An evaluation of the Ultima Genomics sequencing platform: scalable, high-throughput sequencing for low-cost whole genome sequencing

Matthew Coole1, Tom Howd1, Florian Oberstrass2, Martin Sosa2, Sophie Low1, Tyson Clark2, Andrew Bernier1, Bharathi Gandi1, Siobhan Donovan1, Jack Stohlman1, Megan Shand1, Maura Costello1, Corey Nolet1, Yossi Farjoun3, Niall Lennon1, Stacey Gabriel1

1. Broad Institute of MIT and Harvard, Cambridge, MA 02141 2. Ultima Genomics, Newark, CA 94560 3. Lady Davis Institute for Medical Research, Montreal, QC, Canada

**Introduction**

The cost for Human Whole Genome Sequencing (WGS) has stabilized at a little less than $1,000 over the past few years, but the path to significant reduction is not clear. Lower WGS costs offer the chance to dramatically increase the production of population-scale studies and ultimately drive discovery and demonstration of utility of such data in the healthcare system. Ultima Genomics (UG) is a platform designed to enable continual cost decreases from a starting point of $1/Gb and operate at an industrial scale.

Here we introduce and evaluate the performance of the UG novel DNA sequencer in our lab at the Broad Institute and demonstrate an ability to run 10-12 WGS samples per wafer targeting 30-40x mean coverage on the UG 100 (20-24 samples per day, per instrument), we are able to constantly feed the sequencers with its short run times of sub-24 hours. With later advances in the wafer technology, both Ultima and the Broad Institute hope to scale to 25 samples/wafer (50 samples per day, per instrument).

**Wet Lab Workflow**

The Genomics Platform has the ability to generate 96 UG libraries in just three hours. This scaled library construction is outlined below. With the ability to run 10-12 WGS samples per wafer targeting 30-40x mean coverage on the UG 100 (20-24 samples per day, per instrument), we are able to constantly feed the sequencers with its short run times of sub-24 hours.

**Genome in a Bottle Performance**

The Genome in a Bottle (GIAB) metrics as a part of the 231 HapMap study. Sequencing was performed on two UG 100 sequencing systems, using Sequencing Chemistry version 21.1 and analyzed through Pipeline version 4.2.5.20.

**A Scalable Workflow**

Starting from genomic DNA, 96 PCR-free Whole Genome Sequencing (WGS) libraries were made using the NEBNext Ultra II FS DNA Library Prep Kit on an Agilent Bravo liquid handler. After in-process QC’s were performed, the libraries were pooled volumetrically into 6-plexes.

Using an OpenTrons OT-2 system, the pooled DNA was enriched and emulsified. After this, a user set up the automated UG AMP1 system where the pools were electrostatically broken and prepared for sequencing on the Ultima Genomics AMP1 automated system. Bead yields were measured via flow cytometry to ensure that 108 beads were loaded onto the UG 100 sequencer, where roughly 78 beads (raw reads) landed on each wafer.

**Results**

The Ultima Genomics UG 100 is a scalable and high-throughput sequencing system, which can be used for all types of genomics applications. It fits nicely into the Broad Institute Genomics Platforms industrial-scale sample prep workflow, in which we envision running large biobank and GWAS studies. Given run times of <24hrs and a cost of ~$1/Gb, the tools will lend themselves to other research applications such as whole exome sequencing, single-cell genomics, genetic perturbation screens, and CRISPR screening.

For more information on the analysis pipeline, please see Megan Shand’s poster #201 entitled “Optimizing the GATK for the Ultima Genomics sequencing platform: an evaluation of 200 whole genome HapMap samples”. Please also see the pre-print, below, in BioRxiv.org from May 29, 2022.