The Human Body Atlas: High-Resolution, Functional Mapping of Voxel, Vector, and Meta Datasets

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HCA Asia

October 22, 2020

Acknowledgements

HuBMAP Consortium (https://hubmapconsortium.org)

Thanks go to all the **patients** that agreed to volunteer healthy tissue and open use of their data.

NIH National Institutes of Health

Opportunity Pool Awardee
KIDNEY PRECISION MEDICINE PROJECT
kpmp.org

NSF

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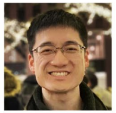

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HuBMAP

Vision

Catalyze the development of an open, global framework for comprehensively mapping the human body at cellular resolution.

https://commonfund.nih.gov/HuBMAP
https://hubmapconsortium.org

Goals

- Accelerate the development of the next generationof tools and techniques for constructing high resolution spatial tissue maps
- Generate foundational 3D tissue maps
- Establish an open data platform https://portal.hubmapconsortium.org
- Coordinate and collaborate with other funding agencies, programs, and the biomedical research community
- Support projects that demonstrate the value of the resources developed by the program

The Human Body at Cellular Resolution:
The NIH Human Biomolecular Atlas Program.
Snyder et al. *Nature*. 574, p. 187-192.

+ 11 new teams!

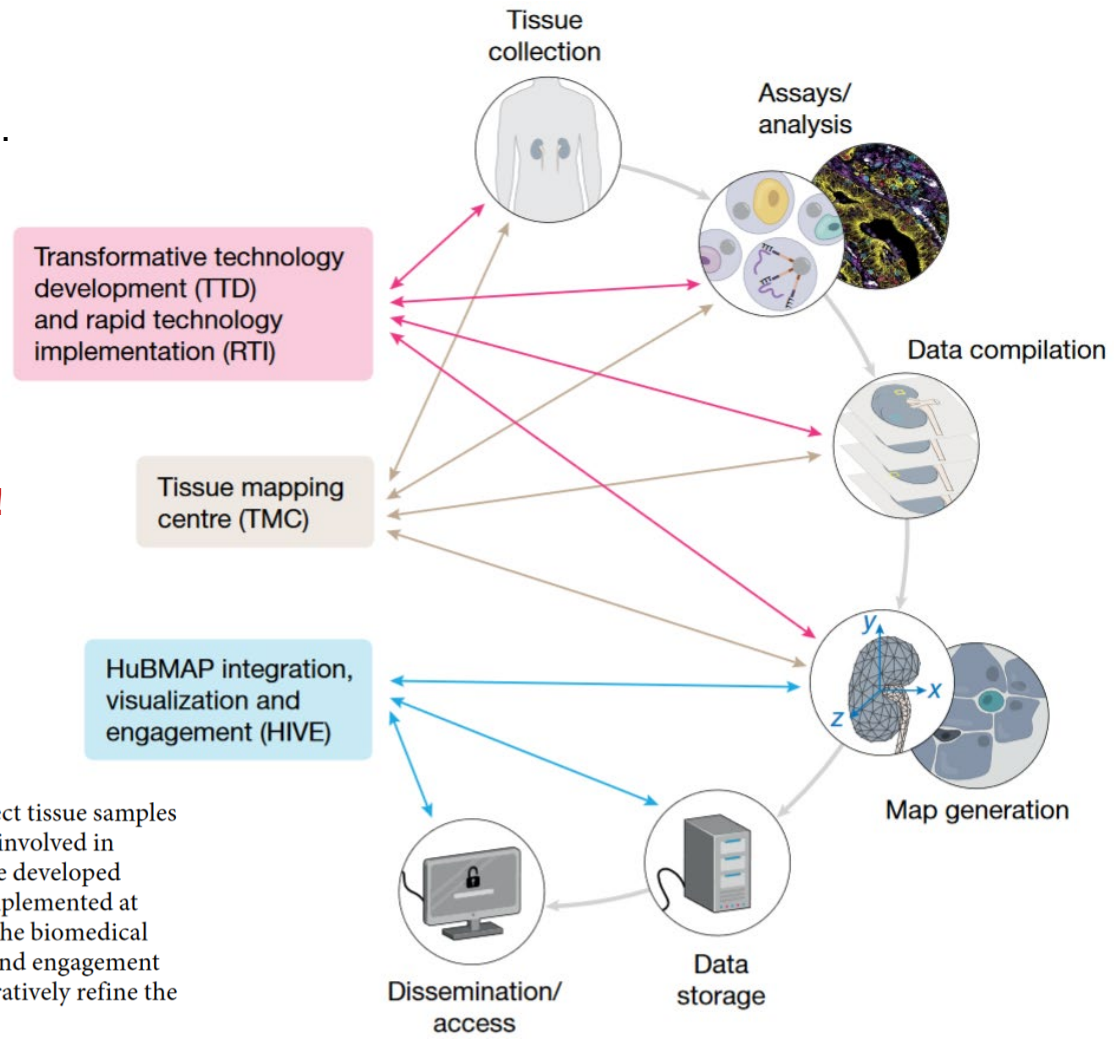


Fig. 1 | The HubMAP consortium. The TMCs will collect tissue samples and generate spatially resolved, single-cell data. Groups involved in TTD and RTI initiatives will develop emerging and more developed technologies, respectively; in later years, these will be implemented at scale. Data from all groups will be rendered useable for the biomedical community by the HuBMAP integration, visualization and engagement (HIVE) teams. The groups will collaborate closely to iteratively refine the atlas as it is gradually realized.

The Human Body at Cellular Resolution:
The NIH Human Biomolecular Atlas Program.
Snyder et al. *Nature*. 574, p. 187-192.

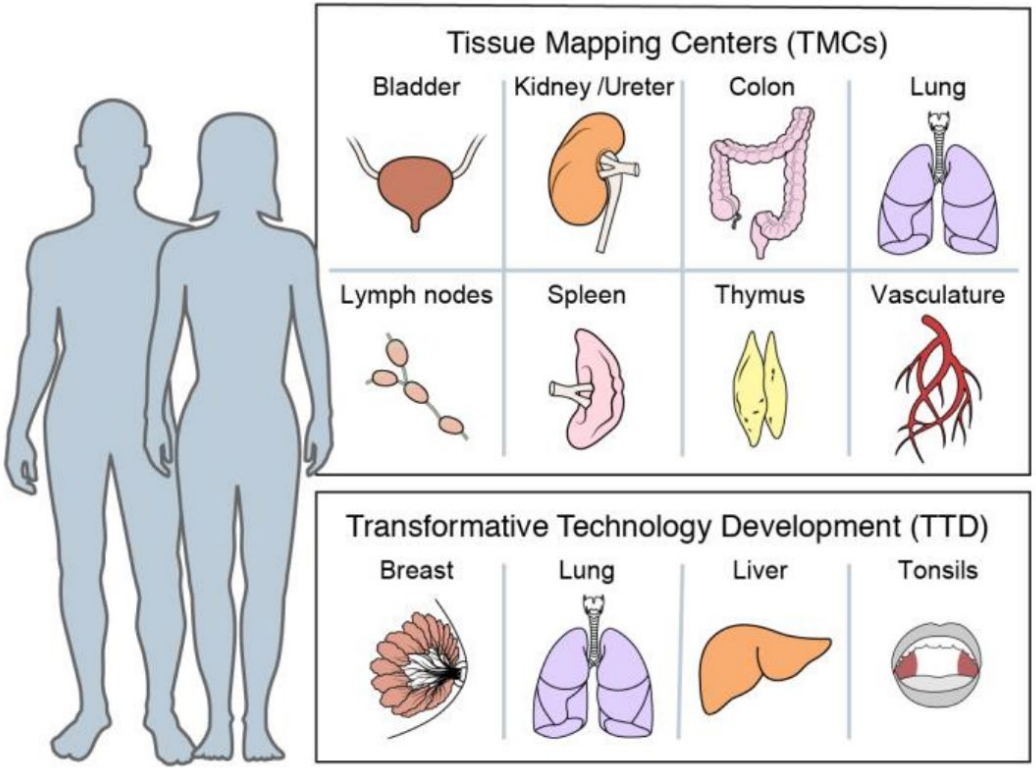


Fig. 2 | Key tissues and organs initially analysed by the consortium. Using innovative, production-grade ('shovel ready') technologies, HuBMAP TMCs will generate data for single-cell, three-dimensional maps of various human tissues. In parallel, TTD projects (and later RTI projects) will refine assays and analysis tools on a largely distinct set of human tissues. Samples from individuals of both sexes and different ages will be studied. The range of tissues will be expanded throughout the program.

The Human Body at Cellular Resolution: The NIH Human Biomolecular Atlas Program. Snyder et al. *Nature*. 574, p. 187-192.

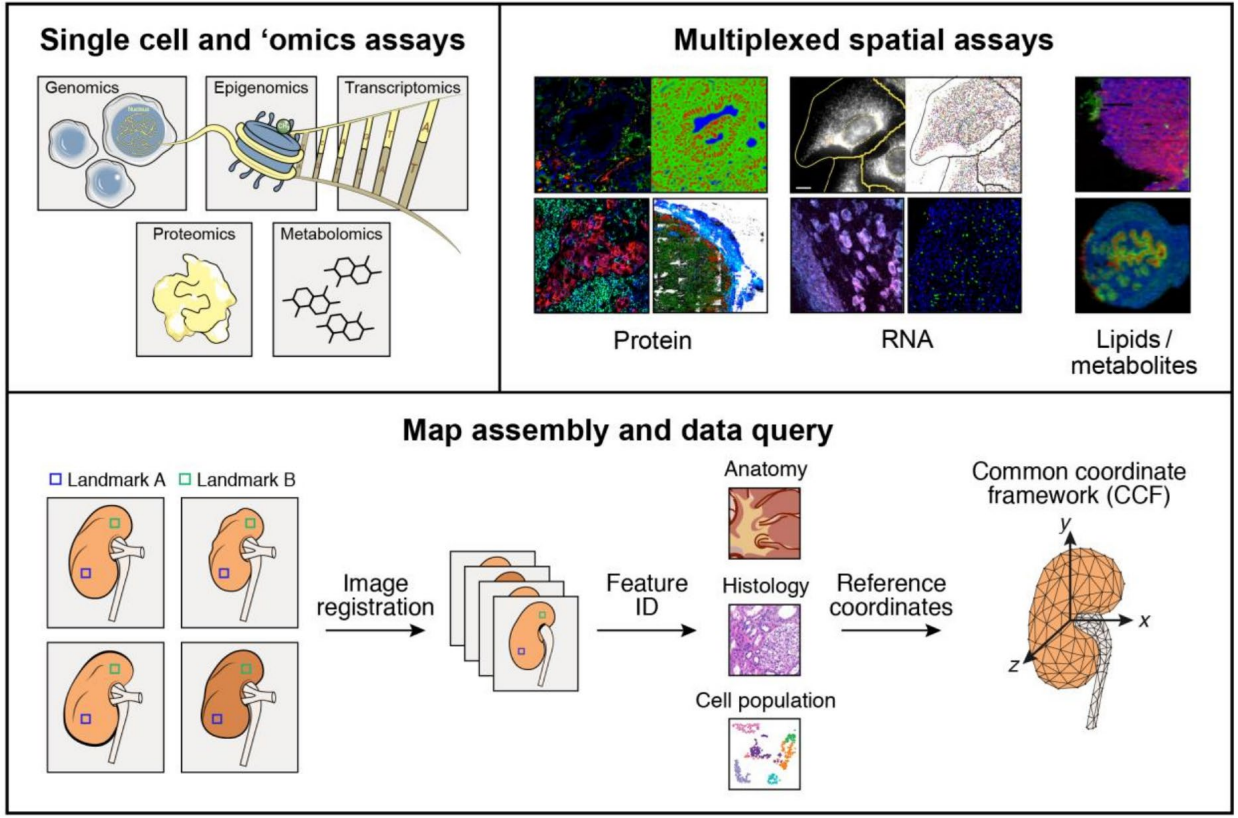


Fig. 3 | Map generation and assembly across cellular and spatial scales. HuBMAP aims to produce an atlas in which users can refer to a histological slide from a specific part of an organ and, in any given cell, understand its contents on multiple 'omic levels—genomic, epigenomic, transcriptomic, proteomic, and/or metabolomic. To achieve these ends, centres will apply a combination of imaging, 'omics and mass spectrometry techniques to specimens collected in a reproducible manner from specific sites in the body. These data will be then be integrated to arrive at a high-resolution, high-content three-dimensional map for any given tissue. To ensure inter-individual differences will not be confounded with collection heterogeneity, a robust CCF will be developed.

HUMAN CELL ATLAS
ASIA

Program

Day 1: Thursday, October 22, 2020

10:30–11:50 **Co-current session-1**

Co-current #1-2: Computational analysis Chair: Jin Gu, Belinda Phipson	Rahul Satija Belinda Phipson Jinmiao Chen	MC-NYGC	ZOOM-2
Co-current #1-4: Atlas Chair: Jay Shin, Katy Borner	Katy Borner Longqi Liu Xinghua Pan	MC-IU	ZOOM-4

HuBMAP Visible Human MOOC (VHMOOC)

Started Aug 4, 2020

To enroll, first **log in**. If you don't have an account, **create an IU Guest account**.

