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COVER ART: ABDUL NAEEM
FRONT: I created the picture to reflect the emergence of medicine and health with technology.
BACK: What I am trying to convey with this piece was to have a crystal ball that is looking in to the future. The base acts as our current standing point looking into the future. The inside of the crystal ball is a bio-mechanical hybrid of a human hand.
Onwards

Laura Hinz (Meds 2011)

When faced with the word “technology,” images of robots, supercomputers, and massive electrical circuits spring to mind. However, the concept of technology stems from Greek thinkers, long before the introduction of any of those devices. Technology encompasses more than gadgets and gizmos, it involves any novel way of thinking, creating, or organizing that aims to solve a problem. Thus Health Technology was an ideal theme for an issue of the UWOMJ, whose mandate has always been to inspire and celebrate new, innovative approaches to medicine.

In this issue, Dhaliwal and Ballantyne describe a technique that uses the body’s own cells to heal articular cartilage injuries. This article illustrates the perfect union between health and technology by suggesting the idea that if manipulated correctly, the body itself can be a source of healing. However, the technophiles will find the more common conception of technology in an eloquent article by MacPherson and Ravichandiran, describing advances in the field of microfluidics engineering.

I approached this issue with a certain degree of trepidation, as circuits and computers remain resolutely beyond my grasp. Those with similar limitations will find hope in Goetheil and Kudlow’s article, which describes an adaptation of a common technology (namely text messaging) to service a health niche. Not only is this a resource-efficient approach to technology, but it puts technological development within the grasp of each individual. You do not need to be an engineer in order to develop technology; you simply need to be inquisitive, observant, and creative.

While the ultimate goal of technology is to solve problems, it can also create new ones in its wake. For instance, the Medicine and the Law editors explore the ethical implications of direct-to-consumer genetic testing. With the development of new technology, we must consider how it will be utilized, who it will affect, and what further changes it will bring.

The introduction of technology can also help to legitimate an ailment by providing a solution. There are several “culture bound syndromes,” those that exist among certain groups only. Several years ago, the medical school curriculum would not have included erectile dysfunction. With very few treatments available, the stigma that shrouded this disorder prevented many men from admitting to symptoms. With new techniques such as those described by Kudlow and Radomska, the prospect of cure has led to erectile dysfunction’s recognition as a legitimate diagnosis.

The phrase “Health Technology” implies a separate part of the whole, a branch of study unto its own. However, innovations in a variety of fields have had an impact on medicine. In his book “The Brain that Changes Itself,” Dr. Doidge suggests that the concept of brain plasticity was initially limited by the prevailing mechanistic view of the brain. Great advances were being made in engineering, which led scientists to liken the brain to a machine. Machines do not grow and change, thus the idea that the brain could adapt after illness or injury was disregarded. With the discovery of electricity, a new conceptualization of the brain unfolded with the suggestion that

nerves relied on changes in current. It is thus reasonable, and perhaps vital, to look beyond medicine for medical technologies.

We have seen countless examples of the impact of technology on medicine—electronic health records, genomic sequencing, robotic surgery. Perhaps less obvious is the impact of technology on each individual’s habits and ways of thinking. This journal is in print form, as many people object to reading off a screen. Why? There is nothing innate in our brain that says that the printed word must be black on a white background, sized 8.5x11 with pages that can turn. If you handed a book to someone accustomed to scrolls, they may regard it with the same disdain as I currently reserve for e-readers. As technology evolves, our determination of what is normal or comfortable will change. If our editors had been asked to wield an old-fashioned pen for this issue, the articles may have been much briefer as they lamented the loss of the quicker and more ergonomic word processor.

As this is my last contribution to the UWOMJ, I would like to thank all of the writers, faculty, advertisers, and readers who make this great publication possible. This issue explores forays into the unknown, attempts to expand our knowledge and improve our ability to heal. To the Class of 2011, this is exactly what we will be attempting to do as we head off on our various residencies. I urge you to take the lessons of four years of clinic, class, and camaraderie and temper it with the sage advice to ‘don’t stop believing.’

REFERENCES

The use of nanotechnology in cancer management

Yuding Wang (Meds 2013)*, Chanseok Rhee (Meds 2013)*, Nianxin Jiang (Meds 2013)*
Suganth Suppiah (Meds 2013)*, Zoya Bahreini (Meds 2013)*

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Drug delivery systems have provided the pharmaceutical industry a means of improving the therapeutic properties of pre-existing drugs. These systems, such as lipid- or polymer-based nanoparticles, alter the pharmacokinetics and biodistribution of the drug that is being carried. A nanoparticle is formally defined as an engineered particle in nanometer size. The inherent properties of the nanoparticle make it an ideal vector to distribute drugs. The submicron size, with diameters less than 200 nm, of the nanoparticles increases its intracellular uptake, ability to penetrate through submucosal layers and cross the blood brain barrier. Both synthetic and organic polymers have been utilized to create biodegradable nanoparticles, like the polyacrylates that undergo hydrolysis upon implantation and broken down to lactic acid. The drugs are released via diffusion across the polymer matrix and through biodegradation of the polymer itself. Nanoparticles conjugated with tissue-specific ligand also allow the delivery of the drug to be more targeted, and reduce the amount of side effects. As a result, nanoparticles have the potential to increase the potency and efficacy of the drugs that are already used in practice.

Nanoparticles could vastly improve the tools we have to fight cancer through a two-fold approach: (1) early detection of cancer and (2) cancer therapeutics. The nanoparticles target the site of the cancer for both diagnostic and therapeutic purposes. The potential of nanoparticles in the field of oncology is holds many promises.

NANOTECHNOLOGY FOR CANCER DIAGNOSIS

Various nanoparticles, such as iron oxide crystals, and QD semiconductor non-crystals, have shown great potential for detecting disease markers, pre-cancerous cells, fragments of viruses, specific proteins, antibodies and other disease indicators.

In the field of oncology, nanoparticles can assist to non-invasively detect tumors at an early stage, perhaps months or even years earlier than the conventional diagnostic tools would make the same diagnosis, and thus result in maximum therapeutic benefit and improve the prognosis of the patients. For instance, in breast cancer, nanomedicine can potentially use molecular imaging to accurately diagnose breast cancer when the tumor mass has only 100-1,000 cells, as opposed to the current imaging techniques like mammography, which require the detection of more than one million tumor cells for accurate clinical diagnosis.

QDs are semiconductor nanocrystals made up of 100-100,000 atoms. QDs contain electrons, which after excitation, can relax to their ground states and release photons in the process, leading to a visible fluorescence. The fluorescent signals of QDs are 10-100 times brighter compared to organic dyes and their emission properties make it possible to overcome tissue autofluorescence. Also, specially-engineered QDs coated with stealth polymers can resist photobleaching and cellular degradation better than conventional fluorophores (molecules capable of fluorescence), allowing studies to be carried out over time. Due to all these unique characteristics, QDs can be conjugated to antibodies that have affinity for tumor-specific antigens, and they will preferentially localize to the tumor cells. The identification of the changes in cellular surface protein concentration can be an early indication of cancer. Other studies have shown that by injecting QD-labelled melanoma cells into mice, one can visualize in vivo the migration of tumor cells to the lungs on imaging. This ability to track tumor micro-metastasis can lead to greater understanding of the behavior of metastatic cancer and discovery of new treatment options.

In practice, identification of the sentinel lymph node (SLN) in breast cancer can be challenging. Currently mapping is done by using blue dye and radioisotopes. This technique obscures the surgical field and can cause radiation to the patients and healthcare providers. Superparamagnetic iron oxide nanoparticles allows pre-operative MRI visualization and intra-operative magnetometer-aided detection of SLNs, removing the need for harmful radioisotopes and obscuring dyes. Nanoparticles can also make important advancements in diagnosing and imaging of brain tumors, through both preoperative and intraoperative brain mass detection, allowing for early detection of precancerous cells and improving the prognostic outcomes of cancer patients. Currently, the most widely used MRI contrast agents are based on paramagnetic gadolinium (Gd(III) ). While still valuable, these ions are not without their problems. They tend to diffuse freely through a tumor and preferentially image areas where there is prominent blood-brain barrier breakdown, providing limited enhancement of the infiltrating tumor margins or areas of poorly vascularized micrometastasis. Also, the permeability of blood-tumor barrier is not homogeneous, which means that the ions cannot enter all areas of the tumor equally. Furthermore, this contrast material has difficulty discriminating tumor from CNS inflammation or infections. Nanoparticles designed to preferentially target tumor areas, such as superparamagnetic iron oxide nanoparticles, have been developed as new MRI contrast agents to avoid many of these problems and provide a wider window of opportunity for tumor imaging and enhancement.

NANOTECHNOLOGY AS CANCER THERAPEUTICS

Many conventional cancer therapeutic agents work by inducing cellular toxicity causing cancer cell death. Although cancer cells are inherently more susceptible to the effects of these agents, these agents also affect normal cells. This puts a constraint on the dosage and frequency of treatment as it inevitably causes injury to normal cells. This constraint often results in suboptimal treatment, which contributes to the persistence and recurrence of cancer after the completion of chemotherapeutic treatment. Current advances in
nanotechnology seek to resolve these therapeutic constraints by allowing for specific targeting of cancer cells helping to increase drug efficacy while limiting unwanted toxicity.

