Health Technology Update

CADTH

A newsletter on new and emerging health care technologies in Canada

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IN THIS ISSUE:

Informing Decision-Makers About Emerging Medical Technologies

This issue of the newsletter coincides with Canada's 150th birthday — and with the publication of 150-plus bulletins in CADTH's *Issues in Emerging Health Technologies* series. Since the first bulletin, in 1997, CADTH's Horizon Scanning Service has covered a diverse range of technologies. Some technologies reviewed almost a decade ago, such as human papillomavirus (HPV) vaccines, are now in routine use. Other technologies, such as artificial blood substitutes, have still not made it to market, while others, such as hip replacement and robotic surgery, continue to evolve and raise questions for decision-makers.

This issue of *Health Technology Update* features the evidence on several new medical technologies — from self-collected sampling in testing for sexually transmitted infections to opening the blood-brain barrier to improve drug delivery in brain cancer treatments.

FOCUS ON:

DIRECT-TO-CONSUMER GENETIC TESTING

FEEDBACK

Have you heard of a new health technology you think will have an impact on health care in Canada?

Please let us know!

Email: **HorizonScanning@cadth.ca.**

CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Self-Sampling for HPV and Other Sexually Transmitted Infections

Despite preventive public health programs, the incidence of sexually transmitted infections (STIs) in Canada is increasing.[1,2] Left untreated, bacterial STIs (like chlamydia and gonorrhea) in women can lead to pelvic inflammatory disease, infertility, or complications during pregnancy. Infection by the human papillomavirus (HPV), a viral STI, usually resolves spontaneously; but some high-risk strains of the virus can lead to cervical cancer later in life.[2,3] Early diagnosis and treatment or monitoring can reduce the spread of these infections, the risk of complications, and the costs of treatment.[4]

Image courtesy of Eve Medical

In 2016, 1,500 new cases of cervical cancer were expected to occur in Canada, and 400 Canadian women were expected to die from this disease.[5] Screening has significantly reduced the incidence of and deaths from cervical cancer, but about 30% of Canadian women who should be regularly screened are not.[5-7] Low-income women, immigrant women, Indigenous women, and women living in remote communities are less likely to receive regular cervical cancer screening.[7,8]

Many women avoid STI testing for various reasons, including the embarrassment and inconvenience of undergoing a pelvic exam, not having a family doctor or a female family doctor, religious or language barriers, and unawareness of the risks associated with STIs.[9-13] Allowing women to collect their own cell samples, at home or in the clinic, improves the uptake of testing and screening for STIs,[1,4,11,14] and is viewed by women as an acceptable and preferable alternative to clinician-collected samples.[13]

Self-sampling for STIs uses small devices — such as brushes, swabs, or tampons — to capture cells from the cervix and vagina for analysis.[7] The cell samples are analyzed in a lab to detect high-risk strains of HPV and other STIs.[7,15] One new self-sampling device is the HerSwab. The HerSwab is available as a medical device, and is also part of the Eve Kit — a direct-to-consumer mail kit that allows women to self-collect cells for STI testing.

HOW IT WORKS

The HerSwab is a brush-type self-sampling device with a plastic applicator handle. After inserting the tip of the device into her vagina, a woman rotates the handle to ensure the brush collects cell samples near the cervix. The brush is then retracted back into the handle of the device (which acts as a sheath to avoid contaminating the sample), sealed in a plastic bag, and sent by mail for testing in the packaging provided.[15]

With direct-to-consumer use of the Eve Kit, women must complete a risk assessment before receiving the test kit. Lab test results are sent directly to the individual within days via a secure online portal. Women who receive a positive test result need to make a medical appointment to discuss the results and, if necessary, receive further testing, treatment, or monitoring. The lab also notifies public health authorities regarding reportable positive results for chlamydia and gonorrhea (Jessica Ching, Eve Medical, Toronto, ON: personal communication, 2017 Jan 30).

AVAILABILITY IN CANADA

The HerSwab (Eve Medical, Toronto, Ontario) was approved as a Class II medical device by Health Canada in 2015, and the Eve Kit (containing the HerSwab, instructions, and packaging for return of the sample) received similar licensing in 2016.[16]

WHAT DOES IT COST?

If used within preventive health programs, the HerSwab device will cost from $3 to $8, depending on the volume, packaging, postage, and customization involved. The direct-to-consumer version of the Eve Kit can be ordered online in Canada at a cost of $85 for a chlamydia/gonorrhea kit and $110 for an HPV kit — which includes the cost of lab testing and shipping (Jessica Ching: personal communication, 2017 Jan).

