National Cancer Policy Forum
February 13th, 2018

Computational Pathology, Artificial Intelligence and Informatics to Enhance Cancer Diagnostics

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Chairman and Distinguished Univeristy Professor, Department of Biomedical Informatics
http://www.dbmi.pitt.edu
University of Pittsburgh School of Medicine

Disclosures of COI for 2017 for MJB

Startup/Public Companies Royalties/Licensing, Equity):

- De-ID Data Corp – de-identification software (licensing agreement) http://www.de-idata.com/
- SpIntellx – Spatial Intelligence for Cancer Diagnostics (founder equity)

Consultancy (honoraria)

- Cancer Center Consulting – Baylor, CINJ, U Colorado, U NM
- CTSA Consulting – MCW, Northwestern, UC Davis, U Chicago, U IN, UC Davis, U NM, U WI
- Biomedical Informatics Consulting – MUSC, Northwestern, UC Davis, U Chicago, U FL

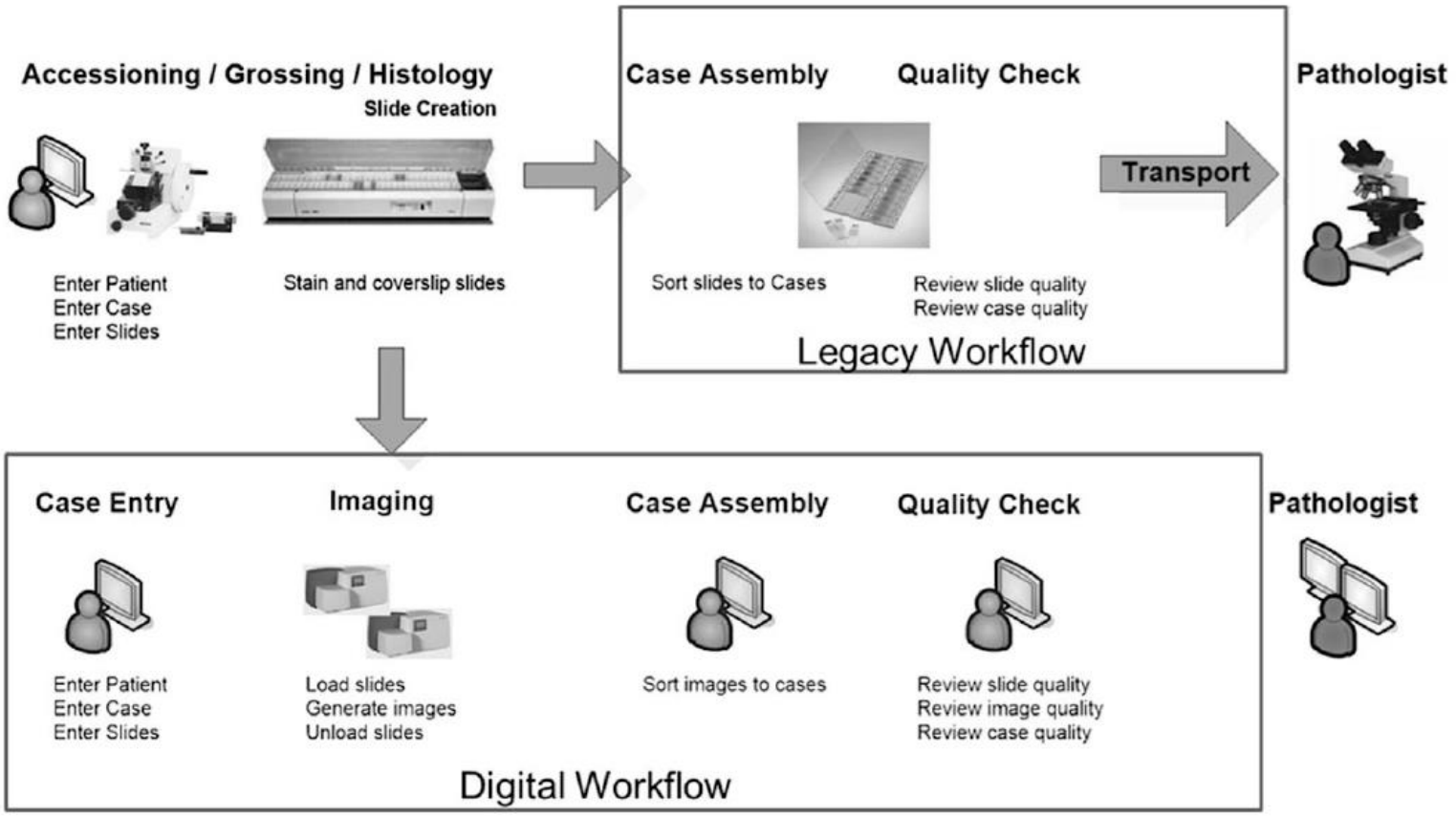
Federal Grants

- CDC NIOSH – National Mesothelioma Virtual Bank
- NCI - CCSG, ITCR and SPORE
- NCATS - CTSA and ACT
- NHGRI - BD2K
- NLM - BMI TP
- PCORI - CDRN

Take Home Messages

- **FDA approval of whole slide imaging is driving Computational Pathology and AI in Pathology**
- **Informatics is key to implementing Computational Pathology and AI in clinical practice**
- **Pathology and Radiology partnership can be enabled through:**
  - TIES – Text Information Extraction System
  - TCRN – TIES Cancer Research Network
- **AI will be enabled through image & data sharing via TCRN and NCI's Cancer Imaging Archive**

Whole Slide Imaging (WSI) Workflow



Hartman et al. J Digit Imaging. 2017. In press.

FDA Approval for Whole Slide Imaging

WSI Regulatory Timeline

Date	Event	Consequence
2000	Commercial WSI devices	Digital Pathology trend started
		Validation of diagnostic applications
2009	FDA advisory panel	High risk (class III) device
		Non-clinical use cases expanded
		Non-US regulatory approval
		DPA & select vendor discussions with FDA
2015	TPA* guideline	Assures manufacturers follow same standards
2017	FDA approval of WSI	For primary diagnosis in surgical pathology

Feldman M et al A Large Multicenter, Retrospective Non-Inferiority Study to Evaluate Diagnostic Concordance Between Optical vs Digital Microscopic Diagnoses in 2000 Surgical Pathology Cases. Mod Pathol 2017; 30(S2):395A

*TPA = Technical Performance Assessment

From Pantanowitz, Path Info Summit, 2017

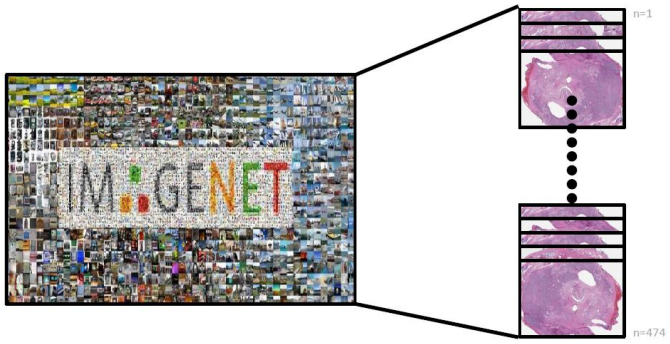
Computational Pathology – What is it?

Computational Path = Big Data Science Meets Pathology

- **Massive Increases in Volume of Digital Data Generated from WSI PLUS genomic sequencing data –**
- **Heralds the rise of computational pathology**
- **Critical for Personalized Medicine, Learning Health Systems, Basic Research and "Big Data/Data Science"**

