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 9a	Dr. Heather Carleton
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

April 5, 2022

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

Dear CLIAC Members:

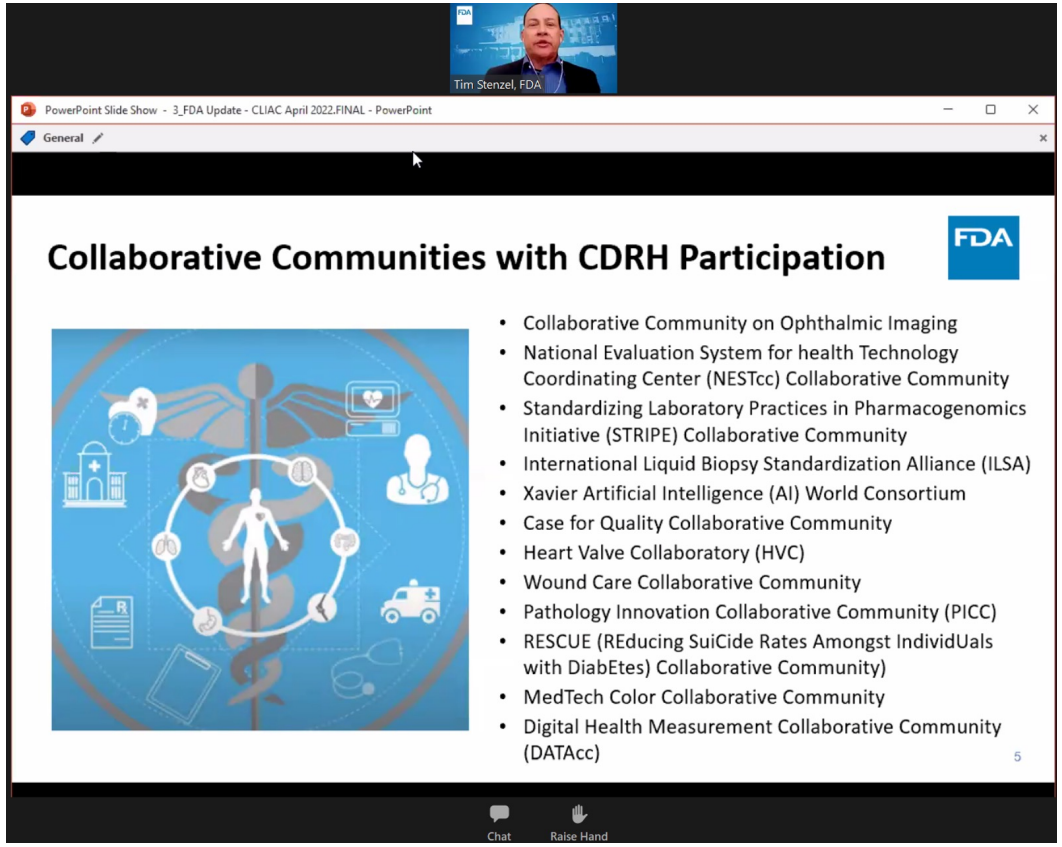
The Association for Pathology Informatics (API) appreciates this opportunity to provide comments to CLIAC concerning the regulation of remote digital review and reporting of pathology slides under CLIA. As the only national organization dedicated exclusively to pathology informatics, the API endeavors 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.

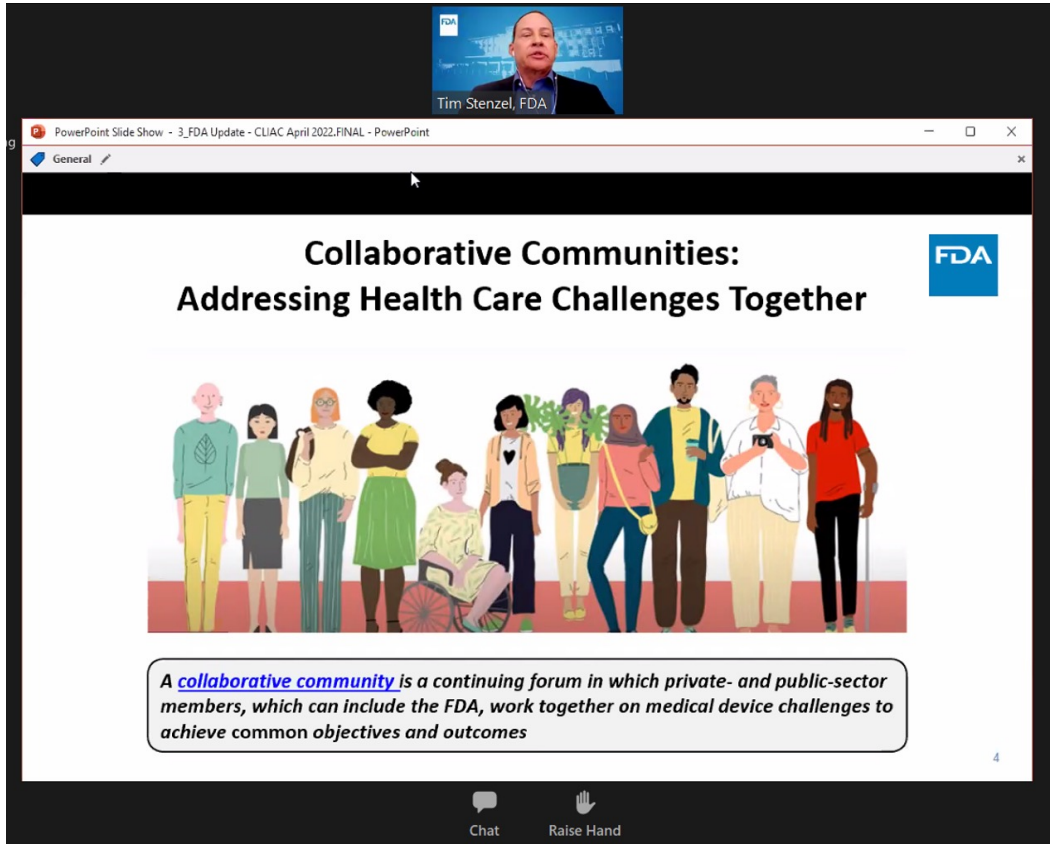
In brief, the API requests that CLIAC recommend extending the current enforcement discretion beyond the end of the COVID-19 public health emergency (PHE) so that a primary clinical laboratory site does not need to obtain separate CLIA certificates or submit multiple CMS 116 forms for all of its affiliated 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]