CURRENT PRACTICE

Canadian guidelines currently recommend that women between the ages of 25 and 69 receive cervical cancer screening by undergoing a Pap test (a pelvic examination to obtain cervicovaginal cell samples for cytology testing) every three years.[6] For an HPV test, cell samples are also collected — either by a health care provider or through self-collection — and these are analyzed to detect whether DNA from high-risk strains of the virus is present. Replacing Pap testing with HPV testing is under consideration in some jurisdictions; but, at present, Canadian cervical cancer screening still relies mainly on the Pap test.[6,8,17,18]

Testing for chlamydia and gonorrhea may also involve either a pelvic examination to collect cell samples, self-collected cell samples, or a urine sample.[1,4]

WHAT IS THE EVIDENCE?

HPV and Cervical Cancer Detection

The recent Cervical And Self-Sample in Screening Study (CASSIS) at McGill University compared the performance of HPV testing using cells collected by three methods — HerSwab, cobas PCR Female Swab (another self-sampling device), and physician-collected samples — in 1,155 women with abnormal Pap test results.[19] Preliminary results, presented at a conference in 2016, found good agreement between the HerSwab and physician-collected samples, and between the HerSwab and the cobas PCR Female Swab, for the detection of high-risk HPV strains.[20]

A second study involving the HerSwab — a randomized controlled trial of HPV self-sampling for cervical cancer screening — has been conducted in Slovenia.[21] The study compared screening uptake rates with various self-sampling devices to uptake with invitation letters. Unpublished data, presented at the European Research Organisation on Genital Infection and Neoplasia (EUROGIN) conference in June 2016, found that the overall response was 37.5% in the self-sampling arm (self-sampling or physician visit) compared with 19.9% in the recall letter arm (physician visit, only). Of the self-sampling devices used, those who received a HerSwab device had a 33.6% response rate compared with 32.4% for the Aprovix Qvintip device, and 27.1% for the Delphi Screener (Jessica Ching: personal communication, 2017 Jan).

Chlamydia and Gonorrhea Detection

A 2016 study from McMaster University assessed user satisfaction and performance of the HerSwab in 189 women who were tested for chlamydia and gonorrhea.[15] Test results with self-collected HerSwab and physician-collected samples had good overall agreement (95%), but the study was not large enough to reliably compare test sensitivity.[15]

Self-Sampling Preferences and Experiences

Women's preferences for self-sampling were also evaluated in the CASSIS and McMaster studies. In the CASSIS study, 55% of women preferred self-sampling using the HerSwab to self-sampling with the cobas PCR Female Swab or physician sampling.[20] In the McMaster study, most women reported that self-sampling with the HerSwab was easy (97%) and comfortable (88%), and most (81%) preferred self-sampling to physician-collected testing.[15] Reasons for preferring self-sampling were similar to those reported in other studies;[11,13] namely, "comfort, privacy, and convenience."[15]

A 2017 study conducted by University of Michigan researchers assessed the acceptability of HPV self-sampling using the HerSwab for indigenous women in Guatemala.[22] Of the 202 women who participated in the study, 178 (88%) women completed the survey and provided a self-sample, 140 (79%) reported that the HerSwab test was comfortable, and 162 (91%) found that the test was easy to use. All of the participants reported that they would be willing to perform the test again, as needed, for future screening.[22]

POSSIBLE ISSUES IN IMPLEMENTING SELF-SAMPLING

Timing for Samples to Reach the Lab

Dry samples collected using self-sampling devices should be processed as soon as possible (within five to seven days).[15,23] This may be a consideration if self-sampling is used in remote areas.

Costs

The cost of distributing self-sampling kits has been noted as a possible limiting factor in their use.[24] Requiring women to opt in to receive self-sampling kits may help reduce distribution costs but may also discourage participation.[14,25-27] Offering kits to underscreened women when they visit clinics or emergency rooms for other reasons may also reduce program costs and increase screening uptake.[28,29]

A recent study of self-sampling for HPV in remote communities in Newfoundland and Labrador reported a cost of $3 for the test kit (a Dacron swab device) and $35 for lab costs, but it did not include the cost of lab staff time or postage (study kits were picked up or dropped off).[30]

