Bringing Researchers Together from Drug Discovery to Delivery

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Advancing Tissue Imaging:

Functional And Morphological Extra-Cellular Matrix Characterization With Stain-Free Non-Linear Microscopy

September 17, 2015 • 1:00pm EDT • Free Webinar

Altering the Microbiome: Can it Impact Health?

September 24, 2015, National Cancer Institute at Frederick MD

Triangle Biotech Research Symposium IV:

Advancing Human Health through Technology Convergence

October 29, 2015 • North Carolina Biotechnology Center, Research Triangle Park

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D3D: Data Drugs Diagnostics

September 10, 2015
11:00 AM EDT

Optimizing Preclinical Imaging Workflows With Online Tools

BRC

James M. Denegre, Ph.D.

Timothy J. Kulbago

The Jackson Laboratory

ImageQuantify.com

Presenters

James M. Denegre, Ph.D.

Project Manager,
Embryonic Lethal Knockout Mouse Project

The Jackson Laboratory

Timothy J. Kulbago

CEO,
President

ImageIQ

Challenges

Bias:

- Inherent to manual analysis
- Non-blind observers shown to over-represent predicted results by 27%[1]
- Automated analysis is completely objective

Irreproducibility:

- $28B of preclinical research conducted each year is irreproducible[2]
- Validated and versioned automated analysis are completely controlled

1. Holman et al., *Evidence of Experimental Bias in the Life Sciences: Why We Need Blind Data Recording*, July 8, 2015.
2. Freedman, Leonard, *Irreproducibility: A $28B/Year Problem with some Tangible Solutions*, June 30, 2015.

Agenda

1. KOMP & IMPC
- Goals & Implications
- Scope
- Challenges
2. Case Studies (3)
- Faxitron X-Ray Analysis
- OCT Layer Analysis
- Mouse Fundus Lesion Analysis
3. Solutions
4. Pass It off to Tim
- The Technology Itself
- Bettering the Quality of Scientific Discoveries

The Knockout Mouse Project (KOMP)

Goal:

- Collaboratively build a comprehensive catalog of mouse gene function
  - First of its kind
  - Utilizes targeted knockout strains
- Deliver a publicly-accessible database of functional genetic insights

The Knockout Mouse Project (KOMP)

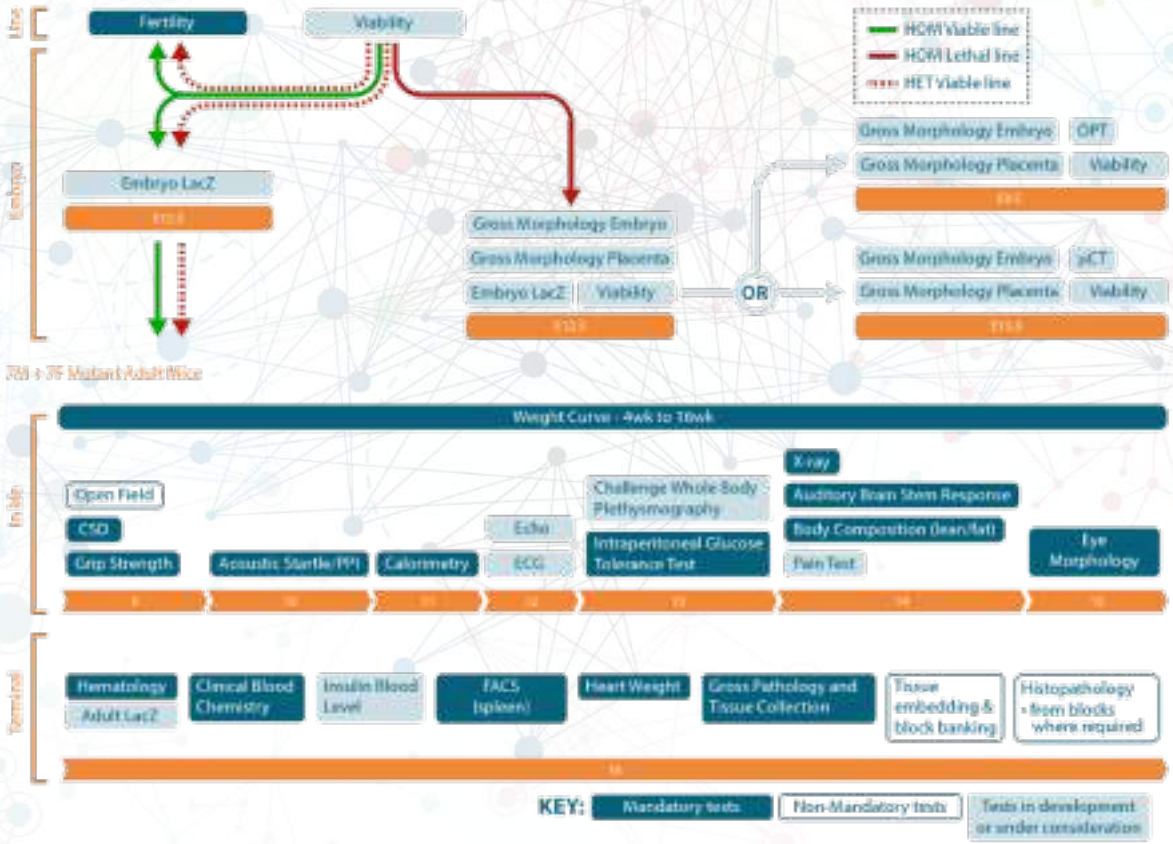
Implications:

- Keeps findings publicly accessible & searchable
- Provides direction for translational research
  - >95% genetic overlap between mice and humans

The Knockout Mouse Project (KOMP)

Mechanics:

- Targeted allele knockout
- Collaborative phenotyping effort
- Data Coordination Center (DCC) aggregates findings

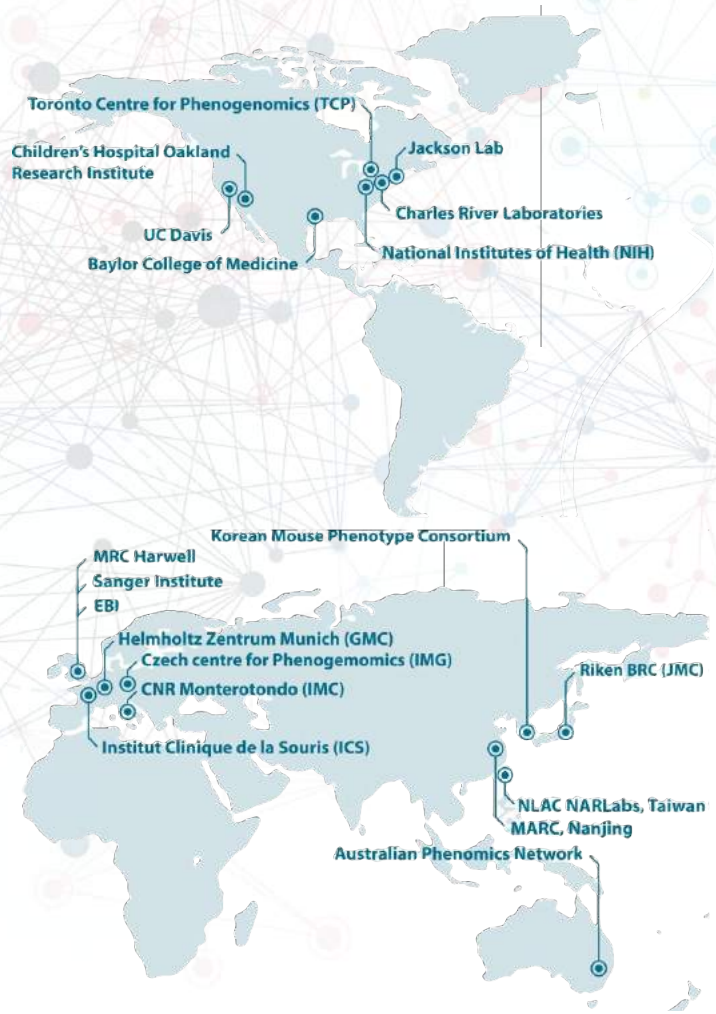


http://www.mousephenotype.org/what-pipelines-are-available-impress

The Knockout Mouse Project (KOMP)

