Whole-Body MRI in Healthcare Screening

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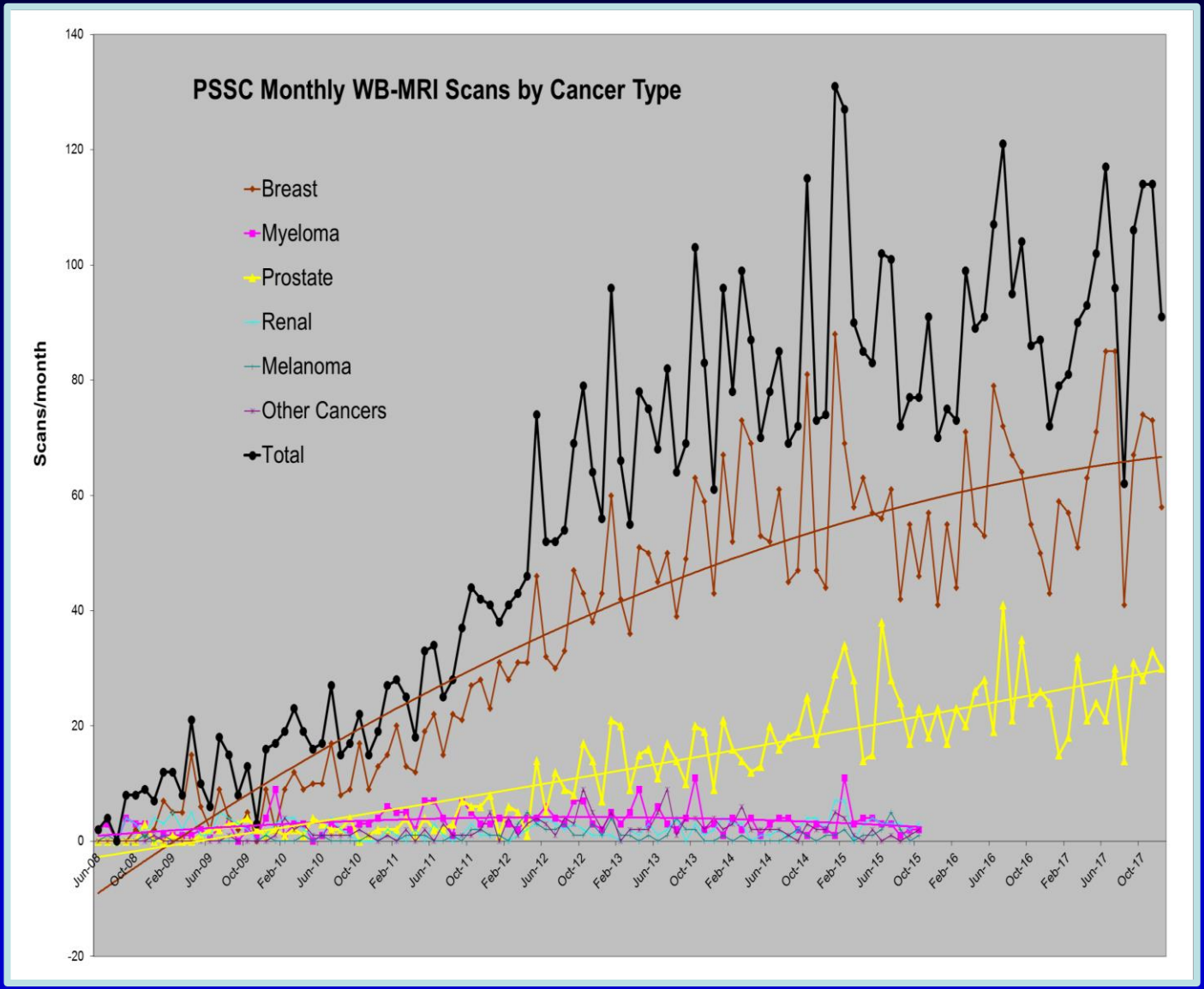
LFS UK 2018, London

WBMRI at PSSC



- Over 6000 examinations
- Developed over 10 years

JAMA Oncology | Original Investigation

Baseline Surveillance in Li-Fraumeni Syndrome Using Whole-Body Magnetic Resonance Imaging
A Meta-analysis

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IMPORTANCE Guidelines for clinical management in Li-Fraumeni syndrome, a multiple-organ cancer predisposition condition, are limited. Whole-body magnetic resonance imaging (WBMRI) may play a role in surveillance of this high-risk population.

OBJECTIVE To assess the clinical utility of WBMRI in germline *TP53* mutation carriers at baseline.

DATA SOURCES Clinical and research surveillance cohorts were identified through the Li-Fraumeni Exploration Research Consortium.

STUDY SELECTION Cohorts that incorporated WBMRI for individuals with germline *TP53* mutations from January 1, 2004, through October 1, 2016, were included.

DATA EXTRACTION AND SYNTHESIS Data were extracted by investigators from each cohort independently and synthesized by 2 investigators. Random-effects meta-analysis methods were used to estimate proportions.

MAIN OUTCOMES AND MEASURES The proportions of participants at baseline in whom a lesion was detected that required follow-up and in whom a new primary malignant neoplasm was detected.

RESULTS A total of 578 participants (376 female [65.1%] and 202 male [34.9%]; mean [SD] age, 33.2 [17.1] years) from 13 cohorts in 6 countries were included in the analysis. Two hundred twenty-five lesions requiring clinical follow-up were detected by WBMRI in 173 participants. Sixty-one lesions were diagnosed in 54 individuals as benign or malignant neoplasms. Overall, 42 cancers were identified in 39 individuals, with 35 new localized cancers treated with curative intent. The overall estimated detection rate for new, localized primary cancers was 7% (95% CI, 5%-9%).

CONCLUSIONS AND RELEVANCE These data suggest clinical utility of baseline WBMRI in *TP53* germline mutation carriers and may form an integral part of baseline clinical risk management in this high-risk population.

- Meta-analysis August 2017
- Clinical utility of WBMRI in germline TP53 mutation carriers (baseline assessment)
- Total of 578 participants
- 13 cohorts in 6 countries
- 42 cancers were identified in 39 individuals
- 35 new localized cancers treated with curative intent
- Overall estimated detection rate for new localized cancers is 7%

Familial Cancer (2017) 16:433–440
DOI 10.1007/s10689-017-9965-1

ORIGINAL ARTICLE

Baseline results from the UK SIGNIFY study: a whole-body MRI screening study in *TP53* mutation carriers and matched controls

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Published online: 16 January 2017

Abstract In the United Kingdom, current screening guidelines for *TP53* germline mutation carriers solely recommends annual breast MRI, despite the wide spectrum of malignancies typically seen in this group. This study sought to investigate the role of one-off non-contrast whole-body MRI (WB MRI) in the screening of asymptomatic *TP53* mutation carriers. 44 *TP53* mutation carriers and 44 population controls were recruited. Scans were read by radiologists blinded to participant carrier status. The incidence of malignancies diagnosed in *TP53* mutation carriers against general population controls was calculated. The incidences of non-malignant relevant disease and irrelevant disease were measured, as well as the number of investigations required to determine relevance of findings. In *TP53* mutation carriers, 6 of 44 (13.6, 95% CI 5.2–27.4%) participants were diagnosed with cancer during the study, all of which would be considered life threatening if untreated. Two were found to have two primary cancers. Two participants with cancer had abnormalities on the MRI which were initially thought to be benign (a pericardial cyst and a uterine fibroid) but transpired to be sarcomas. No controls were diagnosed with cancer. Fifteen carriers (34.1, 95% CI 20.5–49.9%) and seven controls (15.9, 95% CI 6.7–30.1%) underwent further investigations following the WB MRI for abnormalities that transpired to be benign ($p=0.049$). The cancer detection rate in this group justifies a minimum baseline non-contrast WB MRI in germline *TP53* mutation carriers. This should be adopted into national guidelines for management of adult *TP53* mutation carriers in addition

Sibel Saya and Emma Killick—Joint first authorship.

Richard W. Whitehouse, Dow-Mu Koh, S. Aslam Sohaib, D. Gareth Evans and Rosalind A. Eeles—Joint last authorship.

Electronic supplementary material The online version of this article (doi:10.1007/s10689-017-9965-1) contains supplementary material, which is available to authorized users.

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15 St Georges Hospital, London, UK
16 Mater Hospital, Dublin, Ireland

- UK SIGNIFY study 2017
- 44 *TP53* mutation carriers and 44 population controls were recruited.
- In *TP53* mutation carriers, 6 of 44 (13.6, 95% CI 5.2–27.4%) participants were diagnosed with cancer during the study, all of which would be considered life threatening if untreated.
- No controls were diagnosed with cancer.
- The cancer detection rate in this group justifies a minimum baseline non-contrast WB MRI in germline *TP53* mutation carriers. This should be adopted into national guidelines for management of adult *TP*53 mutation carriers to the current practice of contrast enhanced breast MRI imaging.

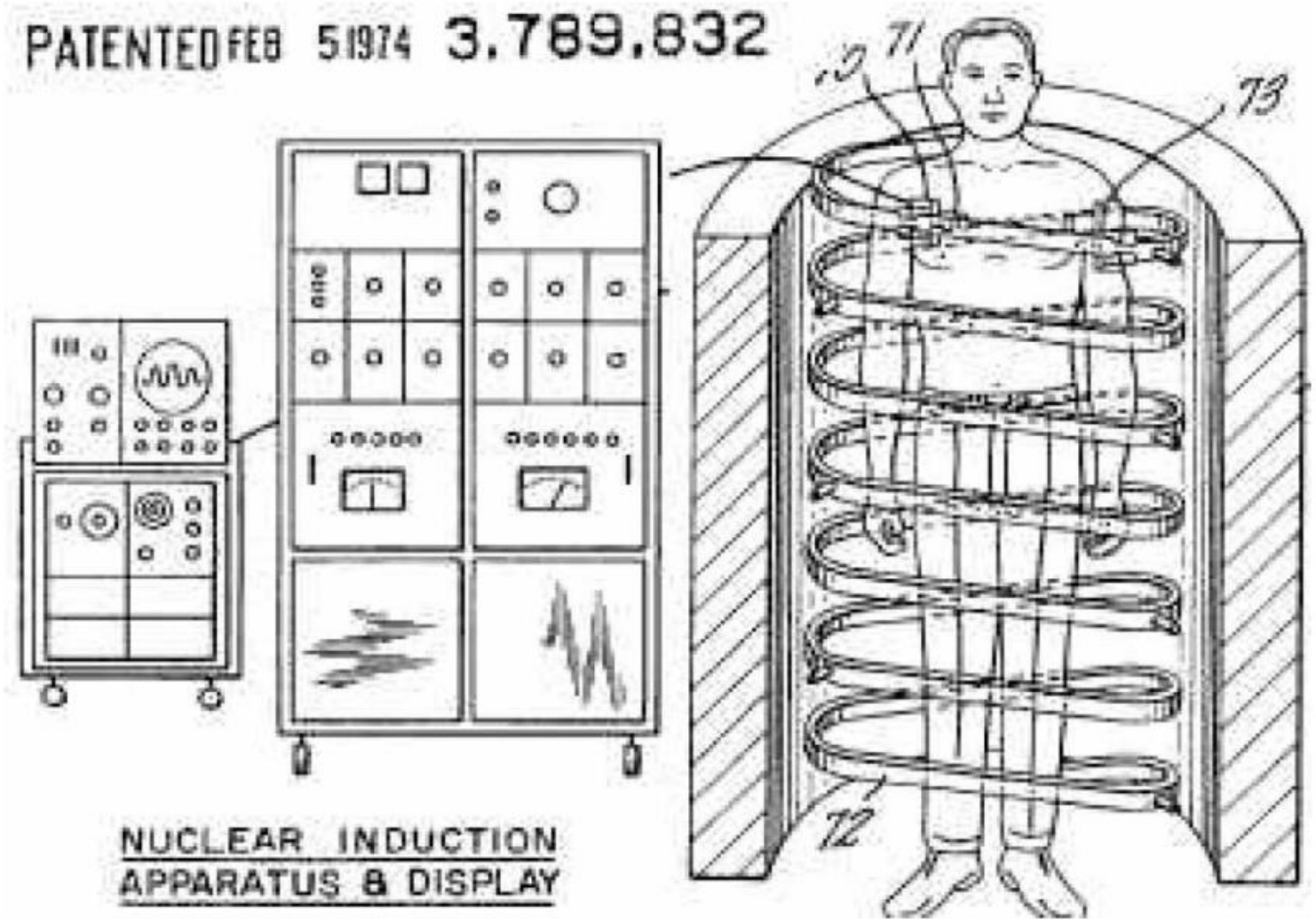
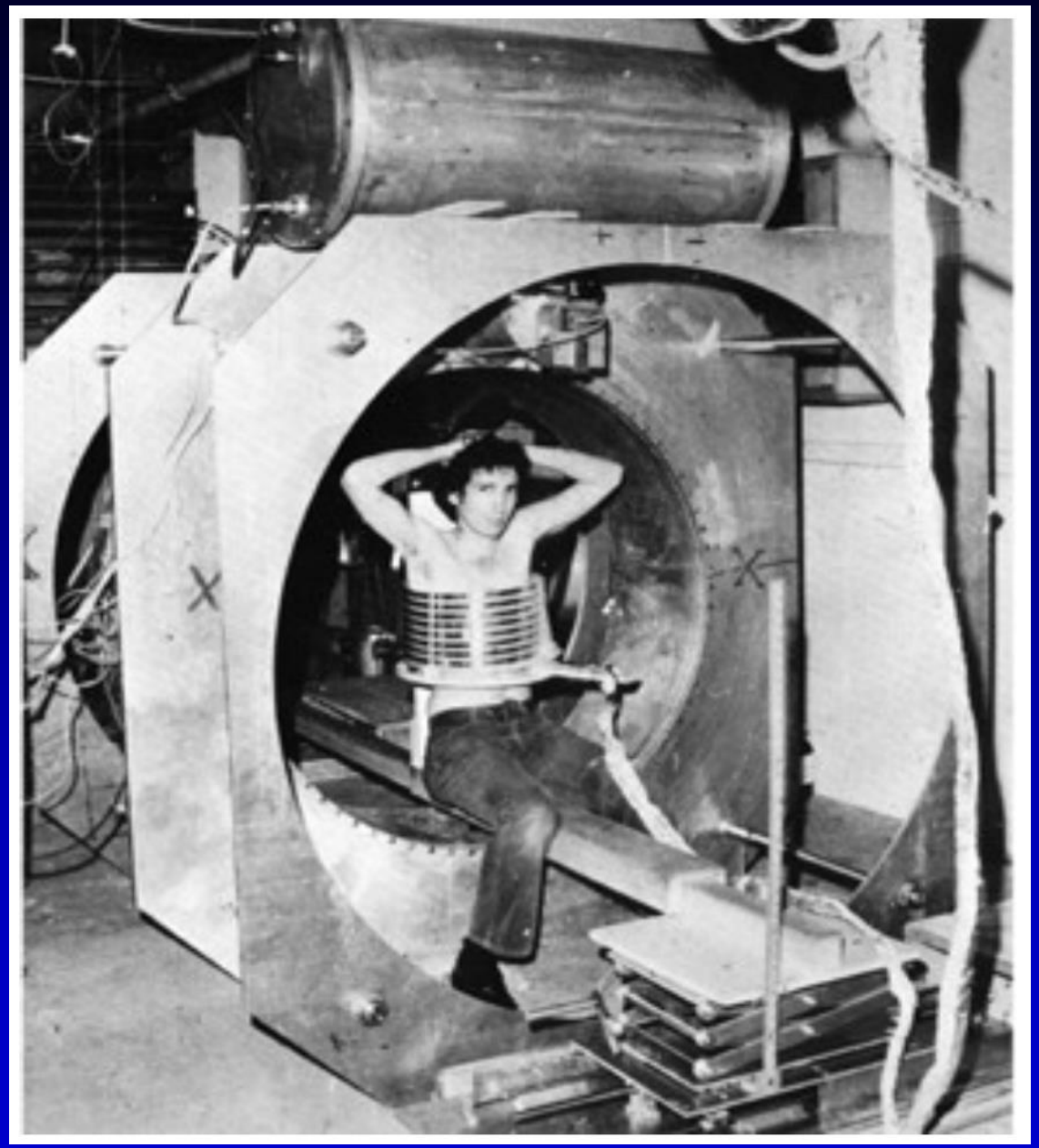
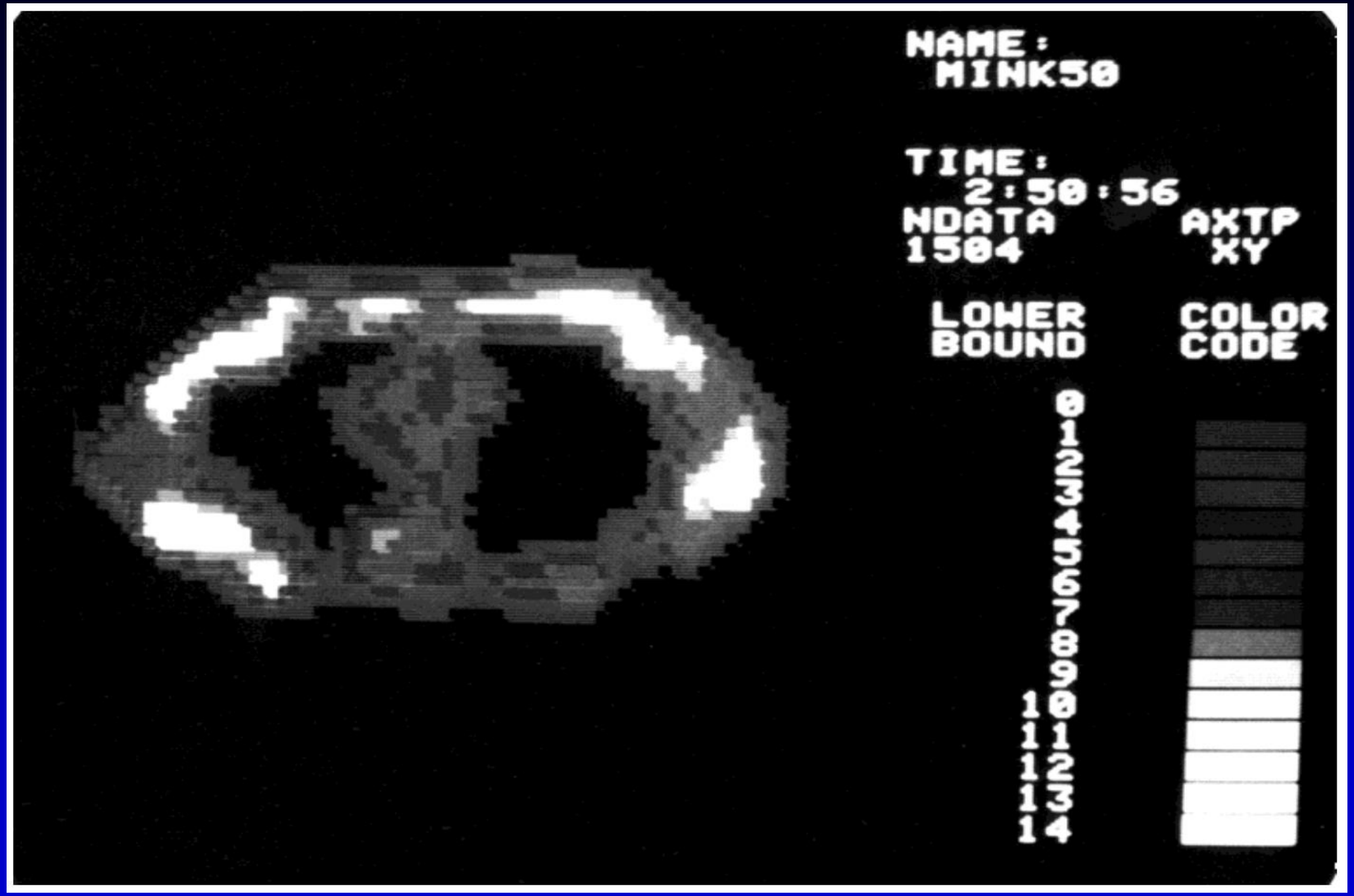


