



Dr. Jeffrey Sunshine

Dr. Sunshine is Professor of Radiology, Neurology and Neurosurgery at Case Western Reserve University recognized for his efforts to promote and advance the use of technology to improve patient outcomes. His research work covers now decades of effort in developing, demonstrating and deploying novel imaging tools for use in particular with acute stroke patients. This work has been long supported by both industry and government, including the National Institute of Health (NIH). Concurrently clinical domains include active practice in both diagnostic and interventional Neuroradiology. His efforts have encompassed many NIH funded trials across the use of functional MRI, imaging changes in chronic

Dear readers and colleagues,

I'm extremely honored to serve as editor for this year's RSNA edition of Siemens Healthineers MAGNETOM Flash journal. This opportunity allows me to share my perspective so fortunately gained from participating in MR developments applied to healthcare for nearly three decades.

My career began as the discovery and availability of MR Diffusion imaging dawned. We were able to pursue its use in the earliest identification of hyper-acute ischemic stroke first in pre-clinical models, and then within just a couple of years into clinical care [1]. The power of rapid diffusion-weighted images to reveal earliest cerebral infarct in a manner never seen before generated enormous enthusiasm, crowded lecture halls, numerous publications by many of you, and most importantly dramatically altered how we can and should care for patients when they face these impactful challenges. For certain, MR diffusion newly showed critical physiology necessary to judge acute intervention, yet additionally it heralded another dimension in MRI, which brings innovation from lab to bedside even today: the power of advanced imaging created with ultra-fast methodologies to confirm health or reveal disease. The likes of simultaneous multi-slice acquisitions, sparse image space acquisitions and high powered novel reconstructions have been developed, made readily available and can be read about today throughout this edition of MAGNETOM Flash – we discuss key examples below.

Simultaneous multi-slice acquisition techniques arose as the demand for image generation over less acquisition time grew considerably beyond initial parallel imaging, whether for greater spatial resolution, greater number of sequences per subject, or larger coverage.

These advancing methods took advantage of special RF pulses that excite multiple slices, encoding mechanisms to distribute signal from simultaneously acquired slices, and reconstruction methods to resolve images from multiple slices [2]. RF encoding and gradient encoding both introduce phase modulation during acquisition in *k*-space, and thus introduce a slice shift in the image domain to shift multiple slices with respect to each other. Subsequent reconstruction methods can separate them and take advantage of the information from the shifted images. Specifically CAIPIRINHA (Controlled Aliasing in Parallel Imaging Results in Higher Acceleration) can use controlled slice shifts and different coil sensitivity from multiple receiver coils to improve artifact reduction and allow higher acceleration factors [3]. A great advantage of these techniques has been mainly in preserving clinical image quality over relatively still anatomic targets, while still supporting important gains in acquisition time efficiency.

Next compressed sensing represents a prime example of high-speed acquisition techniques providing unique clinical advantages most notably under dynamic scans as best represented by cardiac imaging even with irregular or fast rhythms. Compressed sensing reconstructs images from significantly fewer measurements thus reducing scan time by exploiting the sparsity of the images. In this sense sparsity refers to the relatively few meaningful nonzero pixels in an image compared with the many noise pixels. There may also be sparsity in a transfer domain with wavelet transforms exploiting spatial sparsity or Fourier transform exploiting temporal sparsity in dynamic images. Sparse images can be recovered through random under-sampling and non-linear

disease cohorts, and evaluating tools and methods for triage and treatment of hyper-acute and acute cerebral ischemia. Dr. Sunshine has more than 80 peer-reviewed publications including those in the journals *Radiology*, *Science* and *Nature*; he has delivered more than 85 national or international invited talks.

