Multi-Level, Multi-Modal CCF UI for Data Providers and Users within the Human BioMolecular Atlas Program (HuBMAP)

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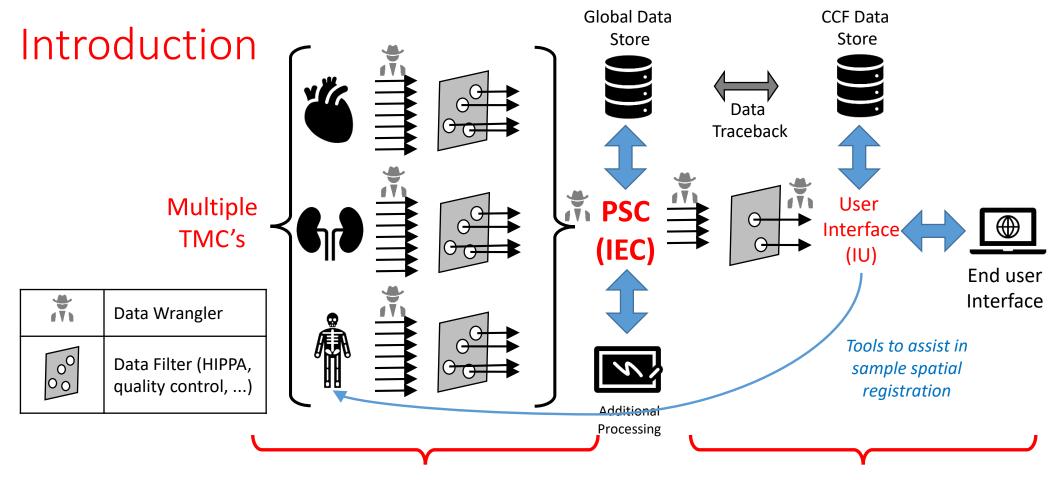
HuBMAP HIVE Q3 Demo Day

Harvard Medical School, Boston, MA

June 27, 2019

Overview

- Introduction
- Y1 Q3 Progress Report
 - CCF Ontology
 - CCF Meta-Data Review
 - CCF Data Wiki
 - CCF User Interface (UI)
- Y2 Plans (June 21, 2019 June 20, 2020)
 - CCF Mapping and Ontologies
 - CCF UI and Tissue Registration UI
 - Visual Human Massive Open Online Course (VHMOOC)
 - User Studies



- Provenance
- Patient
- Sample
- Sample Processing
- Technology (MS, IH, ...)
- Analysis
- Etc.



Propagate needs back to TMC's

 Only the data needed for the GUI

TMC: Tissue Mapping Center

PSC: Pittsburgh Supercomputing Center

CCF User Interface (UI) Tissue Registration UI **CCF** Data **Global Data** Store Store Data Traceback Multiple **PSC** User Interface TMC's (IEC) (IU) End user Interface * Data Wrangler Tools to assist in 000 Data Filter (HIPPA, sample spatial quality control, ...) registration Additional Processing Provenance Only the data

- Patient
- Sample
- Sample Processing
- Technology (MS, IH, ...)
- Analysis
- Etc.

Propagate needs back to TMC's

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Y1 Q3 Progress - Ontology for Kidney

CCF Ontology: some guiding principles

- Reuse existing ontologies and data formats developed for projects similar to HuBMAP to the greatest extent possible
 - GUDMAP / RBK
 - Human Cell Atlas
 - ...
- Reuse domain-specific ontologies and data formats
 - OME-Tiff (Open Microcopy Community advanced image format)
 - MIAME (Minimum Information About a Microarray Experiment)
 - ...
- Leverage HuBMAP domain expertise!
 - Each TMC is an expert in its organ. Capture this in the organ-specific ontologies.
- Use a standard Ontology format and development tools
 - We will use OWL
 - Include test cases in the ontology itself (e.g. both A-box and T-box) for testing, validation and demonstration purposes.
- Cross-link with existing ontologies as much as possible
- Need partOf trees for simplified navigation in GUI.

CCF: Source Ontologies

Anatomic/Phenotypic

- Uberon
- Foundational Model of Anatomy (FMA) (has anatomical terms NOT in Uberon)
- Human Phenotype Ontology (HPO)
- Phenotype and Trait Ontology (PATO)
- Organ specific: Kidney Tissue Atlas Ontology (KTAO) and LungMAP

Tissue/Data Collection

- Biological Spatial Ontology (BSPO)
- Ontology of Biomedical Investigations (OBI)
- EDAM (Bioinformatics concepts)

Open Biological and Biomedical Ontology (OBO)

Foundry is a collective of ontology developers that are committed to collaboration and adherence to shared principles.

BioPortal is a collection of ontologies for biomedical research.

