DICOM
Digital Imaging and Communications in Medicine

DICOM for Small Animal Pre-clinical Imaging & Whole Slide Digital Pathology

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PIXELMED PUBLISHING, LLC

Disclosures

- Editor of the DICOM Standard (NEMA contract)
- Owner of PixelMed Publishing, LLC
- Consulting for AGMednet, Bioclinica, BK Medical, Bracken, Canfield, Carestream, Hologic, Imago, Lunit
- Supported by NCI Leidos BOA 29XS219 Task Order #05

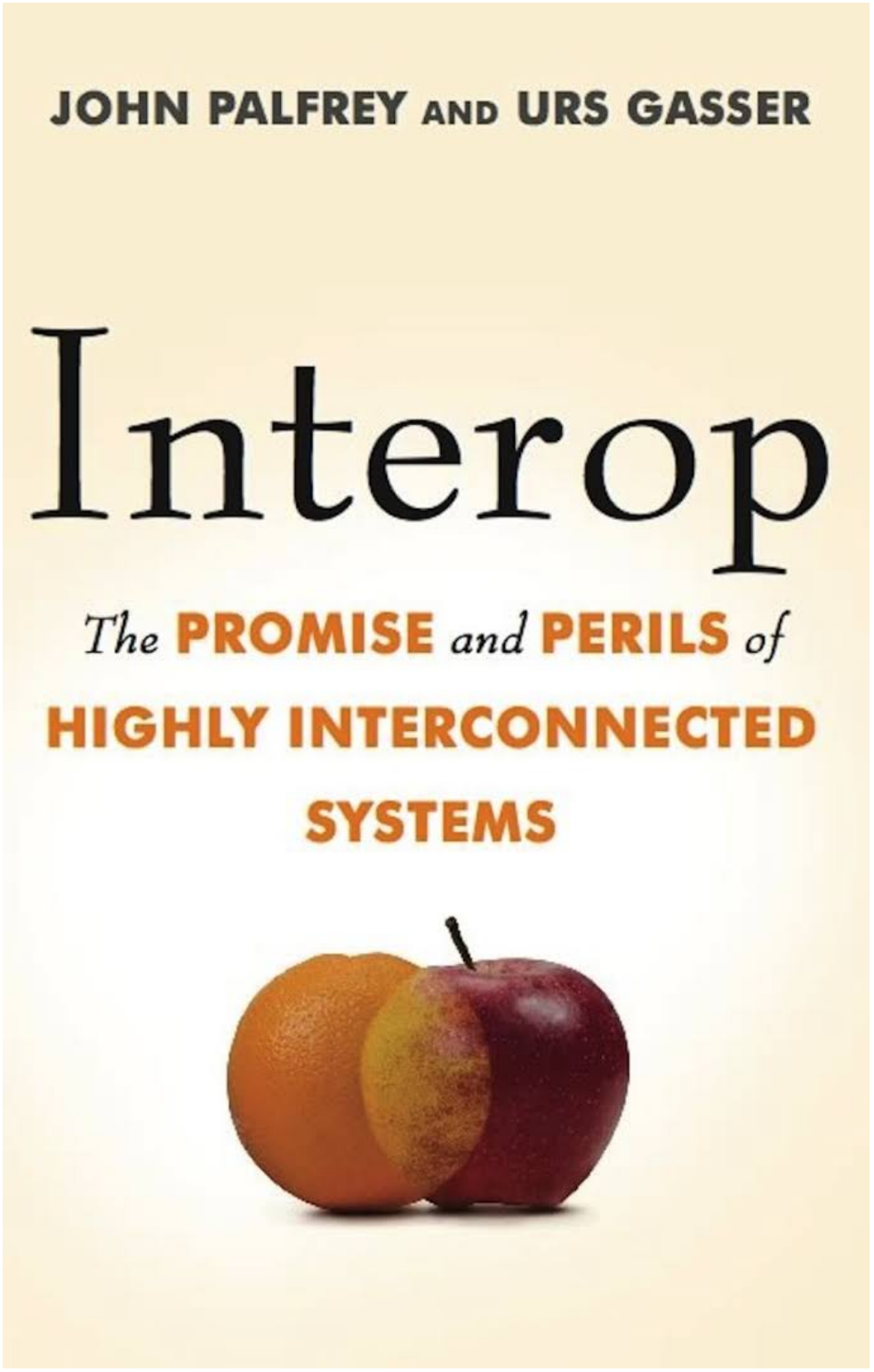
Why Standards?

- Consistency
- Reproducibility
- …
- *Interoperability*

Interoperability

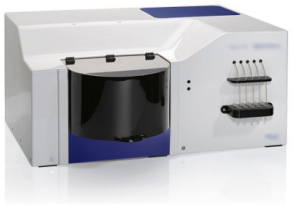
*"the ability of two or more systems or components to **exchange** information and to **use** the information that has been exchanged"*

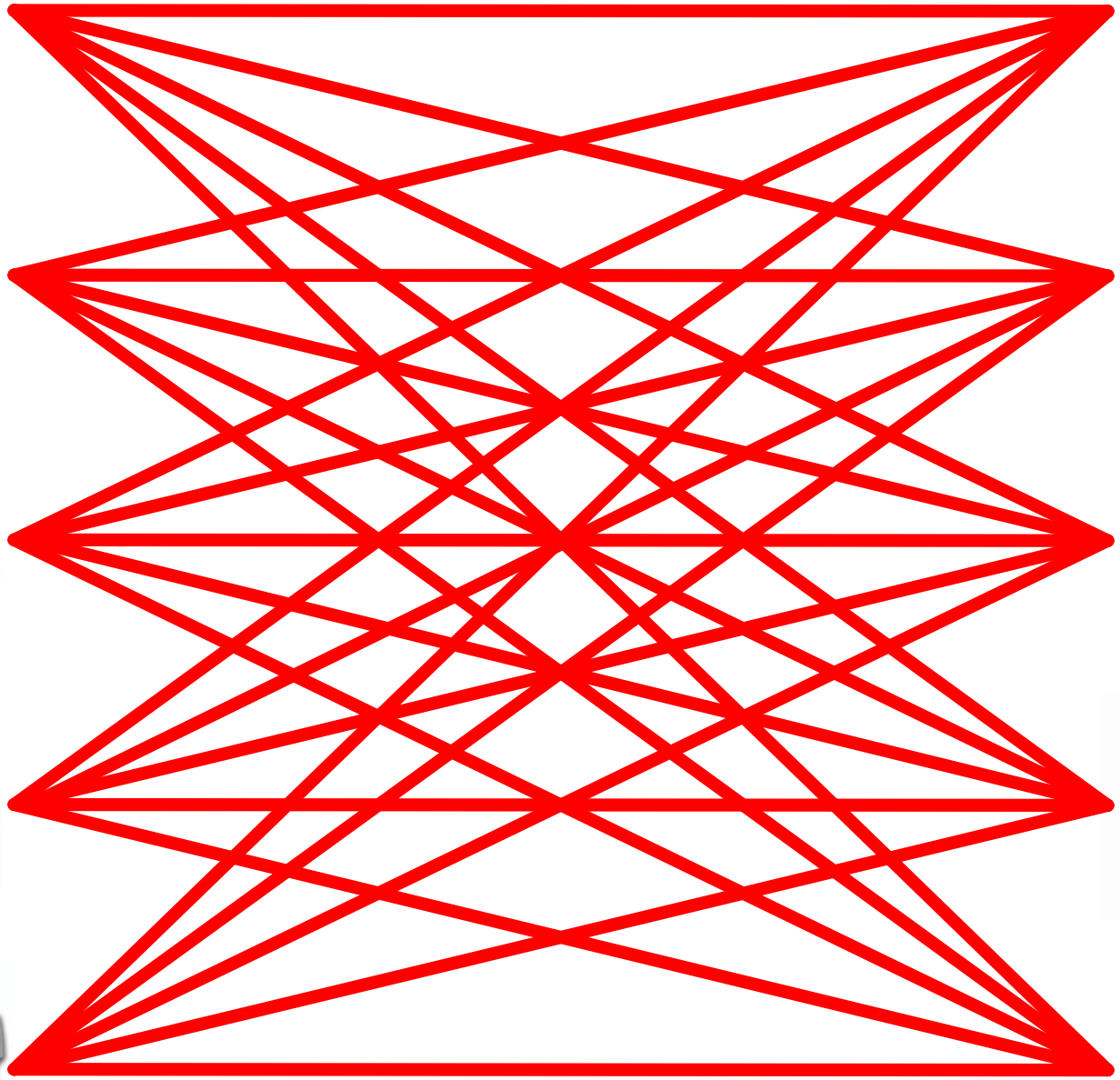
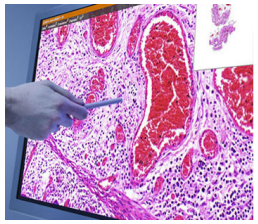
IEEE Standard Computer Dictionary: A Compilation of IEEE Standard Computer Glossaries. 1990



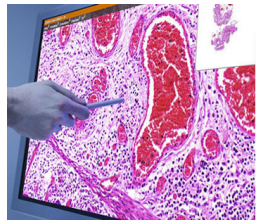
- *layers: technology, data, human, institutional*
- *consumer empowerment*
- *privacy, security*
- *competition, homogeneity, innovation*
- *efficiencies, complexity*
- *by design*
- *over time*
- *architectures*