At University Hospitals (UH) in Cleveland, he is the Chief Medical Information Officer (CMIO) serving as the primary liaison between clinical and IT staff, helping to facilitate the integrated use of their UHCare electronic medical record and many clinical applications across UH. In his tenure as CMIO, Dr. Sunshine has partnered with IT

to optimize and connect electronic medical records (EMRs) and other key clinical systems, advance digital health capabilities and elevate the patient experience through technology. Dr. Sunshine has been named "Best Doctor" by Castle Connolly since 2006 through 2018, "One of 25 Leading CMIOs" by Health Data Management in 2016 and 2017, "Who's Who of Medicine and Health-care" over many years by Marquis. Having contributed to many advances in MRI technology and clinical use, he remains in practice of Diagnostic and Interventional Neuroradiology, and continues service as Professor and Vice Chair of Informatics in Radiology for CWRU & UH.

reconstruction, where the random sampling makes the under-sampling artifacts incoherent so they appear like background noise. The non-linear reconstruction can then recover the sparse coefficients to effectively recover the image. For the clinician, all this translates to rapid acquisition of key information from very dynamic subject tissue, with then heavy additional processing regenerating the entire image. In addition to cardiac applications, compressed sensing advantages 3D Angiography as it typically requires large FOV and high spatial resolution, while the blood vessel information is intrinsically sparse. For example, vessel information can be preserved using only 5% of the transform coefficients, representing a 20-fold acceleration for the scan time [4].

A combination of fast imaging techniques has improved imaging across other motion laden anatomy, as used within abdominal imaging obtained with the patient breathing freely. A key example in this domain, GRASP (Golden-angle Radial Sparse Parallel MRI) combines radial sampling, compressed sensing and parallel imaging methods to support fast volumetric MR imaging. Radial sampling provides incoherent artifacts from under-sampling closely matching an essential requirement from compressed sensing. Sensitivity to motion is diminished as the radii keep sampling the center of k -space with every spoke. The technique then includes parallel imaging reconstruction to recover the under-sampled data and maintain image quality using the different spatial sensitivity information provided from multiple receiver coils. GRASP has been applied to free-breathing 3D abdominal imaging, cardiac cine imaging and 3D DCE imaging of the liver [5]. Techniques such as these

