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March 29, 2013

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By Uduak Grace Thomas

Armed with a $260,000 Small Business Innovation Grant from the National Human Genome Research Institute, SimulConsult is working with researchers at the University of California, San Diego, to develop, test, and validate new features for its Genome-Phenome Analyzer software.

The Chestnut Hill, Mass.-based company, which opened its doors in 1998, launched the Genome-Phenome Analyzer last March. The software helps clinicians combine whole-genome and whole-exome sequencing data with clinical findings and phenotype information and use this information to compute a differential diagnosis for patients using proprietary statistical pattern-matching algorithms (*BI* 5/18/2012).

Also last year, SimulConsult partnered with Geisinger Health System to participate in Boston Children's Hospital's Children's Leadership Award for the Reliable Interpretation and appropriate Transmission of Your genomic information, or CLARITY, challenge. The team was one of the five that received a "special mention" for their contributions (*BI* 11/16/2012).

Since last summer, about 12 laboratories including Geisinger Health System have signed contracts with SimulConsult, Lynn Feldman, the company's CEO, told *BioInform* this week. She said the company expects that number to rise to "well over 20" within the next two weeks. Some of these labs will be paying customers while others will be running pilot projects using the software.

Another SimulConsult customer is UCSD, where, with the help of Joseph Gleeson, a professor of neurogenetics in UCSD's neurosciences and pediatrics department, the company is currently testing its software on patient data provided by Gleeson's lab, as well as on data that was used in the CLARITY challenge, Feldman said.

According to the NHGRI grant abstract, the researchers intend to use the funds to "compute unified severity scores for genome-phenome analysis." This would replace the current methods

used in the software, which are based on "iterative manual modifications of Boolean filtering of variants." The new approach would be a "one pass"
method that would combine "many assessments of gene variants provided by SeattleSeq, including conservation scores, read quality scores, and variant frequency in the population, to automatically construct quantitative severity scores."

Another aim of the project will be to "assess the effectiveness of automated genome-phenome analysis to identify known disease-causing genes" by analyzing data from patients with known disease mutations and their families and judging the accuracy of the system's results based on "the rank of the correct diagnosis and the probability assigned by the software," the abstract states.

A third aim of the UCSD project will be to determine cases where clinicians can identify diseases using only patients' genetic and phenotypic data without having to sequence and analyze additional information from other affected or non-affected family members.

As part of the project, the partners have developed two metrics that they've incorporated into the Genome-Phenome Analyzer, Feldman said.

The first metric ranks the phenotype in the differential diagnosis, which is the list of diseases in the software that are generated based on the clinical and genetic information from the patient. The second metric, dubbed the gene pertinence, measures how much the differential diagnosis would change if information about the patient's gene variants was not included in the analysis.

The partners are currently using UCSD and CLARITY datasets to evaluate which of the two measures "is most predictive, how predictive they are, and under what circumstances," Feldman said.

They've used both to analyze just clinical data from patients; patients' clinical and genetic data; and the patients' clinical and genetic data plus genetic data from family members to see which measure was able to select and rank the right ailments higher in the disease lists generated.

Preliminary results suggest that the gene pertinence metric is the more accurate of the two measures — it ranked the correct diseases higher than the phenotype-driven method could — particularly in cases where patients have more than one disease condition, Feldman told *BioInform*.

So far, the partners have tested the Genome-Phenome Analyzer on data from patients who have already received a confirmed diagnosis, but they plan to test it on data from patients with undiagnosed conditions.

SimulConsult is also working on a second pilot project focused on pediatric rheumatology with researchers at Boston Children's Hospital and other institutions, Feldman said. This project is funded by a grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

According to the grant abstract, the funds will be used to add pediatric rheumatology content to the SimulConsult database, "assess the diagnostic effectiveness and efficiency, and appropriateness of referrals" and finally to assess whether the structure of the data needs to be modified to "deal with issues such as different granularity of information in different areas of medicine, and [to] develop effective approaches to those needs."

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