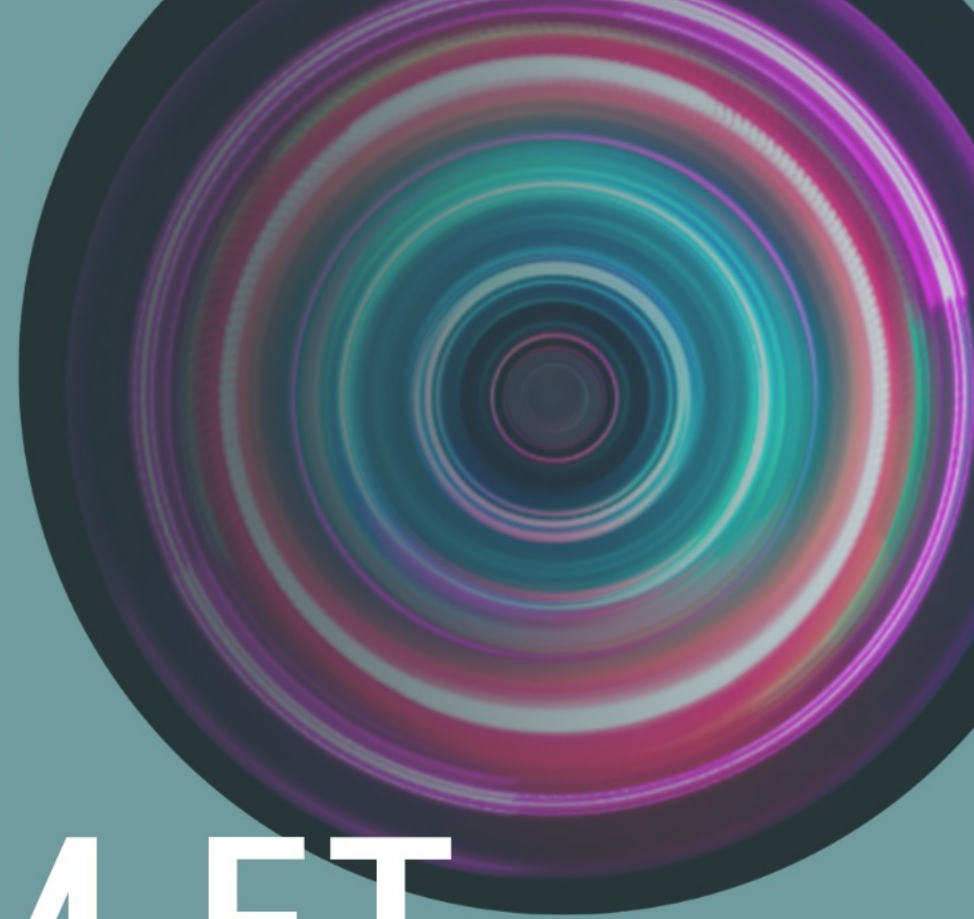


Meeting Summary Available

Monthly Steering
Committee Meetings

April 27
2022 3-4PM ET

Pathology Innovation Collaborative Community



Updates



CLINICAL LABORATORY IMPROVEMENT ADVISORY COMMITTEE

Virtual Meeting by Zoom webinar

Wednesday, April 13, 2022

Time (EDT)	Topic	Speaker/Moderator
11:00	Call to Order/Welcome	Dr. Valerie Ng Dr. Reynolds Salerno
	Recognition of New CDC Ex Officio Ms. Sarah Bennett	
11:20	Introductions/Conflict of Interest	Dr. Valerie Ng
11:30	CDC Update	1 Dr. Collette Fitzgerald
12:00	CMS Update	2 Ms. Sarah Bennett
12:30	FDA Update	3 Dr. Timothy Stenzel
1:00	Report: CDC OID Board of Scientific Counselors Meeting	4 Dr. Donna Wolk
1:30	BREAK (1 hour)	
	THE FUTURE OF LABORATORY MEDICINE IN NON-TRADITIONAL TESTING SITES	
2:30	Introduction to Topic	5 Dr. Collette Fitzgerald
2:40	Current and Future Applications of Point-of-Care Testing – The Industry Perspective	6 Dr. Michael Palm Dr. Norman Moore
3:00	Current and Future Applications of Point-of-Care Testing – The Laboratory Perspective	7 Dr. Sheldon Campbell
3:20	Digital Pathology: The Past, Present, and Future	8 Dr. Keith Kaplan
3:40	Culture Independent Diagnostic Testing Impact on Enteric Disease Surveillance	9 Dr. Heather Carleton 9a
4:00	Committee Discussion	Dr. Valerie Ng
4:50	Personnel Challenges in Non-traditional Testing Sites	10 Mr. Matthew Kossman
5:10	AACC Point-of-Care Testing (POCT) Certification Program	11 Dr. Scott Isbell
5:30	Committee Discussion	Dr. Valerie Ng
6:00	Adjourn	Dr. Valerie Ng

Numerous comments / submissions...
See website



Association for Pathology Informatics

4801 McKnight Road #1069, Pittsburgh PA 15237

www.pathologyinformatics.org

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April 5, 2022

Attention: CLIAC Secretariat
1600 Clifton Road NE
Mailstop V24-3
Atlanta, GA 30333

Dear CLIAC Members:

The Association for Pathology Informatics (API) appreciates this opportunity to provide comments to CLIAC concerning the regulation of remote digital review and reporting of pathology slides under CLIA. As the only national organization dedicated exclusively to pathology informatics, the API endeavors to play an active role in contemporary legal, ethical, social, and regulatory issues related to pathology informatics. It counts amongst its membership many world leaders in informatics and seeks to further its relationships with professional societies, industry, and regulatory partners with similar interests and goals.

In brief, the API requests that CLIAC recommend extending the current enforcement discretion beyond the end of the COVID-19 public health emergency (PHE) so that a primary clinical laboratory site does not need to obtain separate CLIA certificates or submit multiple CMS 116 forms for all of its affiliated remote sites where pathology slides are reviewed. The API recommends that enforcement discretion should continue until CLIA regulations can be amended to provide a permanent exemption for remote review of pathology slides via digital pathology (i.e. telepathology).

Clinical Laboratory Improvement Amendments of 1988 (CLIA) regulations mandate that all laboratory testing is performed on the premises of a CLIA-certified laboratory. Such testing includes the review and reporting of glass pathology slides. To comply with CLIA regulations, pathologists who wish to review and sign out cases with glass slides remotely (e.g. in their home) need a separate CLIA certificate for each additional permanent site. Alternatively, a temporary site exception indicated on Form 116 might be used for non-permanent off-site testing. Until recently, reviewing cases at remote sites was rare given the physical nature of glass slides, but the recent emergence of digital pathology has renewed interest in remote pathology slide review and case reporting (i.e. "signout").

