Health Technology Update

CADTH

A newsletter on new and emerging health care technologies in Canada

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Informing Decision-Makers About Emerging Medical Technologies

This issue of Health Technology Update features brief summaries of information on a broad range of new and emerging medical technologies. Topics covered range from an exoskeleton for stroke rehabilitation to MR-linac — a device that combines image guidance and cancer radiotherapy. These technologies were identified through the CADTH Horizon Scanning Service as topics of potential interest to health care decision-makers in Canada.

TECHNOLOGIES IN THIS ISSUE:

FEEDBACK

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

Please let us know!

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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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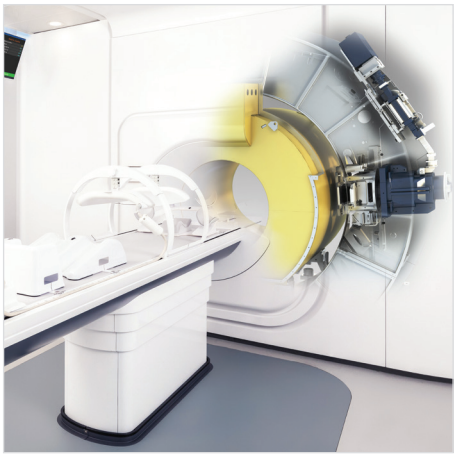

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MR-linac for Radiation Therapy for the Treatment of Cancer

MR-linac is an emerging technology that combines a radiotherapy accelerator and a magnetic resonance imaging (MRI) scanner in a single device.[1] It provides real-time imaging of tumours at the moment of treatment and is intended to deliver radiation beams from the linear accelerator with improved targeting accuracy due to both its enhanced soft tissue visualization and monitoring during radiation delivery.[1]

How It Works

Radiotherapy is an important therapeutic tool used in approximately two-thirds of all cancer patients.[2] It can be used on its own or in combination with chemotherapy and/or surgery.[3] Image-guided radiotherapy using CT is the current standard of care;[4] however, other imaging technologies in radiation oncology are also used including megavoltage planar imaging, static kilovoltage planar imaging, and ultrasound.[5]

MR-linac is a hybrid device that integrates two technologies — a linear accelerator used to deliver external beam radiotherapy and an MRI scanner that guides the delivery of radiation to the tumour.[1] The system enables the delivered radiation dose to be adapted to the current position and shape of the tumour and surrounding healthy tissue. It also facilitates tumour tracking for high-precision targeting.[6] Theoretically, more precise targeting means that higher doses of radiation can be delivered to the cancerous tissue while minimizing damage to the surrounding tissue, which may improve clinical outcomes (increased local control, survival, decreased toxicity, improved quality of life) and reduce hospital stay compared with existing alternatives.[4,6]

MR-linac is the first linear accelerator system that can find tumours and treat them at the same time.[7] It optimizes the visualization of images of tumours located in parts of the body where there is movement. If a tumour moves out of the targeted radiation field due to a patient's normal internal body movement, the MR-linac automatically halts the radiation beam until the tumour returns to its original position, when radiation treatment is automatically resumed.[1]

There are several MR-linac systems available: the Elekta Unity that incorporates a Philips 1.5 Tesla MRI and a 7 megavolt (MV) (acceleration rate) linear accelerator,[8] the MRIdian by ViewRay that integrates a 0.35 Tesla magnet and a three Cobalt-60 source for irradiation,[9] and the MRIdian Linac in which the cobalt sources are replaced by a single 6 MV Linac.[10] Another MR-linac, the Aurora RT radiation therapy system from MagnetTx, combines a 6 MV linear accelerator and a 0.5 Tesla MRI magnet, and has a non-clinical working prototype.[11]

Who Might Benefit?

It is anticipated that MR-linac will initially be used for cancers of the brain, breast, cervix, esophagus, lung, oropharynx, pancreas, prostate, and rectum.[4] However, because it can potentially be used for virtually any type of cancer,[12] its use is anticipated to expand.

Availability in Canada

The first MR-linac system was approved by Health Canada in 2017,[13] and there are three facilities in Canada conducting research with the technology — two in Toronto and one in Edmonton.[5,14]

What Does It Cost?

Canadian costs are not known. In the UK, the installation of an MR-linac at one site cost £5.3M.[15] At a site in the US, the installation costs amounted to US$10M.[16] While the cost of an MR-linac compared to a traditional linac is not certain, it is known that they are more expensive[17] and it is estimated that they may be approximately double the cost of conventional systems.[12] The cost may be offset by other considerations, such as that MR-linac may provide improved outcomes or reduced costs associated with toxicity compared with other image-guided radiation therapy options.[12]

Initially, there may be additional staff-related costs associated with MRI-guided radiotherapy systems which, until the procedures and tools are more mature, are operated by a team consisting of a physician, radiotherapist, medical radiation technologist, and physicist.[18] In contrast, CT-guided radiotherapy only requires radiotherapists to perform the procedure.[18]

Current Practice

CT has been a standard of care as an imaging technique for radiation therapy simulation, planning, and image guidance.[19] While CT revolutionized radiation therapy practice in the early 2000s,[20] it is not the standard of care for all tumour sites and it has some limitations:

- an inability to provide high-quality, soft tissue contrast, which may make it difficult to distinguish cancerous tissue from surrounding healthy tissue[15]
- visualization of tumours is limited by the motion of the body (such as breathing or swallowing)[17]
- it can only be used before or after treatment and not during the procedure[4]
- it exposes patients to additional doses of radiation.[4,5]

Published Studies and Resources

There is a lack of published clinical studies on MR-linac because it is still mostly used for research purposes.[4] A proof-of-concept study involving five patients with painful lumbar spine bone metastases was published in 2017 to determine if high-field, 1.5 Tesla MR-linac is clinically feasible in the patient population.[11]

Most of the ongoing studies focus on dosimetry and the technical performance and/or feasibility of MR-linac rather than on clinical outcomes. Four clinical trials are underway, including a single-arm, open-label study to measure differences between tumour targets and organs at risk volumes visualized on positron emission tomography, CT, and MRI images in lung cancer patients;[21] a single-arm, open-label study to assess the technical feasibility of delivering radical radiotherapy for prostate cancer using the MR-linac;[22] and two observational studies — one investigating the optimal pulse sequence parameters of MR-linac image sequences suitable for patients undergoing radiotherapy[23] and the other to develop MR-linac image sequences suitable for seeing tumour/target and normal tissue at the time of radiotherapy, and to determine variations in image registrations and tissue contouring using the MR-linac images.[24]

Safety

There are some unique safety issues associated with MRI[25] that may not be commonly understood in oncology departments,[16] as some radiation oncologists may be less familiar with MRI than they are with CT. MRI safety issues relate to the projectile capabilities of metallic objects in the strong magnetic field of MRI units, as well as the necessity to screen patients for contraindications such as cardiac pacemakers and neurostimulators.[16]

Issues to Consider

The integration of MRI into radiotherapy practices presents several significant challenges. These challenges include processes for the planning, installation, and commissioning of the technology;[19] workflow practices;[26] human resources;[27] education and training requirements;[27] safety and quality assurance;[16] and the need for collaboration between radiation oncologists, radiologists, medical physicists, pathologists, surgeons, and other staff.[16,28,29]

With a culture change from CT to MRI,[25] significant collaboration and cross-training between radiation therapists and medical radiation technologists will be required.[16] As radiation oncology staff may be less familiar with MRI safety precautions, appropriate safety training will be important.[30] Consideration may also need to be given to whether radiation therapists in the field of medical imaging require more formal qualifications and accreditation.[16] As well, nuances may have to be considered such as the different requirements placed on the therapeutic use of MRI compared with the traditional diagnostic use[31] (for example, compatibility with radiotherapy accessories and the higher geometric fidelity of MR images).

From a system capacity perspective, there is a concern that MR-linac may impede high-patient throughput because workflows are considered to be resource-intensive[32] compared with those used for CT imaging. However, there are potential cost savings associated with MR-linac because it may be able to free up capacity by requiring fewer treatment sessions than conventional linac systems.[15,33]

Related Developments

MR-linac is unique in that it is the only imaging modality that is integrated into a linear accelerator.[1] Other technologies available or evolving for use in informing patient positioning or image-guided therapy include ultrasound visualization, stereoscopic X-ray guidance, CT-based guidance, and continuous intra-fraction position monitoring.[34]

Looking Ahead

It has been predicted that, during the next ten years, MR-linac will become the standard clinical system in radiotherapy.[35] It has also been suggested that it may soon enable radiation oncologists and radiation therapists to image biomarkers during treatment and adapt the treatment plan or even change the treatment objective based on real-time data.[5]

Author: Andra Morrison

See references on page 14.

d-Nav Insulin Guidance System: A New Way to Manage Insulin Requirements

Blood sugar monitoring and insulin dose management are important elements of disease management for many people with type 2 diabetes. The d-Nav Insulin Guidance System aims to make this process easier and more effective by automating the titration of insulin dosing and providing dose guidance to inform the patient which insulin dosage to use.

Source: Green, W, Taylor, M. Cost-effectiveness analysis of d-Nav for people with diabetes at high risk of neuropathic foot ulcers. Diabetes Ther. 2016 Sep;7(3):511-525. Image is licensed under Attribution-NonCommercial 4.0 International (CC BY-NC 4.0)

How It Works

The d-Nav Insulin Guidance System (Hygieia, Livonia, Michigan) leverages proprietary technology to provide personalized guidance prior to each insulin injection.[1] The guidance is provided through an integrated, hand-held device that has a built-in glucose sensor to measure blood glucose levels, or via the d-Nav phone app using glucose data collected by any other available monitoring method from third parties (e.g., continuous glucose monitoring).[1,2] In both cases, the software automatically monitors and analyzes glucose levels and automatically titrates the individual's dosage of insulin based on patterns in their overall blood glucose readings.[1,3] At a minimum, this adjustment in insulin dosing is made weekly.[4] The blood glucose measurements and corresponding insulin requirements are stored in an online cloud, where they can be accessed and reviewed by dedicated nurses who support d-Nav users.[1] These nurses communicate with participants in person or by phone to provide them with individualized support to help manage their diabetes.[1]

Appropriate insulin replacement can help prevent complications of diabetes and potentially reduce costs to both the patient and the health care system.[2] Typically, people with diabetes visit their doctor's offices occasionally to check on the appropriateness of their insulin dose based on blood glucose trends and to determine if adjustments are needed.[2] The intention of the d-Nav system is to provide regular feedback to people with diabetes regarding the appropriate insulin dose required for each injection and to automatically adjust the insulin dose, as needed.[2]

Who Might Benefit?

