

*Midwest Consortium for
Computational Pathology Workshop
January 26th, 2021*

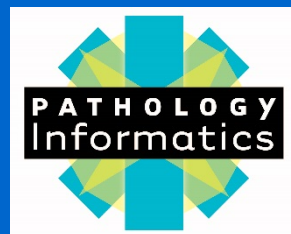
**Computational Pathology and
Improving Predictive Analytics**



**Michael J. Becich, MD PhD - becich@pitt.edu
Chairman and Distinguished University Professor,
Department of Biomedical Informatics**

<http://www.dbmi.pitt.edu>

University of Pittsburgh School of Medicine



Disclosures of COI for 2021 for MJB

Startup/Public Companies Royalties/Licensing, Equity):

- De-ID Data Corp – de-identification software (licensing agreement)
<http://www.de-idata.com/>
- Nexi – Newco by Rebecca Jacobson/TIES/TCRN team (royalties to my Department) to support pharma/biotech – <http://www.nexihub.com>
- SpIntellx (formerly SpDX) – Spatial Intelligence for Cancer Diagnostics (founder equity)

Consultancy (honoraria)

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

Federal Grants

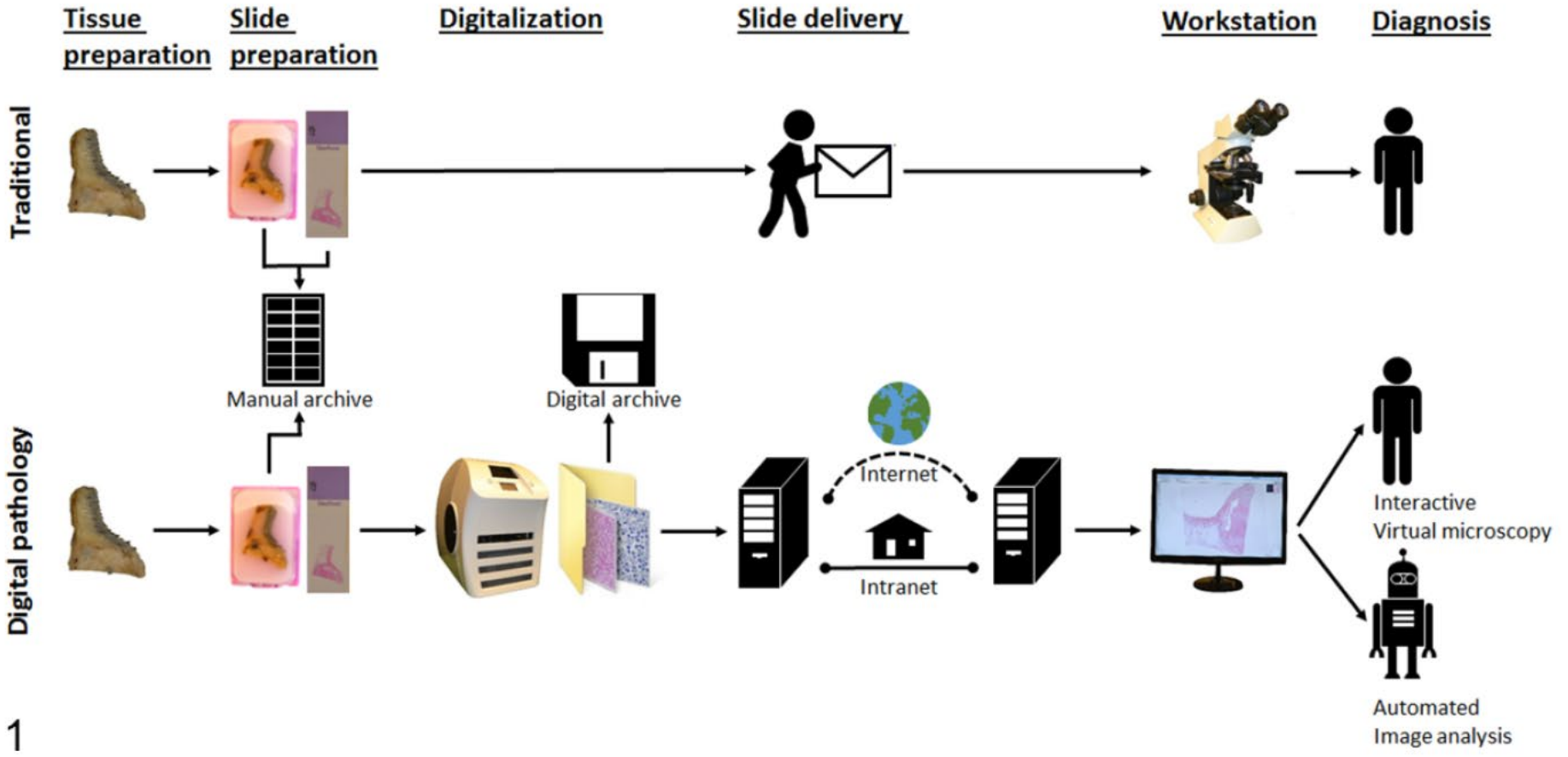
- CDC NIOSH – National Mesothelioma Virtual Bank
- NCI - CCSG – Cancer Bioinformatics Shared Facility
- NCATS - CTSA and ACT
- NLM - BMI TP
- PCORI – PaTH CRN

**Disclaimer: I am a member of
NCI's Board of Scientific
Advisors and Frederic National
Labs Advisory Board Tech WG**

Take Home Messages

- FDA approval of whole slide imaging is driving Computational Pathology and AI in Pathology
- Informatics is key to impact of Comp Path & predictive analytics in clinical practice
- Pathology and Radiology partnerships need to be enabled
- **Key Impact Areas** – Predictive Analytics for health and discovery science via Comp Path!

Whole Slide Imaging (WSI) Workflow

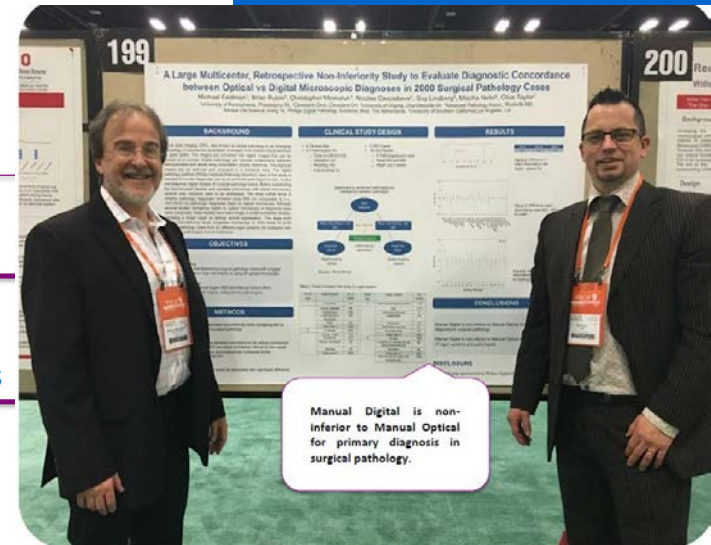


From Bertram and Kopfleish, Vet Path 2017

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(5):395A

*TPA = Technical Performance Assessment

From Pantanowitz, Path Info Summit, 2017

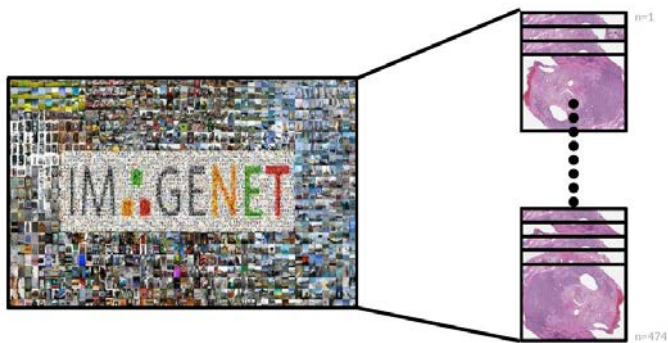
Computational Pathology – What is it?