In November 2019, the mindset of on-site physicality being a necessity of practice started to shift. CLIAC recognized that access to a LIS in a secure environment is the same, whether via a workstation inside a CLIA-certified facility or via a remotely-connected workstation. CLIAC recommended that the CLIA program "consider that, when laboratory professionals provide patient care through selection, interpretation, and reporting of patient results by accessing data remotely in a secure environment, they get deemed as performing those services at the primary site housing the CLIA Certificate." [1]


CLIAC Meeting: Tim Stenzel

PowerPoint Slide Show - 3_FDA Update - CLIAC April 2022.FINAL - PowerPoint

General

Tim Stenzel, FDA

Collaborative Communities with CDRH Participation



- Collaborative Community on Ophthalmic Imaging
- National Evaluation System for health Technology Coordinating Center (NESTcc) Collaborative Community
- Standardizing Laboratory Practices in Pharmacogenomics Initiative (STRIPE) Collaborative Community
- International Liquid Biopsy Standardization Alliance (ILSA)
- Xavier Artificial Intelligence (AI) World Consortium
- Case for Quality Collaborative Community
- Heart Valve Collaboratory (HVC)
- Wound Care Collaborative Community
- Pathology Innovation Collaborative Community (PICC)
- RESCUE (REducing SuiCide Rates Amongst IndividUals with DiabEtes) Collaborative Community)
- MedTech Color Collaborative Community
- Digital Health Measurement Collaborative Community (DATAcc)

5

Chat Raise Hand

PowerPoint Slide Show - 3_FDA Update - CLIAC April 2022.FINAL - PowerPoint

General

Tim Stenzel, FDA

Collaborative Communities: Addressing Health Care Challenges Together



*A **collaborative community** is a continuing forum in which private- and public-sector members, which can include the FDA, work together on medical device challenges to achieve common objectives and outcomes*

4

Chat Raise Hand

CLIAC Meeting

Keith Kaplan
presented “Digital
Pathology: The Past,
Present, and Future”

Keith J Kaplan MD

Recording

Predicted Pathologist Shortage

The diagram illustrates the components of a predicted pathologist shortage. It starts with a cylinder labeled "Demand Year X" on the left. This leads to a series of four boxes, each representing a factor that increases demand:

- Growth of Population:** A box showing a circle increasing in size from "Year X" to "Year X + 1".
- Change in Age and Gender Composition of Population:** A box showing two pie charts. The first pie chart is divided into "Age" and "Gender" (Female/Male) for "Year X". The second pie chart shows a shift in these proportions for "Year X + 1".
- Change in Insurance Status of Population:** A box showing two pie charts. The first pie chart is divided into "Private", "Medicaid", "Medicare", and "Uninsured" for "Year X". The second pie chart shows a shift in these proportions for "Year X + 1".
- Change in Disease Incidence:** A box showing a bar chart where the height increases from "X%" at "Year X" to "Y%" at "Year X + 1".


Each of these four boxes is followed by a plus sign (+). The final result is a cylinder on the right labeled "Future Demand Year X+1".

Audio Settings ^ Chat Raise Hand Leave

Updates continued

- Reminder: CLIA-C waiver project – if interested please e-mail
- Decision summary PAIGE prostate
 - Collaboration with PAIGE regulatory team in progress
- Grand challenges discussion session took place on 4/25
- AACR New Orleans – brief review

Microsoft Teams channel

- Teams channel for Plcc established that enables direct file exchange with FDA 
- Project and workgroup progress GANTT chart to be created
 - Call for assistance from members with web-dev skills


3 layers of project organization

www.pathologyinnovationcc.org

Home About Working Groups News & Events Resources Projects Presentations Publications Join

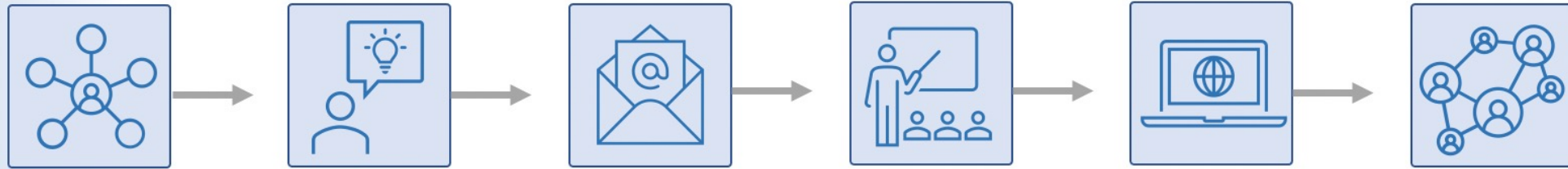
Working Groups. Projects. Presentations.

Concrete practical deliverables

 <p>Information Blocking</p>	 <p>Test Driving VALID2021</p>	 <p>Privacy Pilot Project P3</p>
 <p>SEER Cancer Microscope</p>	 <p>Ethics and Governance of Artificial Intelligence</p>	 <p>A regulatory science approach for morphology-based biomarkers in tissue sections</p>

Pathology Innovation Collaborative Community

The Alliance for Digital Pathology and AI/ML



You value
Collaborations

You have a
Regulatory
Science Project

You propose
your project
to Plcc

You present
to steering
committee

Plcc helps
organize the
project

Plcc is a network
to find interested
collaborators

Focus is NOT on
competitive
product development

Plcc does NOT
actively participate
in your project

Plcc is a collaborative community that provides
the infrastructure to connect stakeholders

What we (can) aim to deliver

- Guidance and Standards
- White papers (peer reviewed publication)
- Research agenda and projects
- Proposed regulation and proposed legislation
- Best practices and tool developments
- Culture change = paradigm shift in digital pathology

Value proposition

- Patient Impact
- Public health impact
- Improved patient services (access)
- Improved patient management (workflows)
- Improved diagnosis (quality)
- Improved diagnosis (quantity)
- Etc...

