

# Incorporating a Clinical Project into Your Core Lab

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OHSU INTEGRATED GENOMICS LABORATORY

Britt Daughtry, Ph.D.

IGL CAP Technical Supervisor | Sr. Core Scientist | Lab Manager

13 October, 2023



# What is CAP?

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## CAP (College of American Pathologists)

- Private, non-profit organization. Provides accreditation and certification services for clinical laboratories.
- CAP accreditation is voluntary. Laboratories choose to seek CAP accreditation to demonstrate their commitment to quality.
- Comprehensive evaluation of laboratory quality, detailed assessments of laboratory processes, quality management systems, and technical proficiency.

# Why We Started – The Healthy Oregon Project

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- CEDAR funding and NIH Moonshot Grant to Paul Spellman, Ph.D. and Jackie Shannon, Ph.D., R.D., M.P.H.
- **No cost** DNA screening for Oregonians.
- Analyze saliva sample by NGS for the pathogenic/likely pathogenic medically actionable variants in 32 genes associated with cancer and heart disease risk.
- Germline not somatic mutations.
- Provide a medical record to patient who has a positive result – **requires a clinical laboratory!**



*Image by Brian Hayes | Salem Statesman Journal*



# Why We Started

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- Knight Diagnostic Laboratory (KDL)
  - Fully operational clinical lab already CAP/CLIA certified and accredited. Sample accessioning group, automated library prep robot, NGS, and bioinformatics. No high throughput extraction robot.
- Integrated Genomics Laboratory (IGL)
  - Research Core with expertise high – throughput DNA extraction & normalization automation. No clinical experience or CAP accreditation.



Qiagen QIA Symphony

*Image by Brian Hayes | Salem Statesman Journal*

# Healthy Oregon Project Workflow

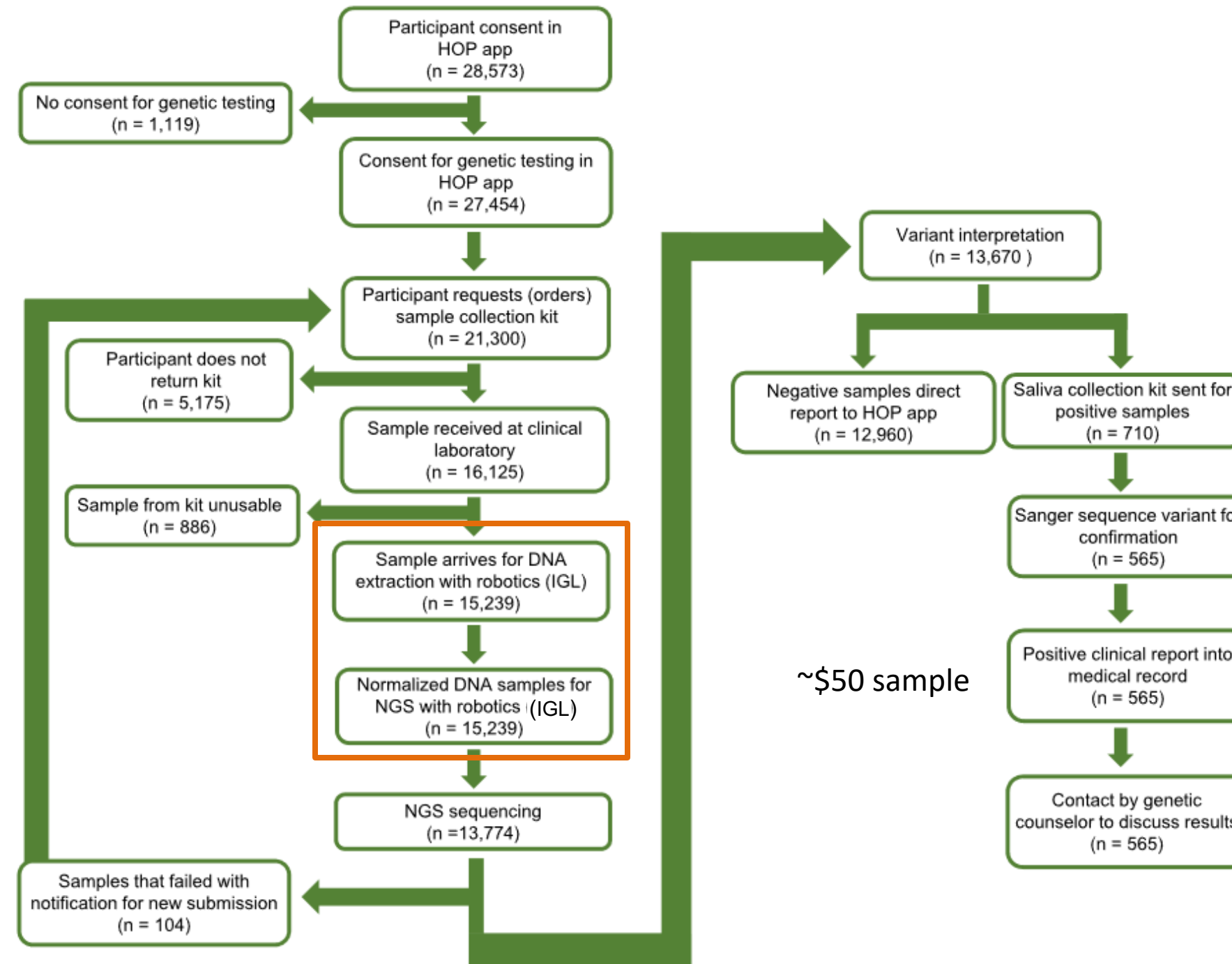


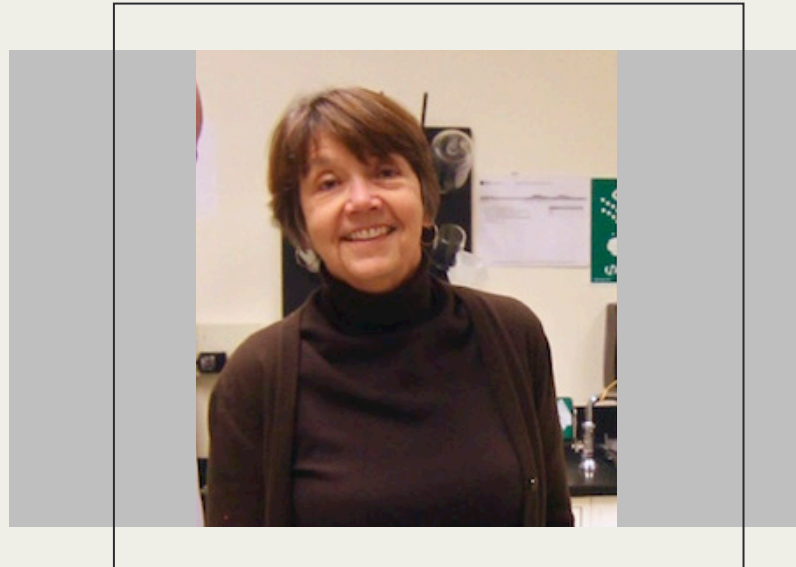
Image by Brian Hayes | Salem Statesman Journal



**Figure 1. Pipeline for the enrollment of HOP participants and sample workflow**  
HOP participants sequenced as of April 15, 2022. Differences in numbers are reflective of the fluid pipeline and time it takes samples to process from consent in the HOP app through next-generation sequencing (NGS) and analysis. IGL, Integrated Genomics Laboratory, core laboratory; KDL, Knight Diagnostic Laboratories, clinical laboratory.

