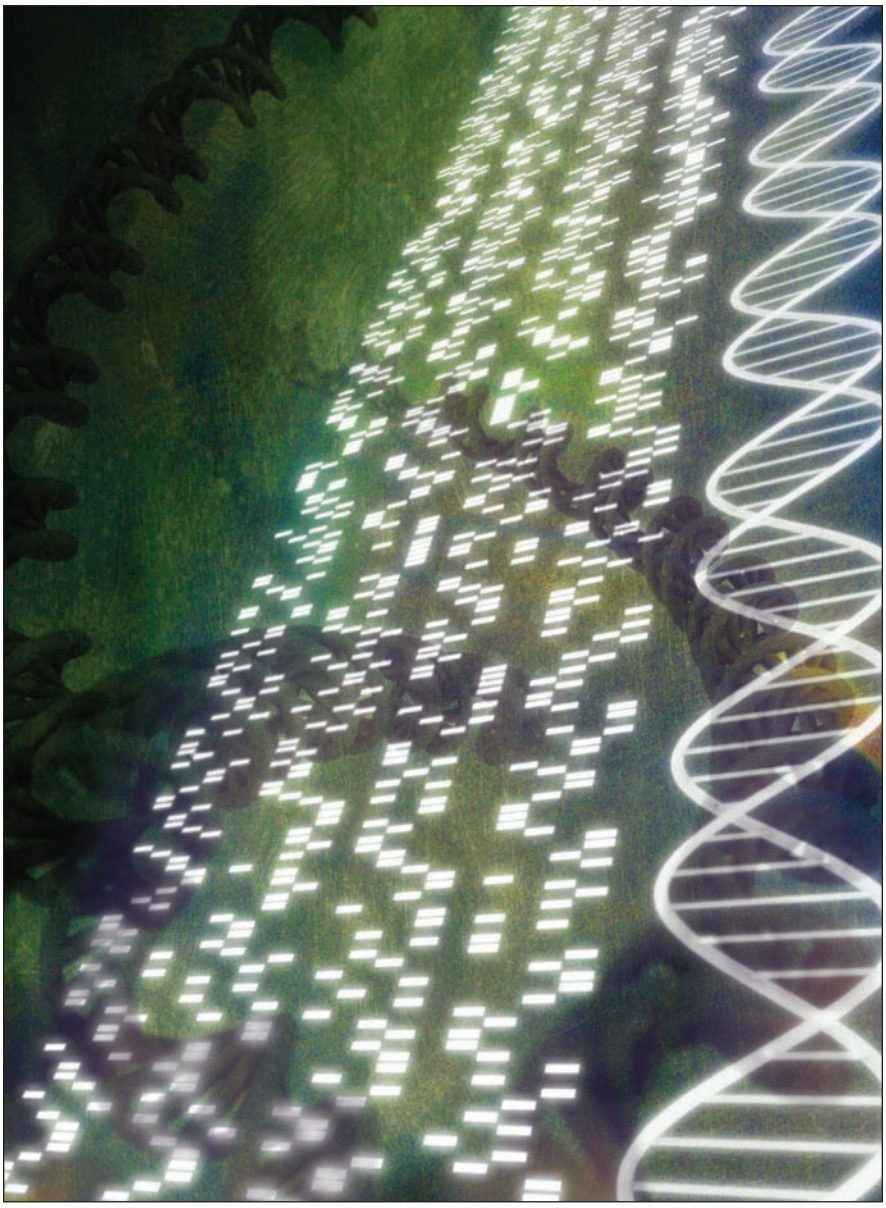
Rare diseases reconsidered

As "personalized" medicine slowly makes its way into clinical settings, clinicians may have to reconsider the boundary between common and rare diseases. Once the tools for parsing the human genome become fast and affordable enough to join the standard diagnostic regime, it will be possible to characterize any given ailment in ways that are unique to the patient in question. And for many observers, that means the same suite of medical resources may come to bear on common and uncommon cases alike.

In Canada, that prospect is quickly coming into view with the latest round of research projects to emerge from a partnership between Genome Canada and the Canadian Institutes of Health Research. Last year, the two organizations assembled $150 million for a funding competition dedicated to personalized health — the tailoring of diagnosis and treatment based on analysis of a patient's genome. From a pool of some 140 applicants, 17 successful initiatives were announced Mar. 26 in Ottawa, Ontario.

