

New York Study Aims to Assess Utility of Clinical Whole-Genome Sequencing Across Diseases

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NEW YORK – A clinical research study recently launched by researchers at Weill Cornell Medicine, New York Presbyterian, and the New York Genome Center, with support from Illumina, aims to determine the diagnostic value of clinical whole-genome sequencing in a variety of disease types.

The initiative, supported with an undisclosed amount of funding from the participating institutions, was announced [last month](#). It follows other efforts to explore the clinical utility of whole-genome sequencing, often for a specific disease type or patient population, such as various projects in the National Institutes of Health's [Clinical Sequencing Evidence-Generating Research \(CSER\)](#) consortium.

"We want to do this in a way that demonstrates, hopefully, clinical utility not only for a very specific set of patients but as broadly as possible," said Olivier Elemento, director of the Englander Institute for Precision Medicine at Weill Cornell Medicine, a project leader.

The goal is to sequence the genomes of more than 3,000 patients over the next year or so, who will be enrolled in a research protocol but also receive back diagnostic results. The study will focus on four disease areas: cancer, heart disease, diabetes and other endocrine diseases, and neurological disorders. Patients are consented to obtain results related to their condition as well as incidental findings in the ACMG-59 genes, while pharmacogenetic variants may be included at a later time.

Recruitment for the study is physician-driven, based on doctors' assessments that whole-genome sequencing would benefit their patients. So far, approximately 200 patients have been enrolled, most of whom are waiting to have their genomes sequenced.

For cancer, Weill Cornell already has significant experience with reporting genomic results from [clinical whole-exome sequencing](#). Genome sequencing would add more information to that, such as structural variants, including their precise breakpoints. "There are lots of translocations or structural variants that are affecting genes that don't necessarily show up in targeted panels or in whole-exome sequencing," Elemento explained. "That's what we want to demonstrate, that this additional layer of information that whole genomes give you has clinical utility and can be used to personalize medicine even more effectively than other things we've done in the past, like whole-exome sequencing."

Marcus DaSilva Goncalves, an endocrinologist and assistant professor of medicine and biochemistry at Weill Cornell Medicine, has been recruiting about 70 patients for the endocrine arm of the study so far, and has had genome results for about 40 percent of them. Most of the patients suffer from type 2 diabetes but some have fatty liver disease, hyperlipidemia, or prediabetes. In addition to whole-genome sequencing, patients receive blood testing for lipids and hormones, he said, and all test results are combined with their clinical history.

Patients who enroll are not necessarily suspected of having a genetic component to their disease. "It was important to us, if we are really going to make this applicable to the field of clinical endocrinology, that we

just take all comers," Goncalves explained. Many patients, in fact, are curious to learn why they developed type 2 diabetes without a family history, he added.

While genome sequencing picks up known disease-causing variants, for example for maturity-onset diabetes of the young (MODY) or familial hypercholesterolemia, there have also been some unexpected results. For example, Goncalves said, one patient with high cholesterol and fatty liver disease turned out to have one known and one novel mutation in the two alleles of a plant sterol transporter gene. In combination with the blood test results, this led to a diagnosis of sitosterolemia, along with a change in medication. "We would never have picked that up because it's not on the standard targeted panels and it was only found because [the patient] had a rare variant in that gene," he said.

Overall, genome sequencing has delivered a result more often than expected. "It's been more than what I thought," he said. "It's very rare that I get a completely 'clean' report back." In about a third of cases, there are no diagnostic or incidental findings, he said, while in about 10 percent, a disease-causing variant turns up. In the remaining patients, a variant of unknown significance in a disease-causing gene or a variant that appears to be "loosely connected" to the disease process are found, which he said are the most interesting cases.

Still, it is challenging to translate the results into something useful for clinicians. "I feel like in other disciplines, they have more experience with interpreting these reports," he said. "Like oncology, they're routinely getting genomic analyses on the tumors. But in endocrinology, there is really no case where we send off for mutational analysis outside of tumor thyroid nodule biopsies, so the results have to be interpreted or the clinician is not going to know what to tell the patient." To help with that, Goncalves and his colleague write a summary of the results for the ordering provider that includes the patient history, blood and genomic test results, and their recommendation for the patient.

Both the blood test results and the genomic report go into the patient's electronic health record, he said, but the investigators also have access to the variants for additional research.