Cancer specific nanoparticle directed drug delivery takes advantage of cancer physiology by both a passive and active drug delivery mechanism. In the passive drug delivery mechanism, nanoparticles are selectively concentrated at the site of the tumour by the enhanced permeability and retention effect (EPR). The EPR works due to the inherent faulty physiology of fast growing tumour. It is known that tumours require angiogenesis for continued growth. However, the growth of these new blood vessels is disorganized and leaky due to enlarged junctions between endothelial cells as well as deficiencies in the underlying basement membrane. While normal endothelium junctions are typically 5 to 10 nm in size, gaps between the leaky endothelium of the tumour are significantly larger and range from 100 to 750 nm. Concurrently, the disorganized growth of the tumour also results in formation of a disorganized lymphatic network. The leaky vasculature and the lack of a lymphatic network result in the accumulation of nanoparticles in the cancer interstitium, passively concentrating drug at the site of the tumour. Novel nanoparticle chemotherapy, Doxil (a pegylated liposomal doxorubicin nanoparticle), takes advantage of the EPR. In vitro experiments have shown Doxil to have a 10-fold increase of doxorubicin concentration (the chemotherapeutic drug (or payload)) within the tumour compared with conventional doxorubicin administration. Although clinical trials comparing Doxil and conventional doxorubicin administration have shown no statistical improvement in survival (overall and disease free), Doxil was nevertheless shown to significantly decrease the risk of cardiotoxic effects of doxorubicin use (a significant side-effect limiting dosing and usage). It should be noted that the pegylation procedure helps the nanoparticle escape from macrophage phagocytosis, while the liposomal core structure helps protect the bound doxorubicin to achieve a significantly longer half-life than free doxorubicin also contributing to the increased concentration of drug seen at the site of tumour.

The active drug delivery mechanism works by targeting specific receptors preferentially expressed on the tumour cell. For example, folate receptors are preferentially expressed in some cancer phenotypes while showing limited expression in normal tissue. Experimental findings in mouse models comparing conventional paclitaxel (given as free drug) with a heparin-folate-taxol (heparin as a carrier molecule and folate as targeting molecule) showed the folate-directed nanoparticles to have more potent activity against tumour growth. Another example is the transferrin receptor. In vitro studies using MCF-7 (human breast cancer cell line) comparing transferrin-conjugated paclitaxel-loaded nanoparticles treatment versus free paclitaxel showed the transferrin-conjugated paclitaxel treatment to have greater inhibitory effect on cell growth.

Although drugs can be delivered to the tumour, another significant impediment remains due to chemotherapeutic drug resistance. The most studied cause of resistance is the membrane associated protein pump p-glycoprotein (p-gp). The p-gp is expressed in a number of cell types in the body and functions to effectively pump chemotherapeutic agents out of the cell, conferring resistance. Nanoparticle drug design could sidestep this impediment by a number of possible mechanisms. One such mechanism is to co-administer a p-gp antagonist along with the therapeutic drug, thus inhibiting the p-gp function. Clinical trials evaluating various potential antagonistic agents have shown disappointing results thus far, though new compounds continue to be discovered with improved binding specificity to p-gp. Another mechanism could rely on receptor mediated endocytosis and subsequent endosomes formation as means for gaining access to the cell cytoplasm, which could effectively mask the nanoparticle until a high concentration of therapeutic drug is released to reach therapeutic effect, essentially overwhelming the p-gp. In vitro and in vivo mouse models have shown that drug resistance can be overcome through this mechanism. Nanoparticles as a means for drug delivery offers many unique benefits in the treatment of cancer compared to other targeted drug therapies proposed such as antibody-drug conjugates. Firstly, nanoparticles could carry a significantly larger drug payload per ligand-receptor binding event compared to antibody-drug conjugates as well as being more versatile in the type of drug it's able to carry since drugs are stored within the nanoparticle, with limited exposure to environment, while the type and number of drugs conjugated to an antibody could significantly affect its kinetics and biodistribution. Secondly, nanoparticles are large enough to target multiple ligands allowing for multivalent binding and selectivity enhancement. Therefore, nanoparticles can use multiple weak ligand interactions to greatly increase the pool of cancer binding targets whereas single ligand recognition offered by antibody-conjugates require strong affinity to be effective. Thirdly, nanoparticle design could allow the rate of release to be tailored for the drug of action. For example, topoisomerase I inhibitors such as the camptothecin-based drugs are reversible inhibitors of the enzyme, and therefore, have better efficacy if exposure of drug is prolonged. Lastly, nanoparticles could allow for the co-localization of different types of agents to work synergistically within the target cell to increase drug efficacy.

CONCLUSION

Nanoparticles holds new promise as means for earlier detection and better treatment of cancer. Imagine a future where nanoparticles can help detect cancer before it even has a chance to manifest and selectively destroy cancer cells while leaving the normal cells unharmed. Cancer, in such a circumstance, could become a highly manageable condition. However, despite our current research there is much we still do not understand. Nanoparticles offer a new avenue to tackle these challenges. More research is needed in this promising and dynamic field of cancer therapeutics.

REFERENCES


Near-infrared spectroscopy to assess penile blood flow: a possible novel technique for the diagnosis of vasculogenic erectile dysfunction

Paul A. Kudlow (Meds 2013), Sidney B. Radomski, MD, FRCSC
Faculty Reviewer: Dr. Gerald Brock, MD, FRCSC (Division of Urology, Department of Urology)

Erectile dysfunction (ED) is defined as the consistent inability to achieve and maintain an erection sufficient to permit satisfactory sexual performance or intercourse. The vast majority of cases of ED are primarily of organic and vascular etiology, although psychological factors also play a role in many cases. Affecting an estimated 2 million Canadians and becoming increasingly common with age, ED has been shown to compromise overall quality of life and is associated with depression, anxiety, and loss of self-esteem. To date, the diagnosis of ED is typically made on history and physical exam. In recent years however, increased understanding of the hemodynamics involved in vasculogenic ED has led to the development of a number of different diagnostic tests. These include penile brachial index, intracavernous pharmacologic testing, penile tumescence monitoring, color duplex ultrasonography, cavernosography and pharmacologic cavernosometry, penile scintigraphy, and selective pudendal arteriography. While each yields information of some diagnostic value, there is yet to be a single test or “gold standard” for diagnosis of ED. Much of this could be due to the fact that many of the current tests are complex, expensive, invasive, and often inaccurate. Given these limitations, and especially in light of advancing efficacious oral therapies readily available, some specialists argue that these tests should be reserved for special cases of ED where a diagnosis is important or surgery is required. However, an opposing view is that a minimally invasive and cost-effective test may still be of value in completing the appropriate management of a patient with suspected vasculogenic ED.

This study was undertaken to examine near-infrared spectroscopy (NIRS) as an approach to study penile blood flow and thereby explore a potential novel diagnostic tool for assessing vasculogenic ED. NIRS has emerged as a new technology within recent years for monitoring blood flow non-invasively and safely. The technology uses photons of light in the near infrared spectrum to assess concentration changes of oxygenated and deoxygenated hemoglobin in tissues. It can provide information concerning both oxygen saturation and relative blood volume changes within the organ of interest. Although NIRS has been widely used to assess muscle and cerebral blood flow, its use in the assessment of penile blood flow has been limited. We examined the use of NIRS to detect penile blood flow and to determine if increases in oxygenated hemoglobin (O2Hb) concentrations correlate with erections.

METHODS
Two groups of men were examined. Group 1 consisted of 10 young men with no erectile difficulties, mean age 19 years (range 18-22). These men allowed us to determine the technical aspects of NIRS monitoring on the penis (i.e. optical sensor placement and how to secure the sensor) and the feasibility of assessing penile blood flow with visual sexual stimulation (VSS). Group 2 consisted of 12 men with prostate cancer undergoing a bilateral nerve sparing radical prostatectomy (RP). Mean age of the patients was 55 years (range 44-66). These men underwent NIRS with VSS preoperatively and at 3 months postoperatively with and without 20 mg of vardenafil. Each completed a validated psychometrically validated questionnaire IIEF (International Index of Erectile Function) pre and postoperatively. During NIRS testing each man was asked to assess if an erection occurred during the VSS.

RESULTS
With Group 1 we were able to create a re-usable NIRS optical sensor probe which was taped to the penis. In 7/10 of the men an erection occurred with VSS and with NIRS testing. O2Hb concentration increased in all 7 men (Figure 1). In Group 2 the mean IIEF preoperative score was 25 (range 5-30) and the postoperative score was 11.1 (range 1-26). With NIRS testing preoperatively without vardenafil, 8/12 men felt they had some erection with VSS, and in 7/8 of these men there was an increase in O2Hb concentration. In the one in which NIRS was unsuccessful the erection was minimal. In this same group, 9/12 men with NIRS testing showed increases in O2Hb concentration with VSS, 2 of which felt they had no erection (Figure 2). When vardenafil was given preoperatively with NIRS testing, 12/12 men felt they had some erection and 10/12 of these men had an increase in O2Hb concentration. Postoperatively without vardenafil on NIRS testing 2/12 men felt they had some erection and 7/12 men were found to have increases in O2Hb concentration including the 2 men that had some erection. When vardenafil was
added postoperatively 7/12 men felt they had some erection and 7/12 men had increases in O₂Hb concentrations on NIRS testing (5 patients with an erection and 2 without). There was a rapid rise in O₂Hb concentration in men with excellent erections.

Figure 2. Patient preop without vardenafil with no erection and no increase in O₂Hb.

DISCUSSION
To date, management of a patient with suspected ED is often centred on a goal-oriented approach. Treatment selection is based on patient preferences following a thorough discussion with a treating physician regarding therapeutic options with minimal diagnostic testing. Reasons for this empirical approach probably stem from the relatively safe and highly effective medications currently available for ED. Despite this, studies completed on outcome analyses of the goal-directed approach, often indicate low patient satisfaction rates. In part, this could be due to the fact that without a thorough understanding of the etiology and pathophysiology of a given patient ED, commonly preferred therapies may be ineffective. Perhaps a diagnosis-based, (pathogenesis-specific) treatment approach to patients with suspected ED may yield better outcomes.

In this preliminary study, we demonstrated that NIRS can be used to assess penile blood flow with sexual stimulation. Accordingly, we performed a series of penile NIRS studies on both healthy subjects, and on patients presenting with various degrees of ED. Upon analysis, a rise in O₂Hb concentration on NIRS was found to correlate very well to patient perceived erections. The results from this early investigation suggest that it may be clinically useful for the practicing urologist. The appeal of this modality is further supported by its perceived advantages: low equipment cost, transportability, operator non-dependence, simple operation, and safety.