Education Needs

Women will need information about the safety and accuracy of self-collected samples to alleviate concerns about their ability to use them.[10,31-33] Clinicians may also need to be educated about the importance of timely referrals for women who test positive for high-risk strains of HPV, regardless of these patients' Pap test results.[34]

Potential for Overdiagnosis and Overtreatment

Establishing mechanisms for women to requisition their own tests will require health systems to develop regulations and practice requirements to ensure such testing is appropriate. Despite its benefits, HPV screening also carries a risk for overdiagnosis and overtreatment.[6] The HPV test is more sensitive than Pap testing and could lead to more false-positive tests and follow-up testing, or detection of harmless infections or cervical lesions that would typically resolve spontaneously.[10,11,30,35] A rise in HPV testing could potentially increase the rate of follow-up testing and invasive interventions, including colposcopy (magnified visual examination of the vagina and cervix) and biopsy, and could lead to unnecessary treatments — all of which carry associated increases in health care costs, and in anxiety and risks for the patient.[36]

LOOKING AHEAD

A 2014 UK review identified 43 self-sampling technologies for HPV testing, including 17 technologies that were commercially available or in development and 26 others that could be used for self-sampling.[9] The findings of the review suggest that the self-sampling device used is not important provided the device is acceptable and inexpensive to women.[9]

HPV vaccination in children and young adults is expected to reduce the number of Canadian women affected by cervical cancer in the next 10 to 15 years.[5,33]

Several countries are introducing HPV testing as the primary cervical cancer screening method,[8,27,37] and Canadian jurisdictions are also considering this change.[8,20] This will require adjustments to cervical cancer screening guidelines, including the frequency of screening, the optimal ages for screening, and the sampling methods used.[24,34]

Self-collected urine specimens are also under investigation for HPV testing and may be an acceptably accurate method of HPV testing that may be preferable for some women.[36,38] However, standardization of HPV urine testing, and studies to assess the feasibility and costs involved, are still needed.[36]

FINAL REMARKS

The evidence does not suggest substituting HPV self-sampling for regular office-based screening.[7,25,39] Rather, offering the option of self-sampling could increase testing for STIs and cervical cancer screening in underscreened women and reduce current inequities in the access to this preventive health intervention.[7,11,25,39]

The HerSwab is a timely addition to the selection of self-sampling devices available. More evidence is needed on how it may best be used in Canada to improve the uptake of testing for HPV and other STIs.

Author: Leigh-Ann Topfer

CADTH is preparing an Optimal Use Report that will assess the evidence for using HPV testing for primary cervical cancer screening. This report is expected to be published in December 2017.[40]

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Neurostimulation for the Treatment of Cluster Headaches

Cluster headaches are a rare type of primary headache — a headache without another medical cause — characterized by frequent, severe attacks that last for less than three hours.[1,2] Attacks may occur for periods of one week to one year, followed by a month of remission (these are known as episodic cluster headaches); or they may last for longer than a year, with shorter periods of remission or no remission at all (these are known as chronic cluster headaches).[3,4] The headaches occur on one side of the head and are accompanied by redness and tearing in the eye on the same side of the head, and by restlessness.[2]

Photo: iStock/Deklofenak

Cluster headaches are usually managed with medication or oxygen — to either treat attacks when they occur or to help prevent future attacks.[2] Using a device to directly or indirectly apply low-level electrical energy to an area of the nervous system, called neurostimulation, may offer patients with cluster headaches an alternative form of pain relief.

HOW IT WORKS

The Sphenopalatine Ganglion

The sphenopalatine ganglion (SPG) is a triangular collection of neurons located in the middle of the face.[5] Because the SPG plays a role in controlling blood flow and the activity of chemical messengers — neurotransmitters — that influence pain, researchers are interested in how stimulating or blocking nerve signals in the SPG can affect pain, including pain caused by cluster headaches.[5]

The Device

The ATI Neurostimulation System (Autonomic Technologies, Inc., Mountain View, California) is a small, implantable device activated by the patient using a hand-held remote control.[6,7] In Europe, the device is marketed as the Pulsante SPG Microstimulator System. When a cluster headache begins, the implant is turned on and emits low-level energy to the SPG area.[6] The implant is self-powered by induction and does not require a battery.[8]

Implantation Procedure

Following preoperative imaging to determine the mid-facial anatomy of the patient and select an appropriate size of implant, patients receive general anesthesia, and then the device is implanted through a small incision in the top of the mouth near the first or second molars.[9,10] The device is implanted on the side of the head where the cluster headaches most often occur.[9] Correct placement of the device is confirmed using imaging during the surgery and again one day after the procedure.[9]

WHO MIGHT BENEFIT?

