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Genomic Singularity Is Near

Once we've uploaded our genomes and the net is abuzz with our biosensor data, virtual doctors and clinics could become very real.

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The explosive growth of DNA-based diagnostics empowers us to take a closer look at our own health and to demand answers from healthcare providers to questions that have never been asked before.

Even if we do not fully understand the clinical relevance of most of the genetic changes, the information that has been validated is significant enough to change the status quo of medical care.

It is only natural that mobile devices are tapped for their unprecedented power and flexibility to deliver physiological data and lab results when and where it is needed most. As the maturing world of mobile devices meshes with the rapidly emerging word of genomics and biosensors, medicine could literally be found at our fingertips. This powerful combination not only gives more tools to treat the existing conditions but could also shift medicine into a true preventative mode.

Some visionaries hypothesize that mobile data will eventually lead to the demise of brick-and-mortar hospitals. One such visionary, geneticist and cardiologist Eric Topol, M.D., advocates the widened use of wearable, wirelessly networked biosensors to advance personalized medicine. In his popular book, "The Creative Destruction of Medicine," Dr. Topol even anticipates that digital tools could empower a consumer-led democratization of medical care.

The data for each individual will be networked to produce a comprehensive picture of disease biology while maintaining the full ability to characterize a particular individual's unique genotype. But for now, genetic data is just beginning to find its way to mobile interfaces, we are still some years away from the fully portable genomic representations needed for the advent of "digital medicine."

Digital Pedigrees, Genetic Risks

Genetic counselors provide risk assessment, education, and emotional support to the individuals and families at risk because of genetic predisposition. Genetic counselors interpret the results of genetic testing and have training and expertise to communicate diagnostic testing results, especially when the results are not immediately applicable or straightforward. To accomplish these tasks, genetic counselors often make use of medical pedigrees. A medical pedigree is a graphical representation of a family's health history.

With the rapid increase of genetic testing and wider availability of whole genome sequencing, medical pedigrees have expanded to capture families' genetic mutations. Pedigrees now capture positive results for

mutations that may potentially render the individual susceptible to cancer, cardiovascular disease, diabetes and other diseases.

“The pedigree’s utility lies in its ability to depict complex relationships at a glance, so that disease patterns, risks, and biological relationships are immediately apparent,” says Jeffrey Miller, lead analyst and programmer at the Center for Biomedical Informatics (CBMi) at The Children’s Hospital of Philadelphia. “Pedigree nomenclature is now fairly standardized. However, to the present day, valuable pedigree information is captured on paper by hand.”

CBMi developed Proband, an app for taking family history pedigrees on an iPad. Available at the iTunes store, Proband carries the motto “Pedigrees Made Simple” and promises to enable pedigree capture at the point of interview, easing the transition from paper to screen. The mobility of the application ensures that a genetic counselor can continue facing the patient while holding an iPad, just as he or she would a paper notepad. The app can capture any level of detail, including confirmed diagnosis.

Users have commented on ease of tracing the diagnosis up the family tree. Creating pedigrees in the electronic format provides obvious benefits of data recovery, interchangeability, security, and uniformity.

Miller asserts that in the future, Proband will be able to incorporate test results and other personal health information stored in electronic health records. “Querying pedigrees based on scientific and medical questions is another near-term goal,” he adds.

In its current release, Proband can be annotated with ICD-10 diagnosis codes and the Human Phenotype Ontology. Despite Proband’s apparent simplicity, development of the app was challenging. It passed through multiple iterations and took almost two years. Miller’s team worked closely with genetic counselors to create an interface that captures complex relationships.

Plant Genomics, Human Diagnostics

The need to compare whole genomes evolved much earlier in plant science than in human genetics. Accordingly, plant science preceded human genetics in the development of visualization software, which may one day allow clinicians the ability to compare a patient’s genetic test on a tablet in the same way a doctor might read results of an MRI or blood panel.

Persephone, a novel genome visualization software developed by Ceres, enables easy switching between reference samples. The software rapidly zooms in from the chromosomal level down to a single nucleotide. On top of this data, users can layer additional relevant annotations. The effect is similar to a geobrower zooming from the whole Earth to the level of an individual street and even a house.

Managing data overload for various sets of users is key. There are only so many pixels on a screen. While a researcher wants access to all possible data, clinicians generally prefer a simplified view, such as a view of SNPs from a particular assay.

“We envision a time when genomics will transition from discovery to diagnostics,” says Timothy Swaller, vice president of genomic technologies at Ceres. “Persephone’s diagnostic view will focus only on informative mutations attributable to a particular trait or disease. A future mobile application would bring this essential information to a patient’s bedside for a physician’s assessment or to an experimental field for a plant breeder to select new hybrids.”

Swaller notes that Persephone can align millions of markers for hundreds of samples, and call every variant based on a public or internal reference. “The only limitation is how much information we can compress to fit onto a screen,” he explains. To develop these capabilities, Ceres programmers had to create multiple proprietary data compression, storage, and retrieval methods.