Current status of the CC

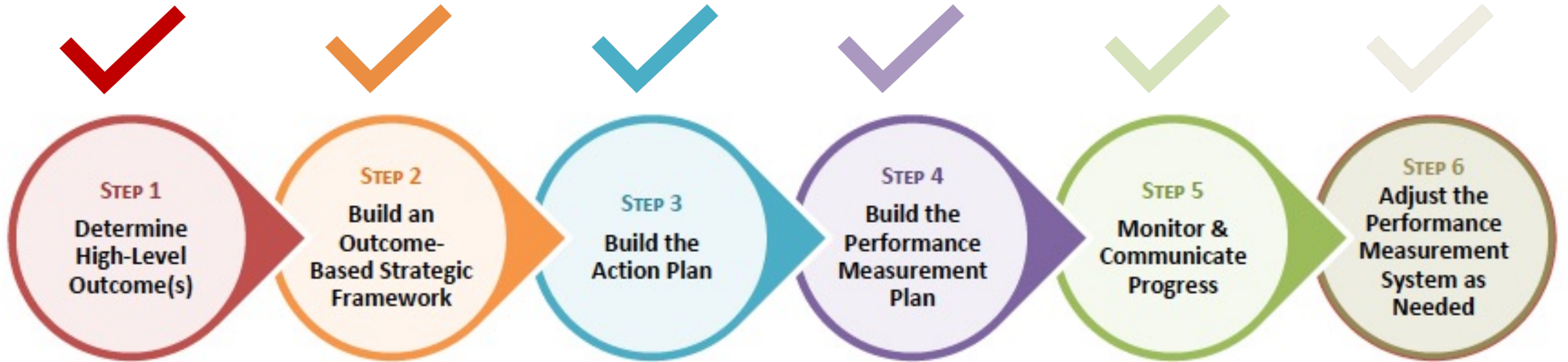


Figure 1. Process from Determining the High-Level Outcome to Implementing the Performance Management System.

Request for help

- Web developer with experience in interactive GANTT charts.

Patient Advocacy

Friends of Cancer Research

- FOCR Annual Report for 2021

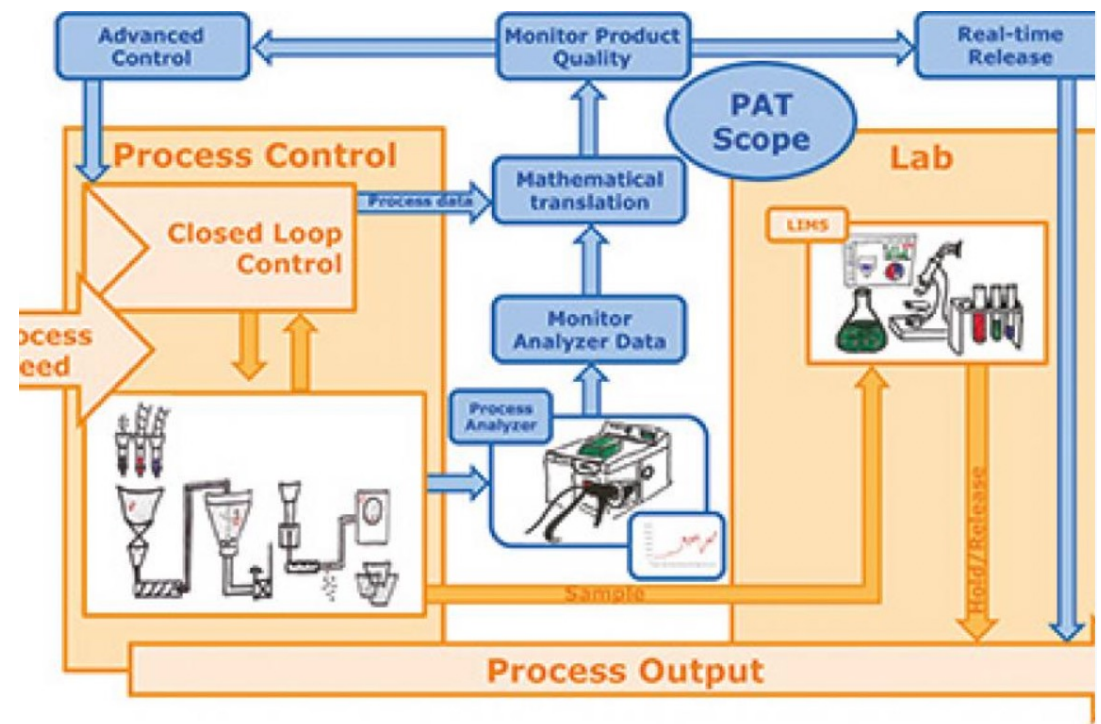


Patient
advocacy
collaborations

- APPIA protocol development (next meeting pending; interest => email join)
- Sepsis alliance (follow-up meeting)

EMA Corner
"Outside the box"

ICH guideline Q14: Intended for analytical procedure development



ICH guideline Q14: Intended for analytical procedure development



31 March 2022
EMA/CHMP/ICH/195040/2022
Committee for Medicinal Products for Human Use

ICH Q14 Guideline

ICH guideline Q14 on analytical procedure development Step 2b

Transmission to CHMP	8 March 2022
Adoption by CHMP	24 March 2022
Release for public consultation	31 March 2022
Deadline for comments	31 July 2022

Comments should be provided using this [template](#). The completed comments form should be sent to ich@ema.europa.eu

43 In certain cases, an established analytical procedure can be applied to multiple products with little or
44 no modification of measurement conditions. For a new application of such *platform analytical*
45 *procedures*, the subsequent development can be abbreviated, and certain *validation tests* can be
46 omitted based on a science- and risk-based justification. Details of the performance characteristics
47 considered for analytical procedure validation are described in *ICH Q2*.

48 In general, data gained during the development studies (e.g., robustness data from a design of
49 experiments (DoE study)) can be used as validation data for the related analytical procedure
50 performance characteristics and does not necessarily need to be repeated.

51

ICH guideline Q14: Intended for analytical procedure development



ICH Q14 Guideline

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49 experiments (DoE study)) can be used as validation data for the related analytical procedure
50 performance characteristics and does not necessarily need to be repeated.