Sequencing for the project is provided by the New York Genome Center, which has a clinical germline (or constitutional) whole-genome sequencing test and a clinical cancer whole-genome and transcriptome sequencing test, both approved by the New York Department of Health.

For other projects, the center has mostly provided clinical genome sequencing for patients with rare diseases, and "this is sort of an extension into more common disease areas, and trying to work with the physicians to figure out what the value is," said Soren Germer, NYGC's senior VP of genomic technologies.

"Overall, it ties into the strategy for expanding the availability of clinical whole-genome sequencing to patients and hospitals," added Vaidehi Jobanputra, NYGC's director of molecular diagnostics. The center also provides clinical WGS for the NIH-funded [NYCKidSeq project](#), for example, which focuses on rare disorders in pediatric patients, completing more than 500 clinical genomes so far.

After a major update in early 2019, NYGC's constitutional whole-genome assay now runs on the Illumina NovaSeq 6000 sequencer, she said, while the cancer WGS assay is undergoing updates at the moment. All informative variants are confirmed by an orthogonal method prior to reporting.

The genome center is in charge of the clinical test from beginning to end, including library preparation, sequencing, alignment, variant calling, and analysis by board-certified lab directors, based on the patient's phenotype and the reason for testing. "Essentially, we follow the ACMG guidelines for constitutional disease, and for oncology, we follow the AMP guidelines for reporting," Jobanputra said. In addition to the

written report, providers can discuss the results with the lab directors and consult with a laboratory genetic counselor when needed.

NYGC also offers case conferences — called tumor boards for cancer patients — to discuss the findings with the providers. "It's a two-way discussion. It allows us to see how the physician is thinking, and any recommendations that we want to make, which we do write in the report, we also have a verbal communication about," she said. "And on the Weill Cornell side, it's a nice teaching opportunity for the fellows and the new providers who are just learning how to order whole-genome sequencing."

According to Elemento, most of the cost for the new initiative is associated with analysis and interpretation rather than sequencing. While analysis software and variant databases have been improved over time and brought costs down, "at the end of the day, there is still a lot of manual review that goes into these analyses," he said.

Diagnostic results already go into patients' electronic health records, another area where Weill Cornell [has experience](#) from its cancer exome sequencing work. "In oncology, we were one of the first centers in the US to integrate genomic results into the EHR as structured data," Elemento said.

He and his colleagues are particularly interested in a genomics module from Epic Systems that promises to help integrate genomic results into the EHR and provide clinical decision support. "We hope that [our] previous experience integrating genomics data into the EHR, combined with this new tool that Epic is making available, will help facilitate this integration in a way that hopefully will make pharmacogenomic usage much, much easier and much more useful than what it used to be before," Elemento said.

At the moment, the report goes into the EHR as a PDF in a non-automated process, but in the future, WGS results will be reported as structured data fields, similar to how Weill Cornell did this for clinical whole-exome sequencing. "This will enable searching for specific patient profiles, for example to look for candidates for clinical trial enrollment, and critically for PGx, it will enable clinical decision support," Elemento said.

"By the end of the project, we're hoping not only to have a lot of results regarding the clinical utility of whole-genome sequencing but also that we'll have worked out many aspects of the integration of whole-genome sequencing into the EHR," he said. NYGC will work with the Weill Cornell team to facilitate workflows and processes related to the integration of the test results into electronic medical records, Jobanputra added.

Beyond diagnostics, the project plans to use the sequencing information in other ways going forward. For example, polygenic risk scores could help predict who is likely to progress from prediabetes to diabetes, though "that will take a bit more time," Elemento said. Also, patients could benefit from having pharmacogenomic results available, should they be prescribed a medication with a PGx label.

Depending on the results of the initiative, the long-term vision is to deploy clinical whole-genome sequencing routinely, and to keep the results in the patient's EHR for future use.

"If we can demonstrate clinical utility, if we have enough data to go back to insurance companies and payors, maybe we can convince them to at least partially pay for clinical whole-genome sequencing," Elemento said. "We're hoping that we can deploy this at scale, and we're hoping that at some point, one day, every patient will get their genome sequenced and put into the EHR, and it can be used throughout their entire life to improve clinical care, from pharmacogenomics to prediction of risk of disease to improve diagnosis."