Figure 2. Damadian's patent filed on 17 March 1972. *Credit*: http://www.fonar.com/pdf/doc_7.pdf

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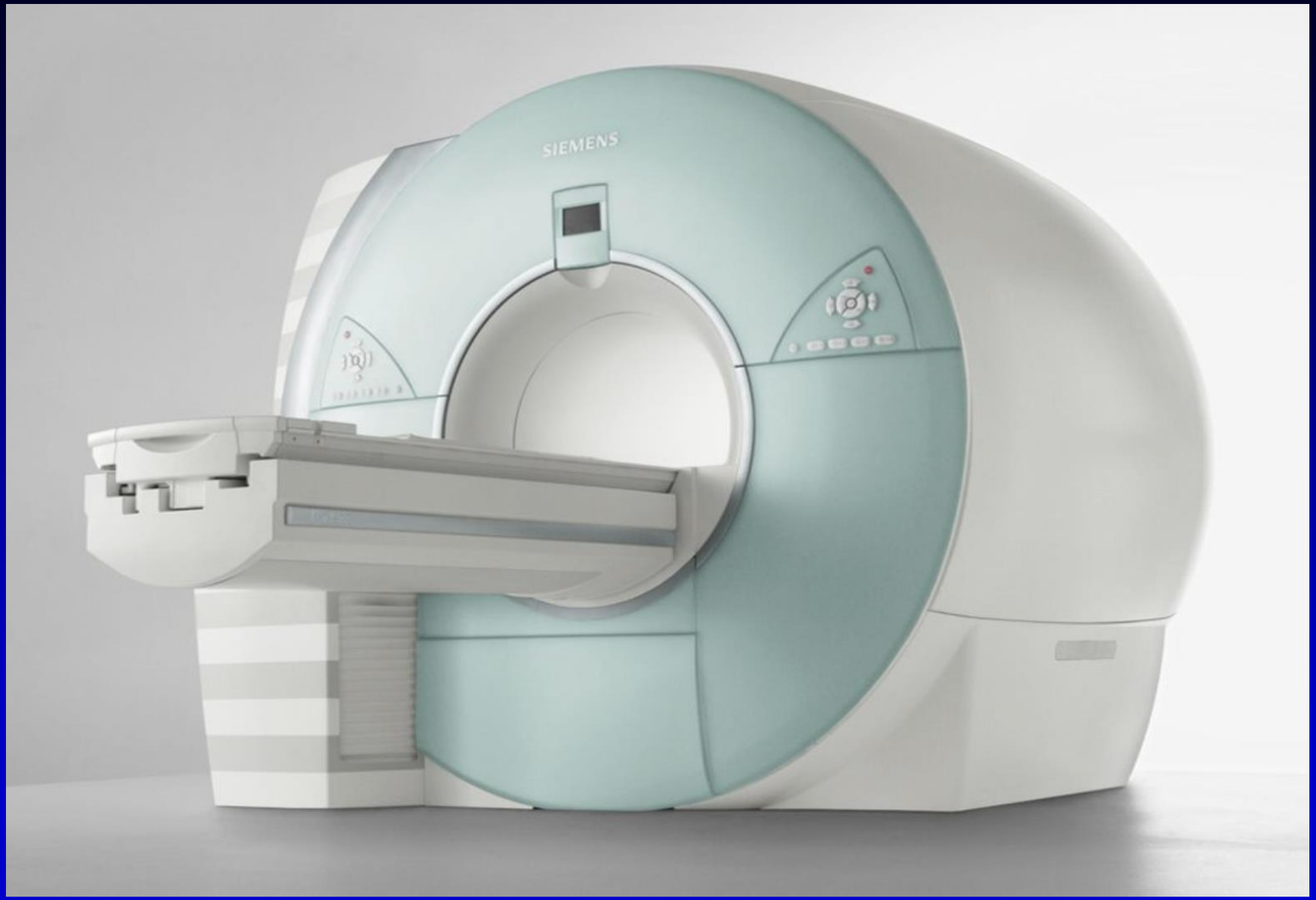

SIEMENS

“Optimal” set-up

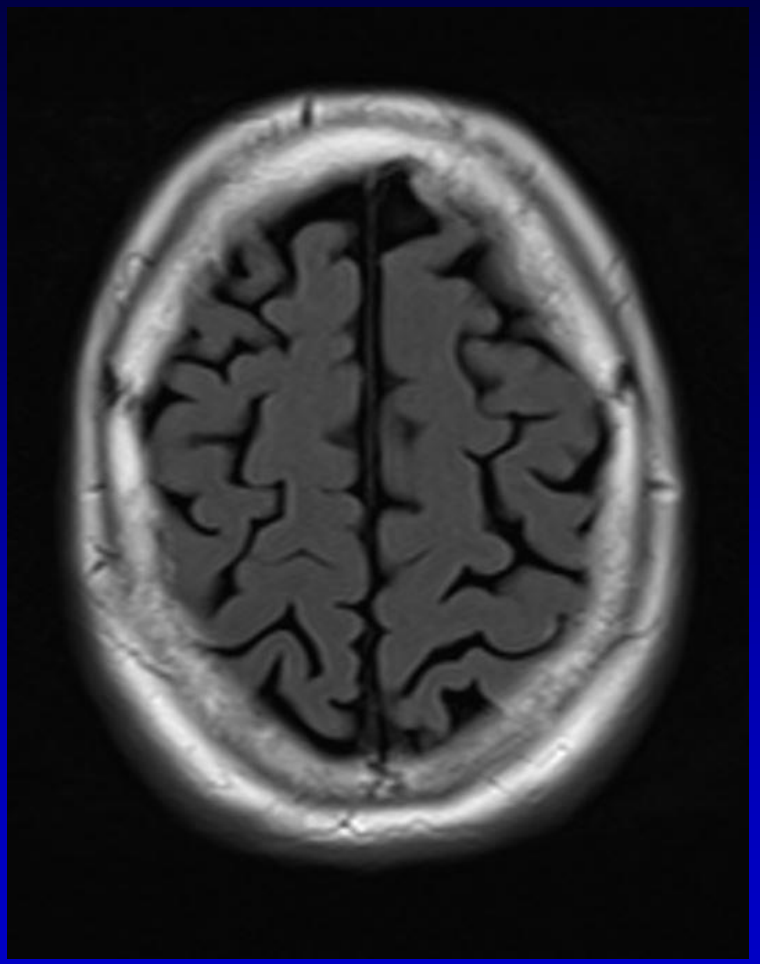
Anterior coils as far as required

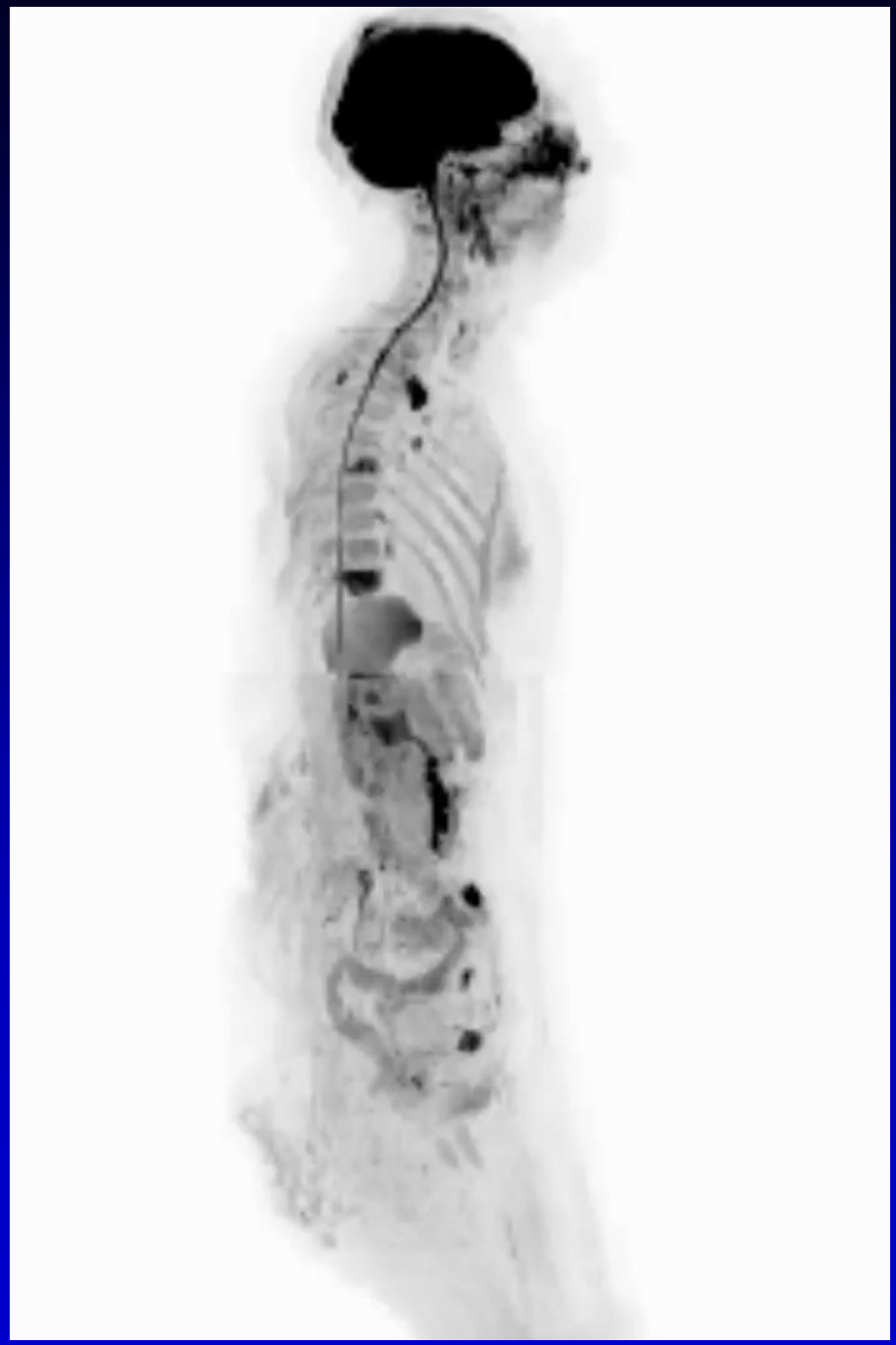
Full head coil

“Comfort” set-up

Anterior coils to thighs

Pillow over posterior head coil





Typical WBMR sequences

Region	Sequence(s)	Plane	Approx. TA	Reason for inclusion
Whole spine	STIR T1	Sagittal	5 min 2 min	Detection of metastases Assessment of activity of metastases Check for impending or actual cord compression
Head	FLAIR	Axial	1 min	Screening for brain metastases Breast cancer: assessment of mandible
Whole body	T1 DIXON GRE	Axial	3 min	Lesion characterisation Fat fraction calculation
Whole body	**DWI**	**Axial** (x4 stations)	**25 min**	**Lesion detection and monitoring** **Tumour volume measurement (ml)**
Lungs	UTE spiral VIBE	Coronal	20 sec BH	Thorax lesion detection
Whole body	T1 DIXON GRE	Coronal	20 sec x3 BH	Lesion characterisation
Whole body	T2 HASTE	Axial	3 min	Lesion characterisation Localisation for DWI
Spine (as required)	T1 and T2	Axial	2 min per	Assessment of any cord compressing lesions
		Approx. total TA:	**45 min**	