# MEET THE IGL CAP TEAM

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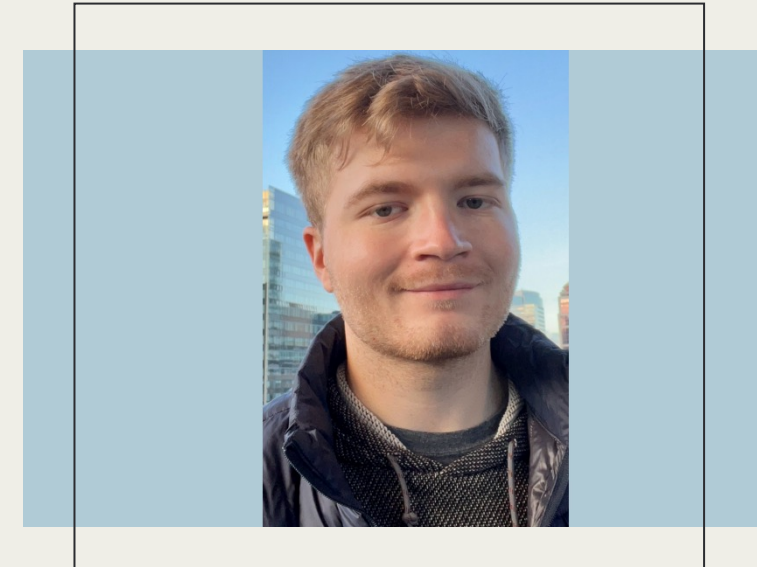
*CAP Section Director*  
**Chris Harrington, Ph.D.**

Dr. Harrington is a Research Associate Professor and Co-Director of the Integrated Genomics Laboratory at OHSU, specializing in RNA and DNA analysis technologies. She has worked on the HOP project since the proof of concept stage and has co-authored HOP publications.



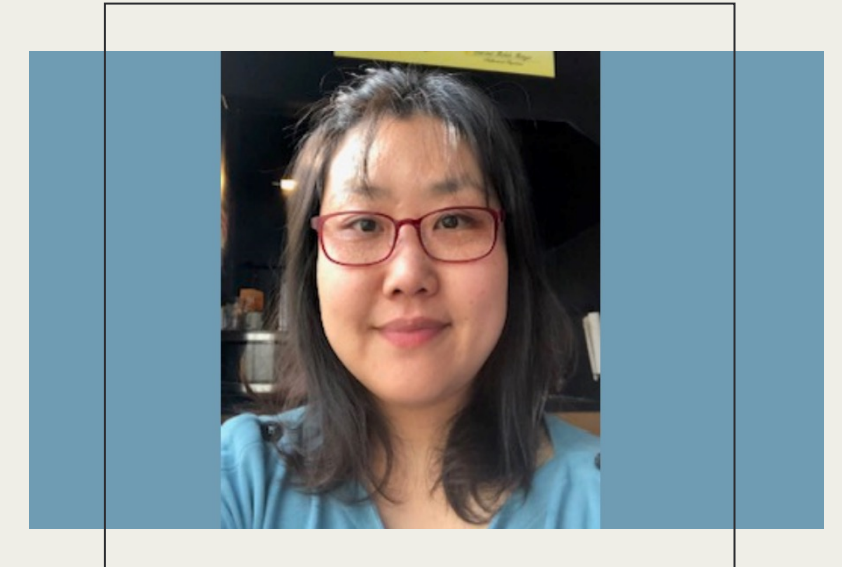
*CAP Technical Supervisor*  
**Britt Daughtry, Ph.D.**

In 2018, Britt joined the IGL team and initiated the implementation of the HOP IGL workflow. Britt's role has been instrumental in ensuring the completion of CAP documentation, training programs, and laboratory operations, all in strict adherence to CAP specifications. During the pandemic, her CAP regulation expertise led her to become the Interim Technical Coordinator at the OHSUCOVID Testing Lab.



*Research Assistant 2*  
**Jake Buitrago**

In the Spring of 2022, Jake became a valuable addition to the IGL HOP team. His contributions have played a pivotal role in maintaining peak throughput and efficiency in HOP sample processing. With Jake's keen attention to detail, strong work ethic, and innovative efficiency ideas, the IGL has achieved rapid turnaround times for sample processing.



*Core Scientist*  
**Jinah Kim, Ph.D.**

Jinah, a proficient scientist, is taking on a supportive role within the HOP team. While currently in training, Jinah is poised to become an important figure in HOP IGL operations.

# HOP Impact – as of October 2023

23,264  
Samples Processed

955  
Positive Reports

5  
Years

## ARTICLE

### Population screening shows risk of inherited cancer and familial hypercholesterolemia in Oregon

Timothy D. O'Brien,<sup>1</sup> Amiee B. Potter,<sup>1</sup> Catherine C. Driscoll,<sup>1,2</sup> Gregory Goh,<sup>1,2</sup> John H. Letaw,<sup>1</sup> Sarah McCabe,<sup>1</sup> Jane Thanner,<sup>3</sup> Arpita Kulkarni,<sup>1</sup> Rossana Wong,<sup>1</sup> Samuel Medica,<sup>4</sup> Tiana Week,<sup>4</sup> Jacob Buitrago,<sup>4</sup> Aaron Larson,<sup>4</sup> Katie Johnson Camacho,<sup>2</sup> Kim Brown,<sup>5,10</sup> Rachel Crist,<sup>5</sup> Casey Conrad,<sup>2</sup> Sara Evans-Dutson,<sup>2</sup> Ryan Lutz,<sup>5</sup> Asia Mitchell,<sup>2</sup> Pavana Anur,<sup>2</sup> Vanessa Serrato,<sup>5</sup> Autumn Shafer,<sup>6</sup> Lisa K. Marriott,<sup>7</sup> K.J. Hamman,<sup>8</sup> Amelia Mulford,<sup>8</sup> Wojciech Wiszniewski,<sup>8</sup> Jone E. Sampson,<sup>8</sup> Andrew Adey,<sup>2,8</sup> Brian J. O'Roak,<sup>8</sup> Christina A. Harrington,<sup>4,8</sup> Jackilen Shannon,<sup>5,9</sup> Paul T. Spellman,<sup>2,8</sup> and C. Sue Richards<sup>1,8,\*</sup>