The d-Nav system is intended for use by any person with type 2 diabetes who requires insulin.[1] In 2018, an estimated 3.5 million Canadians lived with diagnosed diabetes.[5] An estimated 11.4% of the Canadian population will be diagnosed with diabetes by 2025.[6] Based on 2009 to 2014 US data, the percentage of people with type 2 diabetes treated with insulin was 22.2%.[7] No Canadian data on the proportion of insulin use was identified.

Availability in Canada

The d-Nav system is not currently licensed for use or available for sale in Canada and there is no estimated time of entry into the Canadian market available (J. Daniel Prewitt, Chief Revenue Officer, Hygieia, Livonia, MI: personal communication, 2018 Nov 21).

The d-Nav system received US FDA 510(k) clearance in February of 2019.[8] In the US, the d-Nav system is currently available in Michigan for some people with type 2 diabetes through an agreement between the manufacturer and Blue Cross Blue Shield.[2] The d-Nav system has been in use by the South Eastern Health and Social Care Trust in Northern Ireland since 2012 through a partnership with the manufacturer[1] and has CE marking in Europe.[9]

What Does It Cost?

No information on the costs of purchasing and operating the d-Nav system was identified. The manufacturer has not yet established the Canadian cost of the technology (J. Daniel Prewitt: personal communication, 2018 Nov).

One cost-effectiveness analysis was identified examining the use of the d-Nav system for people with diabetes who were at high risk of neuropathic foot ulcers within the UK NHS.[10] In this study, the cost of the d-Nav system (based on 2013-2014 prices) was comprised of an installation fee (£102.17) and a weekly per-patient service fee that decreased, depending on the number of users (£44.96 to £33.72).[10]

The manufacturer of the device suggests that cost savings may be gained through a reduction in diabetes-related complications and hospitalizations, a reduction in outpatient clinic costs, and a reduction in the cost of diabetes testing supplies and glucose-management drugs.[2]

Current Practice

The *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada* outlines current practices for the diagnosis and management of diabetes.[11] They recommend that people with diabetes have their glycated hemoglobin (A1C) levels measured every three months when they are having glucose control issues or when making changes to their methods of diabetes management.[11] Monitoring blood glucose levels using methods such as self-monitoring of blood glucose, flash glucose monitoring, continuous glucose monitoring, and checking A1C levels is recommended as the best methods of gathering information to assess an individual's glucose control.[11] Individual targets are determined in consultation with the patient's health care team. The guideline also recommends collaborative and supportive environments to help facilitate the successful self-management of diabetes.[11] Educational materials and approaches are recommended to be customized based on the individual and their risk factors and life situations.[11]

Published Studies and Resources

One randomized controlled trial (2018) of the d-Nav system and specialist support was undertaken for 181 people with type 2 diabetes whose condition was being managed suboptimally with insulin.[4] Participants using the d-Nav system were compared with participants who received only specialist support.[4] One prospective before-and-after study of the d-Nav system (two publications, 2012) was undertaken for 46 people in the US with type 1 or type 2 diabetes.[12,13]

The studies investigated clinical outcomes including the fraction of dose adjustments made by the d-Nav system without intervention from the study team,[4,12,13] A1C levels,[4,12,13] frequency of hypoglycemic events,[4,12,13] and patient comfort and satisfaction.[4]

In addition, three conference abstracts[3,14,15] and one poster presentation were identified.[16] One of the abstracts[3] appears to be related to the previously mentioned randomized trial. The other conference abstracts may be related to otherwise unpublished work.[14,15] The poster presentation outlines the d-Nav pilot project in Ireland.[16]

The manufacturer noted that there are no ongoing or additional planned clinical trials (J. Daniel Prewitt: personal communication, 2018 Nov).

Safety

None of the identified studies or resources reported on potential safety issues related to the technology.

Issues to Consider

Health care providers may be challenged to process and respond in a timely manner to the large amounts of information produced through cloud-based, remote disease management systems.[17] The requirement for monitoring infrastructure and training providers in supporting patients using the technology may also impact the feasibility of use.[18]

Related Developments

In October of 2018, Health Canada approved a hybrid, closed-loop insulin pump that automatically and continuously adjusts insulin delivery based on continuous glucose monitor readings.[19] Other similar devices are expected to be released in 2019.

Other technologies that support patients with diabetes using insulin are currently on the market or in development. However, unlike d-Nav, none of these technologies provides automatic insulin dose recommendations for the patient.