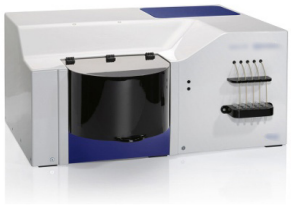




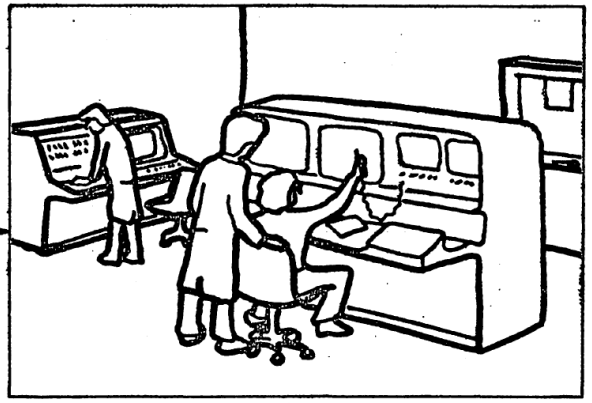






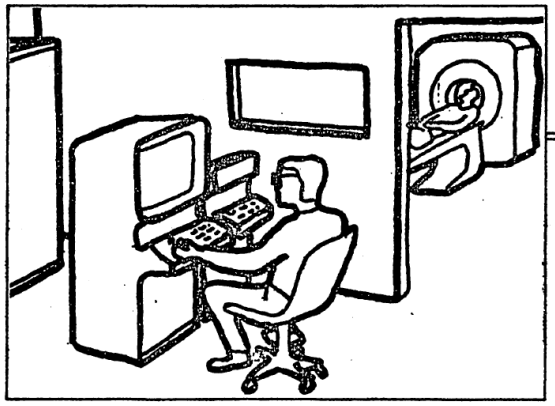




Röntgenuntersuchung

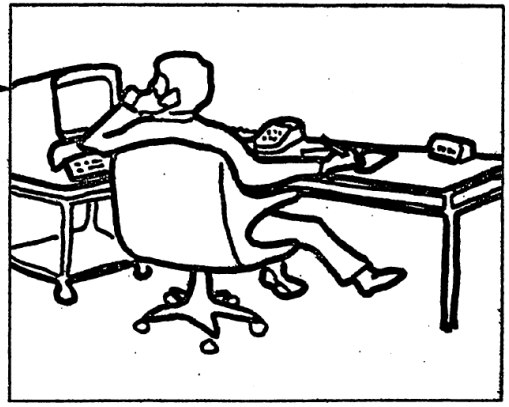


Befundung und automatische Bildauswertung



Computer-Tomographie

Kommunikationszentrale mit Bildarchiv

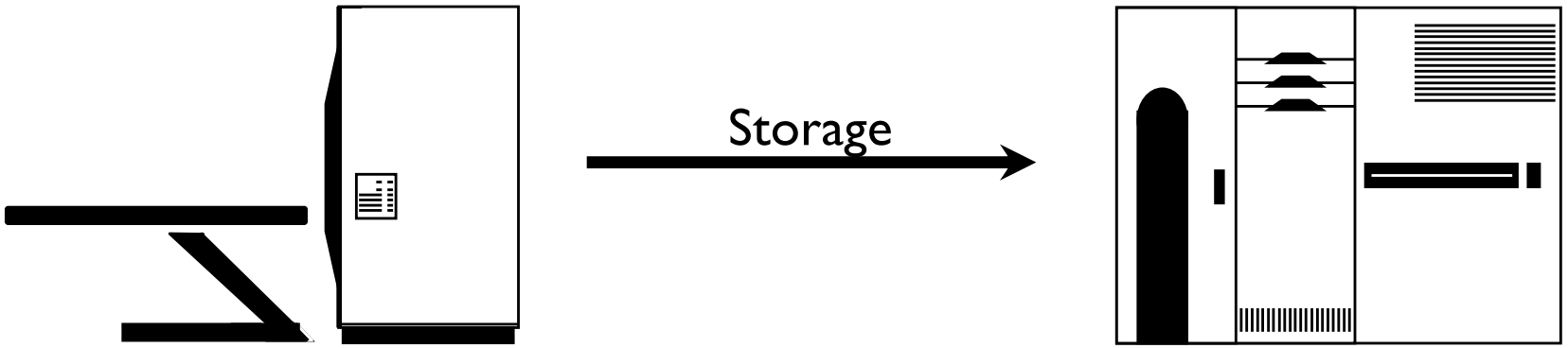


Arbeitsplatzterminal

1973

Meyer-Ebrecht D. [Electronic Archival System for X-Rays Images - Work proposal for a research project in the years 1974 and 1975] Elektronisches Archivierungssystem für Röntgenbilder – Arbeitsvorschlag für ein Forschungsprojekt in den Jahren 1974 und 1975. Hamburg, Germany: Philips Research Labs; 1973 Oct.