#### Summary

The Healthy Oregon Project (HOP) is a statewide effort that aims to build a large research repository and influence the health of Oregonians through providing no-cost genetic screening to participants for a next-generation sequencing 32-gene panel comprising genes related to inherited cancers and familial hypercholesterolemia. This type of unbiased population screening can detect at-risk individuals who may otherwise be missed by conventional medical approaches. However, challenges exist for this type of high-throughput testing in an academic setting, including developing a low-cost high-efficiency test and scaling up the clinical laboratory for processing large numbers of samples. Modifications to our academic clinical laboratory including efficient test design, robotics, and a streamlined analysis approach increased our ability to test more than 1,000 samples per month for HOP using only one dedicated HOP laboratory technician. Additionally, enrollment using a HIPAA-compliant smartphone app and sample collection using mouthwash increased efficiency and reduced cost. Here, we present our experience three years into HOP and discuss the lessons learned, including our successes, challenges, opportunities, and future directions, as well as the genetic screening results for the first 13,670 participants tested. Overall, we have identified 730 pathogenic/likely pathogenic variants in 710 participants in 24 of the 32 genes on the panel. The carrier rate for pathogenic/likely pathogenic variants in the inherited cancer genes on the panel for an unselected population was 5.0% and for familial hypercholesterolemia was 0.3%. Our laboratory experience described here may provide a useful model for population screening projects in other states.

#### Introduction

Early detection of inherited genetic diseases through increased screening in susceptible individuals can potentially increase survival rates and is predicted to decrease healthcare costs for affected individuals.<sup>1–3</sup> However, without a strong family history of disease or other risk factors, an individual is unlikely to meet testing guidelines.<sup>4</sup> Therefore, it may be difficult to identify those individuals at increased risk who may require surveillance due to an inherited genetic variant that leads to increased likelihood of disease.<sup>5</sup> Even with a positive family history, or other risk factors, there may be barriers to the testing required to determine an individual's risk due to costs associated with genetic testing or obtaining a correct referral.<sup>5,6</sup> Cost-free population-based screening can help alleviate these barriers and has successfully been used to generate this information in the past.<sup>7</sup>

Several population screening studies have been implemented from nationwide studies like the All of Us Research Program,<sup>8</sup> eMERGE,<sup>9,10</sup> and the Cancer Moonshot<sup>11</sup> to smaller statewide programs such as the Healthy Nevada Project and the Alabama Genomic Health Initiative.<sup>7,12</sup> These smaller statewide initiatives have demonstrated the utility of population screening to identify at-risk individuals who would otherwise not be identified with standard clinical practice.<sup>7,12</sup>

The Healthy Oregon Project (HOP) is an Oregon Health & Science University (OHSU) IRB-approved (18473) population-based study that aims to build a large research repository and impact the health of Oregonians. HOP is supported by OHSU's CEDAR (Cancer Early Detection Advanced Research) Center. A subsequent federally funded National Cancer Institute Beau Biden Cancer Moonshot initiative clinical trial that utilizes the HOP infrastructure also funds a portion of this work. Goals of

<sup>1</sup>Knight Diagnostic Laboratories, Oregon Health & Science University, Portland, OR 97239, USA; <sup>2</sup>Cancer Early Detection Advanced Research Center, Knight Cancer Institute, Oregon Health & Science University, Portland, OR 97201, USA; <sup>3</sup>Information Technology Group, Oregon Health & Science University, Portland, OR 97201, USA; <sup>4</sup>Integrated Genomics Laboratory, Oregon Health & Science University, Portland, OR 97239, USA; <sup>5</sup>Knight Cancer Institute, Community Outreach and Engagement, Oregon Health & Science University, Portland, OR 97201, USA; <sup>6</sup>University of Oregon, School of Journalism and Communication, Portland, OR 97209, USA; <sup>7</sup>OHSU-PSU School of Public Health, Portland, OR 97239, USA; <sup>8</sup>Department of Molecular & Medical Genetics, Oregon Health & Science University, Portland, OR 97239, USA; <sup>9</sup>Division of Oncological Sciences, Oregon Health & Science University, Portland, OR 97239, USA

<sup>10</sup>Present address: Department of Environmental & Molecular Toxicology, Oregon State University, Corvallis, OR 97331, USA

\*Correspondence: richards@ohsu.edu

<https://doi.org/10.1016/j.ajhg.2023.06.014>

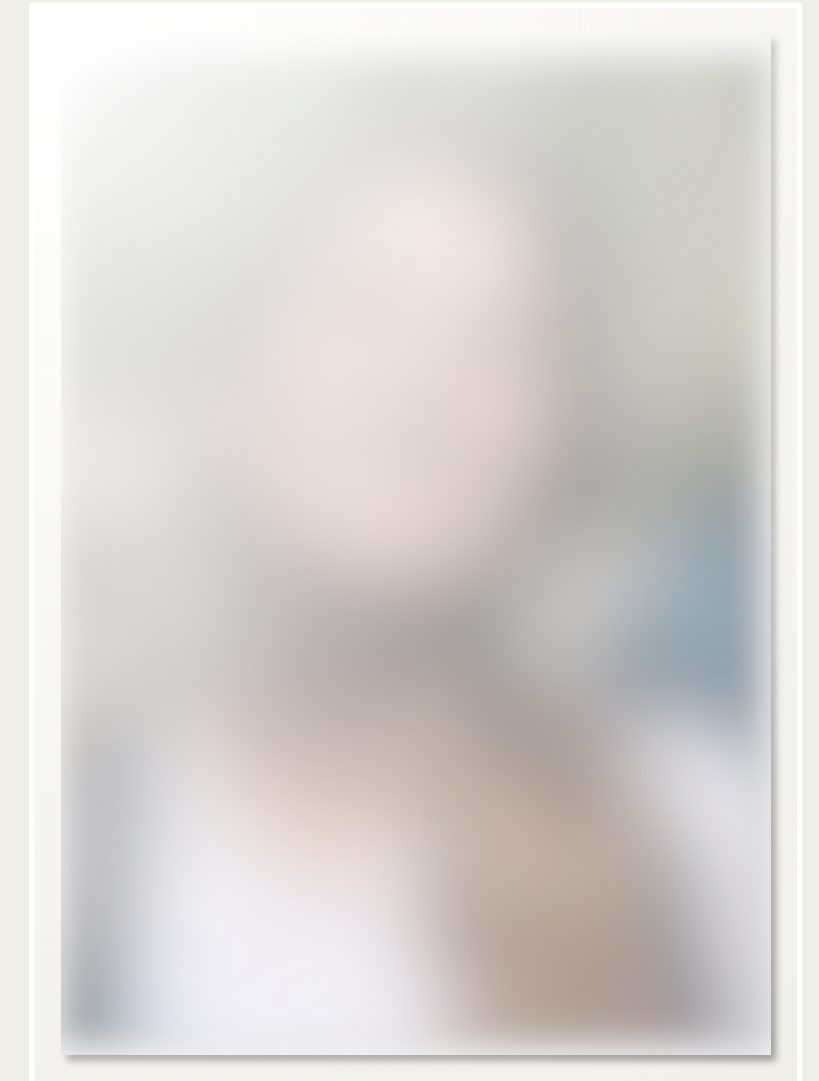
© 2023 American Society of Human Genetics.



