Multiparametric MRI in Prostate Cancer: Open source tools for quantitative analysis and data standardization

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Prostate Cancer

- 1 in 7 men in USA will be diagnosed over lifetime
- PSA, DRE and sextant biopsy are still first line tests
- Clinical challenges
 - Early detection of aggressive disease
 - Therapy selection and monitoring
 - Early detection of recurrence







Bladde

Perinheral

Unethra

- A test to identify fatal disease would spare 80% from treatment
 - \$1.3B cost savings annually
- Localized disease: no significant difference between active Tx vs observation

Aizer et al. Cost implications and complications of overtreatment of low-risk prostate cancer in the United States. *J. Natl. Compr. Canc. Netw.* **13**, 61–68 (2015). Hamdy et al & ProtecT Study Group. 10-Year Outcomes after Monitoring, Surgery, or 2 Radiotherapy for Localized Prostate Cancer. *N. Engl. J. Med.* **375**, 1415–1424 (2016).

Nuclear Magnetic Resonance Imaging of the Prostate

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Summary—Nuclear magnetic resonance (NMR) imaging of the prostate has been done in 25 patients, using a prototype machine developed in Aberdeen. It is a non-invasive technique which demonstrated the anatomical extent and pathological nature of prostatic lesions. The NMR images in both benign and malignant prostatic disease on this machine are comparable with first generation CT scans.

NUCLEAR MAGNETIC RESONANCE IMAGING OF THE PROSTATE



Materials and Methods

⁷²⁷ Twenty-five patients planned for prostatic surgery were studied. The clinical features, pathology and NMR diagnoses were correlated. The Aberdeen NMR imager, which has been described in detail elsewhere (Edelstein *et al.*, 1980; Hutchinson *et al.*, 1980), is based on a 4 coil, air cored magnetic ring producing a static field of 0.04 tesla, giving a proton NMR frequency of 1.7 MHz for the hydrogen proton of body tissue. It is capable of 17.53 mm equivalent thickness requires data to be (collected from 128 electrical signals, each signal being collected during a s interval. Thus all the data for each section are collected in just over 2 min.

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It is concluded that NMR imaging is a non-invasive technique which shows great promise in improving the anatomical and pathological definition of body lesions. It is a technique that has been developed only recently but has advanced very rapidly, and there can be little doubt that further technical improvements will greatly improve the anatomical display and the pathological accuracy of diagnosis. As improvements occur, the use of NMR imaging in the diagnosis and planning of treatment of neoplastic disease, particularly of organs such as the prostate, will develop greatly. Further work is required but there is clear evidence that this is a very promising field of advance

Fig. 1 (a)A proton density section of being hyperplasia with the prostate outlined between bladder and rectum. (b) A T_i section of being hyperplasia; the white area in front of prostate represents bladder urine with a very long T_i time. (c) A proton density section of carcinoma of the prostate with extension posteriorly on the right. (d) A T_i section of carcinoma of the prostate with scattered areas of longer relaxation time.



Prostate Imaging - Reporting and Data System (PI-RADS)



Figure 1. Flowchart showing the PI-RADS version 2 assessment categories. DCE = dynamic contrast-enhanced MR imaging, T2-WI = T2-weighted MR imaging.

Purysko, A. S., Rosenkrantz, A. B., Barentsz, J. O., Weinreb, J. C. & Macura, K. J. PI-RADS Version 2: A Pictorial Update. *Radiographics* 150234 (2016). doi:10.1148/rg.2016150234



PRECISION study

- Multi-center, randomized, non-inferiority trial, 500 biopsy-naive subjects
- Standard biopsy vs MRI w/wo targeted biopsy
- Primary outcome: clinically significant PCa
- Result: MRI and MRI-targeted biopsy is superior to standard biopsy





For men randomly assigned to the MRI-targeted biopsy group, the areas of the prostate were scored with the use of the Prostate Imaging-Reporting and Data System, version 2 (PI-RADS v2). Scores range from 1 to 5, with higher numbers indicating a greater likelihood of clinically significant cancer; a score of 3 indicates equivocal results, 4 results that are likely to be prostate cancer, and 5 results that are highly likely to be prostate cancer. Men who had a score of 3 or higher underwent MRI-targeted biopsy. Clinically significant cancer was defined as the presence of a single biopsy core indicating disease of Gleason score 3+4 (Gleason sum of 7) or greater, and clinically insignificant cancer as a biopsy sample with a Gleason score of 3+3 (Gleason sum of 6). The Gleason score is composed of a primary (most predominant) grade plus a secondary (highest nonpredominant) grade; the range for a primary or secondary grade is from 3 to 5, with the Gleason sum ranging from 6 to 10, and with higher scores indicating a more aggressive form of prostate cancer. Percentages may not total 100 because of rounding.

