

## Introduction

The application of genomics to understand disease in healthcare results in an ever increasing demand for greater sequencing data generation. Despite significant reductions in per-base sequencing cost over the last decade; infrastructure, capital, and reagent costs are still relatively expensive. Best in class sequencers can cost over \$1 million per instrument, and sequencing run costs can be tens of thousands of dollars. With such high costs it is important to maximize capacity utilization and reduce wasteful workflow steps.

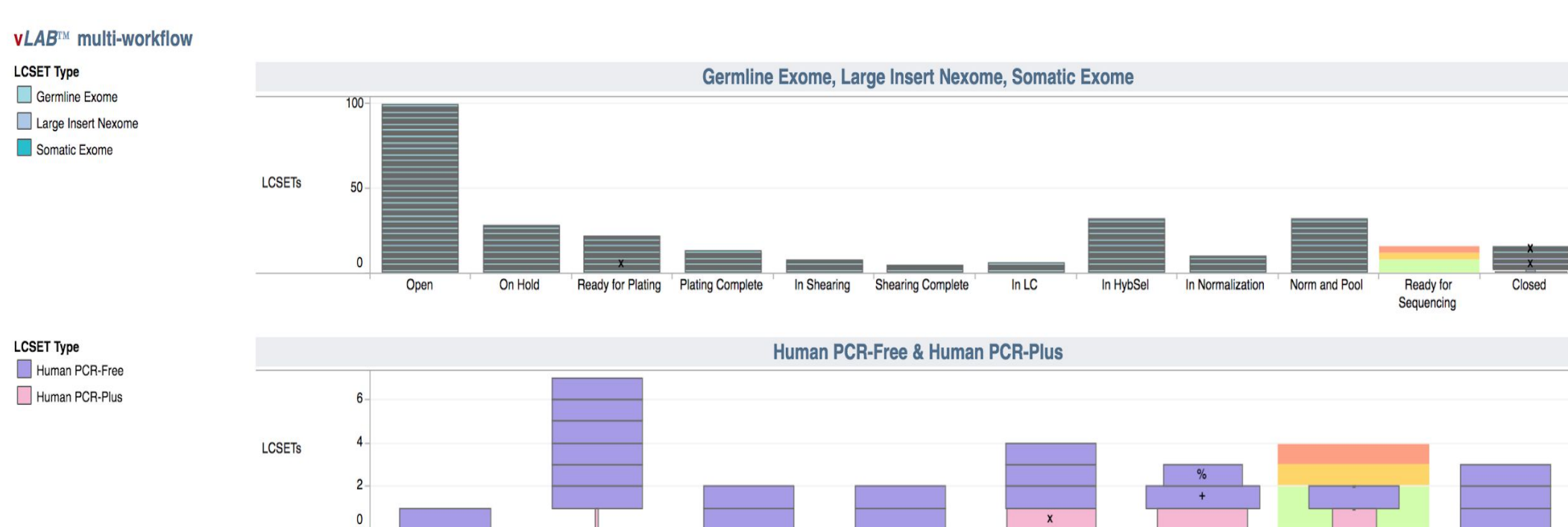
Through detailed observation and capacity analysis of process constraints in our production workflow, Library Construction was identified as a capacity bottleneck (with demand reaching >160% of utilization capacity).

According to Little's Law, running a consistent workflow at or around 100% is unstable. Ideally we would maintain a process or modify our workflows to achieve < 100% utilization based on best practices in the manufacturing field. By applying lean manufacturing methodologies and visual management techniques, we demonstrate a three fold scaling of our library preparation throughput capacity to over 300,000 samples annually achieved in less than a month. Combining the sample preparation methods for exomes and whole genomes into a unified, modularized workflow, samples and reagent supply chains have been optimized, resulting in a more efficient and cost effective processing.

## Key Points

In order to make these changes we had to think critically of our process and question why we did things the way we did. We also needed to be willing to challenge historical ideas about how things should be done to minimize 'waste' in the system.