(Sub-)Cellular

- Cell Ontology (CL)
- Gene Ontology (GO)
- Chemical Entities of Biological Interest (ChEBI)
- RNA Ontology (RNAO)
- Protein Ontology (PR)
- Cell Behavior Ontology (CBO)

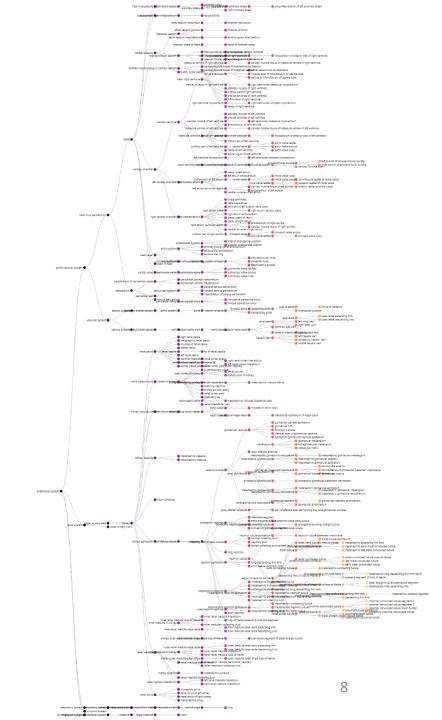
Metadata

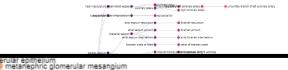
- Basic Formal Ontology (BFO)
- Information Artifact Ontology (IAO)
- Ontology of units of Measure (OM)
- Provenance, Authoring and Versioning ontology (PAV)
- VIVO (Identifying researchers)

