DIRECT-TO-CONSUMER GENOMIC TESTING

Bottom line: Direct-to-consumer genomic testing (DTC-GT) is over-the-counter genomic testing available online to consumers through private companies. Generally, results report an individual's risk to develop a medical condition as being below average/low, average/general population, and above average/high based on genome wide association studies (GWAS). Results may provide medically useful information for consumers and potentially provide support and motivation for lifestyle changes (e.g. weight loss, smoking cessation) or even more vigilant surveillance (e.g. breast cancer screening), reveal carrier status of single gene conditions (e.g. cystic fibrosis), effectiveness and side-effect risk of certain medications, in addition to medically irrelevant information (e.g. curly hair). Currently, DTC-GT is not regulated or accountable to an appropriate governing body. Numerous professional societies express concern about how DTC-GT is marketed to consumers, what and how information is provided and the lack of genetic counselling. **Family health history-based risk assessment is still the gold standard in initial assessment for heritable conditions.**

WHAT IS DIRECT –TO-CONSUMER GENOMIC TESTING?[1,2]

Direct-to-consumer genomic testing (DTC-GT), also referred to as personal genome testing, refers to genomic testing available for over-the-counter purchase without the requirement of health care practitioner involvement. Generally, DTC-GT is marketed with the promise of providing predictive genomic risk assessment for a variety of complex health conditions (e.g. diabetes, cancer, obesity) and information regarding response to and/or side-effect risk of certain medications (e.g. clopidogrel, statins). Additionally, DTC-GT is advertised to assist in diet and exercise planning and can uncover medically irrelevant information such as bitter taste perception or curly hair.

Generally, DTC-GT is available online to anyone for a cost. Genomic testing for DTC-GT is usually performed on a saliva sample.

WHAT DO THE GENOMIC TEST RESULTS MEAN?

Test results for DTC-GT depend on what condition is being tested and what technology is being used. See our resources on Genomic Test Results for more information.

Appropriate pre- and post-test counselling are rarely offered directly by the DTC-GT company or inconsistently accessed by consumers when available[3-6]. Ideally, it should be carried out so that the consumer is informed of what the results might reveal (e.g. risk of multifactorial conditions that arise due to the combined contribution of genetic and environmental factors, carrier status of single gene conditions, including cancer predisposition syndromes) and the potential for results requiring additional medical follow-up not limited to behavioural modifications (e.g. vigilant breast screening and discussion of risk reducing surgery as a result of a *BRCA* gene mutation). The implications for extended family members should be addressed. Genetic counselling would also include the limitations of the test offered as well as incorporate additional personal health and family history information into risk assessment and test interpretation.

Multifactorial disorders and genome-wide association studies (GWAS): GWAS are case-control studies which examine many common variations in our genetic code (single nucleotide polymorphisms [SNPs]). They compare large groups of individuals (unaffected controls versus individuals with symptoms of a specific disease or those experiencing a particular medication response) in an attempt to distinguish between non-harmful changes in the DNA code and pathogenic, disease causing/predisposing changes. SNPs (pronounced 'snips') are the most common type of genetic variation. Each SNP represents a difference in a single DNA building block, a nucleotide. SNPs occur normally in an individual's genome about once in every 300 nucleotides, thus there are about 10 million SNPs in the human genome.

Odds ratios and relative risks are used to categorize an individual as at increased risk (higher than average), average (general population risk), or at decreased risk (lower than average). Results from GWAS may be used to report on an individual's risk for cancer, heart disease or diabetes.

Mendelian disorders and ethnicity-specific testing or next generation sequencing: Single gene disorders (e.g. cystic fibrosis, *HFE*-associated hemochromatosis, *BRCA*-associated hereditary breast and ovarian cancer syndrome) are often screened for by targeting only ethnicity-based gene variations. For example, screening for pathogenic variants* in the *BRCA1* and *BRCA2* genes are limited to the three commonly found in individuals of Ashkenazi Jewish ethnicity, regardless of the consumer's reported ethnicity. In these cases not all clinically relevant mutations or even genes are necessarily included in analysis; possibly resulting in false reassurance with negative results[7].This is of particular importance where there is a known family history.

Additionally next generation sequencing (NGS) may be employed where the entire coding region of a gene is sequenced looking for significant variation as compared to a reference sequence. While some variations are well known to be either pathogenic or benign, some require specialized analysis by a genomic specialist. Genetic changes that are only weakly associated with disease may be reported, possibly leading to anxiety or inappropriate additional testing[7]. Additionally, due to variability in interpretation, there is the possibility of conflicting risk interpretations between companies.

> *pathogenic variant: a change in a gene that disrupts proper function and increases susceptibility to or causes a disease or condition. Formerly called mutation.

Pharmacogenomics: The goal of pharmacogenomics is to identify gene-drug interactions to improve the safety and efficacy of medications[8]. The clinical utility of pharmacogenomics is still be established but looks promising.[9] As of writing, few DTC-GT companies offer pharmacogenomics as part of their testing menu. Most often, privately available pharmacogenomic testing requires health care provider involvement[8]. Like genomic testing for Mendelian disorders, pharmacogenomics testing is highly dependent upon ethnicity-based gene variations[8]. Most often companies are analysing for specific SNPs enzyme genes key to specific drug/drug class metabolism e.g. CYP2D6 and codeine metabolism[10]. Drug and/or dosage response are then predicted. International guidelines have been published and are often referred to on reports[11,12].