Dataset Sizes: Computer Vision vs. Computational Pathology

From Fuchs, 2017

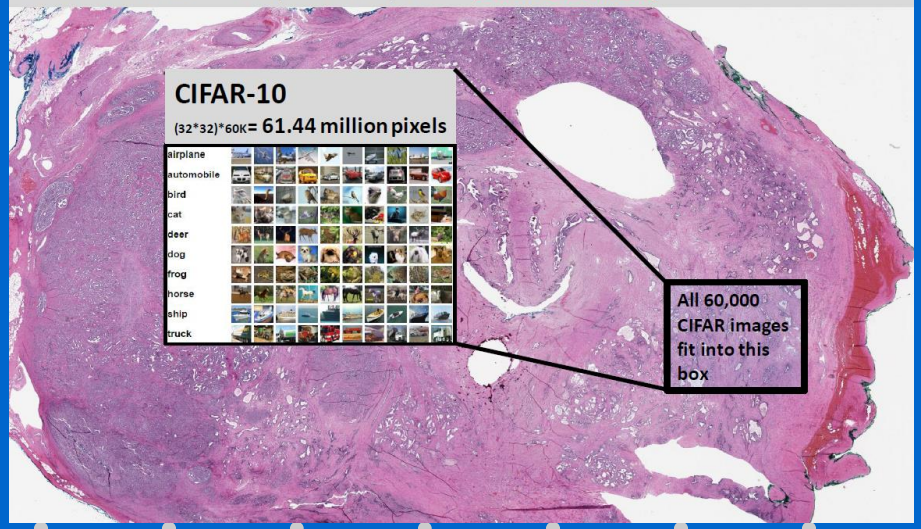


All of ImageNet
482 x 415 * 14,197,122
= 2.8 trillion pixels

474 Whole Slides
100,000 x 60,000 *474
= 2.8 trillion pixels

Dataset Sizes: Computer Vision vs. Computational Pathology

1 Whole Slide = 100,000 x 60,000 = **6 billion pixels**



Definition of Computational Pathology

- **An approach to diagnosis that incorporates multiple sources of data (H&E, IHC, IF & genomic data)**
- **Presents clinically actionable knowledge (big data to knowledge)**
- **Advanced decision support for precision (personalized) medicine**
- **Helps to redefine Pathology from an observational to knowledge engineering discipline hence critical to healthcare data science**

(Louis et al Arch Path Lab Med 2014)

Computational Pathology and Informatics Science

- A Research Data Warehouse (RDW) and robust Biorepository Supported by Informatics Science are key enablers!!!
  - This will require biomedical informatics expertise:
    - Expertise in **database design and query** – ***PCORnet and PaTH***
    - **Natural language processing** of text (H&P, Consults, Discharge, Pathology Reports, etc..) – ***TIES/TCRN and CDP***
    - Structured capture of key medical data will require controlled **vocabularies** and implementation of **ontologies** - ***TIES/TCRN & CDP***
    - **De-identification** of text for sharing with researchers (De-ID Data Corp) – ***TIES/TCRN & CDP***
    - Implementation of **Bayesian** algorithms to make genomic data "actionable" via **Causal Modeling and Discovery – *BD2K – Center for Causal Modeling and Discovery***
      - *Pitt just funded for four years and $11M with CMU, UPMC, Yale*
  - Personalized Medicine critically requires **biorepositories***
    - ***TCRN***

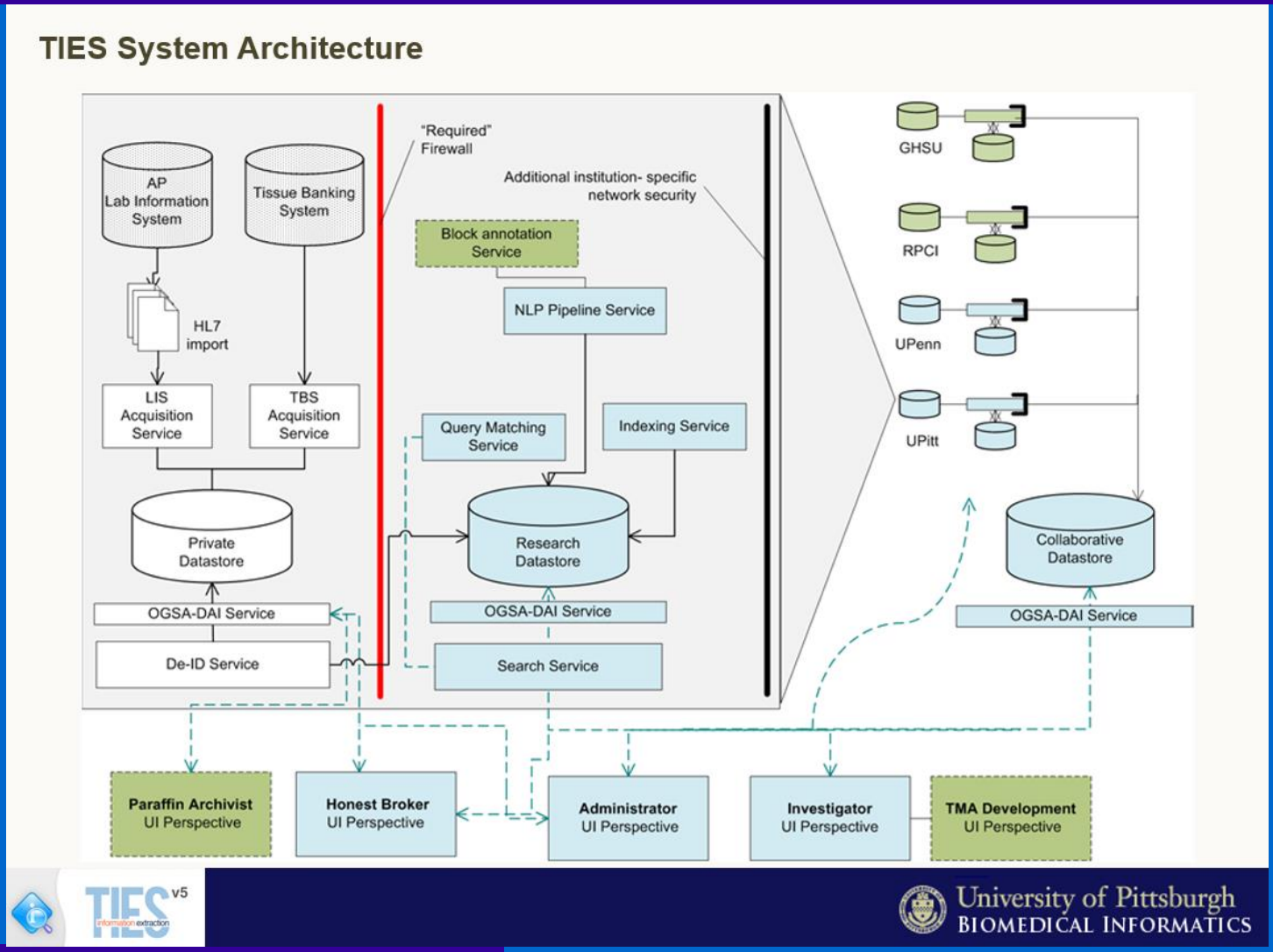
*(U Pitt is #1 contributor to The Cancer Genome Atlas – see subsequent slides)

What is TIES?

- **An NLP and Information Retreival system for de-identifying, annotating, storing and retrieving pathology and radiology documents**
- **A system for indexing research resources (FFPE, FF, WSI) with document annotations**
- **An GUI for querying large repository of annotated documents and obtaining resources locally, using an honest broker model**
- **A platform to support data, biospecimen and both Pathology and Radiology images for sharing among networks of cancer centers and other institutions**