Despite these indications for a diagnostic role of a penile NIRS device, the critical measure of the clinical utility of any new technology rests on its ability to direct appropriate therapeutic management. Given our limited sample size, our study was unable to examine whether penile NIRS can accurately discern blood flow profile differences between vasculogenic and non-vasculogenic ED. Looking ahead, further studies are needed to establish diagnostic ranges that identify psychogenic/neurogenic (non-vasculogenic), mild vasculogenic, and severe vasculogenic causes of ED. As well, more studies are needed to correlate NIRS testing with Doppler studies.

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REFERENCES
Surgical treatment for articular cartilage injuries in the athlete's knee

Sandeep Dhaliwal (Meds 2013), Brennan Ballantyne (Meds 2014)
Faculty Reviewer: Dr. Marie-Eve Lebel, MD (Department of Orthopaedic Surgery)

Articular cartilage injuries of the knee are frequently observed in athletes partaking in high-impact sports, particularly at the competitive collegiate, professional, and world-class level. Additionally, increasing recreational participation in pivoting sports such as football, basketball, and soccer has been associated with a rising number of sports-related articular cartilage injuries in the general population. When left untreated this type of injury results in long-term decline in athletic performance and predisposes the athlete to early joint degeneration. The purpose of medical intervention, therefore, remains twofold: 1) returning the athlete to pre-injury performance; and 2) preserving long-term knee function to ensure a healthy lifestyle can be maintained as the patient ages.

Articular cartilage is a weight-bearing connective tissue consisting of chondrocytes whose primary function is to secrete extracellular matrix. Due to the aneural and avascular nature of this tissue, damage caused by injury or pathogenesis results in very limited ability for self-repair. In this manner, treatment of articular cartilage injuries in the athletic population presents a significant therapeutic challenge. Analgesics, anti-inflammatory medications, activity modification, change in body weight, rest and physical therapy may provide partial symptomatic relief, but they do not restore damaged cartilage to its natural state. Surgical procedures such as total joint replacement may help relieve joint pain, but pose significant limitations to younger patients wishing to pursue vigorous physical activity. Additionally, surgical debridement remains a potential option, but it too is not ideal as it fails to restore cartilage. Therefore, substantial efforts have been devoted to the development of biologic methods for restoring degenerating articular cartilage. Based on the source of the cartilage repair tissue, new techniques can be broadly classified as: 1) marrow stimulation-based techniques; 2) osteochondral transplantation techniques; and 3) cell-based repair techniques. Moreover, the development of new treatment regimens present promising scientific and clinical excitement for the treatment of articular cartilage injury.

Marrow Stimulation

Developed in the early 1980s, a surgical technique known as microfracture is a cost-effective, minimally invasive, and uncomplicated procedure widely used to treat cartilage injury in the athlete's knee. Microfracture hinges on the penetration of the subchondral plate with an awl or drill and filling of the cartilage defect to take place by a blood clot that contains pluripotent marrow-derived mesenchymal stem cells. These cells proliferate and differentiate to produce a cartilaginous repair tissue that eventually fills the chondral defect. The procedure is carried out by placing the patient in a supine position on the operating room table and administering a lower extremity or general anesthetic. A femoral nerve block for postoperative pain relief may also be used. The leg is prepped, draped and has a tourniquet applied which can be inflated if arthroscopic visualization becomes difficult due to intra-articular bleeding. The orthopaedic surgeon carries out a thorough arthroscopic diagnostic examination whereby the lesion is identified and debrided of all loose or marginally attached cartilage using an arthroscopic shaver and a curette. This leaves a stable rim of cartilage surrounding the defect which is an ideal full-thickness border to provide a degree of protection to the regenerating tissue that will form in the treated lesion. A calcified cartilage layer typically remains. With animal studies showing that complete removal is crucial to ensure proper repair, the calcified cartilage layer is removed by the use of a curette or a burr. After preparation of the lesion is complete, an arthroscopic awl is employed to make multiple holes (microfractures) in the exposed subchondral plate. Holes are spaced 3-4 mm apart to ensure that the subchondral bone maintains adequate structural integrity, and a depth of 4-5 mm, or until fat droplets are visibly seen coming from the marrow after tourniquet deflation, is typically achieved.

Osteochondral Transfer Techniques

Osteochondral grafts of autologous or allogenic origin rely on transplantation of intact mature hyaline cartilage containing viable chondrocytes attached to subchondral bone. Although both autologous and allogenic modalities represent complementary paradigms designed to restore the characteristics of native tissue, each pose their own set of unique challenges with regard to tissue availability and safety. Generally, autografts are indicated for relatively small (< 2 cm) focal articular lesions of the femoral condyles. Donor-site harvest is carried out from regions of less weight-bearing structures in the knee such as the medial and lateral trochlear ridge, the intercondylar notch, or the sulcus terminalis of the lateral femoral condyle. Historically these areas were considered non-weight bearing, but recent reports have demonstrated that these areas do bear significant weight and can lead to increased donor-site morbidity, such as osteoarthritis. Advantages of an autologous approach include immediate availability, relatively low cost, and nonantigenic and osteogenic cartilage properties that results in successful osteointegration. However, autologous graft sources are self-limited in their maximal surface area, and donor-site morbidity can add a significant disease burden to the patient. On the other hand, osteochondral allografts are indicated for the treatment of medium to large articular lesions and are highly versatile in treating very complex or multiple lesions without inducing any donor-site morbidity. Drawbacks to the allograft approach include scarcity of donor tissue, potential risk for disease transmission, as well as financial and logistical issues regarding graft procurement.

Autograft transplantation can be performed arthroscopically or through a standard "open"arthroscopy approach. The patient's knee is prepped and a diagnostic arthroscopy is undertaken to debride and...
measure the cartilage defect. Donor grafts are extracted using a T-handled recipient harvester. Plug sizes for the harvester vary from 4 to 10 mm depending on which commercially available instruments are used during the operation. After planning the number, size and placement of specific grafts, the harvester is aligned perpendicular to the donor cartilage and tapped to an appropriate depth. Once tapped, the harvester chisel is disengaged by rotating or "gently toggling" (depending on which system is used) the handle in order to amputate the graft. The recipient socket can be prepared using a core or drill. In general, a socket is created in the area of the defective cartilage by using a slightly smaller circumference T-handled harvester tapped to a depth of equal or greater length than the donor plug extracted. Finally, the graft is implanted under direct visualization using a delivery tube and tapping the impactor with a gentle force. Once the graft is in place, the delivery tube is removed and any resulting margins on the articular surface should fill with fibrocartilage.

Conversely, using an open incision, osteochondral allografting commences by establishing the size of the host knee defect using a sizing cylinder. A sizer is placed over the entire lesion and a guidewire is driven through the center of the sizer perpendicular to the femoral condyle surface. The condyle is then scored to the subchondral bone using an appropriately sized circumferential cutter (reamer) placed over the guidewire. The reamer is typically drilled into the defect to a level of 8-10 mm below the native cartilage surface. Employing the same sizer used on the host knee, the allograft is sized and reamed in the same area of the condyle where the host lesion is located. To avoid any height mismatch, the graft is carefully cut with an oscillating saw to an appropriate height and the edges are slightly bevelled to facilitate placement into the host defect. Finally, a dilator is impacted into the recipient site in order to achieve slight dilation (0.5 mm) which enables graft placement using digital pressure. Additional fixation can be achieved using screws or pins although it is usually not required with this method.

CELL-BASED REPAIR TECHNIQUES

Initially described in the mid-90s, autologous chondrocyte implantation (ACI) plays a major role in treating large full-thickness chondral injuries. ACI is a dual-stage procedure which utilizes the first-step to harvest chondrocytes, and then a second-step to reimplant them following in vitro culture. The initial-stage involves an arthroscopic examination to enable full assessment of the injury to establish the patient's suitability for the procedure. If it is appropriate to continue, slices of cartilage are harvested with a curet. The femoral trochlea and intercondylar notch are recommended as harvest sites based on limited complications and morbidity being associated with the use of those areas. After the slices are removed, they are placed in a sterile vial and transported to the laboratory where chondrocytes will be cultured. The second-stage of ACI is carried out using an arthroscopy to achieve adequate exposure. The defect is debried with care being taken to ensure that bleeding from the subchondral bone is minimal as it can introduce stem cells and fibroblasts into the defect. The defect is measured and a template using sterile paper is made. A parietal flap from the proximal medial tibia is obtained using the template. This flap is harvested and then sutured to the cartilage rim of the defect and the border is sealed using fibrin glue. The cultured chondrocytes are then aspirated into a syringe and are injected under the periosteal graft.

CLINICAL OUTCOMES AND EMERGING TECHNOLOGY

Numerous systematic studies have elucidated improved knee function and increased activity scores for all three types of articular cartilage repair strategies outlined above. Only recently, however, has meta-analysis comparing different repair techniques on returning the injured athlete to sports participation become available. Two separate reviews suggest better outcomes for patients undergoing autologous chondrocyte implantation and osteochondral transfer techniques versus microfracture. Based on a review of 20 studies and 1363 patients, return to sports participation was observed in 73% of athletes with the highest occurring in those who underwent osteochondral autograft transplantation. On the other hand, 65% were actually deemed to have been able to return and perform at a pre-injury level and this was best achieved with autologous chondrocyte repair. It appears that numerous factors, such as age, level of play, lesion size, and duration of symptoms, can impact the clinical outcomes observed in this patient population.