- 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

Dataset Sizes: Computer Vision vs. Computational Pathology

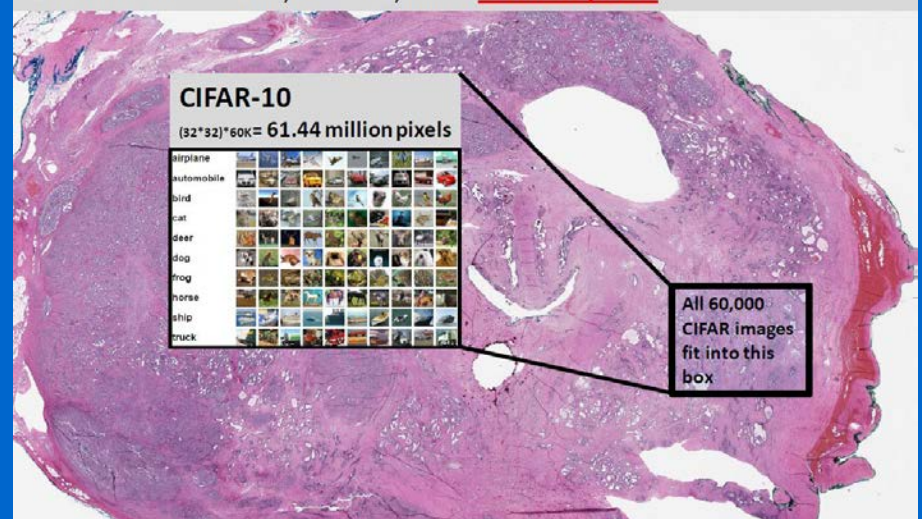
From Fuchs, 2017



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

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



CIFAR-10
(32*32)*60K = 61.44 million pixels



All 60,000
CIFAR images
fit into this
box

Introduction to Whole Slide Imaging

Pipeline for Whole Slide Feature Characterization

- 10^{10} pixels for each whole slide image:
 $10^5 \times 10^5$
- 10 whole slide images per patient
- 10^8 image features per whole slide image
- 10^{15} pixels
- 10^{13} features



1000 scanned slides

3.03 Tbyte

444 registrants



From Saltz, NLM circa 2011



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)

Support for Comp Path – Integration Needed

Data Types Critical to Success for Predictive Analytics

- **Imaging – Rich source of computable information**
 - Need to De-ID WSI and then “deeply” annotate
- **Phenotype – From Anatomic Pathology Lab Info Sys**
 - Structured data from synoptic reports
 - Unstructured data via NLP (Text Info Extract Sys – TIES)
- **Computational Pathology Annotation – more later**
- **Outcomes Data – From Cancer Registry Systems**
- **Data to Integrate – Biobanks, Clinical Pathology & Molecular Pathology**

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)



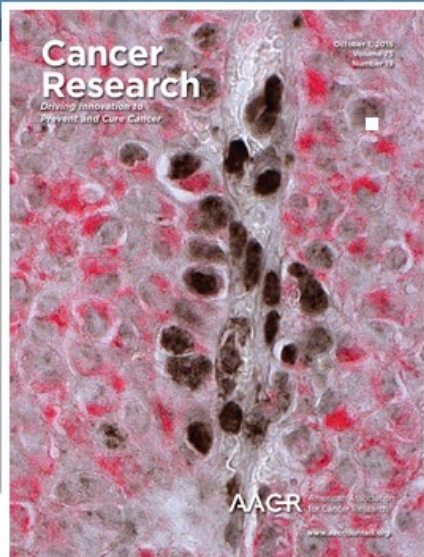
What is the Text Info Extraction System (TIES)?

- An NLP and Information Retrieval 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

Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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Resource

Cancer
Research

A Federated Network for Translational Cancer Research Using Clinical Data and Biospecimens

Rebecca S. Jacobson¹, Michael J. Becich¹, Roni J. Bollag², Girish Chavan¹, Julia Corrigan¹, Rajiv Dhir¹, Michael D. Feldman³, Carmelo Gaudioso⁴, Elizabeth Legowski¹, Nita J. Maihle², Kevin Mitchell¹, Monica Murphy⁴, Mayurapriyan Sakthivel⁴, Eugene Tseytlin¹, and JoEllen Weaver³

Abstract

Advances in cancer research and personalized medicine will require significant new bridging infrastructures, including more robust biorepositories that link human tissue to clinical phenotypes and outcomes. In order to meet that challenge, four cancer centers formed the Text Information Extraction System (TIES)


policies, and procedures, enable regulatory compliance. The TIES Cancer Research Network now provides integrated access to investigators at all member institutions, where multiple investigator-driven pilot projects are underway. Examples of federated search across the network illustrate the potential impact on

- [View the new Impact Factor](#)
- [View the Most-Cited Articles of Cancer Research](#)



<http://ties.dbmi.pitt.edu/>

Computational Pathology and Informatics Science

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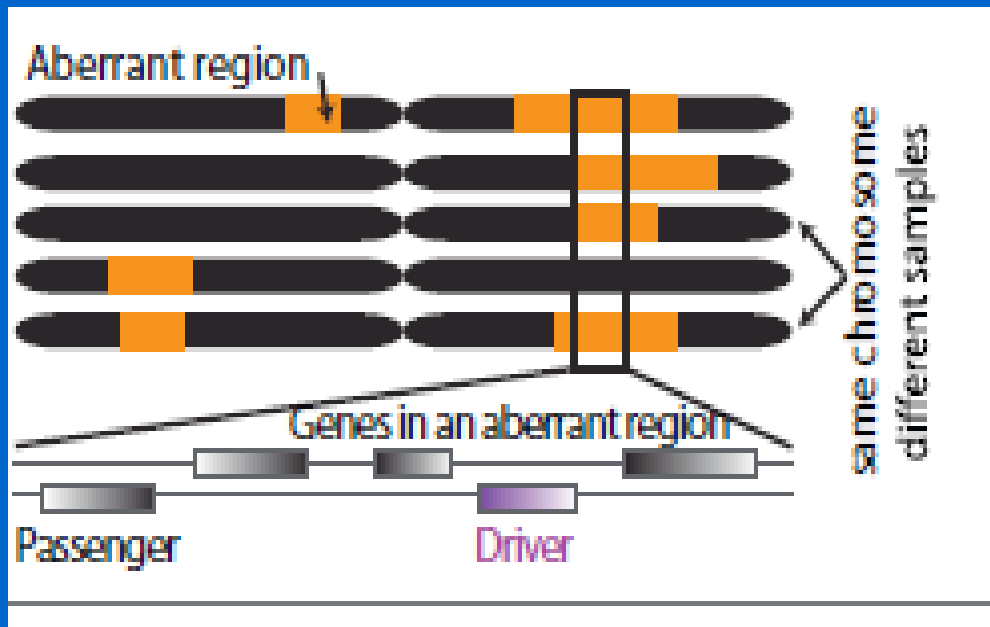
Pitt Center for Causal Modeling and Discovery