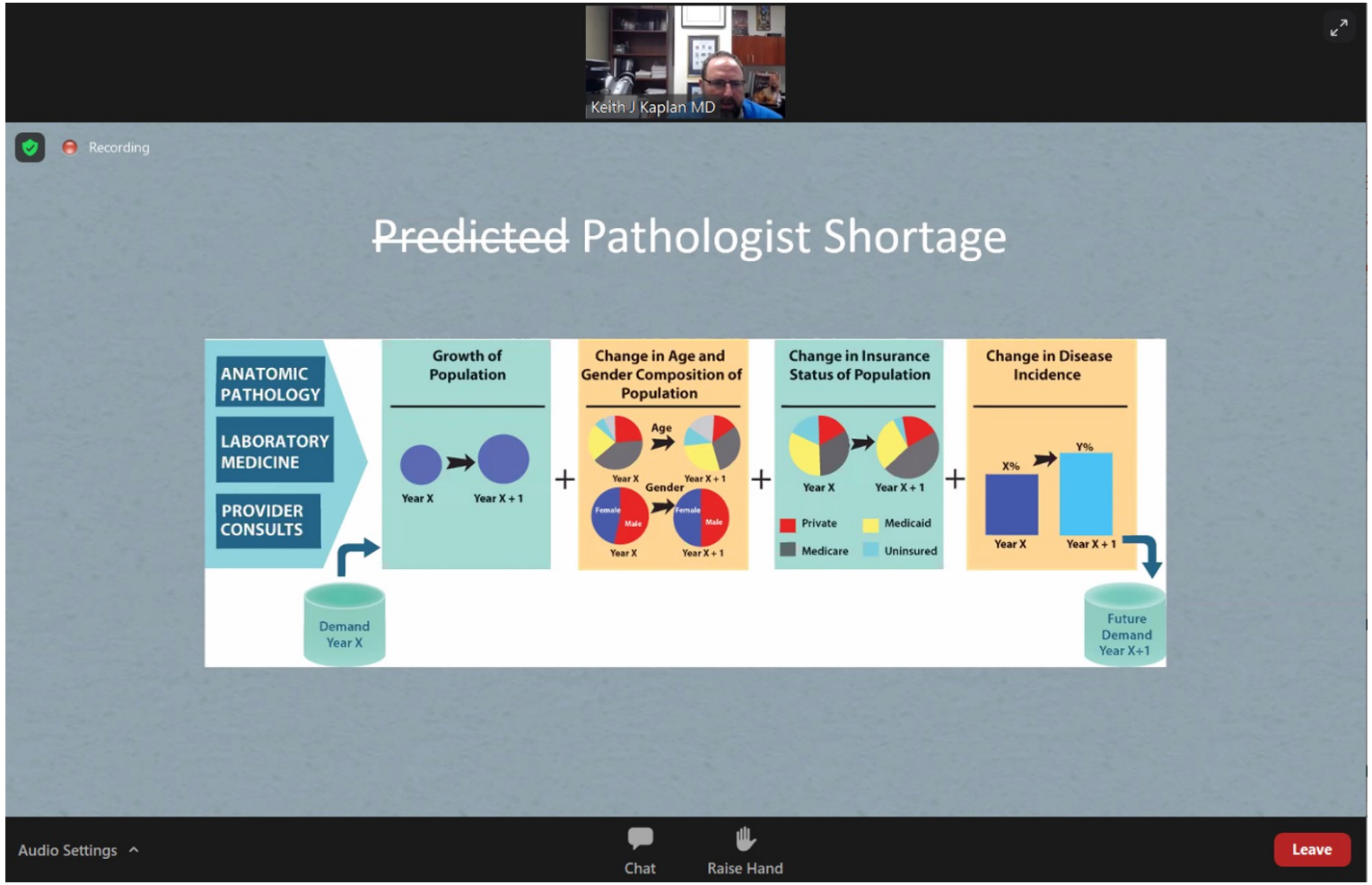
CLIAC Meeting: Tim Stenzel





CLIAC Meeting

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



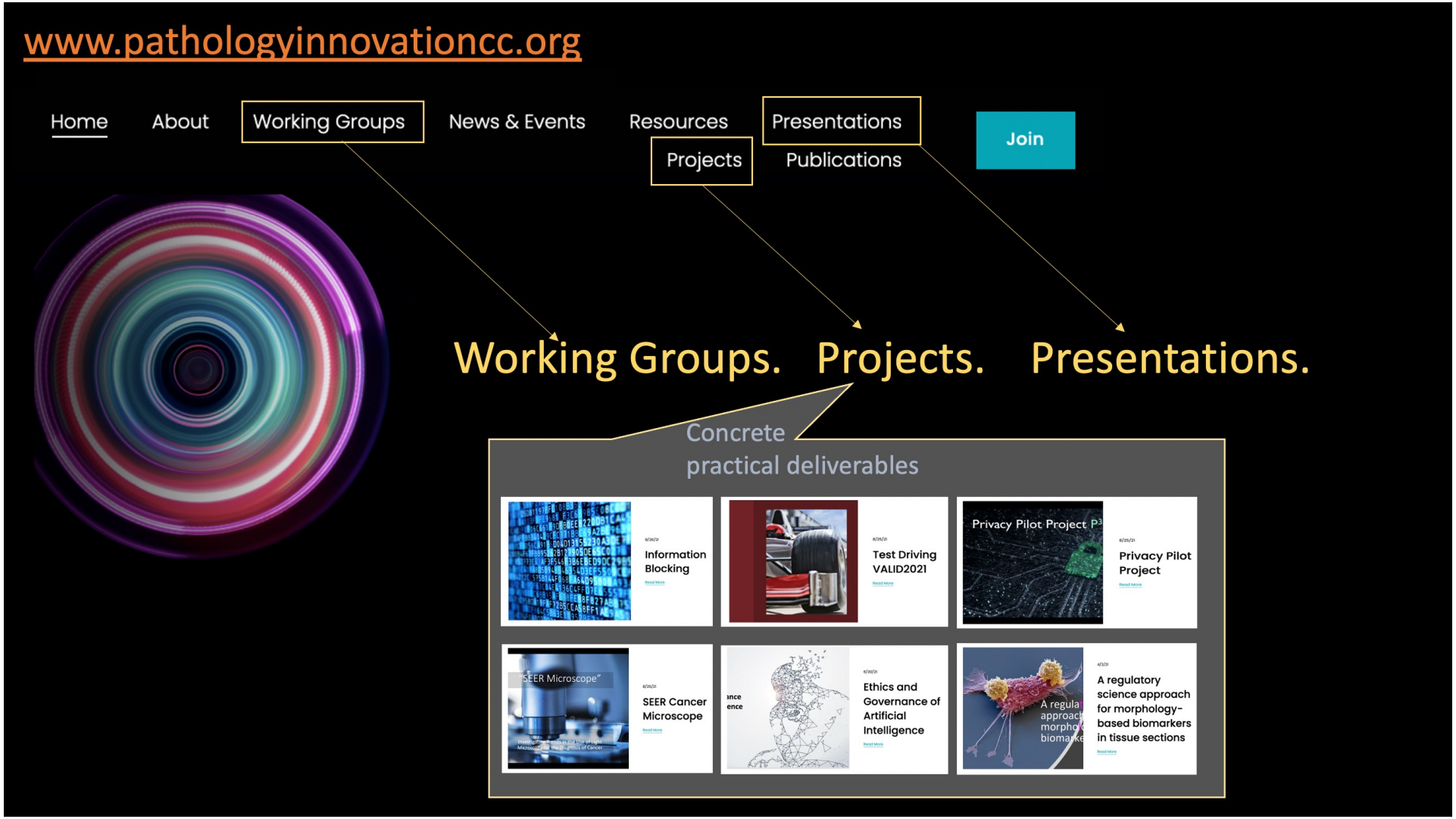
Updates continued

- 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

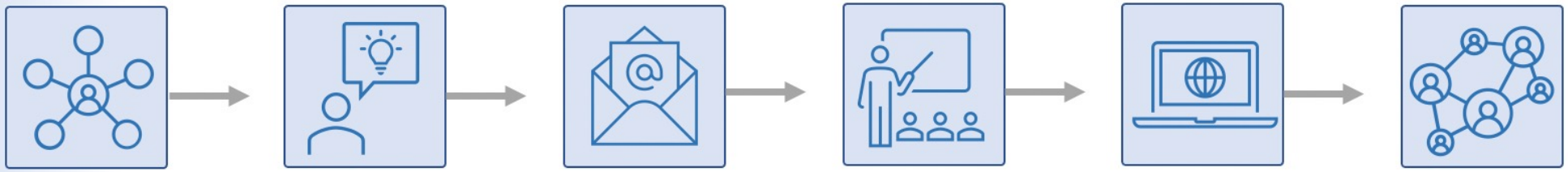
- Teams channel for PIcc established that enables direct file exchange with FDA 
- Project and workgroup progress GANTT chart to be created
  - Call for assistance from members with web-dev skills

3 layers of project organization



Pathology Innovation Collaborative Community

The Alliance for Digital Pathology and AI/ML



You value Collaborations

You have a Regulatory Science Project

Focus is NOT on competitive product development