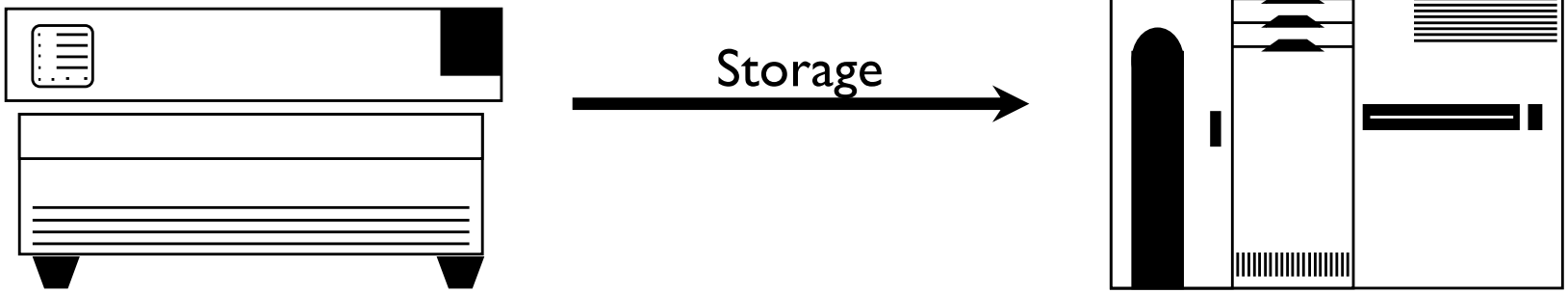
DICOM and Radiology Modality



Modality

PACS

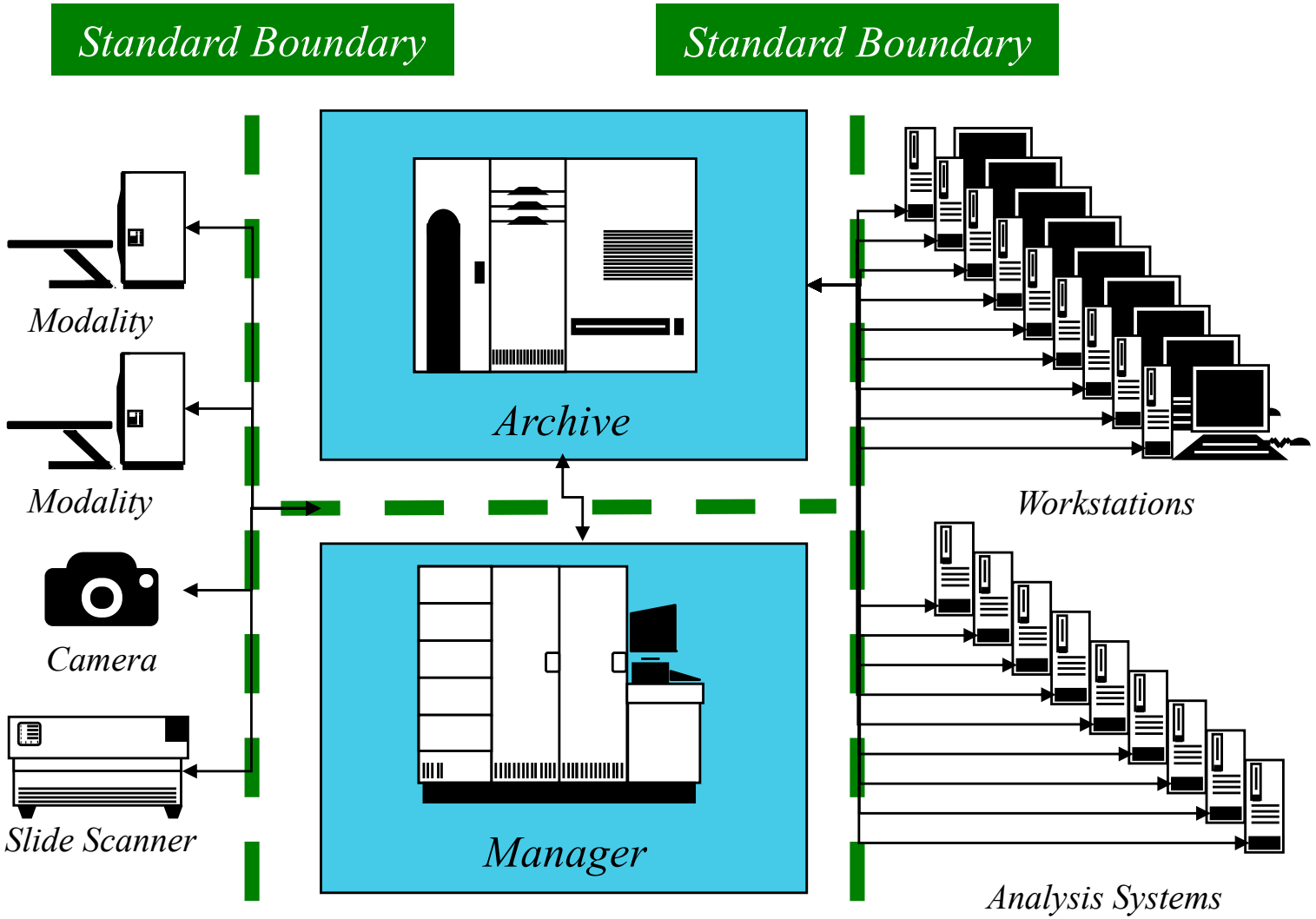
DICOM and Slide Scanner



Slide Scanner

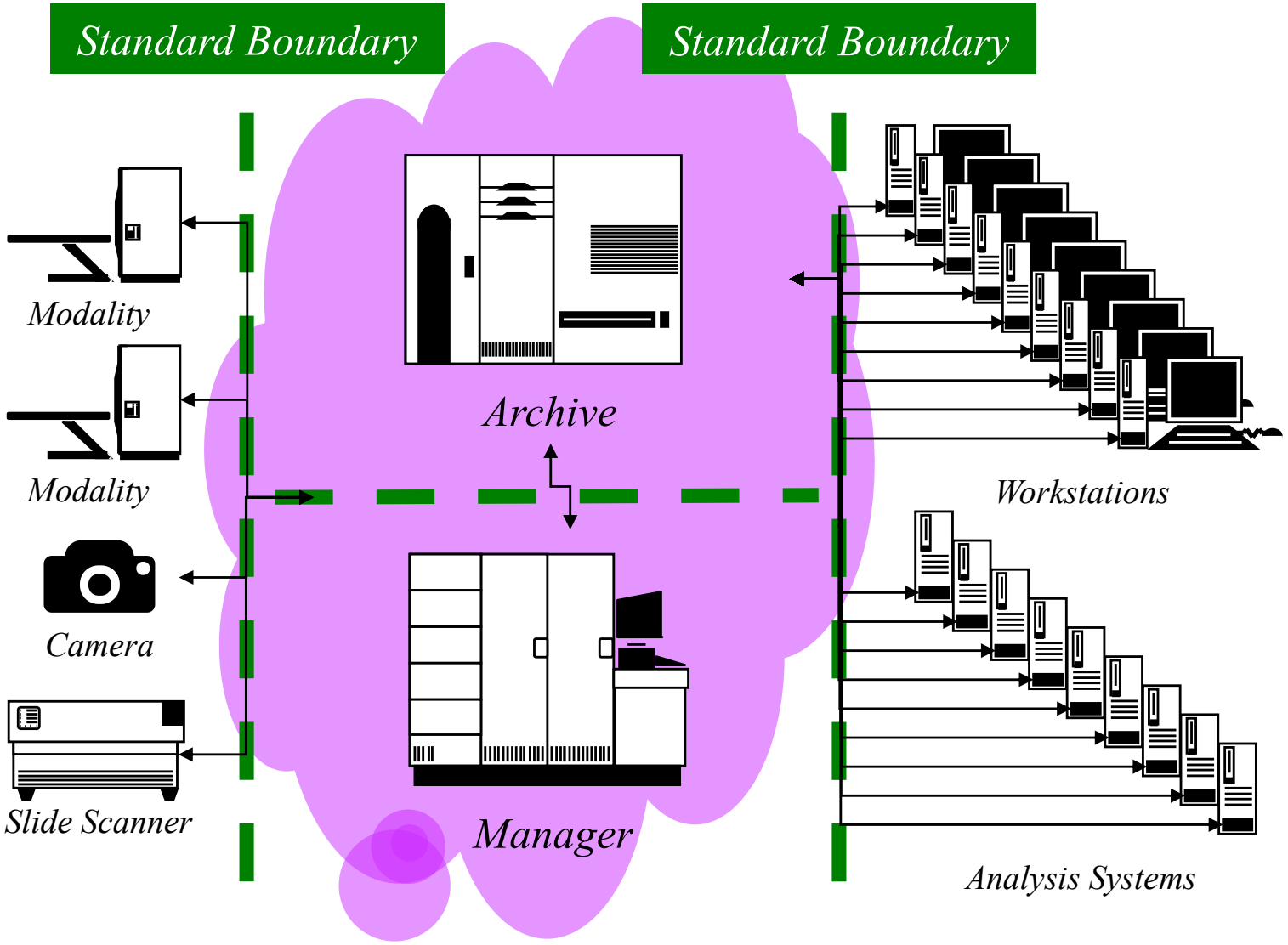
PACS

Deconstructed Enterprise PACS



Single Vendor Black Box

Cloud Distribution and Analysis



Why DICOM?

DICOM℠
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- Enormous experience in radiology and cardiology
- 34 years since ACR-NEMA PS3 Standard (1985)
- A consensus of user and industry representatives. later adopted by ISO as ISO 12052
- 80 million CT studies per year in US (CBS News, 2015) – all DICOM
- Huge supporting infra-structure – for both DICOM file format, protocol and services
- All manner of products essentially commoditized: scanners, archives, workstations, viewers, PACS, toolkits for products, testing, analysis, research
- Both commercial and free, closed and open source tools
- Conformance and interoperability testing venues (e.g., IHE Connectathons)
- Modality agnostic – e.g., XR, MR, NM also Visible Light, esp. Ophthalmology, Endoscopy
- Application agnostic – human, veterinary, small animal research, non-destructive testing (esp. aerospace and nuclear power), security (esp. baggage scanning)
- Emphasis on reliable, consistent, standard metadata (common data elements, value sets)
- Core standard for images in The Cancer Imaging Archive (TCIA)
- Mappings, e.g., Biomedical Research Integrated Domain Group (BRIDG - ISO 14199)

Why not DICOM?

- More effort than most trivial file formats – toolkits are generally required
- Complexity is implicit in the use case more than the "format" per se – harder problems require more effort and discipline to be interoperable
- Population of metadata takes effort – is it worth that effort?
- Traditional DICOM network transport protocols are unique, though TCP/IP based – mitigated through more recent use of HTTP (WADO) using XML, JSON metadata
- Information model not always a perfect match for pre-clinical animal identification
- Pixel data encoding not a perfect match for WSI virtual microscopy – questions of size limits and tile access – multi-frame tiles are a hack (like TIFF), but are workable
- Legacy of use of proprietary (albeit mostly TIFF-based) formats for WSI – why change if downstream users/apps are willing to cope?
- DICOM Conformance is not a panacea – claims of support are limited to query, storage and retrieval, worklists, etc., but NOT necessarily visualization (but DICOM does *enable* viewers and analytic tools)

Status quo for Small Animal Imaging

- Re-use of human scanners, therefore human DICOM images
- Many dedicated animal devices also can produce DICOM
- Not too bad, but …
- Identification difficulties, e.g., "mouse hotel" but one ID field
- Description difficulties, e.g., animal species, strain, model
- Hodgepodge of proprietary file formats for exotic modalities
- Absence of animal metadata -> fragile linkage to out of band sources (database, spreadsheets, mouse management systems)
- When decoupled from environment, lose contextual data
- Often managed as files on filesystem, rather than in "PACS"

DICOM for Animals – 2001 to 2019

- 2001 – Sup 53 – Content Mapping Resource – species of subject
- 2006 – CP 643 – Add veterinary identification tags (breeds)
- 2009 – CP 919 – Add orientation for quadrupeds
- 2009 – CP 922 – Add anatomy, view codes and acquisition context for veterinary use
- 2013 – WG 30 – Small Animal Imaging – formed (NCI initiative)
- 2015 – CP 1457 – Identification of groups of pre-clinical research small animal subjects
- 2015 – CP 1470 – Small animal anatomy for pre-clinical research
- 2015 – CP 1472 – Additional responsible persons
- 2015 – CP 1473 – Transverse positioning of pre-clinical research small animal subjects
- 2015 – Sup 187 – Preclinical Small Animal Imaging Acquisition Context
- 2016 – CP 1478 – Identification of species and strain of pre-clinical research small animal subjects
- 2017 – CP 1619 – Add source mouse strain and genetic modifications for homograft to exogenous substances, and add genetic modifications to patient