Figure 1: The Analytical Procedure Lifecycle

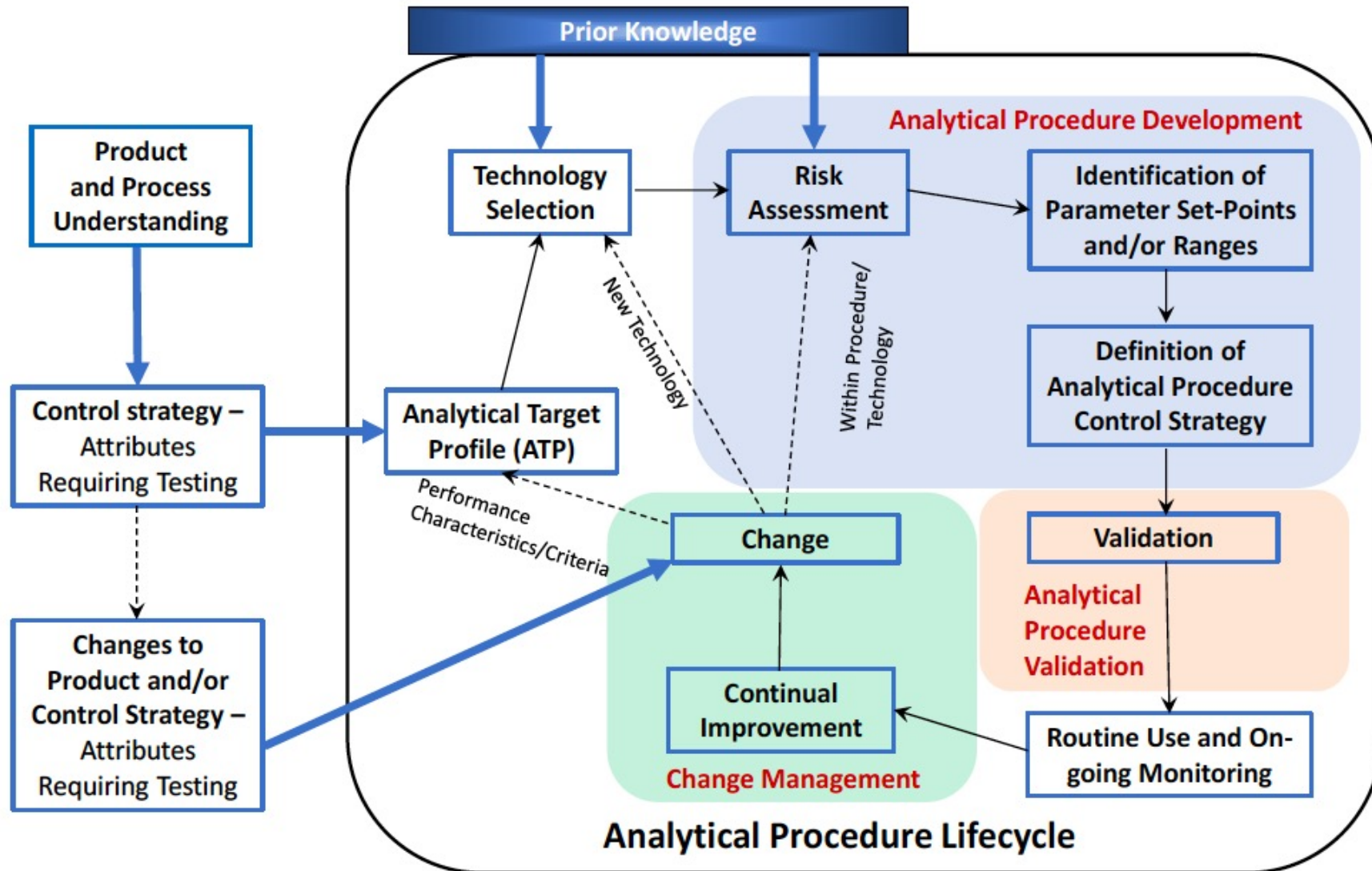






Table 1: Relationship between knowledge, risk and extent of studies for changes to analytical procedures

Knowledge 	Risk associated with the change	
	Low	High
		
		
	Confirmatory study according to previously defined protocol or prior knowledge	In depth study according to previously defined protocol
		
	Confirmatory study including study design	In depth evaluation including study design

FDA

New guidance for certain products between “drug” and “device”

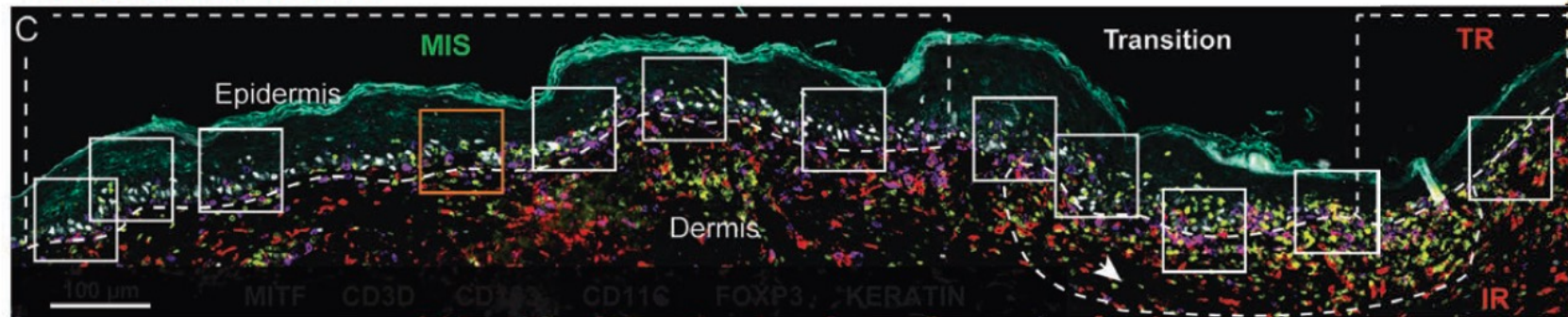
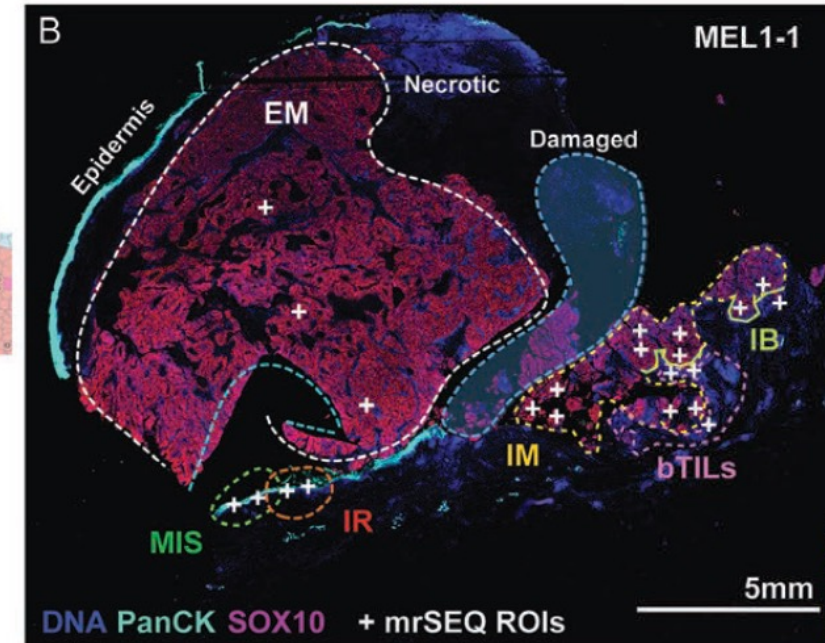
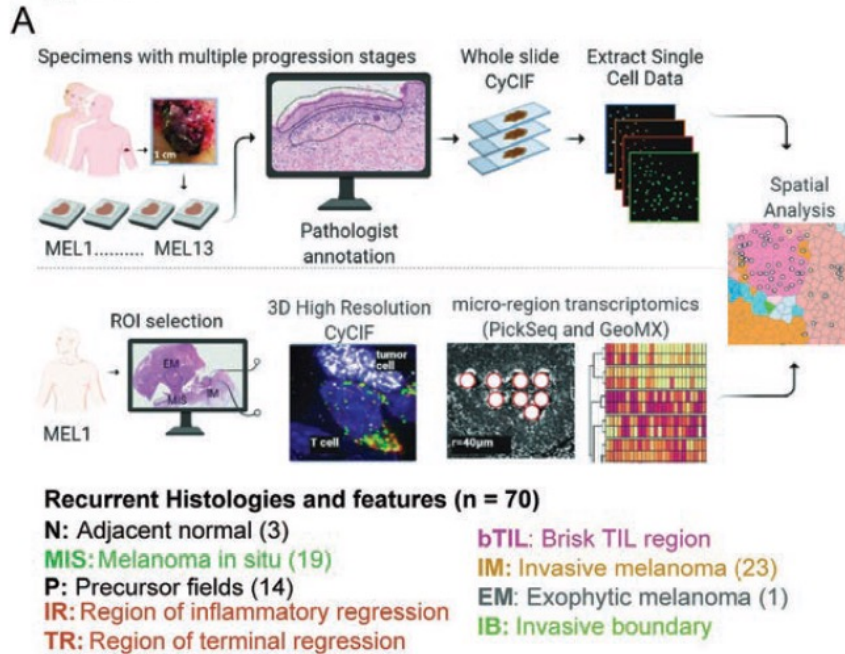
Certain Ophthalmic Products: Policy Regarding Compliance With 21 CFR Part 4 Guidance for Industry