Cluster headaches are estimated to affect about one in 1,000 people worldwide in their lifetime.[11] Men are more than four times more likely than women to be affected.[11] Guidance from the National Institute for Health and Care Excellence (NICE) in the UK concludes that SPG neurostimulation may be an option for patients who do not respond to other forms of treatment.[10]

AVAILABILITY

The ATI Neurostimulation System is not currently available in Canada. The system is CE-marked for marketing in Europe.[12] In the US, the Sphenopalatine Ganglion Stimulation for the Treatment of Chronic Cluster Headache study is underway to collect additional data while the company seeks FDA approval.[13]

WHAT DOES IT COST?

The cost of the ATI Neurostimulation System is not available. A 2015 German cost-effectiveness study funded by the manufacturer reported the estimated cost of the device as €25,000.[14] Additional costs include the implantation procedure, pre- and post-procedure imaging, and follow-up visits during the titration period after implantation.[14]

When compared with drug treatment, the German study found the device to be cost-effective and potentially cost-saving, while noting that further long-term data are required to confirm their costing models.[14]

CURRENT AND ALTERNATIVE PRACTICES

Canadian and US guidelines recommend both acute and preventive drug treatment for cluster headaches.[1,2] The US guidelines also note that SPG neurostimulation is possibly effective for acute attacks, and steroid injections are also listed as an effective option for prevention.[1]

WHAT IS THE EVIDENCE?

In 2013, the UK's National Institute for Health Research (NIHR) Horizon Scanning Research & Intelligence Centre published a *Technology ALERT* on the ATI Neurostimulation System.[12] Since then, additional evidence has become available.

Clinical Efficacy

The manufacturer-funded, randomized, sham-controlled Pathway CH-1 study looked at 28 patients. The study's primary outcome was pain reduction 15 minutes after stimulation was started, and secondary outcomes were pain relief (or freedom from pain) at intervals of 30, 60, and 90 minutes after stimulation began.[7] Results were recorded over a period of three to eight weeks.[7]

Pain relief within 15 minutes

Patients were considered to have achieved the primary outcome of pain relief if their categorical pain score (0 to 4, where 0 is pain-free and 4 is very severe pain) changed from 2, 3, or 4, to 0 or 1 within the first 15 minutes of stimulation.[7] A total of 566 cluster headache attacks were recorded by patients using a headache diary incorporated into the device's remote control.[7] Pain relief was experienced in 67.1% of full stimulation-treated attacks compared with 7.4% of sham stimulation attacks.[7]

Pain relief or freedom from pain after 15 minutes

Patients were also asked to document pain relief or freedom from pain after 15 minutes.[7] Pain relief for headaches treated with full-dose stimulation (one of three stimulation doses, including the sham dose) was achieved in 55.5%, 60.6%, and 60.0% of attacks at 30, 60, and 90 minutes, respectively, compared with 8.0%, 11.5%, and 12.9% of attacks treated with sham stimulation.[7]

Other outcomes

Although the Pathway CH-1 study was not designed to detect a reduced frequency in cluster headaches or a reduction in the use of medication, both these outcomes were noted by the investigators and are now subject to further study.[7,8,15]

Long-Term Effectiveness

Researchers continue to collect data from the study's patients through a registry.[16] Two industry-funded studies of these follow-up data were identified, covering the two years after device implantation.[8,15] Effectiveness of treatment in these 33 patients was defined as being an acute response (pain reduction or freedom from pain in at least 50% of attacks) or a frequency response (at least a 50% reduction in the frequency of attacks) at 24 months. Of the nearly 6,000 attacks recorded, 65% achieved an acute response. However, only 15 patients (45%) were able to effectively treat their headaches at least 50% of the time. A frequency response was reported in 11 of 33 patients (33%), with an 83% on-average reduction in the frequency of attacks at 24 months. Remission (attack-free for at least 30 days) of cluster headaches was also noted in 10 of the 33 patients.[15]

Safety

The Pathway CH-1 study reported five serious adverse events.[7] Three devices were placed incorrectly, including one that was placed in the wrong anatomical structure and required removal. In both of the two other cases, the device required removal: in one, because the implant had moved post-procedure and, in the other, because the wrong-sized implant was used.[7]