Register via:
https://tinyurl.com/vhmooc

INDIANA UNIVERSITY

Course Introduction

This 10h course introduces the HuBMAP project which aims to create an open, global reference atlas of the human body at the cellular level. Among others, the course describes the compilation and coverage of HuBMAP data, demonstrates new single-cell analysis and mapping techniques, and introduces major features of the HuBMAP portal.

Delivered entirely online, all coursework can be completed asynchronously to fit busy schedules. If you have questions or experience issues during registration, please email cnscntr@indiana.edu.

Learning Outcomes

- Theoretical and practical understanding of different single-cell tissue analysis techniques.
- Expertise in single-cell data harmonization used to federate data from different individuals analyzed using different technologies in diverse labs.
- Hands-on skills in the design and usage of semantic ontologies that describe human anatomy, cell types, and biomarkers (e.g., marker genes or proteins).
- Knowledge on the design and usage of a semantically annotated three-dimensional reference system for the healthy human body.
- An understanding of how the HuBMAP reference atlas might be used to understand human health but also to diagnose and treat disease.

Module Topics Include

- HuBMAP Overview: Project Goals, Setup, and Ambitions
- Tissue Data Acquisition and Analysis
- Biomolecular Data Harmonization
- Ontology, 3D Reference Objects, and User Interfaces
- HuBMAP Portal Design and Usage

Meet the Instructors

Katy Börner, Victor H. Yngve Distinguished Professor of Engineering and Information Science. Founding Director of the Cyberinfrastructure for Network Science Center at Indiana University.

Ellen M. Quardokus, staff in the Chemistry Department and research scientist, Cyberinfrastructure for Network Science Center, SICE with expertise in molecular biology, microscopy, anatomy, and interdisciplinary communication.

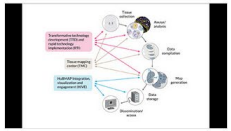
Andreas Bueckle, PhD Candidate in Information Science, performing research on information visualization, specifically virtual and augmented reality.

Length: 10 hours

Department: Cyberinfrastructure Network Science

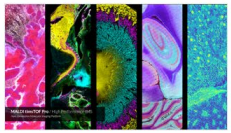
Credit: None

Audience: Biomedical students and professionals interested in single-cell tissue analysis and visualization



HuBMAP Overview

- Project Goals, Setup, and Ambitions

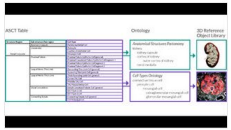


Tissue Data Acquisition and Analysis

- Behind the Scenes at Vanderbilt University

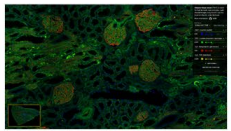
Biomolecular Data Harmonization

- An Introduction to Seurat



CCF Ontology, 3D Reference Objects, and User Interfaces

- Creating an Atlas of the Human Body



Portal Design and Usage

- Datasets and Software in the 1st HuBMAP Portal Release

Open Consent Your Data

- In Support of Research

What is a CCF?

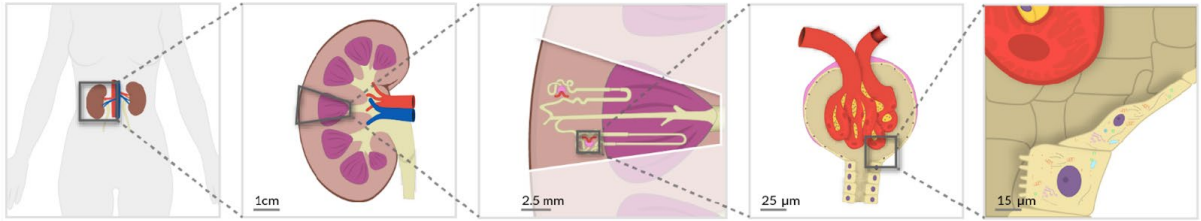
The Common Coordinate System (CCF) consists of ontologies and reference object libraries, computer software (e.g., user interfaces), and training materials that

- enable biomedical experts to semantically annotate tissue samples and to precisely describe their locations in the human body (“registration”),
- align multi-modal tissue data extracted from different individuals to a reference coordinate system (“mapping”) and,
- provide tools for searching and browsing HuBMAP data at multiple levels, from the whole body down to single cells (“exploration”).

CCF Requirements

The CCF must capture major **anatomical structures, cell types, and biomarkers** and their interrelations across **multiple levels of resolution**.

It should be **semantically explicit** (using existing ontologies, e.g., Uberon, CL) and **spatially explicit** (e.g., using 3D reference organs for registration and exploration).



Body	Organ	Functional Tissue Unit	FTU Sub-structure(s)	Cellular
• Body • Kidney (Left, Right) • Aorta • Renal artery • Renal vein • Ureter	• Renal capsule • Renal pyramid • Renal cortex • Renal medulla • Renal calyx • Renal pelvis	• Nephron • Renal corpuscle • Proximal convoluted tubule • Loop of Henle • Distal convoluted tubule • Connecting tubule • Collecting duct	• Bowman's capsule • Glomerulus • Efferent arteriole • Afferent arteriole	• Parietal epithelial cell • Capillary endothelial cell • Mesangial cell • Podocyte

ASCT+B Tables

Anatomical Structures, Cell Types, and Biomarkers (ASCT+B) tables aim to capture the partonomy of anatomical structures, cell types, and major biomarkers (e.g., gene, protein, lipid or metabolic markers).

Structure/Region	Substructure/Subregion	Cell Type	Subset of Marker Genes
Renal Corpuscle	Bowman's Capsule	Parietal epithelial cell	*CRB2*, CLDN1**
	Glomerulus	Podocyte	*NPHS2*, PODXL*, NPHS1**
		Capillary Endothelial Cell	*EHD3*, EMCN*, HECW2*, FLT1*, AQP1**
		Mesangial Cell	*POSTN*, PIEZO2*, ROBO1*, ITGA8**

Partial ASCT Table from

- El-Achkar et al. A Multimodal and Integrated Approach to Interrogate Human Kidney Biopsies with Rigor and Reproducibility: The Kidney Precision Medicine Project. bioRxiv. 2019; 828665. doi:10.1101/828665

Table 3: Cell types and associated markers from KPMP Pilot 1 transcriptomic studies. Asterisk denotes genes detected by more than one technology. *Italics*, genes detected by a single technology.

Structure/Region	Sub structure/Sub region	Cell Type	Abbreviation	Subset of Marker Genes	Pertinent negatives/comments
Renal Corpuscle	Bowman's Capsule	Parietal epithelial cell	PEC	*CRB2*, CLDN1**	
	Glomerulus	Podocyte	POD	*NPHS2*, PODXL*, NPHS1**	
		Capillary Endothelial Cell	GC-EC	*EHD3*, EMCN*, HECW2*, FLT1*, AQP1**	
		Mesangial Cell	MC	*POSTN*, PIEZO2*, ROBO1*, ITGA8**	
Tubules	Proximal Tubule	Proximal Tubule Epithelial Cell (general)	PT	*CUBN*, LRP2*, SLC13A1*, ALDOB*, GATM**	
		Proximal Convoluted Tubule Epithelial Cell Segment 1	PT-S1	*SLC5A2*, SLC5A12**	There is overlap among the segments
		Proximal Tubule Epithelial Cell Segment 2	PT-S2	*SLC22A6**	
		Proximal Tubule Cell Epithelial Segment 3	PT-S3	*PDZK1IP1*, MT1G**	
	Loop of Henle, Thin Limb	Descending Thin Limb Cell (general)	DTL	*CRYAB*, VCAM1*, AQP1*, SPP1**	*CLDN10* low
		Ascending Thin Limb Cell (general)	ATL	*CRYAB*, TACSTD2*, CLDN3**	*AQP1* low to none
	Loop of Henle, Thick Limb	Thick Ascending Limb Cell (general)	TAL	*SLC12A1*, UMOD**	*SLC12A3* low to none
		Cortex-TAL cell	C-TAL	*SLC12A1*, UMOD**	
		Medulla-TAL cell	M-TAL	*SLC12A1*, UMOD**	
		TAL-Macula Densa cell	TAL-MD	*NOS1*, SLC12A1**	
	Distal Convolution	Distal Convoluted Tubule Cell (general)	DCT	*SLC12A3*, TRPM6**	
		DCT type 1 cell	DCT-1	*SLC12A3*, TRPM6*	*SLC8A1, HSD11B2* (low to none)
		DCT type 2 cell	DCT-2	*SLC12A3*, SLC8A1*, HSD11B2*	Has CNT and DCT signature
	Connecting Tubule	Connecting Tubule Cell (general)	CNT	*SLC8A1*, CALB1, TRPV5*	*SLC12A3* low to none. IC or PC without *SLC8A1* could be in the CNT structure
		CNT-Principal Cell	CNT-PC	*SLC8A1*, AQP2*, SCNN1G**	
		CNT-Intercalated Cell	CNT-IC	*SLC8A1*, CA2, ATP6VOD2**	
		CNT-IC-A cell	CNT-IC-A	*SLC8A1*, SLC4A1*, SLC26A7**	
		CNT-IC-B cell	CNT-IC-B	*SLC8A1*, SLC26A4*, SLC4A9**	
	Collecting Duct	Collecting duct (general) cell	CD	*GATA3**	*GATA3* may be in subpopulation of DCT, CNT and vSMC/P. SLC8A1, CALB1, TRPV5
		CD-PC (general)	CD-PC	*AQP2*, AQP3*, FXYD4*, SCNN1G*, GATA3**	
		C-CD-PC	C-CD-PC		
		M-CD-PC	M-CD-PC		
		Outer medulla-CD-PC	OM-CD-PC		
		Inner Medulla-CD cell	IM-CD	*AQP2*, SLC14A2*	
		Transitional PC-IC cell	tPC-IC	*FXYD4*, SLC4A9*/SLC26A7**	(low to none); Low to No *CALCA* and *KIT* in C-CD-IC-A. It may not be possible to assign IC or PC to CNT or CD structures without regional information of their source.
		CD-IC (general) cell	CD-IC	*CA2, ATP6VOD2**	
		CD-IC-A (general) cell	CD-IC-A	*SLC4A1, SLC26A7*, TMEM213**	
		C-CD-IC-A cell	C-CD-IC-A	*SLC26A7*, SLC4A1**	
		M-CD-IC-A cell	M-CD-IC-A	*SLC26A7*, SLC4A1, KIT*, CALCA*	
		CD-IC-B (general) cell	CD-IC-B	*SLC4A9*, SLC26A4**	
		C-CD-IC-B cell	C-CD-IC-B		
		M-CD-IC-B cell	M-CD-IC-B		
Vessels	Endothelial Cells (non-glomerular)	Endothelial Cell (general)	EC	*EMCN*, PECAM1*, FLT1**	
		EC-Afferent/Efferent Arteriole	EC-AEA	*SERPINE2*, TM4SF1**	likely *PALMD*
		EC-Peritubular capillaries	EC-PTC	*PLVAP**	
		EC-Descending Vasa Recta	EC-DVR	*TM4SF1*, PALMD*	
		EC-Ascending Vasa Recta	EC-AVR	*DNASE1L3**	low to none
		EC-Lymphatics	EC-LYM	*MMRN1*, PROX1*	
Structure/Region	**Sub structure/Sub region**	**Cell Type**	**Abbreviation**	**Subset of Marker Genes**	**Pertinent negatives/comments**
Interstitium	Stroma (non-glomerular)	Vascular Smooth Muscle/Pericyte (general)	vSMC/P	*TAGLN*, ACTA2*, MYH11*, NTRK3, MCAM*	
		vSMC/P-Renin	vSMC/P-REN	*REN*	
		Fibroblast	FIB	*DCN*, ZEB2, C7, LUM*	
	Immune	Macrophages-Resident	MAC-R	*CD163*, IL7R**	
		Macrophage	MAC	*S100A9*	
		Natural Killer Cell	NKC	*NKG7*	
		Dendritic Cell	DC	*APOE*	
		Monocyte	MON	*C1QA, HLA-DRA*	
		T lymphocyte (general)	T	*CD3*	
		T Cytotoxic	T-CYT	*GZMA*	
		B lymphocyte	B	*IGJ*	

El-Achkar et al. A Multimodal and Integrated Approach to Interrogate Human Kidney Biopsies with Rigor and Reproducibility: The Kidney Precision Medicine Project. bioRxiv. 2019; 828665. doi:10.1101/828665

	HuBMAP	RBK	KPMP	SPARC	LungMAP	HTAN	HCA	GUDMAP	Gut Cell Atlas	BICCN	Allen Brain	TCGA	Wellcome	MRC	H2020	GTEx	Total
Kidney	1	1	1	0	0	0	1	1	0	0	0	1	1	1	0	1	9
Liver	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	1	3
Spleen	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	1	4
Heart	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	1	4
Lung	1	0	0	1	1	1	1	0	0	0	0	1	1	1	1	1	10
L intestine/Colon	1	0	0	1	0	1	1	0	1	0	0	1	0	0	0	1	7
S intestine	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2
Bladder	1	0	0	1	0	0	0	1	0	0	0	1	0	0	0	1	5
Ureters	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	2
Thymus	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	2
Lymph nodes	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	2
mediastinal lymph node	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Eye	1	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	3
Brain	0	0	0	0	0	0	1	0	0	1	1	1	0	0	1	1	6
Brain stem	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Cerebellum	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	1	3
Spinal cord	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	2
Pancreas	0	0	0	0	0	1	1	0	0	0	0	1	0	0	1	1	5
Breast	0	0	0	0	0	1	1	0	0	0	0	1	1	0	0	1	5
Skin	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	1	3
Pediatric systems	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	2
Ovaries	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	2
Testes	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	2
Cervix	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
Uterus	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	5
Blood	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	2
Bone	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Placenta	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Decidua	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Embryo	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
esophagus	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	1	3
hematopoietic system	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	2
immune system bulk	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Stomach	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	1	3
Thyroid	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	2
Prostate	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	1	3
Adrenal gland	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1	3
Totals	11	1	1	7	1	6	21	4	1	2	2	20	7	5	4	21	114

ASCT+B Table Design

The “CCF Session” at the NIH-HCA joint meeting in March 2020—co-organized with Peter Hunter (SPARC) and James Gee (BICCN)—brought together experts across consortia.