Several reports depicting functional outcomes, as well as return to athletic competition following microfracture can be found in the literature. Despite initial improvements, however, there is conflicting evidence regarding long-term results as some studies suggest that deterioration of knee function occurs in 47% to 80% of athletes 24 months following surgery. These limitations have prompted investigation of new technologies to enhance the results of existing microfracture techniques. For example, the development of a dehydroepiandrosterone sulphate (DHEA-S)-releasing rod that can be implanted into the microfractures has shown promise in improving cartilage in animal models. Other efforts have revolved around the addition of growth factors to promote chondrogenic differentiation, or inhibiting the potential negative effects of cytokines. Finally, the creation of a bioabsorbable using chondroitin sulphate as a primary component has yielded promising results in clinical trials.

In an effort to improve clinical outcomes, new and innovative techniques are rapidly advancing the field of articular cartilage repair. For instance, to avoid the problems associated with osteochondral allografts, syntheic manufactured bioreabsorbable scaffolds have been developed as substitute grafts. Principles of scaffolding have also been applied to autologous chondrocyte implantation which provides a mechanism of delivering chondrocytes into a lesion during a single-stage procedure without necessitating ex vivo chondrocyte culture and expansion. During this procedure, the harvested cartilage is harvested and then embedded into a resorbable scaffold which is then implanted into the knee. Other techniques currently being explored include the use of gene therapy to improve cartilage repair by transfecting chondrocytes with BMP-2, BMP-7 and IFG-1 and neo-cartilage harvesting of juvenile chondrocytes from prepubertal and fetal human cartilage.

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Computed tomography (CT) based calcium scoring in the diagnosis and prognostication of coronary artery disease (CAD)

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Invented by Sir Godfrey Hounsfield in the 1970s, computed tomography (CT) has greatly strengthened the arsenal of imaging technologies that is available to physicians to detect, prognosticate, and treat disease. The fundamental principle underlying CT scanning is the exposure of biological tissues to rotating fine beam X-rays, followed by the detection and processing of the radiation that these tissues attenuate to create a computerized image. The two major types of CT scanning are helical CT and conventional non-overlapping CT. Since its introduction, various enhancements have been made to CT technology which has allowed application across varied medical fields. In cardiac imaging, coronary CT angiography has recently risen to the forefront. As it is a non-invasive method, data in the literature lags behind the well-studied methods to quantify the amount of calcium inside coronary arteries using information obtained from cardiac CT scans, known as calcium scoring. In this article, we explore the use of this specialized CT technology and highlight its advantages and limitations in the diagnosis and prognostication of coronary artery disease.

CT BASED CALCIUM SCORING

In coronary arteries, CT based calcium scoring methods quantify calcium as a parameter termed coronary artery calcification (CAC). Calcium scoring is used to evaluate coronary artery disease since calcium build up in plaques is a key process in atherosclerosis. It should be noted that there is evidence non-calcified plaques are also important, however, they are not evaluated by this method and are thus outside of the scope of this review. Electron beam CT (EBCT) has been a popular method for the assessment of coronary calcium since its development in the 1980s. Nowadays, calcium scoring can also be performed with multidetector or multislice CT scanners (MDCT and MSCT). There is some agreement that the calcium scores obtained from both methods are similar, though this has not been extensively studied. Various methods have been used to compute calcium scores; for example, the Agatston score assigns a weighted value based on the highest density of calcification in the plaque and then multiplies this by the area of calcification. Such scores for all calcifications in all CT slices taken are summed up to provide a CAC score for all the coronary arteries.

Due to certain limitations with Agatston scoring, most notably inconsistent inter-scanner comparability, newer methods such as the volume score and calcium mass score were developed and compared with the Agatston score. Some studies indicate that these methods maybe equivalent to the Agatston method in terms of reproducibility. A more recent method of calcium scoring is known as the lesion specific calcium score in which more specific parameters related to each calcified lesion are included in the final calcium score, such as width, density and distance from major coronary arteries. There is emerging evidence to indicate that the lesion-specific calcium scoring method maybe more accurate than the Agatston method for some purposes; for example, the sensitivity, specificity, and accuracy of the lesion specific calcium score method were shown to be superior to the traditional Agatston score in detecting angiographically confirmed obstructive coronary artery disease.

CORONARY ARTERY CALCIFICATION (CAC) AND CORONARY ARTERY DISEASE

Many studies have shown the association between CAC and coronary artery disease as detected by histopathological or angiographic methods. For example, one histopathological study on autopsyed coronary arteries showed that the EBCT calcium scores correlated well with plaque area. A clinical study of more than 700 patients showed that EBCT calcium scoring had 95% sensitivity in picking up angiographically significant coronary artery disease. CAC has also been studied in relation to myocardial ischemia. Myocardial ischemia most often manifests silently, and this can be detected as stress-induced ischemia with stress testing. One study showed that the likelihood of stress-induced myocardial ischemia increased with a higher CAC score, although the majority of patients (78%) with detectable CAC did not have stress-induced ischemia suggesting a poor positive predictive value of prognosis with CAC scoring. A report from the prospective cohort study known as the multiethnic study of atherosclerosis (MESA) evaluated the relationship between CAC and myocardial ischemia in an asymptomatic population. This study showed that the coronary vasodilatory response (myocardial blood flow with stress) was reduced with a higher CAC, but the resting myocardial blood flow was not affected by increased CAC. These studies provide some indication that CAC maybe associated with impaired myocardial perfusion in a subclinical atherosclerotic state. Overall, there is a good body of evidence to suggest that CAC is associated with structural and functional coronary artery disease.

PROGNOSTIC VALUE OF CAC

Studies have assessed the prognostic value of CAC in both symptomatic and asymptomatic patient populations. There is reasonable evidence to indicate that CAC has good prognostic value in asymptomatic patients. For example, a study of more than 5000 low-intermediate risk, middle-aged adults over a 3 year follow up period found that higher EBCT CAC scores at baseline were associated with a higher risk of developing cardiac events later on in both genders. Another study of more than 1000 patients over a 19 month follow up period showed that higher cut-off levels for EBCT CAC scores were associated with better specificities for predicting cardiac events. Incremental prognostic value of EBCT CAC was observed, in addition to that provided by conventional cardiac risk factors.
One study in a symptomatic patient population consisting of 491 participants referred for coronary angiography found that EBCT CAC scores were moderately predictive of angiographically confirmed coronary artery stenoses and that higher scores were associated with a higher incidence of coronary artery related cardiac events. A similar study on patients referred for coronary angiography followed up after an average time of 7 years found that among conventional risk factors and EBCT CAC, only EBCT CAC (risk ratio 1.72) and age (risk ratio 1.88) were predictive of future hard cardiac events (hard events include non-fatal myocardial infarction and cardiac death). Furthermore, patients with an EBCT CAC score of less than 100 had significantly higher event-free survival rates. Taken together, the prognostic value of CAC has been shown to have a high negative predictive value and a moderate positive predictive value for major adverse coronary events (MACE). Thus, CAC shows promise for aiding in risk stratification.

LIMITATIONS OF CALCIUM SCORING

Although the above discussion has highlighted the value of calcium scoring in detecting and providing prognostic information about coronary artery disease, certain caveats of calcium scoring exist. For example, some results suggest that there is a threshold level of calcium accumulation beneath which EBCT CAC is not predictive of plaque area or severity. Furthermore, studies have reported that EBCT CAC has very good sensitivity for picking up significant angiographic stenoses (greater than 50%), but only moderate specificity. This was confirmed by a consensus document released by the American College of Cardiology in which, based on a meta-analysis by the working group, the sensitivity and specificity of EBCT in detecting coronary artery stenoses were 91% and 47% respectively. Studies have also evaluated whether treating asymptomatic patients with high calcium scores with pharmacotherapy improves outcomes. For example, the St. Francis heart study randomized controlled trial showed that treatment of patients having high calcium scores with statins and antioxidants did not reduce the progression of coronary calcification or the rates of atherosclerotic cardiovascular disease events.

Interestingly, another randomized controlled trial showed that using results from EBCT calcium scores to motivate behavioral change was not successful, as reflected by a lack of improvement in composite cardiac risk measured by 10 year Framingham risk scores. This raises concerns about the utility of EBCT calcium scoring in being an effective screening tool that affects outcomes, but more studies are required in this regard. In addition, there are practical, unresolved concerns about the application of EBCT CAC from a screening perspective; for example, its cost effectiveness and the negative effects associated with false positive tests and radiation exposure are potentially worrisome.

CLINICAL RECOMMENDATIONS FOR USE OF CALCIUM SCORING

The American College of Cardiology Foundation (ACCF) published a consensus document in 2007 to synthesize the evidence and make recommendations regarding the clinical use of CT based calcium scoring. For example, one of the recommendations states that it is helpful to use CAC to risk stratify asymptomatic patients that have an intermediate 10 year risk of developing cardiac events (10-20%), since this may affect how aggressively patients are managed. However, this use of calcium scoring is not recommended for low risk (<10%) asymptomatic patients since these patients are likened to the general population and there is no evidence to support screening the general population with CAC. CAC measurements were also not recommended for high risk (>20%) asymptomatic patients since intensive medical therapy is already suitable for these patients. Also, owing to insufficient evidence, a recommendation was made to not reduce treatment intensity of intermediate risk patients that had zero calcium scores. Furthermore, the recommendations caution against extrapolating findings to populations that have not been well studied; the evidence appears strongest for Caucasian, non-Hispanic men.

CONCLUSION

Despite some limitations in its specificity and concerns about its applicability to patients of varying ethnicities and risk statuses, CT based calcium scoring of coronary artery calcification has emerged as a useful tool that provides added prognostic and screening value, especially in asymptomatic patients with intermediate coronary heart disease risk. Given the prevalence of coronary artery disease and its unparalleled impact on mortality and morbidity, better and innovative methods of cardiac disease screening and prognostication, including calcium scoring, will become increasingly important in providing patient-centred care.