Kasivisvanathan et al & PRECISION Study Group Collaborators. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N. Engl. J. Med.* **378**, 1767–1777 (2018).



INDICATION: XXXXXXX with known prostate adenocarcinoma Gleason 3 + 4 right lateral apex and another focus at the right medial apex. PSA 5.4.

COMPARISON: MR prostate MM/DD/YY.

FINDINGS: Volume of the prostate measures 34.6 mL. There is enlargement of the central gland nodularity which is likely due to benign prostatic hyperplasia. A tiny punctate focus of T1 hyperintensity in the right peripheral zone is likely due to hemorrhage from recent prostate biopsy. Note is again made of 2 areas of abnormality in the right peripheral zone. The first is a 17 x 4 mm area of T2 hypointensity posterior and midline at 6:00 with enhancement and without restricted diffusion. Second is an area of T2 hypointensity in the right peripheral zone at the mid gland without contrast enhancement or restricted diffusion. No extracapsular, seminal vesicle, or bladder invasion is noted. No retroperitoneal lymphadenopathy. Partially imaged pelvic bone marrow signal appears normal.

IMPRESSION: Unchanged areas of abnormality in the right peripheral zone, one posterior at 6:00 with T2 hypointensity and contrast enhancement without restricted diffusion and one in the right peripheral zone at the midgland with T2 hypointensity and no enhancement or restricted diffusion. INDICATION: XXXXXXX with known prostate adenocarcinoma Gleason 3 + 4 right lateral apex and another focus at the right medial apex. PSA 5.4.

COMPARISON: MR prostate MM/DD/YY.

RAF

RAF

75 ± 128

A: 0.11 cm

FINDINGS: Volume of the prostate measures 34.6 mL. There is enlargement of the central gland nodularity which is likely due to benign prostatic hyperplasia. A tiny punctate focus of T1 hyperintensity in the right peripheral zone is likely due to hemorrhage from recent prostate biopsy. Note is again made of 2 areas of abnormality in the right peripheral zone. The first is a 17 x 4 mm area of T2 hypointensity posterior and midline at 6:00 with enhancement and without restricted diffusion. Second is an area of T2 hypointensity in the right peripheral zone at the mid gland without contrast enhancement or restricted diffusion. No extracapsular, seminal vesicle, or bladder invasion is noted. No retroperitoneal lymphadenopathy. Partially imaged pelvic bone marrow signal appears normal.

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Key projects that supported development of the presented tools

- BWH QIN: "Quantitative MRI of Prostate Cancer as a Biomarker and Guide for Treatment" (PI **Fiona Fennessy**, U01 CA151261, 2010-2016)
- DFCI QIN: "Genotype and Imaging Phenotype Biomarkers in Lung Cancer" (PI **Hugo Aerts**, U01 CA190234, 2015-2020)
- DFCI ITCR: "Quantitative Radiomics System Decoding the Tumor Phenotype" (PI Hugo Aerts, U24 CA194354, 2015-2020)
- BWH ITCR: "Quantitative Image Informatics for Cancer Research" (MPI Ron Kikinis, Andrey Fedorov, U24 CA180918, 2013-2018)
- BWH "National Center for Image Guided Therapy" (PI Clare Tempany, P41 EB015898)





NATIONAL CANCER INSTITUTE Informatics Technology for Cancer Research

https://itcr.nci.nih.gov/

https://slicer.org

QI tools delivery platform: 3D Slicer

- Est. 1997
- Free open source
- Research platform, <u>not</u> FDA approved
- Visualization, annotation, analysis, IGT
- Extensible
- Broad adoption across QIN and beyond
- Version 4.8 released Oct 2017





Funding: NAC P41 EB015902, NCIGT P41 EB015898, ITCR U24 CA180918, U24 CA194354, QIN U01 CA151261



3DSlicer

onance Imaging > Most Cited Articles

Most Cited Magnetic Resonance Imaging Articles The most cited articles published since 2012, extracted from Scopus.