You propose your project to PIcc

You present to steering committee

PIcc helps organize the project

PIcc does NOT actively participate in your project

PIcc is a network to find interested collaborators

PIcc 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

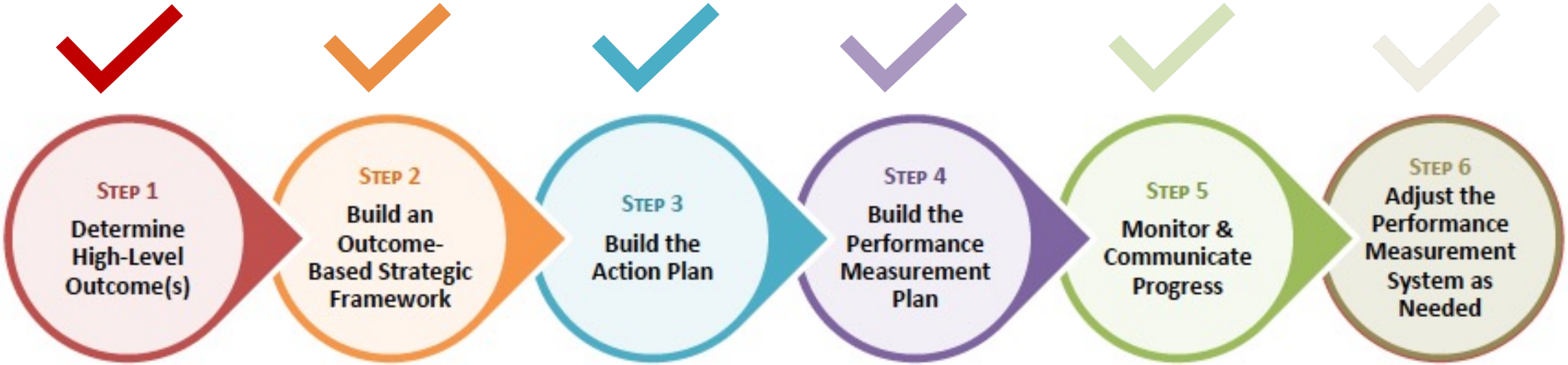


Figure 1. Process from Determining the High-Level Outcome to Implementing the Performance Management System.

Request for help

- Web developer with experience in interactive GANTT charts.

Patient Advocacy

Friends of Cancer Research

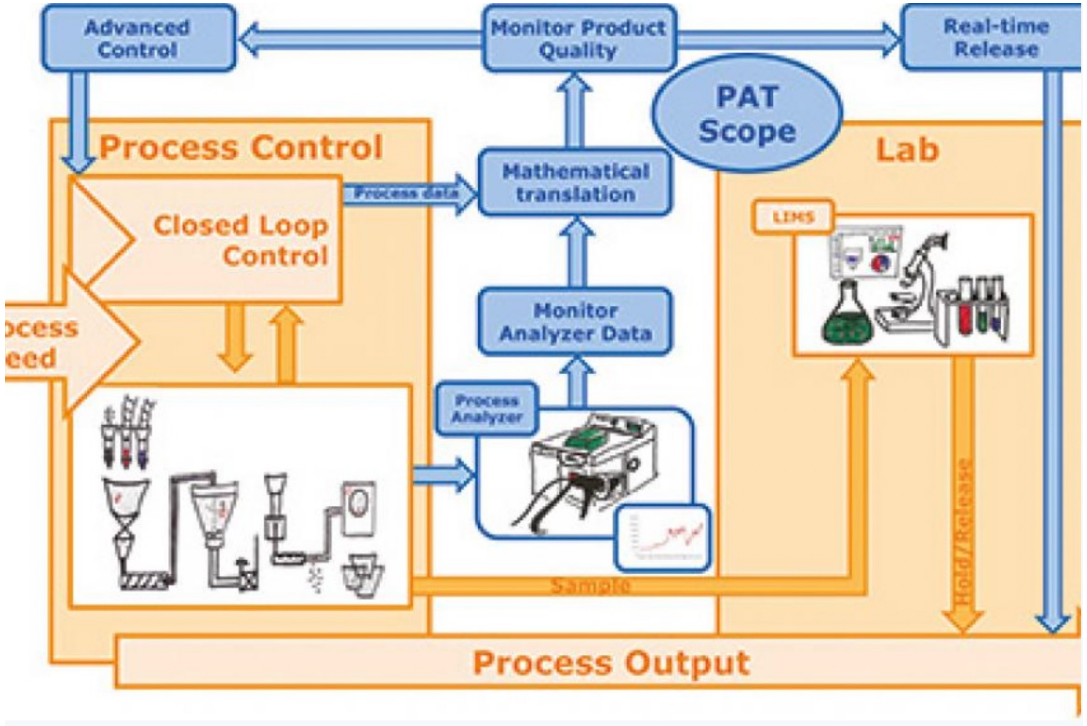
- FOCR Annual Report for 2021

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 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