On April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit issued its decision in *Genus Medical Technologies LLC v. U.S. Food and Drug Administration*, 994 F.3d 631 (D.C. Cir. 2021). The *Genus* court stated “[e]xcepting combination products, . . . devices must be regulated as devices and drugs — if they do not also satisfy the device definition — must be regulated as drugs.”³ In implementing this decision, FDA has determined that the language in § 200.50(c) indicating that ophthalmic dispensers are regulated as drugs when packaged with ophthalmic drugs is now obsolete, because these articles meet the *device* definition. Therefore, FDA intends to regulate these products as drug-led combination products composed of a drug constituent part that provides the primary mode of action and a device constituent part (an ophthalmic dispenser). Because the drug constituent part provides the primary mode of action, generally the Center for Drug Evaluation and Research (CDER) will have primary jurisdiction over these products.⁴

Papers

Nirmal et al., The spatial landscape of immunoediting in primary melanoma at single cell resolution

Figure 1





Article

Tissue schematics map the specialization of immune tissue motifs and their appropriation by tumors

Salil S. Bhate,^{1,2,3,6} Graham L. Barlow,^{1,2,4,6} Christian M. Schürch,^{1,2,5} and Garry P. Nolan^{1,2,7,*}

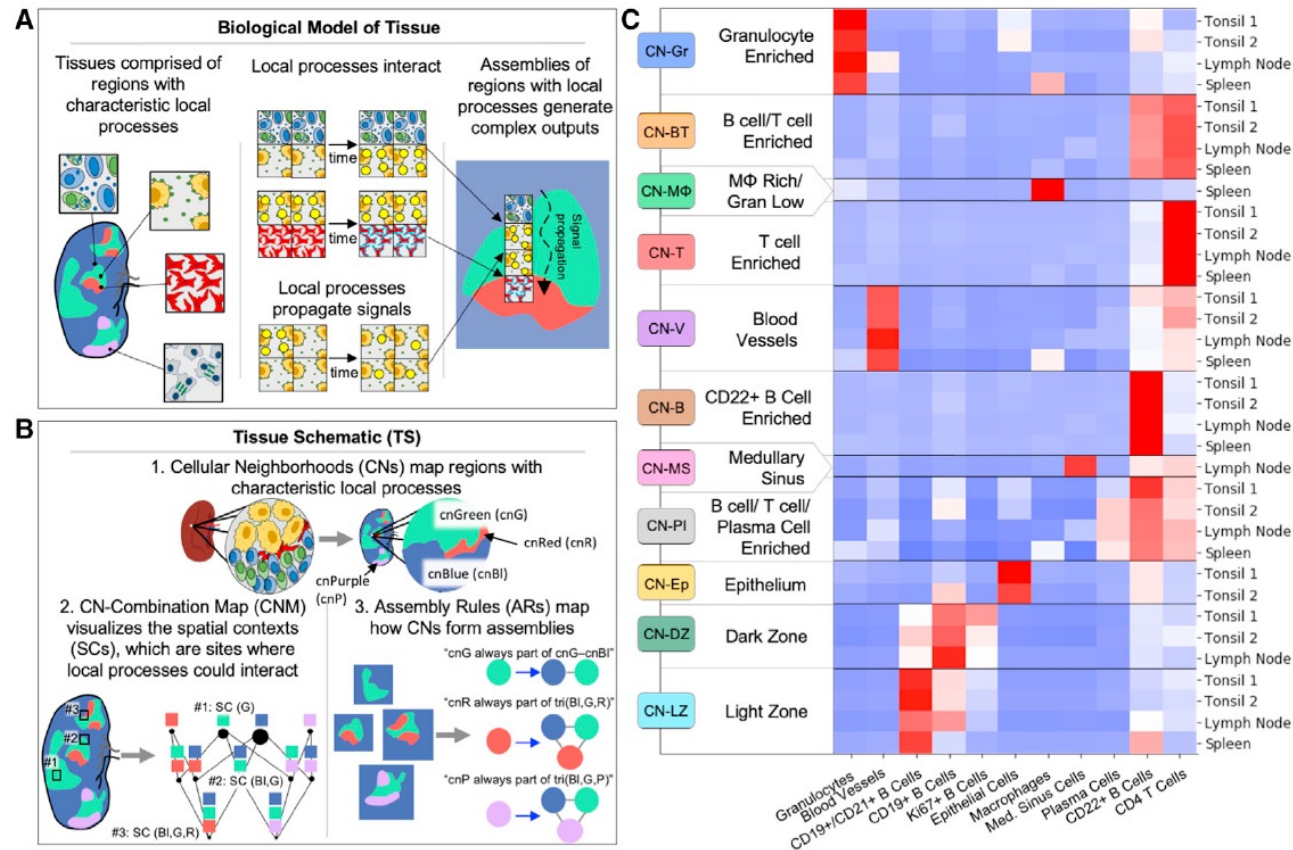


Table 1. Examples of digital biomarkers from published literature.