“The current release of Persephone is ideally suited for exploratory research,” asserts Swaller. “The speed with which our software zooms to selected regions radically improves the ability to manage massive datasets generated by DNA sequencing and genetic testing.”

In house, for example, Persephone was used to identify a compilation of genes responsible for a certain quantitative trait in sorghum samples. Whole genomes of hundreds of plants were rapidly aligned and visualized at the macro level. Once the chromosomal region was identified visually, Persephone zoomed in on a cluster of five genes and then on mutations in a few of those genes that disrupted the amino acid translation. Swaller points out that Persephone reduced the search for mutations from weeks to days.

Unified Programming Interface

“Our applications aim to provide high-definition, relatively comprehensive snapshots of the patient status at any given point of time,” says Gil Alterovitz, Ph.D., director of the Biomedical Cybernetics Laboratory at Harvard Medical School. “Snapshots taken over a period of time help patients maintain their health and interact with physicians regarding their care.

“Each data source has a different system for how its data is formatted, transmitted, and utilized. Getting all the essential data in one place will radically transform the future of medicine.”

Developed as an initiative under a larger $15 million grant from the Office of the National Coordinator for Health Information Technology, a project named Substitutable Medical Apps and Reusable Technology (SMART) Genomics aims to create a unified application programming interface (API). Such an interface would enable programmers to create apps that could work with data from multiple sources, such as electronic health records, sequencers, and genetic lab results without needing to be adapted to each one.

“The SMART Genomics API (http://smartplatforms.org) can be compared to a language translator that enables people speaking in all different languages to understand each other,” continues Dr. Alterovitz. Three apps developed on SMART Genomics platform to date are Genomics Advisor, Diabetes (DB) Bear EMR, and Genomics Precision Medicine.

Genomics Advisor integrates clinical and genomic information in a single user-friendly interface. Users simply log in individually to reach the data sources that they have been cleared to access. The data sources may include Electronic Health Records (EHRs) and personal genomics information obtained via commercial services such as 23andMe. As the log ins progress, more and more information populates the Genomics Advisor app, providing consumers with risk profiles for various diseases, related co-morbidities, and gene-drug interaction information.

The DB Bear EMR app incorporates Genomics Advisor as a module and adds an ability to integrate EHR, genetic, and glucose meter device data to provide live feed to treating physicians. The app incorporates interactive features, such as bear avatars linked to physical toy bears, and screens that engage pediatric patients and help kids to comply with diabetes treatment regiment.

The most recent app, SMART Genomics Precision Medicine, integrates medical and somatic genomic information obtained from sequencing tumor biopsies. Comparing patient's cancer mutations with the known mutations, and examining their impact on cancer progression, is helpful to physicians when choosing the optimal course of treatment.

Geremy Warner, M.D., from the Vanderbilt design and build team, used the technology to display observed genetic variants in lung cancer patients with a KRAS mutation. According to Dr. Alterovitz, both large healthcare organizations and independent physicians may benefit from adopting the SMART Genomics apps for their clinical care, radically transforming the way medicine is practiced.

The Genome at Your Fingertips

"Genomics is now accepted in the everyday practice of medicine, and patients are more comfortable in using genomic data to support their treatment," says Erica Ramos, senior genetic counselor at Illumina. "But as with any relatively young technology, both physicians and patients need to be educated on what it means and how to best use it."

The Illumina MyGenome App was developed as an educational tool for the visualization of genomic data. The elegant graphic interface is designed with the consumer in mind. When demonstrating the app on an iPad, Ramos emphasized the ease of zooming from the whole chromosome view to individual mutations.

Illumina provides interpretation reports for mutations in 1,600 genes covering 1,200 disorders for patients whose physicians have ordered the TruGenome™ Predisposition Screen. The data can be loaded into the MyGenome App.

"To hold your genome literally at your fingertips is a very powerful feeling," continues Ramos. "Patients can browse the app starting with conditions identified as potentially significant in their clinical reports, or they can begin with a specific chromosomal region."

Illumina has been offering the MyGenome App analysis tool with its predisposition screening test for about two years. The service requires a physician's order. Sequencing is performed in the company's CLIA-certified, CAP-accredited laboratory, and the results are interpreted by Illumina's clinical molecular geneticists and genetic counselors. A carefully annotated report is then transferred back to the ordering physician along with the activation key for genome download.

Ramos explains that this process supports the dialogue between physicians and patients: "Because most diseases have complicated genetic context, physicians need to be involved in explaining what the results mean."

Illumina is actively building networks of physicians interested in using genomic data in their practice. The company also facilitates the adoption of clinical whole-genome sequencing via the "Understand Your Genome" conferences. Designed as targeted educational outreach, conferences provide attendees with a hands-on opportunity to learn about the information encoded within the human genome and how it can be used to advance human health.

To "personalize" the discussion, Illumina provides the attendees with TruGenome Predisposition Screen, a clinical report of the findings, and a visual display of their genomic information in the MyGenome App. "In the

future, we see MyGenome App becoming a portal between the company, physicians, and patients that will contain comprehensive medical and genetic information," concludes Ramos.