# HOP Impact – On a Personal Level

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- Friend found HOP through my social media post.
- Genetic counselor informed the mutation increases her lifetime risk of breast cancer up to 40%.
- Now sees a Breast Specialist and a Gynecological Oncologist.
- Obtains yearly breast MRIs and will seek yearly early detection methods for breast and ovarian cancer.
- **“For all of this I am so grateful I learned about the Healthy Oregon Project”**





# Other Opportunities – Project for FDA Petition

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- OHSU Hayflick lab gene expression clinical study for FDA petition.
- Pilot validation study and clinical sample processing workflow performed under CAP accredited laboratories – IGL and KDL.
- RNA extraction from blood and RNA normalization by the IGL → RT-qPCR testing by the KDL.
- The workload for CAP documentation was drastically reduced because HOP documentation sufficed in many instances or served as highly detailed templates.
- Added **additional service fees** for CAP Laboratory documentation, operations, consultations, and covering costs associated with accreditation (5% of total project cost).

## Why They Are Glad They Chose Us.

**Designing and testing of a project/experiment:** “The IGL team offered multiple sessions to discuss experimental design, list of control samples and optimization. We even had multiple chances to run some test samples. IGL did not offer cookie-cutter advice. ***They (the IGL) provided tailored guidance and solutions and had a deep understanding of our project's unique needs.***”

**Convenient sample delivery and fast delivery of results:** “It was absolutely easy to hand samples over to IGL, thanks to meticulous coordination and location (we are in the same building). Also, ***the turnaround time for extraction was very short with efficient data delivery.***”


**Well-coordinated collaboration:** “Our project involved total human blood RNA extraction by IGL and these samples needed to be delivered to KDL for the next step. ***The IGL made the transfer of samples to the KDL extremely easy and I did not need to do anything. All RNA sample data was shared without a single glitch.***”

-Suh Young Jeong, Ph.D. – COASY Project Manager

# Other Opportunities – COVID Testing to Diagnostic Lab

- COVID-19 pandemic starts → IGL HOP members fully shifted to creating and operating the OHSU COVID-19 Testing Laboratory.
- Technical and administrative skills acquired from HOP directly transferred to a CAP lab COVID-19 RNA extraction workflow.
- The construction, stocking and staffing of the lab was done in 14 days.
- This lab that CAP IGL members helped build is now the state-of-the-art, full-spectrum **OHSU Clinical Molecular & Microbiology Lab** – just down the hall from the IGL, and a collaborative partner.

OHSU launches in-house COVID-19



Earn 15 points

Seizing the moment to take a great leap forward

The catalyst occurred mid-day on Feb. 28, 2020. And, three years later to the day, it has culminated in a great leap forward for OHSU.

On Feb. 28, 2023, the full-spectrum OHSU Clinical Microbiology Lab went live, greatly expanding capacity to - and the speed with which OHSU can - identify, treat and, where relevant, contain viruses and diseases, and handle myriad other patient and research samples. The beneficiaries: patients and families, the entire state of Oregon, and all of OHSU's missions.

"The productivity of the full-spectrum lab is astonishing," said John Hunter, M.D., FACS, professor of surgery, OHSU School of Medicine, and CEO of OHSU Health. "Samples that once took days or longer to process can now be done in hours or less, with enormous benefit to patient care as well as to research and education. None of this would be possible if we did not have such a highly skilled and committed cadre of lab team managers

