Optimizing workflows to support genomic medicine efforts

The Health 2030 Genome Center uses Illumina Genomics Architecture and Illumina DNA PCR-Free Prep to maximize throughput for large-scale sequencing studies

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Whole-genome sequencing (WGS) provides a comprehensive view of coding and noncoding variants across an individual's genome in a single assay. Efforts are underway globally to curate data from large-scale WGS studies and translate this genetic information into actionable insights, including identifying disease-causing variants, predicting disease risk, and informing therapeutic strategies. Scalable solutions from Illumina, including Illumina Genomics Architecture (IGA) and Illumina DNA PCR-Free Prep, enable laboratories to optimize their sequencing workflows, reduce turnaround times, and improve efficiency while maintaining a high level of performance.

The Health 2030 Genome Center, based in Geneva, Switzerland, is an ISO 15189–accredited, nonprofit institution serving as a national genomics competence center for the promotion of personalized health and genomic medicine efforts internationally. The center has implemented IGA and Illumina DNA PCR-free Prep to streamline and optimize their WGS workflows. We spoke to Dr Pietro Cattaneo and Dr Cédric Howald from the Health 2030 Genome Center about their experience incorporating IGA and Illumina DNA PCR-Free Prep in their workflows and how deploying these solutions has enabled them to meet the demands of large-scale WGS projects.

Can you provide an overview of the Health 2030 Genome Center?

Pietro Cattaneo (PC): The Health 2030 Genome Center is a nonprofit institution that promotes personalized health and advances genomic medicine by acting as a genomics competence center for clinical diagnostics and biomedical research. Our activities incorporate ISO 15189–accredited DNA and RNA sequencing and data analytics for clinical and population genomics

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research. We provide genomics and transcriptomics expertise for clinical research to universities, hospitals, and companies across Switzerland and Europe. The Health 2030 Genome Center is involved in several Swiss national projects and initiatives, including the Swiss National Data Streams, the Genome of Switzerland project—both of which are funded by the Swiss Personalized Health Network and the Personalized Health Related Technologies Program—and the Swiss National Surveillance Program for SARS-CoV-2. We also provide genomics and transcriptomics expertise to the Swiss Multi-Omics Center (SMOC). The goal of SMOC is to deliver high-quality, integrated genomic, transcriptomic, proteomic, metabolomic, and lipidomic data enriched with expert data analysis and interpretation of multiomic data.

Can you tell me about your partnership with Illumina?

PC: We have successfully worked with Illumina for many years. Partnering with Illumina allowed the Health 2030 Genome Center to implement a functional, cost-effective, automated library preparation method quickly without investing the time and resources to develop the method. Vicky Goody and colleagues in the Illumina Customer Collaboration & Innovation Group had already implemented and optimized an Illumina DNA PCR-Free protocol for the Hamilton Microlab Star robot, which is the liquid-handling platform we use. Using this method developed by Illumina allowed us to benefit from the experience of the global network of labs using the same method.

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Why did you choose IGA and Illumina DNA PCR-Free Prep?

PC: The Health 2030 Genome Center, working with Hamilton, had previously implemented Illumina TruSeq™ DNA PCR-free and TruSeq Stranded mRNA-Seq protocols on our Hamilton liquid-handling robots. Around the time we began considering options for library preparation methods to manage the sample processing needs of a low-coverage WGS application, we were also evaluating the Illumina DNA PCR library reagents to support our high-coverage WGS needs. We were pleased with the performance of Illumina DNA PCR-Free Prep for high-coverage WGS. When we became aware that Illumina had developed and made available to customers Hamilton scripts for library preparation with these reagents, we stopped investigating other possibilities and put our efforts completely behind this Illumina option. Because we were already using two Hamilton Microlab Star workstations and Illumina had an already established automated method with Illumina DNA PCR-Free Prep, it was a natural first choice to install IGA on our premises. Our decision to work with the IGA solution was influenced by the fact that we could use it for both the standard

and low-coverage WGS DNA PCR-Free Prep protocols with no deck modification.

How have Illumina DNA PCR-Free Prep and IGA helped optimize your standard 30× WGS workflows?

