

Supporting the Future of a Genomics-Based Health Care Model

Human Longevity, Inc. is using HiSeq X[™] Ten Systems for various genomic programs designed to one day help customers improve their health so they can live their lives to the fullest.

Founded in 2013, Human Longevity Inc. (HLI) is the brain child of J. Craig Venter, Ph.D., Robert Hariri, M.D., Ph.D., and Peter H. Diamandis, M.D. As the name implies, HLI focuses on extending the healthy human life span. By combining the power of genomics, informatics, and stem cell therapies, the company aims to address challenges related to aging and aging-related diseases. "HLI is going to change the way medicine is practiced by helping to shift to a more preventive, genomic-based medicine model that we believe will lower health care costs. Our goal is not necessarily lengthening life, but extending a healthier, high-performing, more productive life span," states Dr. Venter.

HLI, launched in March, has been building one of the largest human sequencing operations in the world to compile the most comprehensive and complete human genotype, microbiome, and phenotype database available. Accomplishing this enormous task will require massive amounts of sequence data. To obtain it, HLI is using 2 Illumina HiSeq X Ten Sequencing Systems to sequence up to 40,000 human genomes per year, with plans to scale to 100,000 genomes a year.

Recently, we had an opportunity to speak with two of the people leading HLI on this journey from research to clinic, Felix Frueh, Ph.D., Chief Scientific Officer and William Biggs, Ph.D., Head of Genomic Sequencing. We learned that HLI is well-positioned to change the way medicine is practiced in the future.

Q: What made you want to join HLI?

Felix Frueh (FF): I'm a scientist by training and have worked in various health care settings in technology development and diagnostic companies. I worked at the FDA building the genetics and genomics review capabilities for drug and diagnostic development and then at a large pharmacy benefit management organization running R&D oriented towards real-world clinical practice. When the opportunity for HLI came up, it really encompassed my dream to bring all these pieces together. To me, this opportunity is really exciting because it creates the continuum from data creation through interpretation and translation into clinical practice. That's what we are working on here.



William Biggs, Ph.D. is Head of Genomic Sequencing for HLI. He and his team are building the largest genomic sequencing facility in the world.



As Chief Scientific Officer of HLI, Felix Frueh, Ph.D., leads all genomic operations including non-clinical microbiome testing; high-throughput, next-generation genomic sequencing; and research collaborations and partnerships.

"...this opportunity is really exciting because it creates the continuum from data creation through interpretation and translation into clinical practice." William Biggs (WB): Over the past decade, I have built a number of testing laboratories, all with the goal of driving the acceptance and utilization of cutting-edge molecular biology in routine medical practice. That's a very challenging scenario. There are a number of stakeholders related to all aspects of health care. To drive the acceptance of techniques such as whole-genome sequencing in medical practice, one really has to drive that process with all of the stakeholders in mind. It's entities like HLI that have the capability and focus to do that.

Q: With sequencing being such an integral part of what you're doing, was the genesis of the company really that sequencing finally came of age?

FF: I would say yes. Even a year ago, it would have been cost-prohibitive to try to do what we want to do. We're aiming at sequencing about a million genomes within the next 5 to 6 years. The sheer size of the facility needed would not have been possible without the arrival of the HiSeq X Ten System.

WB: Typically, enabling broad-base utilization of wholegenome sequencing technologies is difficult. Evidence is about scale. So the HiSeq X Ten System and robust IT infrastructure are making possible the analysis of large cohorts of individuals that allow us to make the argument that we have the evidence.

Q: What mechanisms or processes are you hoping to uncover by sequencing that many people?

WB: Numbers are important because genetic variation is so individual and the genetic variation driving disease is indeed personal. There are studies out there where many of the large publically financed genome efforts are estimating that you need upwards of 50,000 individuals to have a sufficient statistical power to provide the evidence that's needed. That's how we decided that we needed 500,000 to 1 million genomes in the database. At the end of the day, each individual only cares about his or her own genome. Ultimately, the goal is for all of us to have our genomes sequenced and available as a medical reference for our clinical care.

Q: Where are the samples for sequencing coming from?

FF: The samples are coming from various sources. It's driven by opportunities that we feel are in line with the idea of identifying diseases associated with longevity. By longevity I don't mean as centenarians or super-centenarians, but as extending healthy lives. That also includes the life of someone who is sick or will predictably become sick based on just their genetic predisposition. We're looking at cohorts where we believe that the genetic information will be able to influence medical decisions in a positive manner. Q: Do you have agreements with organizations to have access to those samples? Or are these samples that you're acquiring through testing within your labs? FF: We have fairly substantial agreements with University of California, San Diego (UCSD) and additional ones that we can't disclose publically. Certainly, many pharma companies are interested in looking at larger and larger portions of the genome for their clinical trial populations. We're talking to entire countries for population-wide sequencing. So there are a number of opportunities that we're evaluating. Our company vision goes way beyond being a fee for service sequencing company. We truly have a vision for changing the way we're dealing with molecular, genetic-driven medicine and how we can translate that information into clinical practice.