Scope:

- Domestic – NIH KOMP
  - 3 centers (Jackson Lab, UC Davis, & Baylor College of Medicine)
- International – IMPC
  - "International Mouse Phenotyping Consortium"
  - 18 member institutions



http://www.mousephenotype.org/about-impc/impc-members

The Knockout Mouse Project (KOMP)

Scope:

- 18 Centers
- ~25,000 Knockout Strains
- 14-16 Mice Per Strain
- 100s of Measurements Per Mouse
  - 15 'mandatory' workflows (+ center-specific tests)
  - Many images, measurements, etc. per workflow

Case Study: Faxitron X-Ray Analysis

- Identifies skeletal properties via x-ray imaging
- Analysis and annotation: <u>the single most problematic KOMP bottleneck</u>
- 68 measurement parameters per mouse

Case Study: Faxitron X-Ray Analysis

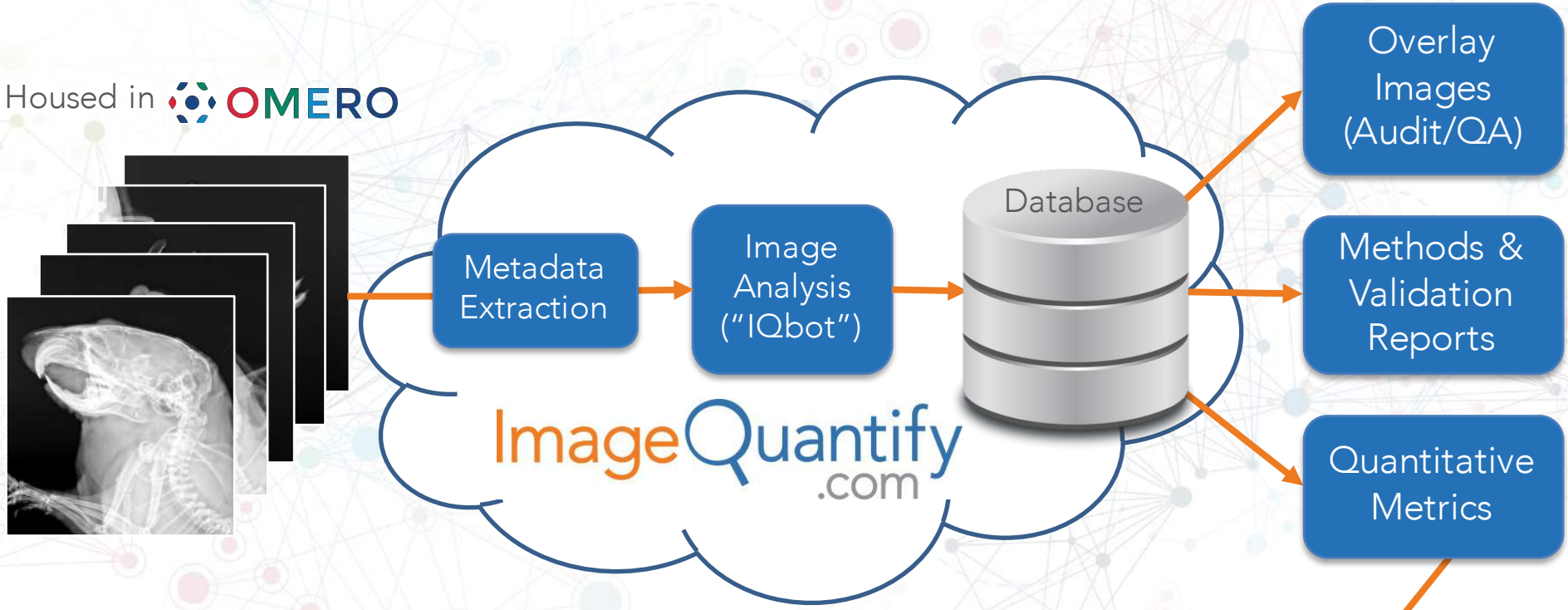
- 5 Images, 68 Measurement Parameters Per Mouse
- Quantitative
  - Digit counts
  - Rib counts (Left, Right)
  - Vertebrae counts (Cervical, Thoracic, Lumbar, Pelvic, Caudal)
- Qualitative
  - Expert designation of features (e.g., normal/abnormal skull shape, presence of syndactylism, etc.)