- 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

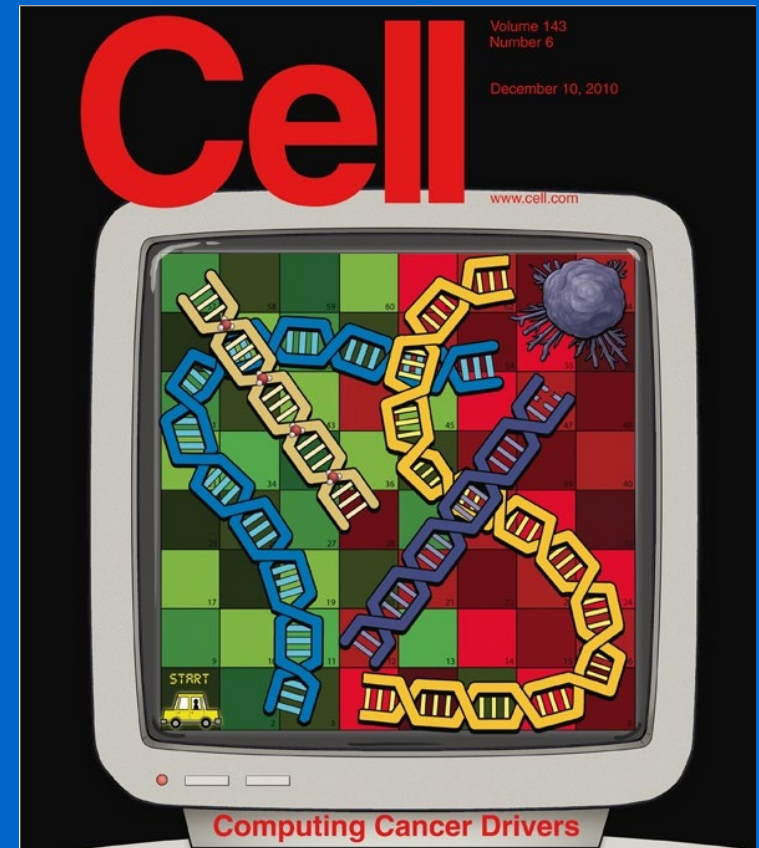


Causal Network Discovery = Computational Pathology

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



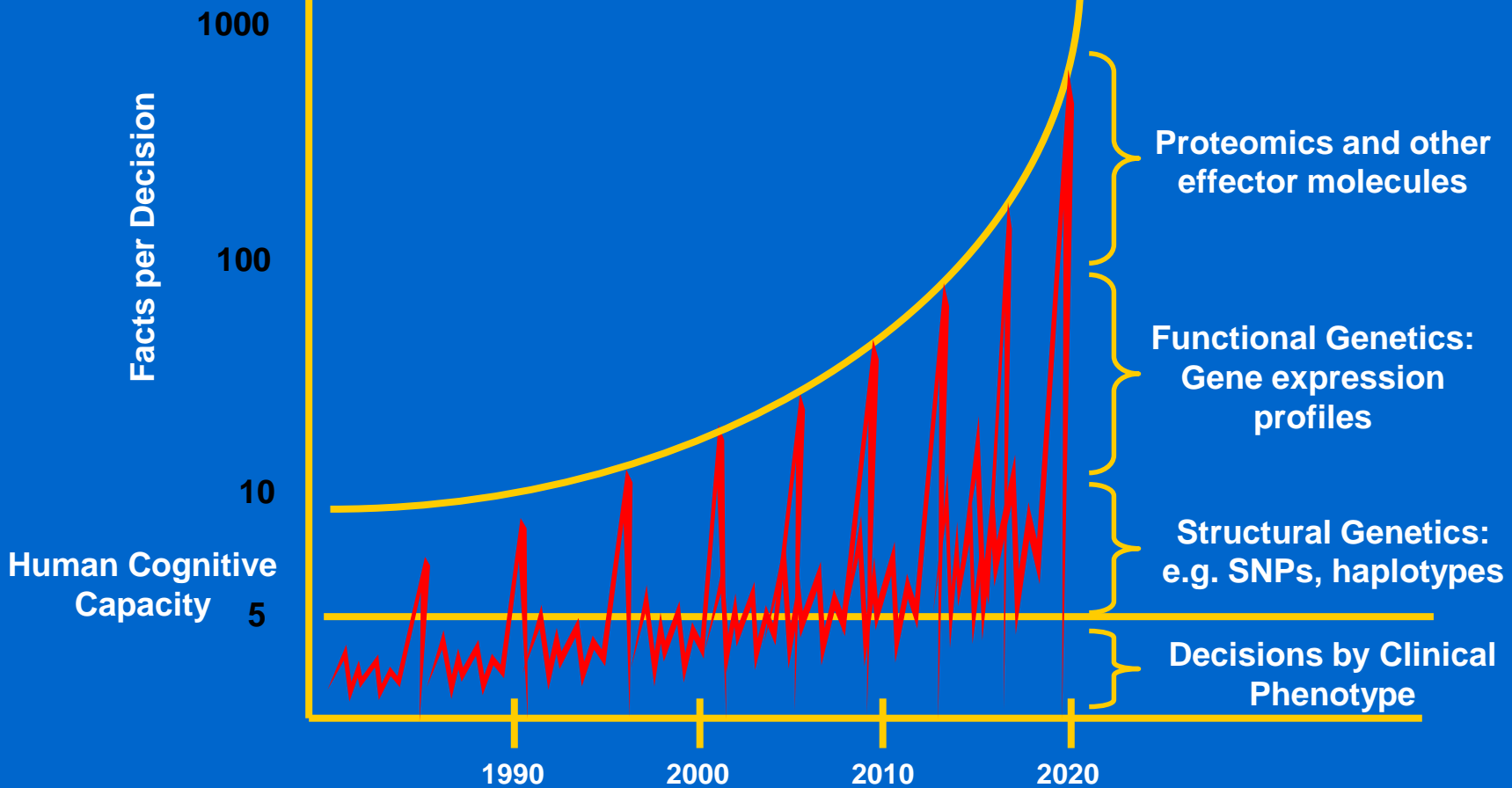
Akavia UD , et al. *Cell* 143 (2010) 1005-1017.
(The figure above appears in this paper)