Other adverse events have been documented both during and following the Pathway CH-1 study.[7,17,18] Over 80% of the patients treated experienced some form of sensory disturbance (e.g., loss of sensation) after the procedure.[7,17,18] Investigators noted that most adverse events were mild or moderate in nature, occurred within 30 days of the procedure, and resolved within three months of surgery.[17]

RELATED DEVELOPMENTS

Other types of neurostimulation to treat cluster headaches are being explored, including occipital nerve, vagal nerve, and deep brain stimulation.[1,19,20]

The use of SPG stimulation for treating migraines, including the use of the ATI Neurostimulation System, is also being investigated.[21,22]

OTHER ISSUES

Patient Selection

It is still unclear which patients will benefit from SPG neurostimulation and would be suitable for ATI Neurostimulation System implants. Consensus guidance has been published to help ensure uniform patient selection and care.[23]

Optimizing the Procedure

Accurately placing the device has been reported to be difficult, and UK NICE guidance indicates that revision procedures or removal occurs in up to 13% of patients.[10,24] Researchers are currently studying ways to improve the implantation procedure. A 2017 retrospective study found that the use of navigation software improved placement of the device.[25] In 2015, researchers recommended using immediate post-operative imaging, in addition to imaging done during the procedure, to reduce additional hospitalizations for incorrect placement of the implant.[24]

FINAL REMARKS

SPG neurostimulation for cluster headaches is an emerging area of research. Additional long-term studies of the effectiveness and safety of the ATI Neurostimulation System will provide a better understanding of which patients might benefit from SPG neurostimulation, as well as a more accurate estimate of the device's potential cost-effectiveness.

Author: Jeff Mason

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Using Ultrasound to Deliver Cancer Therapies Across the Blood-Brain Barrier

The blood-brain barrier is a network of cells and chemical processes that surround the blood vessels of the brain, protecting the central nervous system from toxic agents, viruses, bacteria, and other pathogens.[1,2] However, this barrier also blocks about 99% of drug therapies, preventing the optimal delivery of medications — such as chemotherapies used to treat brain tumours.[3] Temporarily disrupting the barrier can improve drug delivery to brain tumours and adjacent areas of the brain where invasive cancer cells may take hold.[1]

Image courtesy of CarThera

The ability of a drug to cross the blood-brain barrier is affected by several factors, including the size of the molecules, solubility in fats, and the way the drug interacts with certain proteins in the blood.[1]

Different techniques can be used to increase drug uptake to the brain including using osmotic agents (such as mannitol), chemical agents (such as vasoactive drugs that temporarily increase vascular activity), delivering drugs directly to the tumour via catheters, intranasal delivery, and drug-impregnated biodegradable wafer implants.[2,4] However, these methods have risks of serious adverse events, including infection and damage to healthy brain tissue.

One delivery option under investigation is using ultrasound combined with microbubbles in an ultrasound contrast agent.[4-6] Ultrasound waves activate the microbubbles, causing them to expand and contract, forming tiny openings in the blood-brain barrier.[7] The microbubbles are drug-neutral and may improve the delivery of imaging agents, drug therapies, antibodies, and nanoparticles across the blood-brain barrier without damaging the brain.[8] Moreover, ultrasound-activated microbubbles have been shown to disrupt the blood-brain barrier for approximately six to 12 hours, allowing for the increased penetration of chemotherapy drugs without evidence of significant adverse events to date.[5,7]

HOW IT WORKS

The SonoCloud (CarThera, Paris, France) is a small, MRI-compatible, one megahertz ultrasound transducer that emits low-intensity pulsed ultrasound.[9] It is implanted in the skull, near the tumour — either as part of a scheduled surgery to decrease the size of a brain tumour, or in a 15-minute procedure performed under local anesthetic. The microbubble contrast agent, sulphur hexafluoride (with the brand name SonoVue, Bracco Imaging), is injected into the blood and activated by ultrasound to temporarily open the blood-brain barrier.[5,10] Patients receive one ultrasound session each month, followed by intravenous chemotherapy. Follow-up MRI imaging is used to measure the level of disruption of the blood-brain barrier.[9]

While other investigators are evaluating the use of externally applied focused ultrasound,[2] the SonoCloud device allows ultrasound to be applied from within the skull, without needing MRI imaging to monitor the procedure or to adjust for distortion caused by the bone of the skull.[3]

WHO MIGHT BENEFIT?