RESPECT study tolerance questionnaire

Question topic	Criterion	Week 12: response rate 27/40		Week 36: response rate 10/18	
		CT	WB-MRI	CT	WB-MRI
Level of concern	Moderate or Intense	23%	26%	20%	30%
Comfort	Barely acceptable	0%	11%	0%	20%
Helplessness	Moderate or Severe	8%	33%	20%	30%
Pain score	0-10	0.88	1.56	1.50	1.80
Willingness to repeat	Yes	100%	100%	100%	100%
Satisfaction	Good or Very Good	100%	100%	100%	100%
Preference	CT / Neither / WB-MRI	67% / 11% / 22%		80% / 0% / 20%	
Survey method adapted from Schonenberger E, et al. PLoS One 2007; 2(2): e246.					

Kosmin, M. (2017). Personal communication

CCR PEDIATRIC ONCOLOGY SERIES

Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome

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Abstract

Li-Fraumeni syndrome (LFS) is an autosomal dominantly inherited condition caused by germline mutations of the *TP53* tumor suppressor gene encoding p53, a transcription factor triggered as a protective cellular mechanism against different stressors. Loss of p53 function renders affected individuals highly susceptible to a broad range of solid and hematologic cancers. It has recently become evident that children and adults with LFS benefit from intensive surveillance aimed at early tumor detection. In October 2016, the American Association for Cancer Research held a meeting of international LFS experts to evaluate the current knowledge on LFS and propose consensus surveillance recommendations. Herein, we briefly summarize clinical and genetic aspects of this aggressive cancer predisposition syndrome. In addition, the expert panel concludes that there are sufficient existing data to recommend that all patients with LFS be offered cancer surveillance as soon as the clinical or molecular LFS diagnosis is established. Specifically, the panel recommends adoption of a modified version of the "Toronto protocol" that includes a combination of physical exams, blood tests, and imaging. The panel also recommends that further research be promoted to explore the feasibility and effectiveness of these risk-adapted surveillance and cancer prevention strategies while addressing the psychosocial needs of individuals and families with LFS. *Clin Cancer Res; 23(11); e38–e45. ©2017 AACR.*

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Introduction

Li-Fraumeni syndrome (LFS; OMIM #151623) is among the most aggressive cancer predisposition syndromes characterized by a high and early-onset cancer risk. The tumor spectrum is wide and includes brain tumors [choroid plexus carcinoma, Sonic Hedgehog (SHH) subtype medulloblastoma, glioma], adrenocortical carcinoma (ACC), a range of soft tissue sarcomas (STS) and bone tumors, hematologic malignancies, breast cancer (generally very early in onset), and other cancer types, including lung, skin, gastrointestinal tract, kidney, thyroid, as well as neuroblastoma. The tumors most closely associated with LFS are called "core" cancers and include STS, osteosarcoma, premenopausal breast cancer, brain tumors, and ACCs (for review, see refs. 1, 2).

LFS was first described in 1969 by Frederick Li and Joseph Fraumeni Jr based on their observation of a unique spectrum of cancers in four families in whom the index cases presented with rhabdomyosarcoma (3). The original definition of the syndrome was established in 1988 as the result of an analysis of 24 kindreds presenting with an autosomal dominant pattern of transmission of early-onset neoplasms including STS, breast cancers, central nervous system (CNS) tumors, leukemias, and ACCs before the age of 45 years (4). This "classical" definition requires one individual with a sarcoma diagnosed under the age of 45 who has at least one first-degree relative (parent, sibling, or child) with a cancer of any kind diagnosed under the age of 45 and a third family member who is either a first- or second-degree relative in the same parental lineage (grandparent, aunt, uncle, niece, nephew, or grandchild) with any cancer diagnosed under the age of 45, or a sarcoma at any age (4).

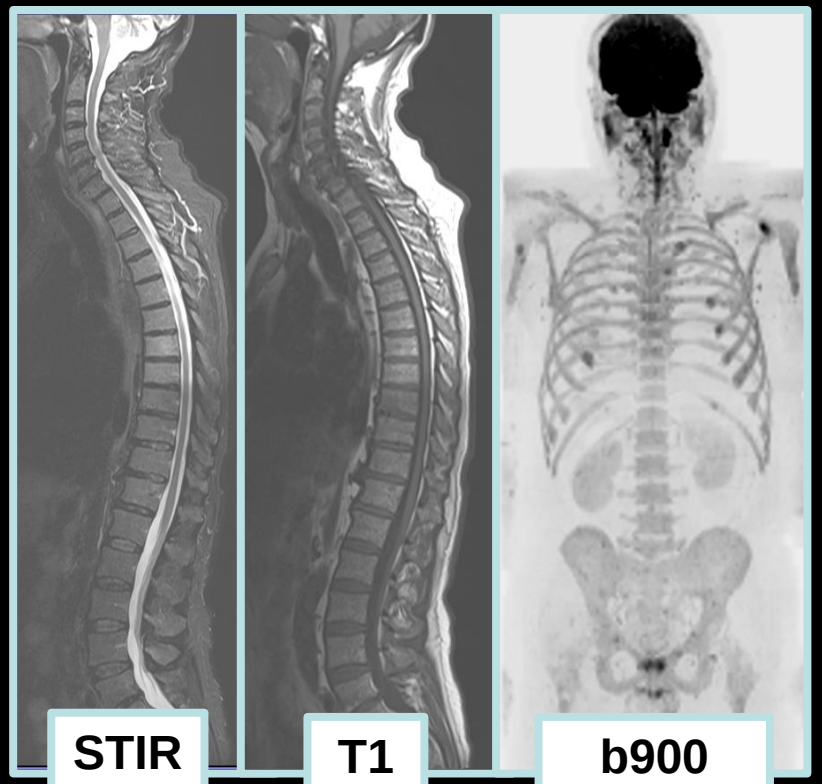
- American Association for Cancer Research meeting of LFS experts. Published June 2017.
- It has recently become evident that children and adults with LFS benefit from intensive surveillance aimed at early tumor detection.
- The panel concludes that there are sufficient existing data to recommend that all patients with LFS be offered cancer surveillance as soon as the clinical or molecular LFS diagnosis is established.
- Specifically, the panel recommends adoption of a modified version of the "Toronto protocol" that includes a combination of physical exams, blood tests, and imaging.

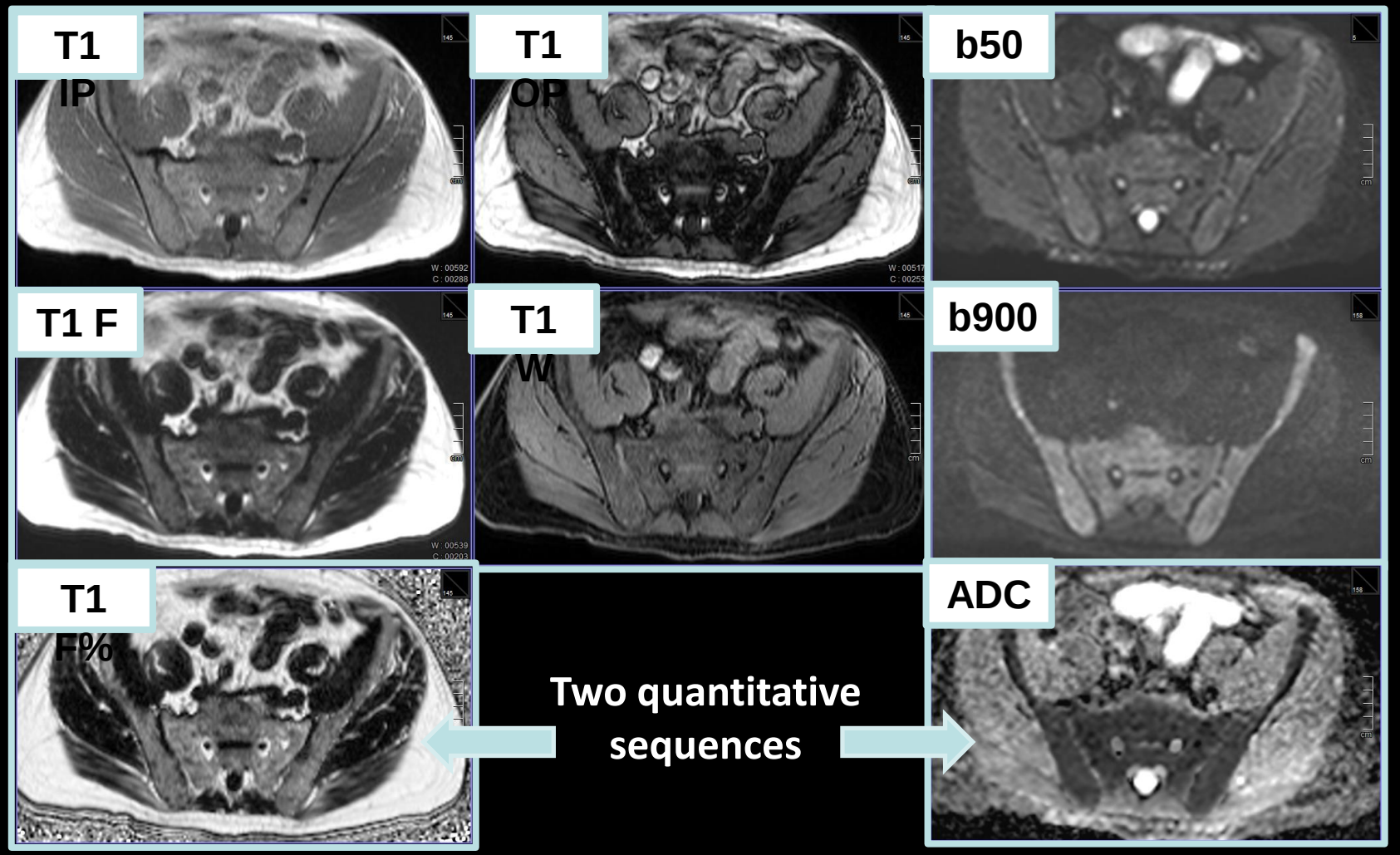
Table 1. Published surveillance protocols for individuals with LFS