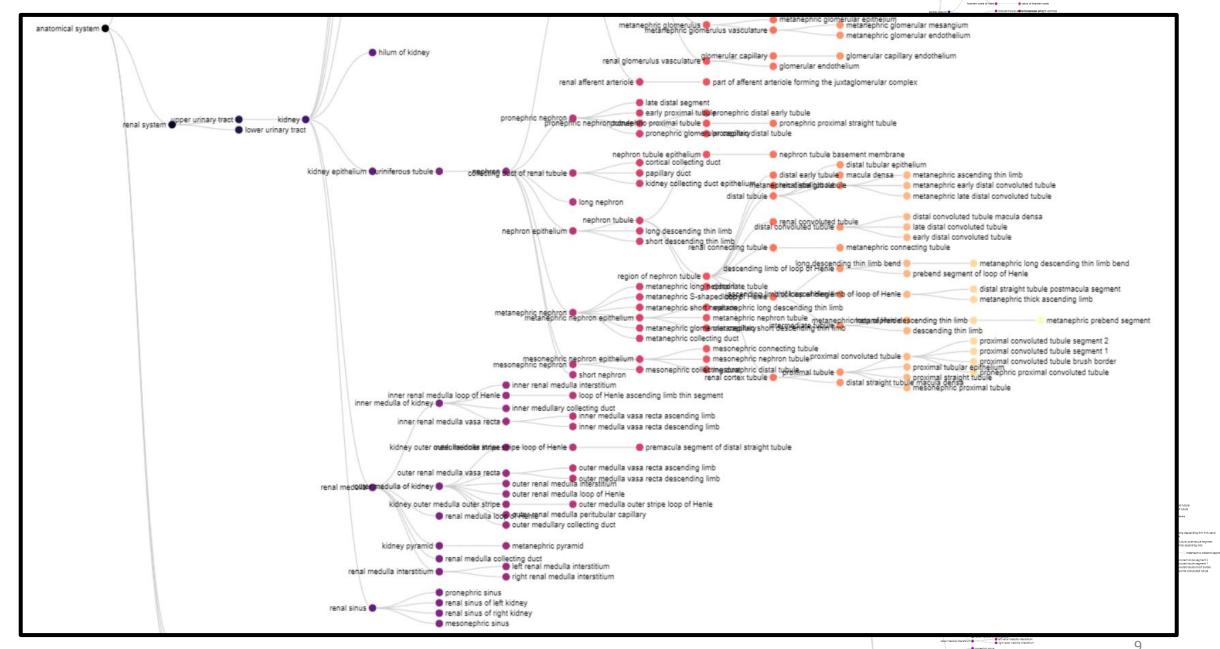
MeSH and NCI Thesaurus

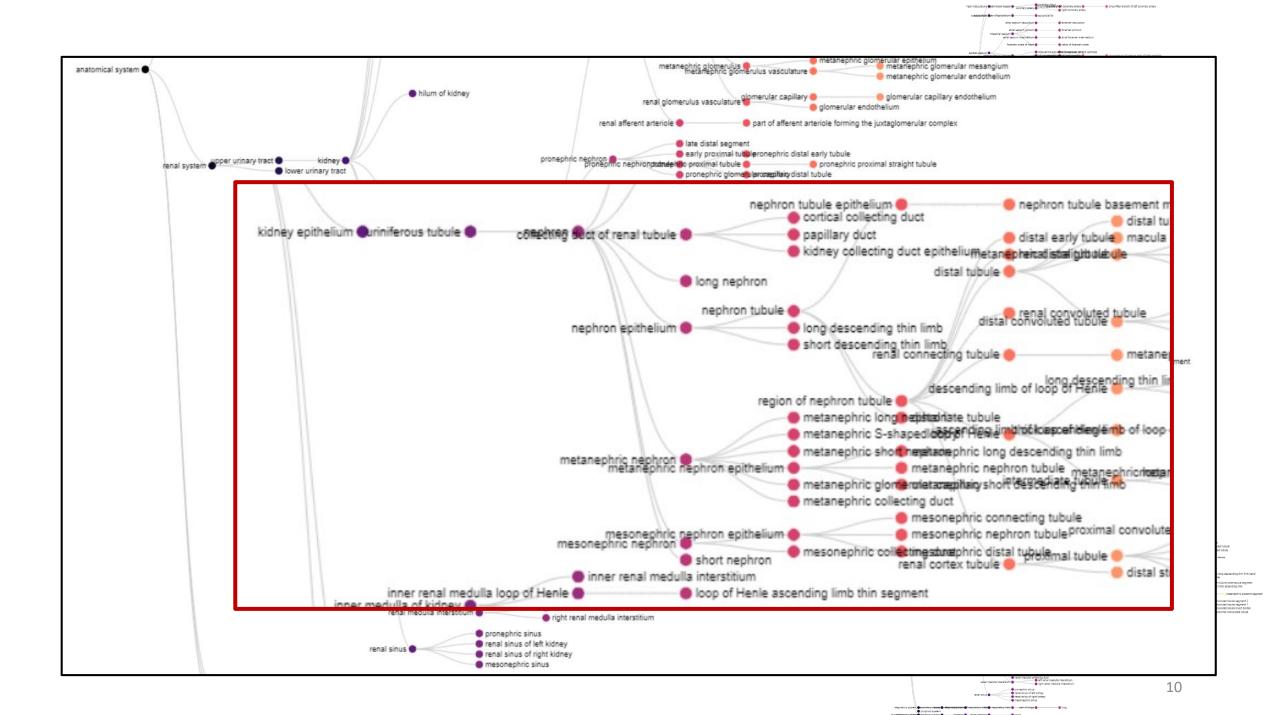
Current CCF Ontology

- Uses Uberon and user-supplied tables of terms to create a SLIM ontology
- Users (initially TMCs) can request missing terms as needed
- "partOf" and other partonomy terms used to help relate concepts
 - Requires domain expertise!
 - Individual TMCs will need to pitch in for their specific organs to refine
- Click here to visualize the current CCF ontology









Y1 Q3 Progress – CCF Meta-Data Review

IU CCF Initial (v0.5.0) Image Formats

Basic image: OME-Tiff as the base "image" format based on:

- 2D to 4D data (includes movies)
- more than three "color channels"
- More flexible "color" data format (int, float, etc.)

Regions of images: SVG with annotations (aligned with a particular OME-Tiff)

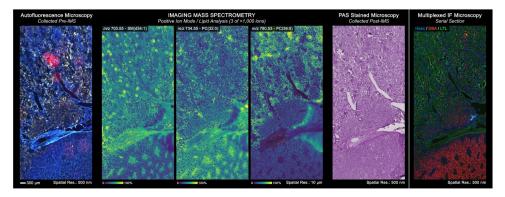
Volumetric (e.g., computed tomography, MR, ultrasound, ...)

Data normally represented as volumes or surfaces

Data. Is very heterogeneous. Must provide guidance.

Kidney: Jeff Spraggins et al., VU

See data on Globus, BIOMIC_patient-64354



Clinical and Spatial Metadata (21 rows)

Cell Types, on right

Cell States (9 rows)

Cell states	Subset A
Proliferating cells	S-phase
	G2/M
Cell cyle arrest	G0
	G1/S
	G2/M

Cell type	Subset A	Subset B	Subset C
Tubular Epithelium	Proximal tubular cells	S1	
		S2	
		S3	
	Loop on Henle	Thin descending limg	
		Thin ascending limb	
		Thick limb	medullary
			cortical
		Macula Densa	
	Distal convoluted tubule		
	Connecting segment		
	Collecting duct	Principal cells	
		Intercalated cells	Type A
			Type B
Glomerulus	Epithelium	Visceral	
		Parietal	
	Mesangial cells		
Vasculature	Endothelium	Glomerular	
		Peritubular	
		Lymphatic	
	Pericytes		
	Juxta Glomerular Cells		
Interstitium	Fibroblasts	Myofibroblasts	
		EPO producing cells	
		Medullary fibroblasts	
	Mononuclear cells	Resident macrophages	
		Dendritic cells	
	Lymphocytes	Ticells	
	Lymphocyces	B cells	
		NK cells	
		THE COMP	

Heart: Shin Lin, UW

<u>Year 1:</u> Tissue data for 1-2cm cubed volumes from 9 sites for 1 heart from 1 individual.

Data Dictionary (115 rows)

Field # Sort Field Label Sort	Field Name Sort	Field Units	Field Data	Lookup Tal	Low Value 1	High Value	Valid value I	sNullable	SParent Fiel Pa	arent Fiel	Can Child b	ReadOnly Sor
9 Donor //ABO:	abo		char(3)	lkup_abo				TRUE				FALSE
10 Donor //Date of birth:	dob		datetime					TRUE				FALSE
11 Donor //Gender:	gender		char(1)	lkup_gende	er		M,F	TRUE				FALSE
12 Details //Age:	age_in_months		smallint		0	1188		TRUE			FALSE	FALSE
13 Details //Age Unit:	age_unit		char(1)	lkup_age_u	unit		M,Y	TRUE	age_in_mont	ths		TRUE
14 Details //Height:	hgt_cm	cm	decimal(5,	2)	1	241.3		TRUE				FALSE
15 Donor hgt_ft //	hgt_ft	ft	int		0	7		TRUE				TRUE
16 Donor hgt_in //	hgt_in	in	int		0	11		TRUE				TRUE
17 Details //Weight:	wgt_kg	kg	decimal(7,	4)	0.454	294.835		TRUE				FALSE
18 Donor wgt_lb //	wgt_lb	lbs	decimal(3,	0)	2	650		TRUE				TRUE
19 Donor //Ethnicity/race:	race		bigint	lkup_race_	subcat_mult	ti		FALSE				FALSE
30 Details //History of diab	e hist_diabetes		smallint	lkup_histdi	ab_dur			TRUE				FALSE
31 Donor //History of cand	e hist_cancer		smallint	lkup_histca	ncer_site			TRUE			FALSE	FALSE
32 Donor History of cancer	cancer_oth_ostxt		varchar(50))	1	50		TRUE	hist_cance	999		FALSE
33 Details //History of hype	er hypertension		smallint	lkup histhy	pe dur			TRUE			FALSE	FALSE