The types of technologies available include mobile applications (apps) that allow people with diabetes to easily enter their blood glucose levels, insulin pump information, activity, nutrition, and lifestyle data into the app in a format that can be shared electronically with their care providers.[20,21] Additionally, there are tracking apps that are paired with glucose testing devices that automatically transfer blood glucose measurements to the app,[22,23] and some also facilitate communication with health care professionals to discuss test results and diabetes management through the app itself.[24-26] Apps exist that are more focused on improving the communication between patient and physician to address gaps in current treatment.[27] A clinical decision support software is available to help make recommendations for the management of in-patient insulin dosage in the hospital setting.[28]

Looking Ahead

There are a number of mobile applications currently available that intend to help people with diabetes monitor and manage their condition. They aim to support self-management and decentralize care; however, few have been proven clinically effective for long-term glycemic control and the management of A1C levels.[9] In order for these applications to be more widely used, longer-term clinical trials are required to adequately demonstrate their benefits for people with diabetes.[9]

Author: Michelle Clark

See references on page 14.

Custom*Flex* ARTIFICIAL*IRIS*: An Iris Prosthesis for People with Aniridia

Aniridia is an eye disorder whereby a person is missing part or all of the coloured part of the eye (the iris).[1,2] A new device — a flexible, customizable iris implant recently approved by the US FDA — may help improve vision and cosmetic issues in people living with the condition.

Fernández-López, Ester; Pascual, Francisco Pastor; Pérez-López, Marta; Quevedo, Alejandro Madrigal; Martínez, Cristina Peris, Sutureless Artificial Iris after Phacoemulsification in Congenital Aniridia, Optometry and Vision Science, 92,4S, S36–S39, https://journals.lww.com/optvissci/Fulltext/2015/04001/Sutureless_Artificial_Iris_after.9.aspx

How It Works

Custom*Flex* ARTIFICIAL*IRIS* (HumanOptics AG, Erlangen, Germany)[3] is a prosthetic iris originally developed by Dr. Schmidt Intraocularlinsen GmbH and is marketed under the name ARTIFICIAL*IRIS* in Europe.[4,5] It is made of a foldable, biocompatible silicone material that can be inserted into the eye through a 2.8 mm to 7.0 mm incision.[6,7] The device is 12.8 mm in diameter, with a fixed-pupil aperture of 3.35 mm.[7] It is available in two models: one with embedded fibre mesh (to add strength if sutured in place) and a more flexible non-mesh version.[6,8,9]

Each device is custom-painted, by hand, based on a photograph of the patient's other iris or, in cases of complete aniridia, the colour of a photograph chosen by the patient.[6,8-10] The back side is a smooth, opaque black.[7]

There are various surgical techniques for implanting the devices.[7] Each technique involves a common basic preparation:

- photographing the remaining iris (the iris of the opposite eye)
- selecting the device model appropriate for the technique to be used
- implanting the device into the ciliary sulcus (the area behind the iris) using forceps or an injector system.

Who Might Benefit?

Defects in the iris can occur at birth or can be acquired later in life (from trauma to the eye, for example).[2,8] In either form, aniridia may affect only a portion of the iris or the iris as a whole.[2] As a congenital condition, aniridia affects an estimated one in 50,000 to 100,000 births worldwide.[1] People born with aniridia are often affected by other conditions of the eye; in particular, glaucoma and cataracts.[11] Vision in people with aniridia can be very good or very poor, and many people with aniridia have large pupils, making them sensitive to light.[11]

Studies of the Custom*Flex* ARTIFICIAL*IRIS* have included people with birth-related partial or complete aniridia, or from aniridia caused by other conditions or trauma.[6] Because the device is intended to be placed in front of an intraocular lens,[12] people receiving the implant must either:

- already have an intraocular lens implant
- have no eye lens at all
- be eligible to have a crystalline (natural) lens removed and replaced with an intraocular lens.[6]

The device is not intended for use in people with a variety of associated conditions such as chronic untreated glaucoma, uveitis, untreated retinal detachment, or types of retinopathy.[6] It is not intended to be used to change the colour of a person's eye.[3]

In the US, the FDA has approved the device for adults and children with full or partial aniridia caused by congenital aniridia or iris damage from other causes or conditions.[6] It was given Breakthrough Devices Designation for meeting a need in a population of patients without other suitable treatment options.[6]

Availability in Canada

Custom*Flex* ARTIFICIAL*IRIS* is not yet available in Canada. It was approved for use in the US in 2018[6] and in Europe in 2011.[9,13]

What Does It Cost?

No information on the cost of Custom*Flex* ARTIFICIAL*IRIS* was identified.

Current Practice

Regular eye examinations are recommended for people with aniridia to monitor changes in vision and detect glaucoma.[11,14] Options to treat aniridia are limited and include tinted glasses, iris reconstruction surgery, coloured contact lenses, and corneal tattooing.[6]

Published Studies and Resources

Two studies of the Custom*Flex* ARTIFICIAL*IRIS* were identified in patients

with full or partial iris defects.[9,15] This includes one multi-centre, prospective, non-randomized, open-label, uncontrolled clinical trial (n = 447 eyes) currently ongoing in the US,[15] with results available in FDA documentation,[6] and one 2016 single-centre, prospective, uncontrolled, before-and-after study (n = 32 eyes) conducted in Germany.[9]

Outcomes reported by authors include:

- best-corrected visual acuity[9]
- intraocular pressure[9]
- light sensitivity and glare[6,9]
- quality of life[6]
- satisfaction with the cosmetic appearance of the implant[6,9]
- safety.[6]

Conference abstracts, case series, and case studies were not included. CADTH completed a Rapid Response on artificial iris prostheses in 2016.[16]

Safety

The US FDA's summary decision lists possible adverse events related to the device or the surgical procedure.[6] These include worsening vision or photosensitivity, elevated intraocular pressure, infection or inflammation, incorrect device positioning, device movement, and the need for subsequent procedures.[6] Device-related, surgery-related, and intraocular lens-related adverse events were all reported in the studies we identified.[6,9]

The device is unsafe for use in an MRI,[6] which may also be an important consideration when selecting patients for the procedure.