In follow-up meetings, 10 ASCT tables have been created via collaborations across consortia. Ontology experts, including Chris Mungall, David Osumi-Sutherland and Mark Musen, provided expert input.

ASCT+B Table Meetings

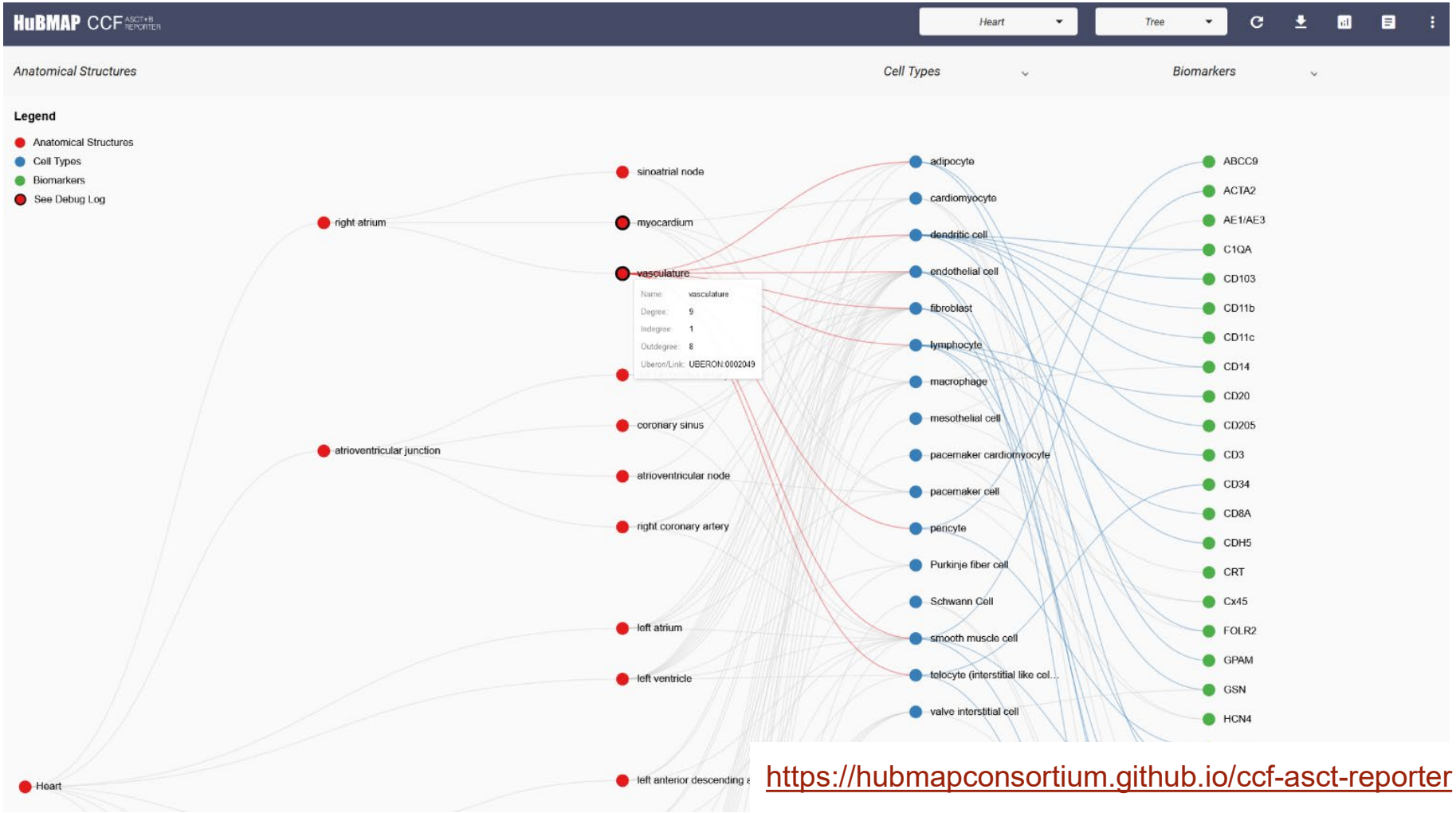
Meetings take place monthly to

- Review and approve tables.
- Formalize and unify table design language.
- Discuss table usage.

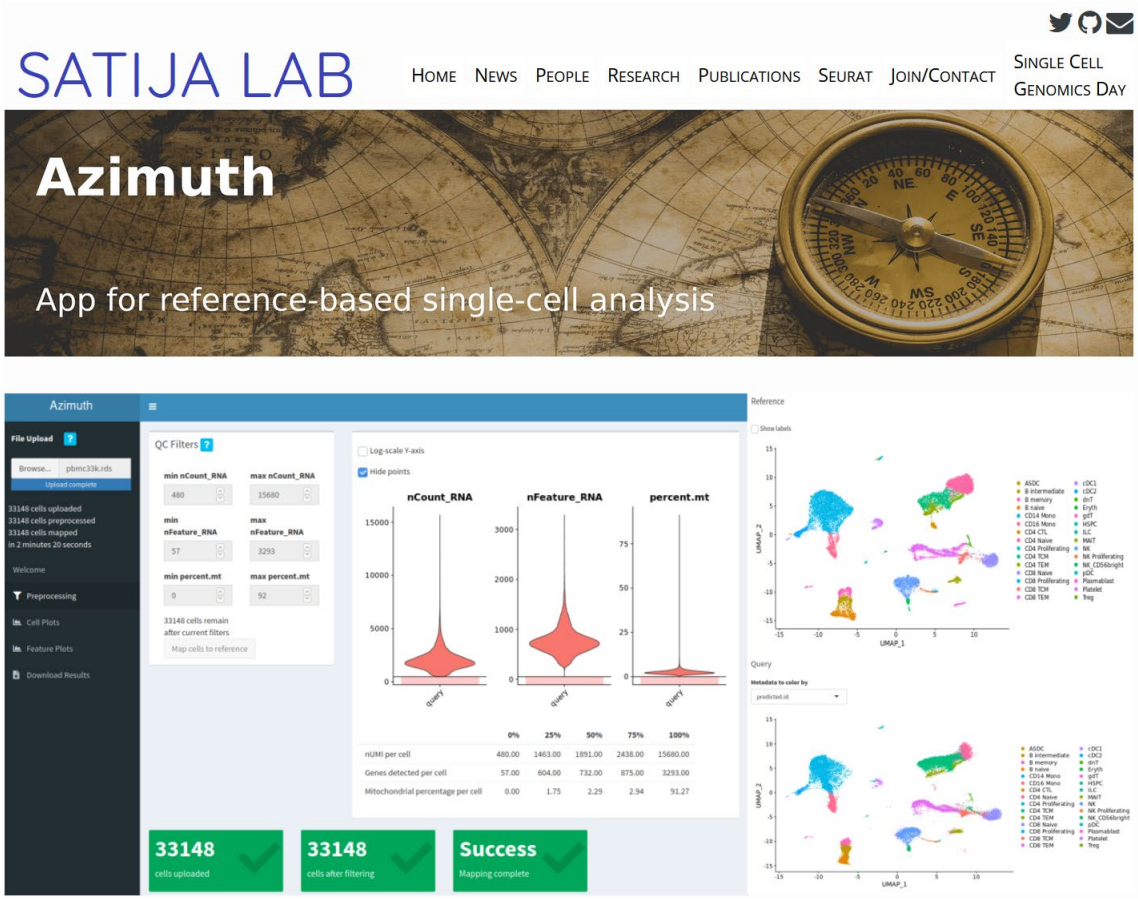
We are working on

- Converting tables into machine readable formats.
- Linking table entries to Uberon, CL, and other ontologies.
- Compare tables against cell types identified in harmonized HuBMAP data and data generated by other efforts.

Experts are welcome to register. Next meetings are on Nov 5 and Dec 3, 1:30p EST.



https://hubmapconsortium.github.io/ccf-asct-reporter



https://satijalab.org/azimuth

SOP for ASCT+B Tables

ASCT+B for 10 organs on 9/14/2020, 9:45am:

Organ Name	#AS	#CT	#B	#AS-CT	#CT-B
Brain	21	127	254	127	346
Heart	23	16	35	73	42
Kidney	39	53	83	55	135
Large Intestine	22	33	45	306	72
Liver	16	27	34	29	35
Lung	18	62	103	110	128
Lymph Nodes	34	30	50	63	110
Skin	14	32	57	37	99
Small intestine	20	32	48	196	57
Spleen	33	26	46	48	72

https://hubmapconsortium.github.io/ccf/pages/ccf-anatomical-structures.html

SOP for Construction, Review, Revision of Anatomical Structure and Cell Types and Biomarker (ASCT+B) Tables

Authors: Ellen M. Quardokus, Lisel Record, Bruce W. Herr II, Hrishikesh Paul, Katy Börner

September 18, 2020

Introduction

Anatomical Structures, Cell Types, plus Biomarkers (ASCT+B) tables aim to capture the nested *part_of* structure of anatomical human body parts, the typology of cells, and biomarkers used to identify cell types (e.g., gene, protein, lipid or metabolic markers). The tables are authored and reviewed by an international team of anatomists, pathologists, physicians, and other experts.

Identification of Subject Matter Experts (SMEs)

- CCF Experts (cross-consortium team lead by MC-IU) invite leading organ experts to contribute to the design of ASCT+B tables.
- Leading organ experts submit information on their expertise and credentials via this online form.
- CCF Experts approve 3-5 experts per organ and give them access to the ASCT+B table forms so they can author and review the forms.

Construction by Subject Matter Experts (SMEs)

- MC-IU provide pre-populated initial ASCT+B table with UBERON and CL ontology IDs.
- A first set of organ experts authors the tables and indicates author contributions.
- Authors use the ASCT+B Reporter to identify/resolve naming and interlinkage issues.
- Completed tables are submitted to the CCF Experts for review.

Review by Subject Matter Experts (SMEs)

- The beginning of each month, all tables ready for review are submitted by CCF Experts to a second set of organ experts for review.
- Review criteria include: scientific rigor (citation of publications, data), coverage and quality of the ASCT+B tables.
- Review results comprise detailed comments together with a rating (accepted, accepted with minor or major revisions, rejected) and are shared back with the author team.

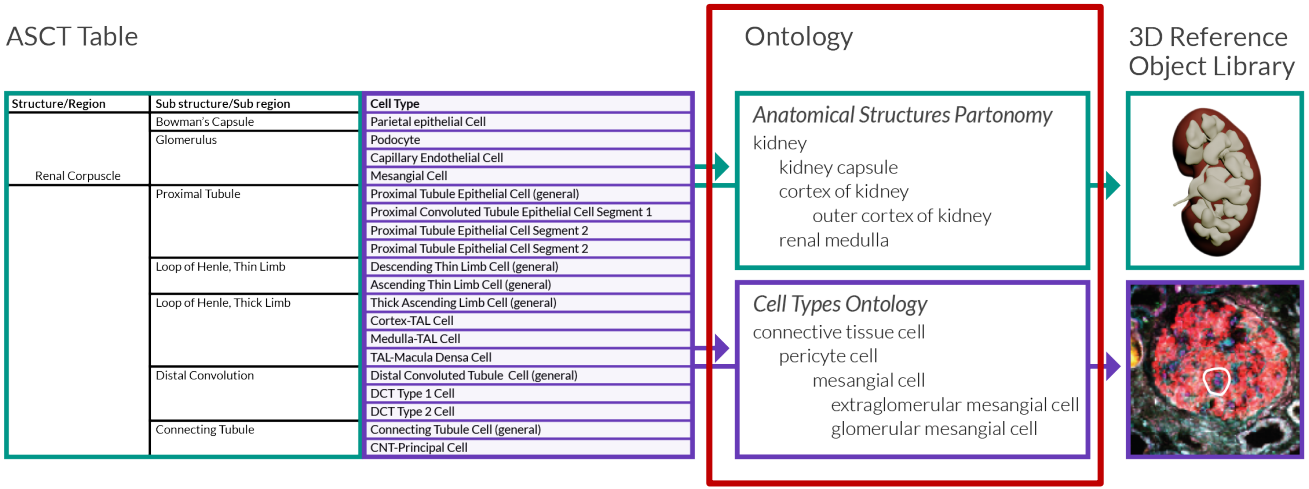
Review by CCF Experts

The begin of each month, all tables ready for review are cross-checked against

1. existing ontologies, e.g., UBERON, CL, to identify any terms that might be missing or that might have different spelling. The goal is to arrive at ASCT+B tables that are in close alignment with existing ontologies so only few changes need to be requested from ontology owners.