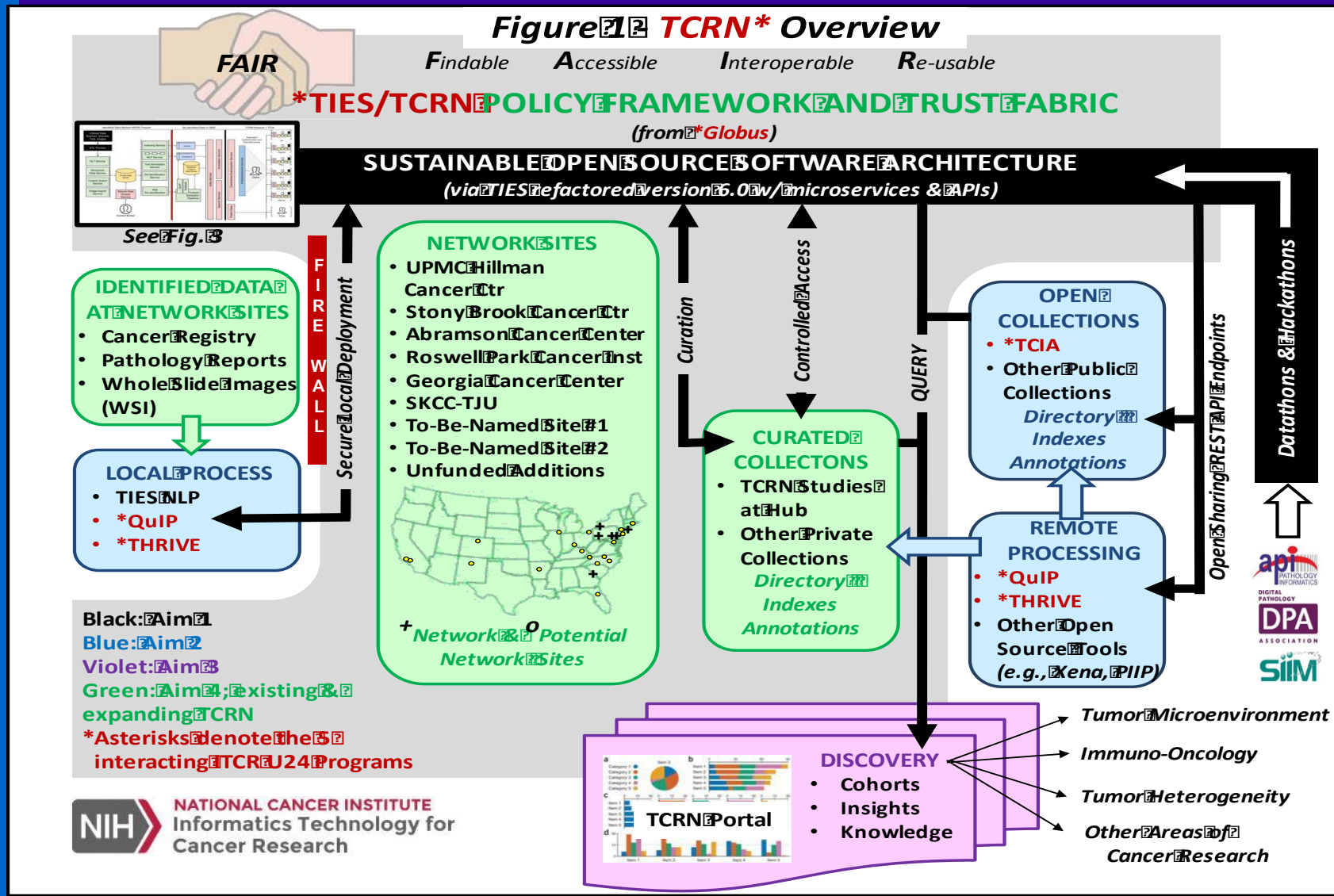
http://ties.upmc.com/

Text Information Extraction System (TIES)



https://cancerdatanetwork.org

TIES Cancer Research Network (TCRN)



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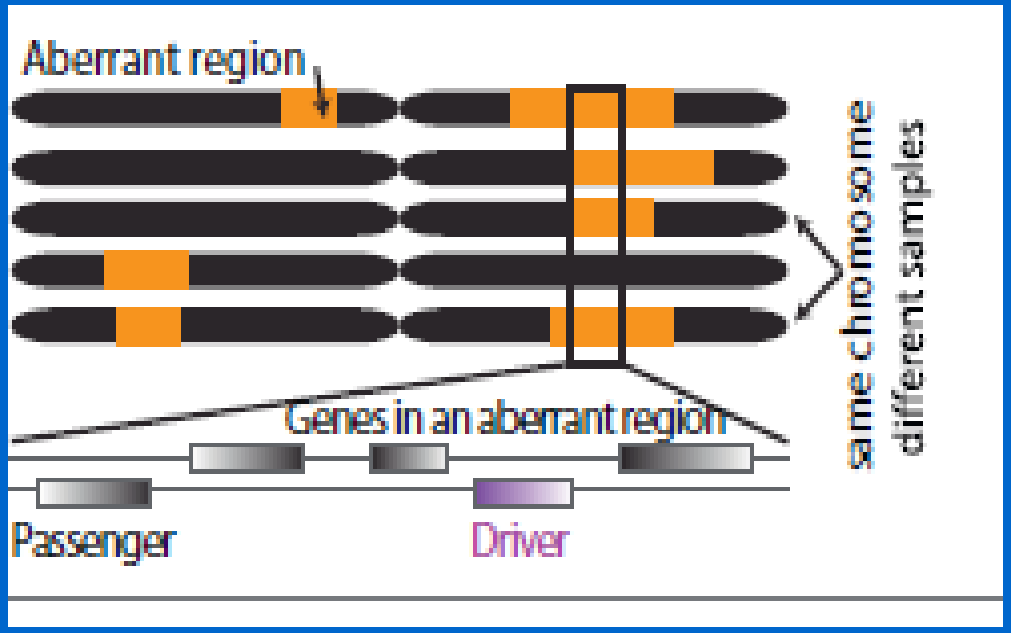
Pitt Center for Causal Modeling and Discovery

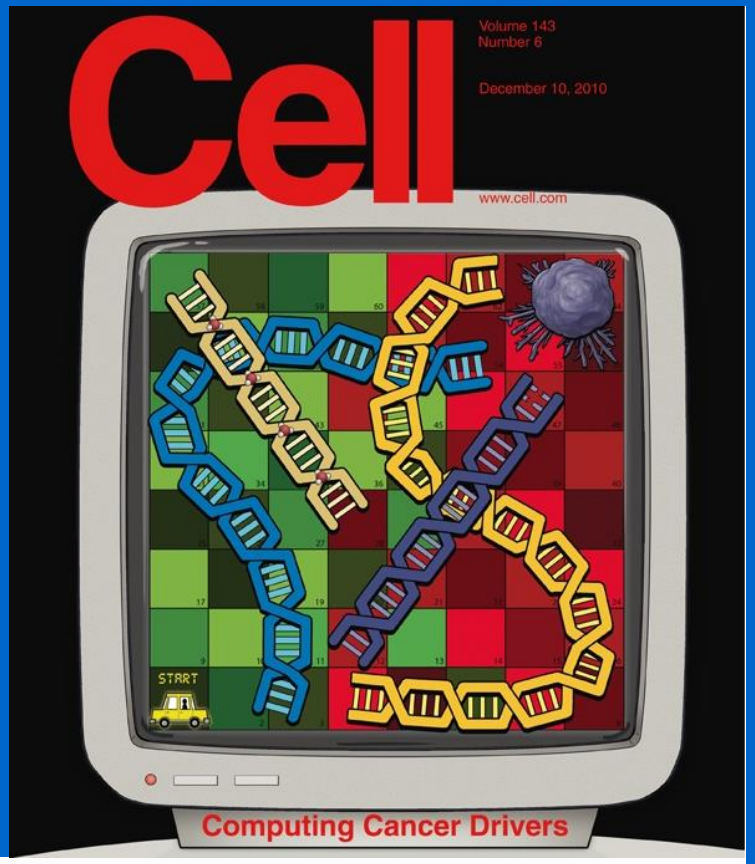
- Led by Greg Cooper, MD PhD (Biomedical Informatics), Ivet Bahar, PhD (Computational and Systems Biology) and Jeremy Berg, PhD (Director of Institute for Personalized Medicine) involves Becich/Crowley – TCGA/PGRR/Computable Phenotypes
- Theme: Modeling and discovery of causal networks from genome and phenome (patient EHR/i2b2 RDW) biomedical datasets including those from clinical trials and other controlled biospecimen based efforts
- Aims
  - ***Represent*** causal knowledge within a unified, formal framework
  - ***Discover*** causal knowledge from biomedical data (both observational and experimental) and background knowledge (e.g., from the literature) using efficient algorithms
  - ***Apply*** causal knowledge to support browsing, answering causal queries, simulating causal processes, and designing experiments to resolve causal uncertainties
- Driving Biological Problem areas: Signaling Pathways in Cancer/TCGA (**Computational Pathology and Genomics/TCGA**), Idiopathic Pulmonary Fibrosis (**Computational Pathology Imaging**) and "Connectome" via fMRI brain imaging

Causal Network Discovery = Computational Pathology

A probabilistic network approach to uncover genetic drivers of melanoma using data on copy number variation and gene expression*