A limitation of the Custom*Flex* ARTIFICIAL*IRIS* is its fixed pupil. Future approaches to managing aniridia could involve using materials that respond to light.

Issues to Consider

Implanting the device is a specialized and technical procedure[7] but no literature was identified discussing accessibility of the procedure for patients living long distances from centres offering the intervention. According to the manufacturer, clinicians wishing to use the device must complete an online training course.[3]

Patient-important outcomes — such as satisfaction with the cosmetic appearance of the device and functional outcomes — were reported outcomes in the studies identified.[6,9] However, using prosthetic iris implants for the purpose of cosmetic improvement may need to be weighed against potential intraoperative and post-operative complications.[2]

Related Developments

People with aniridia often have other eye conditions that require surgery.[1,11] Because of this, the feasibility of conducting pars plana vitrectomy (a procedure to remove the fluid from within the eye to perform other types of repairs) through the pupil of a Custom*Flex* ARTIFICIAL*IRIS* was investigated.[17] Surgeons have also described implanting the device into phakic eyes (eyes with a lens implanted without the removal of the natural lens)[18-20] and other emerging approaches to surgical implantation are also being investigated.[5,21-23]

Other iris replacements and iris implants for the treatment of aniridia exist[10,24-26] and have been used in Europe for more than a decade.[12] We did not identify any studies comparing these devices to the Custom*Flex* ARTIFICIAL*IRIS*. Treating aniridia with an artificial cornea implant has also been described.[27]

Looking Ahead

A limitation of the Custom*Flex* ARTIFICIAL*IRIS* is its fixed pupil.[10] Future approaches to managing aniridia could involve using materials that respond to light.[28-31] Researchers are currently investigating self-dimming contact lenses[28] and iris implants that can change the size of the pupil in response to light.[29-31]

Author: Jeff Mason

See references on page 15.

Photo: iStock/someone25

PolypDx: A Urine-Based Metabolomic Test for Colorectal Cancer Screening

Incidence and mortality of colorectal cancer can be reduced with early detection, but adequate participation in screening programs remains a challenge.[1] PolypDx is a urine-based metabolomic test for detecting and preventing colorectal cancer. It aims to offer ease and accessibility of screening in addition to the current fecal occult blood test options.[2,3]

How It Works

Metabolomics is the identification and quantification of small molecular weight chemicals generated by metabolism.[4] PolypDx (Metabolomic Technologies Inc., Edmonton, Alberta) is a urine-based metabolomic screening test for detecting adenomatous polyps of the large intestine, the precursor to colorectal cancer (CRC).[2] It is intended for individuals at average-to-moderate risk of CRC.[3]

PolypDx was developed through the metabolic profiling of 685 urine samples at the University of Alberta using nuclear magnetic resonance (NMR) technology.[2] PolypDx uses liquid chromatography–mass spectrometry (LC-MS) technology to measure the urine concentration of three key urinary metabolites: succinic acid, carnitine, and ascorbic acid.[2] The urine concentration of these three key urinary metabolites, along with clinical features including age, sex, and smoking history, are interpreted by a machine-learning algorithm to determine the probability of an adenomatous polyp being present.[2] The test results are either positive or negative for adenoma, with positive results requiring a follow-up and a colonoscopy at the care provider's discretion.[2]

Who Might Benefit?

In Canada, CRC is the third most common cause of cancer-related mortality in females and the second most common in males, with lifetime probabilities of CRC mortality of 3.1% for women and 3.5% for men.[5] In 2015, approximately 25,100 Canadians were newly diagnosed with CRC (49 in every 100,000 Canadians).[5]

Individuals who are at risk of CRC could potentially benefit from the PolypDx technology. This includes individuals older than 50 years old — as the incidence of CRC increases with age — and those with a family history of CRC.[5,6]

Availability in Canada

PolypDx is currently unavailable in Canada except in research settings (Dr. Lu Deng, Senior Scientist and Director of Business Development, Metabolomic Technologies Inc., Edmonton, AB: personal communication, 2018 Nov 23). PolypDx is currently available in the US as a laboratory-developed test through Clinical Laboratory Improvement Amendments (CLIA) certified laboratories.[2]

What Does It Cost?

In the US, the commercial price of PolypDx is US$399 per test (Dr. Lu Deng: personal communication, 2018 Nov). In the 2019 clinical laboratory fee schedule published by the Centers for Medicare & Medicaid Services, PolypDx is priced at US$200 by its primary processing Medicare administrative contractors, Novitas Solutions.[7]

In Canada, the price of PolypDx is yet to be determined (Dr. Lu Deng: personal communication, 2018 Nov).