Species encoding in DICOM

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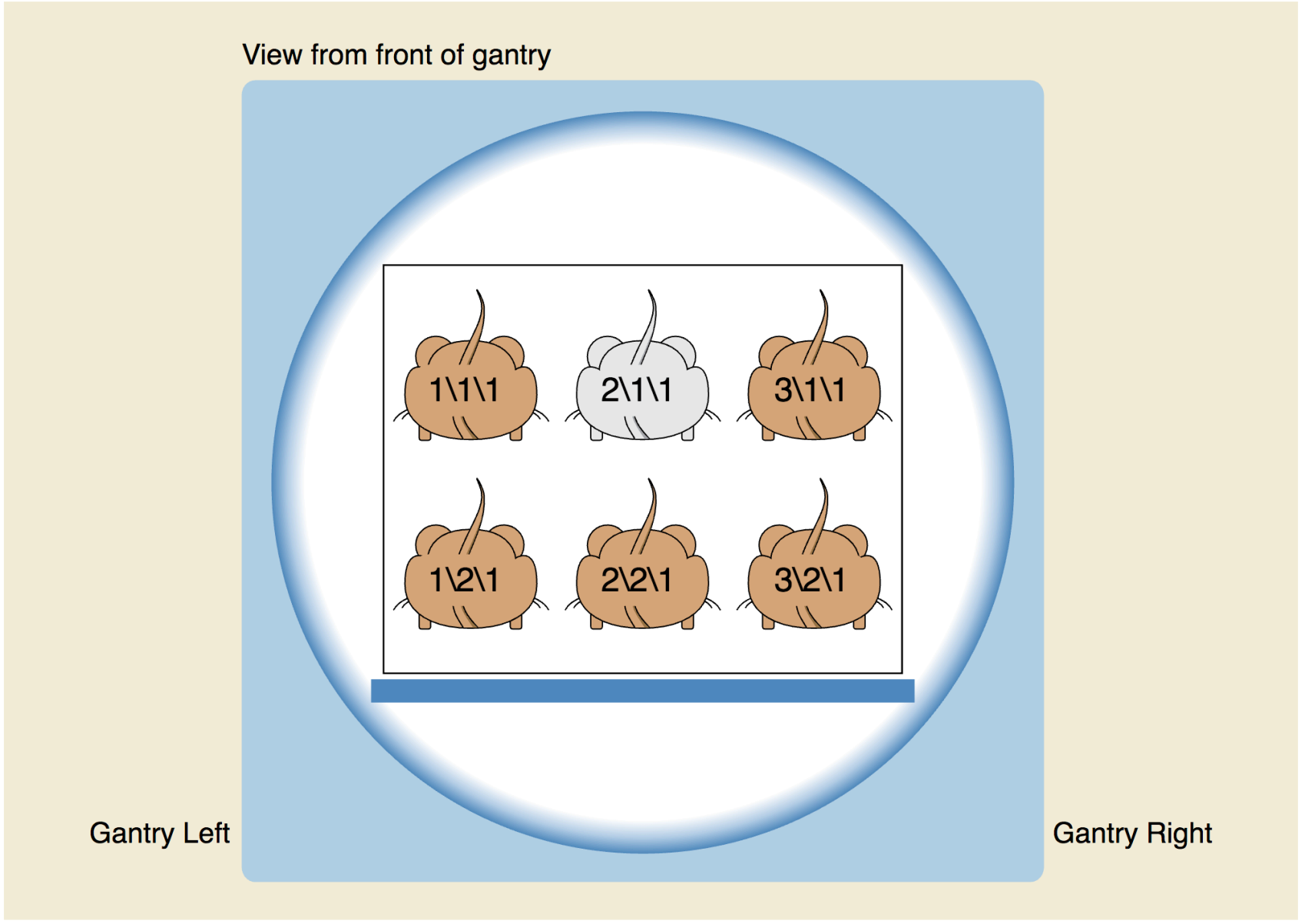
Table CID 7454. Animal Taxonomic Rank Values

Coding Scheme Designator	Code Value	Code Meaning	SNOMED-RT ID	UMLS Concept Unique ID	ITIS TSN
SCT	337915000	Homo sapiens	L-85003	C0086418	180092
SCT	388626009	Felis	L-000F9	C0524517	180586
SCT	448169003	Felis catus (domestic cat)	L-00376	C0007450	183798
SCT	388445009	Equus	L-000A9	C1265527	180689
SCT	35354009	Equus caballus (domestic horse)	L-8A102	C0019944	180691
SCT	388254009	Ovis	L-8C3FD	C0036945	180709
SCT	125099002	Ovis aries (domestic sheep)	L-8C336	C1123019	552475
SCT	388393002	Sus	L-8B1FB	C1265533	180721
SCT	78678003	Sus scrofa	L-8B100	C1135183	180722
SCT	388249000	Capra	L-8C3FB	C1265549	180714
SCT	125097000	Capra hircus (domestic goat)	L-8C306	C0018019	180715
SCT	388490000	Canis	L-881FC	C0524516	180595
SCT	36855005	Canis lupus	L-88121	C1510418	180596
SCT	448771007	Canis lupus familiaris (domestic dog)	L-88124	C0012984	726821
SCT	388168008	Bos	L-8BA18	C1265540	183837
SCT	107007004	Bovinae	L-8B9F9	C0325235	552332
SCT	34618005	Bos taurus (domestic cow)	L-8B941	C1140701	183838
SCT	447482001	Mus genus	L-87830	C0026809	180365
SCT	447612001	Mus musculus (House mouse)	L-87831	C0025914	180366
ITIS_TSN	180278	Peromyscus leucopus (American white-footed mouse)			180278

Strain encoding in DICOM

- *For example, a FVB/N mouse with a Tg(MMTV-Erbb2*)NDL2-5Mul transgene might be identified as:*
  - *Strain Description (0010,0212) = "FVB/N-Tg(MMTV-Erbb2*)NDL2-5Mul"*
  - *Strain Nomenclature (0010,0213) = "MGI_2013"*
  - *Genetic Modifications Sequence (0010,0221)*
  - *>Genetic Modifications Description (0010,0222) = "Tg(MMTV-Erbb2*)NDL2-5Mul"*
  - *>Genetic Modifications Nomenclature (0010,0223) = "MGI_2013"*
  - *>Genetic Modifications Code Sequence (0010,0229)*
  - *>>Code Value = "3793949"*
  - *>>Coding Scheme Designator = "MGI"*
  - *>>Code Meaning = "Tg(MMTV-Erbb2*)NDL2-5Mul"*

Groups of Animals in Single Image



Groups of Animals in Single Image

- *Patient ID (0010,0020) = "Inv234_Exp_56_Group78"*
- *Issuer of Patient ID (0010,0021) = "MyMouseLab"*
- *Group of Patients Identification Sequence (0010,0027)*
- *>Patient ID (0010,0020) = "Inv234_Exp_56_Group78_Mouse01"*
- *>Issuer of Patient ID (0010,0021) = "MyMouseLab"*
- *>Subject Relative Position in Image (0010,0028) = 1\1\1*
- *...*
- *>Patient ID (0010,0020) = "Inv234_Exp_56_Group78_Mouse06"*
- *>Issuer of Patient ID (0010,0021) = "MyMouseLab"*
- *>Subject Relative Position in Image (0010,0028) = 3\2\1*

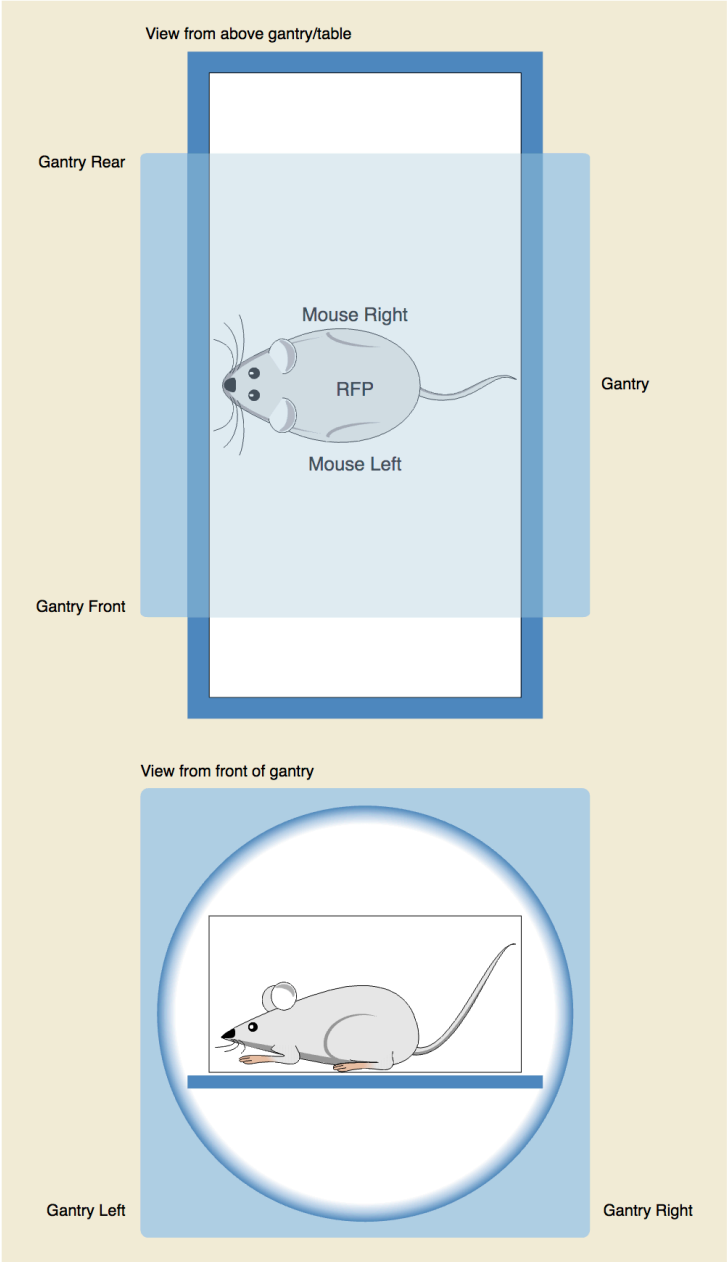
Groups of Animals in Single Image

- *Patient ID (0010,0020) = "Inv234_Exp_56_Group78_Mouse04"*
- *Issuer of Patient ID (0010,0021) = "MyMouseLab"*
- *Source Patient Group Identification Sequence (0010,0026)*
- *>Patient ID (0010,0020) = "Inv234_Exp_56_Group78"*
- *>Issuer of Patient ID (0010,0021) = "MyMouseLab"*