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

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

ICH guideline Q14: Intended for analytical procedure development

ICH harmonisation for better health

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ICH Q14 Guideline

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Figure 1: The Analytical Procedure Lifecycle

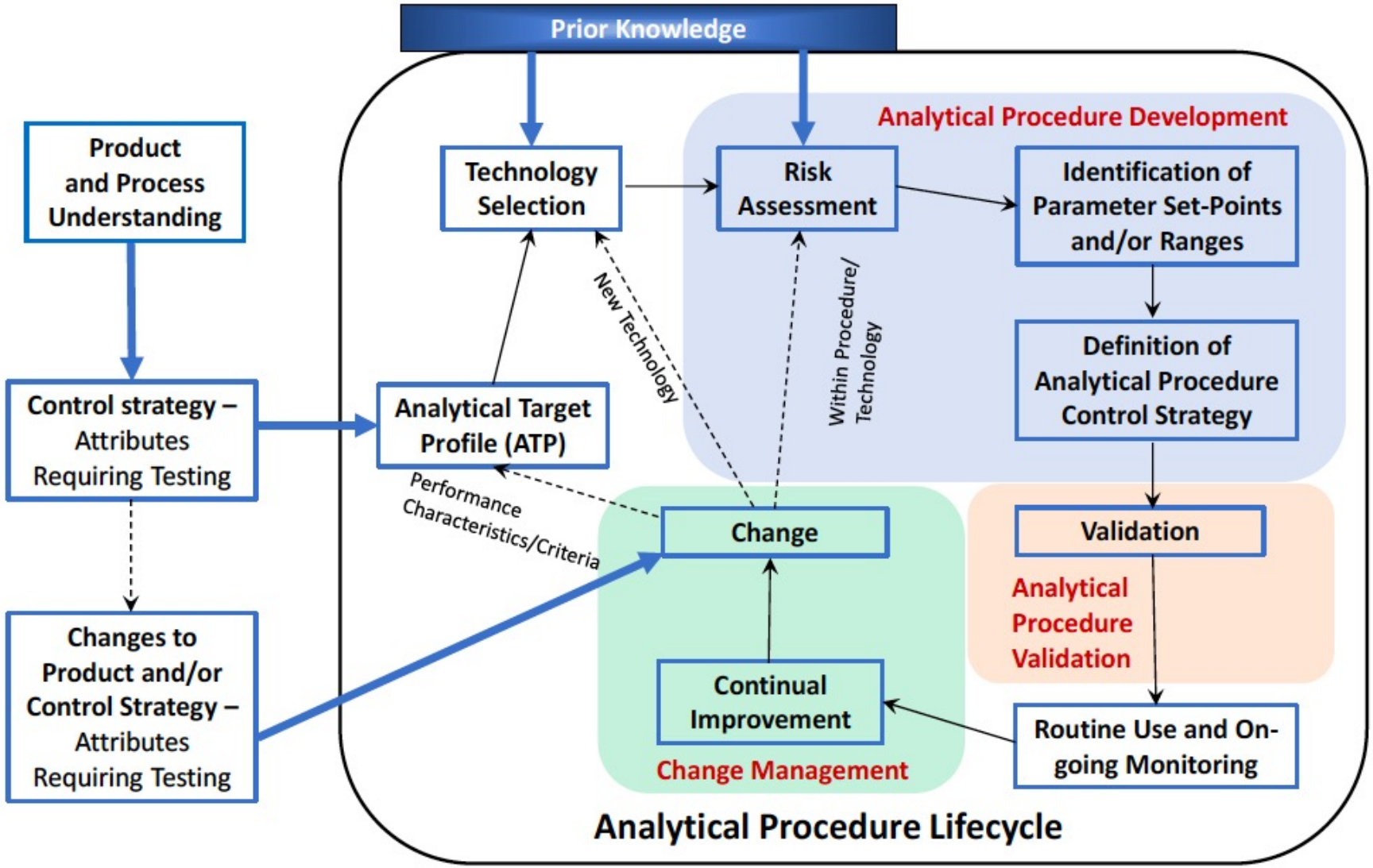
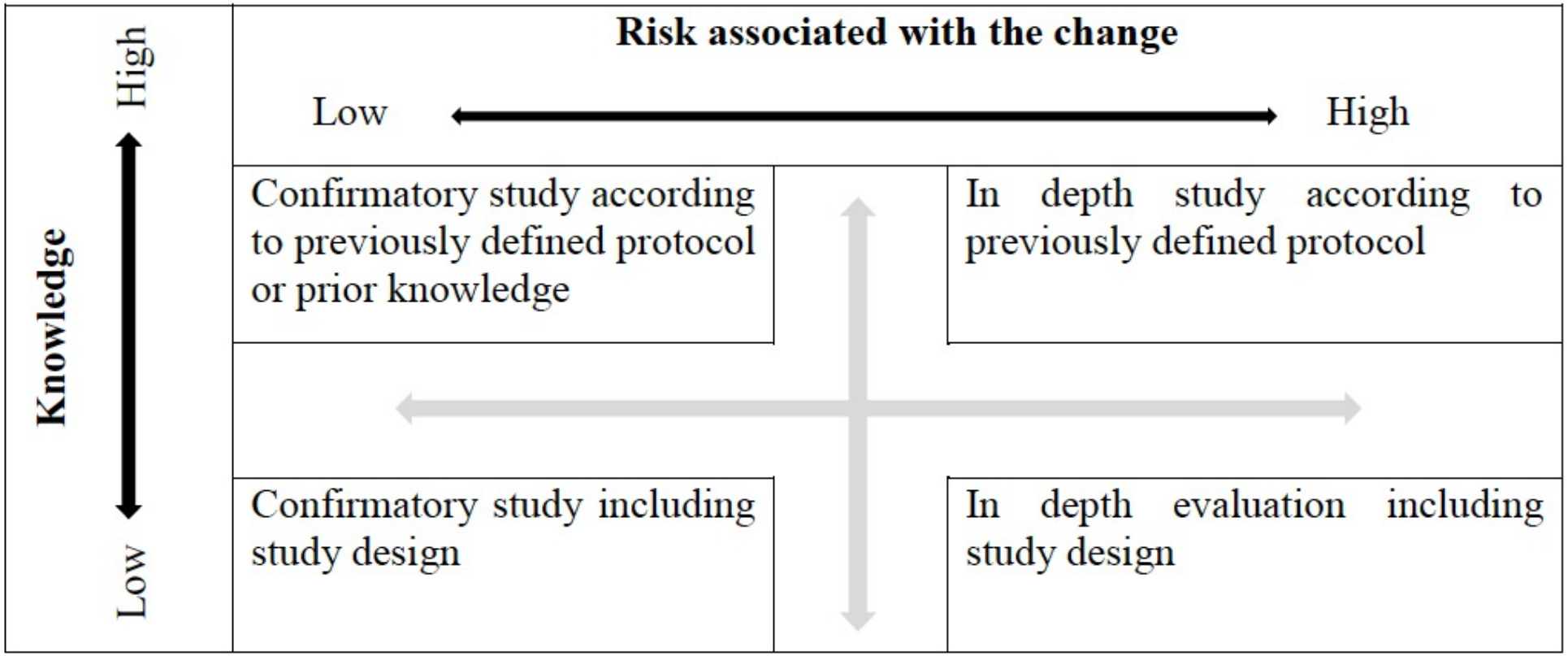