3D Slicer as an image computing platform for the Quantitative Imaging Network

Volume 30, Issue 9, November 2012, Pages 1323-1341

Total citations Cited by 1127



Diffusion Weighted MRI (DW MRI)

- Surrogate measure of tissue cellularity
- Restricted diffusion of water molecules in densely packed tissue
- Parameterized by the selection of b-values
- Strong correlation with prostate cancer Gleason grade
- Assessed qualitatively in clinic

Figure 3

Figure 3: Graph shows the relationship between median ADC, qualitative grade groups, and the normal mirror ROI in the peripheral zone (*PZ*) by using the turnor section with the lowest median ADC. Slope estimate with the linear mixed-effect regression model was -0.18×10^{-3} mm²/sec.



Hambrock et al. Relationship between apparent diffusion coefficients at 3.0-T MR imaging and Gleason grade in peripheral zone prostate cancer. *Radiology* **259**, 453–461 (2011).

DW Modeling in 3D Slicer

Models implemented:

- Mono-exponential
- Bi-exponential: models fast and slow diffusion components
- Kurtosis: estimates deviation from plan water diffusion
- Gamma distribution: models continuous distribution of components
- Stretched exponential



Langkilde F., Kobus T., Fedorov A., Dunne R., Tempany-Afdhal C., Mulkern RV., Maier SE. Evaluation of Fitting Models for Prostate Tissue Characterization using Extended-Range b-Factor Diffusion-Weighted Imaging. *Magnetic resonance in medicine*. 2017

More than model fitting

- Parsing of the b-values from vendor-specific DICOM attributes
- Interactive visualization of the signal curves
- Parameter map overlay
- Model fit visualization
- Fit quality diagnostics maps
- Command line interface for batch mode execution
- Pre-built binaries for Windows, Linux, macOS



Validation

- Single site evaluation
- QIN multi-site collaborative evaluation
 - Physical phantom
 - Clinical data





Fig. 5 Percent difference from reference ADC₄ for Ph4b measurements for (a) GEHC, (b) SM, and (c) PM scans. The reference value for ADC₄ for each individual RO1 is the average of the groups A and B mean ADC₄ values for that ROI. ROIs are ordered from highest ADC (0% PVP) to lowest ADC (50% PVP), left to right, for each AI or group. Concordance is excellent, except for a few measurements on the lowest ADC value (AC < 0.25 × 10⁻³ mm²/s).



FIG. 4. Boxplots of the median, 25th and 75th percentile with whiskers indicating the minimum and maximum ROI values observed for f_{slow} (**b**), ADC_{K} (**c**), K (**d**), DDC (**e**), and gamma distribution mode (**f**) with all *b*-values included. For f_{slow} , ADC_{K} , K, DDC and mode, all tissue types are significantly different from each other (P < 0.05). For D_{slow} tumors in the PZ and TZ do not differ significantly different from both normal PZ and normal TZ (P < 0.05).

Langkilde et al. Evaluation of Fitting Models for Prostate Tissue Characterization using Extended-Range b-Factor Diffusion-Weighted Imaging. *Magnetic resonance in medicine*. 2017

Newitt et al. Multisite concordance of apparent diffusion coefficient measurements across the NCI Quantitative Imaging Network. The journal of medical imaging, 2017

Dynamic Contrast Enhanced MRI (DCE MRI)

- Marker of tissue vascularity
- Increased number and density of small vessels
- Increased permeability of vessel walls
- Treatment response assessment
- Assessed qualitatively in clinic





More details: http://qiicr.org/tool/PkModeling/

DCE Modeling in 3D Slicer

- Tofts' Generalized Kinetic Model
- Individualized or population-averaged Arterial Input Function
- T1 mapping





Tofts et al. Estimating kinetic parameters from dynamic contrast-enhanced T 1-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J. Magn. Reson. Imaging* **10**, 223–232 (1999).