Cell Types (14)

endothelial cells					
	arterial				
	capillary				
	venous				
	lymphatic				
cardiomyocytes					
atrial					
	ventricular				
	nodal				
fibroblasts					
	fibroblasts				
	myofibrob	asts			
immune cells					
	macrophag	ges			

Data: Clinical

Kidney: Jeff Spraggins et al., VU

Clinical and Spatial Metadata (21 rows)

Sample Number:	20
Patient Number:	64354
Procedure ID:	66598
Date:	1/30/2019
Age:	38
Gender:	Female
Race:	White
Height:	165.1 cm
Weight:	115.2 kg
BMI:	42.3
Comorbidities:	Obesity
Type of Procedure:	Total Nephrectomy
Indications for Procedure:	Renal tumor
Laterality:	Left
Tissue Type:	kidney
Dimensions (mm):	L: 19 x W: 13 x H: 7
Anatomical Landmark:	Lower Pole
Distance from Tumor:	7 cm
Sample Processing:	Frozen
Method of Freezing:	Dry Ice/Isopentane Slurry
Embedding Media:	CMC

Heart: Shin Lin, UW

Data Dictionary (115 rows)

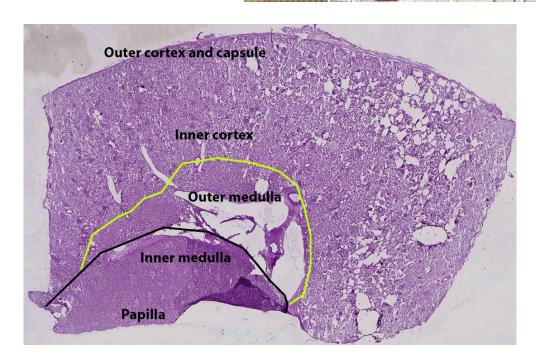
Field # Sort	Field Label Sort	Field Name Sort	Field Units	Field Data	Lookup Tal	Low Value	High Value	Valid value
9	Donor //ABO:	abo		char(3)	lkup_abo			
10	Donor //Date of birth:	dob		datetime				
11	Donor //Gender:	gender		char(1)	lkup_gende	er		M,F
12	Details //Age:	age_in_months		smallint		0	1188	
13	Details //Age Unit:	age_unit		char(1)	lkup_age_u	unit		M,Y
14	Details //Height:	hgt_cm	cm	decimal(5,	2)	1	241.3	
15	Donor hgt_ft //	hgt_ft	ft	int		0	7	
16	Donor hgt_in //	hgt_in	in	int		0	11	
17	Details //Weight:	wgt_kg	kg	decimal(7,	4)	0.454	294.835	
18	Donor wgt_lb //	wgt_lb	lbs	decimal(3,	0)	2	650	
19	Donor //Ethnicity/race:	race		bigint	lkup_race_	subcat_mu	lti	
30	Details //History of diabe	hist_diabetes		smallint	lkup_histdi	ab_dur		
31	Donor //History of cance	hist_cancer		smallint	lkup_histca	ancer_site		
32	Donor History of cancer,	cancer_oth_ostxt		varchar(50)	1	50	
33	Details //History of hyper	hypertension		smallint	lkup_histhy	/pe_dur		

Data: 3D Tissue

Kidney: Jeff Spraggins et al., VU

See data on Globus, BIOMIC_patient-64354

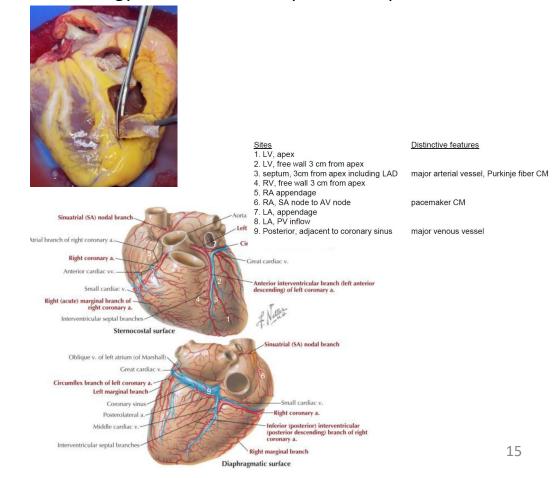




Heart: Shin Lin, UW

Year 1: Tissue data for 1-2cm cubed volumes from 9 sites for 1 heart from 1 individual.

Terminology; Coordinates and photos to spatialize



Data: TMCs x Organs x Data Types x Technologies

BUKMAP, Zhang Group

Organs (10)		Dat	a Types (13)	Technologies (~25)
1.	Bladder	1.	Imaging - Proteins	CODEX;DART-FISHrp;IF;IHC;LRET-IF;MALDI Imaging MS;PER-DEI
2.	Blood Vessel (Heart)	2.	Imaging - RNA	DART-FISH;LRET-ISH;MERFISH;PER-DEI;seqFISH;smFISH
3.	Breast	3.	Imaging - DNA	PER-DEI
4.	Colon	4.	Imaging - Other	Lipid and Metabolite MALDI Imaging MS
5.	Kidney	5.	scRNAseq	snDropseq;scRNAseq
6.	Liver	6.	scDNAseq	scATACseq;scTHSseq;SNAREseq
7.	Lung	7.	scProteomics	IMC
8.	Spleen	8.	bulk-Proteomics	LC-MS/MS
9.	Thymus	9.	bulk-RNA	?
10.	Tonsil	10.	bulk-DNA	?
		11.	Metabolomics	LC-MS/MS;nano-POTS
No E	Bone Marrow	12.	Lipids	LC-MS/MS;nano-DESI
and	Pancreas.	13.	Other	Autofluorescence;PAS stained microscopy