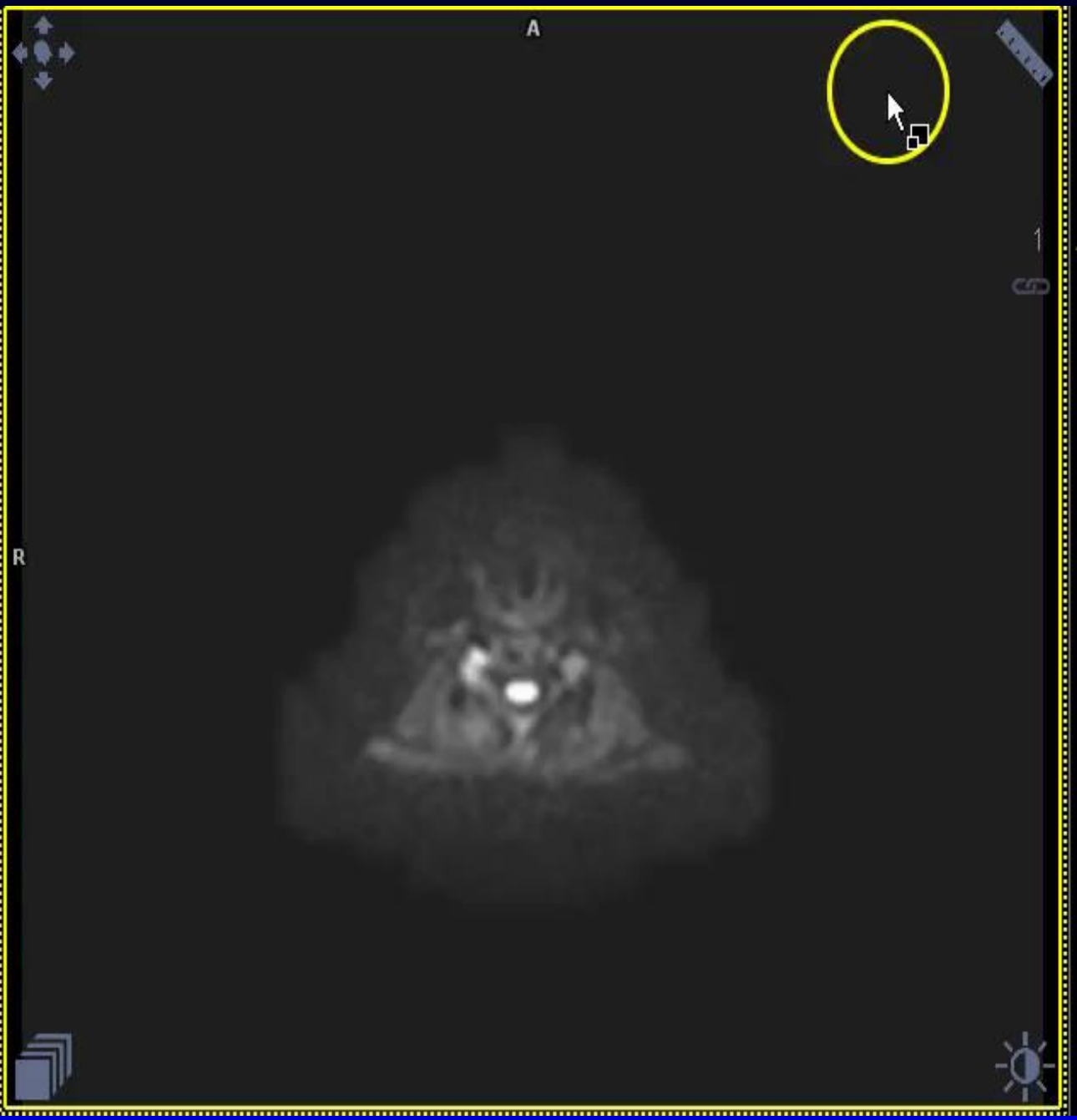
Tumor type	Australia (52, 53)	NCCN (54)	Toronto (55, 56)
ACC	AUS q 3–4 m: birth–10 y	No screening described	• AUS q 3-4 m: birth–40 y • Biochemistry (17-OH-progesterone, total testosterone, DHEAS, androstenedione) q 3–4 m: birth–40 y • 24-h urine cortisol, if feasible
Breast cancer	• BSE: from 18 y • CBE q 6–12 m: from 20–25 y • Breast MRI annually: 20/25–50 y • (Consider annual mammography ± US if not possible) • Discuss risk-reducing bilateral mastectomy	• Breast awareness: from 18 y • CBE q 6–12 m: from 20–25 y • 20–29 y: breast MRI with contrast annually (or mammogram if unavailable) • 30–75 y: breast MRI with contrast and mammogram annually • 75 y: individual recommendations • Continue screening breast cancer survivors with mammogram and breast MRI • Discuss risk-reducing mastectomy	• BSE monthly: from 18 y • CBE q 6 m: from 20–25 y or 5–10 y before earliest case of breast cancer in family • Annual mammography and breast MRI: from age 20–75 y or 5–10 y before earliest case of breast cancer in family • Breast MRI alternates with WBMRI • Breast US with mammography as indicated by breast density • Consider risk-reducing bilateral mastectomy
Brain tumor	• Brain MRI included in annual WBMRI: potentially from childhood • Annual neurologic exam • Prompt reporting of new neurologic symptoms	• The brain may be examined as part of WBMRI or as a separate exam	• Annual brain MRI: from birth
Sarcoma	• Annual WBMRI • Annual comprehensive physical exam • Awareness of new symptoms	• Annual WBMRI (or equivalent)	• Annual rapid WBMRI: from birth • AUS q 3–4 m: from 18 y
Hematopoietic	• Annual CBC: from 18 y	• No screening described	• CBC, ESR, LDH q3-4m: from birth
CRC	• Colonoscopy q 2–5 y: from age 25 or 10 y before earliest onset of CRC in family	• Consider colonoscopy q 2–5 y: from age 25 or 5 y before earliest known colon cancer in family	• Colonoscopy q 2 y: from age 25 or 10 y before earliest onset of CRC in family
Gastric cancer	• Endoscopy q 2–5 y: from age 25 or 10 y before earliest onset gastric cancer in family		No screening described
Skin cancer	No screening described	• Annual dermatologic exam	• Annual dermatologic exam: from 18 y
Other		• Annual comprehensive physical exam, including neurologic exam • Education regarding signs and symptoms of cancer. Apprise pediatricians of childhood cancer risk • Additional surveillance based on family history of cancer • Therapeutic RT should be avoided when possible	• Complete physical exam q 3–4 m, including comprehensive neurologic exam and anthropometric measurements in children • Prompt assessment with primary care physician for any medical concerns

Abbreviations: AUS, abdominal US (abdomen and pelvis); BSE, breast self-examination; CBC, complete blood count; CBE, clinical breast examination; CRC, colorectal carcinoma; DHEAS, dehydroepiandrosterone; ESR, erythrocyte sedimentation rate; h, hour; LDH, lactate dehydrogenase; m, months; q, every; RT, radiation therapy; y, years.

Whole-body MRI Images



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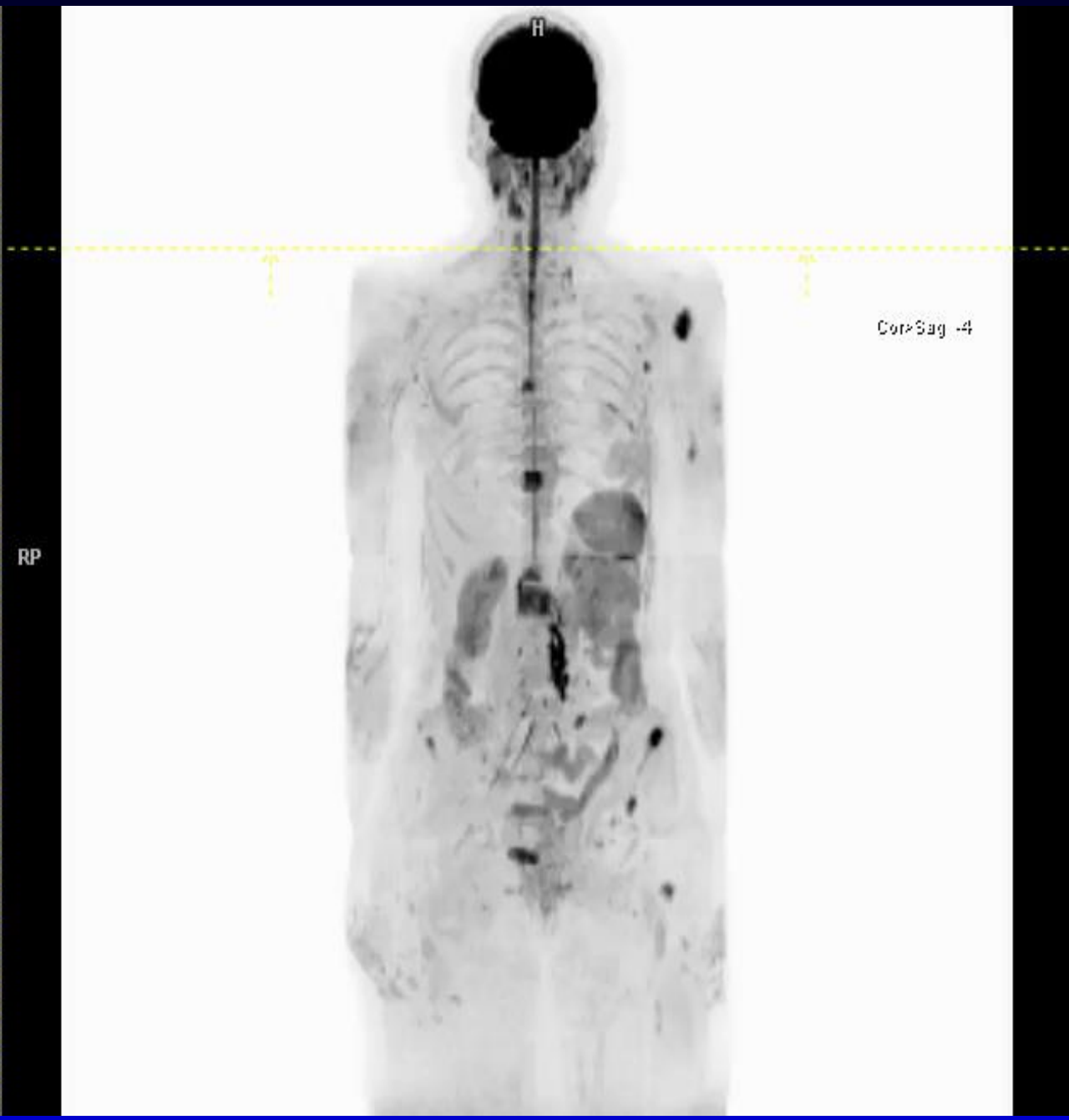
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Delivering WB-MRI for precision medicine by minimising variations

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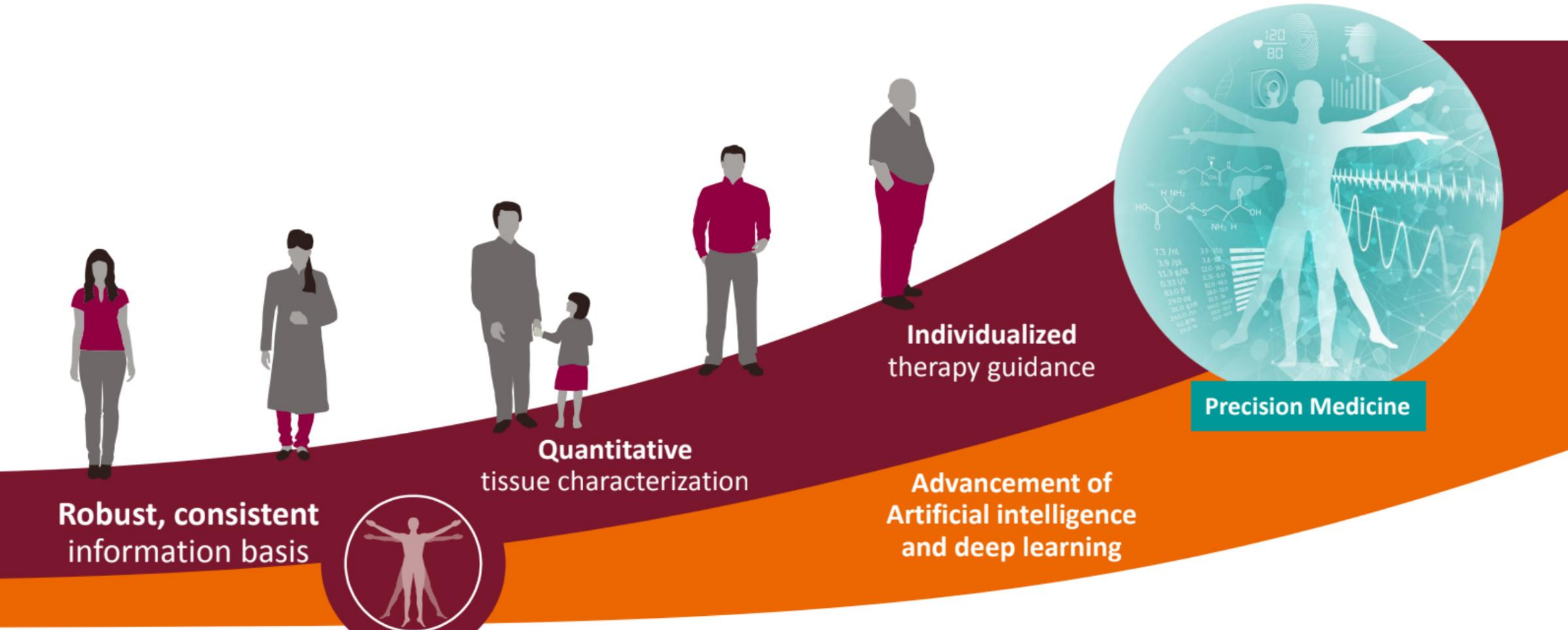

Whole-Body Dot Engine - Highest consistency for follow-up examinations and response assessment

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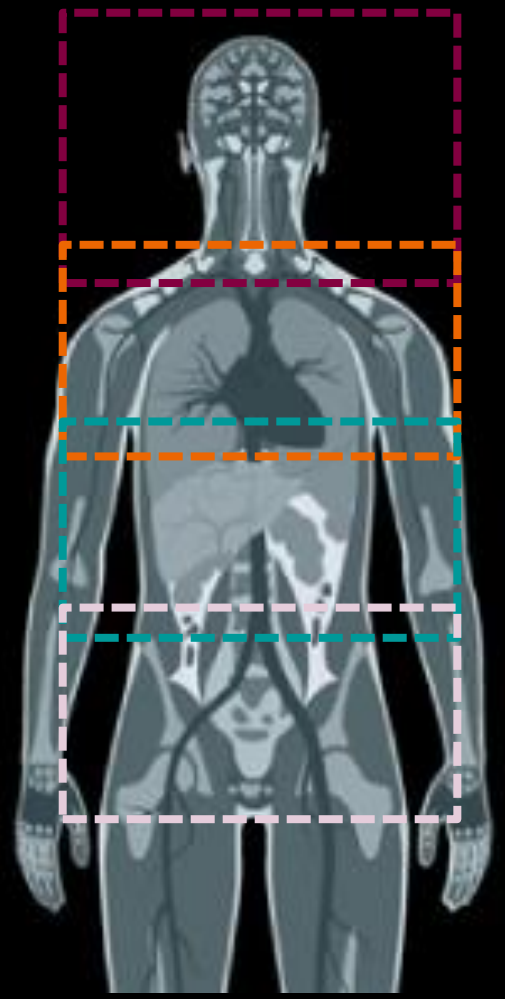
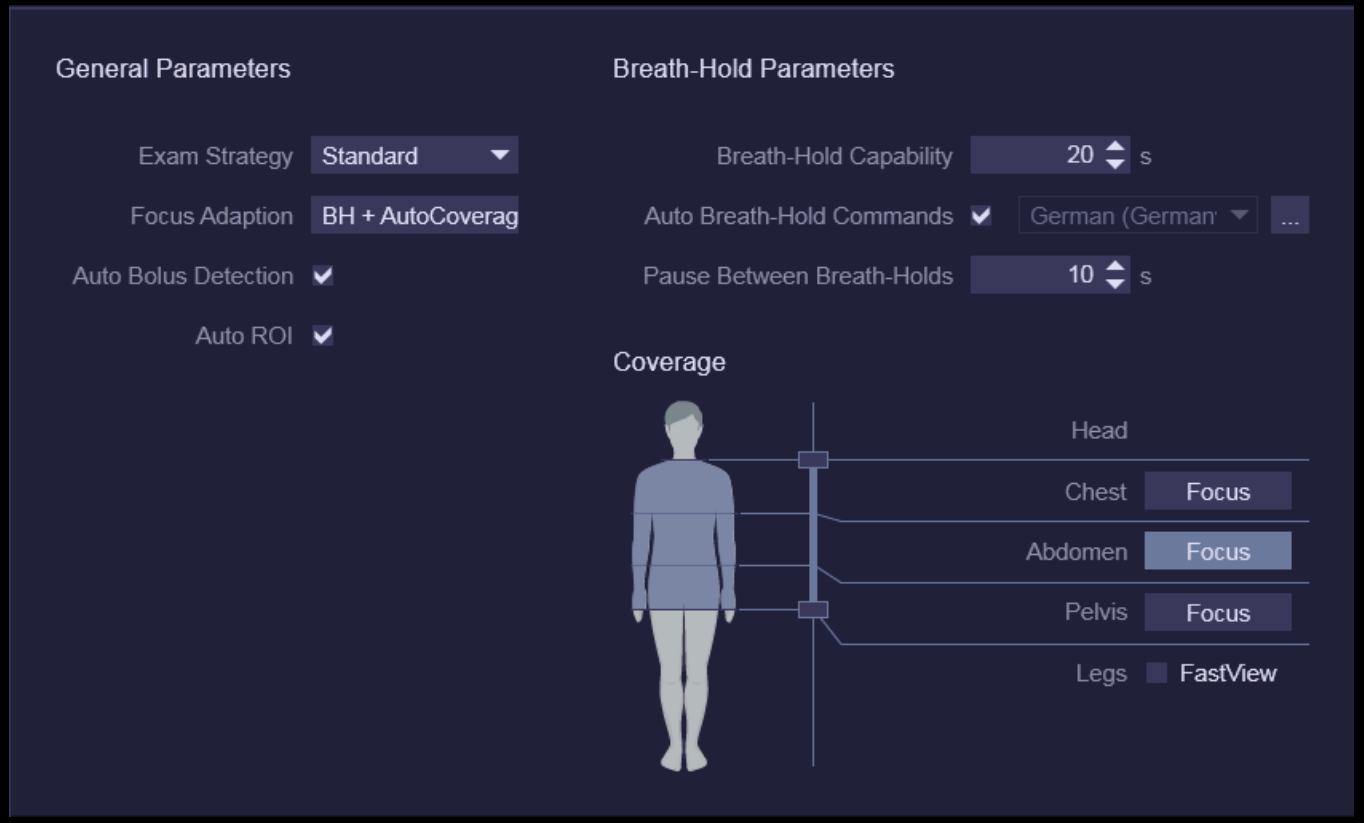