10 December, 2010 Volume 143, Issue 6

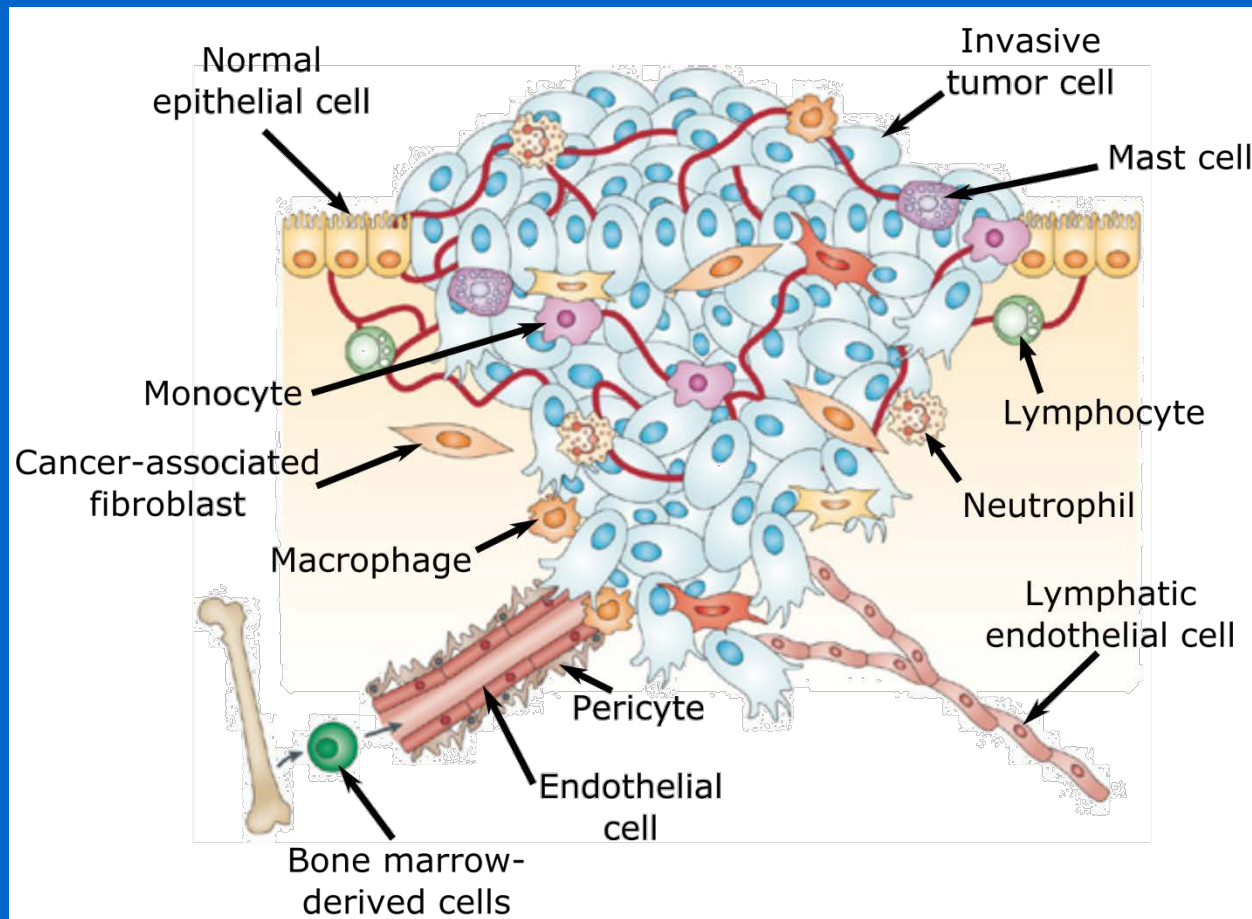
On the cover: In cancer, heterogeneous genetic aberrations frequently result in similar phenotypic outcomes. In this issue, Akavia et al. (pp. 1005–1017) report a computational algorithm that identifies driving mutations and links them with their downstream transcriptional effects. The approach thus 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!!!

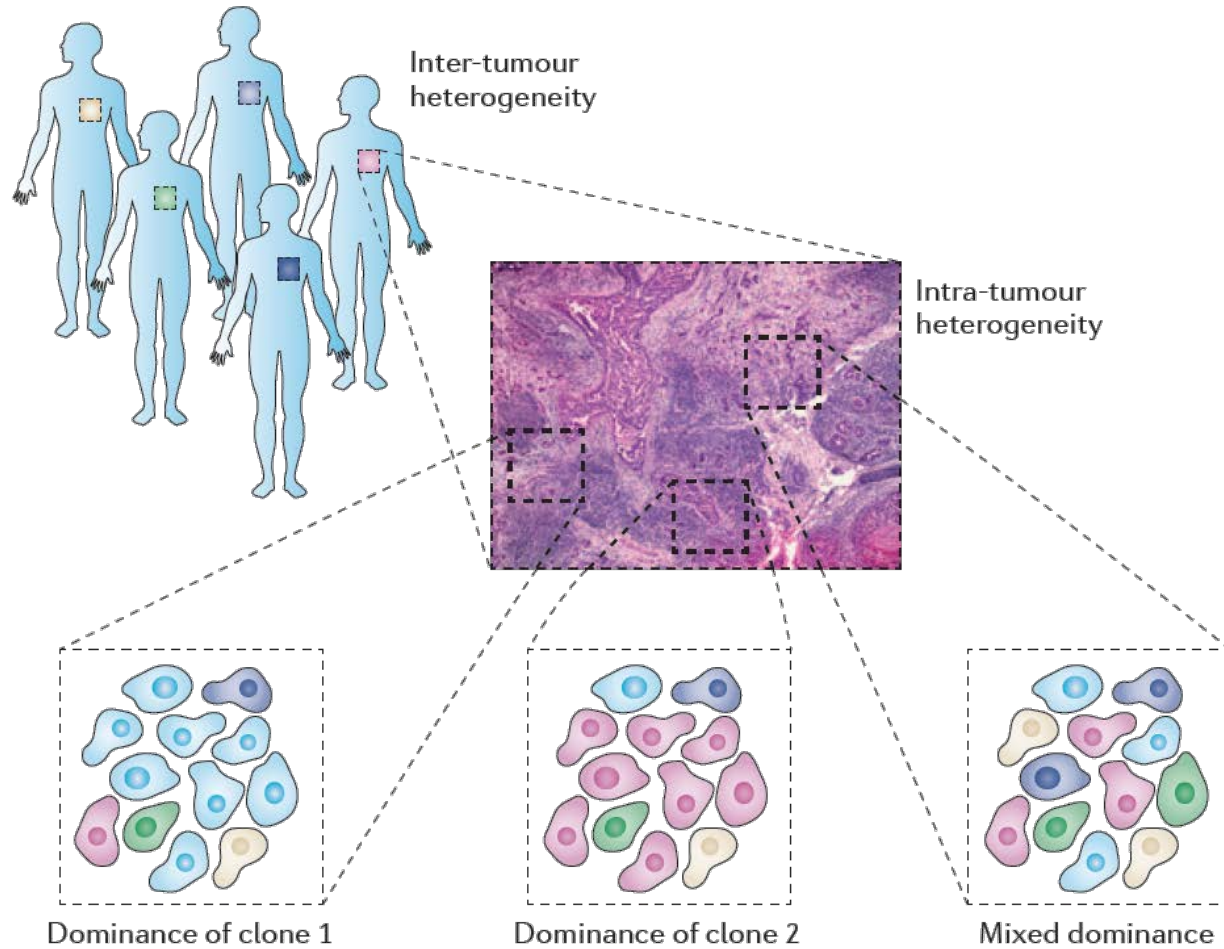


From William Stead: http://courses.mbl.edu/mi/2009/presentations_fall/SteadV1.ppt
& http://www.mbl.edu/education/courses/special_topics/pdf/med_sched09_fall.pdf