PC: The rapid and straightforward Illumina DNA PCR-Free Prep protocol with its lower starting material requirements improves turnaround time and allows for the use of samples with limited amounts of material—two key project performance considerations. Additionally, having an IGA-based version of the protocol automated on our Hamilton robots gives us the capacity to easily manage low-coverage WGS projects with thousands of samples in a cost-effective manner. This existing capability will greatly facilitate the ongoing IGA-based automation of the high-coverage WGS library protocol, thus improving our ability to manage large-scale standard WGS projects (eg, 30× coverage).

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How does low-coverage WGS interact with standard 30× WGS?

PC: WGS at 1× or 2× coverage coupled with variant imputation shows similar performance to standard 30× WGS in both precision and recall for detecting genome-wide genetic variation. The Health 2030 Genome Center recently expanded its services to include low-coverage WGS to support SNP genotyping using variant imputation methods for population and predictive genomics studies, including population-scale genotyping, genetic trait mapping, and polygenic risk score computation. The low-coverage approach is particularly useful for large-scale population studies whereas standard WGS is more appropriate for variants discovery in clinical settings.

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How have you implemented IGA in your low-coverage WGS workflows?

Cédric Howald (CH): We first implemented IGA for low-coverage WGS to respond to the large-scale nature of such projects. It took about six months from the time that we had decided to work with this solution to have it running for production. This included about six weeks for sourcing the new hardware components and a week for upgrading the Hamilton deck to make it compatible with IGA. Another week was needed for the Illumina field specialist to install the method and have it running on our two Microlab Star robots. Pietro then took about four months, working part time, to fine-tune the method and validate the reproducibility and robustness. This was achieved in collaboration with the remote Illumina specialist. The flexibility of IGA allows us to use the standard WGS method

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with minor adaptations. We only had to modify some input files format to make them compatible with our Laboratory Information Management System (LIMS).

What tools do you use to analyze low-coverage WGS data?

CH: We perform mapping and variant calling using both the Broad Institute Genome Analysis Toolkit (GATK) and DRAGEN™ secondary analysis. We use GLIMPSE software[1] for imputation. We have tested imputation using the DRAGEN implementation of GLIMPSE which gave comparable results. The Hap.py software from Illumina is used to estimate the precision and recall.

What impact have Illumina DNA PCR-Free Prep and IGA had on your laboratory operations?

PC: For low-coverage WGS using two Microlab Star robots, we are now able to prep up to 768 samples per day after implementing IGA. This represents a huge throughput increase compared to one operator prepping samples manually. The flexibility given by IGA, which enables prepping from 24 to 96 samples per run, is a major asset to respond to the growing demand for standard WGS. The low-coverage implementation of IGA allows us to perform the Illumina DNA PCR-Free protocol with as low as 150 ng of genomic DNA per reaction without impacting the quality of the results. Our implementation of the standard WGS IGA DNA PCR-Free protocol will allow us to start with a third of the currently accredited TruSeq DNA PCR-Free protocol input material. This is a significant improvement, especially for clinical research samples, which can vary greatly in content and quality.

What role do Illumina DNA PCR-Free Prep and IGA have in the future direction of Health 2030 Genome Center?

CH: We have recently broadened our ISO 15189–accredited WGS workflow to include variant calling and interpretation software. Following library preparation using the Illumina DNA PCR-Free prep reagents and high-coverage sequencing, variants are called with DRAGEN analysis and made available to the Congenica platform, which we run inhouse, so that researchers can prioritize and interpret variants. One key role of the Health 2030 Genome Center is to anticipate and develop clinically accredited services for Swiss hospitals and universities, therefore automating this workflow with the Illumina DNA PCR-Free Prep and IGA is a natural step in this direction.

Learn more

Illumina DNA PCR-Free Prep

Illumina Genomics Architecture

Accelerating NGS workflows with Illumina Genomics Architecture

Health 2030 Genome Center

Hap.py software

Reference

1. Rubinacci S, Ribeiro DM, Hofmeister RJ, Delaneau O. Efficient phasing and imputation of low-coverage sequencing data using large reference panels. *Nat Genet*. 2021;53(1):120-126. doi:10.1038/s41588-020-00756-0

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