Biomarker category	BEST definition	Digital biomarker example
Diagnostic biomarker	A biomarker used to detect or confirm the presence of a disease or condition of interest or to identify individuals with a subtype of the disease ¹	An algorithmic classification of cardiovascular features extracted from optical sensors on wearable devices to identify atrial fibrillation ⁵
Pharmaco-dynamic/ response biomarker	A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent ¹	A wrist-worn DHT may collect accelerometer data and use the data to detect physiological changes (for e.g., tremor and bradykinesia) in response to a pharmacological agent. Mahadevan et al. studied its utility in assessing the response to levodopa in patients with Parkinson's disease ⁶
Monitoring biomarker	A biomarker measured repeatedly for assessing the status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent ¹	An accelerometer-based sensor device that collects data about chest and limb movement to measure gait in patients with Huntington's Disease ⁷

Vasudevan et al., Digital biomarkers: Convergence of digital health technologies and biomarkers



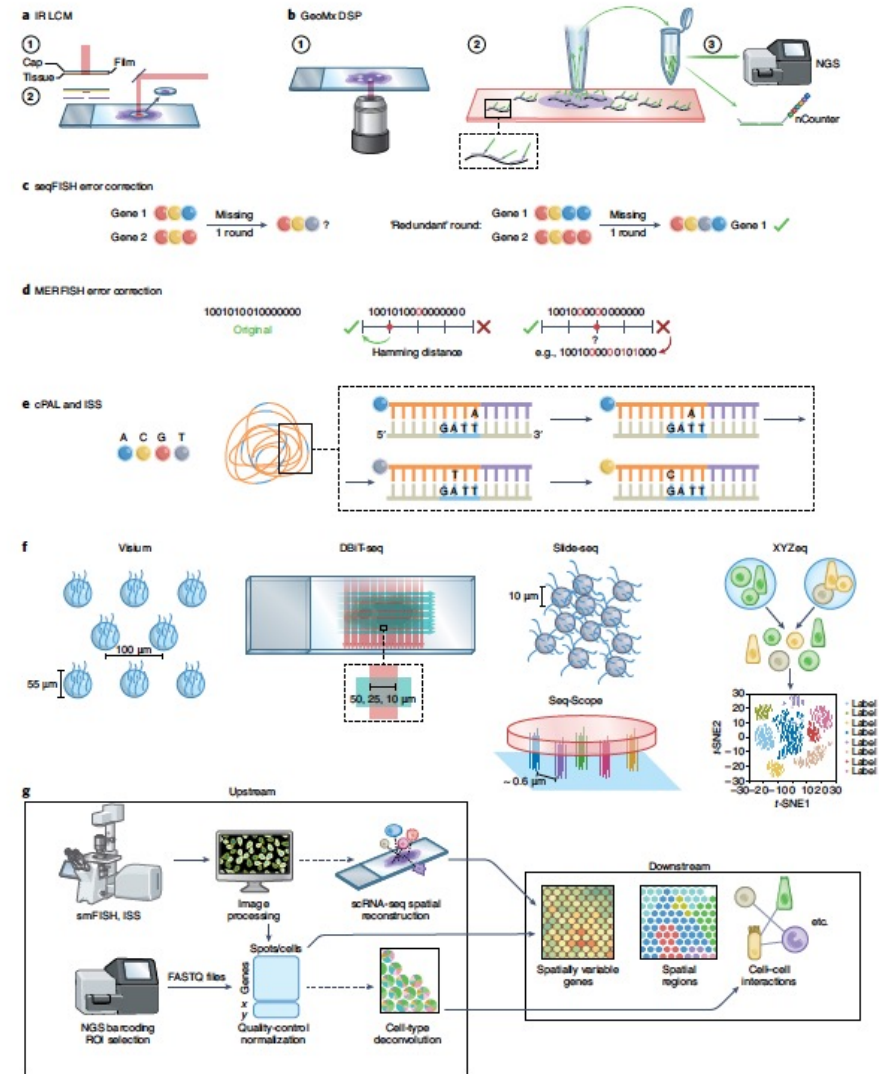
Museum of spatial transcriptomics

Lambda Moses¹ and Lior Pachter^{1,2} ✉

The function of many biological systems, such as embryos, liver lobules, intestinal villi, and tumors, depends on the spatial organization of their cells. In the past decade, high-throughput technologies have been developed to quantify gene expression in space, and computational methods have been developed that leverage spatial gene expression data to identify genes with spatial patterns and to delineate neighborhoods within tissues. To comprehensively document spatial gene expression technologies and data-analysis methods, we present a curated review of literature on spatial transcriptomics dating back to 1987 along with a thorough analysis of trends in the field, such as usage of experimental techniques, species, tissues studied, and computational approaches used. Our Review places current methods in a historical context, and we derive insights about the field that can guide current research strategies. A companion supplement offers a more detailed look at the technologies and methods analyzed: https://pachterlab.github.io/LP_2021/.

without transgenic mice is spatially photoactivatable color encoded cellular address tags (SPACECAT)⁴², which stains cultured live cells or organoids with photocaged fluorophores and photoactivates ROIs for FACS and scRNA-seq. Also using photocaging, ZipSeq⁴³ attaches anchor oligonucleotides with photocaged overhangs to tissue with

antibodies or lipid insertion, and adds spatial 'zipcodes' to photoactivated ROIs hybridizing to the overhangs. A more popular commercial optical ROI-selection technique is the GeoMX Digital Spatial Profiler (DSP)⁴⁴ and whole-transcriptome atlas (WTA)⁴⁵ of Nanostring (Fig. 2b), which shines UV light on ROIs to release photo-cleavable



Nurk et al., Complete sequence of the human genome (3/31/2022)