Individual projects are receiving support ranging from $3 million to $13 million, for investigations into a wide range of diseases, from epilepsy and autism to HIV/AIDS and cancer. All of this work will use the growing knowledge of the human genome to tailor new approaches to individual conditions.

Parents whose children inherited just such a condition, retinitis pigmentosa, were on hand for the announcement. According to Kym Boycott, a geneticist with the Children's Hospital of Eastern Ontario (CHEO), Ottawa, Ontario, they will be among hundreds of families to benefit from the genome sequencing procedures to be conducted by one of the newly funded projects, "Enhanced CARE for RARE genetic diseases in Canada." Boycott is leading this work in collaboration with investigators at CHEO and the University of Ottawa in Ontario.



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As gene sequencing drops in price, researchers are looking to tailor new approaches to individual conditions, including rare diseases and disorders.

"Within weeks we will be able to read their entire genetic code of 23 000 genes and we have an excellent chance of finding the genetic change that is causing their disease," she says. "We will work toward translating these powerful diagnostic methods to the clinic, so that the experience of future families is such that they don't wait two decades for an answer."

Alex Mackenzie, another CHEO geneticist who has now teamed up with Boycott, knows all about the long wait for answers. In the early 1990s, he and his colleague Robert Korneluk successfully identified a genetic mutation linked with spinal muscular atrophy, a discovery that placed both of them at what was then the forefront of this field. They moved

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ahead at a pace that the technology of the day allowed, but he marvels at how dramatically the field had been transformed by 2011, when he got involved with Boycott and other clinical geneticists through FORGE, Finding of Rare Disease Genes, which established a national network for sequencing genetic disorders.

"They emptied their freezers with all the DNA from undiagnosed families, sent them to the various Genome Canada centres for sequencing and identified over 100 new genes," he explains. "What took Bob and me 15 years is now happening in the space of 3 to 6 weeks."

Not so long ago this kind of output would have been an expensive, time-consuming proposition. The first sequencing of a human genome was a multinational venture that cost billions of dollars. In the decade since that milestone, the cost and speed of revealing our genetic code has changed by many orders of magnitude, and promise to keep changing.

The Génome Québec Innovation Centre at McGill University, Montréal, Quebec, did about one genome sequence per week last year, says Genome Quebec President Marc LePage. "If you send in an order, we'll do it for $5200, with some preliminary analysis. Then you'll have to do the data mining."

By next year the price may be half of that, adds LePage. And within a few years, he anticipates that a typical sequencing will cost no more than a few hundred dollars, putting it on par with well established procedures like magnetic resonance imaging scans.

Canada is just beginning to see the implications of this new capability, which is particularly good news for patients with diseases and disorders that do not garner widespread attention. The list includes brain problems like Joubert syndrome or megacephaly, as well as malformations of the joints, such as acrodysostosis or Arkless–Graham syndrome.

Boycott insists that it is no accident that most of us know someone who suffers from one of these disorders. Although particular cases would be classified as rare, meaning they affect fewer than 1 in 2000 people, there are so many disorders that collectively they affect some 3 million Canadians — hardly "rare." Boycott regards the growing power of genomic sequencing as an invitation to explore this significant cohort of the population, which represents a medical frontier that remains largely unknown.

"Of the estimated 7000 rare genetic diseases that are present worldwide, we understand the cause of only half," she says. "And although we can effectively manage many of these symptoms, we can definitively treat only 200 — that's less than 3%."

For Boycott and Mackenzie, this assault on rare diseases captures the essence of how personalized medicine is changing the landscape of diagnosis and treatment. The ultimate appeal of this approach may be a matter of sheer efficiency. The cause of disease can be pinned down to the patient's genetic makeup; drugs may or may not be prescribed, based on a foreknowledge of how well they will work; an awareness of genomic hazards could make it far easier to safeguard an individual's future health.

For Cindy Bell, vice-president of Genome Canada, this new perspective is already altering the way we talk about the most familiar of diseases.

"Even our idea of cancer," she says. "We won't say you have lung cancer or you have liver cancer. We say you have Ras gene cancer. It will be the mutation that defines the type of cancer that you have. That is when you are really putting the technology to work, when you can say things like that." — Tim Lougheed, Ottawa, Ont.

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