Review of Meta-data formats of similar projects

Other NIH Centers

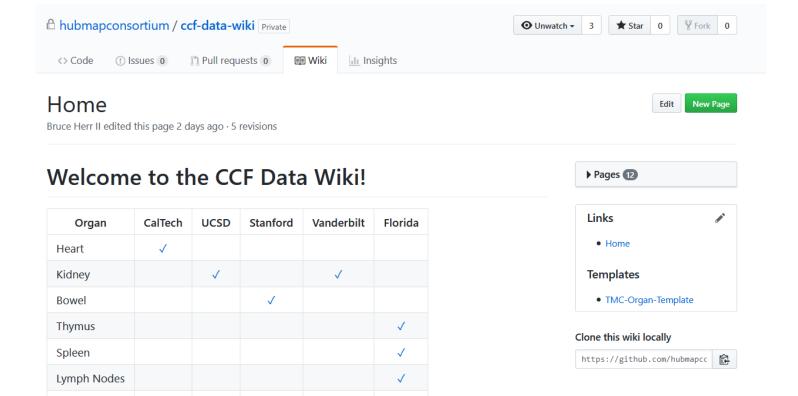
- GenitoUrinary Development Molecular Anatomy Project (GUDMAP)
- (Re)Building a Kidney (RBK)
- Kidney Precision Medicine Project (KPMP)

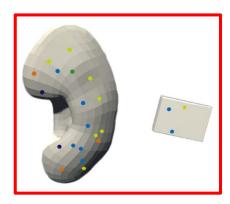
Other Efforts

- Human Cell Atlas (HCA)
- ApiNATOMY

CCF Data Wiki

Minimum Information Standard





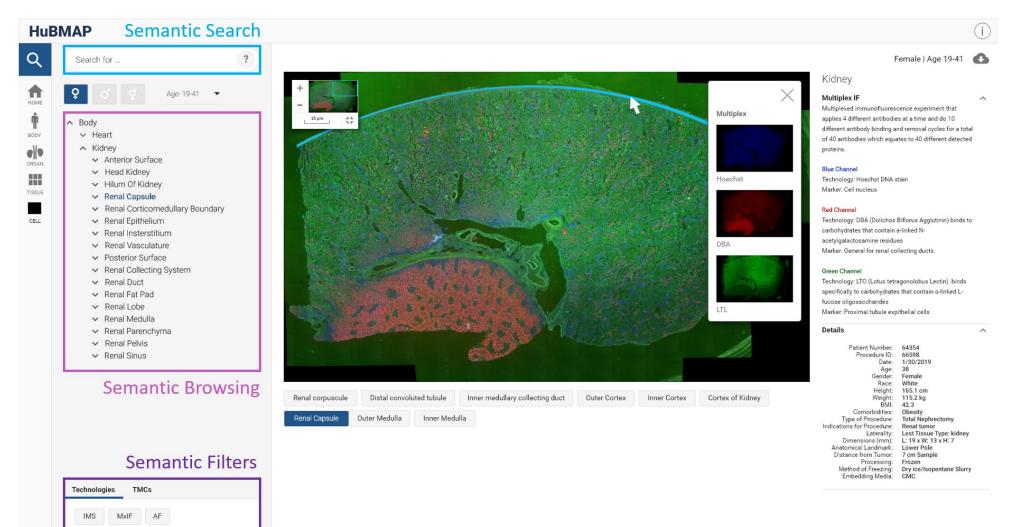
https://github.com/hubmapconsortium/ccf-data-wiki/wiki

Legend:

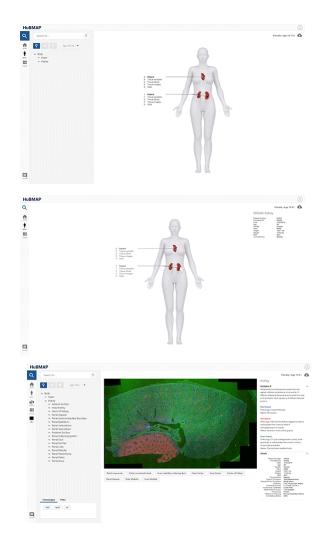
Colon

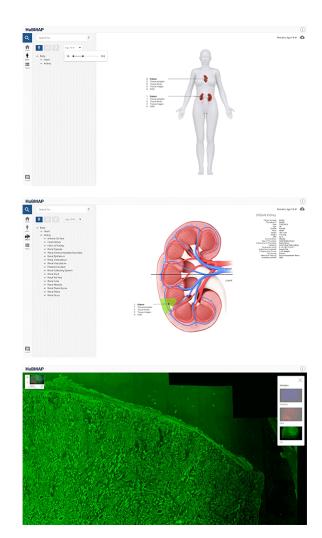
Lung

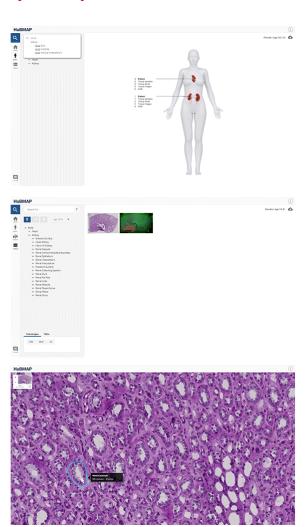
- ✓ Organ proposed and survey submitted
- x Organ was proposed, but no survey has been submitted