ASCT+B Table Usage

ASCT+B tables guide **CCF Ontology** and **3D Reference Object Library** design that semantically name and spatially place tissue data from different donors into one CCF (i.e., mapping).

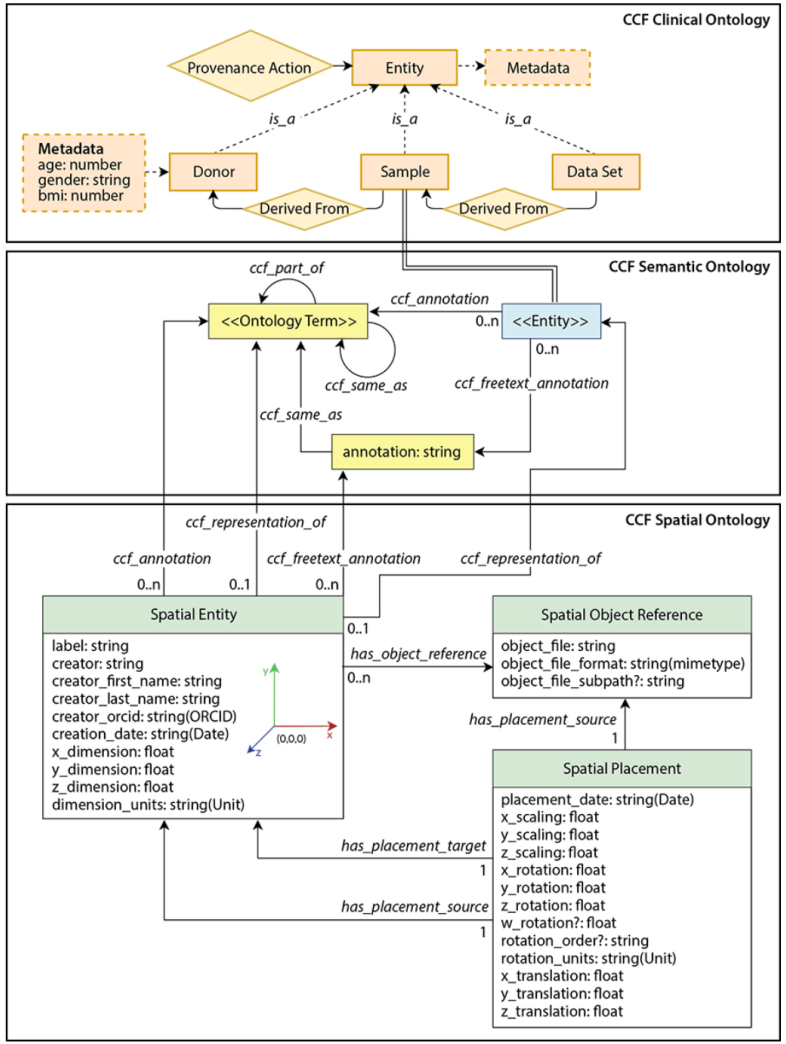


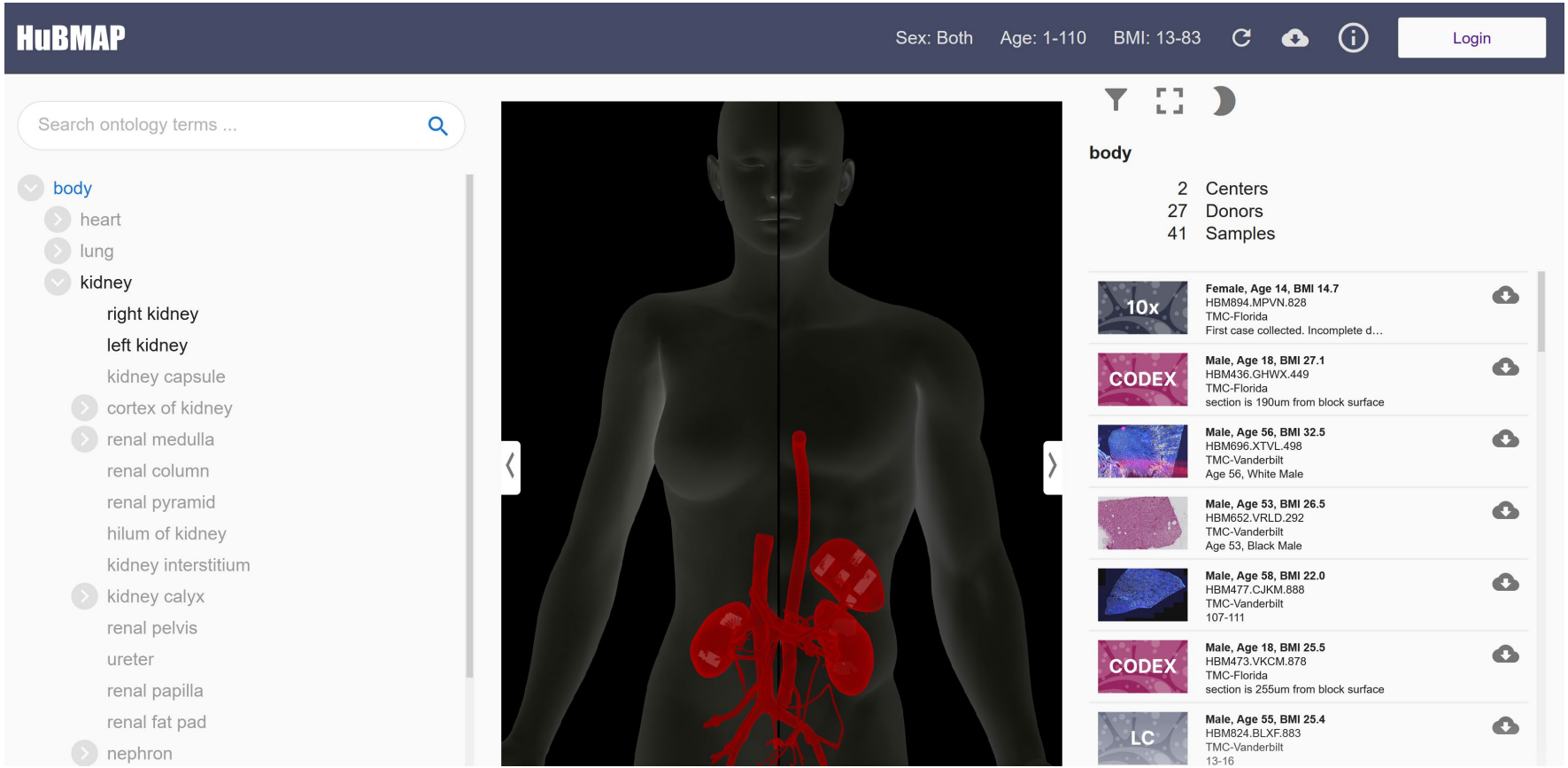
Tissue blocks are registered into the CCF using the Registration User Interface (RUI), and they can be explored via the Exploration User Interface (EUI).

CCF Ontology v1.5.0

References

- Herr II, BW and Börner K. HuBMAP Common Coordinate Framework. https://bioportal.bioontology.org/ontologies/CCF/
- Herr II, BW, Quardokus EM, Cross LE, Record EG, Weber GM, and Börner K. HuBMAP CCF Ontology Source Code Repository.
- Börner K, Quardokus EM, Herr II, BW, Cross LE, Record EG, Ju Y, Bueckle A, Sluka JP, Silverstein J, Browne K, Jain S, Wasserfall CH, Jorgensen ML, Spraggins JM, Patterson NH, Weber GM. 2020. Construction and Usage of a Human Body Common Coordinate Framework Comprising Clinical, Semantic, and Spatial Ontologies. https://arxiv.org/abs/2007.14474.





https://portal.hubmapconsortium.org/ccf-eui

https://hubmapconsortium.github.io/ccf/

The Human Body Atlas: High-Resolution, Functional Mapping of Voxel, Vector, and Meta Datasets

MC-IU team within the HuBMAP HIVE

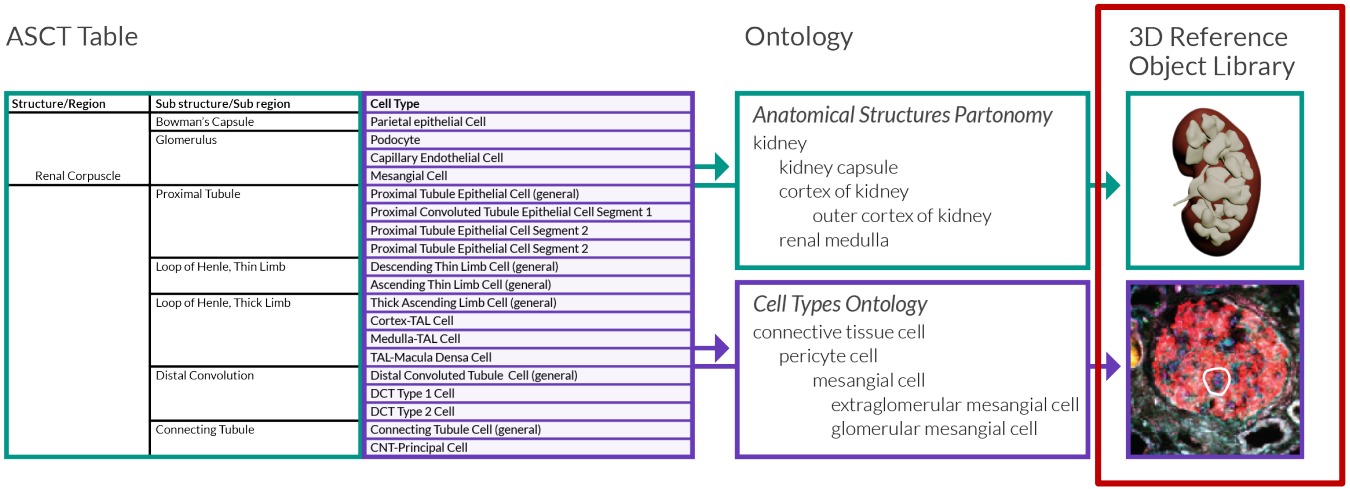
The ultimate goal of the HIVE Mapping effort is to develop a common coordinate framework (CCF) for the healthy human body. This framework will support cataloging different types of individual cells, understanding the functions of and relationships between those cell types, and modeling their individual and collective function. During the initial two years of HuBMAP, the MC-IU team has built many elements of the CCF. We co-organized the design of ASCT+B Tables and implemented a CCF Ontology. We collaborated with NIAID at NIH on the design of a 3D Reference Object Library. Lastly, we developed two interactive user interfaces. The CCF Registration User Interface (RUI) supports tissue data registration. The CCF Exploration User Interface (EUI) supports exploration of semantically and spatially explicit data—from the whole body to the single cell level. For an introduction to HuBMAP goals, data, and code visit the Visible Human MOOC (VHMOOC).

Data and Code Published with 1st HuBMAP Portal Release in August 2020

- CCF Anatomical Structures, Cell Types and Biomarkers (ASCT+B) Tables
- CCF Ontology
- CCF 3D Object Library
- Visible Human MOOC (VHMOOC)
- CCF Registration User Interface (RUI)
- CCF Exploration User Interface (EUI)

ASCT+B Table Usage

ASCT+B tables guide **CCF Ontology** and **3D Reference Object Library** design that semantically name and spatially place tissue data from different donors into one CCF (i.e., mapping).



Tissue blocks are registered into the CCF using the Registration User Interface (RUI), and they can be explored via the Exploration User Interface (EUI).

Document the tissue extraction site by registering tissue blocks within a 3D reference organ.