WHAT ARE THE BENEFITS OF DIRECT-TO-CONSUMER GENOMIC TESTING?

While there are limited data to support the clinical validity (ability to predict clinical outcome) and utility (the likelihood of improving patient outcome), some consumers might benefit from DTC-GT as results may:

- Encourage positive behaviour modifications (e.g. increase exercise, smoking cessation), although data is conflicting as to whether or not this is true[12, 13]
- Provide useful information for medication choice or management
- Provide information to individuals who have no or limited information about their family history (e.g. an individual who was adopted)
- Reveal carrier status of a genetic condition that could have implications for family planning e.g. cystic fibrosis, sickle cell anemia
- Reveal increased risk of adult-onset disorder with published screening and surveillance guidelines e.g. alpha-1 antitrypsin deficiency, *BRCA*-associated hereditary breast and ovarian cancer

WHAT ARE THE LIMITATIONS AND RISKS OF DIRECT-TO-CONSUMER GENOMIC TESTING?

Caution when interpreting DTC-GT should be exercised as:

- DTC-GT does not take into account numerous factors important when interpreting genetic test results such as age, family history, lifestyle (e.g. smoking, obesity) and other environmental factors that are a significant contribution to common complex disease development[14, 15]
- **Family health history-based risk assessment is still the gold standard in the initial assessment for heritable conditions**[16]

Another concern associated with DTC-GT is the unknown impact of privately obtained testing on a publicly funded health care system[1,17]. There are limited prospective studies with actual DTC-GT consumers and longitudinal follow-up that assess health care utilization[1,12,13,18]. While the medical system may be called upon to use limited resources to dismiss incorrectly assigned increased disease risk[17], referral to a specialist or confirmation of test results in a clinical laboratory may be indicated in some circumstances to clarify appropriate surveillance and management.

Additionally, "misattributed equivalence" is a great concern associated with personalised genome testing. There is a fear that if a DTC-GT test were to indicate a lower-than-average lifetime risk for a certain condition, when family history indicated a much higher risk, a consumer could be falsely reassured and not be as vigilant about medical interventions indicated by family history. This phenomenon speaks to the need for knowledgeable health care provider involvement in pre- and post-test counselling.[16]

Some DTC-GT companies will offer access to genetic counselling included with testing or for an added cost. In Canada, genetic counselling is an unregulated profession. To ensure the genetic counsellor providing services to you and your patient has demonstrated a standard level of knowledge, skills, and practice competencies look for appropriate credentials from the Canadian Board Genetic Counselling (CCGC, Canadian Certified Genetic Counsellor/CGAC, Conseiller(ère) en génétique agréé(e) du Canada), or from the American Board of Genetic Counseling (CGC, Certified Genetic Counselor).

WHAT SHOULD I KNOW ABOUT DIRECT-TO-CONSUMER GENOMIC TESTING AND REGULATION?

Numerous health professional organizations and public bodies have published positions statements, policies, and guidelines on DTC-GT. There is variability between publications, however overall there is strong support for: genetic testing laboratories and personnel being accredited/certified by appropriate governing bodies (e.g. Clinical Laboratory Improvement Amendments (CLIA) certification or appropriate provincial licensure bodies for laboratories, board-certification of genetic counsellors and geneticists); pre- and post-test genetic counselling by qualified a health professional to include limitations of testing, for fully informed consent by the consumer.[17,19-21]

Additionally, privacy is a major concern. DTC-GT companies have self-imposed policies that claim a consumer's genomic information will not be shared, although there is no regulation to dictate what happens if/when a company is sold or goes out of business[2]. One study has shown that with the release of even a few genomic markers, they were able to, with high probability; identify multiple participants in public sequencing projects using a technique that entirely relied on free, publicly available resources with only computational tools and an Internet connection. The researchers further demonstrated that this method could lead to the identification of another person who might have no acquaintance with the person who released his/her genomic data[22].

Since the launch of DTC-GT companies in Canada, there have yet to be any regulatory guidelines. Health Canada states that the agency regulates only the safety of the collection kit and not how information from genetic tests is used, further noting that medical information and privacy issues are a provincial responsibility. In Canada diagnostic laboratories are provincially regulated. At the time of writing, no DTC-GT is operating under approved provincial regulation, although some may meet USA federal standards (e.g. CLIA). Companies that are not regulated could have staff performance, test analysis and interpretation of results that may not be certified or licenced by any appropriate governing body.

A recent systematic review by Martins et al. found that while knowledge and experience with DTC-GT has increased over the last two decades, ethical and legal concerns persist.[23]

INSURANCE AND CANADA'S GENETIC NON-DISCRIMINATION ACT (GNA)

There is protection for Canadians under the Genetic Non-Discrimination Act (GNA) passed in May 2017. Some key points of the law are that -

GNA prohibits:

- Discrimination based on genomic characteristics
- Providers of goods and services (including insurance) from:
    - requesting or requiring a genomic test
    - requesting or requiring the disclosure of genomic test results either past or future
- Federally regulated employers from using genomic test results in decisions about hiring, firing, job assignments, or promotions

Note that many insurance companies do ask about conditions and diseases in relatives, and individuals may need to disclose a medical diagnosis (not genomic test results) as family history is not protected e.g. cancer or Huntington disease. A recent commentary in Canadian Family Physician discusses GNA and the implications for healthcare.[24]

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