Groups of Animals in Single Image

- *Patient ID (0010,0020) = "Inv234_Exp_56_Group78_Mouse04"*
- *Issuer of Patient ID (0010,0021) = "MyMouseLab"*
- *Source Patient Group Identification Sequence (0010,0026)*
- *>Patient ID (0010,0020) = "Inv234_Exp_56_Group78"*
- *>Issuer of Patient ID (0010,0021) = "MyMouseLab"*

Animal Positioning – Transverse



Preclinical Small Animal Imaging Acquisition Context

- Things that affect image interpretation and quantitative analysis
- E.g., imaging of an animal in a hybrid PET-CT system where metabolic state matters
- Example use case involves an animal that:
  - lives in an individually ventilated home cage with several other animals in the same cage
  - is (briefly) transported (in its home cage) with its cage mates to the imaging facility, without heating, with an appropriate lid
  - is removed from its home/transport cage for preparation for imaging, involving insertion of a tail vein cannula, performed on an electrically heated pad
  - is induced by (a) placement in an induction chamber with more concentrated volatile anesthetic, or (b) intraperitoneal injection of Ketamine mixture
  - is placed in a PET-CT compatible imaging sled/carrier/chamber for imaging (of one animal at a time), with anesthesia with Isoflurane and Oxygen as the carrier gas, and heated with an electric pad regulated by feedback from a rectal probe
  - is removed for recovery in a separate cage

Preclinical Small Animal Imaging Acquisition Context

1.10	Animal handling during specified phase	
1.10.1	Phase of animal handling	Imaging procedure
1.10.2	DateTime Started	yyyymmddhhss
1.10.3	DateTime Ended	yyyymmddhhss
1.10.4	Animal housing	
1.10.4.1	Housing manufacturer	Acme Inc
1.10.4.2	Housing unit product name	Multimodal Mouse Chamber
1.10.5	Heating conditions	
1.10.5.1	Heating	Electric heating pad
1.10.5.1	Feedback temperature regulation	Yes
1.10.5.2	Temperature sensor device component	Rectal temperature
1.10.5.3	Equipment Temperature	37 C

Preclinical Small Animal Imaging Acquisition Context

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Table TID 8101. Preclinical Small Animal Image Acquisition Context

	NL	Rel with Parent	VT	Concept Name	VM	Req Type	Condition	Value Set Constraint
1			CONTAINER	EV (127001, DCM, "Preclinical Small Animal Imaging Acquisition Context")	1	M		Root node
2	>	HAS CONCEPT MOD	INCLUDE	DTID 1204 "Language of Content Item and Descendants"	1	M		
3	>	HAS OBS CONTEXT	INCLUDE	DTID 1001 "Observation Context"	1	M		
5	>	CONTAINS	INCLUDE	DTID 8110 “Biosafety Conditions”	1	U		
6	>	CONTAINS	CONTAINER	EV (127005, DCM, "Animal handling during specified phase")	1-n	U		
7	>>	HAS CONCEPT MOD	CODE	EV (127006, DCM, "Phase of animal handling")	1	M		DCID 634 “Phase of Animal Handling”
8	>>	CONTAINS	DATETIME	EV (111526, DCM, "DateTime Started")	1	U		
9	>>	CONTAINS	DATETIME	EV (111527, DCM, "DateTime Ended")	1	U		
10	>>	CONTAINS	INCLUDE	DTID 8121 “Animal Housing”	1	U		
11	>>	CONTAINS	INCLUDE	DTID 8122 “Animal Feeding”	1-n	U		
12	>>	CONTAINS	INCLUDE	DTID 8140 “Heating Conditions”	1	U		
13	>>	CONTAINS	INCLUDE	DTID 8150 “Circadian Effects”	1	U		
14	>>	CONTAINS	INCLUDE	DTID 8170 “Physiological Monitoring Performed During Procedure”	1	U		
15	>	CONTAINS	INCLUDE	DTID 8130 “Anesthesia”	1	U		
16	>	CONTAINS	INCLUDE	DTID 9002 “Medication, Substance, Environmental Exposure”	1	U		$ContainerConcept = EV (10160-0, LN, "History Of Medication Use") $CodeConcept = EV (111516, DCM, "Medication Type") $Route = DCID 11 “Route of Administration”

Preclinical Small Animal Imaging Acquisition Context

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Table CID 634. Phase of Animal Handling

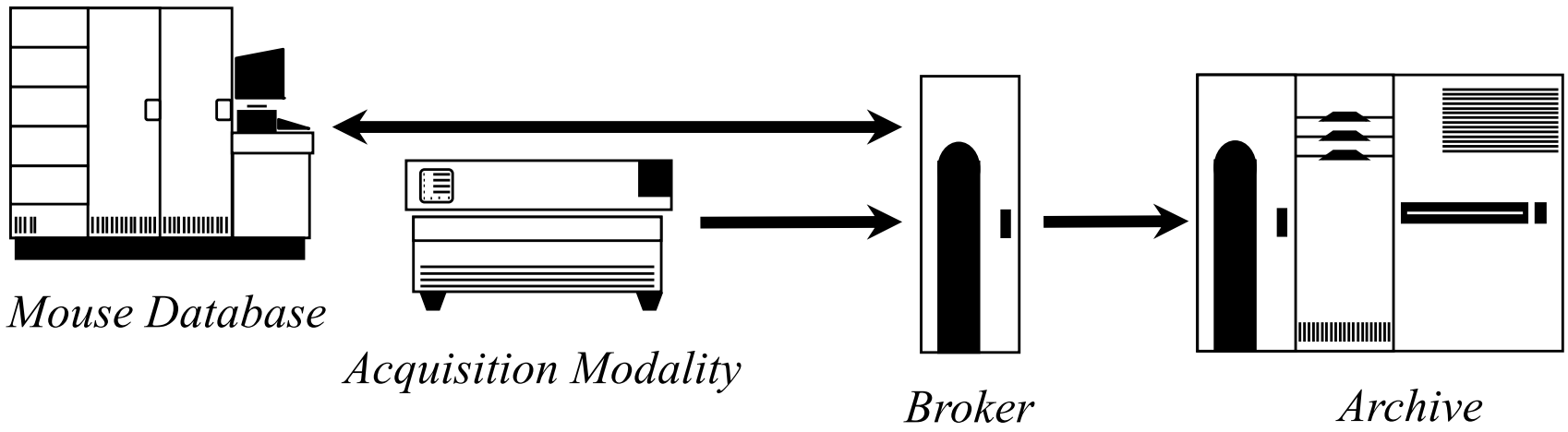
Coding Scheme Designator	Code Value	Code Meaning	SNOMED-RT ID	UMLS Concept Unique ID
DCM	127101	In home cage		
DCM	127102	During transport		
DCM	127103	Staging prior to imaging		
DCM	127104	Preparation for imaging		
SCT	241687005	Anesthesia induction	P1-C0012	C0473960
SCT	363679005	Imaging procedure	P0-0099A	C0011923
UMLS	C0002908	Anesthesia recovery period		C0002908

Status quo post-DICOM updates

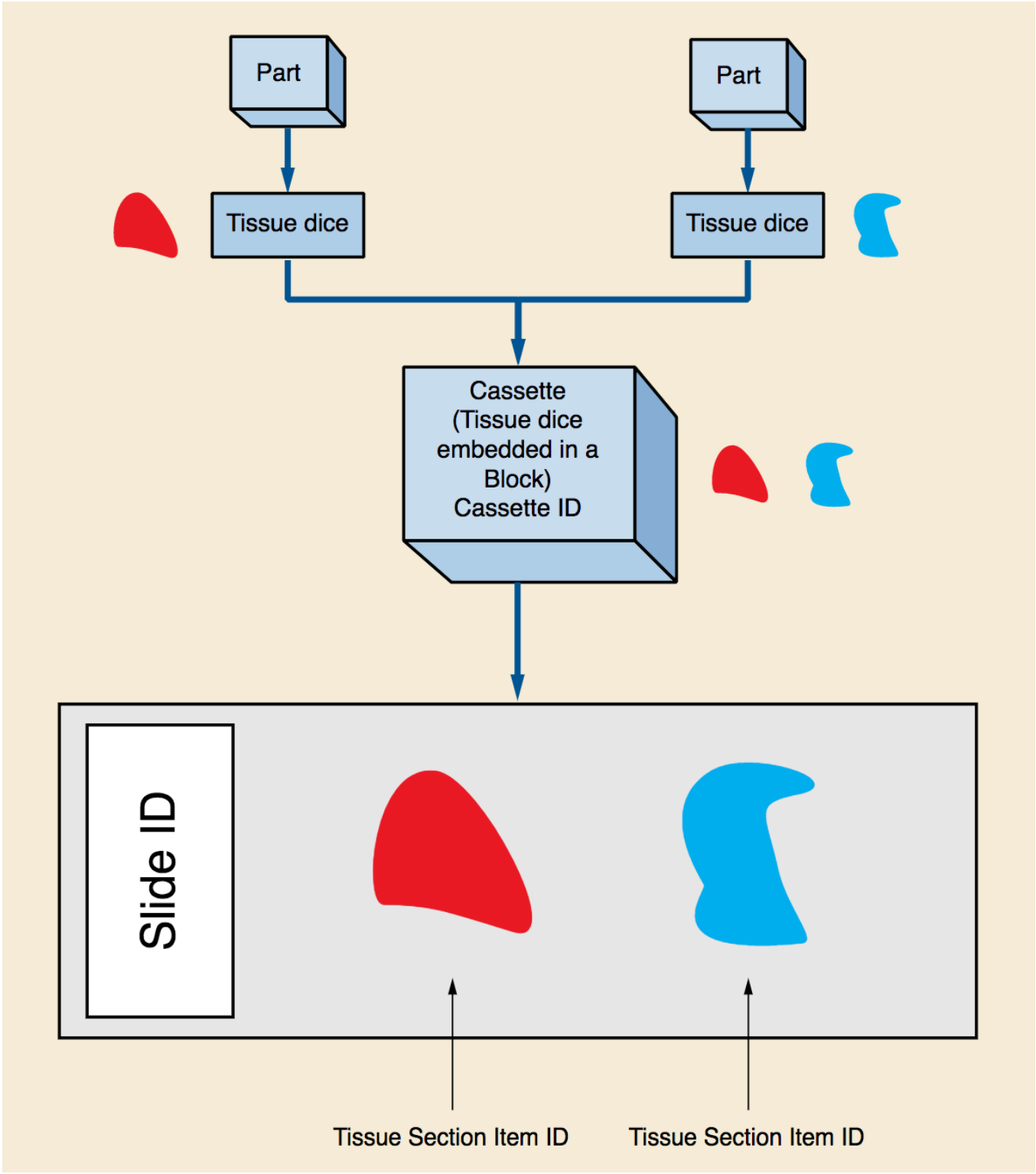
- No/almost no adoption by vendors of small animal equipment
- Obviously no adoption by vendors of human equipment
- But …