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North Perth Family Health Team/Listowel Clinic is recruiting two family physicians. We are a Medical Community of 10 Family Physicians providing a full range of services including ER/OR/OB/Inpatient/Office practice with comprehensive electronic medical records that links Listowel Memorial Hospital, Wingham Hospital & London Hospitals. We have under serviced designation and are located 30 minutes from Stratford and 40 minutes from Kitchener-Waterloo.

A new hospital wing for our 50 bed facility (ER, OR and Diagnostic imaging) was completed in the past 3 years and has attracted a full compliment of surgical, pediatric and internal medicine consultants who regularly visit our site. A new Family Health Facility is being built with a completion date of early 2012. We enjoy the full support of our local community, Family Health Team and Hospital, in this diverse & challenging rural practice.

For more information please visit our FHT website at www.npfht.ca or contact us – 519-291-4200.
Direct-to-consumer genetic testing in Canada

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The goal of this article is to discuss DTC genetic testing in terms of the process of testing, the current regulation of the industry in Canada and the effect the resulting information can have on managing individual and populations in healthcare. This wide-ranging and rapidly evolving topic extends into the fields of genetics, ethics, law and business, each of which have been addressed in the following fashion: the accuracy of testing, the predictive value of the results, the possible effects that the test will have on the consumer and finally the effect that the personal genetics industry will have on physician practice and society. Due to the rapid evolution of the field, testing kits can now be purchased for as little as three hundred dollars, making personal genetic testing highly affordable and accessible.

THE ACCURACY OF THE ASSAY

DTC gene testing companies such as 23andme, deCODEME, Navigenics and Knome (the ‘main players’ in the current market) are private labs governed by the laws in their jurisdiction. In Ontario that licensing body is the Laboratory and Specimen Collection Centre Licensing Act (LSCCLA). However, the majority of these corporations are American and are hence regulated by the Centers for Medicare & Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA). Recently there has been concerns about “faulty lab data analyses, exaggerated clinical claims, fraudulent data, poor clinical study design and a lack of traceability”1. The United States Government Accountability Office recently reported that when samples of DNA were sent to four different DTC testing companies “different companies often provide different results for identical DNA”2. Interestingly, the testing kits themselves are not considered medical devices and are hence not regulated by the Food and Drugs Act3. Additionally, the majority of genetic tests are offered as in-house laboratory services and are similarly not regulated by the federal government through the Health Protection Branch or Therapeutic Products Program4.

THE LINK BETWEEN TESTED GENES AND DISEASE

In contrast to genetic testing in a clinical context, private genetic testing also examines more “personal” genetics traits. According to the website for deCODEME you can “discover your genetic risk for 47 diseases and traits ranging from Heart Attack and Diabetes to Alcohol Flush Reaction and Male Pattern Baldness”5. However disclaimers also state the results may have poor predictive value6 and are not considered diagnostic, leading customers to question the financial value of such test results. Nonetheless, these companies give their customers information about the research that links these polymorphisms to increased probability of developing a given disease.

THE EFFECT OF THE TEST RESULT ON THE CONSUMER

While some DTC companies offer over-the- phone genetic counselling with the results, it is important that all customers understand the information in a contextualized manner. This requires understanding of concepts such as relative and lifetime risks of disease. Physicians have also expressed concern over so called ‘genetic determinism’, where the individual negates environmental risk factors which are contributory to the disease in favour of the test results. For example, a patient’s risk of heart disease is more reflective of their weight, blood pressure and/or cholesterol than genetic factors7. Another ethical concern is testing for conditions where there is no viable treatment or preventative measures. Advocates of DTC testing point to studies such as the REVEAL study, which showed that disclosure of a genetic trait predisposing patients to Alzheimer’s disease “did not result in significant short-term psychological risks” compared to those that were not tested8.

Privacy concerns also exist about third party disclosure of data, especially in regards to health and life insurance, where this detailed information could lead to genetic discrimination. While company policy is generally not to disclose information without explicit consent of the customer, the information itself is not protected to the same standard as information covered by the US Health Insurance Portability and Accountability Act (HIPAA)9,10,11. If a customer discovers that they are positive for a mutation and fails to disclose it to their insurance company, it may serve as grounds for voiding policy if the insurance company finds a way to access the information12,13. Similarly, the Canadian Human Rights Act does not contain a clause protecting against genetic discrimination, though an amendment is currently under consideration in the House of Commons (Bill C-536). On the other hand, Americans are protected from such discrimination by the Genetic Information Nondiscrimination Act (GINA) which does not apply to Canadians using the US based companies.

THE ROLE OF THE HEALTHCARE SYSTEM

Ontario’s Regulated Health Professions Act stipulates that a healthcare professional is responsible for “communicating to the individual or his or her personal representative a diagnosis identifying a disease or disorder as the cause of symptoms of the individual in circumstances in which it is reasonably foreseeable that the individual or his or her personal representative will rely on the diagnosis”. Does the genetic risk assessment offered by these privately owned companies count as a diagnosis? The companies explicitly state that their products are not diagnostic or are substitute for medical advice and that all concerns arising from the test should be referred to your healthcare provider. The onus then lies on the
family practitioner to interpret the information, a burden that could become substantial according to a study by McGuire et al where 78% of respondents said they would consult their family doctor about results of commercial genetic test4. This increased burden on the healthcare system is further complicated by the fact that family physicians are often not trained in genetics counselling and may not be equipped to deal with this extensive genetic information.

CONCLUSION

In 2010, the FDA sent regulation letters to five American commercial genetic testing companies stating that their device is regulated "... under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h) because it is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or is intended to affect the structure or function of the body": It went on to state that the product is classified as a medical device under the Medical Device Act and as such require premarket approval13. Increasing regulation has been occurring in both the United States and many European countries out of concern for inaccurate or misleading test results14.

However, supposing the tests are accurate and relatively specific the next logical question is whether the knowledge of risk factors will translate into better outcomes for patients: reducing risk, earlier screening, prophylactic measures and, in some cases, influence on family planning6. It is difficult to assess this as the industry is relatively new and there is no follow up after the company discloses the results to the customer. Without counselling it may be difficult to put the risk into context for the individual patient and an over or underestimation could be deleterious to a patients' health6. Proponents argue these tests champion patient autonomy and to limit access to one's own genome is paternalistic while detractors are concerned the patchwork regulation does not protect customers purchasing these products. With expanding use of these services the effects of this plethora of information, both positive and negative, will become more apparent.

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Improving healthcare with information technology

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As healthcare costs escalate and the public maintains high expectations about health service delivery, the sustainability of our current public system has become untenable. In 2010, health expenditures comprised 11.7% of Canada’s GDP and 192 billion dollars were spent on healthcare. Furthermore, Canada’s oft-cited aging population—which consumes 44% of all healthcare dollars—continues to grow. In 2005, 13% of Canadians were age 65 or older; by 2036, that figure is expected to reach 24.5%. As policymakers struggle with broad healthcare reform, they are asking hard questions about the marginal returns of further spending on sickness care. For their part, clinical managers and clinician-leaders are working to reorganize the delivery of health services, promote evidence-guided decision-making, and create a culture of inter-professional collaboration and quality improvement.

There is increasing pressure to promote cost-efficiencies in the healthcare system, and health information technology (IT) has enormous potential in that regard. Evidence suggests that such innovations can enhance the efficiency, cost effectiveness, quality, and safety of healthcare delivery. And as the face of health human resources changes, with the adoption of collaborative multi-disciplinary models of care, sharing of health information between providers is all the more crucial.

As of March 2010, an electronic health record is available for 22% of all Canadians, and by early 2011, that proportion is predicted to reach 50%. Canada Health Infoway is an organization charged with managing the development, and promoting the adoption of, electronic health record systems in Canada; its goal is for all Canadians to have an electronic health record by the year 2016. When we compare ourselves to peers in other nations, it is clear that we are not keeping pace. In 2006, Canada ranked last among seven countries based on the use of health IT by primary care physicians. According to a survey of almost 1500 Canadian physicians, only 37% use health information technology. The statistic for our hospitals is more optimistic: approximately 65% have at least one e-health component.

What makes this task so daunting? The complexity of health information technology lies in the amount of data, the sensitivity (and need for privacy) of data, and the high stakes in ensuring the accuracy of data. Banking is an industry with similar information technology needs; according to data from 2004, US financial services spend 5.4% of their total budget on information technology. It is therefore no surprise that we have a long way to go: the average for Canadian healthcare IT spending was only estimated at 1.5-2.0%. In this review article, we will discuss both the potential benefits and challenges to widespread health IT implementation, as well as provide recommendations and future directions for the field.

BENEFITS OF HEALTH IT

Health information technology can deliver a wide range of benefits, including system-level efficiencies (reduced costs and increased productivity), better delivery of care, improved patient safety, more effective communication between providers, and increased access to information. While we have categorized benefits for the sake of discussion in this article, we recognize that these benefits are not truly discrete, and are actually inter-related; for example, when providers communicate more effectively, the resulting decrease in ambiguity leads to improved patient safety, and ultimately, a cost-efficiency through dollars saved treating an adverse event.

Enhanced productivity and long-term cost savings: From an efficiency perspective, upgrades to healthcare IT can help minimize wasted time and resources in a clinical setting. For example, the elimination of paper charts increases the amount of physical space that can be used for patient care. Furthermore, computerization of medical records leads to reduced storage and transcription costs. After a period of training and adjustment, electronic documentation of clinical encounters would be more rapid than handwritten documentation in a paper chart; as such, the amount of time that clinicians spend on administrative tasks is reduced, freeing up valuable time for productive clinical care. A single electronic patient record can result in smoother hand-offs and tighter connections between health providers along the continuum of care, leading to an overall more efficient care process. Furthermore, health information technology can be used to optimize the scheduling of procedures and diagnostic tests, reducing overbooking and bottlenecks, thus allocating resources more accurately.