Validation

- QIN multi-site collaborative project
- Concordance of QIN DCE MRI analysis
- Phantom and clinical data (breast treatment response assessment)
- Result: good to excellent prediction of pathologic response with K^{trans}% change





Despite the considerable variances in parameter values obtained with different algorithms, it is rather encouraging within the context of therapy response assessment, however, that nearly all 12 algorithms provided good to excellent (ULR $c \ge 0.8$) early prediction of pathologic response using V2 K^{trans} and $k_{\rm ep}$ or their corresponding percentage changes (V2 relative to V1) as predictive markers (Table 6).

Huang et al. Variations of dynamic contrast-enhanced magnetic resonance imaging in evaluation of breast cancer therapy response: a multicenter data analysis challenge. *Translational oncology*, 2014.

Radiomics analysis



- Pyradiomics: python library for radiomics feature extraction
 - First order statistics, shape, variety of texture features
 - Preprocessing: normalization, LoG, wavelets
 - Command line interface for batch processing
 - Available in Docker, Jupyter examples
 - 3D Slicer extension for interactive

usage

van Griethuysen et al. Computational Radiomics System to Decode the Radiographic Phenotype. *Cancer Res.* **77**, 104–108 (2017).



Repeatability of mpMRI Radiomics features

- Can be highly sensitive to extraction parameters (normalization, binning, pre-processing)
- Features identified as predictive in the literature may not be reproducible
- Further investigation is needed!



Fedorov et al. Multiparametric Magnetic Resonance Imaging of the Prostate: Repeatability of Volume and Apparent Diffusion Coefficient Quantification. Investigative radiology. 2017 Schwier M, van Griethuysen J, Vangel MG, Pieper S, Peled S, Tempany CM. Repeatability of Selected Multiparametric

Schwier M, van Griethuysen J, Vangel MG, Pieper S, Peled S, Tempany CM. Repeatability of Selected Multiparame Prostate MRI Radiomics Features. Proc. of ISMRM 2018.



ADC features

Deformable image registration

- Intensity-based
 - Hierarchical up to b-spline, mutual information, ROI-constrained
 - Evaluated for MR-guided biopsy applications
- Contour-based
 - Hierarchical up to b-spline
 - Segmentation distance map
 - Evaluated for MR-TRUS fusion
- Other tools
 - Elastix
 - ITK, SimpleITK, itk-python

Fedorov et al. Image registration for targeted MRI-guided transperineal prostate biopsy. *J. Magn. Reson. Imaging* **36**, 987–992 (2012).

Fedorov et al. Open-source image registration for MRI-TRUS fusion-guided prostate interventions. *Int. J. Comput. Assist. Radiol. Surg.* **10**, 925–934 (2015).



More details: <u>https://github.com/SlicerProstate</u> <u>https://github.com/SlicerProstate/SliceTracker</u> 20

Validation





Poulin, E., Boudam, K., Pinter, C., Kadoury, S., Lasso, A., Fichtinger, G. & Ménard, C. Validation of MRI to TRUS registration for high-dose-rate prostate brachytherapy. *Brachytherapy* (2018). doi:10.1016/j.brachy.2017.11.018

A lot more 3D Slicer tools that I did not cover ...

- Annotation tools
- Deep learning models (promising results for automatic prostate segmentation, disease characterization)
- End-to-end solution for targeted in-bore MRI-guided biopsy
- Integration with devices and scanner control

More details: <u>https://slicer.org</u> <u>https://discourse.slicer.org</u> <u>http://deepinfer.org</u>

Data harmonization along the PCa management continuum



*START: Standards of Reporting for MRI-targeted biopsy studies; **PI-RADS: Prostate Imaging - Reporting and Data System; ***PRECISE: Prostate Cancer Radiological Estimation of Change in Sequential Evaluation.



What data scientists spend the most time doing





TCIA Collections

TCIA is a service which de-identifies and hosts a large archive of medical images of cancer accessible for public download. The data are organized as "Collections", typically patients related by a common disease (e.g. lung cancer), image modality (MRI, CT, etc) or research focus. DICOM is the primary file format used by TCIA for image storage. Supporting data related to the images such as patient outcomes, treatment details, genomics, pathology, and expert analyses are also provided when available.