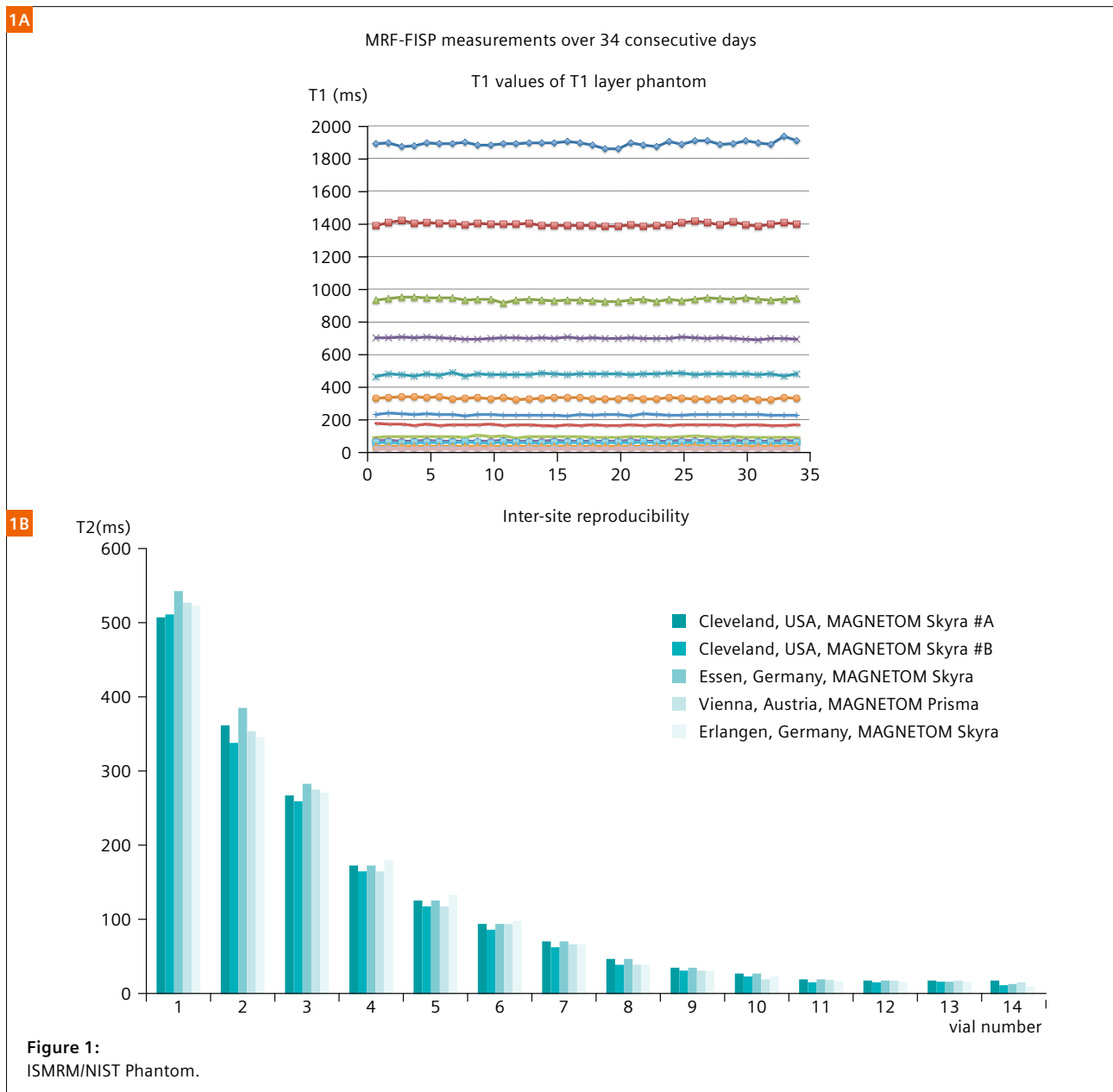
permit imaging across a much wider number of patients including the more infirm or elderly who otherwise could not hold breathes sufficient to support consistent diagnostic image quality.

I believe that now as I write to you we witness the dawn of another age beyond fast advanced imaging alone, we enter excitedly the time of quantitative image output, with all its potential to provide specificity of tissue, diagnoses and importantly broad data linkage to machine assisted analyses. In this wave of ongoing innovation, we have reported the ideas and prototypical implementations of MR Fingerprinting (MRF)¹ [6]. The MRF framework has three main components: data acquisition, dictionary generation and pattern recognition. MRF uses a pseudorandomized acquisition that makes the signal from different tissues have a unique signal evolution, simultaneously a function of multiple parameters of interest. This is accomplished by varying parameters such as flip angle and phase of RF pulses, TR, TE and sampling patterns during the acquisition to generate spatial and temporal incoherence. For this technique, one constructs a dictionary that contains signal evolutions from all foreseeable combination of relaxation and system-related parameters. Then one uses a pattern recognition algorithm to match the acquired signal to the dictionary, the results of which identifies the parameter combination in each of the voxels, and can then be translated to quantitative maps.

¹WIP, the product is currently under development and is not for sale in the US and in other countries. Its future availability cannot be ensured.