1. Intra-tumoral spatial heterogeneity

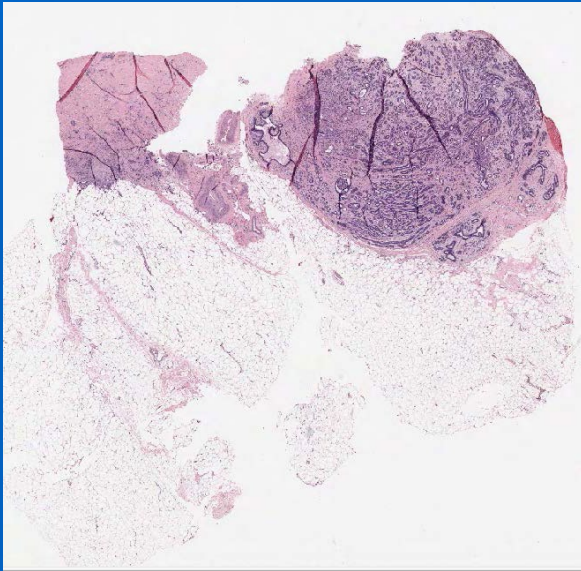


1. Quantify Heterogeneity for Diagnostics, Prognostics & Immunotherapy



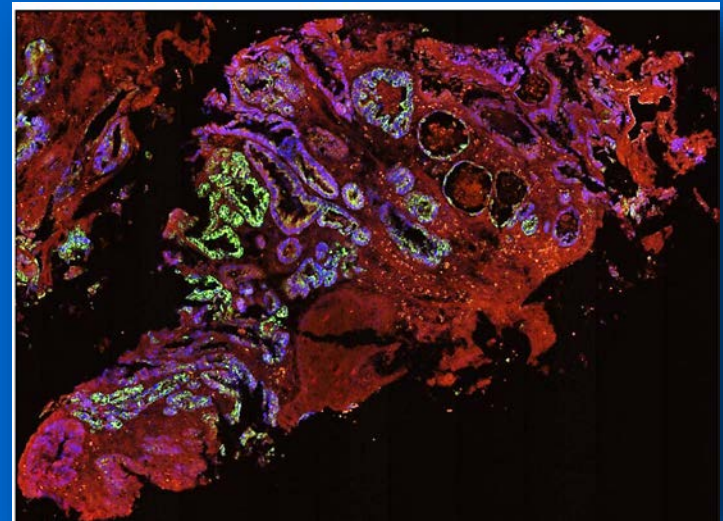
2. Integration of H&E, IHC and IF

H&E in transmitted light



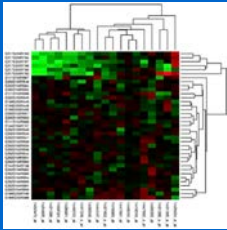
- Universal method
- Limited molecular measurements in transmitted (IHC)
- Complex tissue “scenes”

Multi to hyperplexed

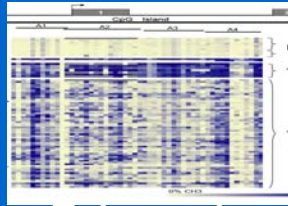


- Emerging method with potential to measure many DNA/RNA/proteins in the same tissue section/TMA
- Structural biomarkers
- Quantify biomarker expression levels and tissue based spatial relationships.

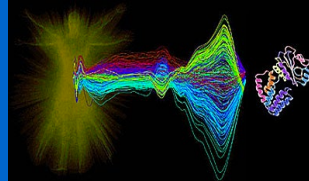
3. Histopathomics: Spatial ITH



Genomics



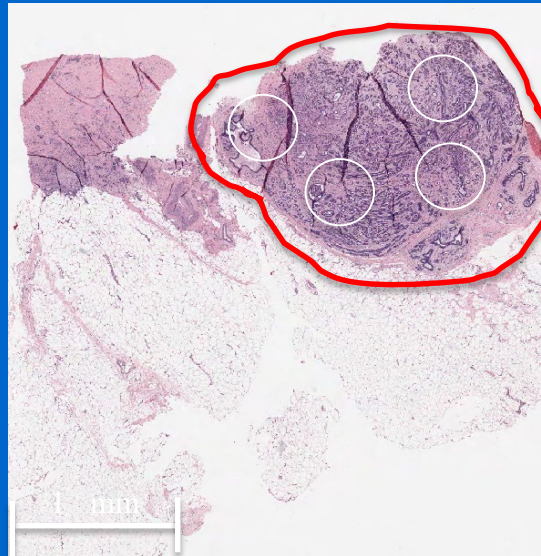
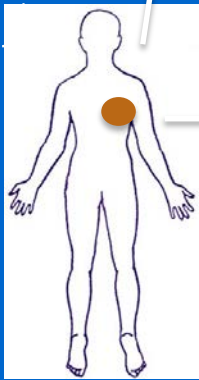
Epigenomics



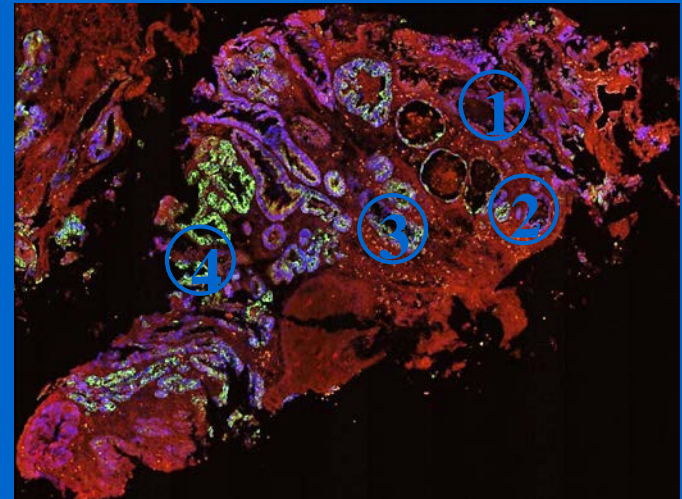
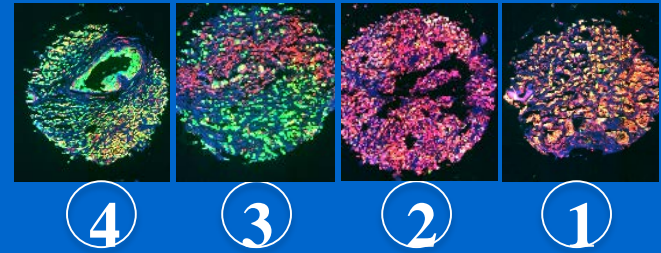
Proteomics