GitHub demo site: https://hubmapconsortium.github.io/ccf-ui/







MC-IU has released CCF user interface v0.5.0, a proof-of-concept version of the CCF UI. The user interface supports:

- Visual browsing of tissue samples and metadata at the whole body, organ, tissue, and cell level.
- Filtering by metadata (age, gender, TMC, and technology), results are presented at all views.
- Submission of questions and comments on the CCF UI.
- Semantic search by ontology, results are presented at all levels.
- Data download at the whole body, organ, tissue, and cell level, i.e., link to https://sampledata.hubmapconsortium.org.

See also:

Recorded demo: https://www.youtube.com/watch?v=rWMqKQc_00w&feature=youtu.be

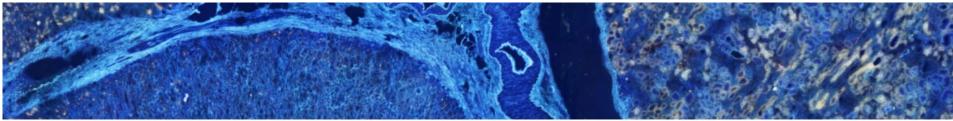
GitHub link to code: https://github.com/hubmapconsortium/ccf-ui

GitHub demo site: https://hubmapconsortium.github.io/ccf-ui/

Original specs: https://drive.google.com/open?id=1tqUzmVLxwqcGprtRlevfY86YvHHPEsDR

Live Demo!

CCF Workshop





COMMON COORDINATE FRAMEWORK WORKSHOP CCFWS-01

Time & Date

9:00am-5:00pm EDT on May 9, 2019

All slides, video recordings are at https://ccfws.cns.iu.edu

Goals

HuBMAP will develop a common reference map or coordinate system called the Common Coordinate Framework (CCF). As stated in the Common Coordinate Framework Meeting (CCFM) document, a CCF makes it possible to uniquely and effectively define and name any location in the human body. A set of robust origin points (serving as landmarks) make it possible to reference organs, tissues, cells over different anatomical scales, tolerate human variability and function across lifespan and disease, and help integrate heterogeneous data layers and a wide range of reference maps such as whole body spatial maps, genetic variant maps, and coordinate systems that align with vascular pathways.

This CCF workshop will focus on a kidney-specific CCF and atlas but also discuss other relevant CCF/atlas efforts. It will feature presentations and discussions on:

- CCF metadata—what data are currently captured, how can they be unified across tissue mapping centers (TMCs), what additional data are needed to meet stakeholder (research) needs.
- CCF ontologies—what ontologies exist and are used in what part of the data pipeline; what 'desirable properties' and 'success criteria' exist?
- CCF mapping and numerical construction—including dealing with human variation and using CCF user interfaces as a means to properly register data and review data completeness.
- General principles and processes that can inform CCF design for other organs and continuous adaptation of CCF to emerging technologies and ever changing user requirements.

The ultimate goal is a set of draft guidelines for TMCs detailing what data to provide in which formats to maximize CCF mapping accuracy and data utility.

Y2 Plans

- CCF Mapping and Ontologies
- CCF UI and Tissue Registration UI
- Visual Human Massive Open Online Course (VHMOOC)
- User Studies

Y2 Plans: CCF Mapping and Ontologies

- Complete kidney ontology and switch to "part of" hierarchy
- V1.0.0 Data format specifications for image data including specification of identified regions
- Patient, sample and technology metadata ontologies in collaboration with the tissue centers
- Lung ontology

Y2 Plans: CCF UI and Tissue Registration UI

CCF User Interface (UI) Tissue Registration UI **CCF** Data **Global Data** Store Store Data Traceback Multiple **PSC** User Interface TMC's (IEC) (IU) End user Interface * Data Wrangler Tools to assist in 000 Data Filter (HIPPA, sample spatial quality control, ...) registration Additional Processing Provenance Only the data

- Patient
- Sample
- Sample Processing
- Technology (MS, IH, ...)
- Analysis
- Etc.

Propagate needs back to TMC's

Only the data needed for the GUI

TMC: Tissue Mapping Center

PSC: Pittsburgh Supercomputing Center

Tissue Registration UI: Heart (depending data availability)

Align 9 tissue samples in 3D heart using a combi of

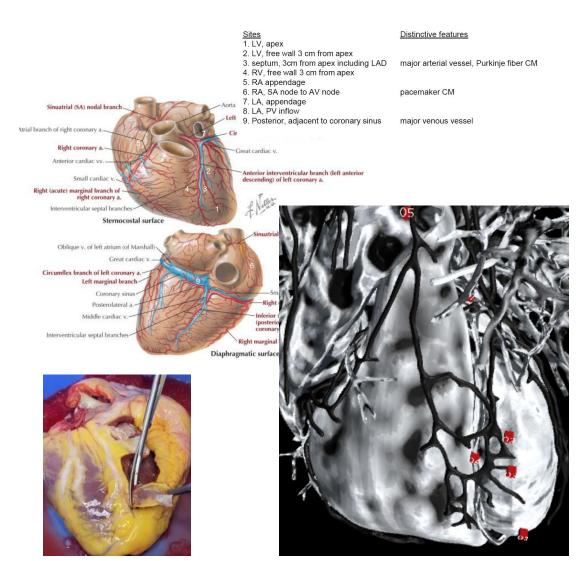
- Rough placement using human expertise/3D pattern matching and
- Fine adjustments using machine learning

Virtual tissue samples will be sized 1-2cm cubed, numbered (1 ... 9), and oriented (left-right, top and bottom tissue slice of z-stack).