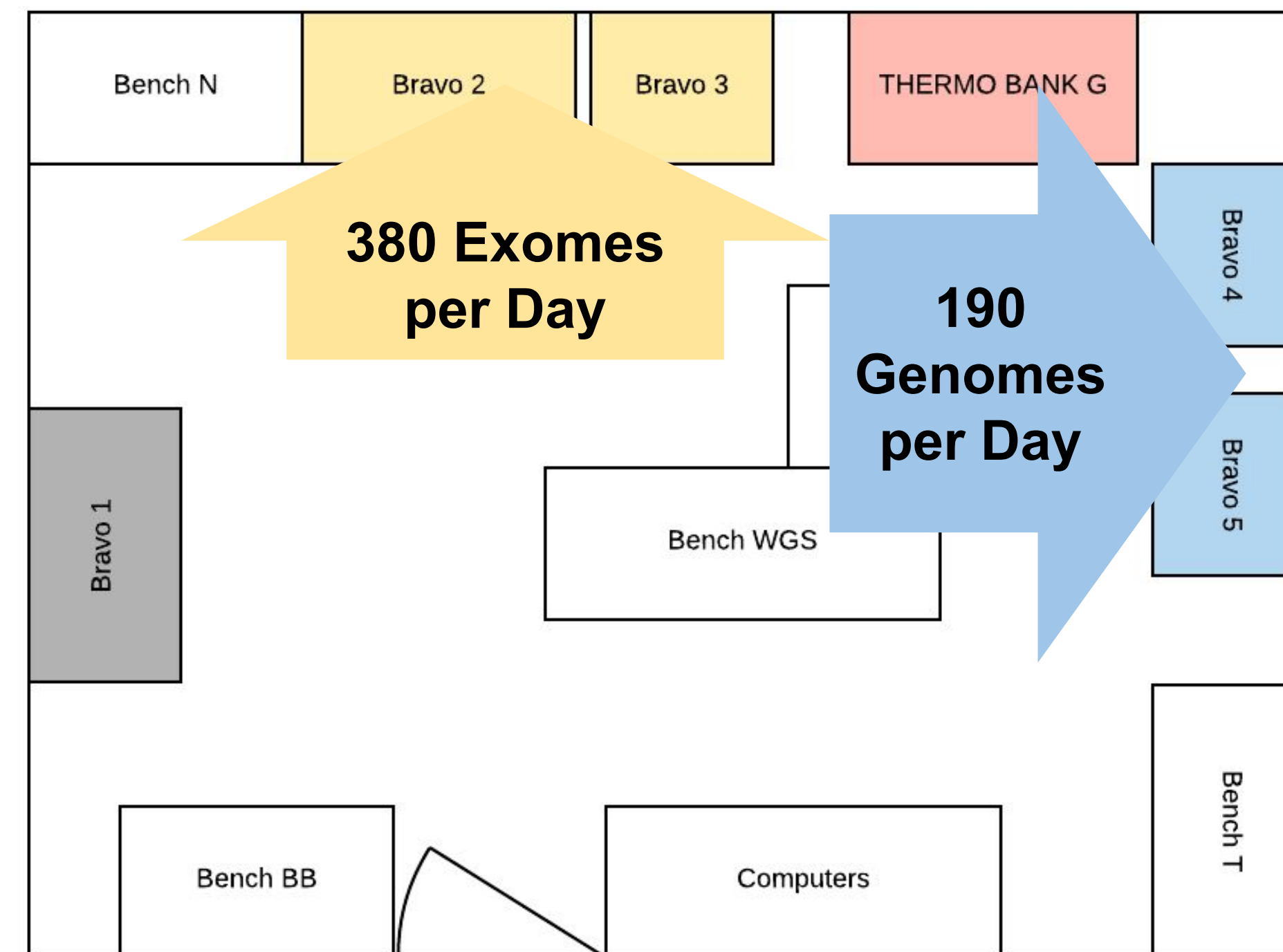
- Capacity Mapping - Identify and locate bottlenecks within the system
- Smaller Batch Sizes - Reduced process time yields greater utilization
- Pull system - Reduce inventory and over-processing
- Demand Leveling - Produce at the pace of the slowest subprocess
- Visual Management - Keep track of sets in new high volume setting
- Spaghetti Diagrams - Identify 'non-value added' movements
- Poka-Yoke - Error proofing to reduce wasted production