As MRF arises it can achieve the requisite burdens of proof that its quantitative output is indeed efficient and reproducible across time, subjects and machines. These characteristics remain fundamental. We have had measurement of T1, T2 and other parameters for some time, but we haven't had them with sufficient rigor to allow wide consistency across the varying circumstances of acquisition across time, place and subject. Such consistency to standards of measurement, i.e. precision, will allow us to generate broad, deep data domains through which we expect to find parameter patterns

with true specificity to the underlying human situations. We can envision our future where the end result of our imaging experiments evolve beyond the image and radiologist's necessarily loose consideration of tissue diagnoses currently framed as a differential diagnosis, perhaps including terms like moderate or severe, or descriptions of intensity. We begin to see a world where images become more complete with specific reproducible parameters of the tissue under study, where those same data permit us to create the very same weighted images as derived necessarily from the core physical



parameters. Most anticipated of all by me, we will allow the radiologist's conclusions to morph to newly enabled forms such as "the tissue in question represents tumor A with calculated probability X, and if not that then B with probability significantly lower of Y" or "the organ reveals diffuse changes compatible with normal aging of the matched age and gender in our population within two standard deviations, and this pattern has been seen in a disease C but only with significantly lower probability of Z." What a new world we create together to see ever better what's happening, what may be wrong and how we might intervene to adjust the health of our patients.

Inherent to MR Fingerprinting design then remains the focus on generation of measurements from rapid acquisition centered on the early time courses of parameter curves richest in distinguishing among tissues. The output of MRF then isn't initially targeting image quality, rather the numerical distinctions needed for specific characterization. These data must be vigorously reproducible with at least great precision to support broad implementation and comparable utilization. Some early examples of this necessary groundwork are shown in Figure 1A, where the consistency of measured T1 from the ISMRM/NIST standard phantom (NIST – US National Institute for Standards and Technology – those who bring us time from the atomic clock) is demonstrated [7]. Note that these measurements show the consistency across a month of days with all the environmental variations

of a single scanner and room. In Figure 1B we see the reliability of measured T2 from those standard phantoms across a range of T2 values with inter-site reproducibility from 5 sites, 2 machine types, and 4 cities in 3 countries. This need for consistent precision extends naturally across physiologic variations for example in heart rate. My colleagues have shown no parameter value changes through simulations across heart rates from as low as 40 bpm to as many as 120 bpm [8].

Once the quality of the quantified imaging output has been established, then the now known measured parameter values can be used to create the predicted companion T1 or T2 weighted images given the base data. Indeed we have identified a color mapping standard that allows visual distinction of T1 from T2 maps and allows our visual spectrum to better align with the apparent progression of the numeric scale as shown for MRF calculated brain images in Figure 2. Necessary data can be acquired with rapidity in as few as 15 or 16 heartbeats, then constructing images comparable to previous techniques permitting comparison of images and parameter values. As consistency holds, images can now come with additional quantified output of normal myocardial tissue prior to or following intravenous gadolinium based contrast injections. The technique has been applied preliminarily to hypertrophic cardiac myopathy where the muscle walls show typical thickening, and we receive the additional data of muscle T1 and T2 values. As we expect true change of muscle