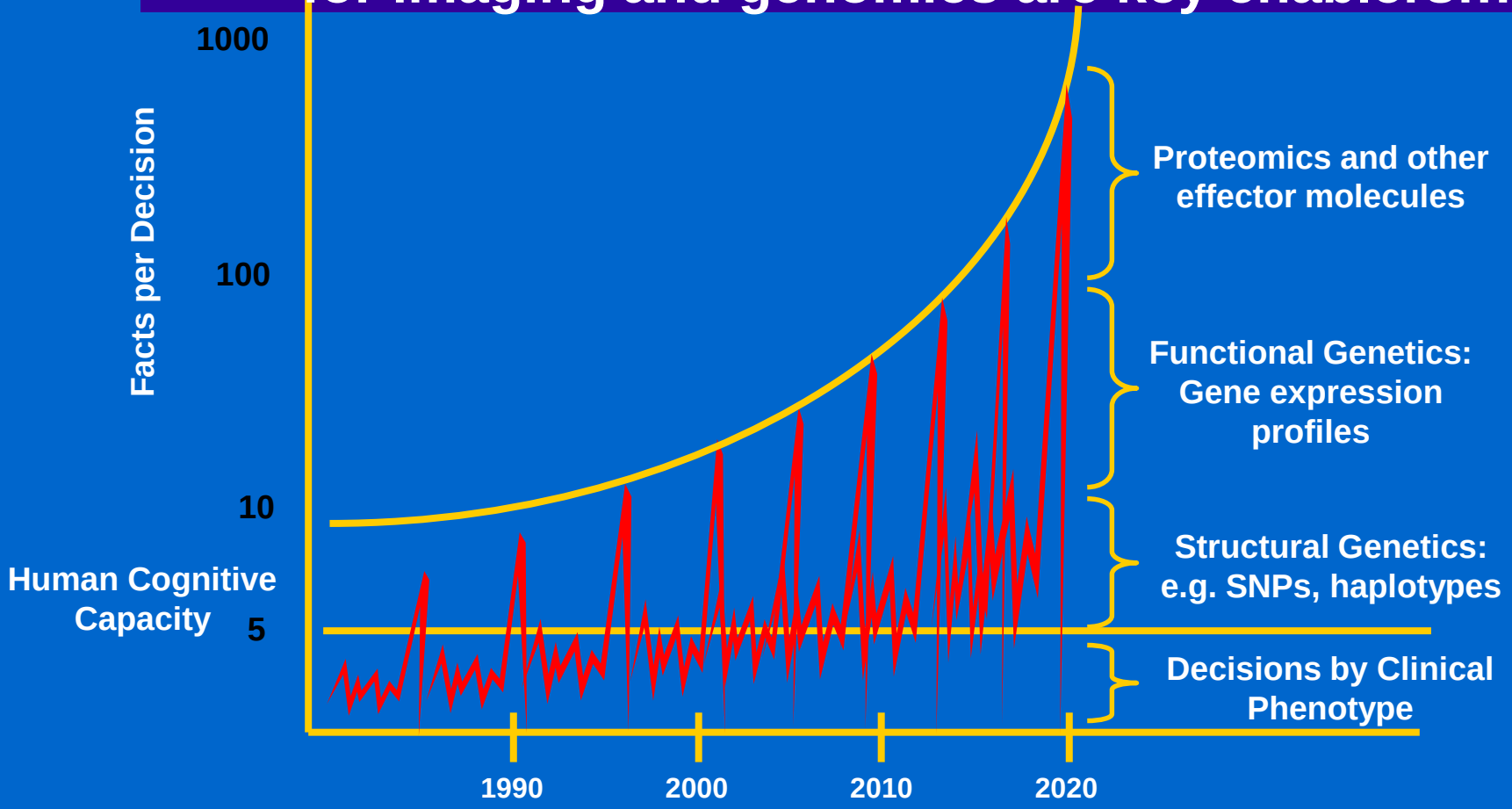
Akavia UD , et al. *Cell* 143 (2010) 1005-1017.
(The figure above appears in this paper)



10 December, 2010 Volume 143, Issue 6

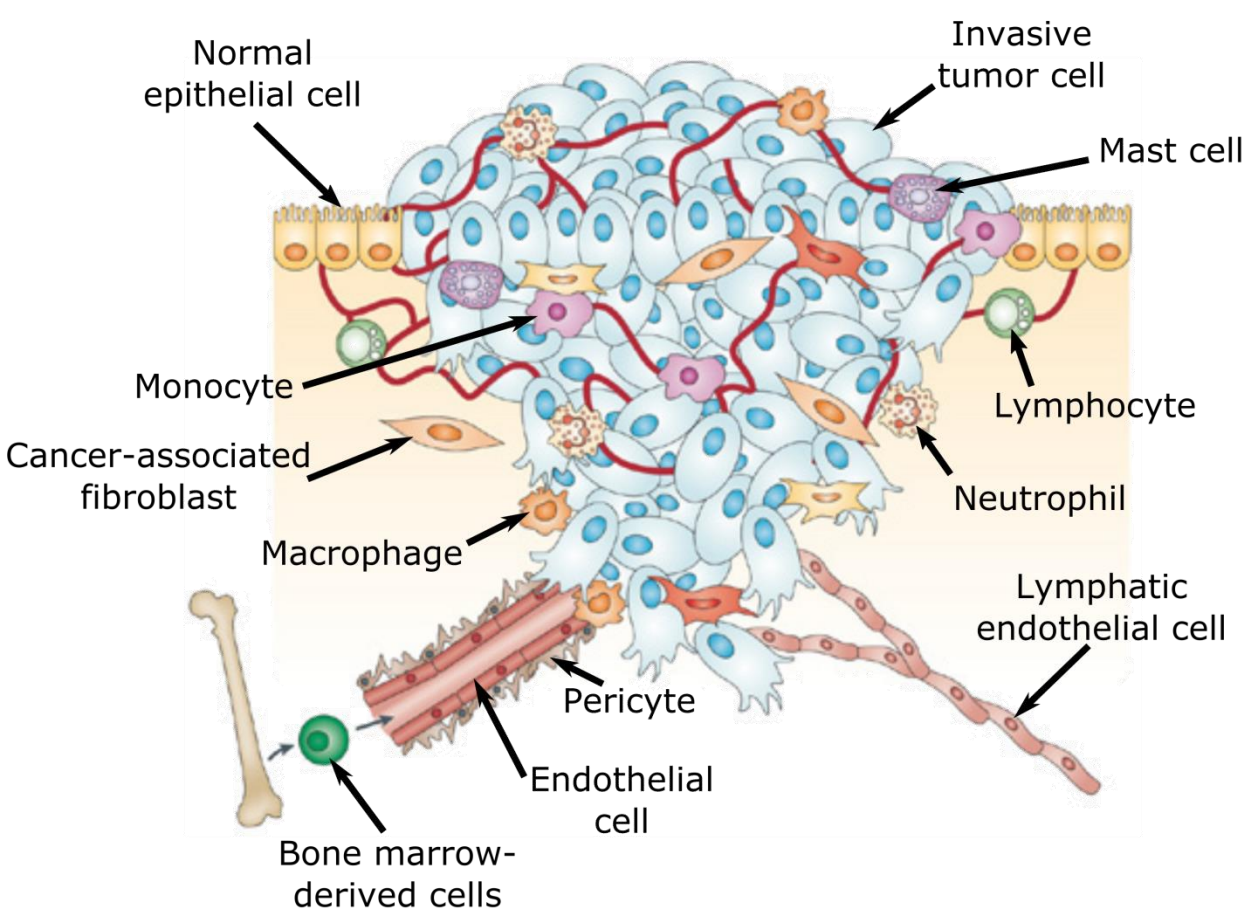
On the cover: In cancer, heterogeneous genetic aberrations frequently result in similar phenotypic outcomes. In this issue, Akavia et al. (pp. 1005–1017) report a computational algorithm that identifies driving mutations and links them with their downstream transcriptional effects. The approach thus allows the authors to begin disentangling the complex mechanisms by which genetic aberrations drive transformation. The cover shows a driver with many DNA-mediated paths to a tumor.

Computational Pathology Algorithms like those in CCD for imaging and genomics are key enablers!!!