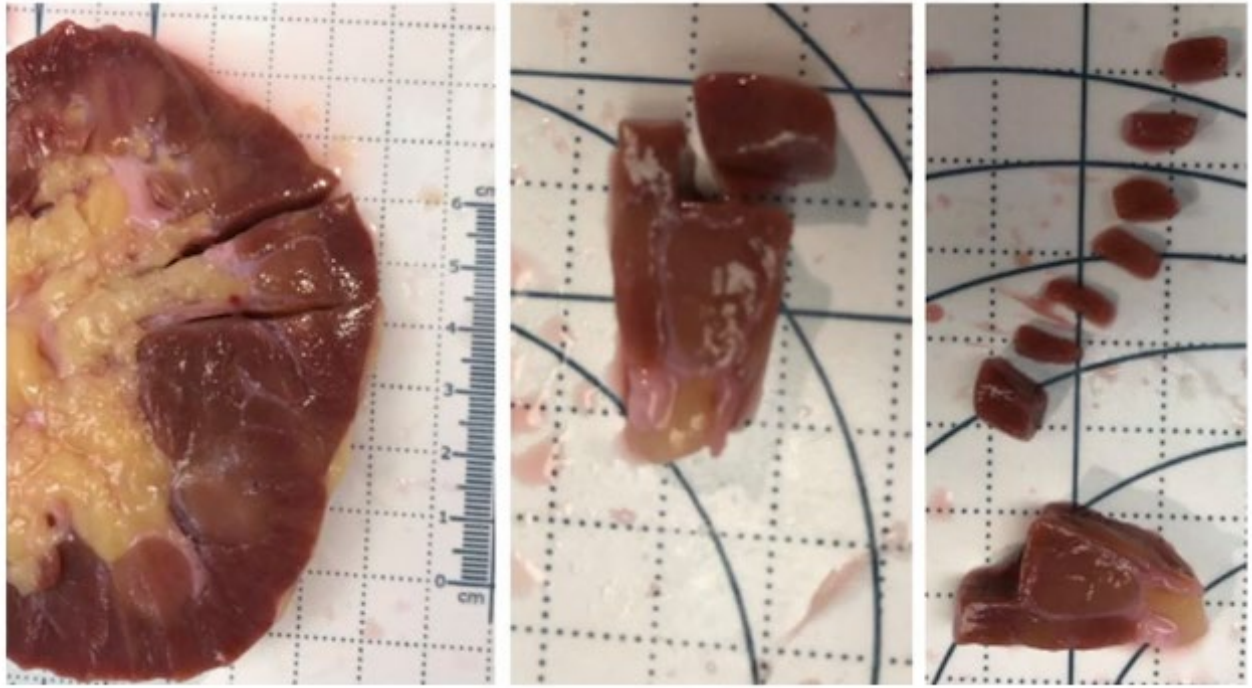
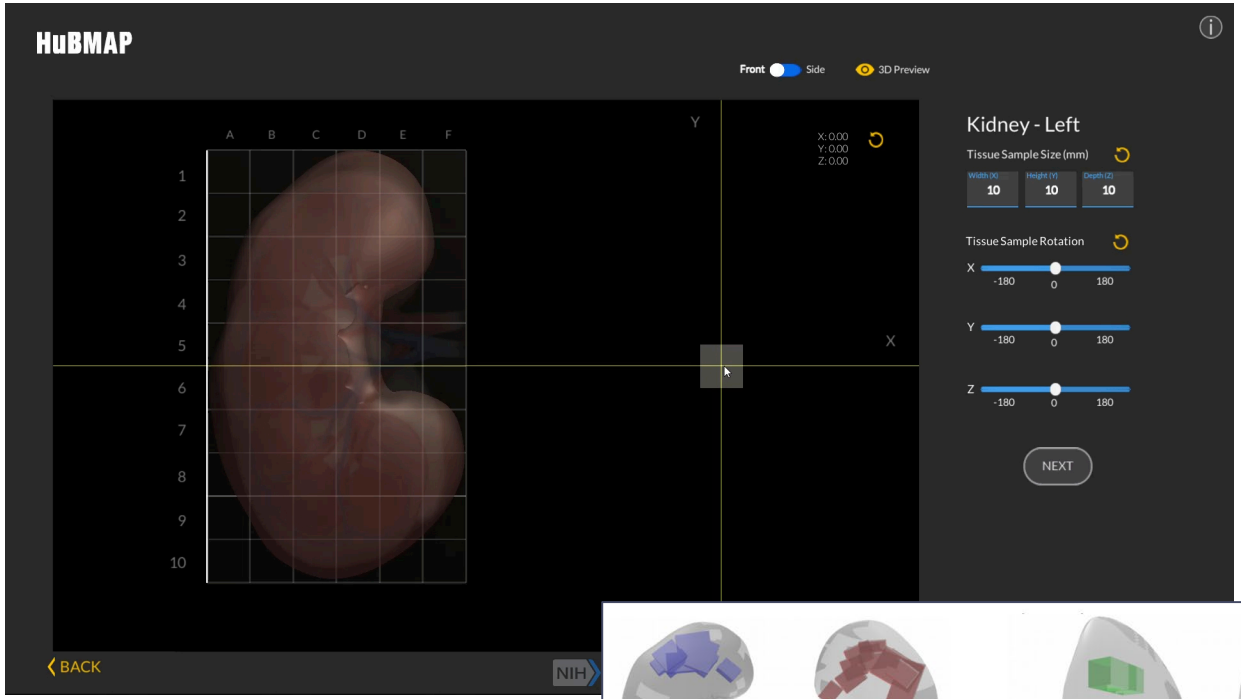
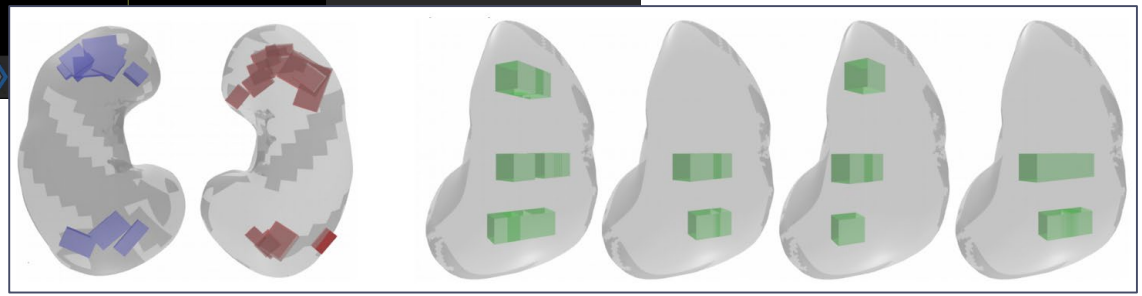


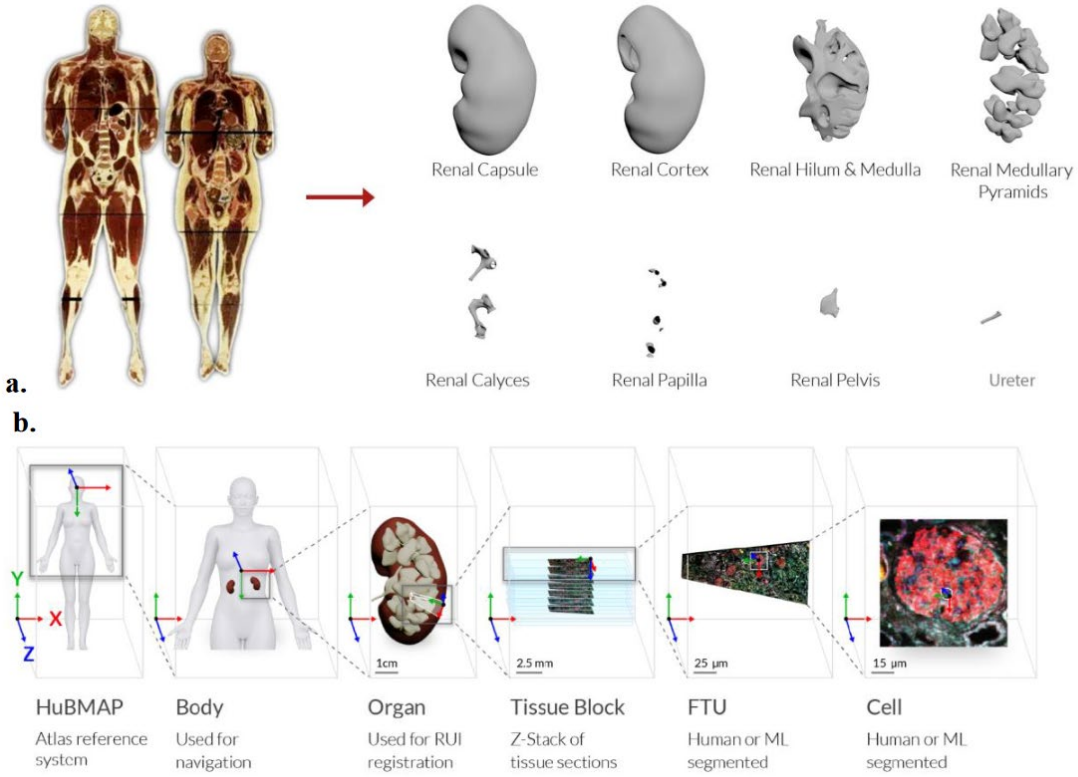
Image provided by Sanjay Jain, TMC-UCSD





For the first HuBMAP portal release, 48 tissue blocks were registered.

Figure 3. Spatial Representation of a Kidney. (a) The CCF Spatial Ontology leverages a 3D Reference Object Library to define the dimensions and shapes of ASTC entities in 3D space. (b) Construction of the CCF Spatial Ontology involves relative positioning of objects from whole body down to individual cells.

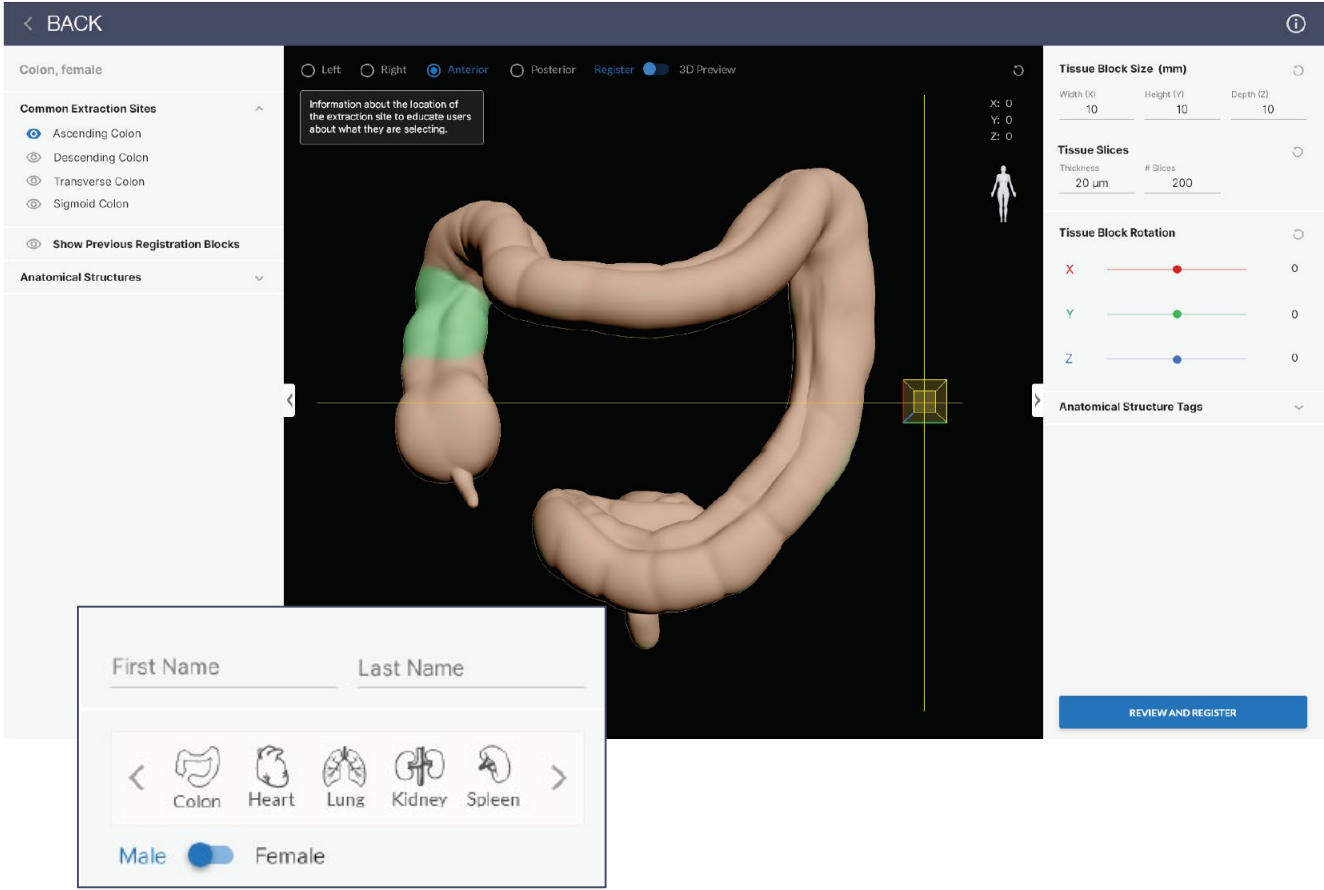


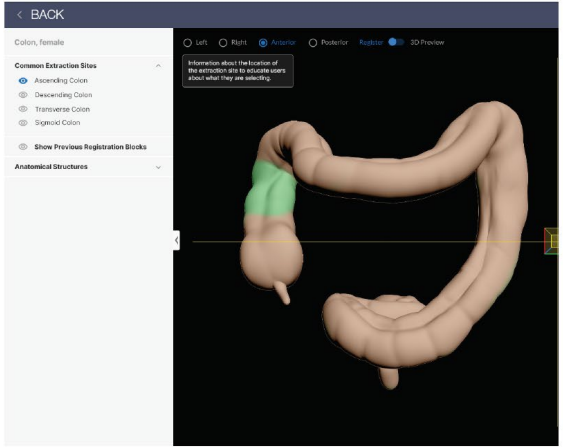
https://hubmapconsortium.github.io/ccf/pages/ccf-3d-reference-library.html