- Opportunity to post-process DICOM headers to add missing data by merging from other sources
- Then subsequent distribution (e.g., via TCIA) achieves greater degree of interoperability
- Ongoing TCIA query changes (index animal metadata in database), e.g., species is mouse
- Will use for Patient Derived Models Repository (PDMR) project, e.g., identification of split mouse-specific images, strain of mouse, identifier of model (source of xenograft)

Add missing animal metadata



Broker "improves" DICOM object with database metadata


Part
Part
Tissue dice
Tissue dice
Cassette
(Tissue dice
embedded in a
Block)
Cassette ID
Slide ID
Tissue Section Item ID
Tissue Section Item ID

Status quo for WSI

- Hodgepodge of proprietary file formats, e.g., SVS
- Some (Big-)TIFF-based (good), some not (bad)
- Some with extensions to TIFF (e.g., JPEG 2000 compression)
- Some disclosed publicly, some not
- Usually used with vendor-supplied viewer or proprietary SDK
- Possibly readable by open source or 3rd party (OpenSlide, OME)s
- Limited integration of scanners with Anatomical Laboratory Information Systems (APLIS), if at all, perhaps requiring expensive customization
- No metadata: fragile linkage to contextual data (patient, slide, handling, staining) by filename or scanned slide identifier only
- When decoupled from environment (APLIS, proprietary PACS), lose contextual data

DICOM WSI – 2005 to 2019

- 1999 – Sup 15 – Visible Light including Microscopy
- 2005 – WG 26 got to work on WSI etc.
- 2006 – IHE Anatomic Pathology Domain
- 2008 – Sup 122 – Specimen Module (identify, describe)
- 2008 – IHE Anatomic Pathology Workflow
- 2010 – Sup 145 – Whole Slide Microscopic Image IOD
- … *seven years of silence* …
- 2017 – 1st premarket approval for primary diagnostic use
- 2017 – 1st WG 26 Digital Pathology Connectathon (PV)
- 2019 – five Connectathons so fars (PathInfo, ECDP/NDP, PV)
- 20XX – IHE Acquisition Workflow profile (APLIS integration)

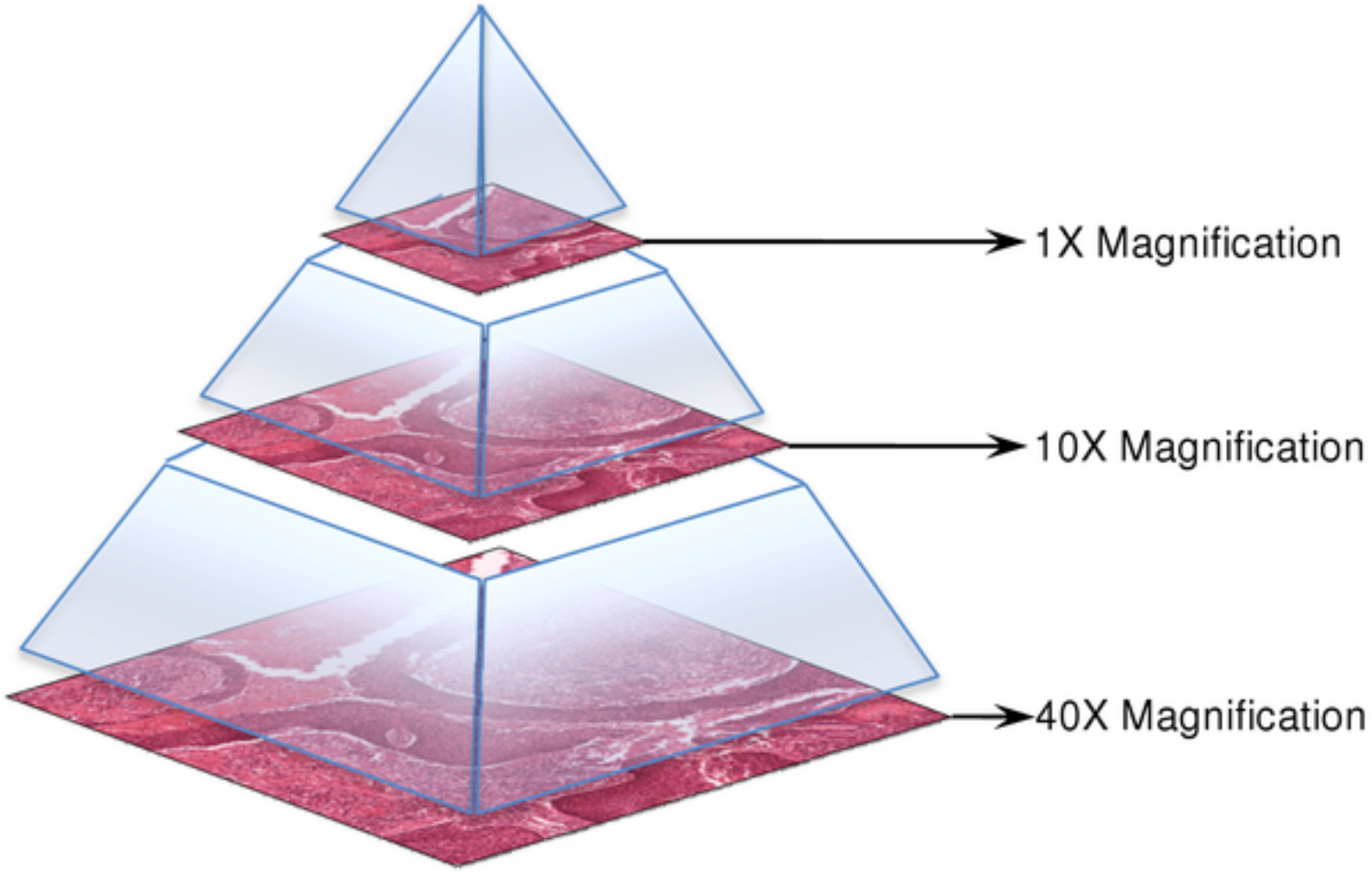
DICOM WG 26 WSI Connectathons Participation to date

	PV'17	PI'18	ECDP'18	PV'18	ECDP'19
AidPath	View		Archive, View		
Corista		Analyze			
Gestalt				Archive, View	
Neagen				Archive, View	Archive, View
PathCore	Archive, View	Archive, View		Archive, View	
Sectra		View	View	View	
3DHistech					Scan
Hamamatsu		Scan	Scan		Scan
Leica	Scan	Scan		Scan	
Motic				Scan	
Philips	Scan		Scan	Scan	Scan
Roche	Scan	Scan	Scan	Scan	Scan