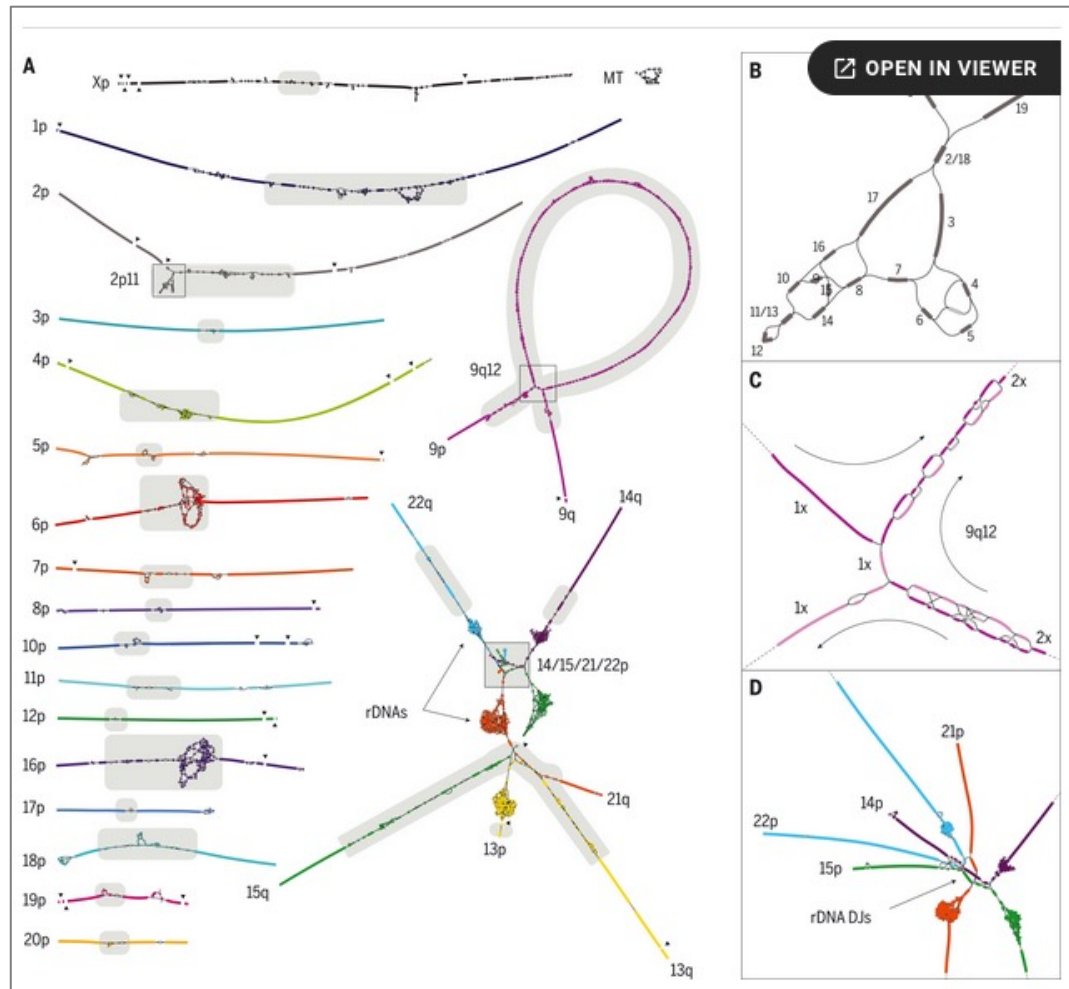


FIG. 2. High-resolution assembly string graph of the CHM13 genome.

(**A**) Bandage (60) visualization, where nodes represent unambiguously assembled sequences scaled by length and edges correspond to the overlaps between node sequences. Each chromosome is both colored and numbered on the short (p) arm. Long (q) arms are labeled where unclear. The five acrocentric chromosomes (bottom right) are connected owing to similarity between their short arms, and the rDNA arrays form five dense tangles because of their high copy number. The graph is partially fragmented because of HiFi coverage dropout surrounding GA-rich sequence (black triangles). Centromeric satellites (30) are the source of most ambiguity in the graph (gray highlights). MT, mitochondria. (**B**) The ONT-assisted graph traversal for the 2p11 locus is given by numerical order. Based on low depth of coverage, the unlabeled light gray node represents an artifact or heterozygous variant and was not used. (**C**) The multimegabase tandem HSat3 duplication (9qh+) at 9q12 requires two traversals of the large loop structure. (The size of the loop is exaggerated because graph edges are of constant size.) Nodes used by the first traversal are in dark purple, and nodes used by the second traversal are in light purple. Nodes used by both traversals typically have twice the sequencing coverage. (**D**) Enlargement of the distal short arms of the acrocentrics, showing the colored graph walks and edges between highly similar sequences in the distal junctions (DJs) adjacent to the rDNA arrays.

Resources

HAL: Nicolas Rougier, Scientific
Visualization

Python ML

Report 2022: Clinician of the Future

Bruce Quinn 2022: Cancer Patient
and Access to Molecular Diagnostics

Python ML



Example

Predict the speed of a car passing at 17 P.M:

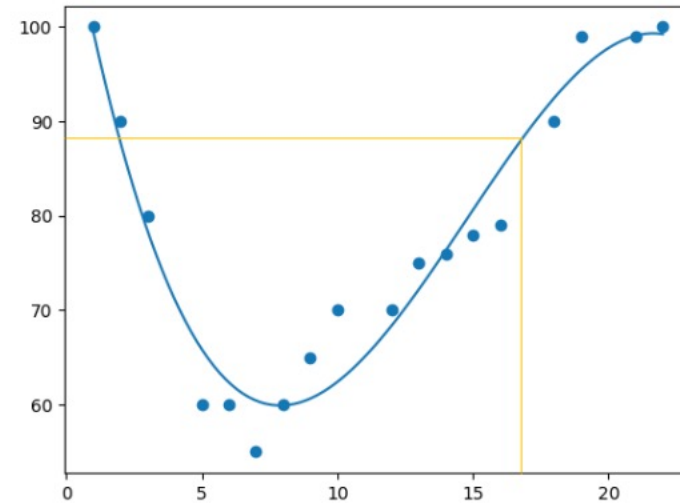
```
import numpy
from sklearn.metrics import r2_score

x = [1, 2, 3, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 18, 19, 21, 22]
y = [100, 90, 80, 60, 60, 55, 60, 65, 70, 70, 75, 76, 78, 79, 90, 99, 99, 100]

mymodel = numpy.poly1d(numpy.polyfit(x, y, 3))

speed = mymodel(17)
print(speed)
```