Table 1: Relationship between knowledge, risk and extent of studies for changes to analytical procedures



FDA

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

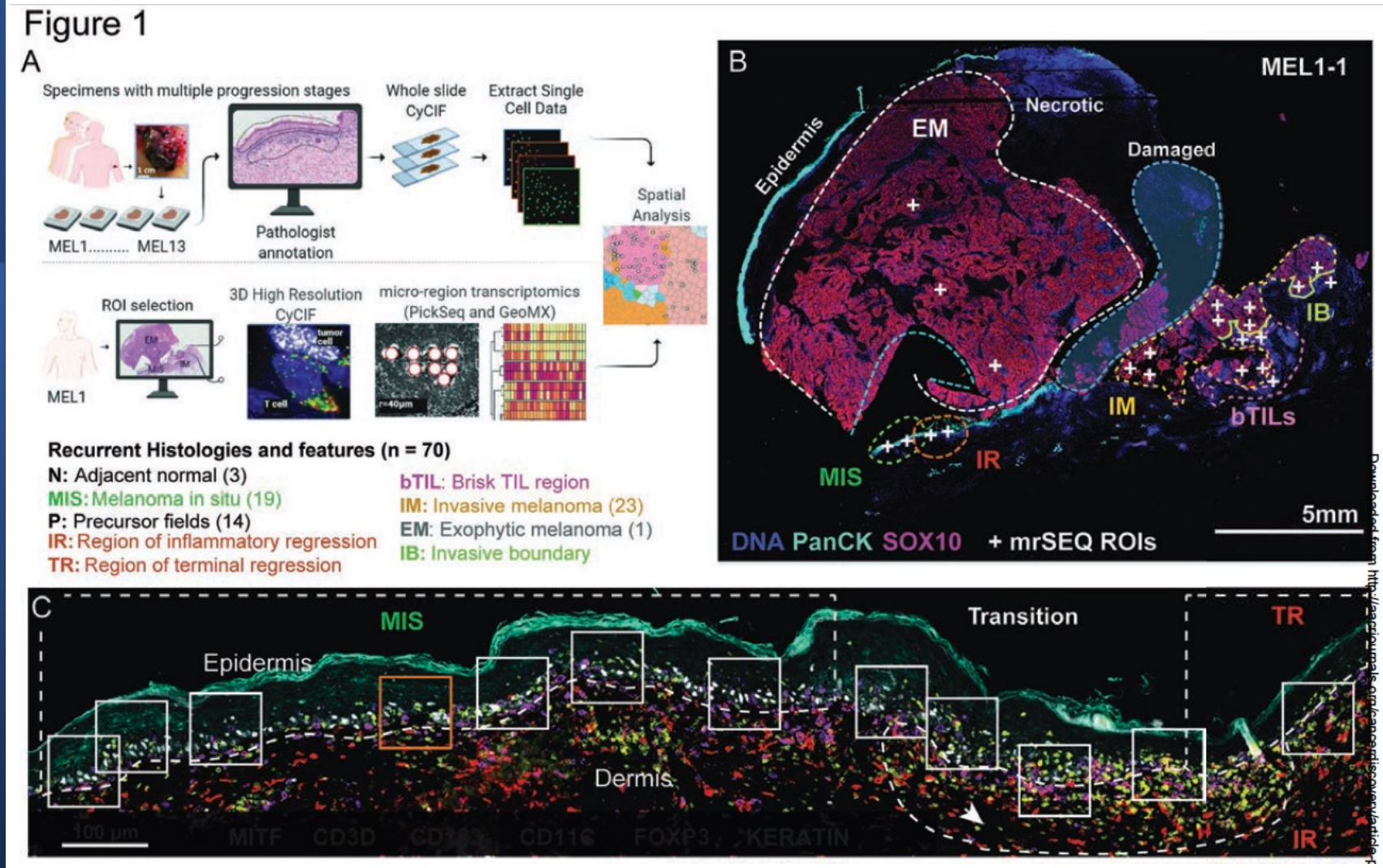
Certain Ophthalmic Products: Policy Regarding Compliance With 21 CFR Part 4

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



Cell Systems

CellPress

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,*]

