgments regarding bias and applicability.

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:

- ❖ Was a consecutive or random sample of patients enrolled? Yes/No/Unclear
- ❖ Was a case-control design avoided? Yes/No/Unclear
- ❖ Did the study avoid inappropriate exclusions? Yes/No/Unclear

Could the selection of patients have introduced bias?RISK: LOW/HIGH/UNCLEAR

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):

Is there concern that the included patients do not match the review question?
CONCERN: LOW/HIGH/UNCLEAR

DOMAIN 2: INDEX TEST(S)
If more than one index test was used, please complete for each test.

A. Risk of Bias

Describe the index test and how it was conducted and interpreted:

Were the index test results interpreted without knowledge of the results of the reference standard? Yes/No/Unclear

If a threshold was used, was it pre-specified? Yes/No/Unclear

Could the conduct or interpretation of the index test have introduced bias? RISK: LOW /HIGH/UNCLEAR

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW /HIGH/UNCLEAR

DOMAIN 3: REFERENCE STANDARD
If more than one index test was used, please complete for each test.

A. Risk of Bias

Describe the reference standard and how it was conducted and interpreted:

Is the reference standard likely to correctly classify the target condition? Yes/No/Unclear
Were the reference standard results interpreted without knowledge of the results of the index test? Yes/No/Unclear

Could the reference Standard, its conduct, or its interpretation have introduced bias? RISK: LOW /HIGH/UNCLEAR

B. Concerns regarding applicability
Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW /HIGH/UNCLEAR

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference Standard:

Was there an appropriate interval between index test(s) and reference standard? Yes/No/Unclear
Did all patients receive a reference standard? Yes/No/Unclear
Did patients receive the same reference standard? Yes/No/Unclear
Were all patients included in the analysis? Yes/No/Unclear

Could the patient flow have introduced bias? RISK: LOW /HIGH/UNCLEAR

The AMSTAR checklist for systematic reviews

1. Was an 'a priori' design provided?
The research question and inclusion criteria should be established before the conduct of the review.
Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."
□ Yes
□ No
□ Can't answer
□ Not applicable

2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.
Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.
□ Yes
□ No
□ Can't answer
□ Not applicable

3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.
Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).
□ Yes
□ No
□ Can't answer
□ Not applicable

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.
Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.
□ Yes
□ No
□ Can't answer
□ Not applicable

5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided.
Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."
□ Yes
□ No
□ Can't answer
□ Not applicable

6. Were the characteristics of the included studies provided?
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.
Note: Acceptable if not in table format as long as they are described as above.
□ Yes
□ No
□ Can't answer

□ Not applicable

7. Was the scientific quality of the included studies assessed and documented?
'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.
Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).
□ Yes
□ No
□ Can't answer
□ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.
Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.
□ Yes
□ No
□ Can't answer
□ Not applicable

9. Were the methods used to combine the findings of studies appropriate?
For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).
Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.
□ Yes
□ No
□ Can't answer
□ Not applicable

10. Was the likelihood of publication bias assessed?
An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).
Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.
□ Yes
□ No
□ Can't answer
□ Not applicable

11. Was the conflict of interest included?
Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.
Note: To get a "yes," must indicate source of funding or support for the systematic review AND for each of the included studies.
□ Yes
□ No
□ Can't answer
□ Not applicable

Shea et al. BMC Medical Research Methodology 2007 **7**:10 doi:10.1186/1471-2288-7-10
Additional notes (in italics) made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010.

Checklist for potential ethical, organisational, social and legal aspects

1. Ethical	
1.1. Does the introduction of HistoScanning™ and its potential use/ nonuse instead of the defined, existing comparator(s) give rise to any new ethical issues (equal access to the treatment, resource allocation/shortage etc.)?	No
1.2. Does comparing HistoScanning™ to the defined, existing comparators point to any differences which may be ethically relevant?	No
2. Organisational	
2.1. Does the introduction of HistoScanning™ and its potential use/ nonuse instead of the defined, existing comparators require organisational changes in terms of training in procedure, need for facilities, equipment and resources?	Yes
2.2. Does comparing HistoScanning™ to the defined, existing comparators point to any differences which may be organisationally relevant (e.g. shift from primary to secondary care, transportation, etc.)?	No
3. Social	
3.1. Does the introduction of HistoScanning™ and its potential use/ nonuse instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing HistoScanning™ to the defined, existing comparators point to any differences which may be socially relevant?	No
4. Legal	
4.1. Does the introduction of HistoScanning™ and its potential use/ nonuse instead of the defined, existing comparator(s) give rise to any legal issues?	Yes
4.2. Does comparing HistoScanning™ to the defined, existing comparators point to any differences which may be legally relevant?	Yes