			Read m	ore				
Show 100 \$ entri	es					Filter table	e:	
Collection \$	Cancer Type	Modalities	Subjects +	Location	Metadata	Access 🖨	Status 🜲	Updated 🗘
National Lung Screening Trial	Lung Cancer	СТ	26254	Chest	Yes	Limited	Complete	2013/03/01
CBIS-DDSM	Breast Cancer	MG	6671	Breast	Yes	Public	Complete	2017/09/27
LIDC-IDRI	Lung Cancer	CT, CR, DX	1010	Chest	Yes	Public	Complete	2012/03/21
CT Colonography	Colon Cancer	СТ	825	Colon	Yes	Public	Complete	2011/10/31
NSCLC-Radiomics	Lung Cancer	CT, RTSTRUCT	422	Lung	Yes	Public	Ongoing	2016/05/20
PROSTATEX	Prostate Cancer	MR	346	Prostate	Yes	Public	Complete	2017/03/30
MyelomaTT3PET	Myeloma	PET	300	Whole Body	Yes	Public	Coming	2016/04/16

https://www.cancerimagingarchive.net/

Research data harmonization

- Images
- Derived data
 - Image-like (e.g., segmentations, parametric maps)
 - Non-image-like Quantitative, qualitative, categorical (e.g., measurements, impressions)





	Segment	Mean [{SUVbw}g/ml]	Minimum [{SUVbw}g/ml]
1	primary tumor	10.6175	5.0406
2	lymph node 1	5.18311	3.76263
3	lymph node 2	8.29498	3.88878
4	lymph node 3	3.38146	0.353775
5	lymph node 4	6.27497	3.60357
6	lymph node 5	8.73281	4.22884
7	lymph node 6	8.50875	3.00571



Standard for images

Digital Imaging and Communication in Medicine (DICOM) is the standard for communication of medical imaging information and related data

- compatibility with acquisition and archival tools
- harmonized with other standards (HL7, JSON, XML, REST, WADO)
- History of development and adoption since 1983
- Adopted by virtually all manufacturers of medical imaging equipment
- Open international community of stakeholders
- Continuously evolving standard

Standard for images and image-related evidence

Digital Imaging and Communication in Medicine (DICOM) is the standard for communication of medical imaging information and related data

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- harmonized with other standards (HL7, JSON, XML, REST, WADO)
- History of development and adoption since 1983
- Adopted by virtually all manufacturers of medical imaging equipment
- Open international community of stakeholders
- Continuously evolving standard
- Can be used to store images and results of analysis
 - <u>clinical and pre-clinical!</u>

DICOM - preparing for the unknown, since 1983

- Standard for images and image-related evidence
- Information object definitions CT, MR, RT ... SEG, PM, SR!
 - Object type defines required and optional attributes
- For all object types: *Composite context* is formalized and required
 - Dates, patient IDs, study, series for every object
- Unique identifiers
- References to related evidence
 - Provenance of data acquisition
 - Provenance of data analysis
- Fixed syntax
 - (hierarchical) list of attribute/value pairs
- Normalized semantics
 - Common data elements / lexicons / ontologies



Conversion to DICOM

dcmqi: An Open Source Library for Standardized Communication of Quantitative Image Analysis Results Using DICOM 12

Special Article

Christian Herz^{1,2}, Jean-Christophe Fillion-Robin³, Michael Onken⁴, Jörg Riesmeier⁵, Andras Lasso⁶, Csaba Pinter⁶, Gabor Fichtinger⁶, Steve Pieper⁷, David Clunie⁸, Ron Kikinis^{1,2,9,10}, and Andriy Fedorov^{1,2}

DICOM Source code, binaries for Win/Mac/Linux, Docker Composite context is propagated from the source image data DICOM dcmgi non-DICOM Analysis-specific metadata is Segmentation image volume defined by the user and in any format readable by ITK **JSON** parametrized by a JSON-Schema (NRRD, NIfTI, Analyze, MHD) More details: netadata metadata https://github.com/giicr/dcmgi

29

Promoting and evaluating adoption of the standard

DICOM4QI: DICOM for Quantitative Imaging

- Demonstration and connectathon at RSNA
- Goals:
 - Promote adoption of the DICOM standard for Quantitative Imaging applications
 - Develop best practices for storing QI analysis data using DICOM
 - Understand and lower adoption barriers
- Educate vendors so they adopt standards
- Educate customers so they demand standards

* This is not an official IHE or DICOM connectathon. We use the word "connectathon" to describe the essence of the activity, and not our affiliation to official connectathons that are already established in the field.