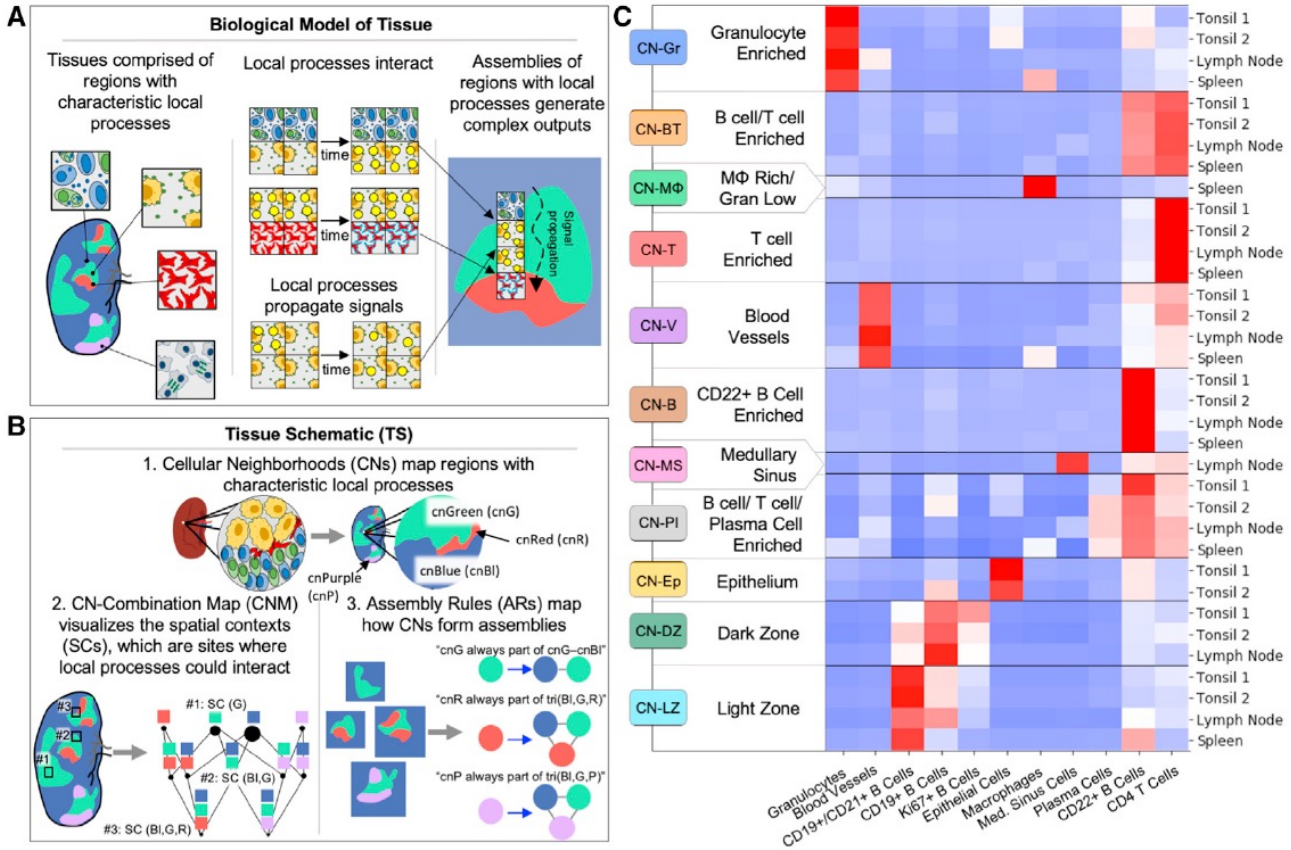


Table 1. Examples of digital biomarkers from published literature.

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 ccelerometer-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

nature methods

REVIEW ARTICLE

https://doi.org/10.1038/s41592-022-01409-2

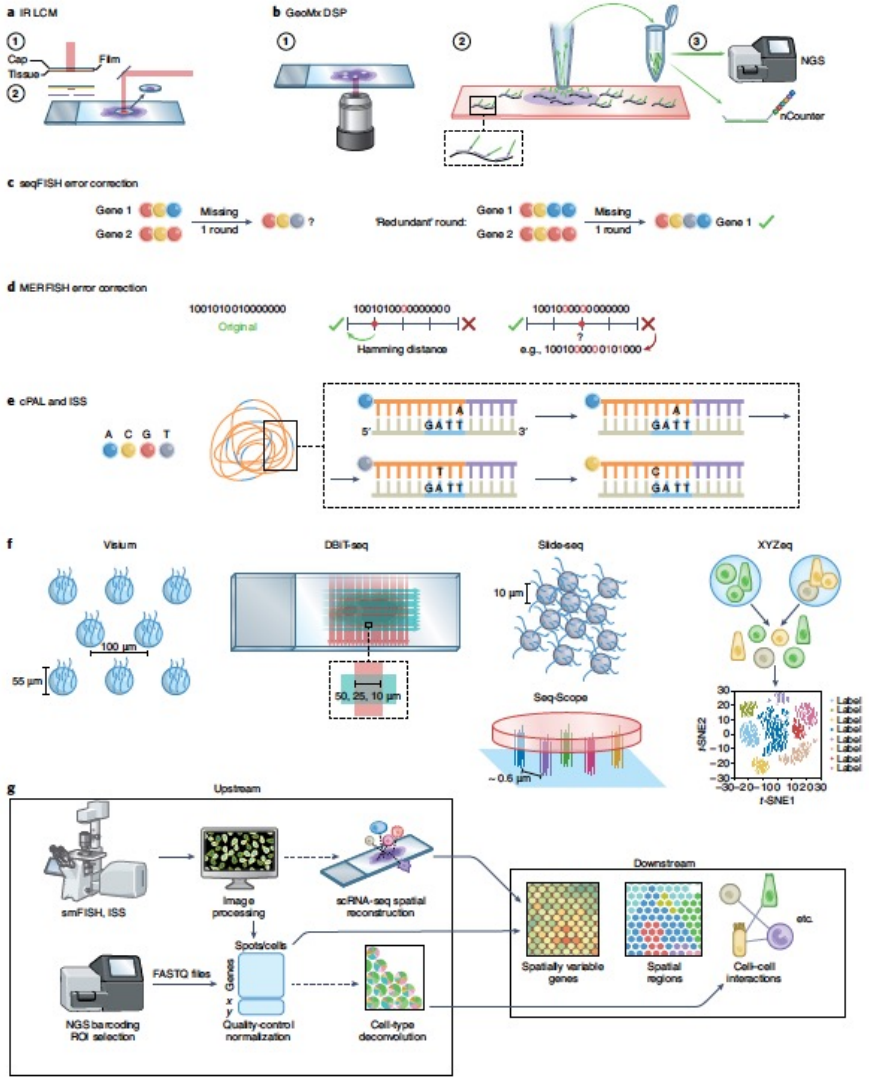
Check for updates

Museum of spatial transcriptomics

Lambda Moses[1] and Lior Pachter[1,2] ✉

The function of many biological systems, such as embryos, liver lobules, intestinal villi, and tumors, depends on the spatia organization of their cells. In the past decade, high-throughput technologies have been developed to quantify gene expressio in space, and computational methods have been developed that leverage spatial gene expression data to identify genes wit spatial patterns and to delineate neighborhoods within tissues. To comprehensively document spatial gene expression tech nologies 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, an computational approaches used. Our Review places current methods in a historical context, and we derive insights about th field that can guide current research strategies. A companion supplement offers a more detailed look at the technologies an 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, ZipSeq[43] 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)