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

4. Ground-truth & Annotation

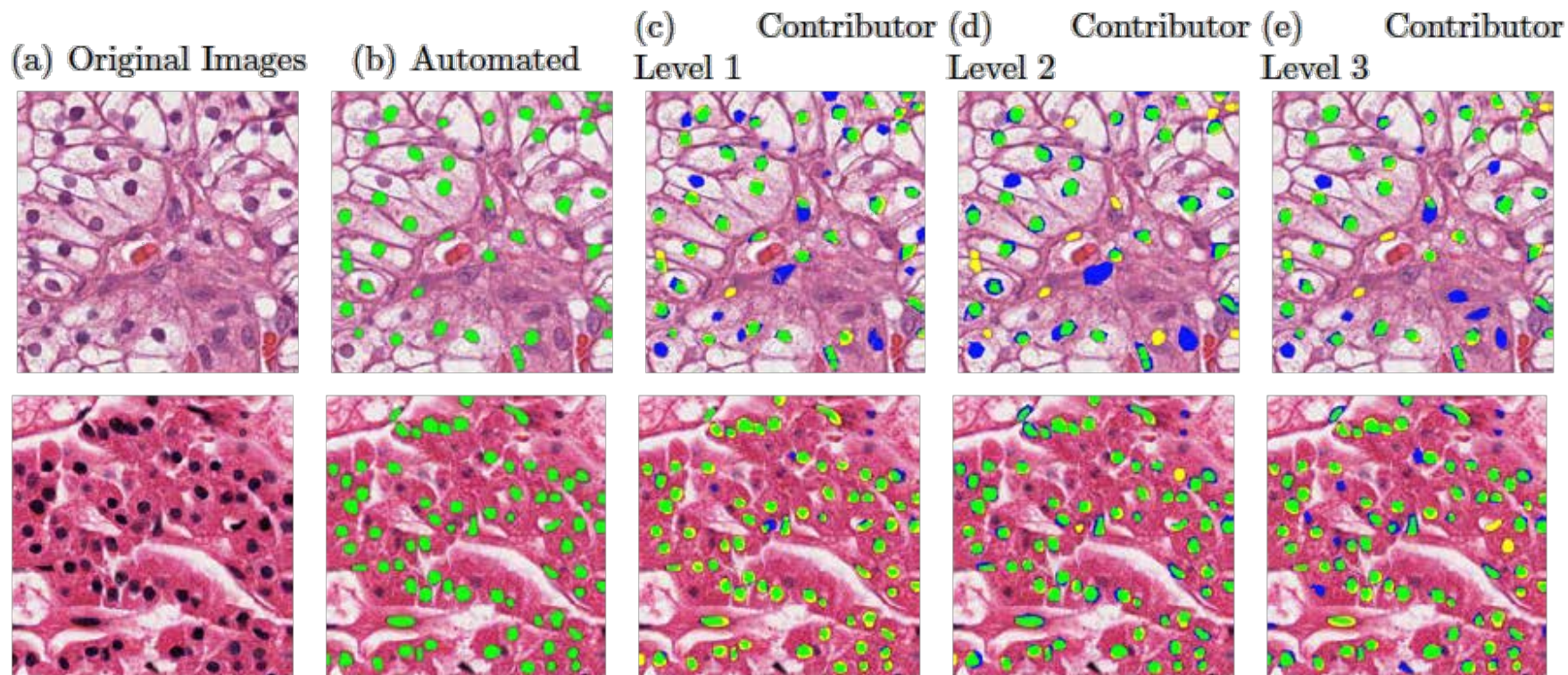
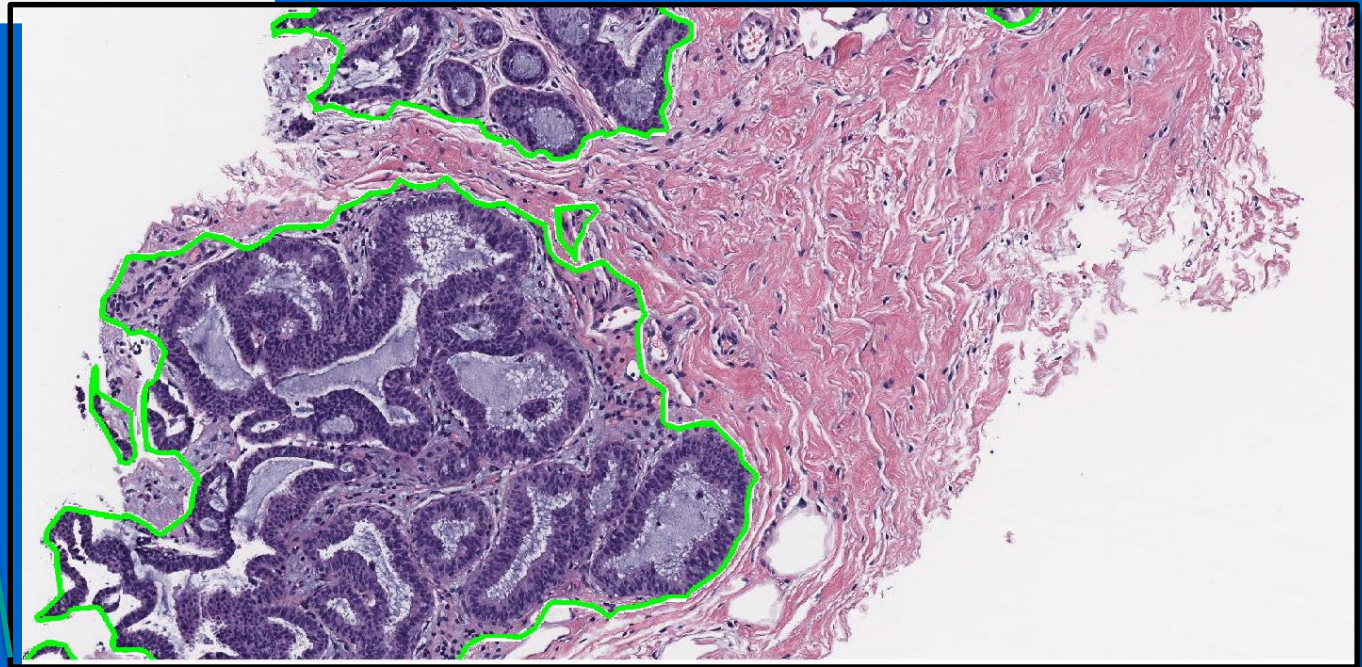
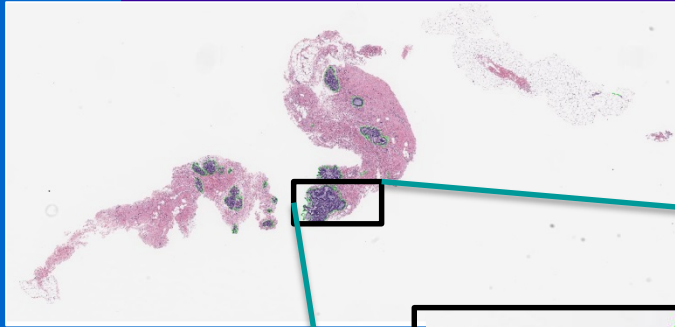
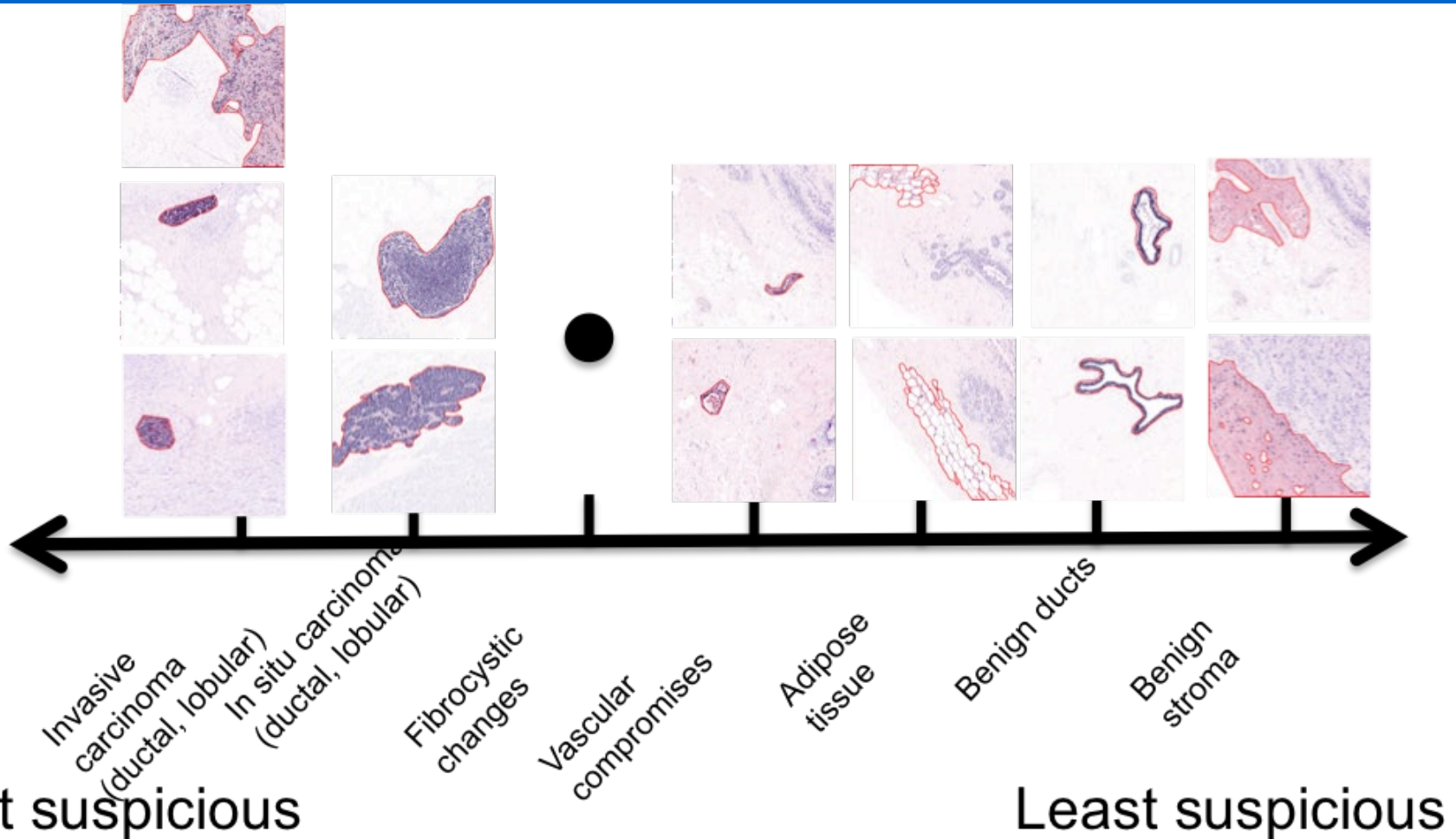