Easy, push-button workflow with Whole-Body Dot Engine

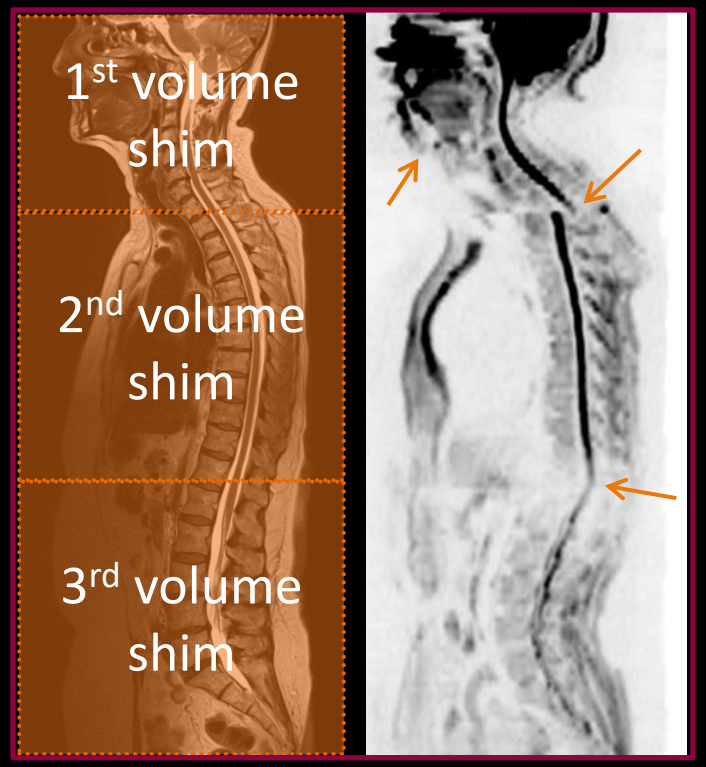


"True" whole-body coverage in 4-5 stations (MET-RADS compliant protocol)

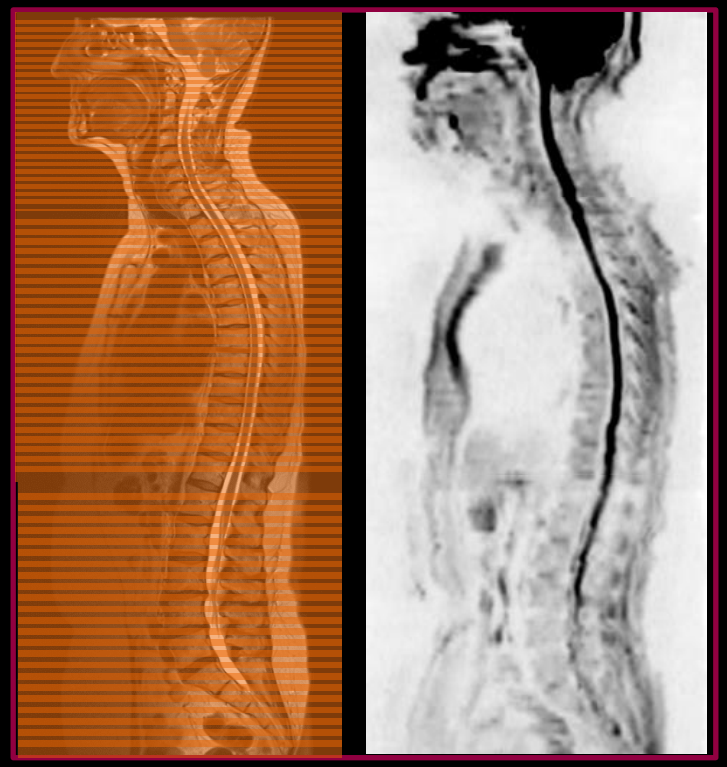
5 x 3:13 min DWI b50_800
5 x 0:42 min T2 HASTE STIR
7 x 0:12 min T1 VIBE Dixon
3 x 1:24 min T1w Spine
3 x 1:41 min T2w Spine

Σ 29:30 min

iSHIM-SliceAdjust enables distortion free Whole-Body DWI



3D Shim =
global, static compromise



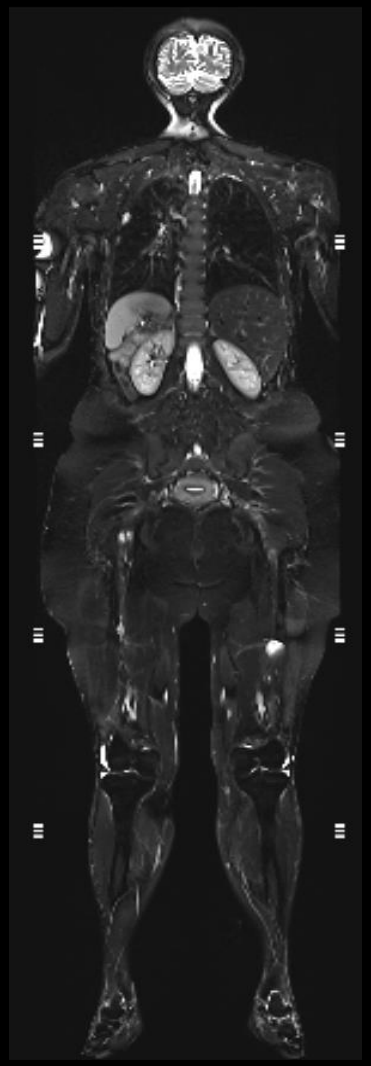
SliceAdjust =
local, dynamic optimum

Excellent correlation of DWI information with anatomical scans due to the absence of “broken spine” artifact

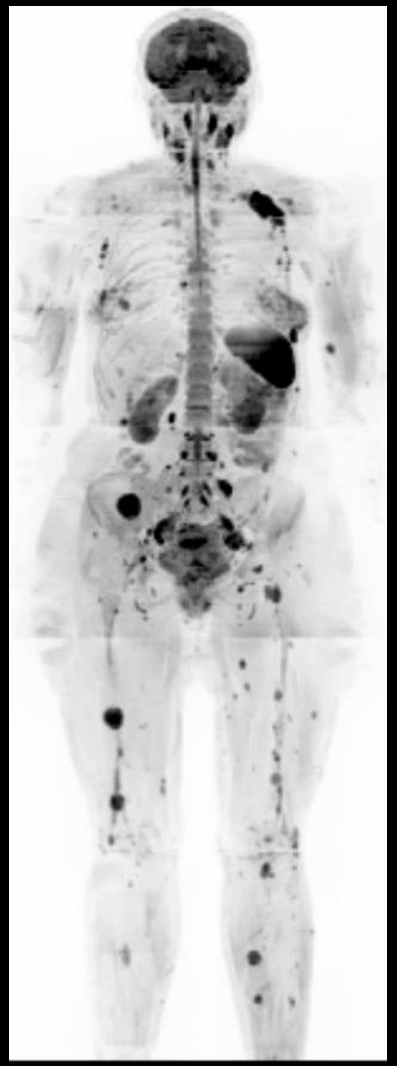
510(k) pending. The product is still under development and not commercially available yet. Its future availability cannot be ensured.

Whole Body MRI in patient with multiple myeloma
Excellent homogeneity and fast execution

SIEMENS Healthineers



T2 HASTE STIR



b800 DWI, MIP

T1w TSE

STIR TSE

"True" whole-body coverage in 5 stations (MET-RADS compliant)

5 x 3:13 min DWI b50_800
5 x 0:42 min T2 HASTE STIR
7 x 0:12 min T1 VIBE Dixon
3 x 1:24 min T1w Spine
3 x 1:41 min T2w Spine