The costs of implementing a health information strategy are high. However, evidence suggests that the payoff can be equally impressive. In Canada, for example, the estimated productivity gains and savings from a fully implemented electronic health record are estimated at $6 billion. There is a growing body of literature that presents detailed cost-benefit analyses of health IT implementation. One study used US data to demonstrate potential net efficiency and safety savings of $81 billion each year, after widespread and effective e-health adoption. These gains in efficiency will ideally lead to the transfer of labour to more productive activities. The authors analyzed other industries for productivity gains as a result of widespread IT implementation, and estimated potential gains for healthcare between 1.5 and 4%.

Another paper assessed the value of a fully standardized and interoperable nationwide health IT system in the US. Despite the high cost associated with this ambitious task (estimated ten-year rollout costs of $276 billion), the authors projected a net value of $77.8 billion annually after implementation is complete. A third study performed a cost-benefit analysis of an ambulatory care
Enhancing the delivery of safe, high-quality patient care: The Canadian Adverse Events Study tabulated 70,000 adverse events that occur in our hospitals each year, resulting in as many as 23,000 deaths.11 British Columbia has implemented a drug information system (DIS), with great success: if these results are used to make projections for all of Canada, we can expect an electronic DIS to reduce inappropriate prescriptions by 55 million, and to identify 20 million drug interactions.12 This positive impact on patient safety can also translate into cost-savings. In one study, adverse drug events were associated with an increase in costs of $2,262, primarily due to a 1.9-day increase in length of stay.13 Data cited in another report7 suggest that drug-related events cost the average 200-bed hospital between $1.6 million and $3 million a year.

The potential for health information technology to reduce errors is three-fold: by preventing the errors upfront, by alerting clinicians and allowing a more rapid correction of the error, and by reporting and generating feedback about the adverse event.14 In a controlled trial evaluating the effect of computerized medication order entry by physicians, the investigators found a 55 percent reduction in serious medication errors; a follow-up study later evaluated the addition of enhanced levels of clinical decision support to the electronic application, and noted an 83 percent reduction in the overall medication error rate.14 A fundamental advantage to electronic health records is the elimination of issues that plague written documentation, such as illegible handwriting and incomplete medication orders. Communication breakdowns, most notably during poor “handoffs” between clinical team members, are another common risk factor for adverse events.13 Health IT can facilitate effective communication among providers, particularly with the use of hand-held wireless devices with access to the electronic patient chart.

The capacity for electronic information systems to facilitate effective clinical decision-making is increasingly being recognized. Order entry systems can limit dosage or route of administration for potentially unsafe medications; for example, in patients with renal dysfunction, computerized calculations of safe drug dosages are particularly beneficial.13 IT can specifically improve patient monitoring. For example, IT systems can alert clinicians to potentially serious lab abnormalities that may otherwise be overlooked, and promote earlier correction: in one trial, this strategy decreased the duration of dangerous patient conditions by 29 percent.15 In another approach, technology-enabled remote monitoring of intensive care lead to a reduction in mortality of up to 68 percent, and a reduction in average length of stay and associated costs of about 33 percent.16 Finally, health information technology can increase linkage to clinical references and best practice recommendations, allowing clinicians to make evidence-informed decisions.

Increased access to information: Increasing access to information leads to myriad benefits, at the level of patients, providers, and the health system alike. Many of these benefits have already been realized by provincial initiatives.17 Firstly, providers can develop a common understanding of patient conditions, leading to more seamless care for patients. For example, ONE Mail is an email server that allows for transfer of patient medical records back to the family physician upon discharge from a hospital. Currently, 55,000 Ontario healthcare workers have ONE Mail accounts.18 Second, health information technology can also facilitate communication and collaboration between providers, which is particularly relevant to the enhancement of rural healthcare delivery. One example, Telestroke, is an emergency telemedicine application that uses two-way communication and digital imaging to connect local physicians with remote neurologists located at large urban centers, to obtain urgent diagnosis and treatment recommendations about their stroke patients. Thus far, 1200 patients have received urgent care that saved their lives.18 Thirdly, when health information is shared, redundancy and the need for duplicate testing are decreased; this is beneficial to patients, who will no longer have to undergo unnecessary repetition of tests, and as a system-wide cost-efficiency since additional expensive tests can be avoided. A local success story in this arena, the South Western Ontario Digital Imaging Network (SWODIN) provides regional healthcare providers electronic access to a patient’s medical imaging results, when taken at any hospital in the network.19

Beyond these local success stories, there are other intriguing potential outcomes of increased access to health information. In one scenario, where patients are to receive access to their electronic health record, they could use this information to manage their chronic conditions on a day-to-day basis, identify risk factors, and for self-care. One important benefit that can be felt on both a system- and patient-level is reduced wait times. The use of health IT to coordinate and manage wait lists, and to make wait time information accessible to the public in real time, is well documented. In the UK, for example, their national health system reports wait times data that is less than one month old.20 As such, patients can make an informed decision about where to go for care. A related benefit of health IT is the wealth of data that are made readily available; this is useful both for reporting of health status to the provincial government, and for reporting of performance indicators (e.g. length of stay and mortality rates) to increase hospital accountability.

BARRIERS TO SUCCESS

One review21 provided a succinct classification of four types of barriers to the implementation of health information technology. Situational barriers include time and financial concerns; cognitive and/or physical barriers include physical disabilities and insufficient computer skills; liability barriers include concerns about confidentiality; and knowledge and attitudinal barriers include apprehension about change or lack of awareness of potential benefits.

With respect to financial concerns, it is no surprise that widespread health information technology implementation comes with a hefty price tag. The costs of implementation include software and hardware, training, workflow process redesign, historical paper chart abstracting, and ongoing maintenance and support. There are also indirect costs as a result of the transition from a paper to electronic system, such as the temporary decrease in provider productivity after implementation, as they adjust to a new system.10 The creation of an electronic health record for all Canadians is projected to cost $10 billion.22 In Ontario alone, the estimated total cost of a three-year e-health strategy—which focuses on diabetes management, medications, and wait times—is over $2 billion.19 Compounding this high cost is the fact that the presumed financial payoff is delayed: one review including 82 studies with cost-benefit analyses showed the time to break-even on health IT investment was between 3 and 13 years.23 In some cases, the financial payoff may also be uncertain—particularly for physicians operating in a small group or solo practice, where the return on investment is less substantial, and there is no formal organizational support for training and restructuring.24 Moreover, the task of performing a cost-benefit analysis can itself pose difficulties, given the challenge of assigning dollar values to productivity gains or improvements in patient care.

With respect to attitudinal barriers, Poon et al25 noted the perception that health information technology could have a negative impact on clinical processes. This speaks to the fact that technology cannot be applied to a clinical area without careful workflow analyses; where necessary, updated protocols should be implemented.
that are in sync with the new technology. The authors also noted that product and vendor immaturity was a barrier; many current software offerings were not compatible with hospital needs, and various modifications were necessary to accommodate the hospital's current workflow.

Hersh reported that system and data interoperability was a major concern, noting the "information silos" pervasive in managing healthcare data. Further to this, smaller, pilot projects are often more affordable, and thus, desirable from a management perspective; this becomes a problem when a health system has multiple incompatible electronic medical records, and an expensive standardization process must be undertaken. Hersh also identified the need for a workforce trained sufficiently in clinical informatics to roll-out such a complex implementation process. A related cognitive barrier is the lack of IT knowledge and training in health professional education; this can certainly impede front-line clinicians' acceptance of technological trends in their workplace.

CONCLUSIONS

Recommendations: An electronic health information system has a large impact on the day-to-day work of both clinicians and hospital administrators. As such, there is a clear need to engage, and ensure buy-in from, these stakeholders early in the decision process. Health professionals in particular should be consulted in order to select and build an electronic system that is compatible with clinical needs and patient flow. One approach is to designate key physicians as "champions" of the process, who can then help motivate other clinicians and administrators, and promote acceptance and adoption of the IT system. Often times, there is resistance among front-line staff when a change is seen as coming from administrators who are not familiar with clinical processes; if the process is supported by a respected clinical colleague, however, other clinicians tend to be less wary. It is also important not to underestimate the scale of such an implementation process. The process may include modifications to the software architecture and the establishment of new standards of care or changed medical practices. Change management itself requires resources and time; for example, in one Canadian hospital system, approximately 30 percent of the total project budget was allocated to this stage. Another approach is to implement an information technology system in a succession of phased pilots; the project team can identify lessons learned and apply them to subsequent rollouts. If pilots are successful, other clinical areas will be eager to undergo the same change. Increasing education and awareness about the benefits of health information technology will boost acceptance of change on the part of the general public and health providers alike. Data elucidating these benefits are required for such endeavours; clinical settings where IT systems have been implemented should be encouraged to collect, analyze and publish data on the results. Finally, having diverse applications and software platforms increases complexity, raises costs, and lengthens implementation timeframes. As such, at a time of rapid adoption of health IT, it is crucial to implement a simple, unified system. It will be important to maintain an integrated e-Health Ontario strategy to facilitate this.

The path ahead: Health information technology has created endless opportunities and has enormous potential to transform the delivery of healthcare. The possibilities even surpass the biomedical model: an electronic health record has the capacity to link clinical data to indicators of socioeconomic status, allowing a remarkable understanding of the impact of social determinants of health. However, this changing landscape has also challenged us with important questions. Who will have access to this wealth of information? Will patients be able to view their own electronic record? If data are anonymized, are they then ethically for government reporting and public use? Will health information technology be used to increase transparency, by providing outcomes data to the general public? Will clinicians feel comfortable operating in such a system, where their post-operative mortality rate is widely published? And perhaps most importantly, will the myriad stakeholders embrace the opportunity to collaborate and use information for the advancement of health? We look forward to learning the answers to such questions, and hope that innovations in health information technology will be embraced across Canada.