Fig. 2. Examples of nuclear segmentation using an automated method and increasing contributor skill level, ranging from 1 to 3. (Green region indicates TP region, yellow region indicates FN region and blue region indicates FP region). The automated nuclei segmentation used as ground truth.

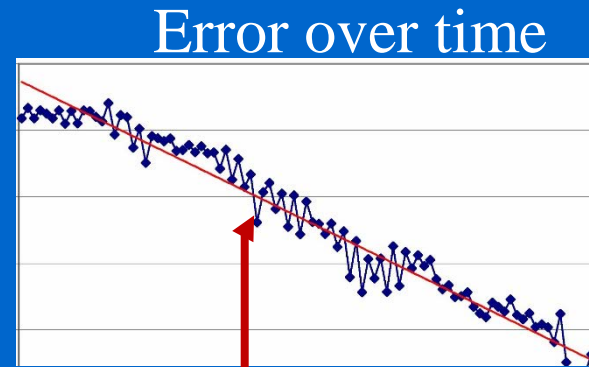
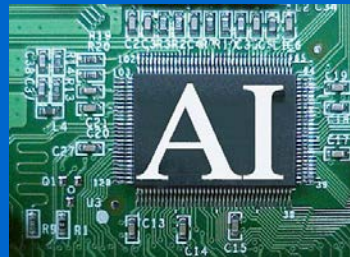
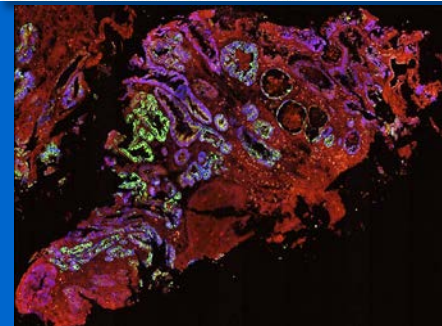
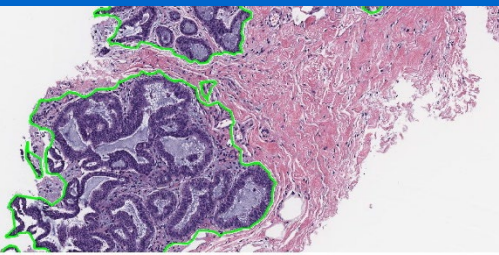
5. "Callable" ID of Histologic Features



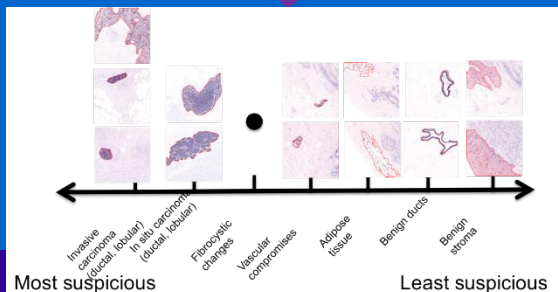
6. Triaging ROIs



7. Computational Pathology and AI



Intervention



Pathology and Radiology Must Partner!

A Joint Effort for Personalized Medicine

From Fuchs, 2017



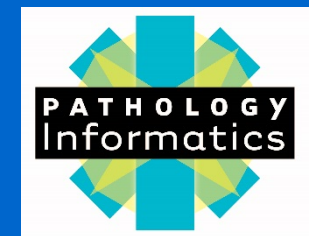


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-
- End of Talk – e-mail me at becich@pitt.edu if you have
- questions/clarifications not covered in the discussion.

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



**Thank you for organizing this
MCCP Workshop!**



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...”

Slide 27

The screenshot shows the website for the Association for Pathology Informatics (API). The header includes the API logo and the text "Association for Pathology Informatics". Below the header is a navigation menu with links for Home, Membership, Membership Benefits, Meetings, Journal, Awards, Training, Donate, Resources, Sponsors, Contact Us, and LIS Toolkit. The main content area is divided into several sections:

- Job Opportunities:** Fellowship Posts, Other Job Posts.
- 2015 Conference Diamond Level Sponsor:** sunquest.
- Corporate Sponsors:** Cerner, General Data, HAMAMATSU, Leica, BIOSYSTEMS, omnyx.
- Pathology Informatics Summit - May 5 - 8, 2015 in Pittsburgh:** ALL ONLINE REGISTRATION ENDS WEDNESDAY, APRIL 29, 2015. Register now: <http://pathologyinformatics.com/content/registration>. Deadline for reservations at the meeting discount is Monday, April 20, 2015. Make your reservations at the Wyndham here. 2015 Schedule: <http://www.pathologyinformatics.com/content/pathology-informatics-summit-2015-schedule>. A PDF link is provided: "Click here for the PDF."
- New Webinar: Digital Pathology Meets Surgical Pathology:** The Association for Pathology Informatics (API) and Sunquest Information Systems sponsored a webinar titled, "Digital Pathology Meets Surgical Pathology" on Thursday, March 5, 2015, at 1 PM EDT/10 AM PDT, presented by Stephen M. Hewitt, MD, PhD, FCAP, FASCP, Clinical Investigator in the Laboratory of Pathology, Center for Cancer Research, National Cancer Institute. View the Webinar.
- New Webinar: 10 Years of Direct Access Genetics: What Have We Learned?:** The Association for Pathology Informatics (API) and Sunquest Information Systems sponsored a webinar titled, "10 Years of Direct Access Genetics: What Have We Learned?" on Thursday, February 19, 2015, at 12 PM EDT/9 AM PDT, presented by Jill Hagenkord, MD, FCAP, Chief Medical Officer of 23andMe.
- Teaching Institution Sponsors:** EINSTEIN (Albert Einstein College of Medicine of Yeshiva University), Beth Israel Deaconess Medical Center, Cleveland Clinic, COLUMBIA UNIVERSITY (IN THE CITY OF NEW YORK), DALHOUSIE UNIVERSITY (Inspiring Minds), Duke University School of Medicine, EMORY UNIVERSITY (Department of Biomedical Informatics Emory University School of Medicine), EMORY UNIVERSITY SCHOOL OF MEDICINE, Henry Ford HEALTH SYSTEM, Icahn School of Medicine at Mount Sinai, ROBERT WOOD JOHNSON MEDICAL SCHOOL.