Initial trials focus on using SonoCloud in people with glioblastoma multiforme (also called glioblastoma) — the most common type of primary brain cancer in adults.[11] In North America, glioblastoma affects an estimated three in every 100,000 people.[11] It is a particularly aggressive cancer that contains different types of cancer cells that can proliferate throughout the brain, including in the vascular system, where a blood-tumour barrier can form.[1,12]

AVAILABILITY IN CANADA

The SonoCloud device is in clinical trials in France and is not yet licensed for use in Canada. The company anticipates the SonoCloud may be commercially available in Europe and the US by 2020.[13]

WHAT DOES IT COST?

The potential cost of SonoCloud is not yet known.

CURRENT PRACTICE

Treatment of glioblastoma usually involves surgically removing as much of the tumour as possible, followed by radiation therapy and chemotherapy. However, the chemotherapy drugs have limited ability to cross the blood-brain barrier;[11,14] and, despite treatment, the cancer usually recurs or progresses.[1,11,12]

WHAT IS THE EVIDENCE?

Opening the blood-brain barrier

The ongoing phase I/IIa clinical trial of SonoCloud at a hospital in Paris, France, will enrol 20 to 30 patients with recurrent glioblastoma.[5,6] The trial is a dose escalation study, assessing the feasibility and safety of opening the blood-brain barrier using different intensity levels of ultrasound. It is not designed to assess cancer progression or survival.

Each patient is implanted with the SonoCloud device and receives up to six rounds of ultrasound in combination with carboplatin chemotherapy.[5] The trial is expected to be completed in 2017.[5] Preliminary results with 15 patients were published in 2016.[6] The patients received different, increasing doses of acoustic pressure ultrasound with each monthly cycle of chemotherapy.

Blood-brain barrier disruption was seen in 28 of 41 applications of focused ultrasound (sonications).[6] Disruption was seen only at higher levels of acoustic pressure (measured in megapascals or MPa).[6] Blood-brain barrier disruption occurred at 0.8 MPa (8 of 11 sonications), 0.95 MPa (6 of 7 sonications), and in all 14 applications at 1.1 MPa.[6] The extent of opening the blood-brain barrier, assessed using MRI, was greatest at 1.1 MPa. In patients where opening was apparent, the average increase was 15%, observed through contrast-enhanced MRI imaging.[6]

The small size of the ultrasound field — which may be increased in future versions of the device — was considered a limitation, as it was not sufficient to cover the entire desired volume of the tumour, and region around the tumour, in the patients treated. The investigators noted that ultrasound may have other benefits beyond an effect on the blood-brain barrier; for example, an increase in immune system antitumour responses, as seen in breast cancer research.[6] As the trial continues, higher acoustic pressure levels will be used to determine optimal levels for future phase II/III trials.[6]

Safety

The preliminary trial results noted no serious treatment-related adverse events and patients did not report any sensation during the 2.5-minute ultrasound sessions.[6] Two minor adverse events were reported: one patient experienced pain during placement of the transdermal needle used to activate the device, and one patient felt faint during infusion of the microbubble contrast agent.[6]

CONCURRENT DEVELOPMENTS

Researchers at Toronto's Sunnybrook Health Sciences Centre are investigating focused ultrasound under MRI guidance, combined with microbubbles of contrast agent, as a non-invasive way to temporarily open the blood-brain barrier for better drug delivery.[7]

Another new treatment for glioblastoma is the Optune system (Novocure, Portsmouth, New Hampshire, US), which delivers low-intensity electricity to the brain.[1] New formulations of chemotherapy drugs and nanoparticles that enhance their ability to cross from the blood to the brain are also in development.[1,14]

Ultrasound in combination with microbubbles is also being investigated as a way to remove the amyloid beta-protein that accumulates in the brain of people with Alzheimer disease.[15]

LOOKING AHEAD

Using ultrasound to improve penetration of the blood-brain barrier could benefit people with many conditions, including other types of brain cancers and neurodegenerative diseases.[6]

Author: Leigh-Ann Topfer

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Focus On: Direct-to-Consumer Genetic Testing

Direct-to-consumer (DTC) genetic testing is the analysis of human DNA that is directly marketed to consumers via the Internet, TV, or other media.[1] Unlike traditional genetic testing provided within a health care setting, DTC genetic testing offered by private companies does not require that customers be referred by health care providers.[1]