DICOM WSI – What and How

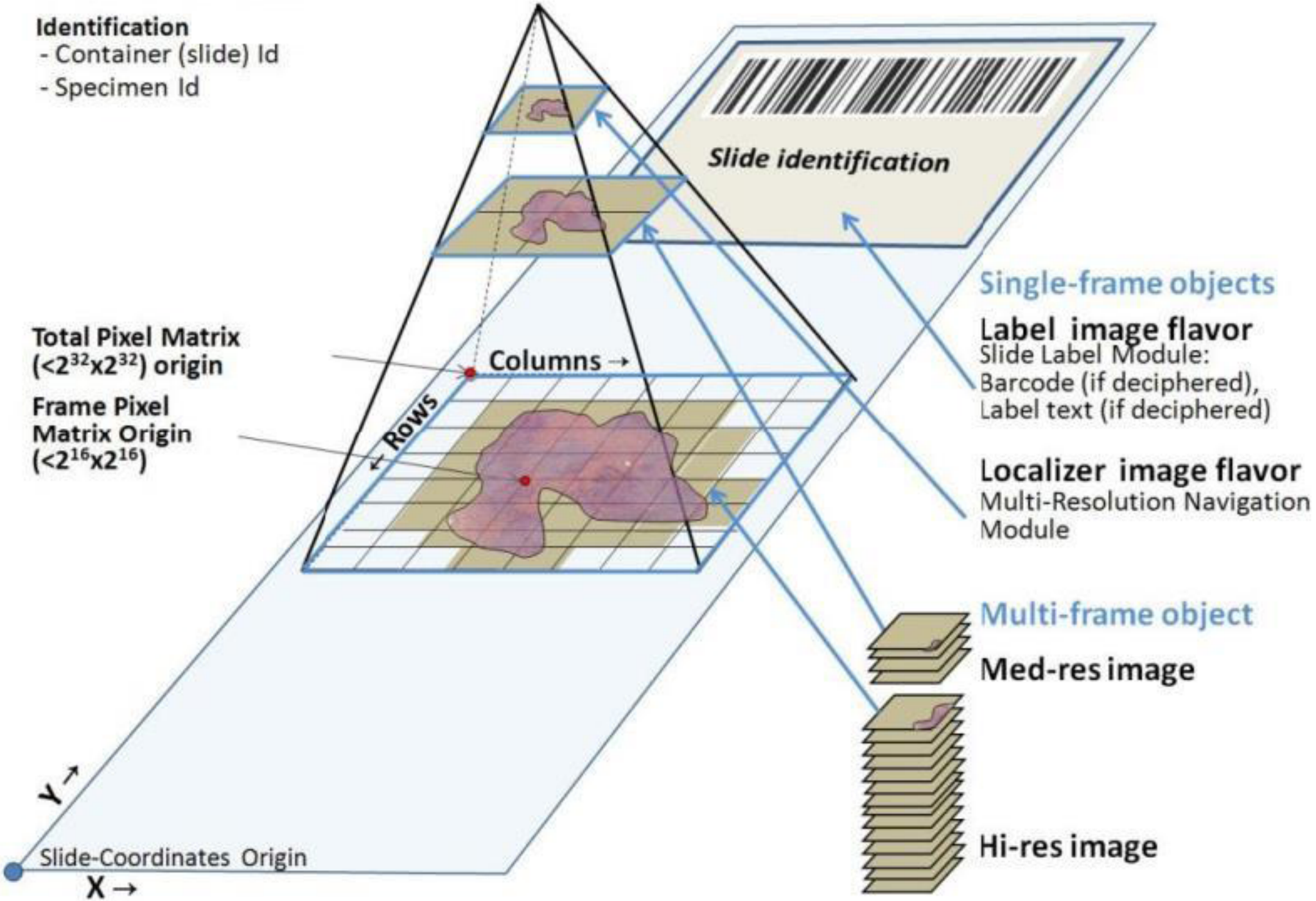
- File format for:
  - whole slide images (tiled pyramid)
  - single fields – slide microscopy
  - gross microscopy
- File contains:
  - compressed pixels (JPEG or JPEG 2000)
  - metadata – identifying AND descriptive
- Protocol for sending and receiving, etc.
- Other stuff like workflow, annotation, segmentation, structured reports, …

How digital slides are stored in a pyramid structure.



Wang Y, Williamson KE, Kelly PJ, James JA, Hamilton PW (2012) SurfaceSlide: A Multitouch Digital Pathology Platform. PLOS ONE 7(1): e30783. https://doi.org/10.1371/journal.pone.0030783
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0030783

Garcia-Rojo et al. 2016

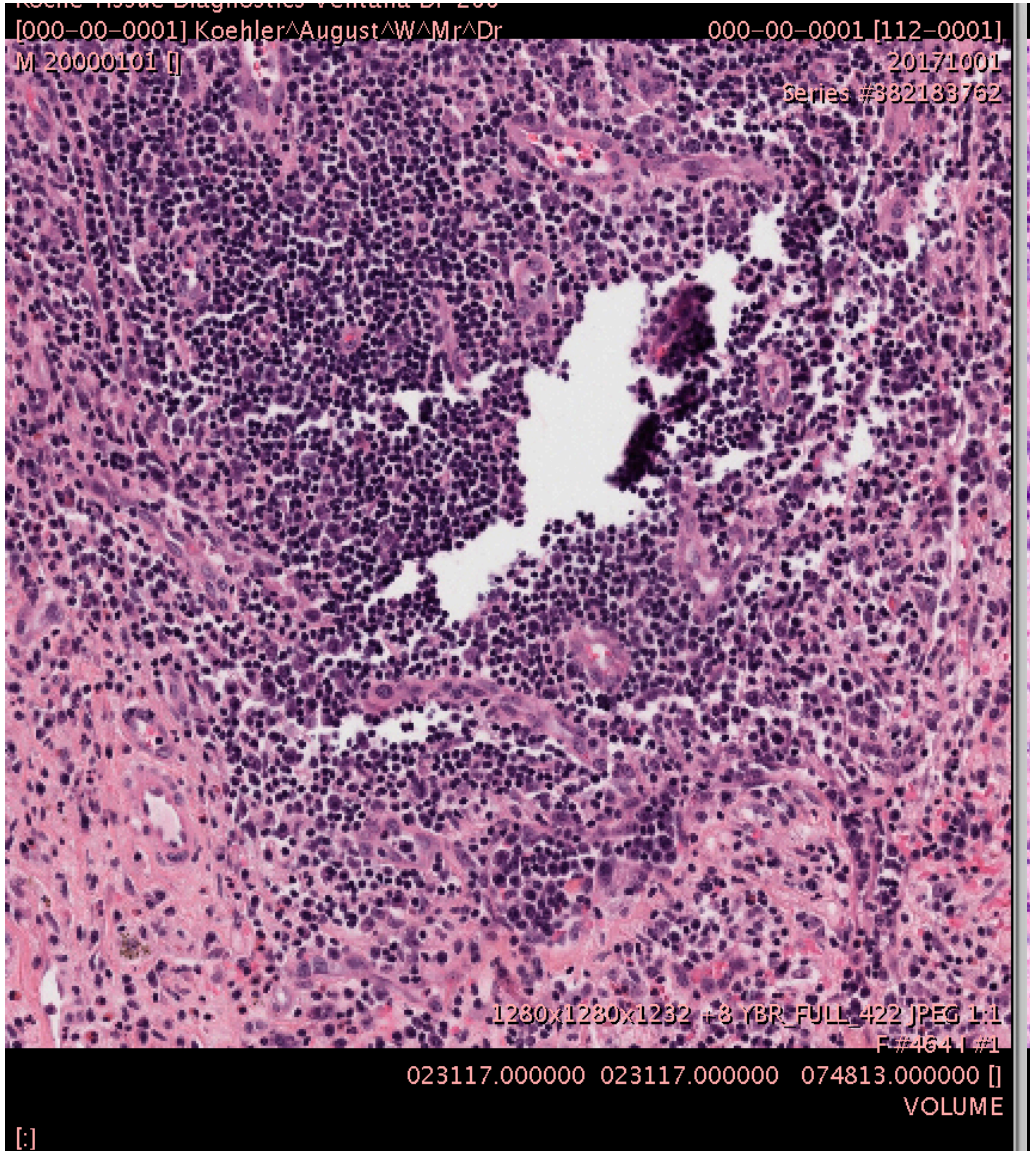


DICOM WSI: Why tiled pyramids?

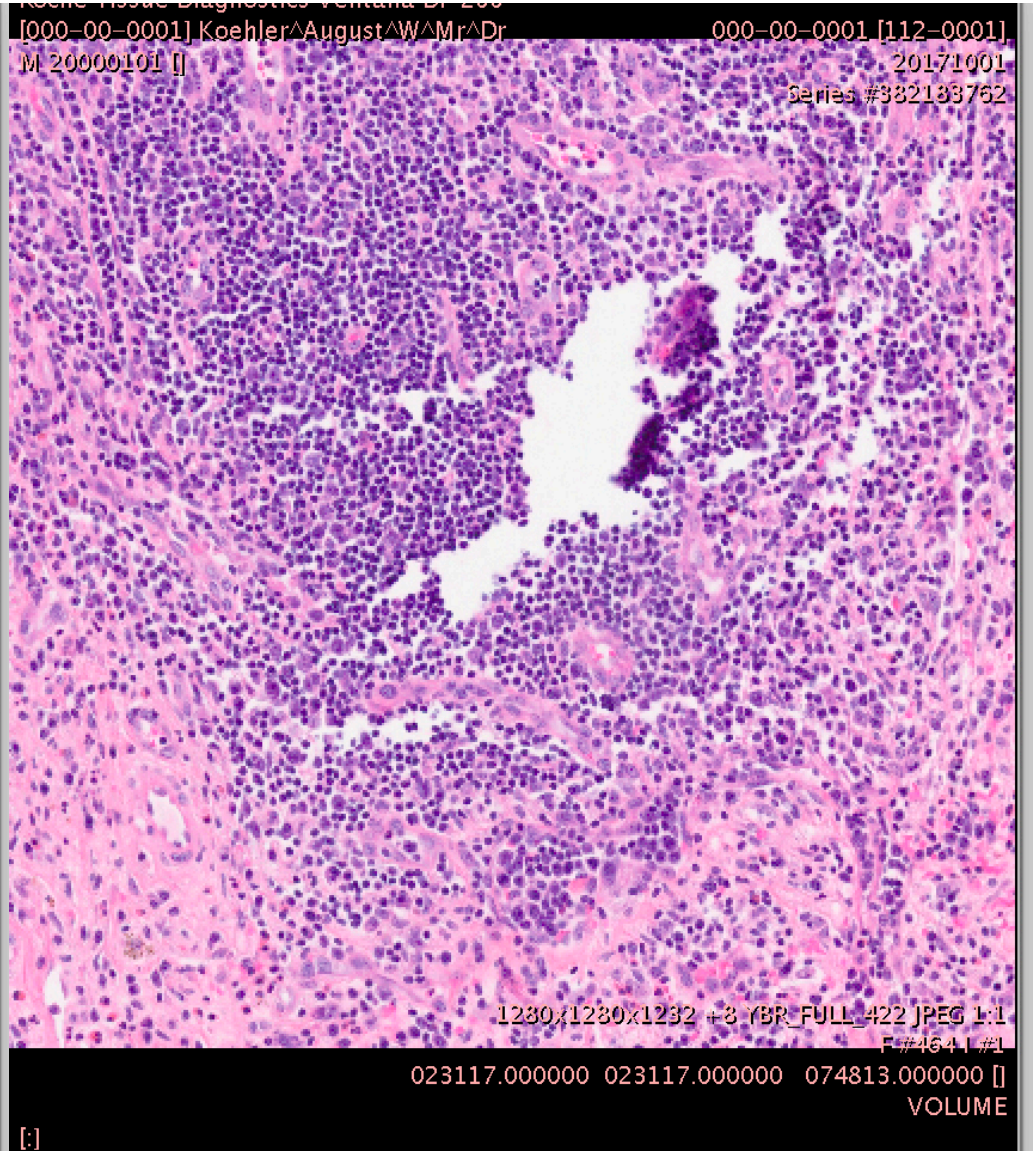
- Goal is simplicity of access simulating a microscope
- Zoom and pan
- Tiles (frames): allow access to rectangular sub-regions of each resolution layer (without loading entire huge object)
- Pyramid: entire highest resolution layer is very large, so storing lower magnification layers (for faster zooming) takes negligible extra space
- Works around DICOM single frame size limitations (64k x 64k): no change to underlying DICOM encoding, no change to existing DICOM toolkits and archives
- Do need services for metadata (index: which tile is which frame) and frame-level retrieval – WADO-RS