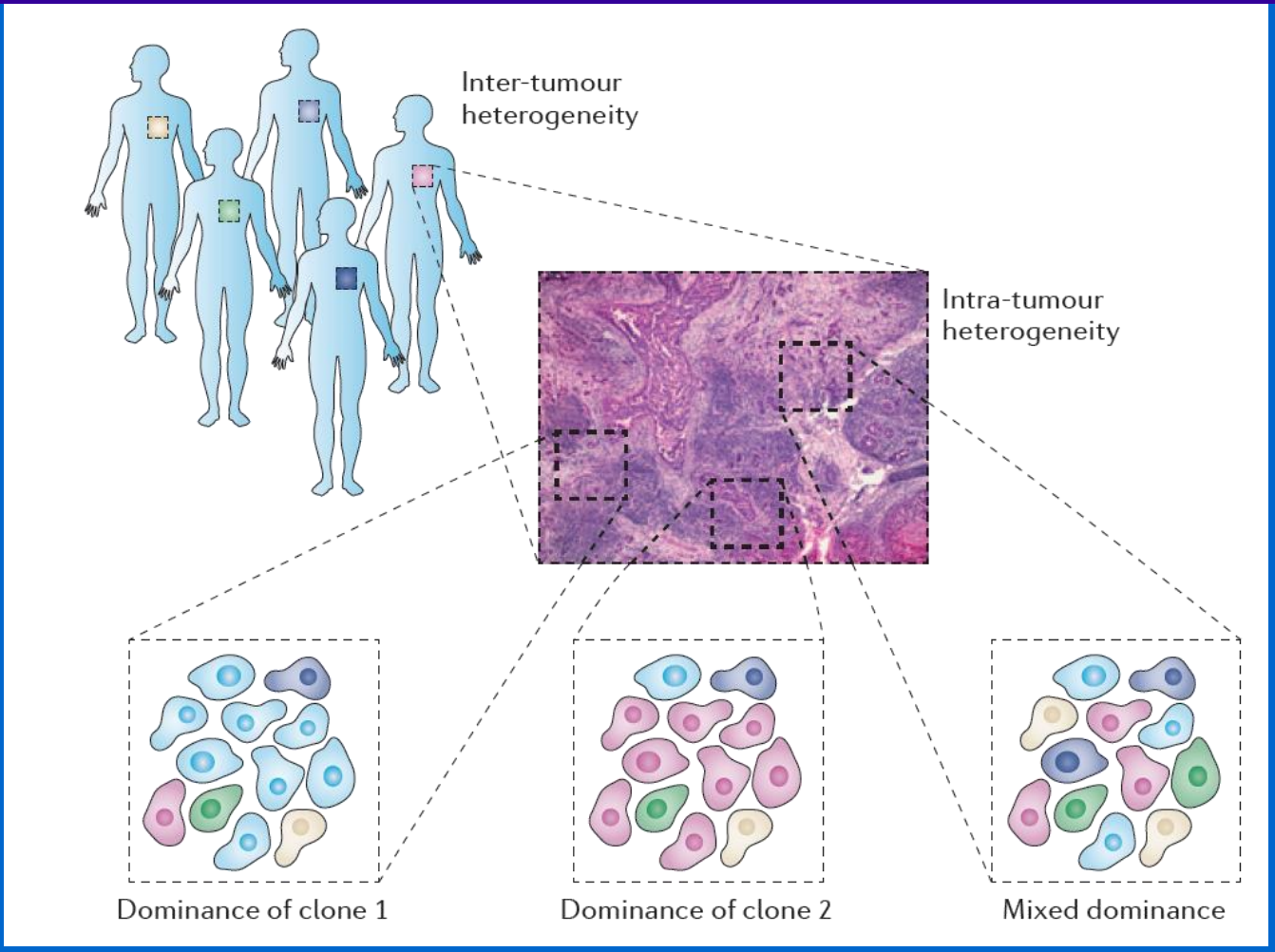
From William Stead: http://courses.mbl.edu/mi/2009/presentations_fall/SteadV1.ppt & http://www.mbl.edu/education/courses/special_topics/pdf/med_sched09_fall.pdf

1. Intra-tumoral spatial heterogeneity



Nature Reviews Cancer (2009) 9:239–252

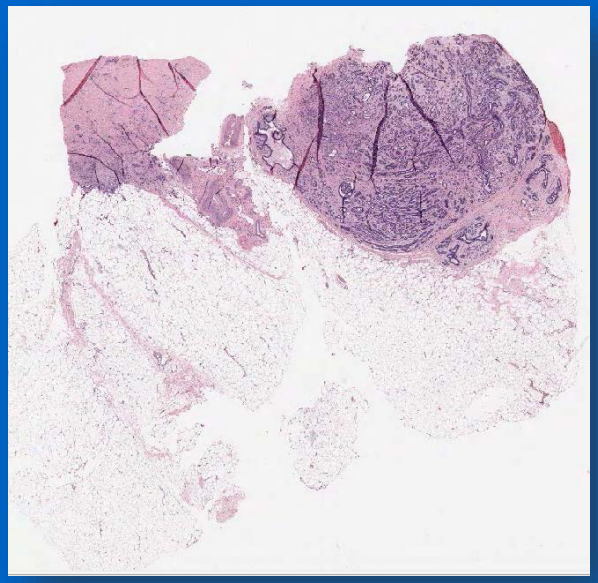
1. Quantify Heterogeneity for Diagnostics, Prognostics & Immunotherapy



Marusyk A. Nat Rev Cancer. 2012 Apr 19;12(5):323-34

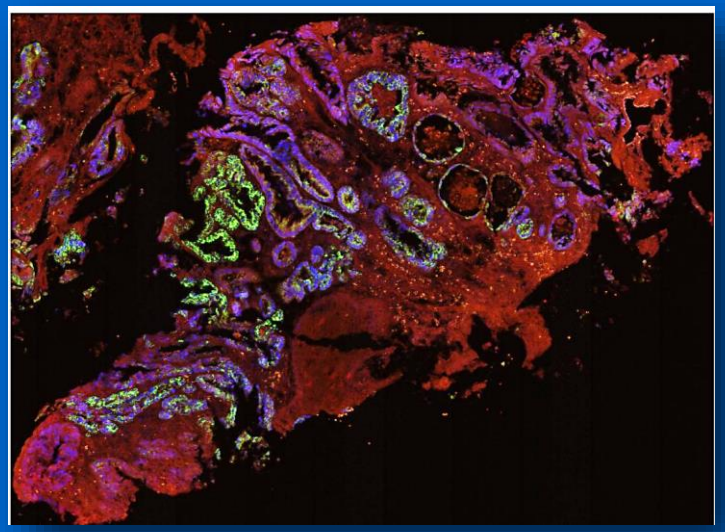
2. Integration of H&E, IHC and IF

H&E in transmitted light



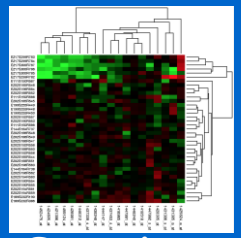
- Universal method
- Limited molecular measurements in transmitted (IHC)
- Complex tissue “scenes”

Multi to hyperplexed

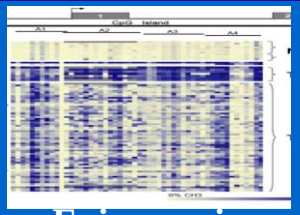


- Emerging method with potential to measure many DNA/RNA/proteins in the same tissue section/TMA
- Structural biomarkers
- Quantify biomarker expression levels and tissue based spatial relationships.

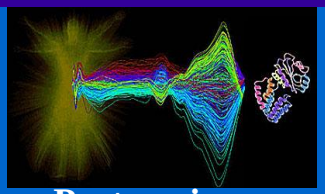
3. Histopatholomics: Spatial ITH



Genomics

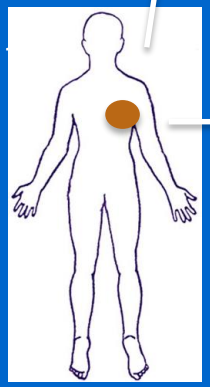


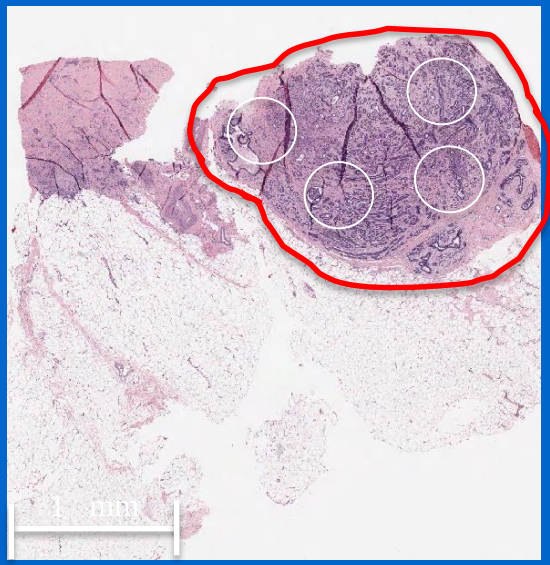
Epigenomics



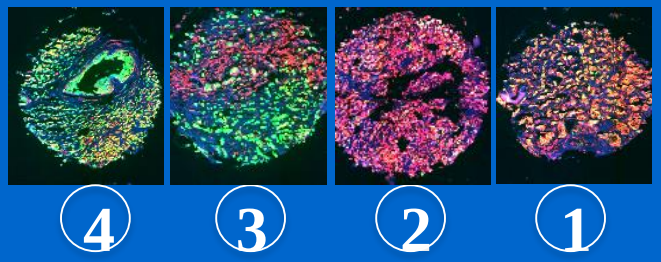
Proteomics

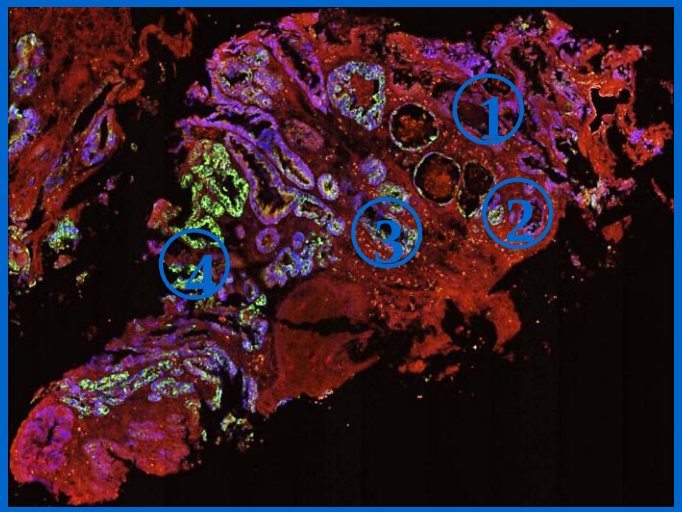
Metabolomics





H&E stained whole tissue section from FFPE tumor sample





Multi to hyperplexed fluorescence imaging of whole section for higher spatial resolution and tissue context