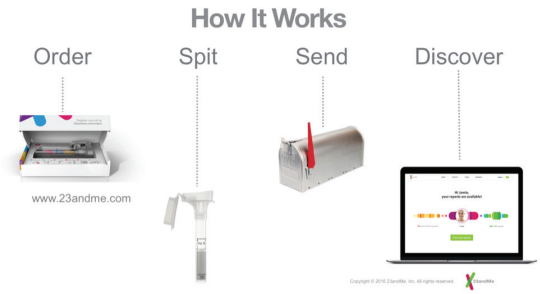
Advertising for DTC genetic testing began in the early 2000s with Myriad Genetics' BRACAnalysis — a genetic test for hereditary breast and ovarian cancers.[2] Other biotechnology companies soon followed suit with their own DTC genetic test offerings. In 2015, there were 77 companies offering DTC genetic testing to Canadians.[3]

Many of the first DTC genetic tests were curiosity-driven projects. These tests employed a set of benign genetic markers used for "recreational" purposes to help consumers uncover their ancestry and understand innocuous personal characteristics, such as their ability or inability to smell asparagus in urine.[4] The array of offered tests has since expanded to include medical indications, such as risk information for hereditary cancers,[5] and carrier testing intended to help individuals with their reproductive decision-making by assessing whether they are at a heightened risk of having a child affected by a certain genetic condition or disease.[6]

HOW IS DIRECT-TO-CONSUMER GENETIC TESTING REGULATED?

The move to medical uses of DTC genetic testing to predict disease risk and drug response has come under scrutiny from the US FDA.[7] In July 2010, the FDA announced a plan to regulate DTC genetic tests and contacted 20 biotechnology companies, asking them for data to support their medical claims.[2] One of those companies, 23andMe, was an early provider of online DTC genetic testing. In November of 2013, the FDA and 23andMe made headlines when the regulatory body warned the California-based company to stop selling its US$99 DNA collection kit (see Figure 1).[8] For two years following the warning, 23andMe was allowed to provide only ancestry information to its US customers.[9,10] 23andMe subsequently received FDA approval to provide carrier testing for 36 inherited conditions or diseases[10] and to begin the marketing of tests that estimate a person's risk of developing 10 conditions, including Parkinson disease and late-onset Alzheimer disease.[11] Today, its DNA collection kit sells for US$199.[12]

Figure 1: The Process for Obtaining 23andMe DNA Collection Kit Test Results



Reproduced with permission from 23andMe

In 2014, 23andMe began selling its DNA collection kit to Canadians at a cost of C$249, providing customers with information on more than 100 health conditions. Because the analysis of DNA samples is performed in laboratories located outside of Canada, Health Canada considers the 23andMe DNA collection kit to be a Class I medical device (i.e., low risk and not requiring a medical device licence) that is used only to transport samples of saliva to a testing facility and does not serve any diagnostic function itself.[9]

In the absence of stricter federal regulations specific to DTC genetic testing, other means may be used to regulate the industry at the federal level (e.g., via marketing or privacy regulations) or at the provincial level (e.g., via health laws or consumer protection

or other privacy regulations).[13] In many Canadian provinces, medical diagnostic tests, by law, must be prescribed by a physician.[14,15] In addition, if performed in Canada, the tests would be considered a Class III in vitro diagnostic device (i.e., moderate risk and requiring a medical device licence).[16] Recognizing these inconsistencies between DTC genetic testing and traditional genetic testing provided within a health care setting, in 2015, the Canadian College of Medical Geneticists wrote to the Federal Minister of Health,[17] and the Doctors of BC issued a position statement, both calling for stricter regulation of DTC genetic testing, as is the case in the US.[18]

WHAT ARE THE POTENTIAL BENEFITS OF DIRECT-TO-CONSUMER GENETIC TESTING?

Compared with traditional genetic testing provided within a health care setting, DTC genetic testing may be more accessible to the public, as DNA collection kits can be ordered online and delivered at a relatively low cost, with no need for referrals from health care providers.[1,6] In addition, DTC genetic testing may empower individuals who, given the new information that DTC genetic testing provides, may make healthier choices to prevent disease, potentially saving downstream health care costs — although evidence on any cost savings is still lacking.[1] Further, DTC genetic testing users may draw individual value, as they fulfill their desire to be in the forefront of adopting new technologies and their test results may also contribute to medical research.[19]

> "There are also concerns around inaccurate test results, which could lead to unnecessary actions and costs or misplaced assurance."

WHAT ARE THE POTENTIAL HARMS OF DIRECT-TO-CONSUMER GENETIC TESTING?