Current Practice

Established non-invasive tests, such as fecal occult blood tests (FOBT), are the main components of most CRC screening programs, which identify individuals who should receive a colonoscopy.[8] These current non-invasive FOBT tests have high specificity (94.2 to 99%) but low sensitivity (2.6 to 17.6%), especially for the detection of CRC precursors like adenomas.[2,4] A colonoscopy is the gold standard for the detection and removal of pre-cancer and cancerous tissues.[4] However, barriers to consider are that it is invasive, costly, and inconvenient for patients.[4]

The 2016 guideline published by the Canadian Task Force on Preventive Health Care recommends screening adults aged 50 to 74 years for CRC with FOBT (either a guaiac fecal occult blood test or a fecal immunochemical test) every two years or flexible sigmoidoscopy (examination of the lower portion of the colon)[9] every 10 years.[6]

Published Studies

Three diagnostic test accuracy studies of PolypDx in patients enrolled in a CRC screening program were identified.[2,8,10] These include two validation studies — one conducted in Canada (n = 633)[10] and one in China (n = 661).[8] The studies compared an NMR-based metabolomics test — a precursor to PolypDx technology — with commercially available fecal-based tests for their ability to detect adenomas based on a reference standard of colonoscopy.[8,10] The third validation study,[2] conducted in Canada (n = 685), compared PolypDx (both NMR and LC-MS-based) and commercially available fecal-based tests with a reference standard of colonoscopy.[2] The identified studies report on diagnostic accuracy outcomes such as sensitivity and specificity.[8,10]

In addition, one systematic review[4] was identified that included 41 studies (including the three diagnostic test accuracy validation studies listed previously)[2,8,10] investigating the diagnostic performance of metabolomic biomarkers in blood, urine, and feces for the early detection of colorectal neoplasms.

Safety

While no published information was identified on the safety of the PolypDx technology, like many screening tests, CRC screening technologies are associated with a potential risk of overdiagnosis and false-positive test results.[11] Overdiagnosis applies to the proportion of cases that may not have progressed to symptom presentation if not detected via screening.[11] As these cases are not distinguishable from those with poor prognosis, patients may be subjected to the adverse effects of cancer therapy with unclear benefit.

Issues to Consider

Generally, compared to blood serum samples, urine samples are more susceptible to lifestyle factors such as diet and exercise, which can affect urinary biomarker composition and affect test results.[4]

PolypDx uses a machine-learning algorithm to determine the probability of an adenomatous polyp being present.[2] The ability of machine-learning algorithms to determine the likelihood of a polyp being present depends on the amount and quality of data available for training.[12]

To date, the studies have been done in individuals who are enrolled to receive a colonoscopy, so the screening and diagnostic performance in general asymptomatic populations that may be at risk of CRC is unclear.[2,4,8,10]

PolypDx may increase access to screening in rural and remote settings when compared with colonoscopy, and may provide an alternative to FOBT. The mass spectrometers required for PolypDx are commonly available in clinical laboratory settings, whereas a colonoscopy requires in-person testing.[2] Urine samples can be easily collected and sent to central labs for analysis, negating the need to travel.

Related Developments

Metabolomic Technologies Inc. is working with researchers at the University of Alberta, Memorial Sloan Kettering Cancer Center, and Obafemi Awolowo University on a point-of-care, real-time, urine metabolomics test for the diagnosis of polyps and cancer.[13] The test aims to incorporate biomarkers for the diagnosis of CRC into the current biomarker panel for PolypDx (Dr. Lu Deng: personal communication, 2018 Dec).

A number of metabolomic screening tests for CRC are being developed with dried blood spot-based and plasma-based testing.[4]

The C-Scan Cap system developed by Check-Cap is an orally ingested, X-ray-based imaging that scans and records the structure of the colon as it passes through the digestive tract.[14]

Looking Ahead

There is significant interest in combining machine-learning algorithms and diagnostic tools.[15] The introduction of PolypDx into clinical practice may offer more insight into the application of machine-learning methodology in the development of screening and diagnostic tools.

As PolypDx is currently unavailable in Canada, the impact on health care human resources and financial resources for CRC screening in the Canadian health care system is unclear. The Canadian Assessment of PolypDx (CAP) project was announced in October 2018.[16] It is intended to assess a new CRC screening program using PolypDx in 3,000 patients, in five regions throughout Alberta.[16] The results of the new screening program will be assessed by a national working group that consists of key provincial and national leaders in CRC screening.[16]

Author: Ke Xin Li

See references on page 15.