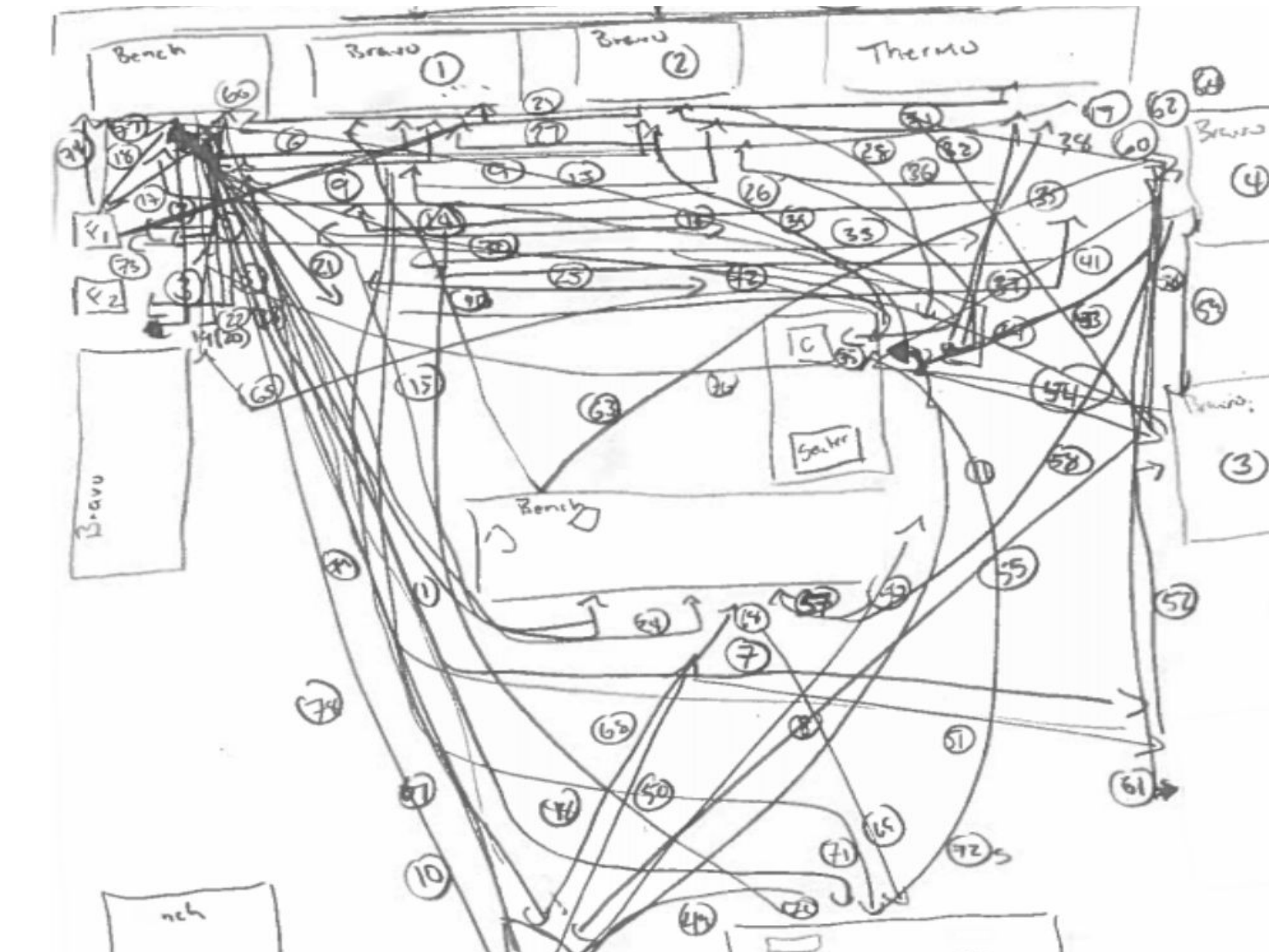
Above: Visual Management systems similar to this one are utilized throughout our processes. By creating a modular workflow it allows for us to easily choose which product gets the higher workload based on current demand.

## Elimination of Waste and Creation of Flow

### BEFORE



Above: A diagram of the Library Construction room, showing the layout of the room the room was organized to process segregated workflows, ultimately under utilizing the equipment