The clinical utility of some DTC genetic tests is unclear.[7,20,21] In addition to genetic tests for single-gene disorders that almost always occur in those carrying a mutation, such as Tay-Sachs disease or cystic fibrosis, DTC genetic tests target multigene conditions that may or may not occur in those carrying a mutation, such as heart disease or diabetes.[2] The predicted risk of such multigene conditions can vary drastically, based on the mutation tested, the test used, and the individual company's interpretation of the test result.[22,23] Further, there may not be effective interventions for disease prevention or treatment, as is the case with Huntington disease.

There are also concerns around inaccurate test results, which could lead to unnecessary actions and costs or misplaced assurance.[24] For example, a false-positive result for breast cancer may lead to preventive mastectomy, and a false-negative result for colorectal cancer may lead to a person foregoing a colonoscopy that may otherwise prove beneficial.

Without sophisticated genetics knowledge, customers and their health care providers may also be confused by the information they receive,[7,25] which is often provided without genetic counselling.[6,7] In fact, there is evidence that users of DTC genetic testing are sharing their results with their health care providers,[26] identifying a need to ensure that health care providers are equipped with sufficient genetics knowledge to be able to guide their patients appropriately.[27]

There are also questions surrounding the privacy of genetic information, including the misuse of personal genetic information by third parties. For example, the information may be used by health insurance companies and employers to justify discrimination[7,28] or by researchers without obtaining proper consent from DTC genetic testing users.[29] In fact, a 2016 study found that DTC genetic testing companies do not consistently meet international transparency guidelines related to confidentiality, privacy, and secondary use of data.[30] A 2015 report to the Office of the Privacy Commissioner of Canada also found that, in 2013, up to half of the 86 companies offering DTC genetic testing services to Canadians had no privacy policy posted on their websites and, of those that did, many addressed only aspects related to the use of their websites.[3] In the US, the *Genetic Information Nondiscrimination Act* ensures customers experience no impact on health insurance policy and employment status as a result of pursuing genetic testing.[1] However, Canadians do not have similar legislative protection, although Bill S-201, the *Genetic Non-Discrimination Act*, has, at the time of writing, passed a third reading in the House of Commons and is now before the Senate for consideration.[31,32]

WHAT ARE THE ACTUAL IMPACTS OF DIRECT-TO-CONSUMER GENETIC TESTING?

Currently, there is little evidence of either significant benefits or significant harms associated with DTC genetic testing.[33-35] For example, a 2011 study, where 2,037 individuals were provided with genetic risk information on 23 health conditions — including heart attack, breast and colon cancers, and diabetes — reported no significant change in psychological health (e.g., anxiety) or health behaviours (e.g., diet, exercise, or screening) following genetic testing.[36] A 2010 Cochrane Review on the effects of communicating DNA-based disease risk estimates also reported little or no change in smoking and physical activity following genetic testing.[37] A 2015 systematic review also reported no behavioural change up to one year after DTC genetic testing.[35]

FINAL THOUGHTS

While there is much hype surrounding DTC genetic testing, little evidence currently exists to demonstrate either significant benefits or significant harms associated with it.[33,34] Nevertheless, the global DTC genetic testing market continues to grow, highlighting the need to monitor its progress, update and fill in any gaps in research, and educate consumers to help them make informed choices.[3]

Author: Joanne Kim

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CADTH *Issues in Emerging Health Technologies* Bulletins

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- Outpatient (Same Day) Hip Replacement
- Ifunny Channel Inhibitors: An Emerging Option for Heart Failure
- Wearable Artificial Kidneys for End-Stage Kidney Disease
- Point-of-Care Testing for Influenza
- PAR-1 Antagonists: An Emerging Antiplatelet Drug Class
- GPS Locator Devices for People With Dementia

CADTH Horizon Scan Roundup 2016

The CADTH *Horizon Scan Roundup* for 2016 (Part 1 and Part 2) is now available. The two parts list reports on new and emerging technologies published by CADTH and other agencies in 2016.

Recent Horizon Scanning Reports From Other Agencies

Agencies included in the mini-roundup that follows:

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- ECRI Institute, US
- Health Policy Advisory Committee on Technology (HealthPACT), Australia
- Innovation Observatory (NIHR-IO), UK
- Institute for Safety, Compensation and Recovery Research (ISCRR), Australia

Selected Recent Horizon Scanning Reports From Other Agencies

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- NeuroBlate System for Precise Brain Tumour Treatment (NIHR-IO)

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