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Q: In addition to whole-genome data, you're looking at data from the microbiome and the metabolome. Why are these "-omes" important?

FF: If you think about what impacts disease, there are genetic and genomic factors, and also environmental factors that are critical not only for disease development, progression, and treatment, but also for maintaining a healthy state. We're trying to get molecular characterization to the level where we can accurately, reproducibly, and specifically measure anything that has to do with disease.

We know we can sequence the genome and we have learned a lot about the impact of the microbiome on human health over the last 2 to 5 years. Craig and the team at the Venter Institute have been analyzing the microbiome for nearly a decade now so we have a lot of depth of knowledge in this area. We believe that the metabolome is at the point where we do have reference information that might be useful. We're exploring that in collaboration with the company Metabolon looking at how we can build the correlations between what we see on the genetic, genomic, and microbiomic or metagenomic level, and the phenotypes that we measure. Then we can see whether those metabolic data contribute to the decision making overall. WB: We have to keep in mind that human disease is a complex process and, depending on the stage of the disease, can manifest itself in various changed ways during that disease process. The inclusion of the microbiome, metabolome, and genome in this process, as well as other more standard clinical measurement techniques, is simply an effort to be inclusive. We want to look at the potential of all of the different analytical methods that may yield value in any algorithmic manner in that final data set.

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Q: HLI is also performing stem cell research. Does sequencing play a role in those studies?

FF: We're talking about longevity and healthy life so the idea of stem cell therapy is not farfetched. It's one way that we believe we can reconstitute homeostasis in the cell and extrapolate that to organs and, ultimately, the body to get back to a healthy state. To do this right, I would strongly argue that sequencing of stem cells is a key quality component for every future stem cell therapy. Before we even think about what these stem cells really can do for us on a more routine clinical care side, we need a better handle on the molecular characterization of the stem cells themselves.

Q: In addition to the HiSeq X Ten Systems, what other sequencers do you have?

WB: We have a HiSeq[®] 2500 System that is used primarily for microbiome sequencing and a MiSeqDx[™] System that is going to be used for cystic fibrosis testing as well as other tasks.

Q: How have installation and training been?

WB: It's been great because the team that's supporting us started working with us before we actually had a lab. It's a smooth process.

Q: How long did it take to start running studies on the HiSeq X Ten instruments after they were installed? WB: We're now beginning to process external samples, but we've done a considerable amount of work with known samples to prove to ourselves and our customers how great the data looks.

Q: What's your goal for sequencing coverage?

WB: Our goal will depend on the intended use of the sequencing results. From the perspective of clinical utility, we want to be sure that the ~6,000 genetic loci linked to heritable forms of human disease are sufficiently covered to allow for accurate identification of potentially disease-causing

sequence variants. For this "clinical" genome, we're initially targeting 30× coverage, which is the standard for a single HiSeq X Ten run. Other uses of the sequencing results (ie, somatic variant identification in cancer), will likely require significantly deeper coverage.

Q: As you begin to ramp up, what throughput are you seeing?

WB: We typically are able to run about 16 samples per instrument, so 32 samples per instrument per week is what we're targeting. The processes that we've put in place upstream of the HiSeq X Ten Systems can meet those needs.

Q: Could you have believed 10 years ago that we would be at this level of sequencing today?

WB: Probably not. I certainly have my own 10 kB Sanger sequencing merit badge and I know that Felix has his own, too. There's certainly a lot that's gone on, but there's been amazing progress. We're really looking at the potential to accelerate that and take advantage of the capabilities of the HiSeq X Ten so we can push sequencing technology in a way that benefits patients.

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Q: What are the next steps for HLI?

FF: We have three key business areas of focus-sequencing genomes and compiling the resulting genotype information, collecting phenotype data, and putting this all together. We're well-equipped and up and running in the lab. Now we're focusing on developing the database and tools to use this information. That's no small task considering the amount of information that we're trying to manage, and the correlations we're trying to find. It's at a scale that nobody has ever attempted. The third area we are targeting is developing state-of-the-art health information centers where we can begin to translate what we're finding into practice and start piloting some of those efforts. All of these factors are important for our business model. At the front end, we have the phenotyping. The back end goal is the actual delivery of care and the ability to push towards the outcomes that we believe are triggered by use of molecular-driven clinical decision making.

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