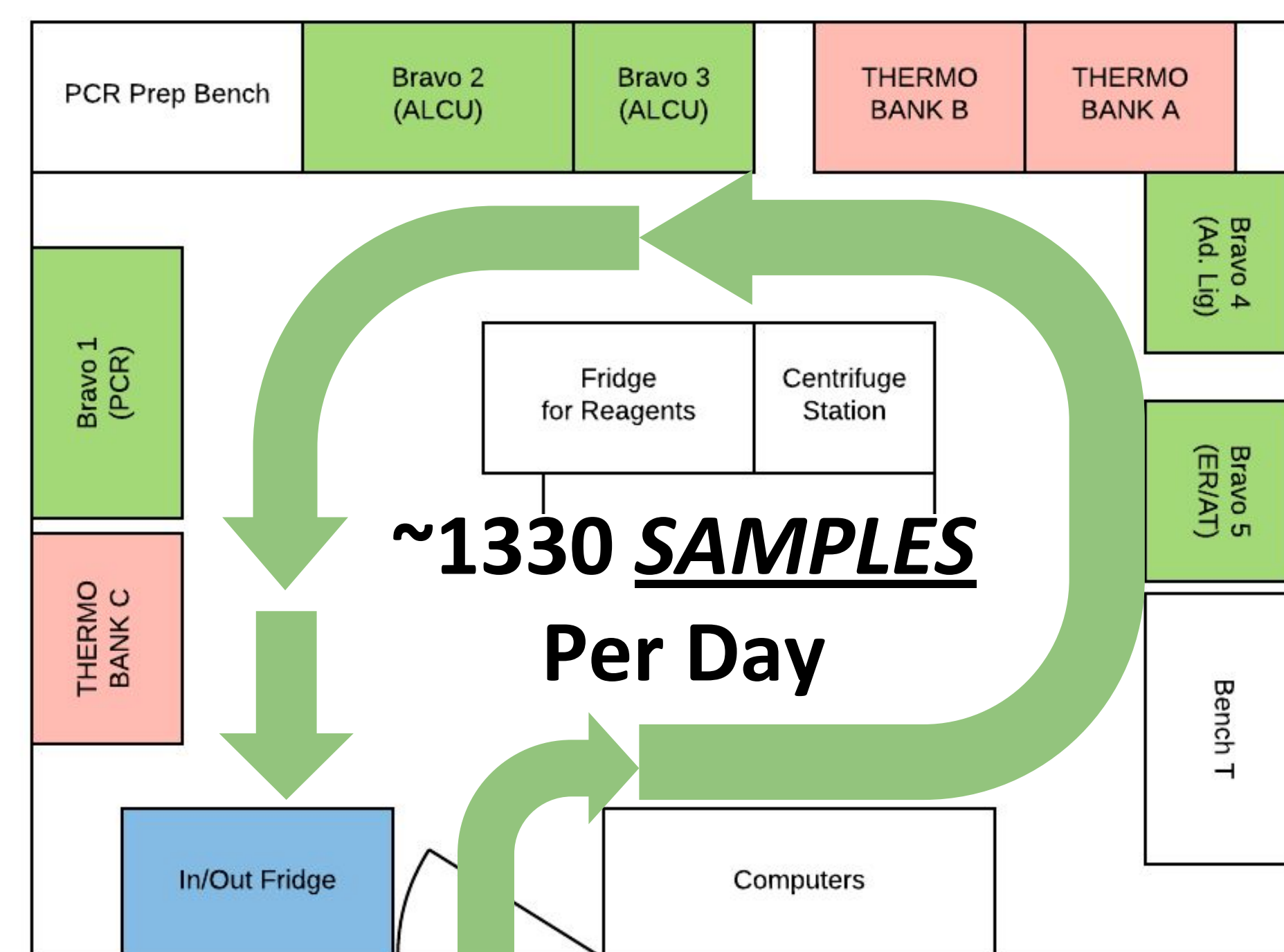


Above: A Spaghetti diagram produced by observing the movements of a single operator performing Exome Library Construction. The Diagram is very busy and messy, a reflection of the excessive movements operators had to make.