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!!!



The screenshot shows the homepage of the Journal of Pathology Informatics. At the top, there is a navigation bar with links for JOURNAL, EDITORIAL BOARD, BROWSE ARTICLES, INSTRUCTIONS, SUBMISSION, SUBSCRIBE, and ADVERTISE. Below this is a banner with the journal's title and a small image of a pathology slide. The main content area features a large URL: <http://www.jpathinformatics.org>. Below the URL, there is a section for "Latest published articles" with three entries. Each entry includes the article title, authors, a brief background, the journal issue information, and links to the abstract, full text, PDF, and Epub versions. The first article is "Distance reporting in digital pathology: A study on 950 cases" by Aleksandar Vodovnik. The second is "Imaging file management to support international telepathology" by Liron Pantanowitz et al. The third is "Default settings of computerized physician order entry system order sets drive ordering habits" by Jordan Olson et al. To the left of the articles, there is a "Submit your manuscripts to the journal" section with a list of benefits: Online submission, Wider visibility through open access, Higher impact with wider visibility, and Prompt review. Below this are buttons for "Submit article", "Follow us on Twitter", and "PubMed". At the bottom of the page, there is a footer with a sitemap, contact information, and various accreditation logos like Open Access, RoMEO, and W3C.

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Editorial and Ethics Policies

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Thanx to the Pitt team! SpIntellx™



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Lương Nguyễn



Maurice Marx



Dr. Om Choudhary



Dr. Filippo Pullara



Akash Parvatikar



Nathan Ong



Chakra



Alex Andonian



Tammy Ma

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

Drug Discovery Institute/CSB

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UPMC/Magee/Pathology

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Center for Commercial Applications of
Health Care Data/DBM

Dr. Michael Becich

Dr. Don Taylor

GE Global Research

Brion Sarachan

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Dr. Fiona Ginty

Magee-Womens Research Institute

Dr. Adrian Lee

Dr. Rekha Gyanchandani

CSB

Dr. Takis Benos

Dr. Dimitrios Manatakis

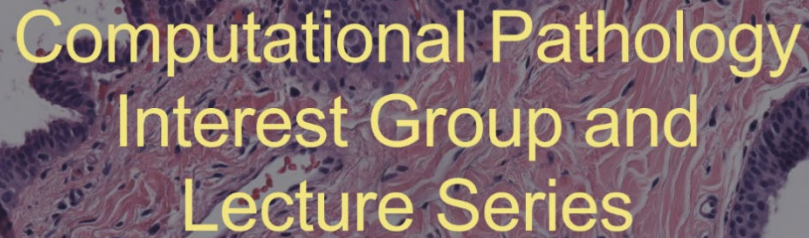
Dr. Joe Ayoub



Spatial Pathology Powers Precision Oncology

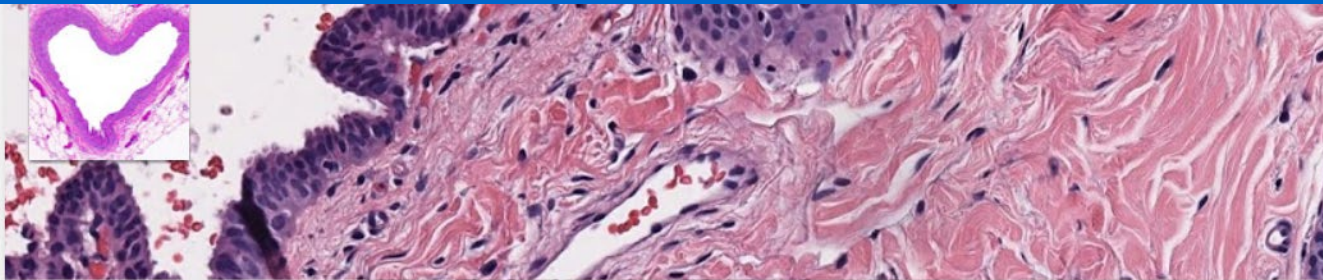
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Thank to Chakra Chennubhotla, PhD & Burak Tosun, PhD



Computational Pathology
Interest Group and
Lecture Series

<http://www.csb.pitt.edu/comppath/>
Youtube Channel for Lectures



Pittsburgh CompPath Lecture Series

Pittsburgh Computational Pathology Interest Group and Lecture Series is a special group formed to bring focus on developing basic compute... [Show more](#)

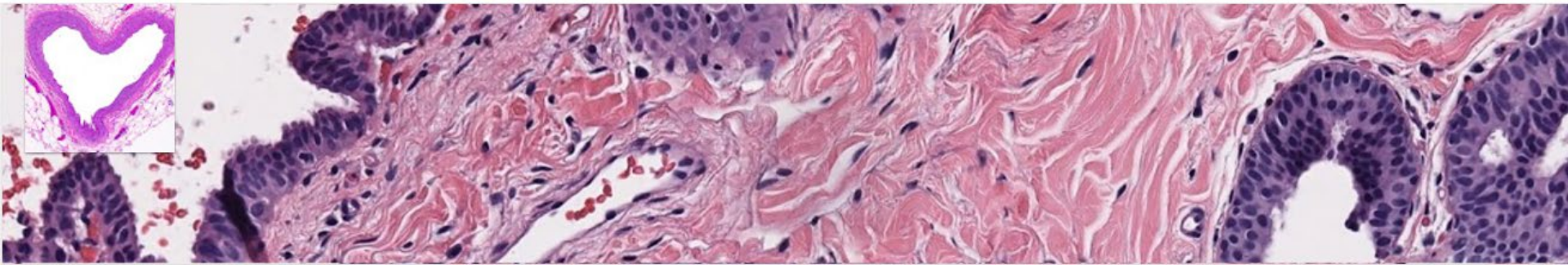
<https://www.youtube.com/watch?v=Xrvxc0YNcAM&feature=youtu.be>

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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 & Duquesne Universities



Pittsburgh Computational Pathology Lecture Series

Subscribe 32

Pittsburgh Computational Pathology Interest Group and Lecture Series aims to bring focus on developing basic computer vision and machine learning algorithms for transmitted light and fluorescence microscopy imaging data from histopathology and on highlighting the translation role of computational pathology research in interfacing with genomics, personalized medicine and microbiomics.

Our goal is to promote a vibrant community of computational pathology research and education practices here in Pittsburgh by engaging researchers and clinicians across Pitt, CMU and Duquesne campuses, and the local industrial partners.

<http://www.csb.pitt.edu/comppath/>
Show less

Uploads



Computational Pathology Interest Group and Lecture Series
52:07
CompPath Dr. Shikhar Uttam, Ph.D. Lecture (April 14th 2017)
21 views • 1 month ago



Computational Pathology Interest Group and Lecture Series
51:03
CompPath Dr. Shandong Wu, Ph.D. Lecture (March 14th 2017)
24 views • 1 month ago



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1:37:28
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