Case Study: Faxitron X-Ray Analysis

Current State:

- Manual analysis not high-throughput enough to prevent backlogs
  - At The Jackson Lab alone, ~10,000 mice to be analyzed over 5-year term
- Highly susceptible to user error and fatigue, mix-up of animals IDs
- Drains expert phenotyper resources

Case Study: Faxitron X-Ray Analysis

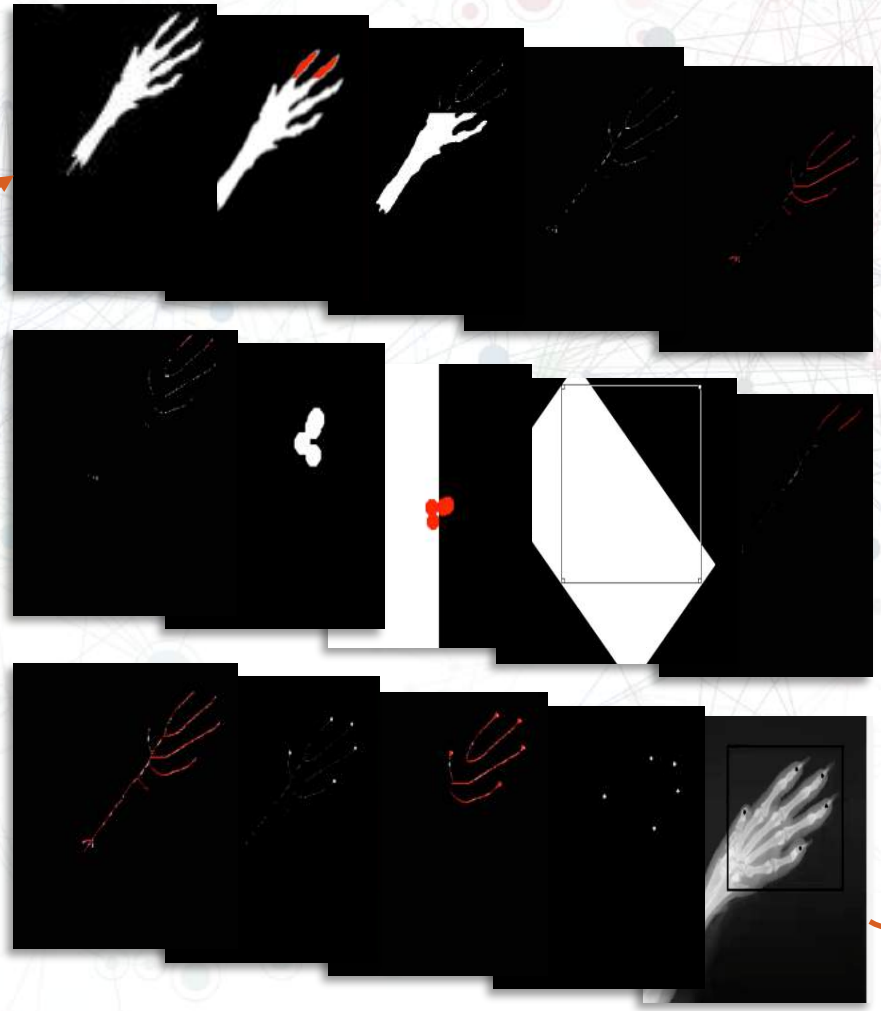


	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U
1	Filename	Upper-Right Paw Digit Count (Forepaw)	Upper-Right Paw Digit Count (DorsoV)	Upper-Left Paw Digit Count (DorsoV)	Bottom-Right Paw Digit Count (DorsoV)	Bottom-Left Paw Digit Count (DorsoV)	Caudal Vertebrae (DorsoV)	Caudal