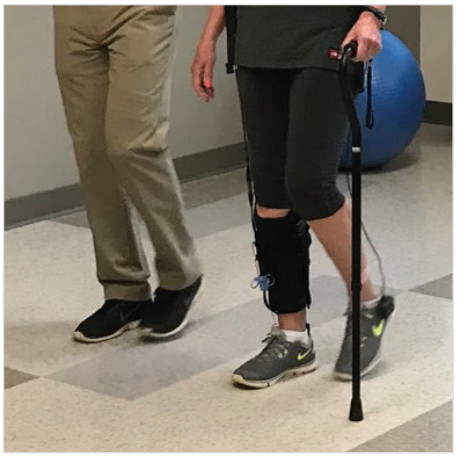

Image courtesy of ReWalk Robotics

A Robotic Exoskeleton for Gait Rehabilitation After Stroke

Stroke rehabilitation aims to reduce disability and help patients regain their ability to carry out the activities of daily living — one of the foundations of which is walking.[1-3] Combining manually guided therapies with robot-assisted rehabilitation may reduce the fatigue of the therapist and ensure exercises are provided in a controlled manner and at an optimal level.[4]

How It Works

There are two main types of robotic, or electromechanical-assisted, gait therapy systems:

- end-effector systems, such as the G-EO System (REHA Technology), and the Gait Trainer GT1 (Reha-Stim Medtec AG), which move the patient's feet using foot plates[2,5,6]
- exoskeleton systems, such as the Lokomat (Hocoma), which move the hips, knees, and ankles.[6-8]

Established robotic exoskeleton gait systems are based on workstations that include treadmills with overhead body weight support and bilateral exoskeletons.[6,9] Newer, mobile exoskeletons can be used with or without body weight support or a treadmill.[10] The new generation exoskeletons, or "exosuits," are intended to provide assistance for specific areas of weakness.[11]

The ReStore soft exosuit is a lightweight garment worn unilaterally on the affected leg, with a fabric sleeve that wraps around the calf and an insole under the foot. The leg and foot components are attached by cables to an activation unit and battery pack that can be worn around the waist for overground walking or placed adjacent to a treadmill. The ReStore can be used for both tethered (where the patient is connected to a system that supports their body weight during treadmill training) and untethered rehabilitation exercises.[12,13] The device has built-in sensors to detect load and force of delivery, and the activation unit motor provides power to the weakened leg to assist in bending the ankle, raising the foot up and down for ground clearance (dorsiflexion and plantar flexion), and propelling the leg forward for walking.[12]

Who Might Benefit?

Stroke is a leading cause of death and long-term disability in Canada.[14] Each year, more than 62,000 Canadians experience a stroke, and about 405,000 Canadians are living with the after-effects of stroke.[15] Following a stroke, most patients will have some functional disabilities, many of which will improve within six months; however, in many patients, functional impairment, including difficulty walking, will persist beyond this period.[2,16] As Canada's population ages and new treatments improve survival rates, it is estimated that the number of people living with disability due to stroke will increase to 726,000 throughout the next 20 years.[10,14,15]

Availability in Canada

The ReStore exoskeleton (ReWalk Robotics, Inc.) is not currently commercially available.[17] ReWalk Robotics first plans to apply for regulatory clearance in Europe and the US, where it anticipates ReStore may be commercially available in the first-half of 2019.[17]

What Does It Cost?

The different capabilities of current gait rehabilitation systems compared with the ReStore exoskeleton are not yet clear. A 2018 news item on the ReStore exoskeleton noted the company plans to price the system at under US$20,000.[18] Based on the very limited cost information available, this may be less than the cost of other exoskeletons used in rehabilitation.[19-21]

Current Practice

Lower limb rehabilitation involves repetitive, task-oriented movements to improve strength and coordination.[4] The focus is on relearning to walk using a combination of treadmill walking (with or without body weight support), community-based (overground) walking, and intensive repetition of functional mobility exercises, such as getting up from a chair.[3] Rehabilitation is supervised by

trained therapists, but the combination and application of exercises and the duration of therapy varies.[3,4]

Rehabilitation may differ in the sub-acute (within the first three to six months following a stroke) versus chronic (beyond six months) periods of rehabilitation.[2] In the sub-acute phase, rehabilitation may focus on restoring the ability to walk independently, whereas the chronic phase may focus on improving walking ability.[10] Neuroplasticity enabling recovery is believed to be greater during the sub-acute period.[8,22]

Canadian stroke rehabilitation guidelines recommend that robotic-assisted gait training may be used to complement, but not replace, conventional gait therapy, and should be considered for patients who might otherwise not practice walking.[1]

Published Studies

Results of three small, US, pilot, uncontrolled before-and-after studies of the ReStore exosuit were published in 2017 to 2018.[12,13,23] These studies likely all used the same group of patients (a total of nine patients). The studies assessed the impact of the ReStore exosuit on walking speed, energy cost, muscle activity, forward propulsion, and ankle flexion for ground clearance.

Several recent systematic reviews of robotic-assisted gait training in stroke rehabilitation have been published but studies of the ReStore exoskeleton were not included.[6,8,22,24,25]

Safety

No studies on the safety of ReStore were identified. A single-arm, open-label safety study of ReStore involving 40 participants at five US rehabilitation hospitals was expected to be completed in November 2018.[17,26] Each participant used the ReStore exoskeleton during a period of four weeks as part of their rehabilitation program.[26] The primary outcome was the incidence of device-related adverse events, and secondary outcomes were the number of device malfunctions, injury to the therapist caused by the device, gait-related measures, and patient and therapist satisfaction.[26] Study results are not yet available.