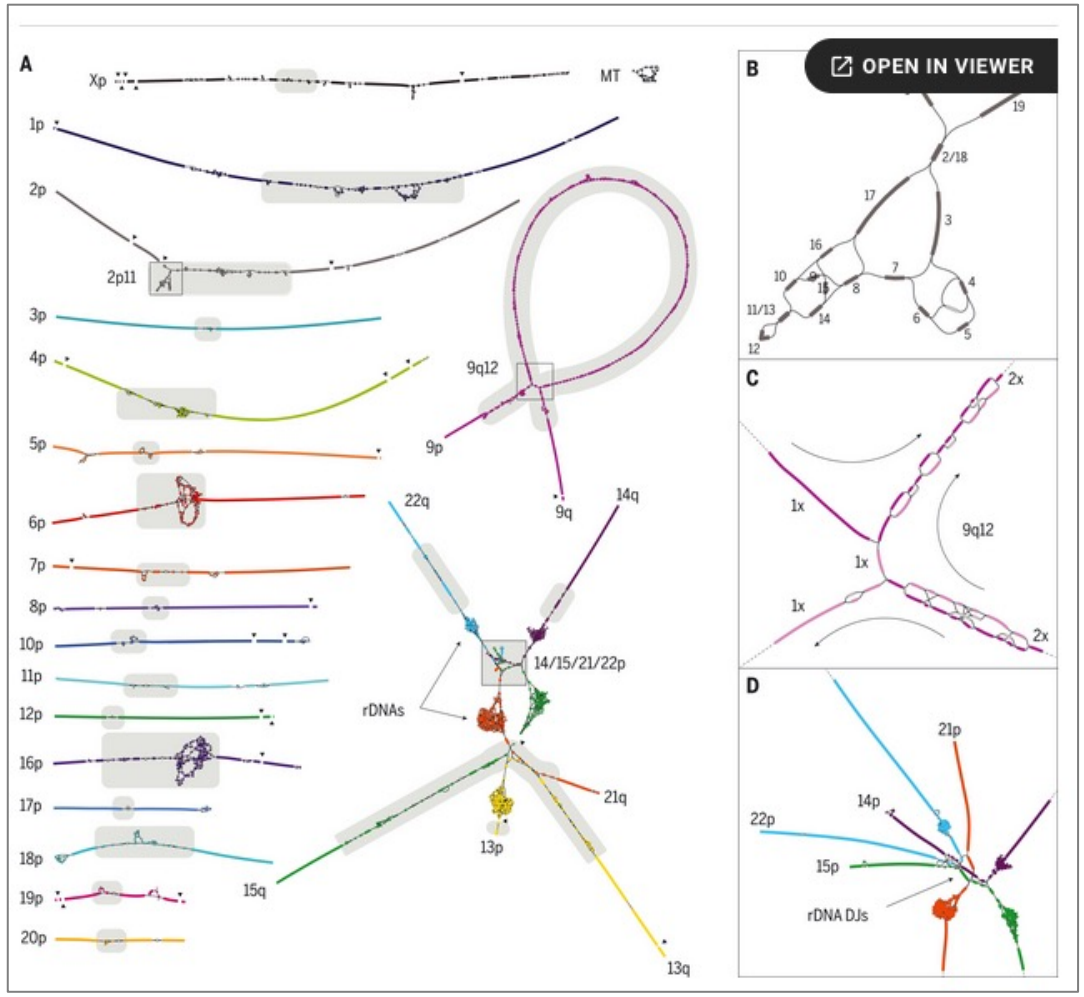


FIG. 2. High-resolution assembly string graph of the CHM13 genome.

(**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:

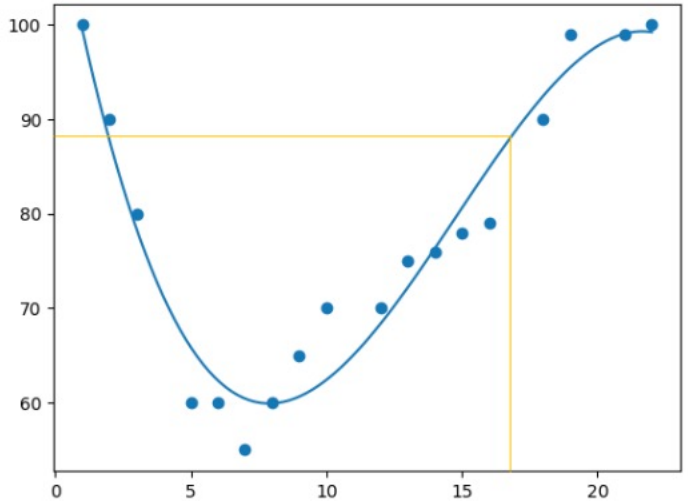
```
import numpy
from sklearn.metrics import r2_score

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)
```

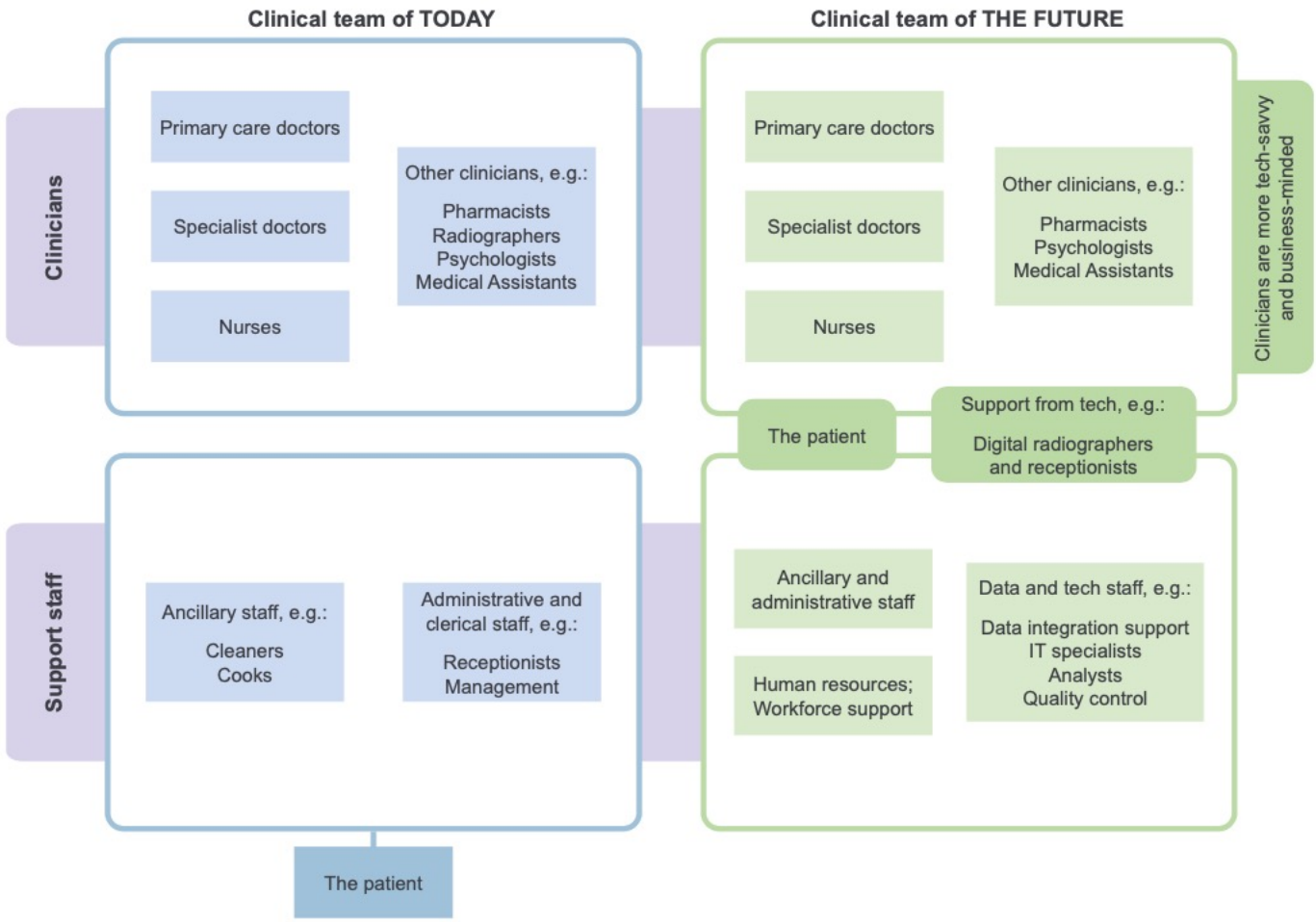
The example predicted a speed to be 88.87, which we also could read from the diagram:



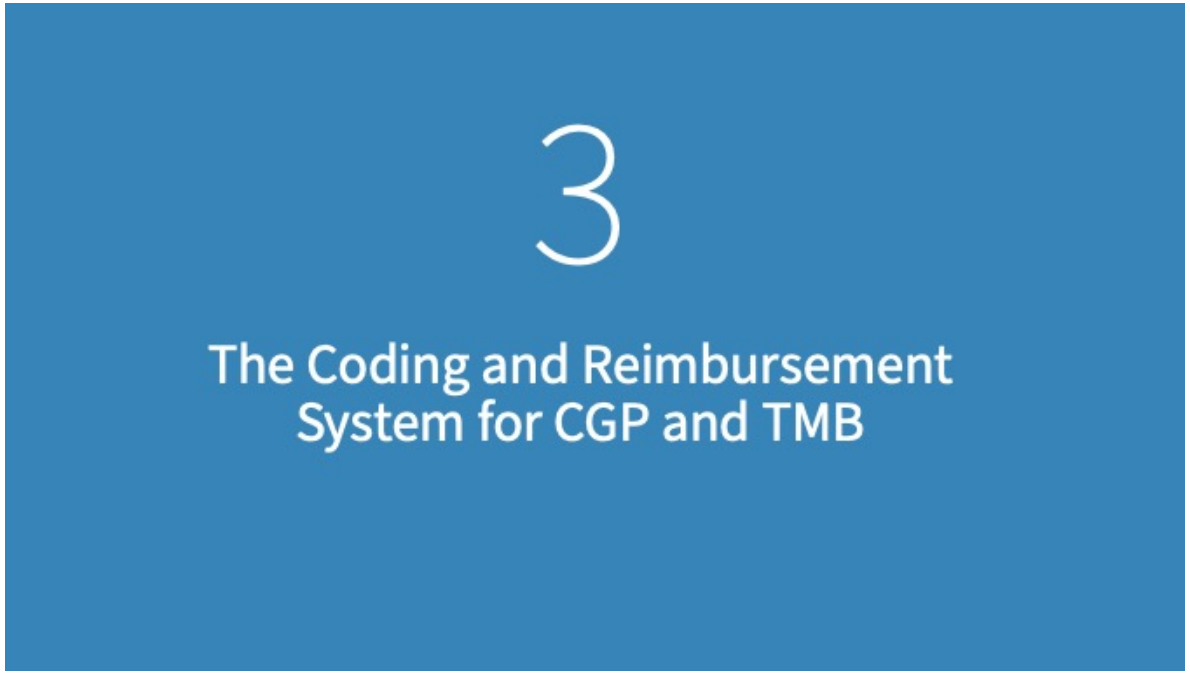
Bad Fit?

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

Report 2022: Clinician of the Future



Bruce Quinn 2022: Cancer Patient and Access to Molecular Diagnostics



HAL: Nicolas Rougier, Scientific Visualization

HAL open science

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.

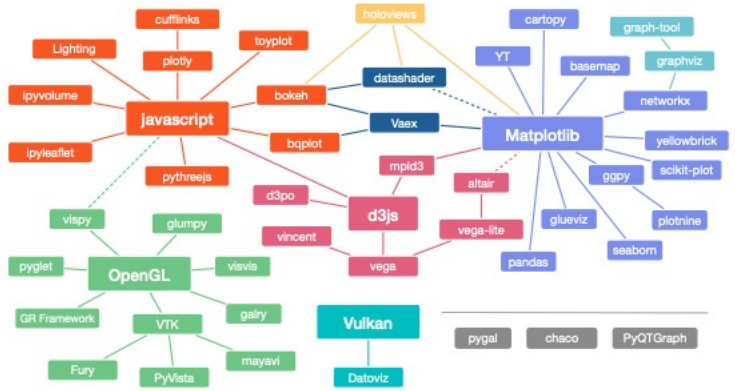


Figure 1
Python scientific visualisation landscape in 2018 (not exhaustive). Adapted from the original idea of Jake Vanderplas. **Sources:** github.com/rougier/python-visualization-landscape

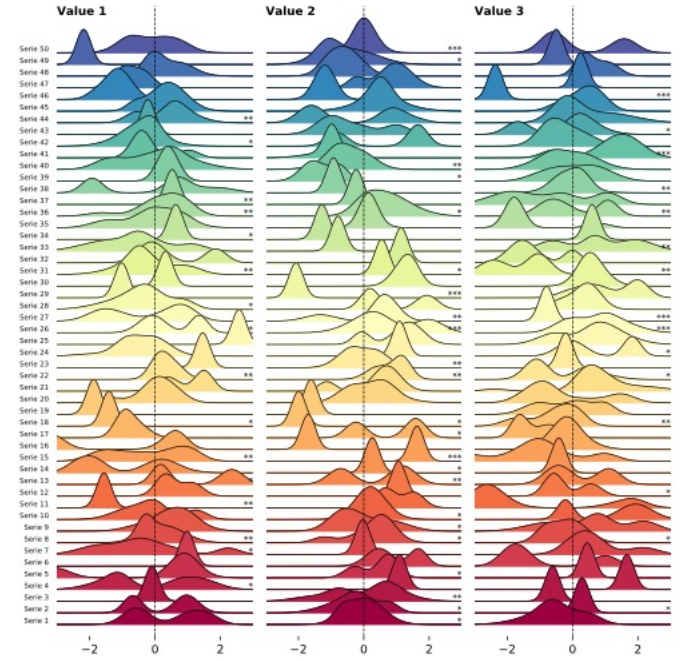
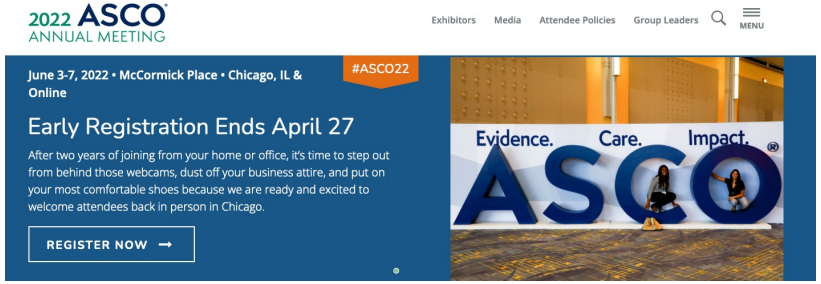


Figure 1.10
Multiple plots partially covering each other (**solution**: anatomy/zorder-plots.py).

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 Umeton, 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
MENU
June 3-7, 2022 • McCormick Place • Chicago, IL & Online
#ASCO22
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
Evidence. Care. Impact.
ASCO

Thank you

See you next month