Status

More details: <u>https://qiicr.gitbooks.io/dicom4qi/</u>

- RSNA Quantitative Imaging Reading Room exhibit since 2015
- RSNA 2017
 - **4 types of QI DICOM objects** (segmentations, parametric maps, volumetric measurements, tractography)
 - **11 platforms participated** (including 5 commercial)
- Free open source tools that support the standard for QI analysis results
 - 3D Slicer (desktop platform and application)
 - ePAD (browser-based application)
 - MITK (desktop platform and application)
 - OHIF LesionTracker / Cornerstone (browser-based application and toolkit)
 - vtk-dicom (desktop)

73DSlicer





Open Health

Example data collection: Head and neck cancer

- Methods paper: Medical Physics 2016
- Data paper: PeerJ 2016
 - PET SUV, segmentations, measurements, clinical data
- Data: TCIA QIN-HEADNECK collection
- Demonstration/tutorial: <u>http://giicr.org/dicom4miccai/</u>





Semiautomated segmentation of head and neck cancers in 18F-FDG PET scans: A just-enough-interaction approach

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Beichel et al. 2016. Semiautomated segmentation of head and neck cancers in 18F-FDG PET scans: A just-enough-interaction approach. Medical physics 43:2948. DOI: 10.1118/1.4948679.

✓ PEER-REVIEWED

DICOM for quantitative imaging biomarker development: a standards based approach to sharing clinical data and structured PET/CT analysis results in head and neck cancer research

Bioinformatics Clinical Trials Oncology Radiology and Medical Imaging

Andry Fedorov^{11,2}, David Clunie³, Ethan Ulrich^{4,5}, Christian Bauer^{4,5}, Andreas Wahle^{4,5}, Bartley Brown⁶, Michael Onken⁷, Jörg Riesmeier⁸, Steve Pieper⁹, Ron Kikinis^{1,2,10,11}, John Buatti¹², Reinhard R. Beichel^{4,5,13}

Published May 24, 2016

I Note that a Preprint of this article also exists, first published November 26, 2015.

PubMed 2725754

Example data collection: Repeatability of mpMRI

- Confirmed or suspected treatment naive PCa
- Quantitative measures: image-based volume and mean Apparent Diffusion Coefficient
- Standard-of-care repeat mpMRI performed within 2 weeks, with e-coil
- 189 men approached, 40 consented, 15 completed the study
- DICOM dataset to be released on TCIA (images, segmentations, measurements, radiomics features later) under review!



 Table 1
 Repeatability of the region of interest volume measurements for different structures segmented on T2-weighted axial images, and ADC and SUB maps.

	RC%	RC, cc	Mean difference, cc (% mean difference)	ICC	
PZ tROI					
ADC	112.2	0.4	0.1(42.4%)	0.7	
SUB	119.4	0.4	0.1 (42.8%)	0.57	
T2AX	70.5	0.2	0.08 (25.5%)	0.86	

 Table 2 Repeatability of the mean ADC measurements (b0-1400) for the segmented structures.

	RC%	RC, ×10 ⁻⁶ mm ⁻² /sec	Mean difference, ×10 ⁻⁶ mm ⁻² /sec (% mean difference)	ICC
WG	29.5	359	83 (6.85%)	0.72
PZ	22.3	305	88 (6.45%)	0.68
nPZ	30.2	471	175 (11.27%)	0.46
PZ tROI	41.8	447	170 (15.93%)	0.3

Conclusions

- mpMRI is a promising biomarker for PCa assessment
- Challenges remain in refinement, validation, deployment of decision support tools
- A spectrum of free open source tools are available for mpMRI analysis of PCa
- Improved data harmonization and management can be enabled by judicious use of standards
 - tools, reference datasets, implementations are available

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- Ron Kikinis, Clare Tempany, Hugo Aerts
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- Collaborators and colleagues beyond immediate team
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Thank you!

These slides: http://bit.ly/aapm2018-fedorov



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