Vertebrae (LateralO)	Sacral Vertebrae (DorsoV)	Sacral Vertebrae (LateralO)	Lumbar Vertebrae (DorsoV)	Lumbar Vertebrae (LateralO)	Thoracic Vertebrae (DorsoV)	Thoracic Vertebrae (LateralO)	Cervical Vertebrae (DorsoV)	Cervical Vertebrae (LateralO)	Cervical Vertebrae (SkullLateral)	Left Ribs (DorsoV)	Right Ribs (DorsoV)	Left Ribs (LateralO)	Right Ribs (LateralO)
2	A9237	5	5	5	5	5	23	23	4	4	6	6	13	13	7	7	7	13	13	13	13
3	A9238	5																			
4	A9239	5																			
5	A10347	5																			
6	A15496	5																			
7																					
8																					

Case Study: Faxitron X-Ray Analysis

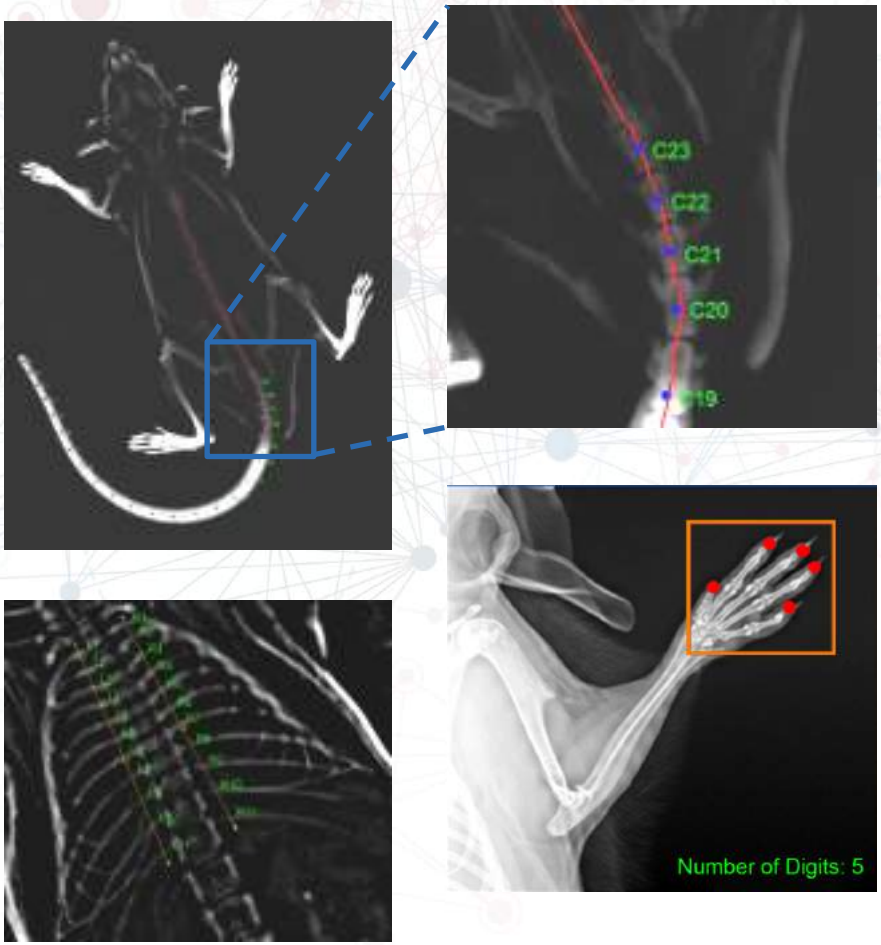
Solution:

Automated Analysis



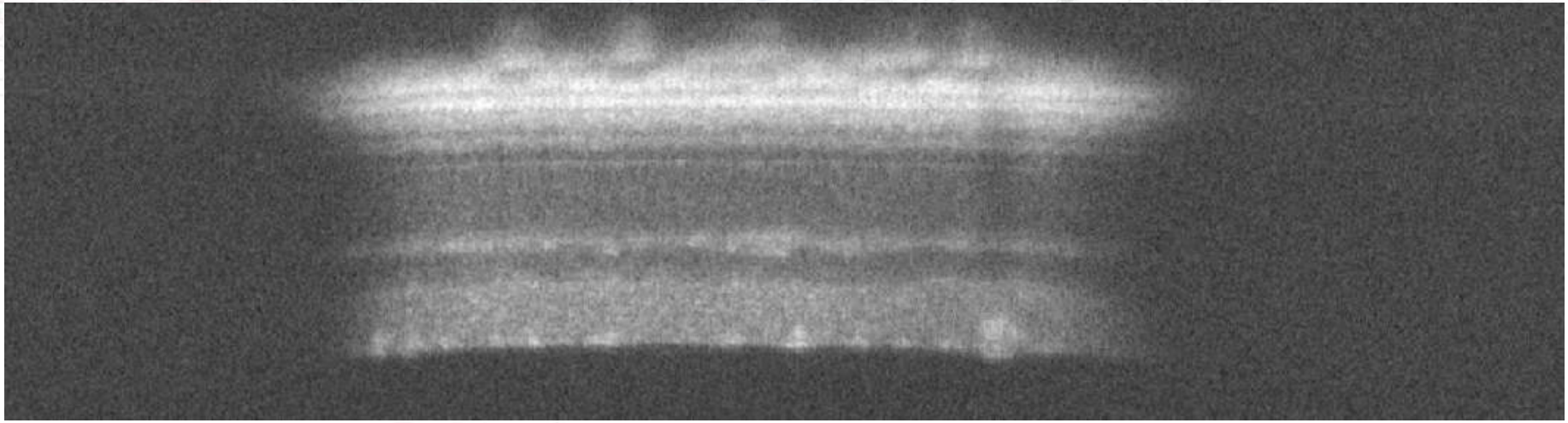
Case Study: Faxitron X-Ray Analysis

- Automates quantitative measurements
- Flags abnormal qualitative phenotypes for further review
- Allows for visual QA by experts
- Reports data directly to the DCC and in accessible Excel spreadsheets