Thanks to Dr. Joe Ayoob for HPlomics

4. Ground-truth & Annotation

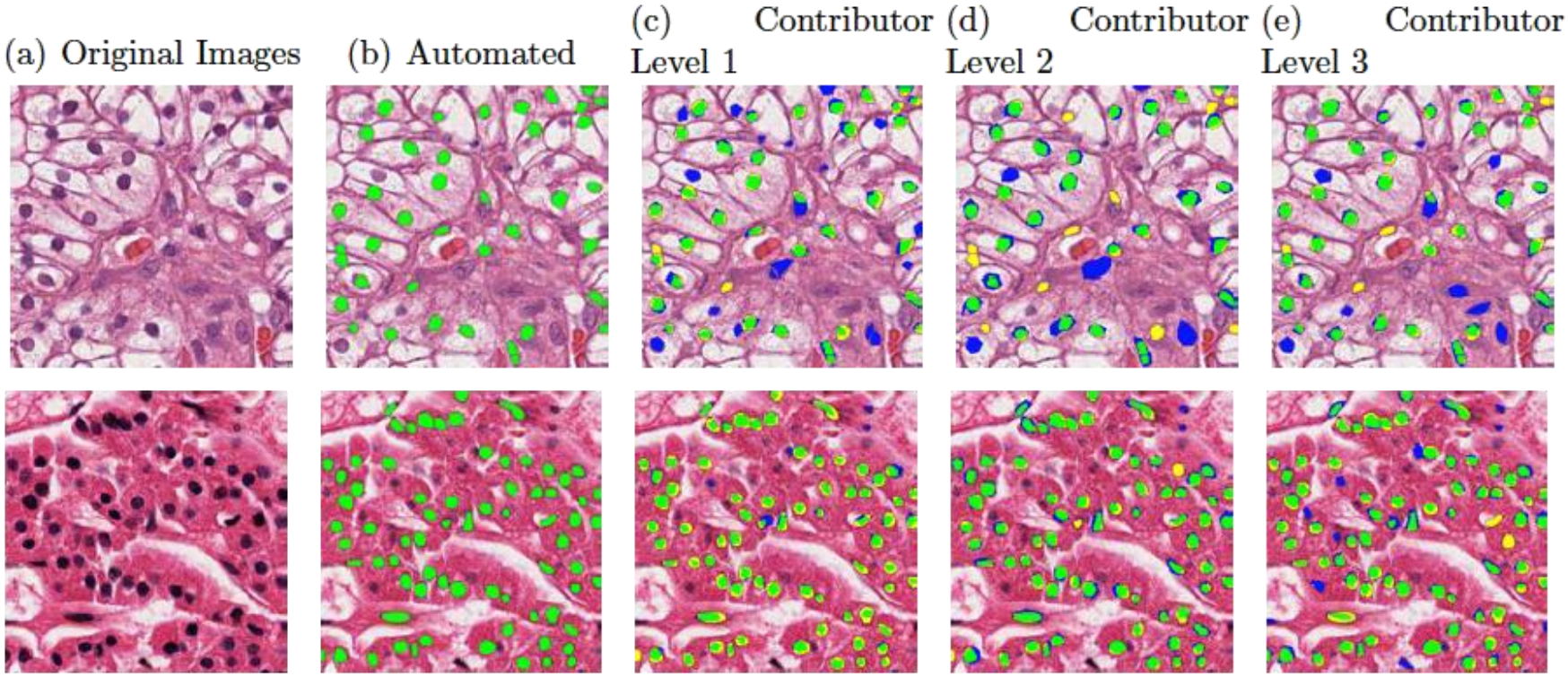
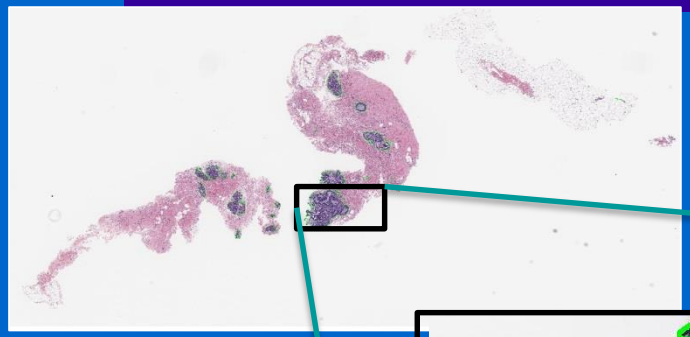
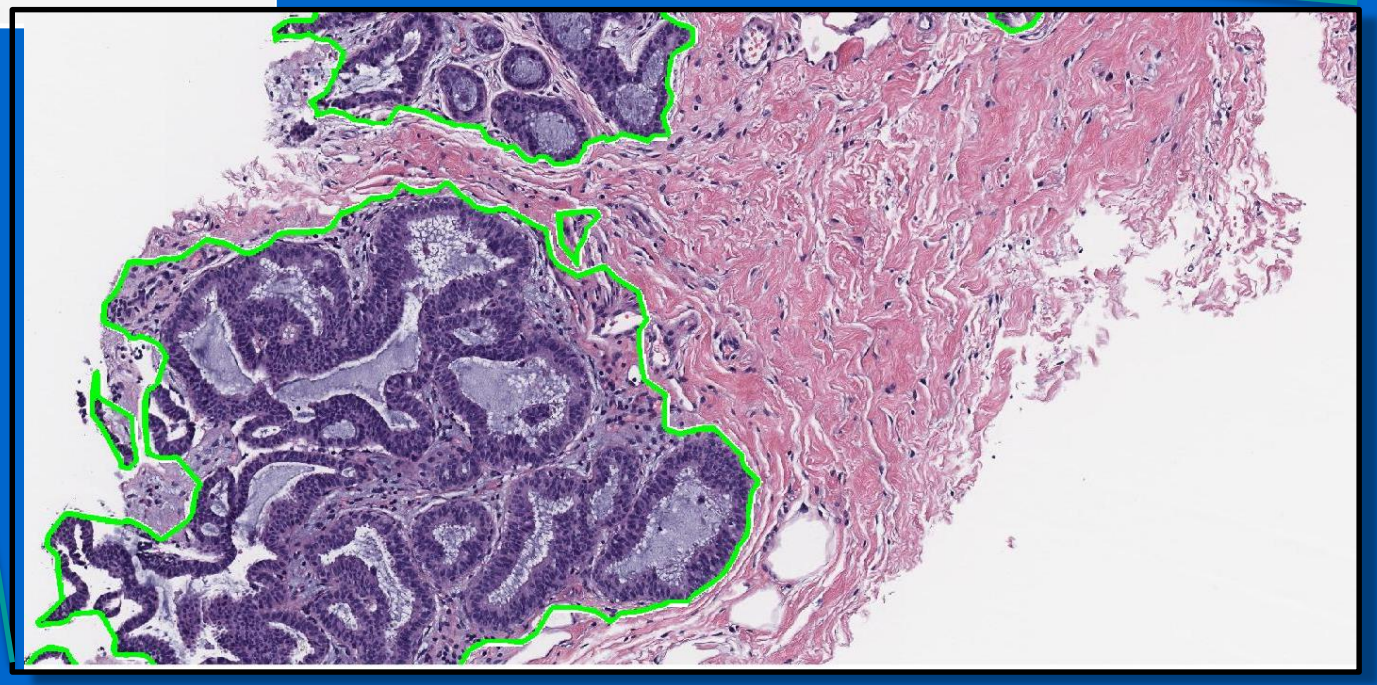