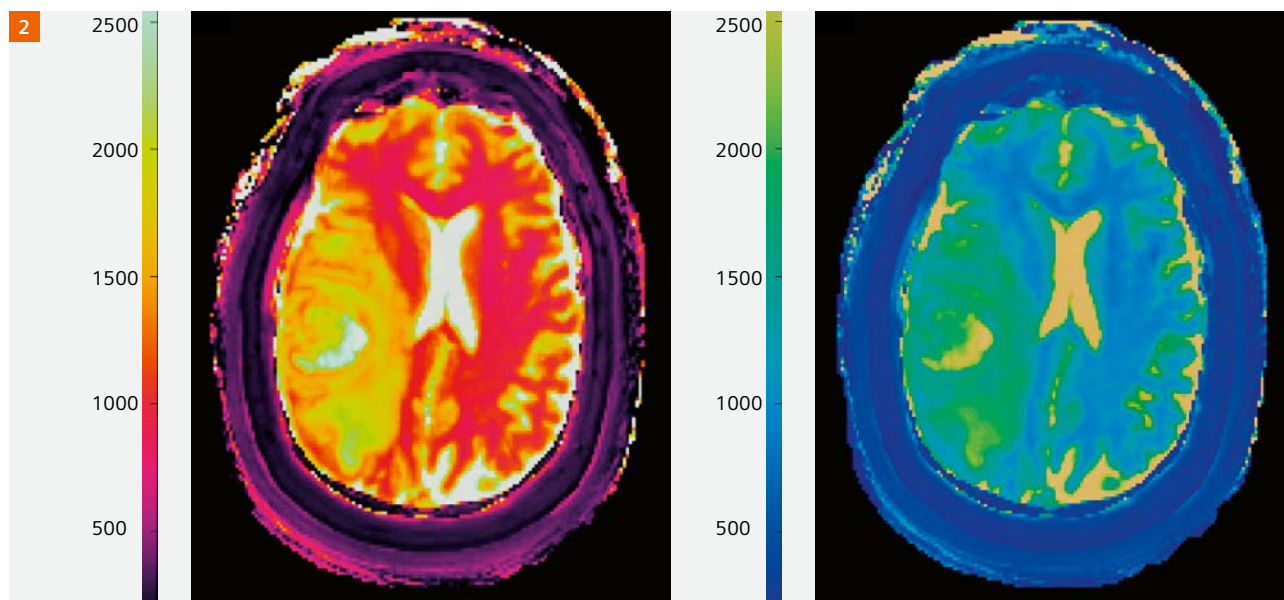


Figure 2:
Quantitative T1 and T2 maps with distinct colors.

tissue has occurred with this myopathy, we aren't surprised to learn these parameters have shifted and are distinct from those measured in dilated cardiac myopathy. Our future will reveal whether we can detect such diseases ever earlier than the thickening or dysfunction to allow intervention to slow down or avoid harmful progressions.

Combinations of MRF measured parameters and accompanying derived images allow characterization of other normal and specific disease tissues, and colleagues have published results from MRF generated over patient abdominal tissues [9]. Specific T1 and T2 normal ranges have been measured and as expected vary by tissue types across renal cortex, renal medulla, spleen, skeletal muscle, fat and liver, yet stay consistent in different organ's parenchyma. When further compared in a single tissue such as liver, a clear, significant numerical distinction with metastatic adenocarcinoma can be revealed. We look to the wider analyses needed to show how well and reliably different tumor types can be mapped between one another.

Quantitative relaxometry results can also allow us to identify changes in tissue which otherwise appears unchanged through conventional MR image acquisition, in other words increasing the dimensionality of output from MRI. Colleagues with me have used MRF to measure the T1 and T2 parameters of brain gray and white matter that has no visible lesions across changing ages and between genders [10]. This exposed a generally rising T1 value of certain brain tissues, with concomitant generally decreasing T2 value in other brain regions. There is an initial age related decrease in T2 values of frontal white matter that then increases in the later years, and this pattern is higher in males compared to females.

Given that specific quantified values have been obtained, we can combine them for analytical distinctions among otherwise conventionally similar abnormal tissues. By using both T1 and T2 values and plotting them simultaneously, valuable groupings become apparent, as when evaluating brain tumor lesions from metastases, low grade gliomas or glioblastomas [11]. The tissues may align such that only tumors display parameters above lower thresholds. Similarly when the peritumoral tissue surrounding the tumor is measured we can clearly distinguish areas with overlap to normal white matter from those that have tissue with parameters aligned to tumors. The initial analysis proceeds further and from T2 a threshold allows separation of low grade glioma from metastasis, and from T1 a separation in peri-tumoral tissue between low grade glioma and glioblastoma. Once the measures are complete they enable even further evaluations, for example textural analysis which suggests that with derived factors such

