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Table E1: mpMRI Prostate and PI-RADS Research and Development Proposals

Data acquisition & analysis
• Multiparametric MRI versus biparametric MRI–potential roles for asymptomatic screening and for diagnosis in suspected cancer
• Biparametric MRI (bpMRI)–quality standards for data acquisition (should they be higher than for mpMRI?); should the number of assessment categories for bpMRI be changed (merge 3/4 categories). Should reader requirements be different (double reading of nonsuspicious cases). Are clinical performance indicators (see below) retained using the bpMRI approach?
• High b-value diffusion imaging roles (what values are optimal; acquired or computed, zonal value)
• Dynamic contrast enhancement (DCE-MRI) added value for detection and characterization for other PI-RADS assessment categories
• Role of quantitative diffusivity and DCE measurements
• Size distinction between PI-RADS 4/5 lesions–is the 1.5 cm cut-off optimal?
• Assessing background changes of the prostate–value?
• Refine imaging assessment criteria weighted for the number of sequences on which abnormalities are observed
• Improve upon transition zone category 3 assessment criteria that include examining patterns of enhancement and/or diffusion characteristics
Radiologic/pathologic correlations
• Improved definition of what MRI can and cannot detect
• PI-RADS categories versus detected/undetected lesions according to GS, size, index lesion status, including sensitivity analysis according to % GS4 in GS3+4 (GGG2) disease
• Suspicion scores versus detection rates according to prostate zonal anatomy
• Documentation on the range of specific pathologies including prevalences for individual PI-RADS assessment categories
• Multireader performance of PI-RADS criteria against whole mount histopathology, including dominant sequence concept and the contribution of DCE-MRI on observer performance
• Radiologic/pathologic correlations on prostatectomy specimens/high density sampling of in-situ glands
• Oncologic equivalence between MRDB and TRUS biopsies compared with final pathology–what are the rates of over and under-grading
PI-RADS validations
• MRDB in various population groups to obtain robust estimates of likely probability for all cancers and clinically significant cancers per assessment category
• Data on rule-out capability of mpMRI and bpMRI with correlation studies using high density prostate sampling including saturation/template biopsies
• Studies evaluating multireader performance of the PI-RADS criteria with whole mount histopathology, evaluating the dominant sequence concept and the contribution of DCE-MRI for each assessment category
• Studies evaluating PI-RADS and MRDB use in multiple population groups (biopsy naïve, prior negative TRUS, AS cohorts, Eastern/Western populations) to develop robust estimates of category biopsy yields
Value based care–performance indicators comparing mpMRI-MRDB pathway to PSA-TRUS pathway
• The magnitude of reduction of the number of patients undergoing mpMRI; influence of risk calculators and molecular biomarkers in the serum, urine and tissues of patients at risk
• The magnitude of reduction of biopsies by employing mpMRI & MRDB approaches in all patient groups, including for patient on AS
• The potential for reducing the over-diagnosis of insignificant cancer and how that would impact on the numbers of patients over-treated and undergoing active surveillance
• What is the effect on time to reach definitive diagnosis and to start treatment for relevant patient groups according to health systems
• Changes in risk-stratification of patients diagnosed with prostate cancer–risk migration toward higher risk categories, with fewer low-risk disease and the favorable subgroup of intermediate risk patients
• Changes in the proportion of patients undergoing radical therapies for appropriately chosen patients
• Changes in the number of patients undergoing gland sparing procedures including focal treatments and active surveillance
• Changes in the active surveillance results related to early and late drop-out rates because of improvements in initial patient selections
• Quality of life (QoL) measurements related to avoidance of biopsy, surety of pathologic state and therapy related side-effects including sepsis rates and anxiety
• Costs & effectiveness of the mpMRI first approach for different health care systems, and whether appropriate reimbursed costs utilizing modeling with actual patient flows
Expansion of PI-RADS guidance
• Quality standards of MRDB procedures