Measure error from

- precision of tissue sample procurement and
- placement in the 3D browser

We hypothesize that placement accuracy will improve when additional information (e.g., landmarks, major scaffolds, MR/CT scan of heart after 9 samples were extracted) is being visible in virtual organ.

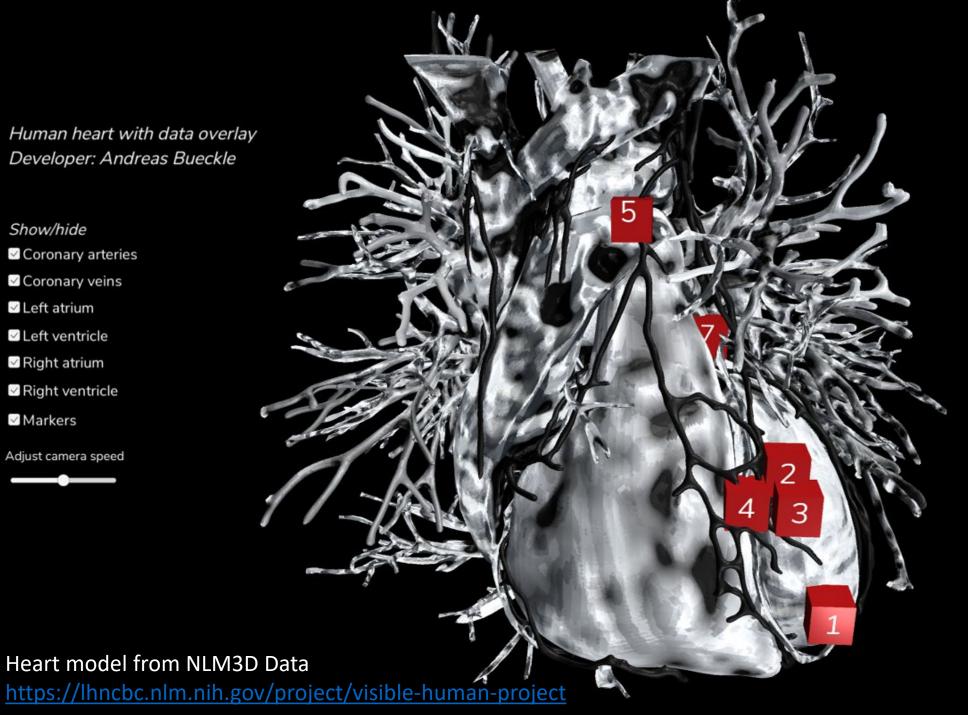


Human heart with data overlay Developer: Andreas Bueckle

Show/hide

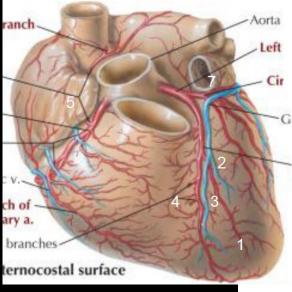
- ✓ Coronary arteries
- ✓ Coronary veins
- ✓ Left atrium
- ✓ Left ventricle
- ✓ Right atrium
- ☑ Right ventricle
- ✓ Markers

Adjust camera speed



Currently Selected

Please click any of the red markers!



Tissue Registration UI: Kidney

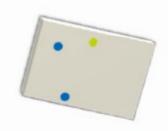
(depending data availability)

- Exploit human pattern recognition and fine motor skills (by surgeons) to register tissue in organs.
- Add info on anatomical landmarks, cell types, molecular data to support alignment.
- LATER: Use human alignment data as training data for machine learning algorithms, to better support manual alignment OR to possibly fully automatize alignment.



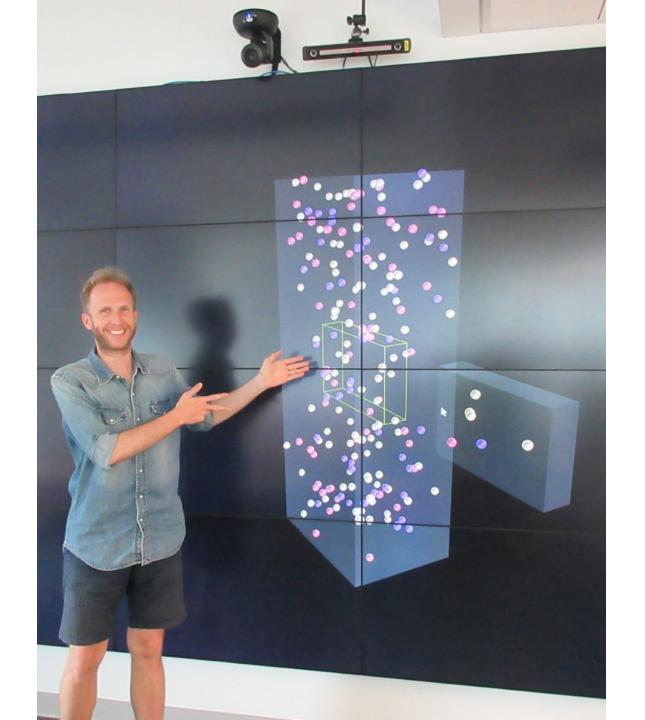


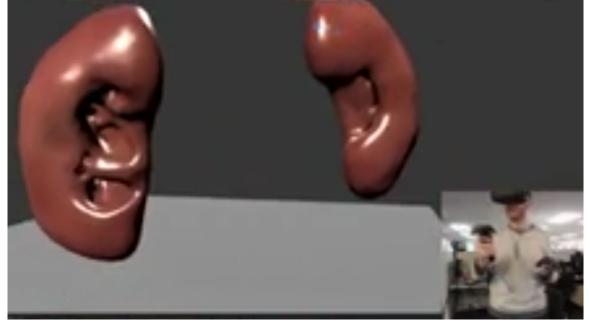
How many of you have used a VIVE or space mouse?