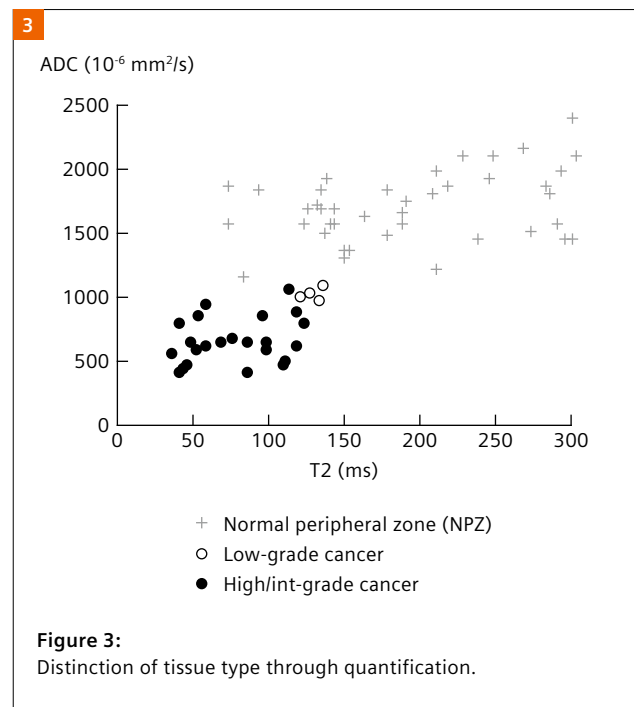
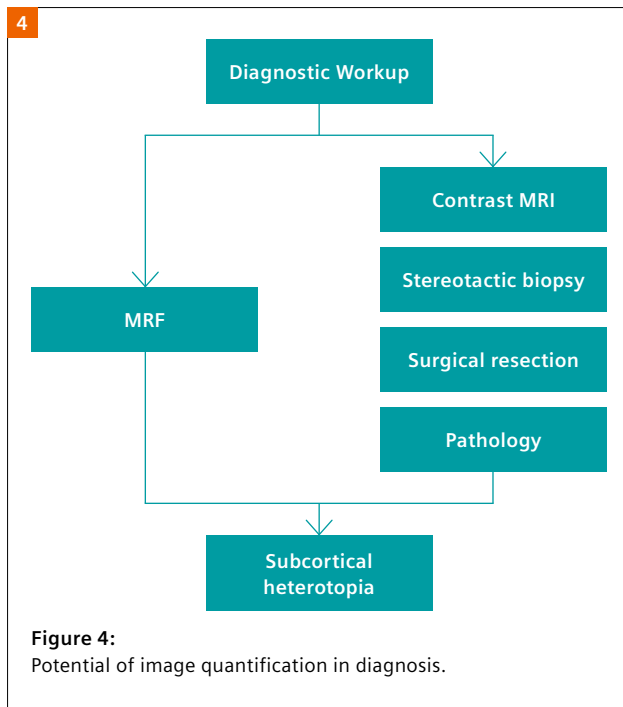


Figure 3: Distinction of tissue type through quantification.

as T1 correlation or T2 homogeneity, low grade glioma tumors can be distinguished from glioblastoma.

Combining measurements across sources can provide other pathways to identify disease. Colleagues' work has shown in prostate cancer that combining T2 values determined from MRF acquisition with ADC values from typical MR diffusion studies generate high significant difference between normal tissue and cancer in prostate peripheral zone disease [12]. Using the combination of parameters also remarkably drives the diagnostic area under the ROC curve in separating low grade from grouped intermediate and high grade lesions (the grouping reflecting need for treatment) above 0.9. When these data are used in conjunction with conventional ADC maps and calculated MRF images, biopsy can be guided, and the resultant tissue falls into distinct clusters across ADC and T2 (Fig. 3).