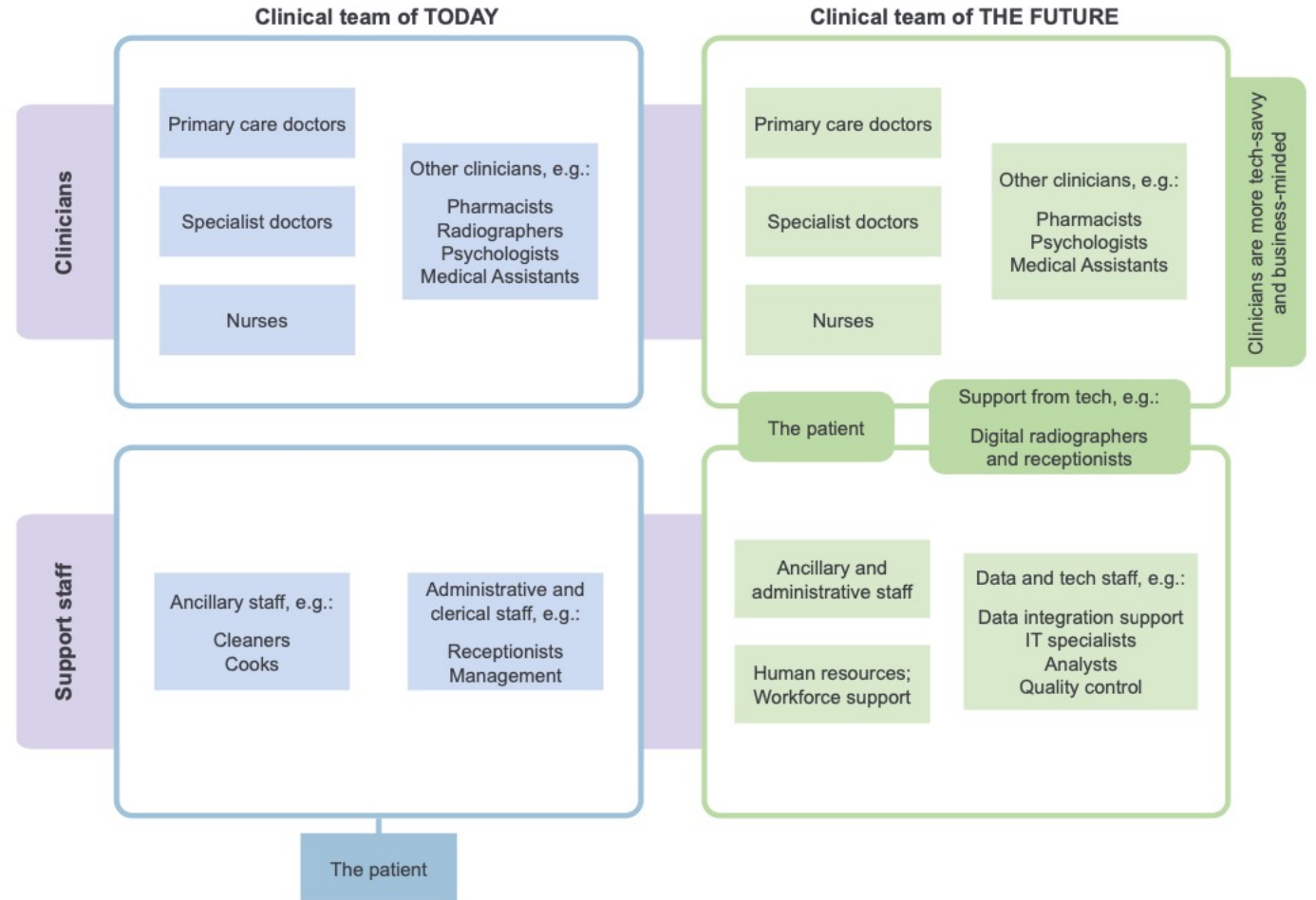
The example predicted a speed to be 88.87, which we also could read from the diagram:



Bad Fit?

Let us create an example where polynomial regression would not be the best method to predict future values.

Report 2022: Clinician of the Future



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MADE REAL.

Cancer Patients and Access to Molecular Diagnostics

Understanding the Transition Toward Comprehensive
Genomic Profiling and Tumor Mutation Burden Testing

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LOS ANGELES | SAN FRANCISCO

April 2022

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3

The Coding and Reimbursement
System for CGP and TMB

HAL: Nicolas Rougier, Scientific Visualization



Scientific Visualization: Python + Matplotlib
Nicolas Rougier

The Python scientific visualisation landscape is huge (see figure 1). It is composed of a myriad of tools, ranging from the most versatile and widely used down to the more specialised and confidential. Some of these tools are community based while others are developed by companies. Some are made specifically for the web, others are for the desktop only, some deal with 3D and large data, while others target flawless 2D rendering.

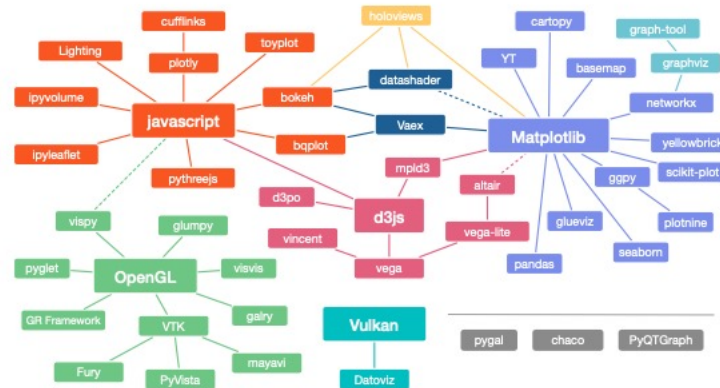


Figure 1
Python scientific visualisation landscape in 2018 (not exhaustive). Adapted from the original idea of Jake Vanderplas. Sources: github.com/rougier/python-visualization-landscape

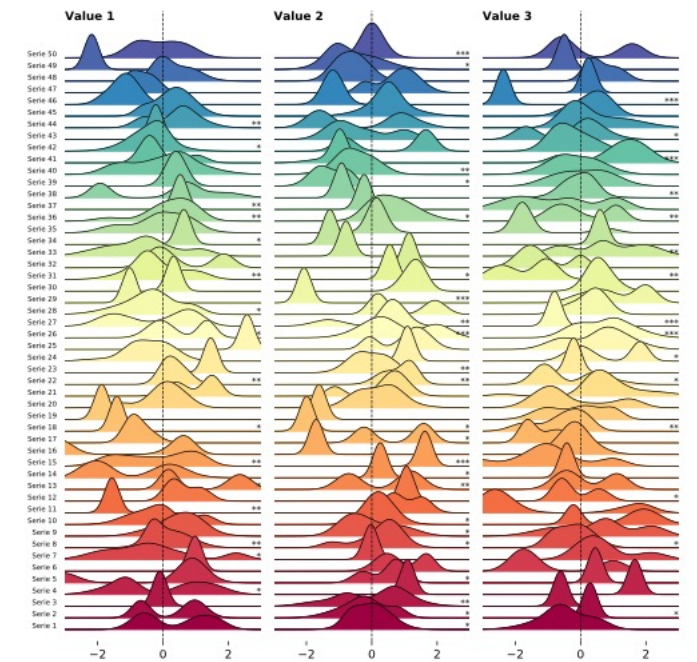


Figure 1.10
Multiple plots partially covering each other (solution: [anatomy/zorder-plots.py](https://github.com/anatomy/zorder-plots.py))

News & Events

Pathology
Informatics
Summit 2022

Innovate Connect Inspire

May 9-12, 2022

Pittsburgh, PA

David L. Lawrence Convention Center

Brought to you by the Association for Pathology Informatics.

Join top thought-leaders and immerse yourself
in rapidly evolving topics essential to clinical
laboratory and anatomic pathology informatics.

PATHML

An open-source software
toolkit for computational
pathology research

Presented by Renato Umeiron, PhD &
Jacob Rosenthal, MSc

Monday, June 6, 2022

10:00-11:00 AM Eastern Time



2022 ASCO
ANNUAL MEETING

Exhibitors Media Attendee Policies Group Leaders

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Early Registration Ends April 27

After two years of joining from your home or office, it's time to step out
from behind those webcams, dust off your business attire, and put on
your most comfortable shoes because we are ready and excited to
welcome attendees back in person in Chicago.

REGISTER NOW →



Thank you

See you next
month

Monthly Steering
Committee Meetings

May 25
2022 3-4PM ET

Pathology Innovation Collaborative Community