Issues to Consider

Robot-assisted gait training provides quantitative data on patient performance, such as walking speed and muscle strength, which may not otherwise be available.[8,9]

Older treadmill-based robotic systems may not be as beneficial as exoskeletons that allow overground walking — which is more challenging and demands more balance and control on the part of the user.[9,10,22] Whether there are advantages to any particular exoskeleton system is not yet known and comparative studies are needed. There is also a lack of evidence on the optimal duration of training; whether benefits are maintained in the long term; and the impact on quality of life, activities of daily living, and falls.[6,25]

Other considerations include:

- the features of the different exoskeletons
- the type, level, and variability of assistance they provide
- whether the assistance is provided at the hip, knee, or ankle (or a combination of all)
- how the step is triggered
- the level of strength required by the patient
- whether the gait assistance is motor-driven or provided through functional electrical stimulation (Vickie Buttar, Glenrose Rehabilitation Hospital, Edmonton, AB: personal communication, 2019 Jan 28)

More evidence is needed on the impact of robotic exoskeletons on therapist fatigue and injury, and whether they can provide more intensive rehabilitation therapy (for example, a higher number of repetitions in a more accurate gait pattern). It has yet to be determined whether robotic systems can reduce the number of therapists needed during a rehabilitation session or increase the number of patients who can be treated during a session.

Related Developments

Examples of other mobile exoskeletons in use or under investigation for lower-body stroke rehabilitation include EksoGT (Ekso Bionics, US), Indego Therapy (Parker Hannifin, US), and HAL (Cyberdyne, Japan).[2,4,7,27]

In January 2018, the US FDA expanded approved indications for the Indego exoskeleton to include the treatment of lower-limb paralysis due to stroke.[28,29] The Exoskeleton for Post-Stroke Recovery of Ambulation (ExStRA) study, underway at three Canadian centres, is assessing gait rehabilitation outcomes in 40 patients using the EksoGT system.[30] Other exoskeletons are being studied as a way to reduce musculoskeletal workplace injuries.[31]

Looking Ahead

A systematic review of the economic costs of robotic rehabilitation in adult stroke patients is underway at the Joanna Briggs Institute in Australia.[32]

The ReStore developers are investigating further uses of the exoskeleton for other conditions that affect mobility, such as multiple sclerosis and Parkinson disease.[33] A multi-centre clinical study of ReStore in stroke rehabilitation is underway at five US centres.[34]

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See references on page 16.

Mini-Roundup: Recent Reports From CADTH and Other Agencies

CADTH

- Health Technology Update, Issue 22, October 2018: Artificial Intelligence Issue
- *Issues in Emerging Health Technologies:* An Overview of Clinical Applications of Artificial Intelligence

Recent Reports From Other Agencies

Agencies Included in the Mini-Roundup below:

- Cleveland Clinic Innovations, US
- Healthcare Improvement Scotland, Scottish Health Technologies Group (SHTG) National Health Service, National Services Scotland, UK
- The King's Fund, UK
- National Institute for Health and Care Excellence (NICE), UK
- National Institute for Public Health and the Environment, the Netherlands
- Medgadget, US

Cardiovascular

- Cerebrotech Visor for Detecting Stroke (NICE)

Cancer, Imaging, and Radiology

- Colon Capsule Endoscopy (CCE-2) for the Detection of Colorectal Polyps and Cancer in Adults With Signs or Symptoms of Colorectal Cancer or at Increased Risk of Colorectal Cancer (SHTG)
- Outpatient Biopsy for Diagnosis of Suspicious Lesions of the Larynx, Pharynx, and Tongue Base (SHTG)
- Robot-Assisted Surgery Compared With Laparoscopic Resection for the Treatment of Rectal Cancer (SHTG)

Gastroenterology and Liver

- LiMAx System for Assessing the Functional Capacity of the Liver (NICE)

Infectious Disease and Infection Control

- Beta-D-glucan (BDG) Tests for Invasive Candida Infection (SHTG)

Kidney and Urology

- Axonics Sacral Neuromodulation System for Overactive Bladder and Faecal Incontinence (NICE)

Nervous System and Neurology

- gammaCore for Cluster Headache (NICE)
- RT300 for Spinal Cord Injury Rehabilitation (NICE)

Respiratory

- myAIRVO2 for the Treatment of Chronic Obstructive Pulmonary Disease (NICE)
- OxyMask for Delivering Oxygen Therapy (NICE)
- Servo-n With Neurally Adjusted Ventilatory Assist (NAVA) for Babies and Children (NICE)
- The Vest for Delivering High-Frequency Chest Wall Oscillation in People With Complex Neurological Needs (NICE)
- Video Laryngoscopes to Help Intubation in People With Difficult Airways (NICE)

Trends, Forecasts, and Strategic Initiatives

- *Horizon Scan of Medical Technologies: Technologies with an Expected Impact on the Organisation and Expenditure of Healthcare* (National Institute for Public Health and the Environment)
- Medgadget's Best Medical Technologies of 2018 (Medgadget)
- Top 10 Medical Innovations for 2019 (Cleveland Clinic)
- *New Models of Home Care* (The King's Fund)

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