The power from quantified image output again provides synergies as one considers additional diagnostic complexities. After all patients don't present as simply as normal versus tumor, they may have symptoms possibly related to any of the multitude of disorders. So within the example of prostate analyses one may consider normal findings, tumor or commonly prostatitis. Separation among these appears best combining measures: a higher ADC value can sensitively select the group which excludes all worrisome cancer, while a lower value can specifically identify those which are almost always cancer needing treatment. That then leaves a middle group,



which can still be any of the lesions. First let's note that's not all bad – we've reduced the unknowns as the high values need treatment for benign conditions, and the low more aggressive care – the middle group is much smaller than the initial cohort. Further when colleagues introduce a second parameter, T2 value, another threshold appears that can stratify even this middle cohort between prostatitis and more aggressive tumors. Availability of additional quantification may also add to our ability to evaluate early response to therapy, lack of response or disease progression. Preliminary evidence from my colleagues suggests that although early decrease in breast cancer tumor volume may signify response, confirmation by change in T1 and T2 values provides clearer distinction of true responders among all those with some early shrinkage.

Specificity of tissue typing through rapid precise measurement of tissue physical characteristics including T1 and T2 offer high efficiency in healthcare. Consider a brain lesion that has appearance under conventional MRI that could represent congenitally displaced gray matter heterotopia, or less likely low grade glioma, which if so ought best be resected. Colleagues have such an example in which an initial biopsy returned consistent with a tumor, leading to full open resection. Of interest here, MRF acquisition obtained during the initial imaging generated T1 and T2 numerical values aligned only with gray matter and quite distinct from the range found in low grade gliomas. Full pathologic evaluation

of tissue after resection revealed only heterotopic gray matter with no evidence of neoplasm. Diagnostic workup of today (Figure 4, right column) included three resource intensive steps of i) enhanced conventional MRI ii) stereotactic biopsy and iii) surgical resection to learn the true diagnosis, which of itself needs no surgery. The workup of tomorrow enabled by quantitative imaging output ought well engage only the single step of MR Fingerprinting or similar to confirm the sole tissue present and forego any need of intervention.

I couldn't conclude my discussions here without acknowledging the extraordinary privileges afforded to me at Case Western Reserve University and University Hospitals in Cleveland, Ohio, USA. In particular as a long active clinician here, my partners from the science of MR Physics sequentially moved along the lines here connecting Mark Haacke, Jeffrey Duerk, Mark Griswold and Nicole Seiberlich, Ph.D.s all; few indeed have been impacted so deeply over such a continuum of gifted MR minds. There remain many other collaborators here gifted in their own right that stand too numerous to mention all, yet our MR Fingerprinting work could not have succeeded as it has without the vision and leading contributions from Vikas Gulani M.D. and Dan Ma Ph.D. (with special acknowledgement for their exceptional efforts shaping our clinical vision with MRF, and assisting in preparation of this editorial respectively). I'd also note, again representing my extraordinary opportunities, the decades long partnership with Siemens Healthineers Magnetic Resonance group and its many individual contributors.

Finally, I conclude again with excitement around the expansion of quantified image output occurring now, which will provide rich data already aligned to computational analysis, pattern recognition, and machine assisted learning of many varieties. These growing quantifications can unlock the vast repository of information derived from ongoing patient imaging in healthcare to analysis under 'artificial intelligence' (perhaps which may ultimately prove neither artificial nor intuitively intelligent in the human representation of that word). So relish all going on about the MR field as represented here, join in the wonder of the age of quantitative image output with all it may do to alter how we create images, and explore what we learn through the additional content, and define further how we will use these standardized data to augment our care through advanced machine processing across many domains.