# The CAP Accreditation Process

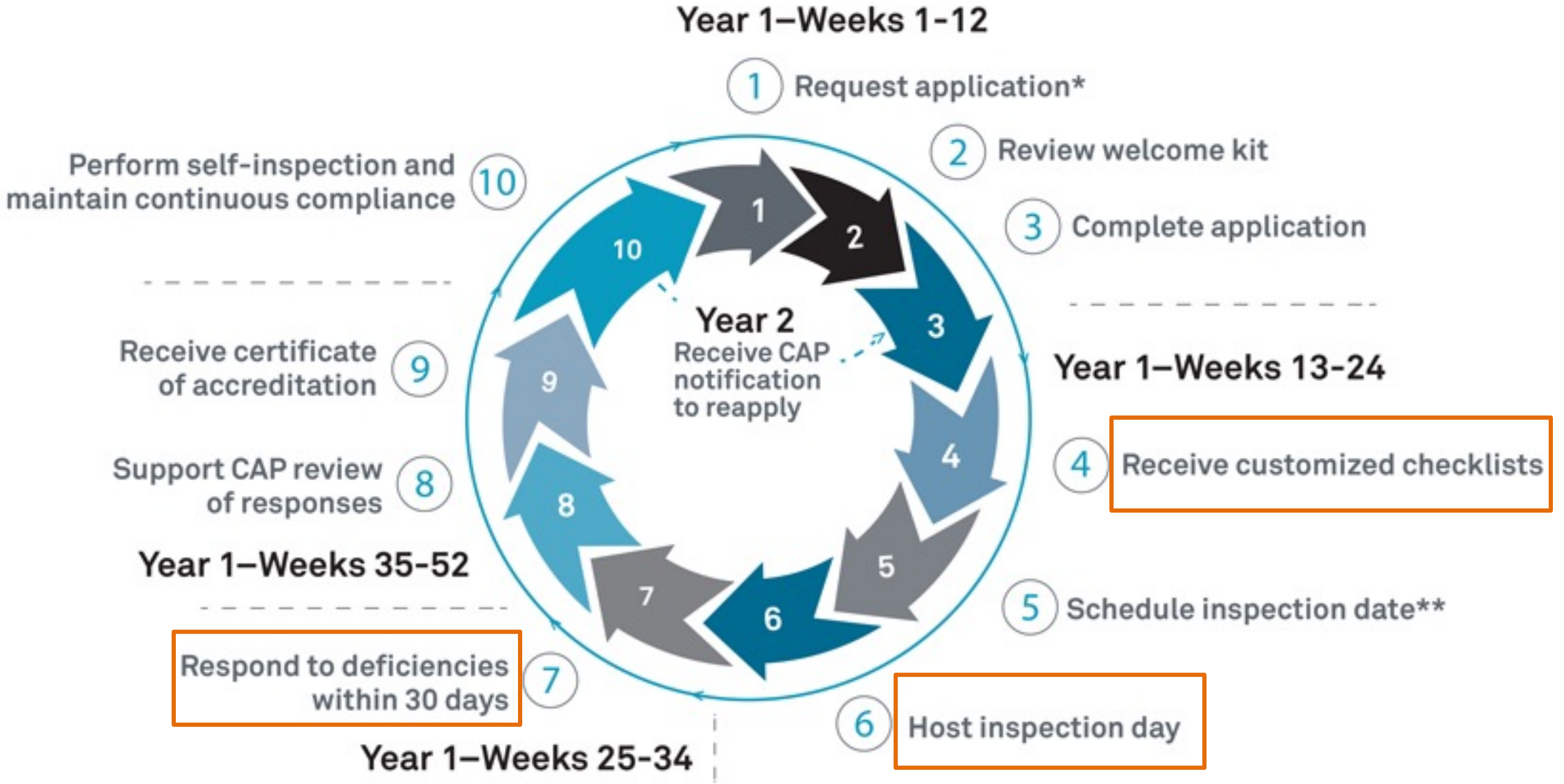
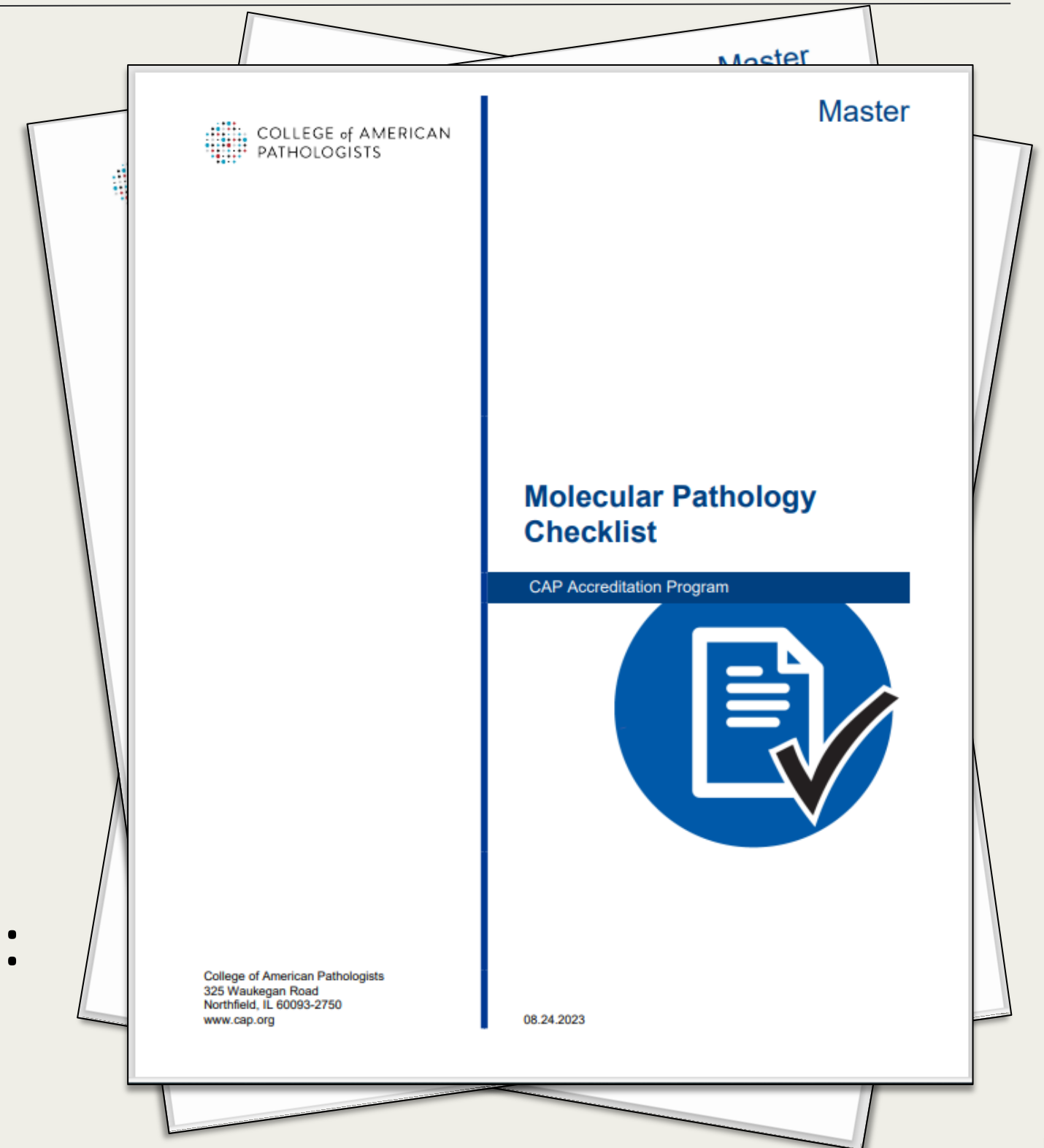


Image from <https://www.cap.org/laboratory-improvement/accreditation/accreditation-process>

# CAP Checklists

- Comprehensive sets of guidelines and standards.
- Designed to help laboratories ensure the accuracy, quality, and safety of their services.
- Depending on the work you are doing, you will be assigned customized checklists.
- The IGL CAP lab has the following checklists:



# CAP Checklists – What Do They Cover?

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## Laboratory General:

- Quality management system
- Specimen collection and handling
- Specimen chain-of-custody
- Specimen transport and tracking
- Personnel qualification and requirements
- Training and competency
- Physical facilities
- Laboratory safety