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Using texts for safe sex: technology in adolescent sexual health

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Risky sexual behaviour among adolescents is a significant cause of infection and morbidity, as well as unwanted pregnancy. In the United States, 25% of females between 14-19 have acquired a sexually transmitted infection (STI) and adolescents between 10-24 account for more than 20,000 new cases of HIV/AIDS annually. While many STIs are easily treatable, they can also lead to pelvic inflammatory disease, chronic pain, or cervical cancer and infertility. As well, there are over 745,000 teenage pregnancies in the US every year. Therefore, promoting sexual health through youth-specific interventions is an important topic of research and concern.

In the past, sexual health promotion interventions (SHPI) have been provided through school programs and sexual health clinics. Through this medium, information is typically given face-to-face by health care workers and is complemented by print materials. While these strategies have shown moderate success, they are limited by cost, time, and accessibility. Face-to-face SHPI have not been shown to substantially impact STI infection rates, unplanned pregnancy rates, or number of sexual partners, although they have been shown to increase knowledge about sexual health and condom use. The introduction of new technology allows for a less expensive and more efficient way of promoting sexual health to the largest number of people. The most successful technology-based SHPI to date have involved either internet-based interventions or text-messaging-based interventions. Since 93% of US adolescents have a computer at home and 85% of 14-18 year olds own a cell phone, these media provide excellent access to the adolescent population. Technology-based SHPI have not only been shown to reduce risky sexual behaviour and increase knowledge of sexual health, but can reduce costs and time spent by healthcare workers by shifting the burden to more automated technologies.

Sexual health promotion consists of providing individuals with the tools to make informed decisions about their sexual well-being. The overall goal is to improve the sexual health of a population through community-based interventions. In order to do so, however, one must first identify the reasons that individuals, especially adolescents, engage in risky sexual behaviour. Recent research into adolescent motivation found that the four main factors that contribute to these behaviours are: low perceptions of risk, lack of confidence, the influence of social norms, and inaccurate knowledge. Most interventions aimed at adolescents focus on this last factor by providing information on STIs and contraception; however these strategies have shown only marginal success. Sexual health promotion interventions must not only focus on biological outcomes, such as STI incidence rates or teen pregnancy, but on behavioural and emotional outcomes – increased self-efficacy, motivation to change, and confident decision-making.

Technology-based strategies can incorporate this research by providing population-specific interventions that touch on multiple aspects of sexual health. Studies have shown that interventions are more effective when they are based on behavioural theories and address the social and psychological causes of risky sexual activity. Internet-based and text-messaging-based interventions have the ability to promote behavioural change by using the convenience, speed, and ubiquity of these technologies to access at-risk adolescents.

Internet-based SHPI are promising because they allow for anonymous, repeatable, convenient, and inexpensive interventions that can reach populations that are more resistant to mainstream medical care. Almost 50% of youth surveyed have already used the Internet to search for sexual health information. A recent Cochrane Review meta-analysis of interactive, computer-based SHPI found significant effects on both behavioural measurements, such as condom use, and psychological measurements, such as confidence and self-efficacy. Fifteen RCTs with 3917 participants were reviewed. In keeping with previous findings on the importance of motivation and decision-making in behaviour modification, the review focused only on interventions that required user contribution and provided personalized feedback. The most successful interventions were tailored to an individual’s level of knowledge and involved role-playing or situational exercises. Studies that focused specifically on adolescents were also more successful if they avoided negative messages and scare tactics, and targeted specific behaviours. Many of these interventions exemplify the principles of health promotion because they not only educate, but also provide users with the confidence and motivation required to make safe decisions in the future. Other websites provide users with anonymous and accessible ways of improving sexual health via mail-in STI tests or online contact-tracing after STI diagnosis.

Using text messaging to promote adolescent sexual health has many advantages. Text messages are fast, convenient, and inexpensive; they can be sent to multiple individuals at the same time; they are very popular among adolescents, and text messaging rates are similar between socioeconomic groups. Text messaging has been incorporated into sexual health care in numerous ways, with encouraging results. Sexual health clinics in the UK have begun providing results of STI tests via text message if desired – 70% of adolescents preferred this to booking a follow-up appointment. The UK has also begun a text messaging “Grab a Condom” campaign, where individuals can request condoms and have them home-delivered. Other clinics have begun providing daily text message reminders to patients about taking oral contraceptives, and have seen a significant improvement in reported compliance. The most promising intervention, implemented in San Francisco, allows individuals to text “SEXINFO” from any mobile phone and receive
information about sexual health, relationships, and nearby clinics. In
the first 6 months, SEXINFO received more than 4500 text messages
and those who remembered seeing advertisements for the service
were significantly more likely to be concerned about STIs.11 While
not yet widely used, text messaging shows promise as an effective
SHPI that can be used to target adolescents directly.

The use of technology-based SHPI is relatively new, although
its effectiveness has been demonstrated in numerous studies.
However, there are still concerns that these strategies may be saving
time and money at the expense of accuracy and holistic care. A recent
study of 177 sexual health websites showed that 17% contained one
or more medical errors, and the number of errors was correlated with
the complexity of the topic at hand.12 Sexual health websites focus
strongly on STIs and contraception, but often only contain a cursory
treatment of how to express sexuality, body image, and the positive
aspects of sex.13 A recent study of 30 “Positive Youth Development”
interventions — those that focused on empowerment of disadvantaged
youth — showed that all successful interventions involved a
supportive environment containing parents, teachers, or health care
providers.1 Can technology-based interventions provide this same
level of support and intimacy? Nearly half of teenagers cited their
parents as the people with the most influence in their sexual decision-
making, yet very few of the internet- or text messaging-based
interventions encourage parental involvement.5 Moreover, providing
STI results via text messaging led to a decrease in follow-up visits,
which was hailed as a success by the UK sexual health clinics
involved.14 However, if these interventions lead to fewer
conversations between adolescents and their health care providers, is
this really something to celebrate?

Media and communication technologies, like Internet and text
messaging, have the potential to be used as far-reaching and cost-
effective methods of promoting sexual health among adolescents.
Initial studies demonstrate that these interventions can successfully
provide knowledge, motivate people to change behaviour, and
courage adolescents to seek medical care when necessary.
However, few studies have measured their effects on long-term
outcomes, such as STI infection or pregnancy rates. As well, some
concern remains that technology-based SHPI cannot fully address
the emotional needs of adolescents in the same way as face-to-face
conversations with a healthcare provider. Nevertheless, it is thought
that reaching adolescents “on their own turf”, by using media they
are comfortable and familiar with, may encourage them to seek care
when necessary and feel more motivated to practice safe sexual
practices.

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The complex organization of the Canadian health care system has led to fragmented care, and challenges in interdisciplinary communication. Advances in technology, however, are rapidly enhancing the potential for multiple disciplines to communicate and integrate information. Many of these advances have been fostered under the leadership and influence of radiology.

Innovation is described as having two components: the development of new technologies, and their adoption into clinical practice. Both are required for a real impact in medicine. Beginning with Roentgen's discovery of x-rays, innovation in new imaging techniques like ultrasound, CT and MRI has propelled radiology to the forefront of cutting edge medical science. Furthermore, leaders in radiology have pioneered efficient communication and electronic storage strategies to more efficiently adopt these imaging modalities into clinical practice, accessible to a larger group of caregivers. Picture Archiving and Communication System (PACS) is just one example that has now been implemented in hospitals across the country and throughout the world.

The field of radiology has been exemplary in using innovation to facilitate multidisciplinary care. Often, however, these innovations are adopted or completely taken over by other specialties resulting in "turf wars," which create animosity, hindering collaboration on a fundamental level. In addition, it is possible that since technology has reduced face-to-face time in non-medical realms (e.g. Facebook, online chat, blogs), it could also negatively impact communication in medicine. This article argues, however, that an increase in computerized communication is a positive development for interdisciplinary collaboration owing to the nature of the technologies used. This article will also outline some examples of current technology that have come to symbolize the concept of computerized clinical integration.

Despite literature that bemoans the decreased clinical presence of radiologists caused by technology, its advantages to patient care cannot be ignored. A radiologist stated, "the saying *tempora mutantur* is as true today as it was in the days of the Romans: times change, and we must change with them." Radiologists have been pivotal in developing these modern technologies and now must adapt to best reap their rewards.

**PICTURE ARCHIVING AND COMMUNICATION SYSTEM**

PACS refers to the electronic storage of multimodal data including imaging studies, reports and patient identification information. PACS replaces hard copy data (films and paper records) and allows the integration of imaging with other systems such as the Electronic Medical Record (EMR). There are several storage formats for PACS, which all generally include images (which can be CT, MRI, US, PET, endoscopy, mammography, ophthalmology, etc), a secure network, multiple workstations (which can exist at multiple hospital sites), and patient archives. PACS facilitates remote access, and is used by radiologists to perform teleradiology, or off-site image interpretation. Integrated into PACS is a workflow management system, which allows for an efficient asynchronous communication system. In other words, once the image is acquired, preliminary comments can be made by the technician or referring physician. In addition, if a diagnosis is made immediately and acted upon, say in the ED, this is recorded and can be later re-evaluated by the radiologist who can either agree or disagree with the original impression. This allows for a system where discrepancies can be recorded and later studied for particular patterns of error.

In the study by Mates et al., an additional communication tool was implemented alongside PACS, called Collaborative Notification System (CNS), which was used in the setting of urgent or emergent radiology. CNS consists of a pager notification system between the radiologist and referring physician, and allows for images to be read immediately, and the diagnosis paged to the referring physician who can then acknowledge its receipt. The system was shown to improve documentation, and provided an exact record of the communication, which would not be available with person-to-person communication. CNS is just one way in which PACS has been shown to facilitate radiologist workflow.