Σ 29:30 min

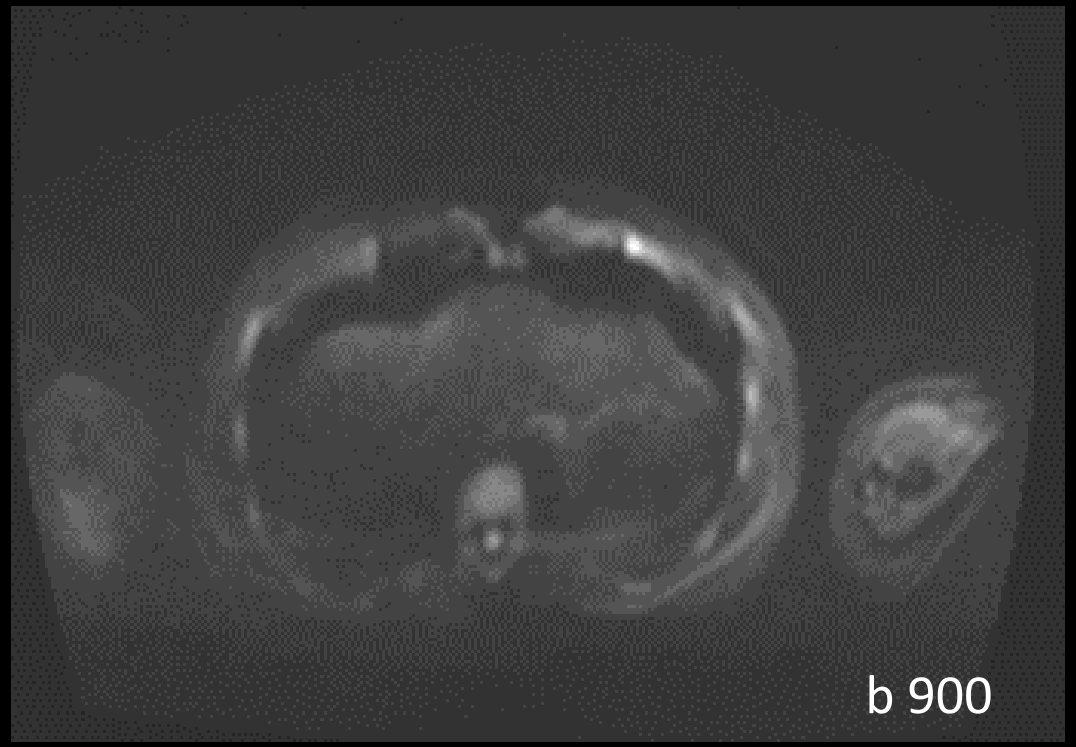
University Hospital Tübingen, Germany

Magnetic Resonance

SliceAdjust
WholeBody mode

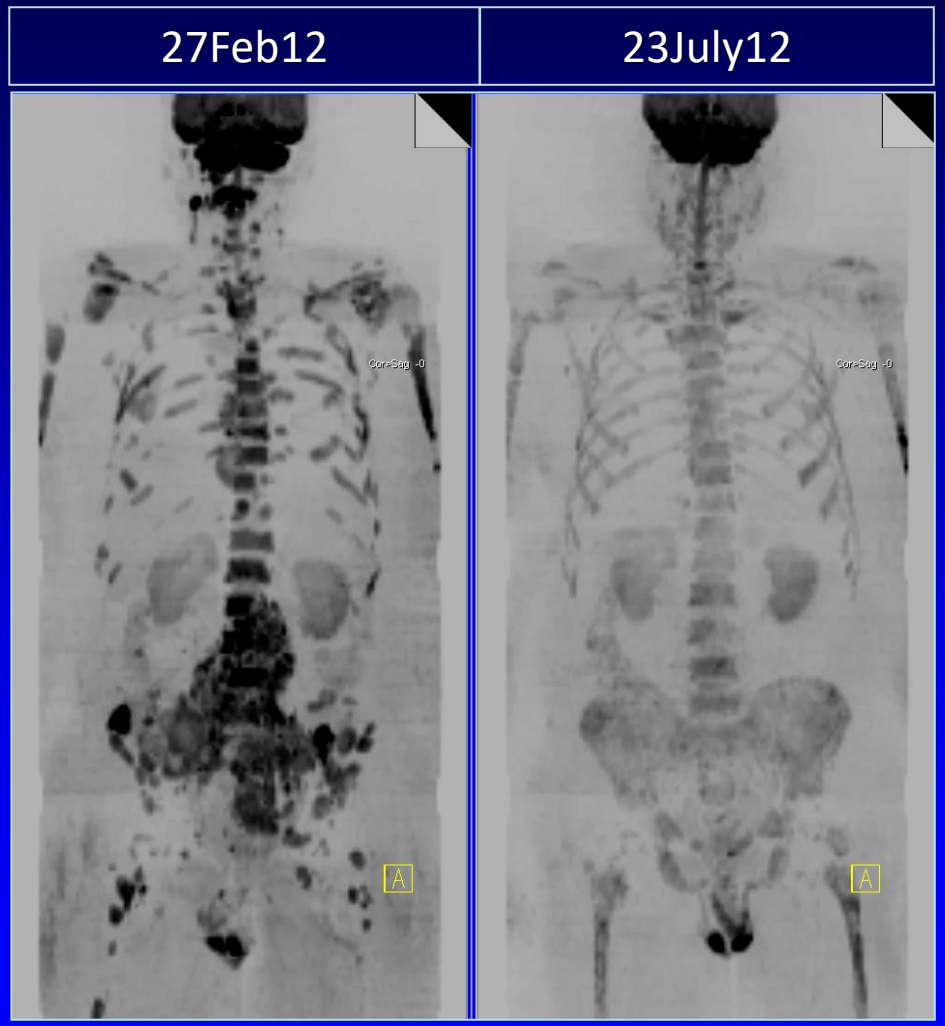
SIEMENS Healthineers

Without
SliceAdjust

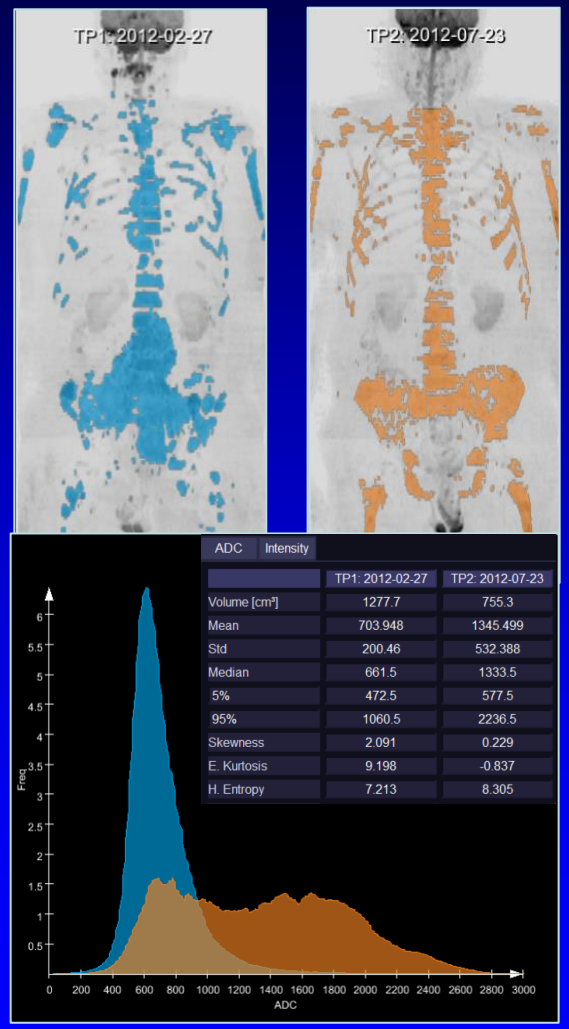


With
SliceAdjust

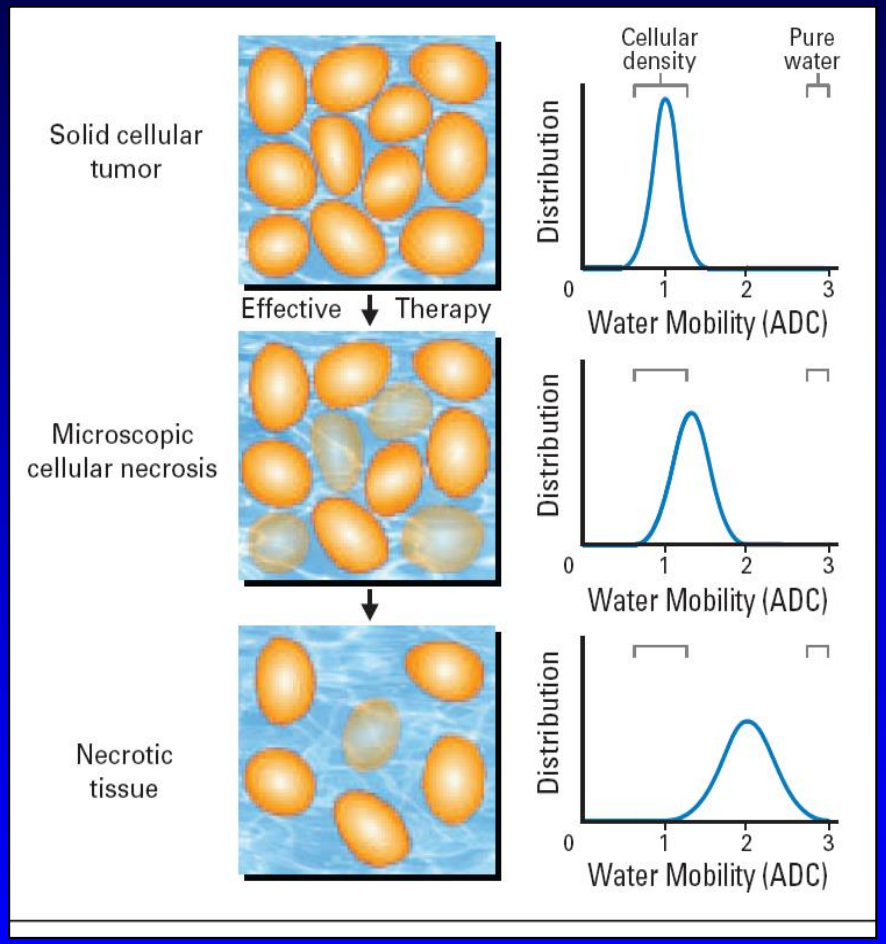
Quantitative ADC values are related to cell viability



Metastatic prostate cancer (x4 docetaxel, goserelin & prednisone)

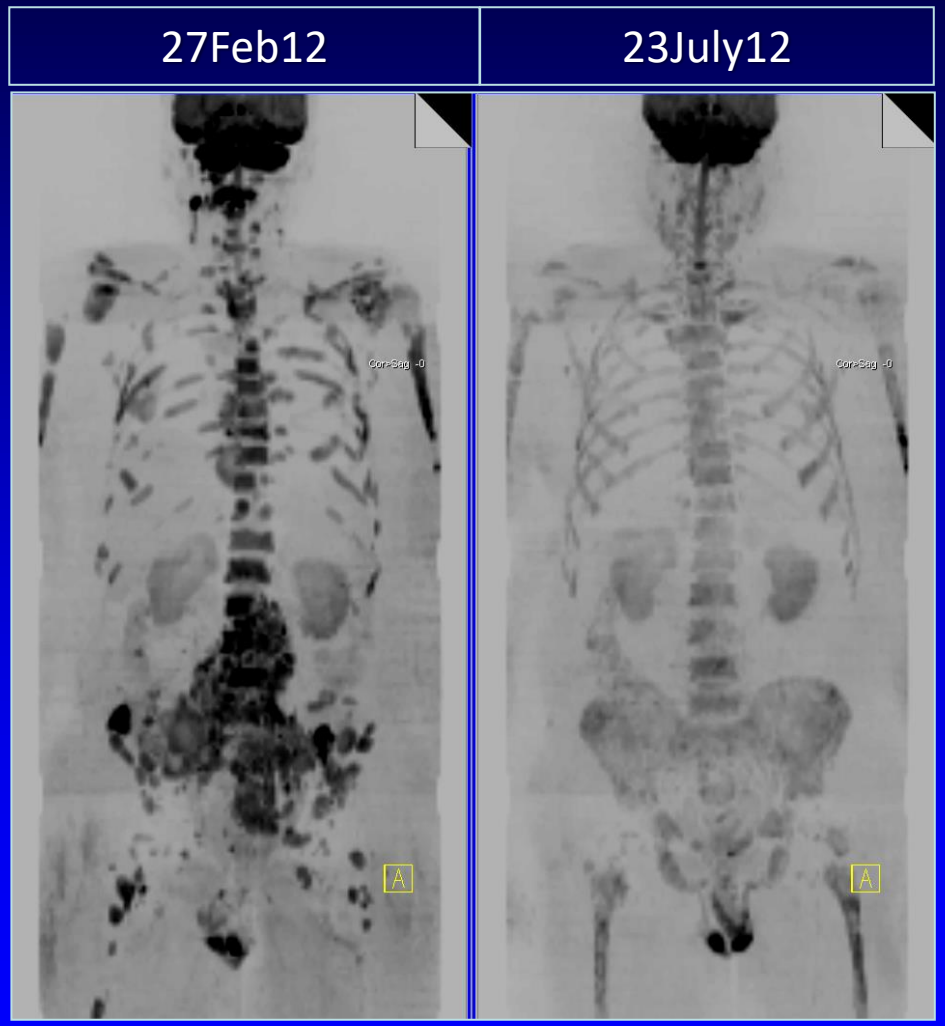


Syngo.via Frontier MR Total Tumor Load software v1.3; Siemens Healthineers

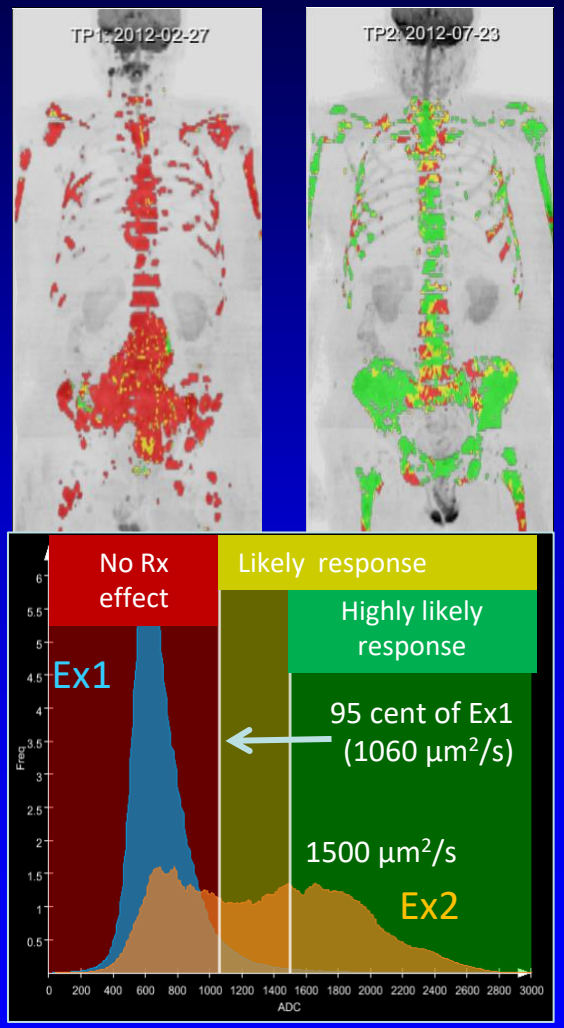


Hamstra DA, et al, J Clin Oncol 2007: 25:4104-4109

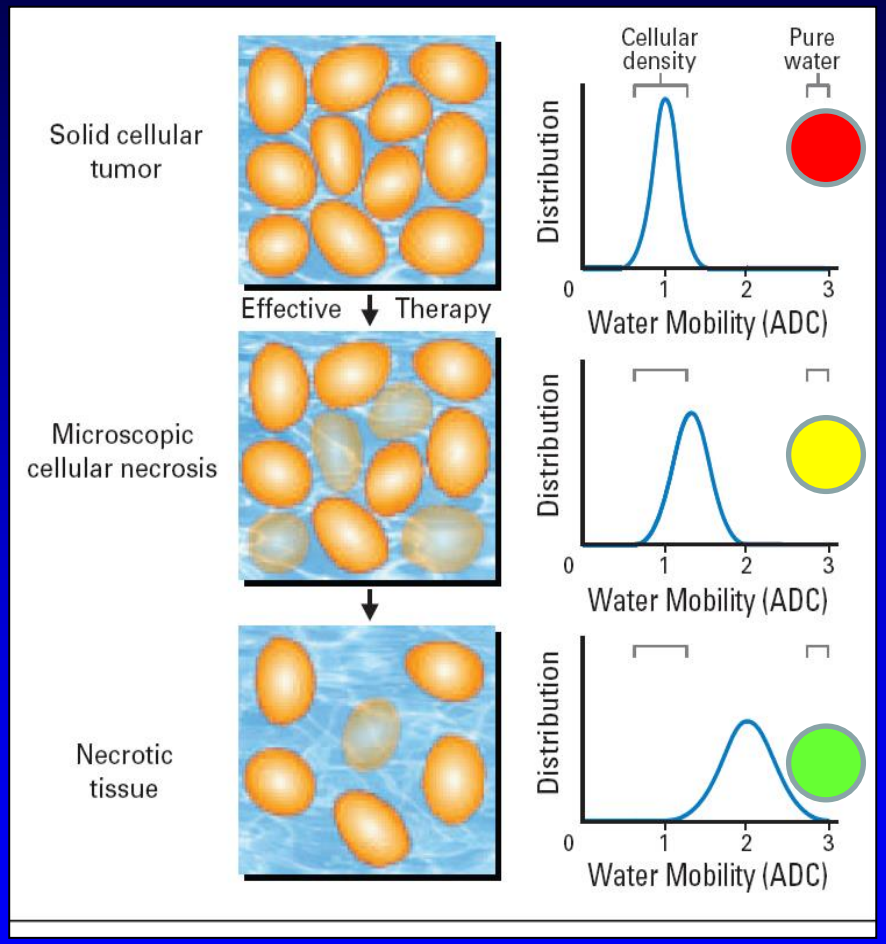
Cellular viability habitats can be spatially mapped



Metastatic prostate cancer (x4 docetaxel, goserelin & prednisone)



Syngo.via Frontier MR Total Tumor Load software v1.3; Siemens Healthineers



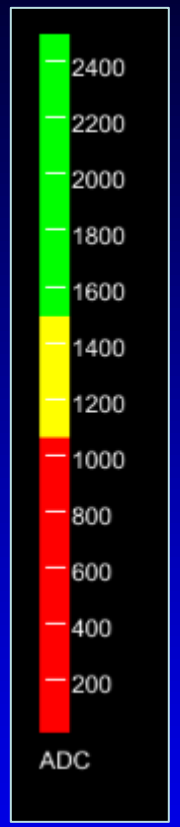
Hamstra DA, et al, J Clin Oncol 2007: 25:4104-4109

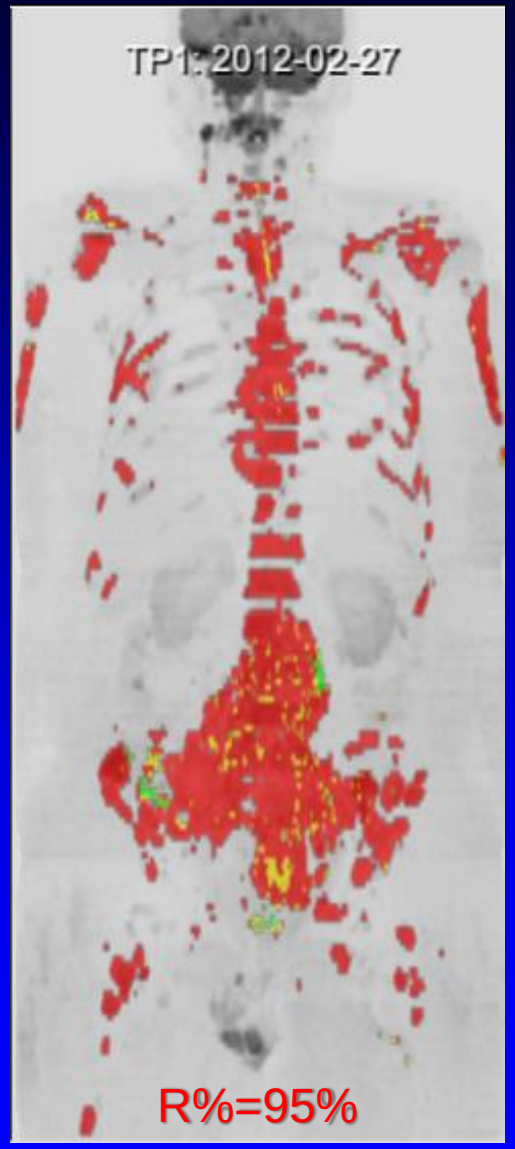
Viability habitats: mapped & quantified (ADC distribution/spatial heterogeneity)