• Screening
• Active surveillance
• Risk-stratification and staging of known disease
• Prognostic impacts of PI-RADS scoring
• Recurrence
mpMRI-MRDB pathway implications
• Management implications of different PI-RADS scores; currently, ranges of percent likelihoods have not been assigned to each PIRADS v2 assessment category, which inhibits management recommendation for each PI-RADS assessment category.
• Management implications per PI-RADS category in all examined populations
• Should PI-RADS be combined with other metrics to inform on management plans
• What do we do about mpMRI nonsuspicious patients? Who should follow nonsuspicious mpMRI patients not undergoing biopsy–what should be the regimen for follow-up? What are the exceptions?
• Optimal management of PI-RADS 3 (equivocal) patients; should clinical biomarkers influence decision for biopsy & follow-up after negative histology
• Who should follow-up PI-RADS 3–5 patients with negative biopsies?
• Should negative MRDB directed biopsies for PI-RAD 4, 5 lesions have immediate higher sampling density biopsy, if no adequate benign explanatory histology is obtained; what biomarkers should influence decision making?
• Should only targeted biopsies, or focal saturation biopsies or targeted + systematic biopsies be undertaken for positive MRI for biopsy-naïve patients and relative trade-off for over-diagnosis
• Define who benefits from MRDB approaches. Decision curve analyses of systematic and targeted biopsy approaches for clinical and imaging features that predict patients likely to benefit (detecting significant cancers) versus gaining no benefit (side-effects and over-diagnosis); sensitivity to a variety of pathologic definitions.
• Consensus recommendations preferably using RAND methodology to define biopsy implications of PI-RADS categories, follow-up strategies when biopsies are deferred, use of multivariate tools to inform on the need for mpMRI and/or biopsy
mpMRI integration with emerging next generation prostate cancer diagnosis tools
• Multivariate risk assessments with biomarkers such as PSAD, PSA isoforms, urinary genomics and risk calculators to select patients for mpMRI and/or biopsy.
• Decision curve analyses of the contributions of MRI to biomarkers to improve prostate cancer diagnostics
• Multivariate imaging before biopsy (MRI/PET/US/other).
• Delineation of prostate gland habitats based on quantitative imaging likely to harbor cancer.
• Accurate lesion sampling with US/MRI fusion or in-bore targeted Bx.
• Computer/robotic targeted tissue sampling for histology, IHC, genomic analyses.
• Nomograms to select patients for mpMRI
• Nomograms to improve the rule-out ability of mpMRI
Computer aided diagnosis/machine learning and artificial intelligence solutions
• Image quality control and remedial tool according to machine type and software levels
• Role in determining who needs contrast medium enhancement for those preferring biparametric MRI approaches
• Determination of normal cases–those not requiring biopsy
• Define roles in detection, classification & localization of suspected cancer locations
• Second reader role for intermediate cases
• Ability to adapt performance to match patient clinical priorities (biopsy avoidance versus increasing biopsy yields)
• Integration of clinical biomarkers
Quality standards for mpMRI (data acquisitions, reporting and biopsy)
• Develop objective quality standards for mpMRI sequence components (DWI is particularly urgent)
• Technologist training SOPs
• Defining levels of mpMRI reading competence and specific tasks enabled by training
• Define competencies for MRI-directed biopsies

MRDB = site-specific MRI-directed biopsy using US/MRI fusion technique or in-bore technique, TRUS = 10–12 systematic transrectal US-guided core biopsies as per international standards. Saturation biopsy using transrectal or transperineal sampling (eg, Ginsburg approach). TPMB-transperineal mapping biopsy, mpMRI = PI-RADS-compliant multiparametric MRI, MRDB = MRI-directed biopsy, PI-RADS = Prostate Imaging Reporting and Data System, 4 K score = incorporates a panel of four kallikrein protein biomarkers (total PSA, free PSA, intact PSA, and human kallikrein-related peptidase 2) and other clinical information in an algorithm that provides a percent risk for clinically significant (Gleason grade ≥ 7) cancer on TRUS biopsy, PHI = prostate heath index, PCA3 = Prostate

cancer gene 3, FH = family history, PSAD = Prostate specific antigen density (ng/mL/cm^3), IHC = immunohistochemistry.