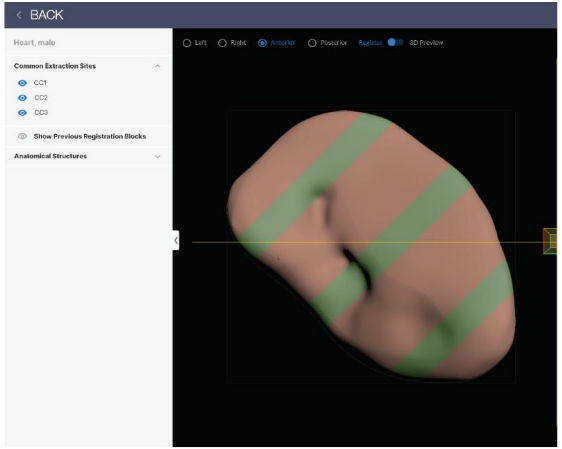
CCF Registration User Interface (RUI) v1.0.0

New Features:

- Organ carousel with 4 reference organs
- Support for tissue extraction sites
- Expanded ontology
- Semantic annotation via collision detection & manual annotation
- Support for non-HuBMAP usage







Kidney

- Bisection Line

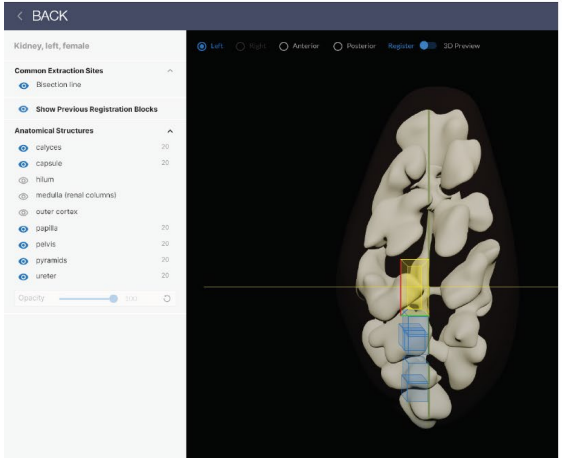
Spleen

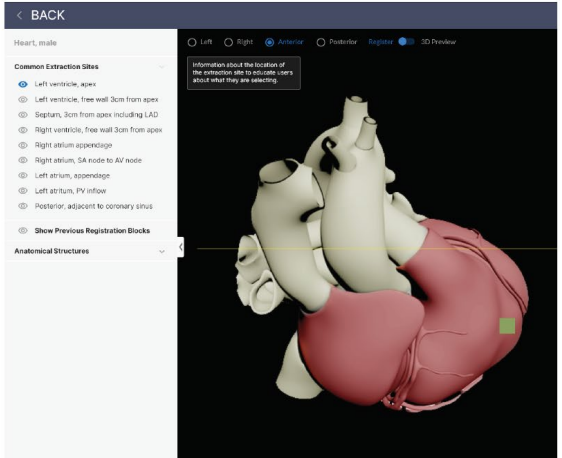
- CC1
- CC2
- CC3

Colon

- Ascending Colon
- Descending Colon
- Transverse Colon
- Sigmoid Colon

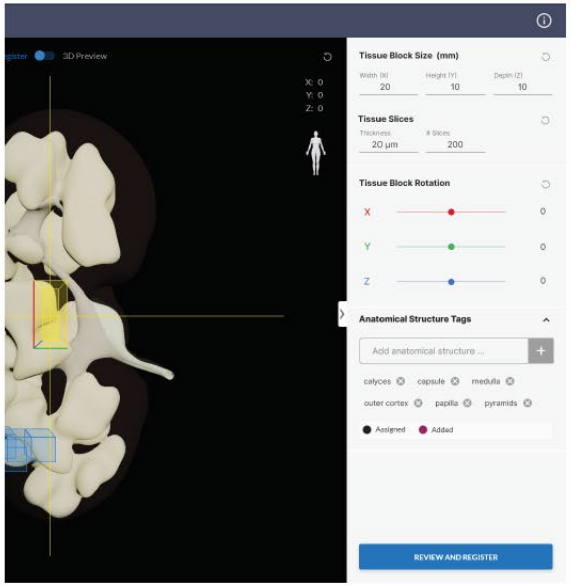
Heart	Extraction Site Mapping
Left atrium, appendage	7
Left atrium, PV inflow	8
Left ventricle, apex	1
Left ventricle, free wall 3cm from apex	2
Septum, 3cm from apex including LAD	3
Posterior, adjacent to coronary sinus	9
Right atrium appendage	5
Right atrium, AV (atrioventricular) node	6a
Right atrium, SA (sinoatrial) node	6b
Right ventricle, free wall 3cm from apex	4



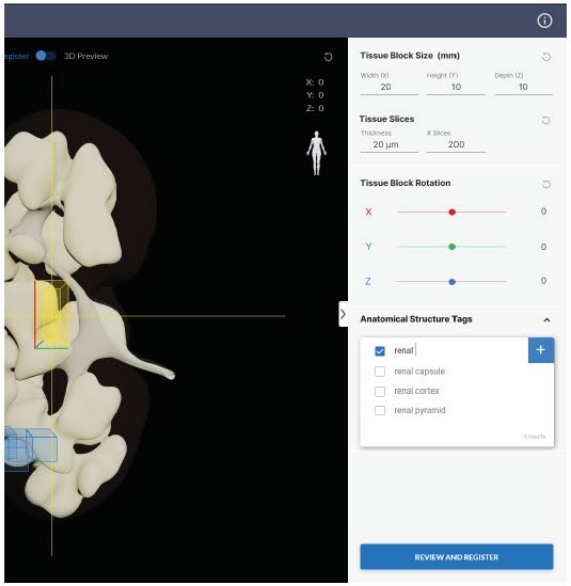


CCF Registration User Interface (RUI) v1.0.0 cont.

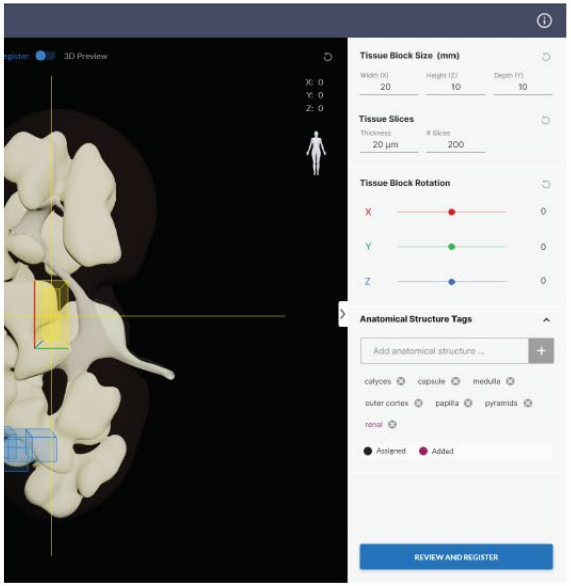
Collision when Tissue Block hits Reference Organ



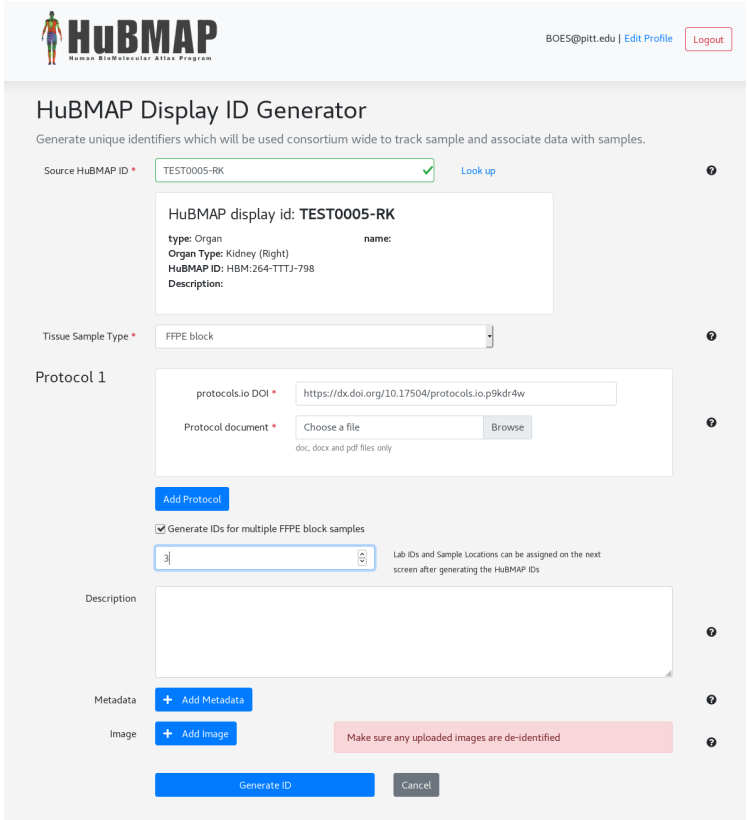
Tag Search behavior

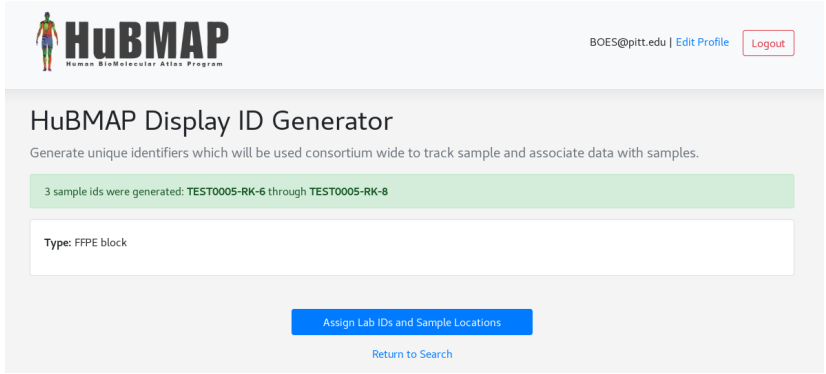


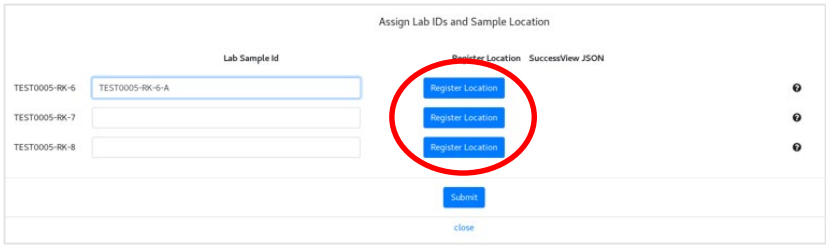
Custom tag added to list



1st Portal Release: Upload Portal







Implemented by the HIVE IEC

SOP for Approval of 3D Reference Objects

CCF 3D Reference Object Library

Overview

The CCF 3D Reference Object Library provides anatomically correct reference organs. The organs are developed by a specialist in 3D medical illustration and approved by organ experts, see SOP.

Initially, reference objects were created using data from the Visible Human male and female datasets provided by the National Library of Medicine. The male dataset comprises 1,871 cross-sections at 1mm intervals for both CT and anatomical images at a resolution of 4,096 pixels by 2,700 pixels. The female data set has the same characteristics as the Visible Human Male but axial anatomical images were obtained at 0.33 mm intervals resulting in 5,189 cross-section anatomical images. The male was white, 180.3 cm (71 inch) tall, 199-pound and was 38 years old. The female was white, 171.2 cm (67.4 inch) tall, obese, and 59 years old.

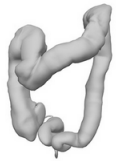
For the 1st HuBMAP Portal Release, kidney and spleen reference organs are freely available in GLB format. They can be viewed and explored using free web browsers such as Babylon.js. Screenshots and major properties of the nested reference organ objects are given in table below.

For selected organs, 3D extraction site objects are provided. Some extraction sites resemble geometric objects (e.g., cuboids for heart) while others take the shape of one or more whole or partial anatomical structures (e.g., in spleen). The 3D extraction sites do not restrict registration to specific regions, instead they provide "expert defined landmarks" to help guide tissue registration. The extraction site objects are also used for automatic semantic annotation of tissue samples via collision detection during registration.