Jeff Sunshine

References

- 1 Sunshine JL, Tarr RW, Lanzieri CF, Landis DM, Selman WR, Lewin JS: Hyperacute stroke: ultrafast MR imaging to triage patients prior to therapy. *Radiology*. 1999 Aug;212(2):325-32.
- 2 Barth M, Breuer F, Koopmans PJ, Norris DG, Poser BA: Simultaneous multislice (SMS) imaging techniques. *Magn Reson Med* 2016; 75:63–81.
- 3 Breuer F a, Blaimer M, Heidemann RM, Mueller MF, Griswold MA, Jakob PM: Controlled Aliasing in Parallel Imaging Results in Higher Acceleration (CAIPIRINHA) for Multi-Slice Imaging. *Magn Reson Med* 2005; 53:684–91.
- 4 Lustig M, Donoho DL, Pauly JM: Sparse MRI: The Application of Compressed Sensing for Rapid MR Imaging. *Magn Reson Med* 2007; 58:1182–95.
- 5 Feng L, Axel L, Chandarana H, Block KT, Sodickson DK, Otazo R: XD-GRASP: Golden-angle radial MRI with reconstruction of extra motion-state dimensions using compressed sensing. *Magn Reson Med* 2016; 75:775–788.
- 6 Ma D, Gulani V, Seiberlich N, et al.: Magnetic Resonance Fingerprinting. *Nature* 2013; 495:187–192.
- 7 Jiang Y, Ma D, Keenan KE, Stupic KF, Gulani V, Griswold MA: Repeatability of magnetic resonance fingerprinting T1 and T2 estimates assessed using the ISMRM/NIST MRI system phantom. *Magn Reson Med* 2017 Oct;78(4):1452-1457.
- 8 Hamilton JI, Jiang Y, Chen Y, Ma D, Lo WC, Griswold M, Seiberlich N: MR fingerprinting for rapid quantification of myocardial T1, T2, and proton spin density. *Magn Reson Med*. 2017 Apr;77(4):1446-1458.
- 9 Chen Y, Jiang Y, Pahwa S, Ma D, Lu L, Twieg MD, Wright KL, Seiberlich N, Griswold MA, Gulani V. MR Fingerprinting for Rapid Quantitative Abdominal Imaging. *Radiology*. 2016 Apr;279(1):278-86.
- 10 Badve C, Yu A, Rogers M, et al.: Simultaneous T1 and T2 Brain Relaxometry in Asymptomatic Volunteers Using Magnetic Resonance Fingerprinting. *Tomography* 2015 Dec;1(2):136-144.
- 11 Badve C, Yu A, Dastmalchian S, et al.: MR Fingerprinting of Adult Brain Tumors: Initial Experience. *Am J Neuroradiol* 2017 Mar;38(3):492-499.
- 12 Yu AC, Badve C, Ponsky LE, Pahwa S, Dastmalchian S, Rogers M, Jiang Y, Margevicius S, Schluchter M, Tabayoyong W, Abouassaly R, McGivney D, Griswold MA, Gulani V.: Development of a Combined MR Fingerprinting and Diffusion Examination for Prostate Cancer. *Radiology*. 2017 Jun;283(3):729-738.

The statements by Siemens' customers presented here are based on results that were achieved in the customer's unique setting. Since there is no 'typical' hospital and many variables exist (e.g., hospital size, case mix, level of IT adoption), there can be no guarantee that other customers will achieve the same results.

We appreciate your comments.

Please contact us at magnetomworld.team@siemens-healthineers.com

Editorial Board



Antje Hellwich
Editor-in-chief



Rebecca Ramb Ph.D.
Head of Global MR
Collaborations



Dr. Sunil Kumar. S. L.
Clinical & Product Specialist MRI
Dubai, UAE



Wellesley Were
MR Business Development
Manager Australia and
New Zealand



Gary R. McNeal, MS (BME)
Advanced Application Specialist,
Cardiovascular MR Imaging
Hoffman Estates, IL, USA

Review Board

Katja Böhm

Global Segment Manager
Pediatric and Musculoskeletal MRI

Daniel Fischer

Head of Outbound Marketing
MR Applications

Christian Geppert, Ph.D.

Head of Cardiovascular Applications

Berthold Kiefer, Ph.D.

Head of Oncological Applications

Heiko Meyer, Ph.D.

Head of Neuro Applications,
Head of Musculoskeletal Applications

Efrén Ojeda

MR Marketing Application Center

Gregor Thörmer, Ph.D.

Global Segment Manager
Oncological MR imaging