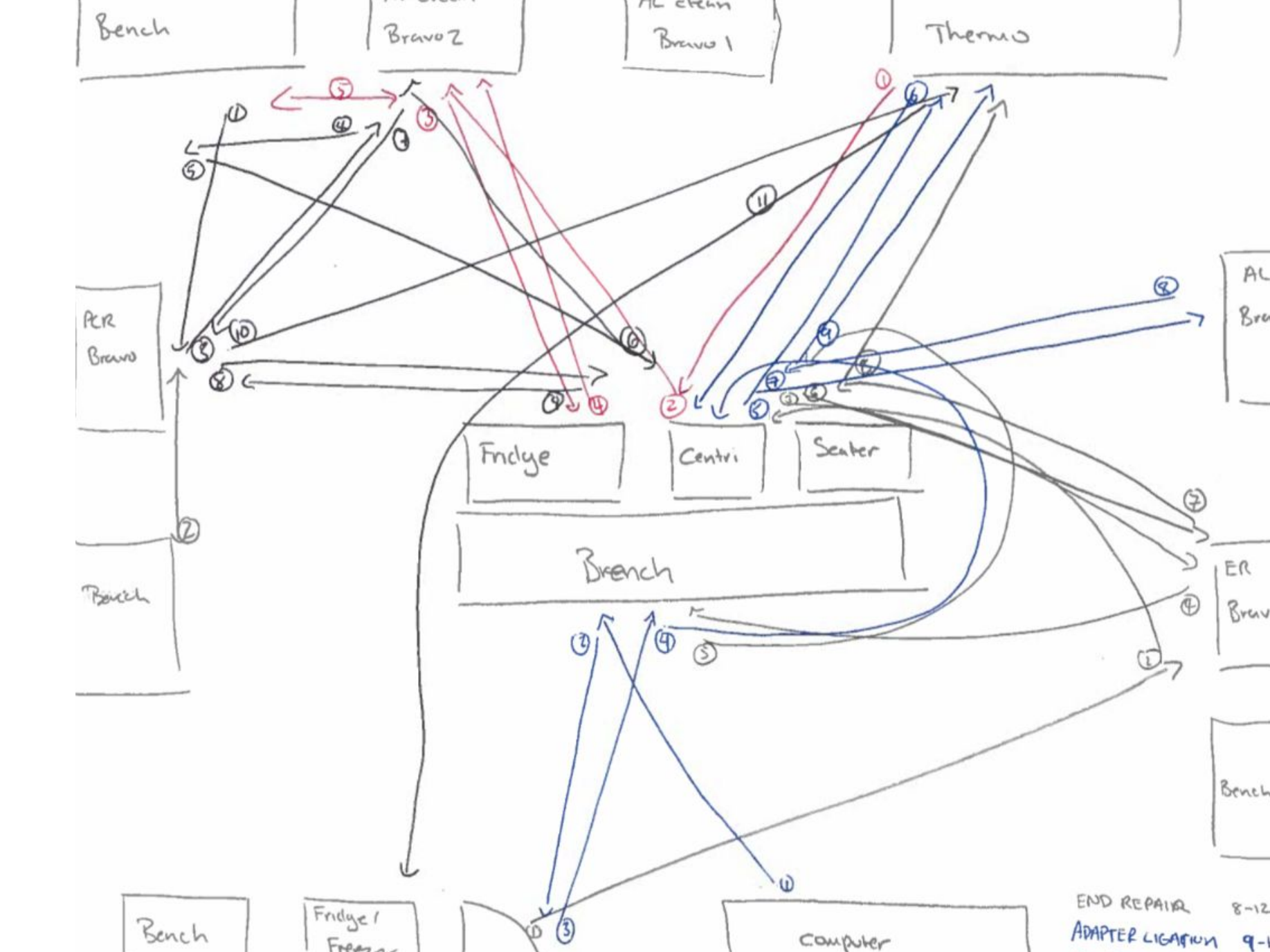
**Define** - We started our transformation process by defining an end goal - 300k samples annually  
**Measure** - Shadowing the lab to creating process and capacity maps and monitoring movement of samples  
**Analyze** - We found that to achieve our throughput goal of processing 300k samples/year we would need to operate at greater than 100% utilization of our capacity with the existing workflow and batch size. However, we noticed our machines were not running at even half their maximum uptime, and identified specific protocols that were bottlenecks within the process.

ER	ER Thermo	Adapter Ligation	AL Thermo	AL Cleanup	AL Cleanup (Genome)	PCR	PCR Thermo	PCR Clean-up	Pond Pico	Entire Process
26.79%	34.82%	28.02%	15.23%	75.29%	14.22%	22.05%	21.31%	33.07%	22.05%	162.3%

### AFTER



Above: The LC Room after changes. Each Bravo is now used for one step of LC, allowing for higher throughput processing.