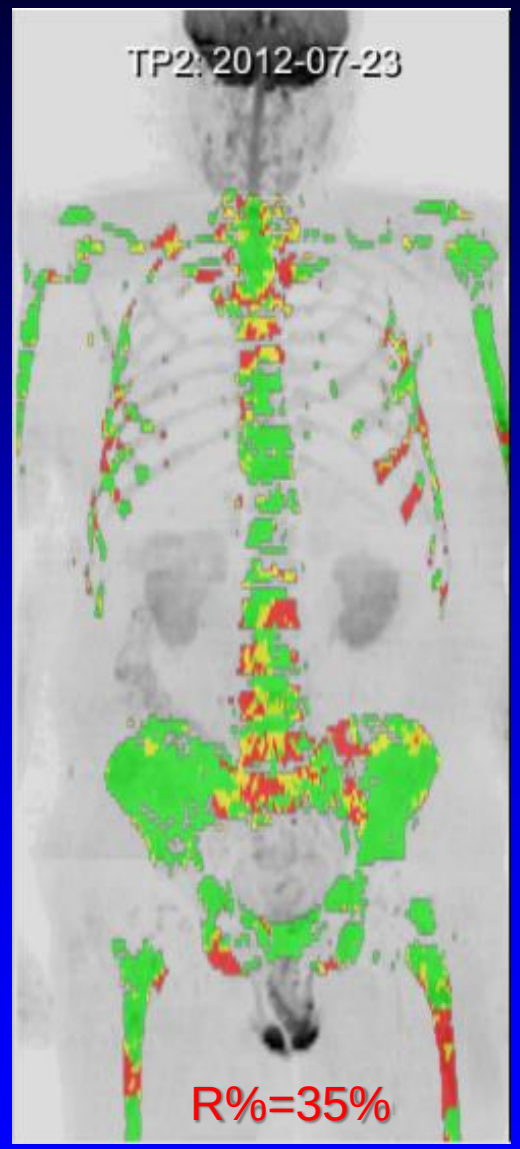
b900 MIP with superimposed ADC value classes

1500 µm²/s

1060 µm²/s





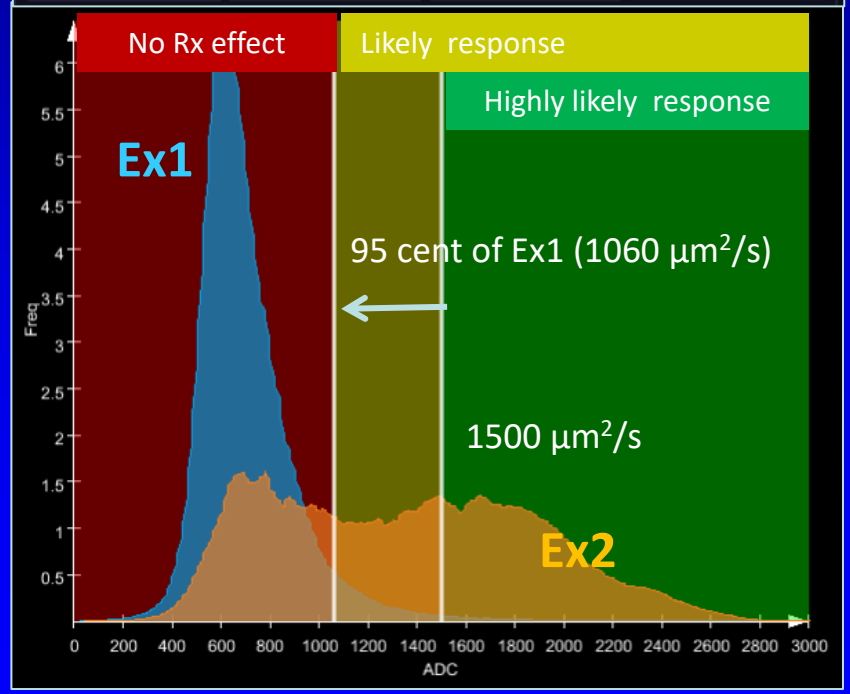


Syngo.via Frontier MR Total Tumor Load software v1.3; Siemens Healthineers

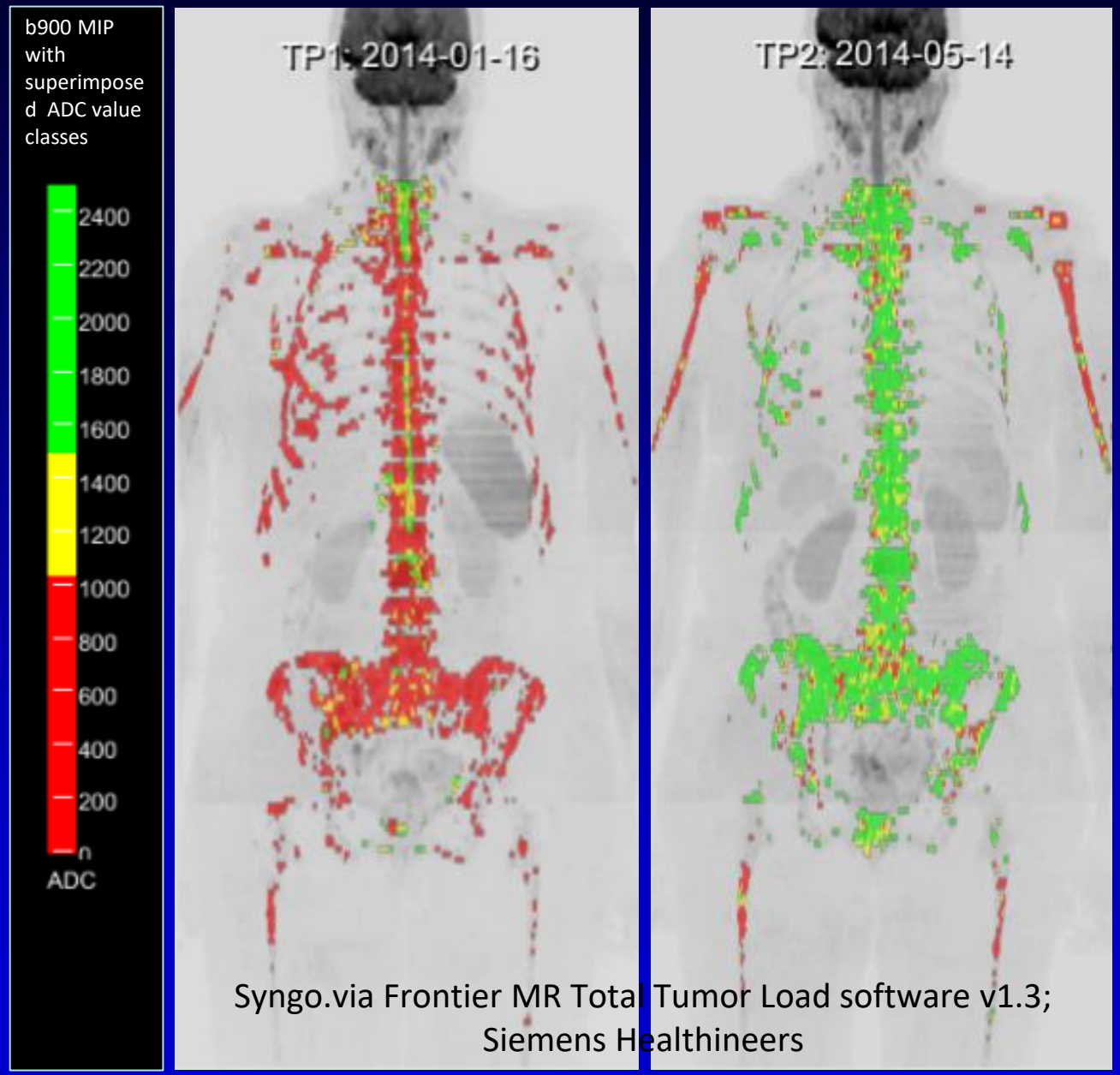
Metastatic prostate cancer (x4 docetaxel, goserelin & prednisone)

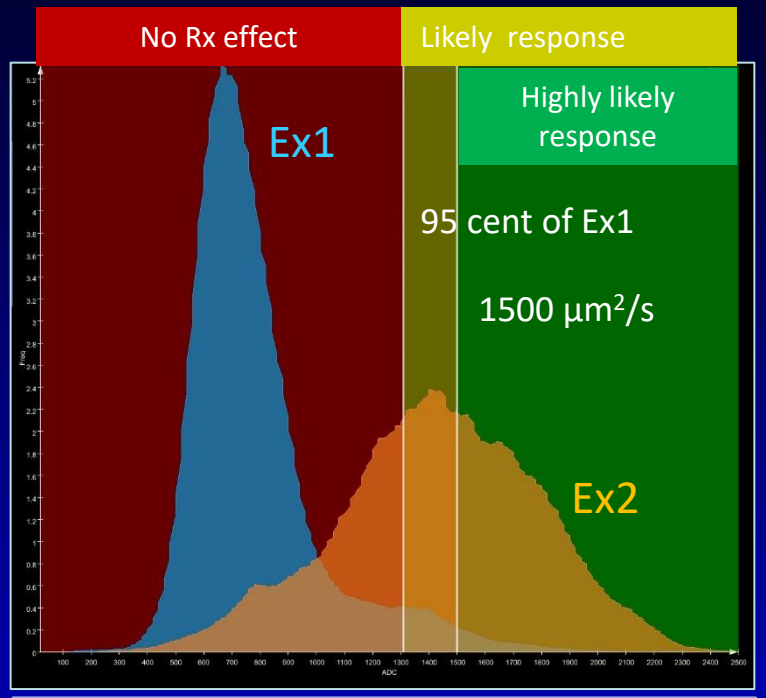
ADC | Intensity

	TP1: 2012-02-27	TP2: 2012-07-23	Difference
Volume [cm³]	1277.7	755.3	-40.9%
Mean	703.948	1345.499	+91.1%
Std	200.46	532.388	+165.6%
Median	661.5	1333.5	+101.6%
5%	472.5	577.5	+22.2%
95%	1060.5	2236.5	+110.9%
Skewness	2.091	0.229	-89.0%
E. Kurtosis	9.198	-0.837	-109.1%
H. Entropy	7.213	8.305	+15.1%
% Low	94.7	35.2	-62.8%
% Mid	4.4	23.7	+432.9%
% High	0.8	41.1	+432.9%



51 yo female with metastatic breast cancer. Rx Erubulin chemotherapy x 6 cycles. Progression on morphology & but response on DWI/ADC maps





ADC | Intensity

	TP1: 2014-01-16	TP2: 2014-05-14	Difference
Volume [cm³]	588.6	391.5	-33.5%
Mean	813.127	1427.905	+75.6%
Std	272.794	358.137	+31.3%
Median	756	1428	+88.9%
5%	516	780	+51.2%
95%	1356	2004	+47.8%
Skewness	2.524	-0.202	-108.0%
E. Kurtosis	13.145	-0.221	-101.7%
H. Entropy	7.451	7.98	+7.1%
% Low	92.9	29.5	-68.2%
% Mid	4.5	26	+473.9%
% High	2.6	44.5	+473.9%

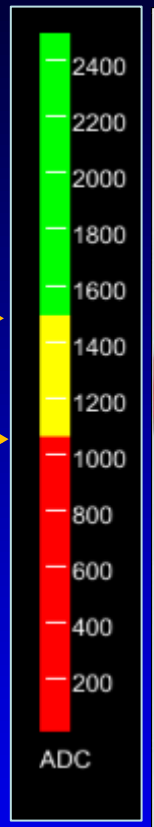
Syngo.via Frontier MR Total Tumor Load software v1.3; Siemens Healthineers

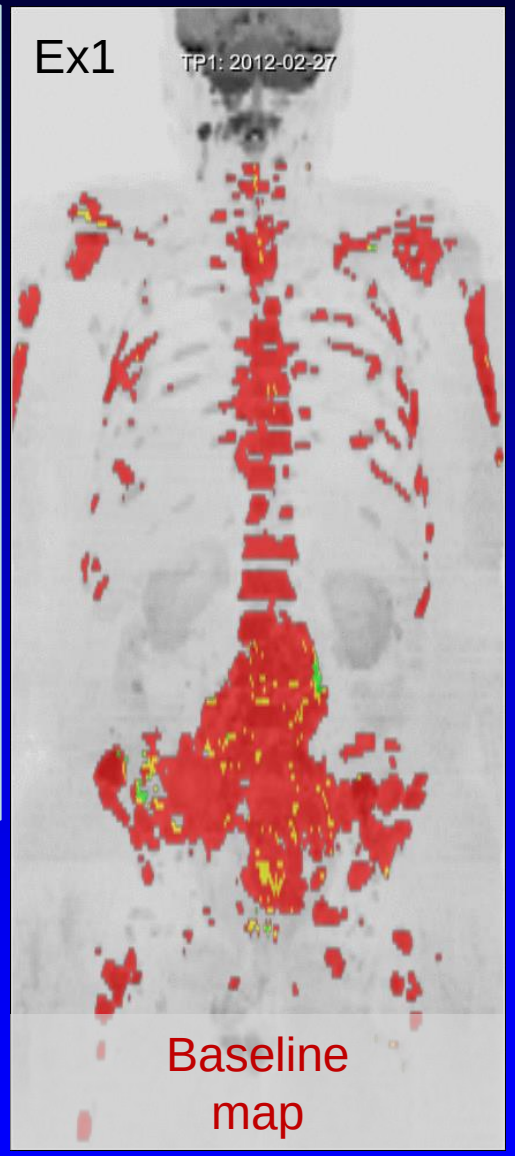
Viability habitats mapping for biopsy guidance

