Genetic testing of patient constitutional DNA (i.e., their genome) is increasingly performed in medical practice. Sequencing an entire human genome (about 3.2 billion nucleotides) is now possible to complete in days to weeks, and at a similar cost to some advanced imaging tests or to a brief admission to hospital. Genome sequencing is being integrated into health care systems internationally, most notably in the United Kingdom. Starting in 2021, genome sequencing is being performed as a clinical genetic test in Ontario, Canada.

What is genome sequencing?

Genome sequencing (or whole genome sequencing) is a comprehensive test capable of detecting nearly all DNA variation in a genome. Sequencing can diagnose most of the > 6000 conditions listed in the Online Mendelian Inheritance in Man database (www.omim.org) for which the genetic basis is currently understood. These include cystic fibrosis, Duchenne muscular dystrophy, familial hypercholesterolemia, hemophilia A, Lynch syndrome, Marfan syndrome and multiple endocrine neoplasia. Most diagnoses are individually rare (i.e., < 1 in 2000 live births) or ultrarare (i.e., < 100 people reported in the medical literature), and thus less likely to be suspected a priori (e.g., Kabuki syndrome; Figure 1). Patients may present with unusual constellations of features, or with common diseases like autism spectrum disorder, cardiomyopathy, congenital heart disease, epilepsy, cancer, schizophrenia or dementia, although this list is not comprehensive.

Genome sequencing is broader in scope than other commonly used genetic tests (Box 1), and data can be analyzed in both hypothesis-driven and hypothesis-generating ways. For these reasons, genome sequencing will likely eventually supplant exome sequencing, large next-generation sequencing gene panel tests and chromosomal microarray analysis.

How is genome sequencing delivered?

Genome sequencing is a 3-stage process (Figure 1). First, a medical geneticist or other health care professional collects the necessary information on phenotype and family history. Second, the genome data are generated and reviewed by a clinical laboratory geneticist. Third, a physician correlates the genetic findings with the clinical phenotype. Primary findings are genetic variants that may explain all or a component of the clinical presentation. Identifying such results is the main purpose of genome sequencing as a clinical diagnostic test. In North America, some laboratories will also actively look for secondary findings, namely disease-causing variants in specific genes associated with medically actionable conditions that are unrelated to the reason for testing. Communication of results is embedded within the framework of genetic counselling (Box 2) and is often facilitated by a medical geneticist and genetic counsellor.

DNA sequencing is becoming less expensive and more accurate because of technological advances. However, the cost of offering genome sequencing as a clinical test is still in the range of several thousand Canadian dollars per family-based investigation, not including up-front investments in personnel, equipment and infrastructure.

Who is eligible for genome sequencing?

Genome sequencing is a consideration for children and adults with suspected genetic disorders for whom a targeted genetic testing approach is unlikely to succeed or has already failed. In Ontario, genome sequencing is undergoing a 2-year pilot assessment as part of the Genome-wide Sequencing Ontario project (www.gsontario.ca), with publication of interim results pending. Testing can be ordered only by a medical geneticist or other physician with comparable expertise. The approval criteria currently favour individuals with multiple unexplained congenital anomalies or a moderate-to-severe developmental disability, and affect scenarios where a unifying diagnosis is expected to impact management.
What are the harms?

The procedure of sequencing is safe; however, possible negative consequences are tied to how results are interpreted and disclosed. First, genome sequencing can be misconstrued as a diagnostic panacea. Accurate clinical information and family history remain important for interpreting results. A positive result may not explain all of the patient’s features, and a negative result does not rule out a genetic contribution or invalidate an unambiguous clinical diagnosis. Second, the classification of a genetic variant can change over time as new information becomes available. Certain ethnic groups remain under-represented in the large-scale reference databases of genomic variation that guide interpretation, and therefore misdiagnosis is a possibility for these groups. Third, genetic test results can
reveal unexpected information about the individual, family members or their relationships to one another. These considerations underscore the importance of detailed pre- and post-test counselling and the need for trained genetics professionals (Box 2). An additional safeguard against harms is Canada’s Genetic Non-Discrimination Act, which became law in 2017 and is intended to protect individuals from genetic discrimination on the basis of their test results.13

What is the evidence so far?

Most data are from prospective observational trials of testing in clinically heterogeneous populations with suspected rare genetic diseases.1,2,4,5,14,15 Primary outcome measures are usually diagnostic yield or time to diagnosis. Clinical utility and cost-effectiveness are secondary outcomes of interest. Genome sequencing has a higher diagnostic yield than exome sequencing and chromosomal microarray analysis, including 2 randomized controlled trials showing increased timely diagnostic yield and clinical utility relative to routine testing.4,14

What can be expected in the future?

Genome sequencing is anticipated to become a first-tier investigation in children and adults with suspected genetic conditions that have high genetic heterogeneity (i.e., a broad genetic differential diagnosis with many candidate genes or loci).2,4,5,14,15 This will curtail the longstanding practice of ordering multiple genetic tests sequentially and shorten many diagnostic odysseys. Results returned to patients may also include pharmacogenetic profiles, reproductive carrier status information and genetic risk profiles for later-onset conditions.16 The role for genome sequencing as a preventive health tool in ostensibly healthy individuals remains unclear.16

Further evidence is needed regarding the clinical utility, cost-effectiveness and possible unintended downstream consequences of genome sequencing within our health care system. The added yield of genome sequencing over exome sequencing remains modest in some cohorts; however, this gap will widen with advances in data analysis and larger data sets to compare against.2,11,15 The anticipation of additional clinically relevant information arising from as-yet-unexplored areas of the genome is also driving investments in genome sequencing technology.2,5,11

Appropriate adoption of genome sequencing as a diagnostic test in Canada would be facilitated by a coordinated national strategy for genomic medicine that couples basic and clinical research, as exists in the United Kingdom and Australia. Translational genomics projects, such as Care4Rare Canada (www.care4rare.ca), the CAUSES Clinic at BC Children’s Hospital, the Integrated Centre for Pediatric Genomics in Montréal, the Silent Genomes Project (www.bcchr.ca/silent-genomes-project), Genome Canada’s All-for-One initiative (www.genomecanada.ca) and the efforts from individual tertiary hospitals (e.g., The Hospital for Sick Children) continue to evolve. These disease-focused initiatives would benefit from a parallel genome sequencing effort of the national population to study the genetic determinants of health. Delivering diagnostic genome sequencing in Canada will also require that more staff be trained, including medical geneticists, clinical laboratory geneticists and genetic counsellors, to enhance the genetic literacy across the diverse population of Canada. Ensuring equitable access to care informed by the DNA code, irrespective of postal code, is a challenge in countries that span a large geography, such as Canada and the United States, but we suggest that this be a priority for policy-makers.
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