Reference Organs

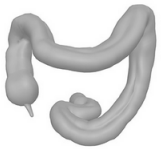
COLON | HEART | KIDNEY | SPLEEN

MALE: Colon



# Anatomical Structures	10
Appendix	1
Ascending Colon	1
Cecum	1
Descending Colon	1
Hepatic Flexure	1
Ileocecal Valve	1
Rectum	1
Sigmoid Colon	1
Splenic Flexure	1
Transverse Colon	1

FEMALE: Colon



# Anatomical Structures	10
Appendix	1
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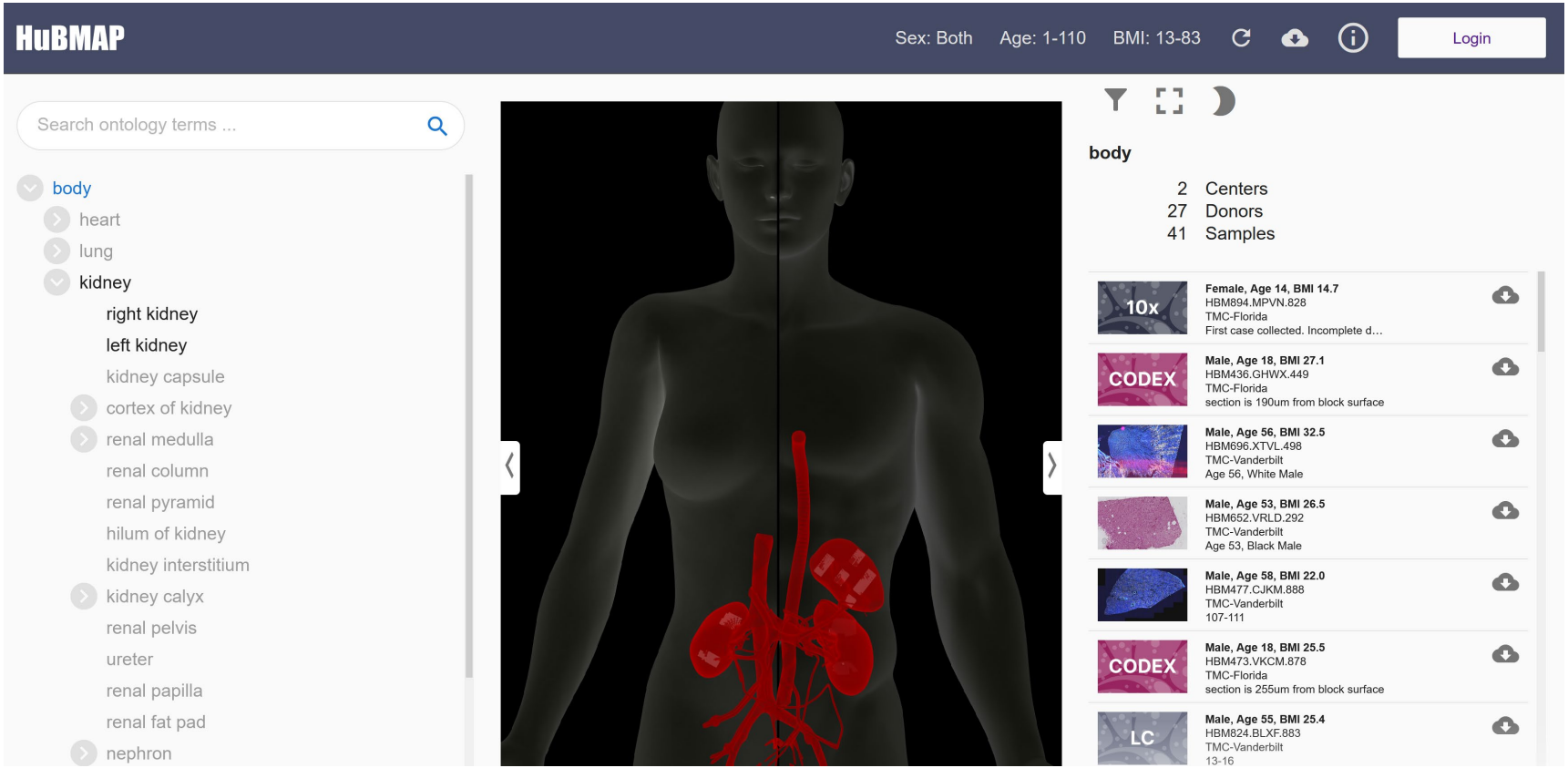
Descending Colon	1
Hepatic Flexure	1
Ileocecal Valve	1
Retum	1
Sigmoid Colon	1
Splenic Flexure	1
Transverse Colon	1

https://hubmapconsortium.github.io/ccf/dld/SOP-3D-Reference-Object-Approval-v1.0.1.pdf

CCF Exploration User Interface (EUI)



https://portal.hubmapconsortium.org/ccf-eui

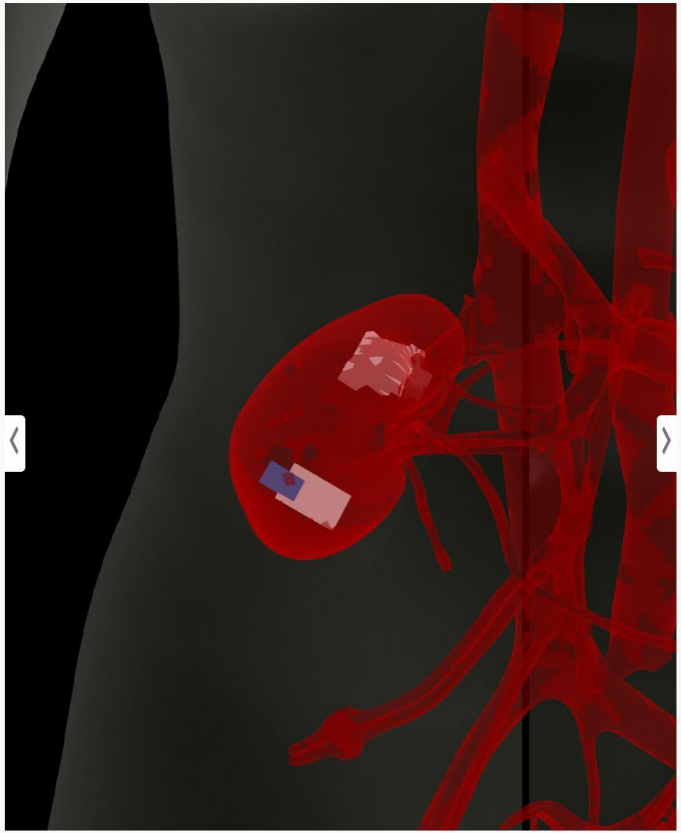
HuBMAP

Sex: Both Age: 1-110 BMI: 13-83

Logout

Search ontology terms ...

- body
  - heart
  - lung
  - kidney
    - right kidney
    - left kidney
    - kidney capsule
    - cortex of kidney
    - renal medulla
    - renal column
    - renal pyramid
    - hilum of kidney
    - kidney interstitium
    - kidney calyx
      - major calyx
      - minor calyx
    - renal pelvis
    - ureter
    - renal papilla
    - renal fat pad
  - nephron
  - spleen
  - colon

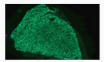


body

1 Centers
9 Donors
40 Samples

Male, Age 55, BMI 25.4
HBM695.RTLJ.484
TMC-Vanderbilt
13-16

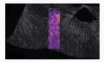
Male, Age 21, BMI 21.8
HBM634.MMGK.572
TMC-Vanderbilt
Age 21 , White Male, Trauma Patient



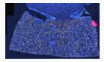
Female, Age 44, BMI 28.0
HBM457.NNQN.252
TMC-Vanderbilt
Age 44, white female.

Female, Age 44, BMI 28.0
HBM465.VKHL.532
TMC-Vanderbilt
Age 44, white female.

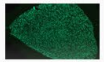
Male, Age 21, BMI 21.8
HBM693.HFFJ.752
TMC-Vanderbilt
Age 21 , White Male, Trauma Patient



Female, Age 58, BMI 23.0
HBM536.LDTZ.757
TMC-Vanderbilt
Age 58, White Female

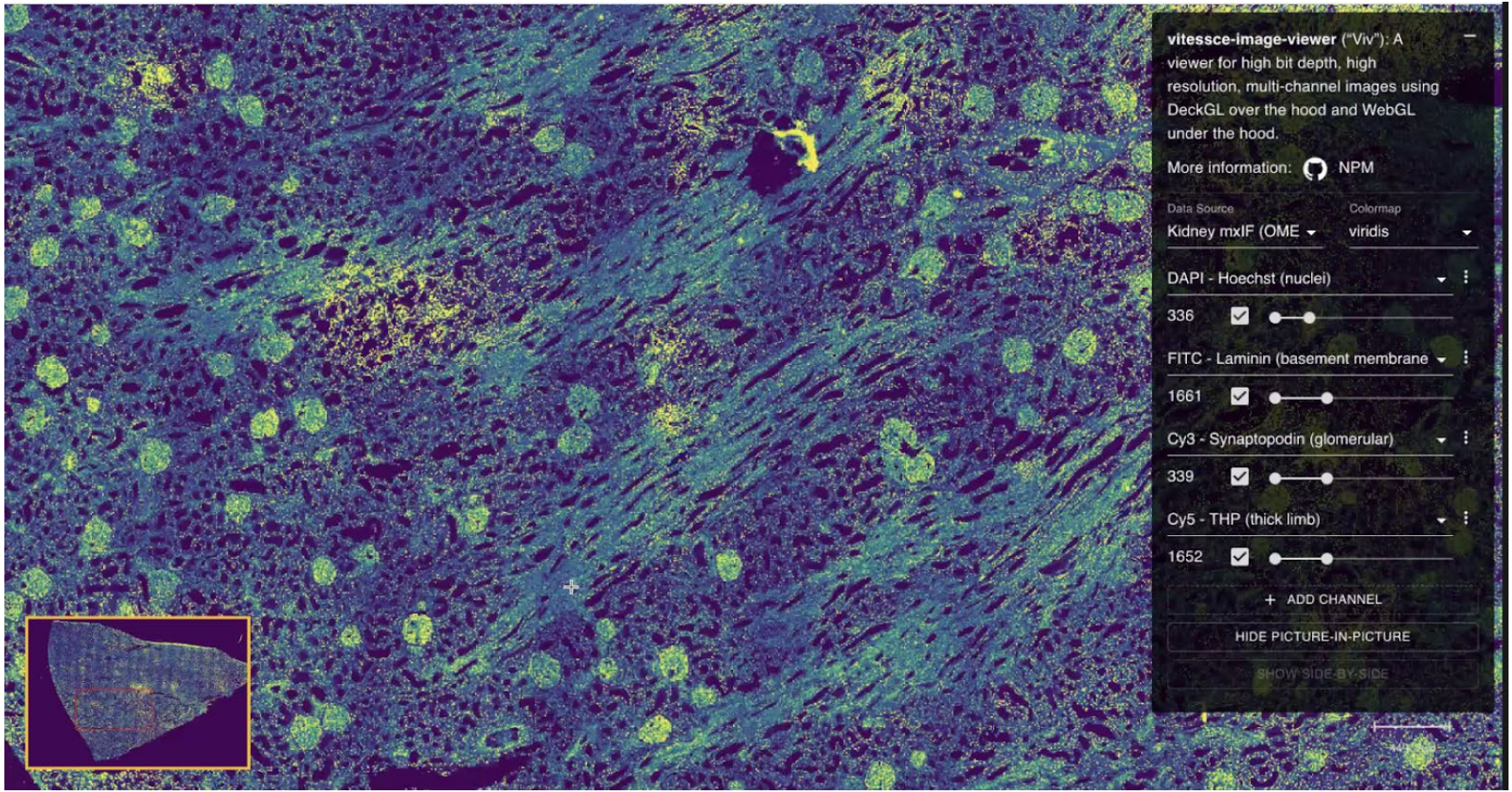


Male, Age 48, BMI 35.3
HBM334.GCCX.874
TMC-Vanderbilt
Age 48, White Male



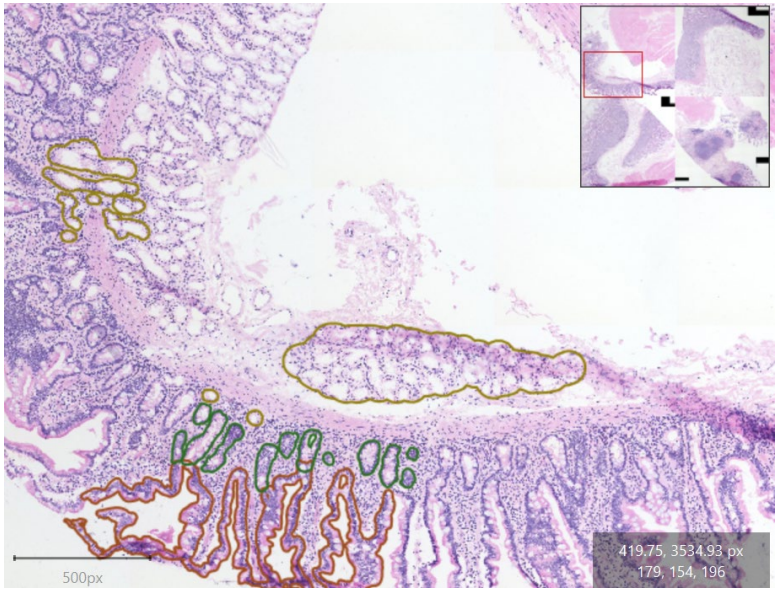
Male, Age 31, BMI 32.6
HBM776.PKJF.786
TMC-Vanderbilt
Age 21, White Male

Female, Age 66, BMI 31.3
HBM284.TRCV.726



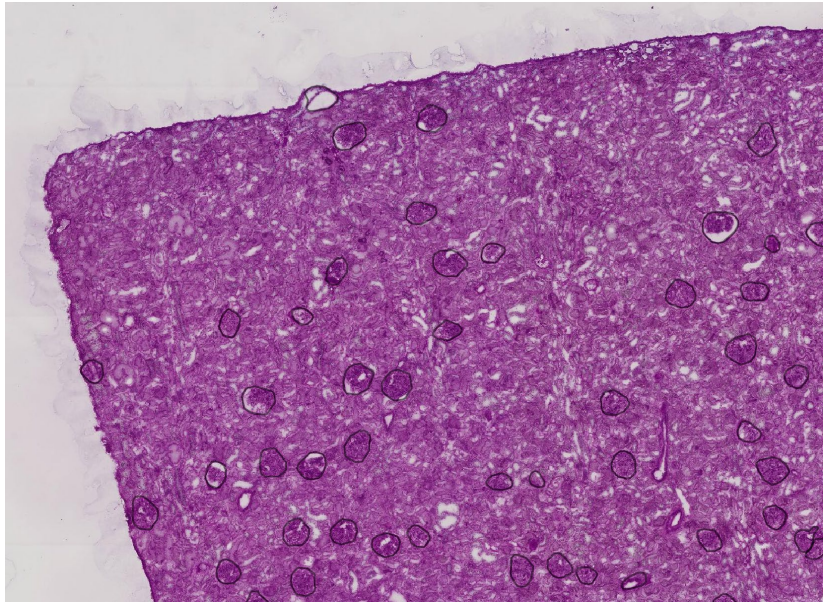
http://gehlenborglab.org/research/projects/vitessce/

Small Intestine
Provided by Jeanne Shen, TMC-Stanford



Red brown: Small intestinal villus epithelium
Green: Small intestinal crypt
Brown: Small intestinal Brunner's gland

Kidney
Provided by Heath Patterson, TMC-VU



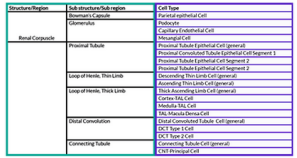
Black: Glomeruli

Also used in HuBMAP Hackathon

Get Involved!