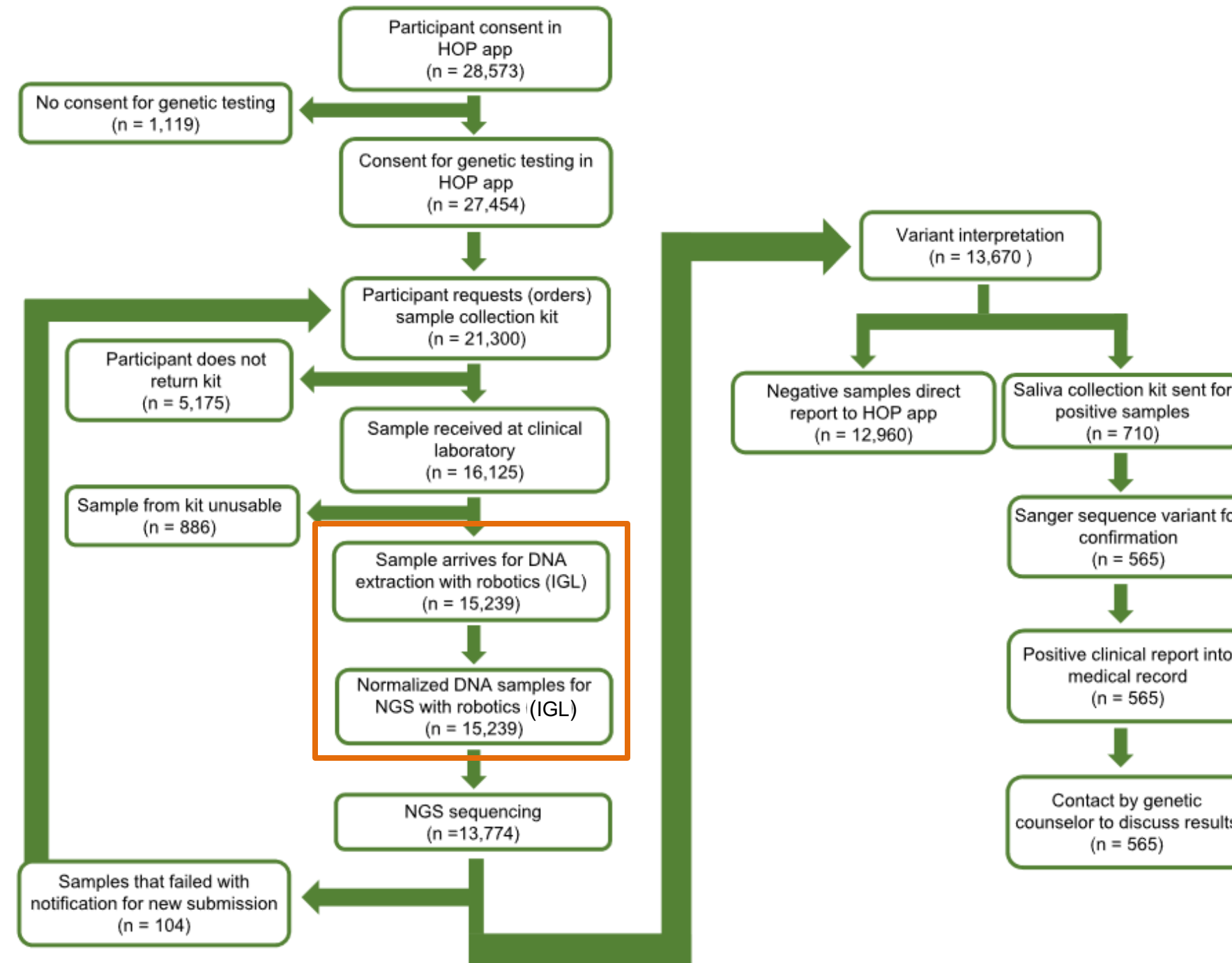
## All Common:

- Policy and procedure manuals
- Reagents labeling, storage, handling, disposal, etc.
- Instruments and equipment maintenance
- Thermometers and temperature dependent equipment and environments
- Pipette calibrations
- Test method validation
- Individualized quality control plans

## Molecular Pathology:

- Molecular assay validation
- Turnaround time
- Specimen records
- Metrics for specimen quality and quantity
- Specimen storage and retention
- Positive and negative controls
- Assay performance monitoring

# Healthy Oregon Project Workflow



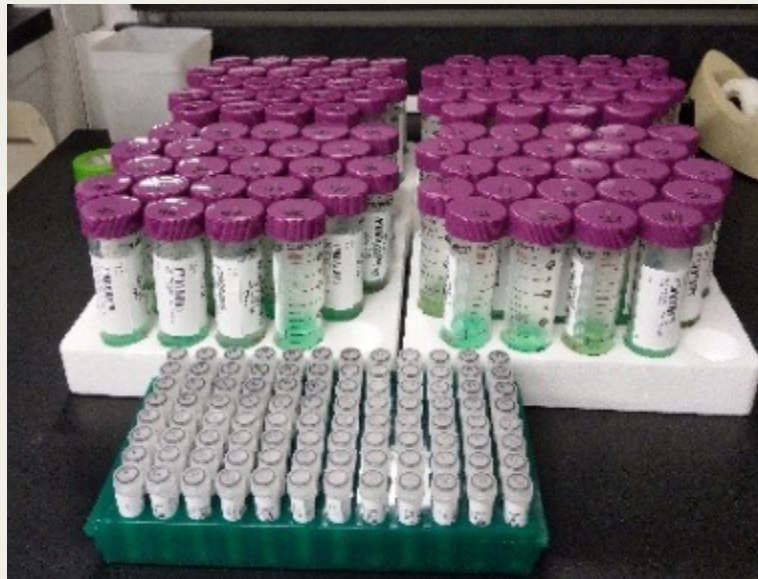
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# CAP Requirements for IGL HOP Workflow

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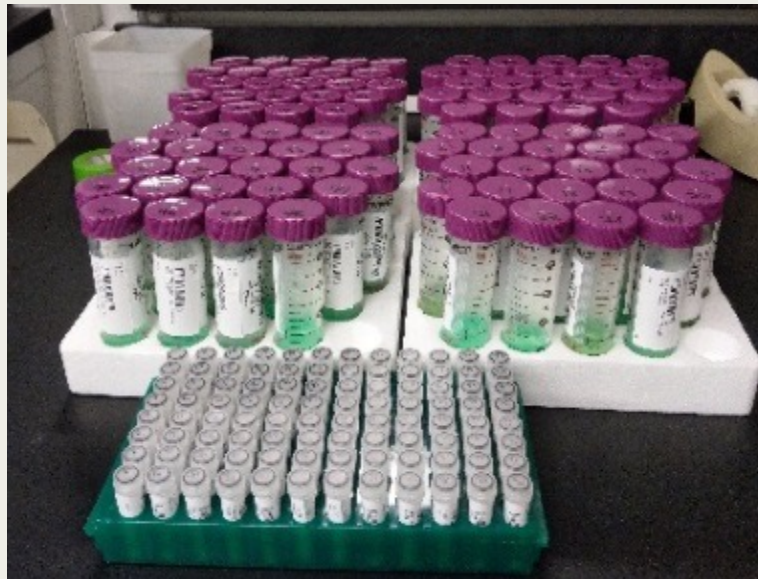
Receive samples from  
KDL via courier



- SOP for sample transfer/receiving/transport
- Policies for sample storage and environmental monitoring
- Policies for sample rejection criteria
- Error log for rejected samples
- Designated, secure storage area
- Temperature monitoring for storage areas (4°C, -20°C, and RT) checked daily
- Trained personnel with training and competency documents on file
- Chain of custody documentation

# CAP Requirements for IGL HOP Workflow

Receive samples from  
KDL via courier



Concentrate saliva cells,  
lyse, barcode check and  
transfer to robot-  
compatible tubes