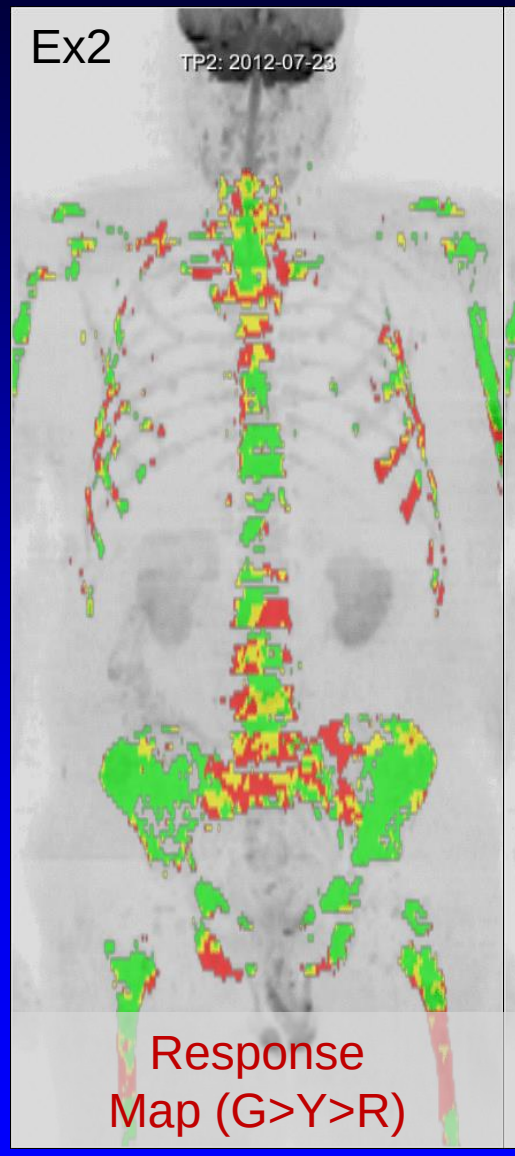
b900 MIP with mapped ADC classes

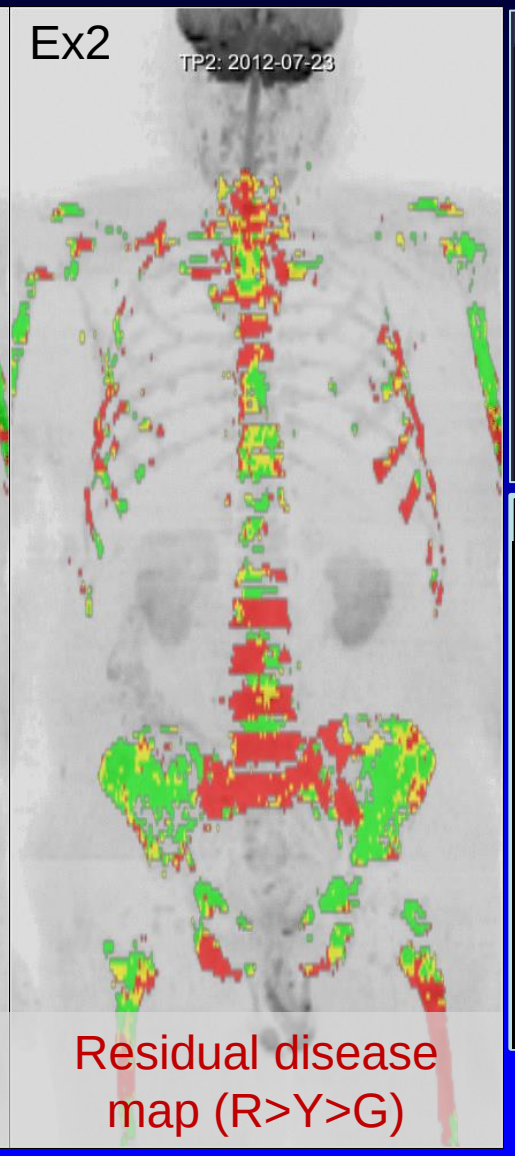
1500 µm²/s

1060 µm²/s









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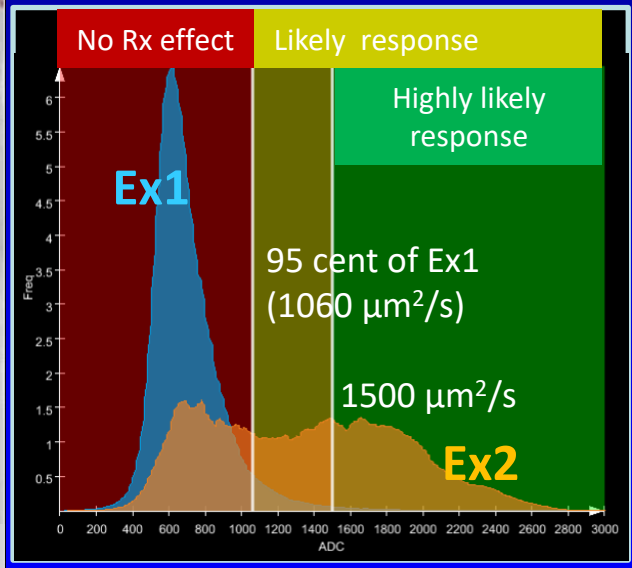
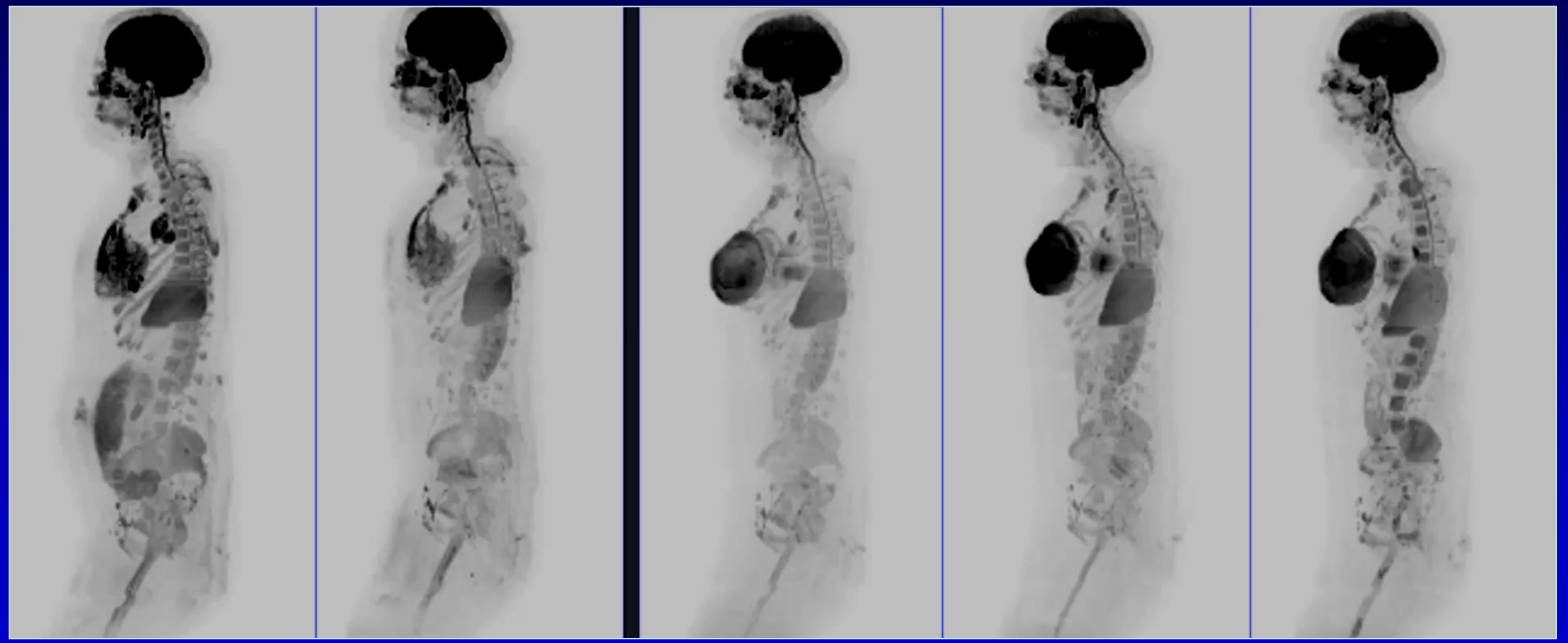


Syngo.via Frontier MR Total Tumor Load software v1.3.3; Siemens Healthineers

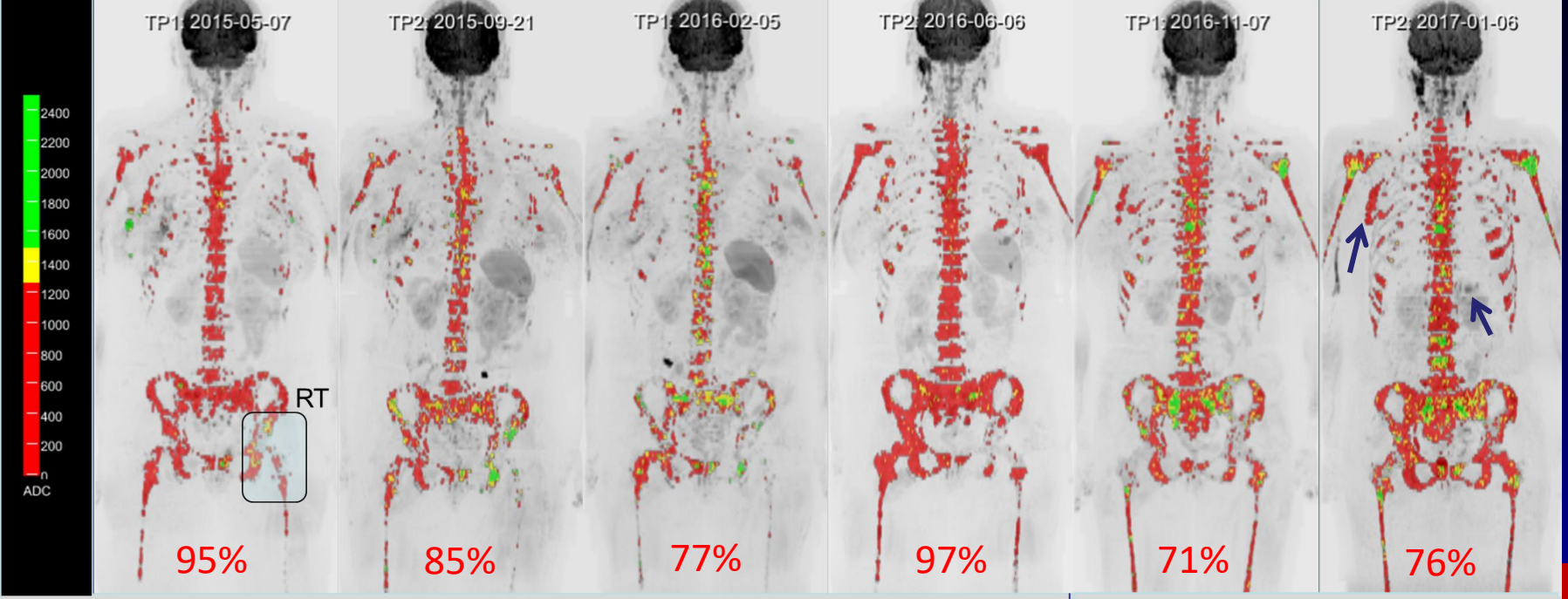
Metastatic prostate cancer (x4 docetaxel, ADT, prednisone)

Triple Negative MBC in Pregnancy: staging & follow-up

34F with triple negative breast cancer (G3, T4, N1) diagnosed in pregnancy (26/40) – presentation & follow-up



Precision oncology application of quantitative WB-MRI in metastatic breast cancer



Exemestane, Goserelin & Zoledronic acid

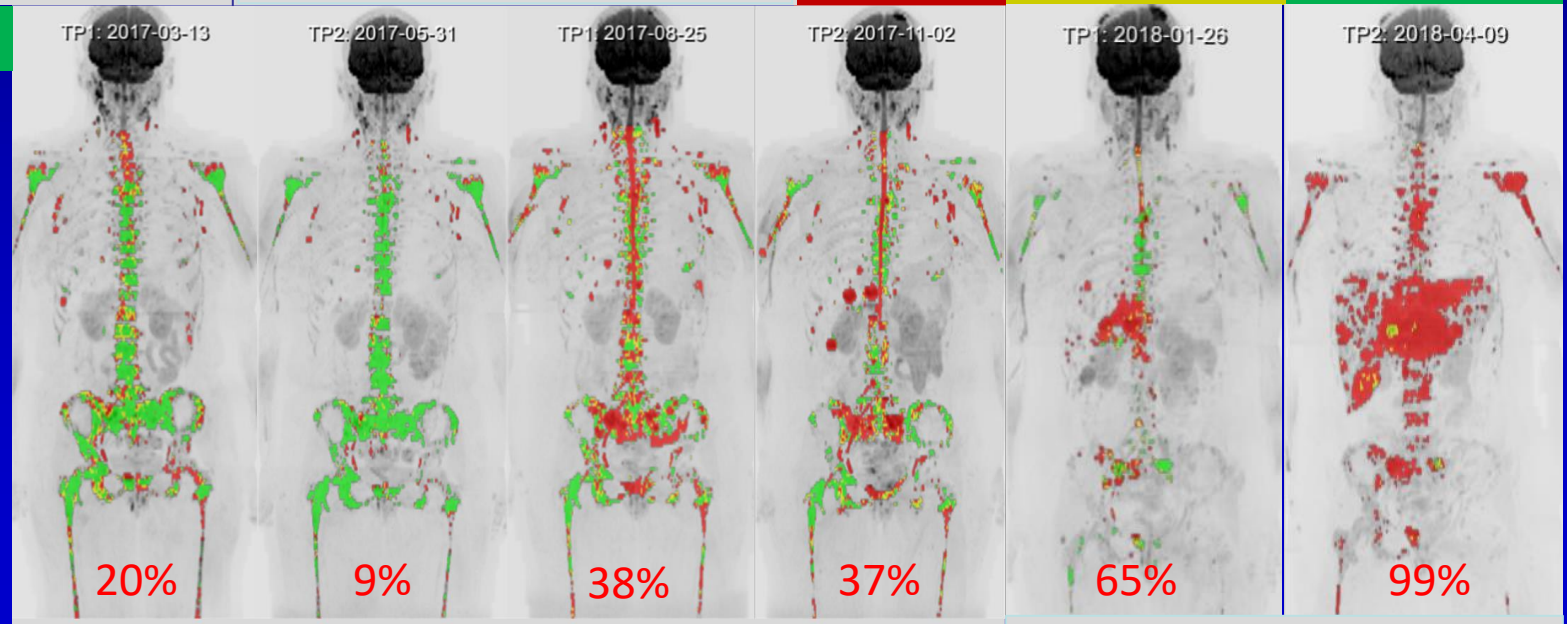
Fulvestrant & Zeledronic acid

No Rx effect | Likely response | Highly likely response

50 yo female ER+ HER2- MBC

- Heterogeneity of response to hormonal Rx
- Uniform but non-sustained response to chemotherapy
- Emergence of multi-drug resistance in the liver

Syngo.via Frontier MR Total Tumor Load software v1.3, Siemens Healthineers



Capecitabine & Zoledronic acid

5FU, Epirubicin, Cyclophosphamide

No Rx effect | Likely response | Highly likely response

Acknowledgements:

Prof. Anwar Padhani and Will McGuire for allowing the use of their slides