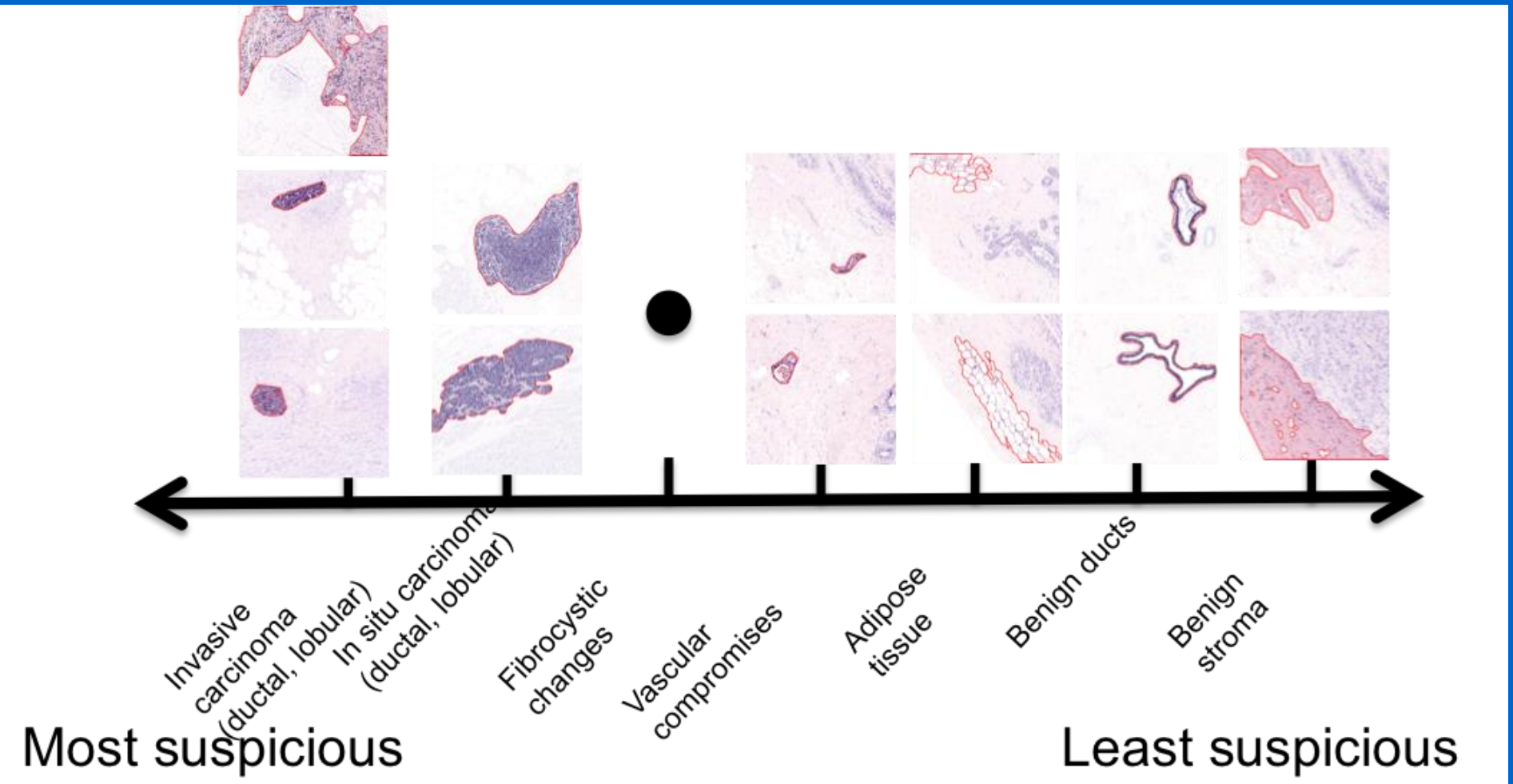
Fig. 2. Examples of nuclear segmentation using an automated method and increasing contributor skill level, ranging from 1 to 3. (Green region indicates TP region, yellow region indicates FN region and blue region indicates FP region). The automated nuclei segmentation used as ground truth.

4. ”Callable” ID of Histologic Features

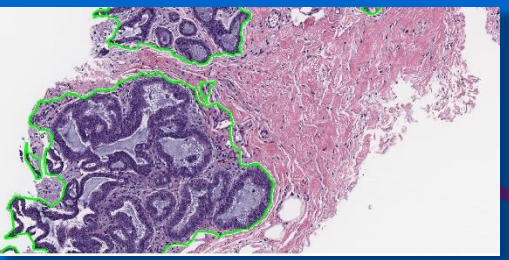


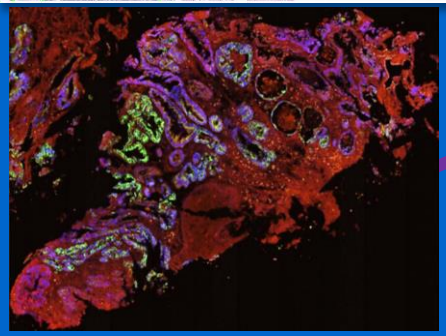


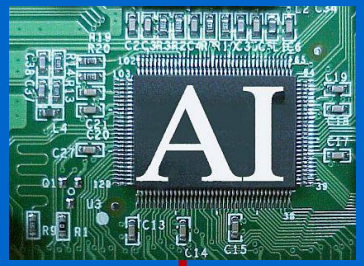
5. Triaging ROIs



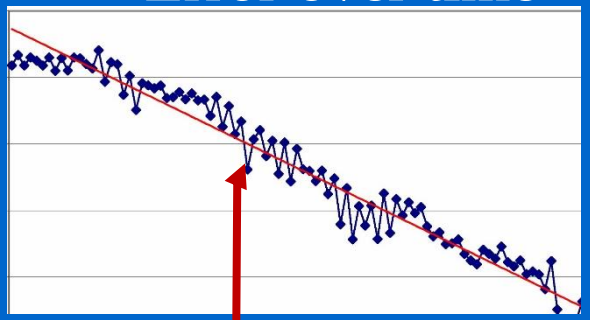
6. Computational Pathology and AI



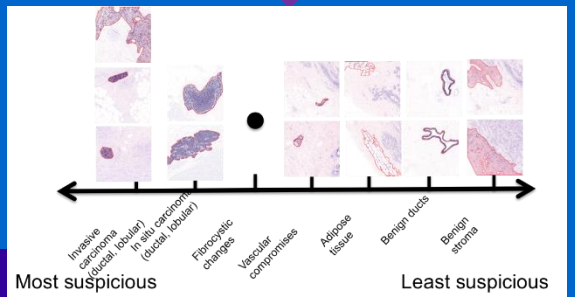




Error over time



Intervention

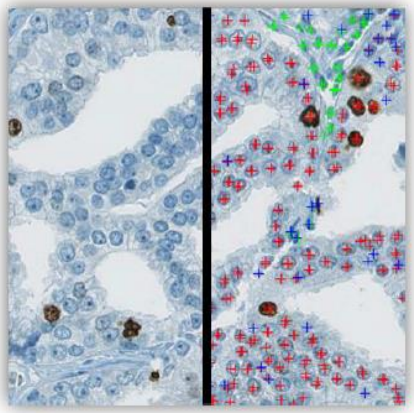


Pathology and Radiology Must Partner!

A Joint Effort for Personalized Medicine

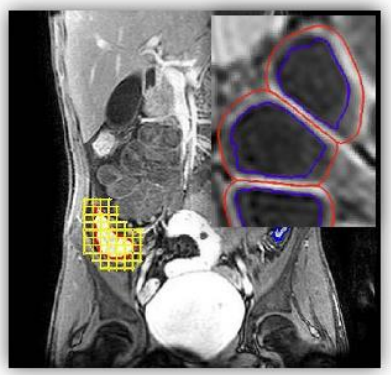
From Fuchs, 2017

Pathology



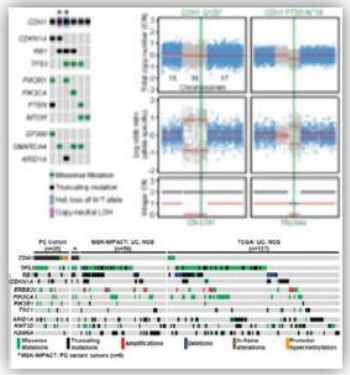
Computational Pathology

Radiology



Radiomics @ MSKCC

Genomics



cBioPortal @ MSKCC

Combining quantitative analyses from pathology, radiology and genomics facilitates true **personalized medicine.**

End of Talk – e-mail me at becich@pitt.edu if you have questions/clarifications not covered in the discussion.