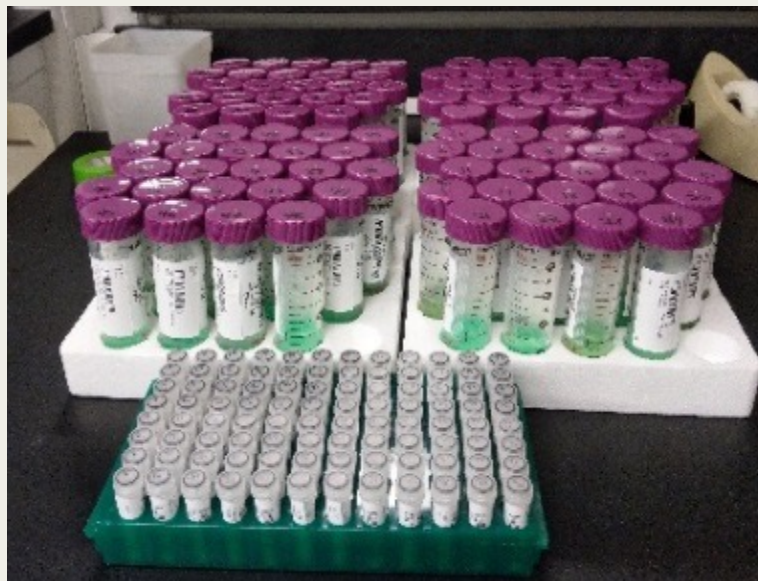


- Initial pilot validation study on file
- SOP for sample processing workflow
- Barcode/sample ID check file
- Certification documentation for biosafety cabinet and centrifuge PMs
- Safety policies and posted signs for biohazardous samples
- Inventory and specimen tracking documentation
- Chemical hygiene plan
- Maintenance logs for equipment cleaning
- Calibration documentations for pipets
- Separate, “clinical use only” consumables, stored in secure location.



# CAP Requirements for IGL HOP Workflow

Receive samples from KDL via courier



Concentrate saliva cells, lysed, barcode check and transfer to robot-compatible tubes



Extract DNA next day using QIA Symphony.



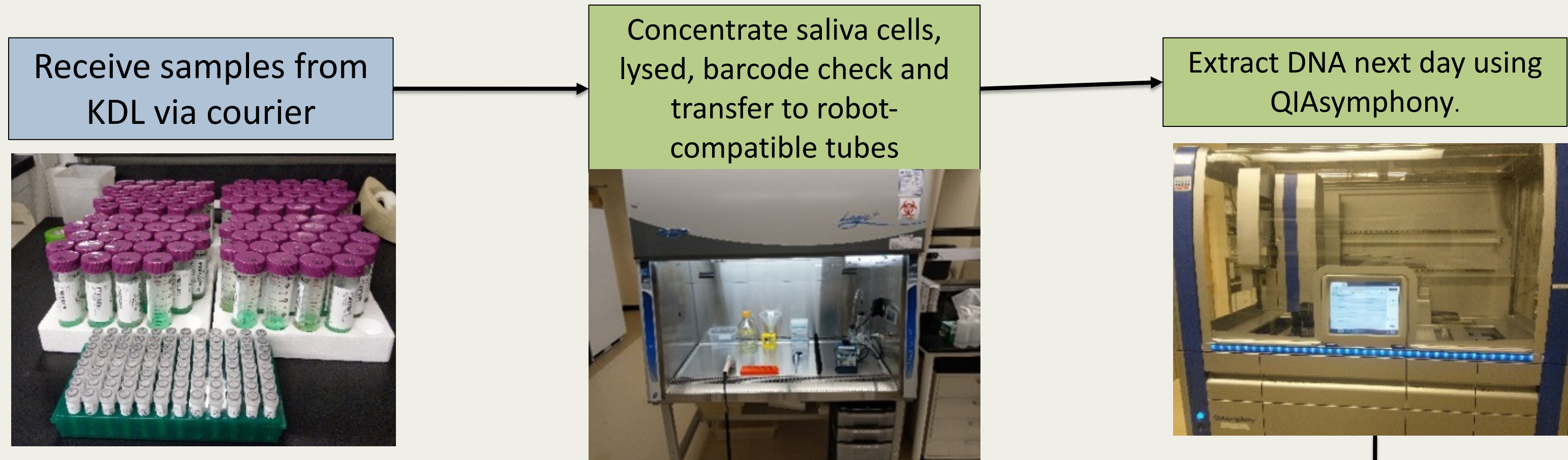
Quantify & Normalize DNA with using Liquid handling robot and Plate Reader



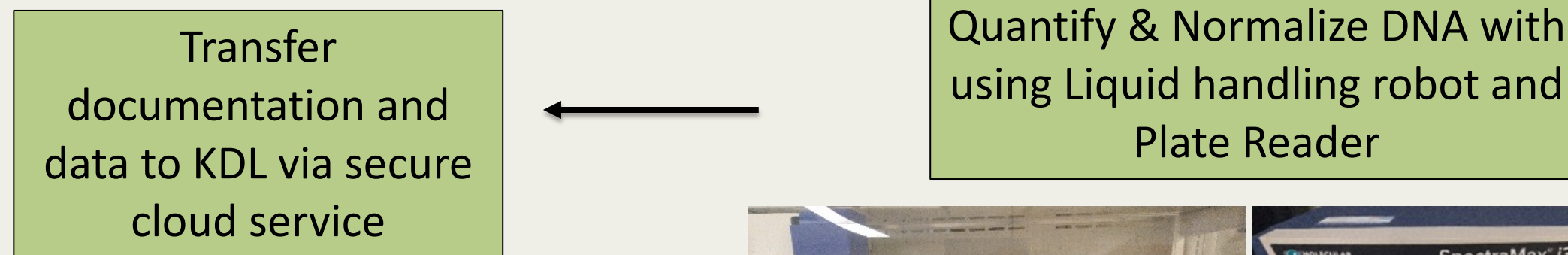
- Consumables lot recalls & actions taken
- Logs and reports for instrument crashes and errors
- Documentations for PMs and repairs

- Reagent lot tracking
- Reagent lot tests with “+” and “-” controls
- Failed standard curves and control testing stored on file