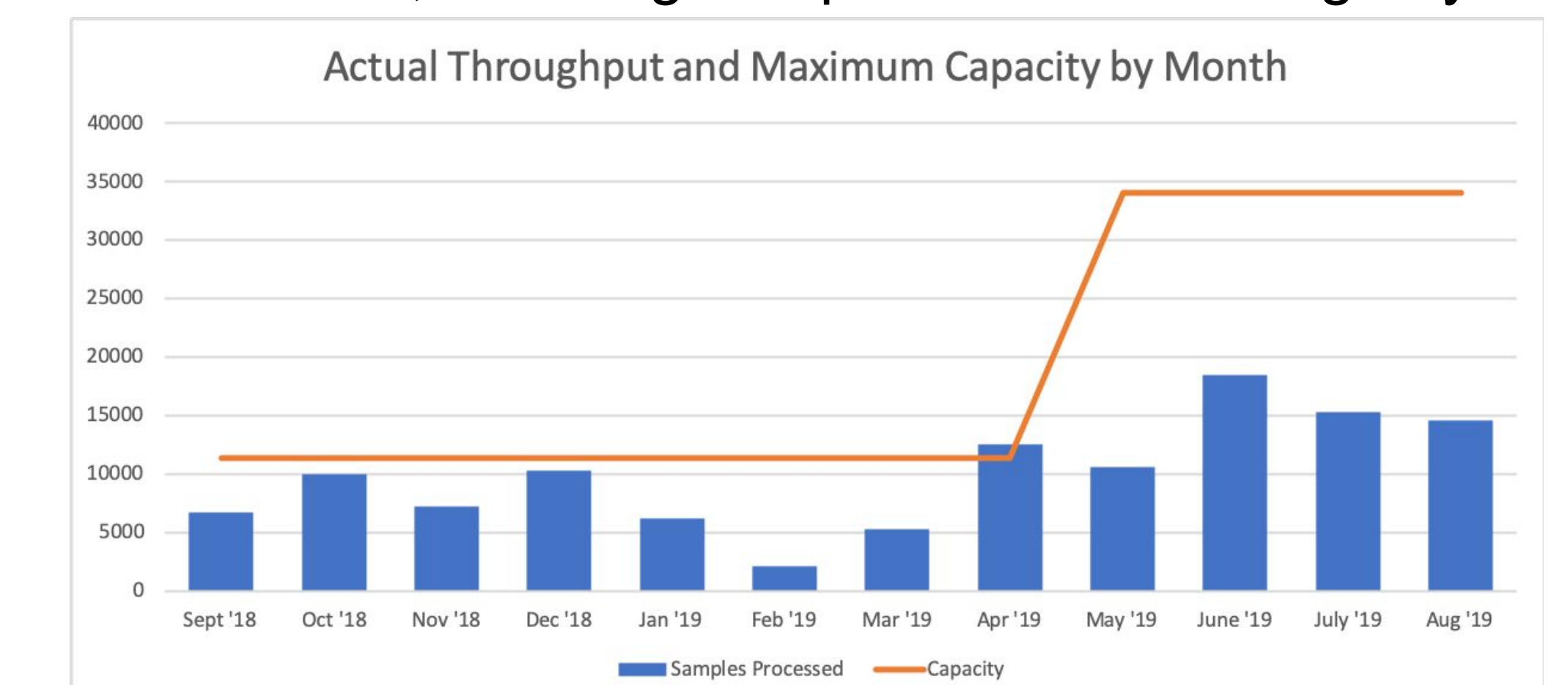


**Improve** - Library Construction team executed the proposed changes. Machines were reorganized and the lab was rearranged to reduce excess operator movements. As a result, we were able to reduce the burden of our bottleneck, and reduce the % utilization of our total capacity (enabling higher throughput if needed).

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26.79%	34.82%	28.02%	15.23%	55.38%	14.22%	22.05%	21.31%	33.07%	22.05%	66.67

## Changes Made

- Reorganized lab to reduce operator movement
- Made Bravos universal: any script can be run on any bravo.
- Split 1 large thermocycler bank into 3 smaller banks, one for each step of Library Construction (End Repair/A-Tail, Adaptor Ligation, PCR).
- Placed an in/out box adjacent to the entrance door.
- Added a second computer in the room, allowing both operators to use Jira LIMS.
- Reduced batch size from 4(Exomes) and 2(Genomes) to 1. This allows flexibility and modularity in the amount of samples processed on a given day.
- Created system for creation and storage of reagent plates.
- Began prepping for the next days LC in the afternoons, reducing setup time the following day.



## Conclusion

Historically, genomics research and the principles that tie into manufacturing at scale have not been widely associated together. As the demand for genomics research continues to climb, however, we are forced to respond by creating industrialized workflows.

Applying lean manufacturing practices and streamlining our workflow has realized a three fold increase in our Library Construction throughput without additional equipment or personnel. Previously our Library Construction step was viewed as a major bottleneck in our genome and exome sequencing workflows, but this is no longer the case.

We have removed library construction as a bottleneck and in doing so, also created free time for technicians to address newly revealed bottlenecks in other areas of our sequencing workflow, which present the team with a clear path to processing 1 million samples annually.

## Acknowledgments

Data used in this poster was generated at the Broad Institute, for more information please visit: <http://genomics.broadinstitute.org/>