Contribute your expert experience and time.

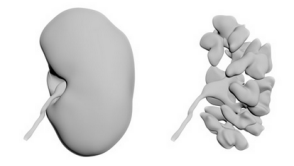
Register via:
https://tinyurl.com/vhmooc



Structure/Region	Sub-structure/Sub-region	Cell Type
Renal Corpuscle	Bowman's Capsule	Parietal epithelial Cell
	Glomerulus	Podocyte
		Capillary Endothelial Cell
		Mesangial Cell
	Proximal Tubule	Proximal Tubule Epithelial Cell (general)
		Proximal Convoluted Tubule Epithelial Cell Segment 1
		Proximal Tubule Epithelial Cell Segment 2
		Proximal Tubule Epithelial Cell Segment 3
	Loop of Henle, Thin Limb	Descending Thin Limb Cell (general)
		Ascending Thin Limb Cell (general)
	Loop of Henle, Thick Limb	Thick Ascending Limb Cell (general)
		Cortex TAL Cell
		Medulla TAL Cell
		TAL Macula Densa Cell
	Distal Convolution	Distal Convoluted Tubule Cell (general)
		DCT Type 1 Cell
		DCT Type 2 Cell
	Connecting Tubule	Connecting Tubule Cell (general)
		CNT Principal Cell

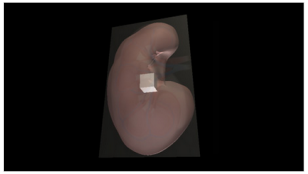
Author or Review ASCT+B Tables

Anatomists, pathologists, biomolecular and other experts are invited to author, edit and/or review Anatomical Structures, Cell Types, and Biomarkers (ASCT+B) tables. Please register to participate.



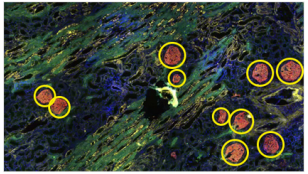
Explore 3D Reference Organs

Download kidney or spleen objects from the HuBMAP Reference Object Library, explore them in a web-based 3D viewer, answer a simple question. Optional: Provide expert comments on the reference organs.



Register Tissue Block via RUI

Use the Registration User Interface (RUI) Prototype to spatially and semantically register three-dimensional tissue blocks within reference organs.

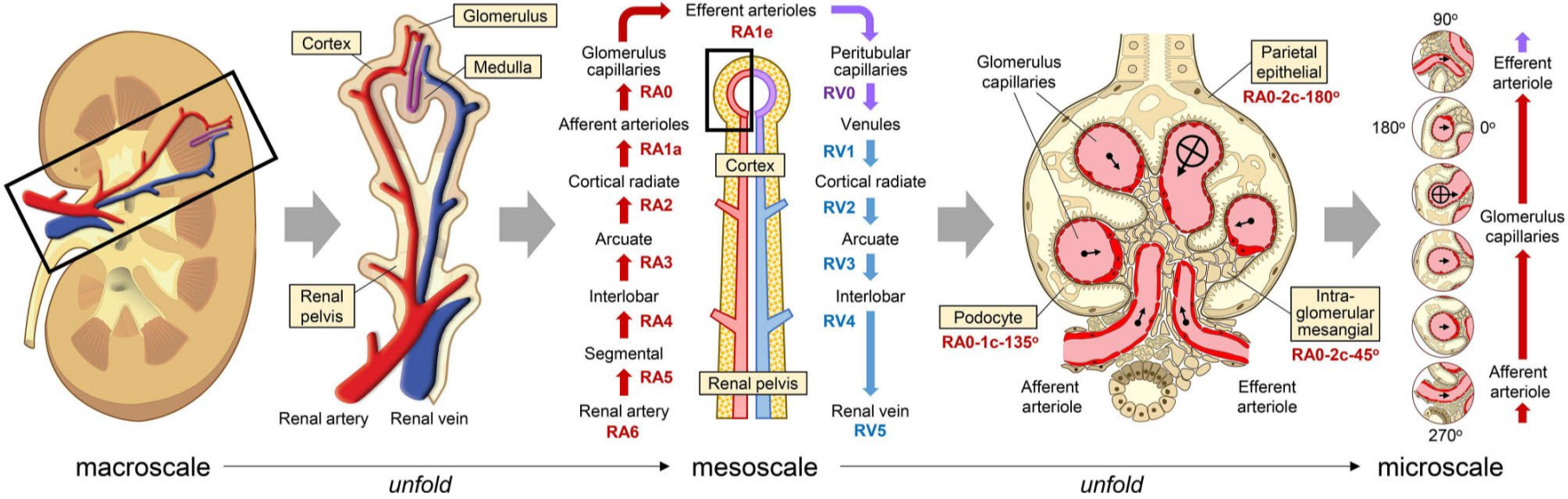


Manually Annotate Human Tissue

Learn how to visually identify functional tissue units in different organs, use human intelligence to annotate them in tissue samples. The resulting data will be used to train machine learning algorithms.

QuPath, https://qupath.github.io

Capturing vasculature details from macro to micro scale is critically important for a vasculature based CCF



Weber, Griffin M, Yingnan Ju, and Katy Börner. 2020. "Considerations for Using the Vasculature as a Coordinate System to Map All the Cells in the Human Body". *Frontiers in Cardiovascular Medicine* 7 (29): doi: 10.3389/fcvm.2020.00029.

Example: Converting tables into machine readable formats – Kidney vasculature

Vasculature	renal atery [L/R]				Endothelial Cell (general)	EC	*EMCN*, PECAM1*, FLT1**
		segmental arteries [superior, inferior, anterior, posterior]					
		interlobar aterties					
		arcuate aterties					
		cortical radiate ateries {cortex}	afferent arterioles {nephron}		EC-Afferent/Efferent Arteriole	EC-AEA	*SERPINE2*, TM4SF1**
				glomerulus capillaries {glomerulus}	Capillary Endothelial Cell	GC-EC	*EHD3*, EMCN*, HECW2*, FLT1*, AQP1**
			efferent arterioles {nephron}		EC-Afferent/Efferent Arteriole	EC-AEA	*SERPINE2*, TM4SF1**
				peritubular capillaries	EC-Peritubular capillaries	EC-PTC	*PLVAP**
				descending vasa recta	EC-Descending Vasa Recta	EC-DVR	*TM4SF1*, PALMD*
				ascending vasa recta	EC-Ascending Vasa Recta	EC-AVR	*DNASEIL3**
	renal vein [L/R]	cortical radiate veins {cortex}	venules		Endothelial Cell (general)	EC	*EMCN*, PECAM1*, FLT1**
		arcuate veins					
		interlobar veins					

Vasculature	renal artery [L/R]				Endothelial Cell (general)	EC	EMCN*, PECAM1*, FLT1*
Vasculature	renal artery [L/R]	segmental arteries [superior, inferior, anterior, posterior]			Endothelial Cell (general)	EC	EMCN*, PECAM1*, FLT1*
Vasculature	renal artery [L/R]	interlobar arterties			Endothelial Cell (general)	EC	EMCN*, PECAM1*, FLT1*
Vasculature	renal artery [L/R]	arcuate arteries			Endothelial Cell (general)	EC	EMCN*, PECAM1*, FLT1*
Vasculature	renal artery [L/R]	cortical radiate arteries {cortex}			Endothelial Cell (general)	EC	EMCN*, PECAM1*, FLT1*
Vasculature	renal artery [L/R]	cortical radiate arteries {cortex}	afferent arterioles {nephron}		EC-Afferent/Efferent Arteriole	EC-AEA	SERPINE2*, TM4SF1*
Vasculature	renal artery [L/R]	cortical radiate arteries {cortex}	afferent arterioles {nephron}	glomerulus capillaries {glomerulus}	Capillary Endothelial Cell	GC-EC	EHD3*, EMCN*, HECW2*, FLT1*, AQP1*
Vasculature	renal artery [L/R]	cortical radiate arteries {cortex}	efferent arterioles {nephron}		EC-Afferent/Efferent Arteriole	EC-AEA	SERPINE2*, TM4SF1*
Vasculature	renal artery [L/R]	cortical radiate arteries {cortex}	efferent arterioles {nephron}	peritubular capillaries	EC-Peritubular capillaries	EC-PTC	PLVAP*
Vasculature	renal artery [L/R]	cortical radiate arteries {cortex}	efferent arterioles {nephron}	descending vasa recta	EC-Descending Vasa Recta	EC-DVR	TM4SF1*, PALMD
Vasculature	renal artery [L/R]	cortical radiate arteries {cortex}	efferent arterioles {nephron}	ascending vasa recta	EC-Ascending Vasa Recta	EC-AVR	DNASEIL3*
Vasculature	renal vein [L/R]	cortical radiate veins {cortex}	venules {nephron}		Endothelial Cell (general)	EC	EMCN*, PECAM1*, FLT1*
Vasculature	renal vein [L/R]	cortical radiate veins {cortex}			Endothelial Cell (general)	EC	EMCN*, PECAM1*, FLT1*
Vasculature	renal vein [L/R]	arcuate veins			Endothelial Cell (general)	EC	EMCN*, PECAM1*, FLT1*
Vasculature	renal vein [L/R]	interlobar veins			Endothelial Cell (general)	EC	EMCN*, PECAM1*, FLT1*

Weber, Griffin M, Yingnan Ju, and Katy Börner. 2020. "Considerations for Using the Vasculature as a Coordinate System to Map All the Cells in the Human Body". *Frontiers in Cardiovascular Medicine* 7 (29): doi: 10.3389/fcvm.2020.00029.

Human Reference CCF Atlas: Data Checklist

Common Coordinate Framework (CCF) Design (see CCF Portal):

1. **Make sure the Anatomical Structures, Cell Types, and Biomarkers (ASCT+B) that you use/submit are listed in the ASCT+B tables. The tables are authored and reviewed by an international team of anatomists, pathologists, physicians, and other experts, see this SOP.**
2. Spatially register all tissue samples using the CCF Registration User Interface (RUI) in the Ingest Portal. End of October 2020, kidney, spleen, heart, colon registration are supported. For other organs, see SOP.
3. After submitting data, review data in the CCF Exploration User Interface and make sure spatial, semantic, and other metadata are correct.
4. For functional tissue unit (FTU) segmentation, submit a list of FTUs for your organ(s) and make sure FTU names and all relevant cell types (CT) are captured in the ASCT+B table. Use assays/biomarkers (B) that make it possible to identify FTUs—initially manually, later automatically. Submit tissue with 1000 FTUs manually identified FTUs.
5. In support of the Vasculature-based CCF, provide cell segmentation data for blood vessels and different cell types.

For questions, email infoccf@indiana.edu.

General Human Atlas Questions by Jay W. Shin

- How to build an “**Anatomical Structure**-based" Atlas?
- What is the strategy to define **Cell Types**, in the context of building a anatomical atlas?
- Are **Biomarkers** sufficient? Or how can we define cells and states (e.g. ontological) relative to 3D space, age, disease?

so we can better understand cell types, function and disease by establishing a global picture of the human body?

First Answers:

- Agree on AS, CT, B nomenclature—revise existing ontologies (e.g., Uberon, CL, HUGO) accordingly.
- Collaborate on 3D scaffolds.
- Register tissue using the RUI, explore tissues via the EUI.

Q&A