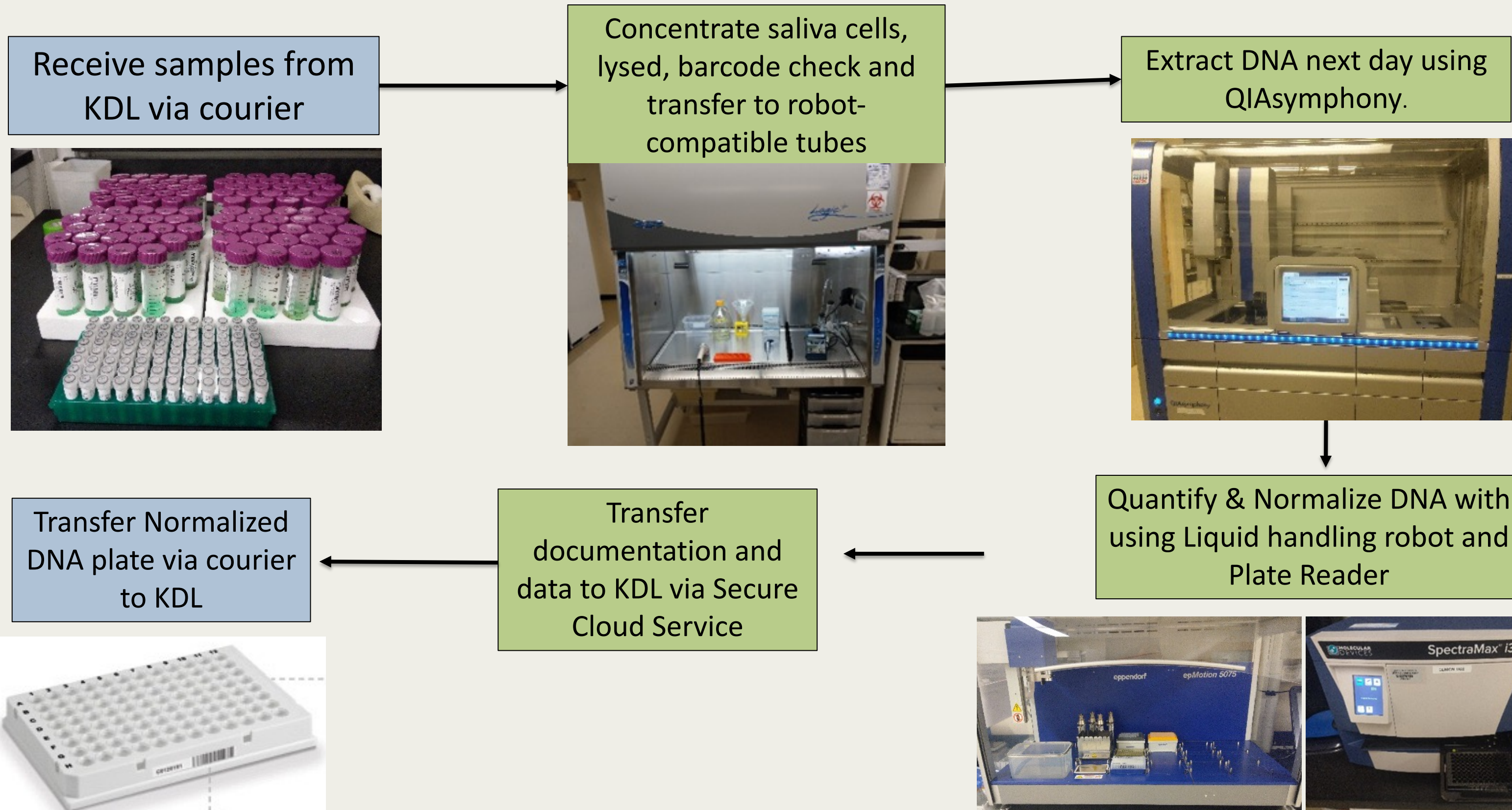
# CAP Requirements for IGL HOP Workflow



- Patient data transfer must be secure & HIPAA compliant
- Policies for retention of records and materials that must comply with laws and regulations



# CAP Requirements for IGL HOP Workflow



# The Inspection

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- First inspection *should* be announced, on-site, and pre-arranged with the inspection team leader.
- Window of inspection will be ~6 months after you complete online application.
- CAP inspector will review the laboratory's policies and procedures, observe personnel performing services, and review records.
- All checklist items relevant to your CAP lab are open for review.



# The Inspection

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All subsequent inspections\*:

- Every 2-years
- You need to reapply
- Unannounced
- 1 hour notice given
- Within 90 days of inspection anniversary
- You can request blackout dates
- Self-inspections the year in between



# CAP Deficiencies

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- Inspectors want to find deficiencies, big or small.
- 30-days to officially respond to deficiencies.
- **Phase 1** deficiencies compromise the quality of the services without endangering the health and safety of patients, clients, or personnel.
  - Written response describing corrective action.
- **Phase 2** deficiencies may have a serious impact on the quality of services or may endanger the health and safety of patients, clients, or personnel.
  - Response of corrective action and supporting documentation.
- Potential consequences of failing to correct deficiencies are risk of not obtaining or losing CAP accreditation and/or probation.



# CAP Deficiencies - Examples

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- **Failure to monitor room temperature. Phase 1.**
  - Action: Installed Aeroscout room temperature monitors. Perform daily checks of temps, alert system set up if temps out of range, monthly environmental monitoring summary reports.
- **Failure to lot validate diagnostic grade extraction kits. Phase 2.**
  - Action: Implemented lot testing SOP for DNA extraction kits using pooled positive controls. QC metrics developed for determining satisfactory lots for extraction kits.



# Lesson Learned & Advice!

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- CAP accreditation improves your laboratory operations for research projects too.
- Find mentors and collaborators.
- Negotiate sharing instrument service contract expenses and personnel FTEs.
- Shared space/equipment used for clinical work is open to inspection.
- Understand if your lab will also need to be regulated by CLIA (Clinical Laboratory Improvement Amendments).
- Obtain copies of the CAP checklists to get a sense of what is required.
- Have the required documentation, operations, a validation study in the works.
- Perform a mock inspection.



# Thank you!

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## **Current & Past IGL Team Members:**

- Chris Harrington, Ph.D.
- Trevor McFarland
- Samuel Medica
- Tiana Weeks
- Jacob Buitrago
- Syber Haverlack
- Jinah Kim, Ph.D.

## **KDL/CEDAR Team Members:**

- Sarah McCabe
- Christopher Corless, MD
- Katie Johnson-Camacho
- Madeleine Matheis
- Gregory Goh
- Travis Hayes
- Other members of KDL/CEDAR

## **Qiagen Members:**

- Karen Fortenberry
- Tony Stepan

# Questions?

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Britt Daughtry, Ph.D.

CAP Lab Technical Supervisor | Sr. Core Scientist | Lab Manager

13 October, 2023

# Other CAP Checklists

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- Anatomic Pathology
- Biorepository
- Chemistry and Toxicology
- Clinical Biochemical Genetics
- Cytogenetics
- Cytopathology
- Flow Cytometry
- Forensic Drug Testing
- Hematology and Coagulation
- Histocompatibility
- Immunology
- Microbiology
- Urinalysis

# OBJECTIVES

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- What is CAP?
- Why We Started a CAP Lab
- Healthy Oregon Project Workflow
- The IGL CAP Team
- HOP Impact
- Other Opportunities
- The CAP Accreditation Process
- CAP Checklists
- CAP Requirements for IGL HOP Workflow
- The Inspection
- CAP Deficiencies
- Lesson Learned & Advice