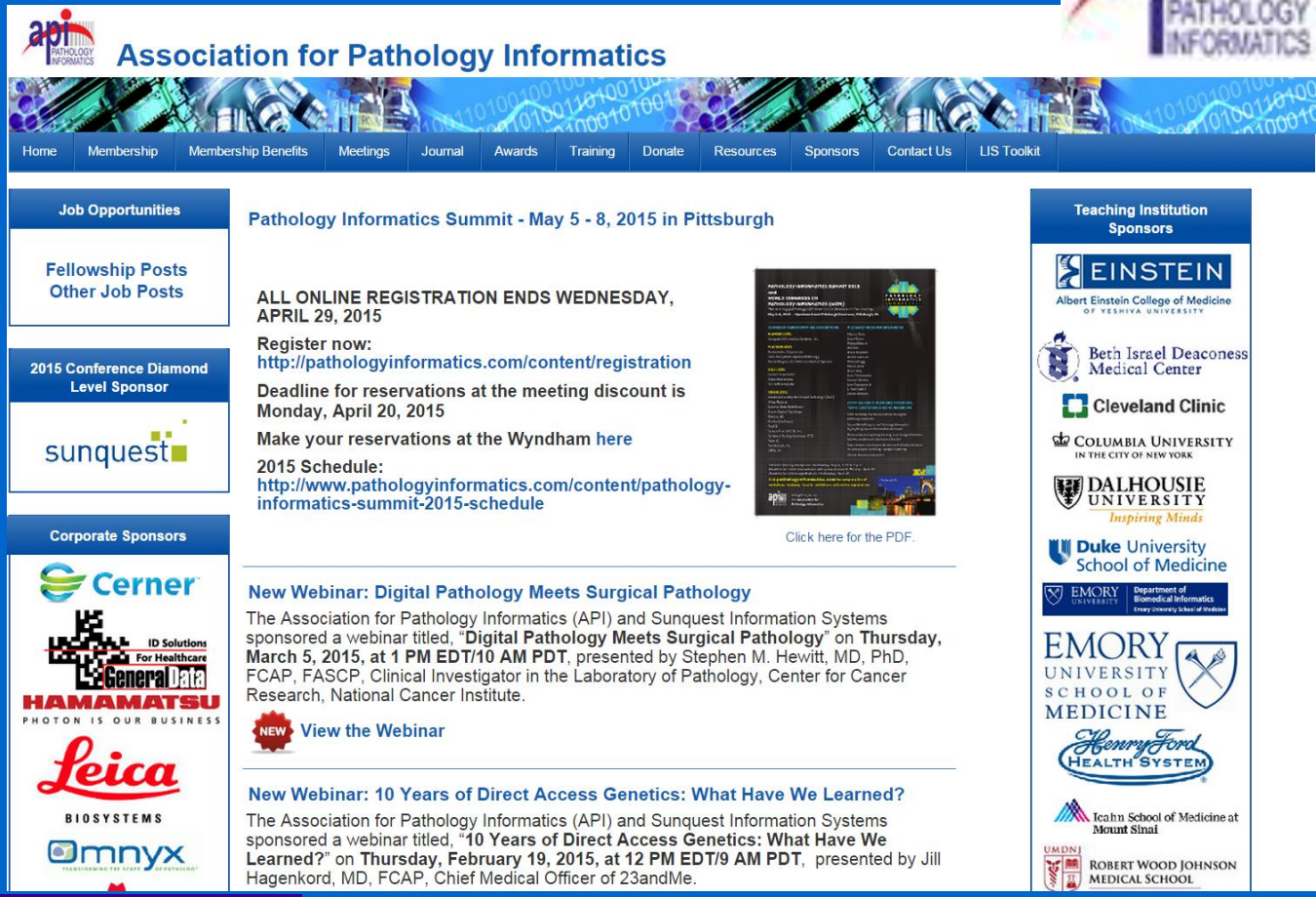
NOTE: E-mail me if you want PDFs of articles or presentation.

Thank you for organizing NCPF

Association for Pathology Informatics (API)

http://www.pathologyinformatics.org

"…to advance the field of pathology informatics as an academic and a clinical subspecialty of pathology…"



Journal of Pathology Informatics

Co-Editors Liron Pantanowitz, MD PhD and Anil Parwani, MD PhD

Please support JPI, API and Pathology Informatics as the Home for Digital Pathology - Great Academic and Strategic Partnership with Multiple Benefits!!!

Thanx to the Pitt team!


Dan Spagnolo


Dr. Shikhar Uttam


Dr. Burak Tosun


Lương Nguyên


Maurice Marx


Dr. Om Choudhary


Dr. Filippo Pullara


Akash Parvatikar


Nathan Ong


Chakra


Alex Andonian


Tammy Ma

Drug Discovery Institute/CSB
Dr. Lansing Taylor
Dr. Andy Stern
Dr. Bert Gough
Dr. Tim Lezon

UPMC/Magee/Pathology
Dr. Jeffrey Fine

Center for Commercial Applications of
Health Care Data/DBMI
Dr. Michael Becich
Dr. Don Taylor

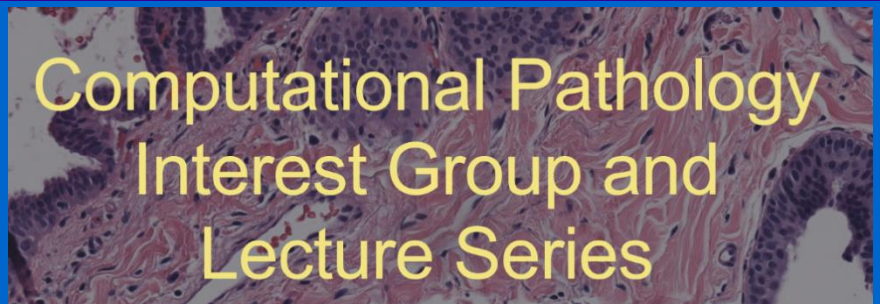
GE Global Research
Brion Sarachan
Dr. Yousef Al-Kofahi
Dr. Fiona Ginty
Magee-Womens Research Institute
Dr. Adrian Lee
Dr. Rekha Gyanchandani
CSB
Dr. Takis Benos
Dr. Dimitrios Manatakis
Dr. Joe Ayoob

- UPMC & Center for Commercial Applications of Healthcare Data Grant #711077
- NIH-NCI U01 CA204826
- NHGRI BD2K U54HG008540 (Lung DBP)

SPDx

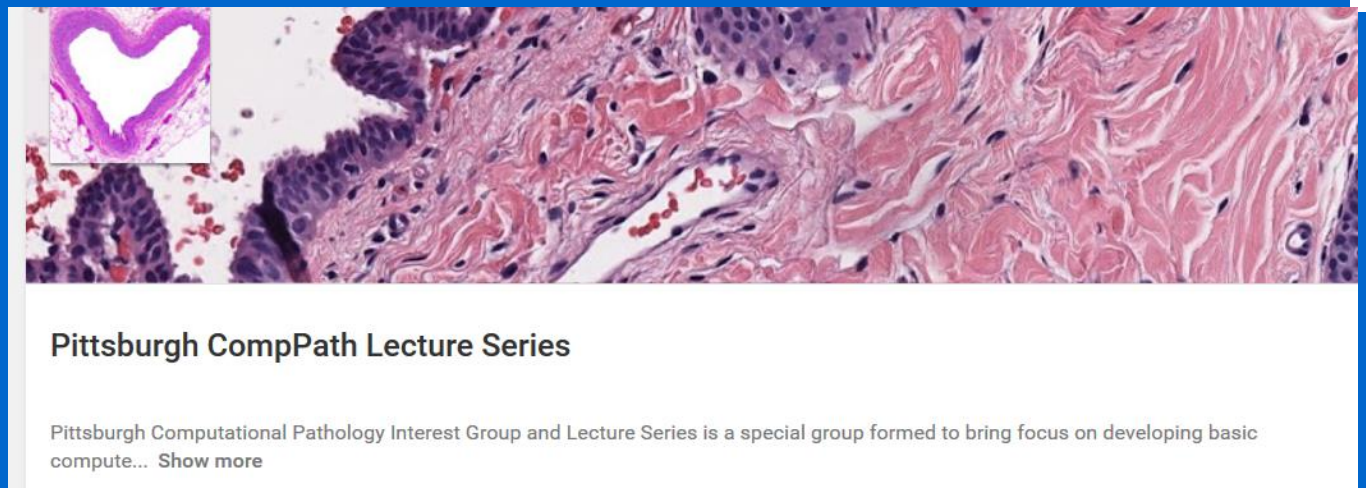
Spatial Pathology Powers Precision Oncology

Thanx to Chakra Chennubhotla, PhD & Burak Tosun, PhD



http://www.csb.pitt.edu/comppath/

Youtube Channel for Lectures



https://www.youtube.com/watch?v=Xrvxc0YNcAM&feature=youtu.be

Comp Path Team Profile - Pittsburgh

- **Special Interest Group Members (n=93):**
  - Bioengineering (5%)
  - Biomedical Informatics (10%)
  - Computational and Systems Biology (10%)
  - Computer Science and Machine Learning (20%)
  - Industry and Entrepreneurs (20%)
  - Medicine (10%)
  - Pathology Informatics (10%)
  - UPMC (15%)

Participation from Carnegie Mellon & Dusquene Universities