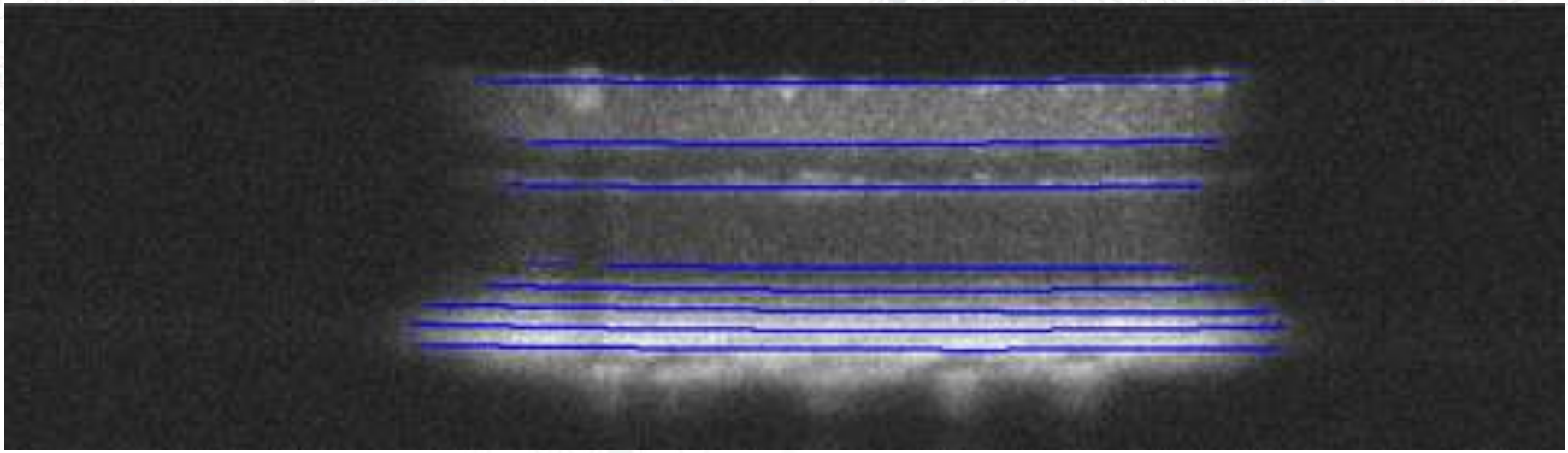
Case Study: OCT Layer Analysis

- Not yet a mandatory test (i.e., not common to all sites)
- Measures relative characteristics of different ocular layers that have relevance to eye disease



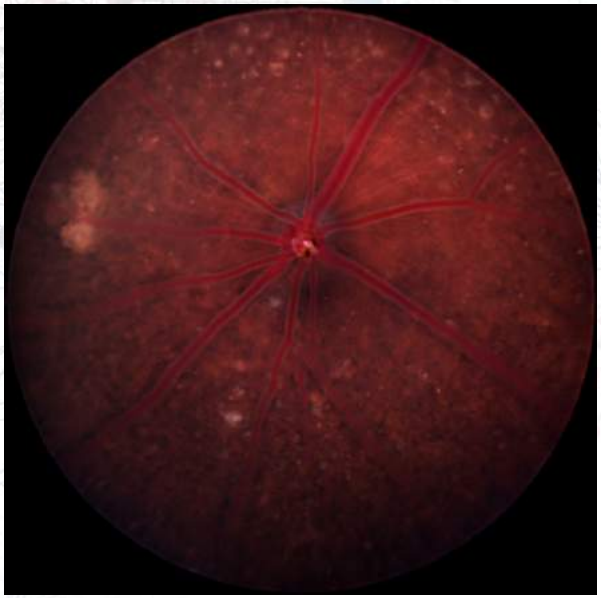
Case Study: OCT Layer Analysis

- Automated analysis enables sites to adopt this more useful procedure while removing both bias and the need for expert reviewers



Case Study: Mouse Fundus Lesion Analysis

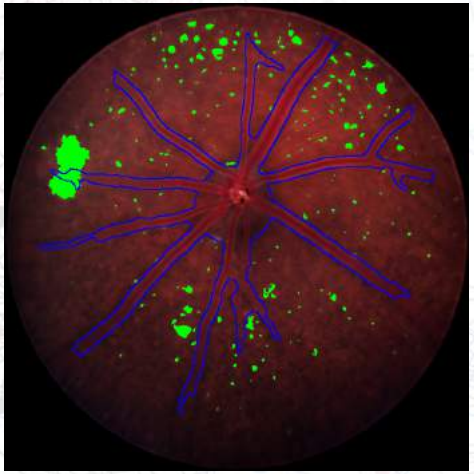
- Funduscope image of the mouse eye
- Investigating lesion presence, size, and location
- Opportunity: quantify lesions in funduscope images to derive more value from each image, increasing the functionality of the funduscope

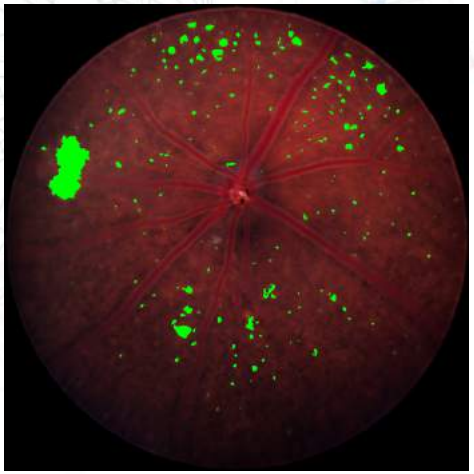


Case Study: Mouse Fundus Lesion Analysis

Challenges:

- Curvature of the eye, uneven shadowing
- Non-standardized image center or coordinate system
- Vasculature and optic nerve trigger false identification of lesions





Solutions

Automated analysis via online tools enables The Jackson Lab's KOMP research to:

- Provide high-throughput processing
- Remove bias
- Take weight off of experts
- Reduce the need for manpower
- Allow for seamless data, result, and tool access
- Access for all IMPC sites

Technology Summary

- Automated preclinical image analysis
- Data management
- Hosted in the secure cloud
- Quantitative data
- Measurement Overlay Images
- References
- Validation Information
- GLP compliance documentation

Enablers (i.e., “Why Now?”)

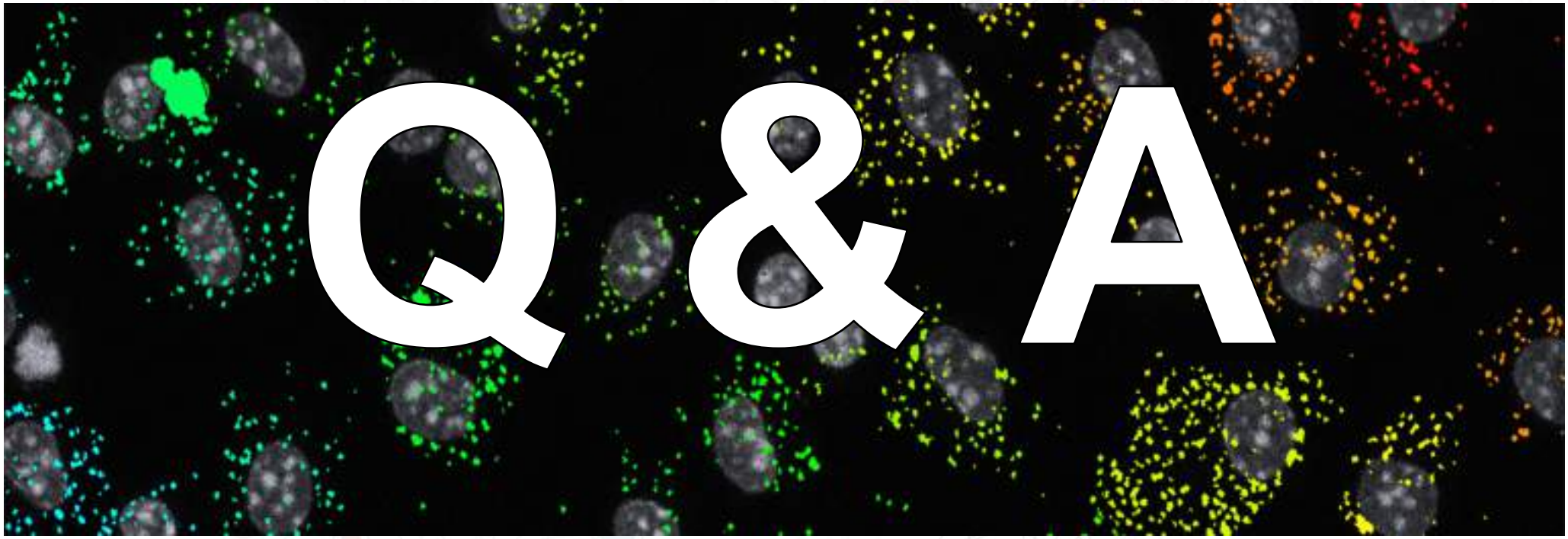
- Algorithm maturity
- Computer capability
- Internet speed
- Cloud computing
- Security technologies
- Connectivity

Capability

- Globally accessible
- Scalable
- Deployable instantly
- No hardware

Enabling Better Science

- Speeds the time-to-analysis
- Yields objective, reproducible results
- Reduces costs
- Creates consistent standard of practice for image analysis across multiple collaborative institutions
- Simple online interface allows non-experts to produce better-than-expert results, anywhere


Q & A