DICOM WSI – What next?

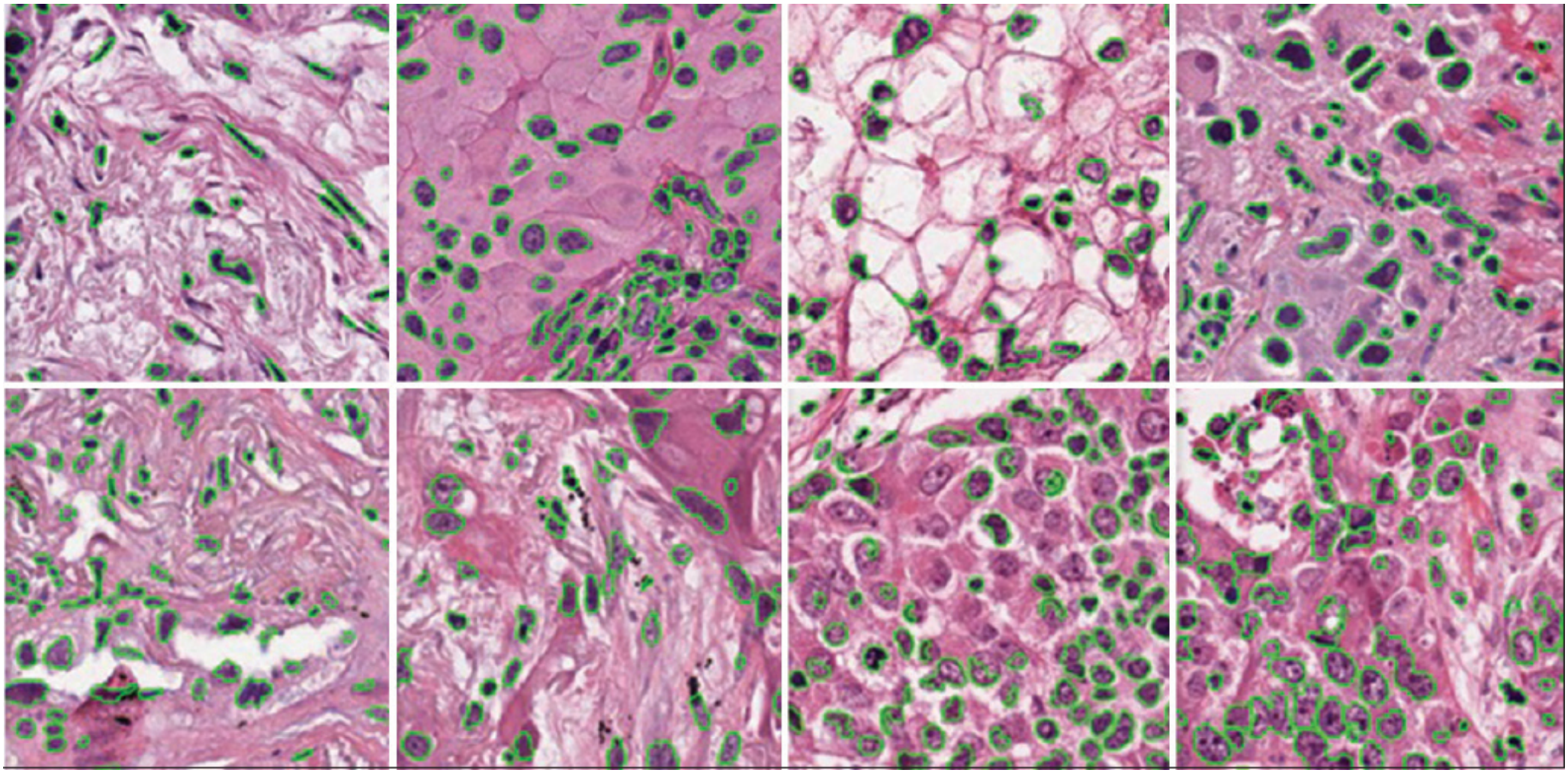
- Color management
  - color normalization
  - color consistency - ICC profiles
  - services for application of ICC profiles to simplify (Internet browser based) viewers
- Workflow management
  - provision of identification and specimen preparation
- Annotations
  - input ("hot spots") and output from analysis algorithms
  - DICOM Segmentations
  - DICOM Structured Reports
  - ? something new in DICOM that scales to millions of nuclei, membranes, etc.



No ICC Profile Applied



With ICC Profile Applied



Wen et al. A methodology for texture feature-based quality assessment in nucleus segmentation of histopathology image. JPI. 2017.

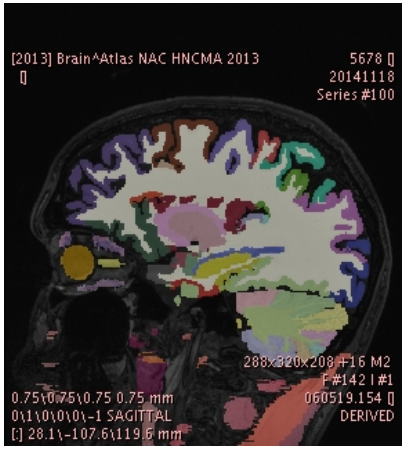
Annotation – Granularity

- Patient (Animal)/Case
- Imaging Study
- Series/Acquisition
- Image
- Frame (pixel data array at one place in space/time/…)
- Region ("of interest" – ROI)
- Single point (label each/every voxel/pixel)

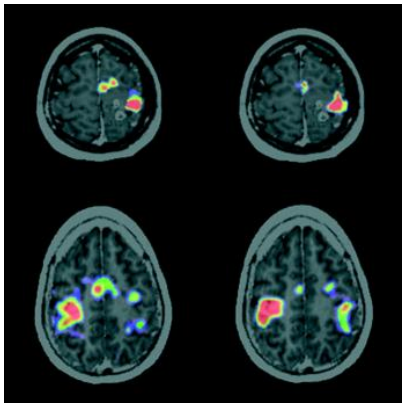
- Can all be encoded in DICOM Structured Report (SR)

Segmentations and Parametric Maps

- Per-voxel encoding of numeric or label values
- "Images", but not just "pretty pictures"
  - modality-specific or secondary capture; single or multi-frame
- Segmentations
  - binary, probability, fractional occupancy
  - multiple segments (multiple labels)
- Parametric maps
  - pixel value "means something" – real world value map (RWVM)
  - integers +/- (linear) rescaling to floats (usable by any viewer)
  - "derived" images of modality-specific SOP Class
  - recently added floating point voxels and SOP Class (Sup 172)
- Leave "fusion" (superimposition) to application
  - e.g., PET SUV on top of CT
  - can use Blending Presentation State to specify what to fuse



Harvard Brain Atlas NRRD Label Map converted to DICOM Segmentation



Meyer P T et al. J Neurol Neurosurg Psychiatry 2003;74:471-478

Conclusion

- DICOM is maturing, both for pre-clinical small animal research and whole slide imaging
- Can use DICOM to leverage existing off-the-shelf commercial and research storage, viewing and analytic tools that salready support DICOM
- Can use DICOM in new developments, e.g., by writing wrappers and brokers using existing toolkits to create appropriate project-specific objects
- Can use DICOM to serve infrastructure needs for completely different modalities, radiological and pathological
- Not just for input – can store quantitative output in DICOM too
- Ideal for co-clinical imaging, because same tools can be used for both human and animal indexing, storage, analysis and quantifications