Kidney model from NLM3D Data

https://lhncbc.nlm.nih.gov/project/visible-human-project

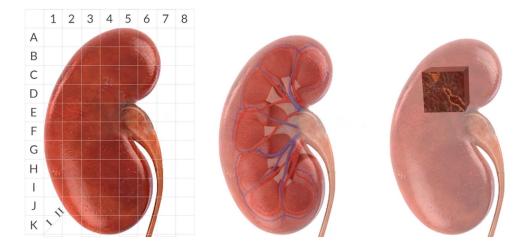




Kidney model from NLM3D Data https://lhncbc.nlm.nih.gov/project/visible-human-project



For the kidney, there exist no predefined tissue extraction sites. The current kidney Registration UI uses a grid system and a picture of a kidney slice to guide placement, see **Fig. 3 left and middle**. Funding of this GLUE grant will make it possible to use 3D image volumes collected from intact kidney tissue within KPMP that feature anatomically meaningful structures of different cell types, see **Fig. 3 right**.



KPMP GLUE grant proposal in progress.

Figure 3: 3D grid system (left), 2D image (middle), 3D tissue reconstructions from KPMP (right)

Using the 3D grid system, a user can use 3D coordinates to refer to a particular area in the kidney, e.g., A-4-II would correspond to the lower-middle part of the kidney, on the inside (occluded in this view). Using the 2D image, sample placement within a semi-transparent reference kidney object is guided by anatomical structures. Using KPMP data, it will be possible to show complex volumetric structures inside the 3D reference kidney to allow for more granular alignment at the molecular level.

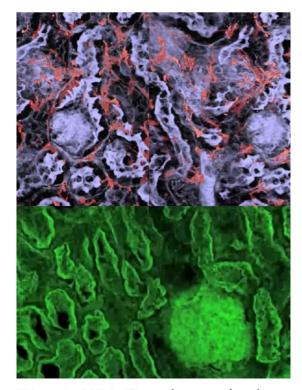


Fig. 4. KPMP volumetric data.

See presentation by Seth

Winfree for details

https://ccfws.cns.iu.edu

Y2 Plans: CCF UI

- Use the CCF UI to serve a Kidney Micro Atlas.
- Go from Proof of Concept to fully-realized application
 - Fully integrate heart and kidney data
 - Integrate Tissue Registration UI data
 - Integrate expanded CCF Ontology
 - Connect to data/queries via IEC APIs and infrastructure
- Collaborate on a common Tissue Viewer

Y2 Plans: Visual Human Massive Open Online Course (VHMOOC)

Research and develop a Visual Human Massive Open Online Course (VHMOOC) hat helps communicate the

- quality and coverage of HuBMAP data,
- utility and proper usage of CCF Tissue Registration, CCF UI, and HuBMAP tools, and
- demonstrate new single-cell analysis and CCF mapping techniques.

First interviews with experts will be run at the HuBMAP meeting at Stanford U. Please let MC-IU know if you are interested/available to showcase your work.

Y2 Plans: User Studies

Conducting in-depth interviews with experts to understand user needs (Y1Q3, will continue in Y2Q1)

Information gathered will inform both the Tissue Registration UI and the Common Coordinate Framework UI.

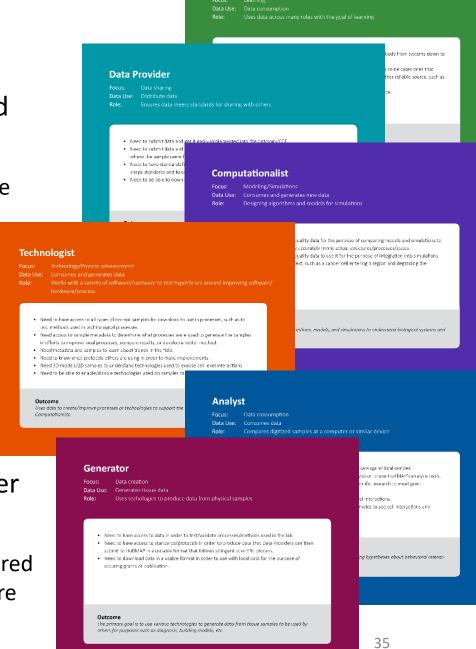
Identified 6 draft personas (Y1Q3, will refine in Y2)

Generator, Analyst, Technologist, Computationalist, Data Provider, Educator/StudentBased on interviews, user stories, surveys, and comparisons with similar projects (HCA, KPMP)

We welcome your feedback on their applicability across the project. Review and provide feedback at https://bit.ly/2ZFHwYW.

Developed methodology and obtained IRB approval for user studies to be conducted in Y2 (Y1Q3)

Task-oriented user testing to improve the CCF user interface. Administered online, with HuBMAP members and other biological researchers who are representative of users based on their research interests.



Educator/Learner