Additional benefits of PACS include an increase in image availability as well as a decrease in time spent travelling to the radiology department. Another report demonstrated that PACS enhanced communication between radiologists and referring physicians by decreasing errors related to incorrect patient identification, and increased the efficiency of meetings by providing readily available images and reports. More manageable workflow and increased efficiency of inter-physician communication are undeniable here. Unfortunately for radiologists, however, more accessible image data may lead to an increase in the number of non-radiologist physicians who interpret radiological studies.

**SPEECH RECOGNITION REPORTING**

Speech Recognition Reporting (SRR) has been widely available in health care worldwide for the last 15 or so years, but recently improvements have been made such that the voice recognition systems are more sophisticated, requiring less voice-training time with increased word-recognition accuracy. Radiologists have been a major consumer of SRR as it has been shown to significantly reduce the time between examination and report finalization. Traditionally, radiologists would dictate reports, which were recorded and transcribed at a later time, and finally verified by the radiologist and signed off for inclusion in the patients chart or EMR. With SRR, voice is converted directly to text after the SRR software has been trained to the particular user's voice. The report then appears immediately in the EMR and as part of the hospital’s PACS. The use
of SRR alongside PACS has been shown to significantly reduce report completion time as well as significantly increase the number of reports which are available within 24 hours.\(^6\)

Another benefit of SRR, shown by Bhan et al., is the decrease in overall hospital operating costs.\(^6\) The same report, however, published data showing that SRR actually increased the amount of time taken to produce individual reports, and was prone to inaccuracies in certain settings, for example, when used by practitioners for whom English was a second language. Speech Recognition Reporting was shown to have no effect on the overall number of reports produced. Despite some of its shortcomings, SRR has recently shown vast improvement and will undoubtedly continue to do so. It has become a mainstay for many radiologists and other specialties alike and has the unique ability to be combined with systems such as PACS to provide a more complete composite of patient data, benefitting all members of the interdisciplinary team.

**THE FUTURE OF RADIOLOGY**

Since many technologies have improved the efficiency and accuracy of radiological reporting, there has been a parallel increase in the adoption of radiological techniques by other specialties. This is known to many as radiology "turf wars". The most prominent examples over the past 40 years are in vascular surgery and coronary angiography. One author speculated that the reason for the total cessation of radiologists performing these procedures was their lack of specific knowledge in the clinical aspects of coronary artery disease (especially electrocardiology and cardio pharmacology) as well as the ability of cardiologists to self-refer.\(^8\) Palma notes that since radiologists are not trained in the catheter lab and do not conduct research in coronary disease, they are less adept to perform coronary angiography. Thus, radiologists have largely abandoned this practice. One study showed that the total number of intravascular procedures performed by radiologists fell from 63.6% to 49%, while those performed by cardiologists rose from 25% to 36% from 1997 to 2002.\(^9\) Radiologists, however, have longer and more highly specialized education that includes in-depth radiation safety training, familiarity with all imaging modalities, and ability to detect incidental findings, which suggests that they are better suited for these procedures. The previously mentioned phenomenon of self-referral has also been explored and shown to lead to an increasing and unnecessary utilization of radiological services by non-radiologists.\(^9\)

The high level of technical ability inherent in radiology has led to a real or perceived weakening of the clinical relationship between radiologist and patient. Therefore, there has been a recent push towards solutions termed "clinicalisation", which reinforce the clinical role of radiologists and their technologies.\(^5,8,11\) Clinicalisation also seeks to help radiologists better communicate with other disciplines by recommending training for radiology residents in specific organ pathologies, and supports the physician-patient relationship by encouraging radiologists to maintain contact with the patient in all phases of treatment.\(^11\) Additionally, centers in the United States have explored the possibility of using online images to increase patient access. This was found to increase patient satisfaction, and support the relationship with and identification of the radiologist as a professional responsible for diagnosis and treatment.\(^11\)

**CONCLUSION: WILL TECHNOLOGY HELP OR HINDER RADIOLOGISTS?**

Innovation in radiology is influencing many aspects of medicine that include communication, management, diagnostics and therapy. The future of radiology undoubtedly involves further development of PACS and SRR systems and their becoming so widespread that transmission of images and reports to patient smart cards, nationally or internationally is possible.\(^11\) Telemedicine and videoconferencing will also enhance large-scale communication. The next few decades will see further advances in nanotechnology, molecular imaging, and new forms of percutaneous treatment. Radiologists who have expertise in electronics and informatics, a foundation of specialized clinical pathology and excellent bedside manner will help shape the way innovation is implemented in day-to-day medicine.

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One of the greatest challenges in modern medicine is the ability to provide accurate diagnostic laboratory tests in developing countries and in remote areas where conventional analytical laboratories are lacking. Imagine running a clinic in a remote area of rural Africa, the Canadian arctic, on a military field base or even in a small rural community in Ontario and having the ability to provide accurate, rapid, point-of-care diagnostic lab tests without the infrastructure of a full analytical laboratory! There’s no need for a cumbersome or expensive mass spectrometer, a spectrophotometer, a flow cytometer or even a centrifuge because the application of microfluidics engineering to medical diagnostics has enabled laboratory tests to be performed on a small microchip the size of a credit card that you can carry around in your pocket and may only require the use of a battery as a power source for analysis! As futuristic as this idea seems, the application of microfluidics engineering to the development of medical diagnostic tests is very much a reality.

Microfluidics engineering is a multidisciplinary field of engineering where the intersection of the fields of physics, chemistry, engineering and biotechnology have come together to develop chips on which the analysis of fluids can occur on a microscale level. A particularly interesting application of microfluidics engineering technology is the development of a lab-on-a-chip, a platform on which one or more laboratory tests are integrated onto a small chip a few square centimetres in size that uses a very small volume of fluid for analysis. Several microchannels of a variety of biological fluids including blood, cerebrospinal fluid, urine, feces or saliva can be added to the lab-on-a-chip for analysis. These chips utilize a wide variety of techniques for analysis. The most successful lab-on-a-chip applications integrate all aspects of sample preparation, sample separation, signal amplification and signal detection on a single chip.

These chips can be easily adapted for use in remote regions since specialized laboratory personnel are not needed for analysis - you simply need to apply the sample to the chip and the technology takes care of the rest. In addition to their small size and portability, the applications of lab-on-a-chip platforms have a wide variety of advantages to the field of medicine and are listed in Box 1 (adapted from references [1-3]). A variety of molecular biology, immunology and biochemical techniques have been adapted for use on lab-on-a-chip platforms including protein assays, nucleic acid assays, cell sorting, and biological analyte detection. Since lab-on-a-chip technology has a wide variety of applications in medicine we will now focus on two areas of interest where we feel the technology will be rapidly applied; the detection of infectious microorganisms from biological samples and the microscale detection of biological analytes.

Arguably, one of the most important and exciting applications of these devices is in the early and accurate diagnosis of infectious diseases in the developing world. The ability to rapidly detect an infection, assess an infected patient’s health status and the application of this technology to epidemiological studies in the field are invaluable. In order to be a useful tool in the developing world several design challenges need to be overcome; the reagents and the chip itself need to be stable at a wide variety of temperatures since refrigeration of the components may not always be feasible in the developing world, the cost of the chips needs to be low and the chips need to have a small power source for operation since reliable electrical infrastructure is not found in all parts of the world.

Research and development work is being undertaken to adapt lab-on-a-chip technology for the detection of many microorganisms from biological samples including: HIV (reviewed in [5]), malaria, tuberculosis, diarrheal diseases, pertussis, and dengue fever. One exciting lab-on-a-chip application for the detection of enteric infections is the Disposable Enterics Card (DEC) which is able to detect the presence of Campylobacter jejuni, Escherichia coli O157:H7, Shigella dysenteriae, Shiga Toxin-producing Escherichia coli (STEC) and Salmonella from a sample of feces all on one microchip. The DEC lab-on-a-chip technology combines several laboratory assays to detect the bacteria (see Figure 1 and Figure 2 for a schematic of the chip). Briefly, a sample of feces is applied to the chip and bacteria from the sample are captured on the chip by using specific antibodies to each bacteria of interest. These antibodies are located in several different areas of the chip. The bacteria are subsequently lysed using buffers and the bacterial DNA is captured on a silica resin contained within the chip. The purified bacterial DNA is subsequently amplified using a standard molecular biology technique called the polymerase chain reaction (PCR) with DNA primers specific for a gene in each bacterial species of interest. The end of each primer has been designed to contain a fluorescent molecule. After the amplification of the bacterial DNA using PCR, fluorescent molecules are now found at the ends of each DNA fragment.
amplified molecule of bacterial DNA. The next step in the process is to detect the amplified bacterial DNA. To do this, a laser light is directed at the sample. The fluorophore emits fluorescent light which can be detected if the sample is positive for the bacteria. Unfortunately, the DEC testing still requires the use of a small machine for the PCR reaction and PCR product detection which limits its ability to adapt to field conditions. This technology would be useful in a small analytical laboratory or clinic but its usefulness would be limited under field conditions.

A second application of technology to lab-on-a-chip capability is the detection of analytes such as electrolytes from a small sample of blood. The iSTAT, a device manufactured by Abbott Diagnostics, has the capability of rapidly analyzing analytes in a few drops of blood. The developers of the iSTAT have miniaturized electrodes by depositing electrode arrays onto silicon cartridges to create a biosensor. A few drops of blood deposited into a sample chamber are able to enter the cartridge by capillary action. Once the sample is in the cartridge it can be treated with chemical reagents prior to analysis. At the analytical stage the cartridge is inserted into a handheld electromechanical read-out device that provides a power source and controls the temperature of the chip. The electrode arrays deposited on the silicon membrane can then be used to measure the concentration of various blood electrolytes, gases, and other analytes using potentiometry (measuring the electric potential),

**Box 1: Advantages of lab-on-a-chip technology**

- Small size (credit card or smaller), portability
- Small sample volumes, less invasive
- Rapid analysis, short processing times
- Low cost
- No need for highly trained laboratory technicians to perform the test
- May run using a battery for power (no need for electrical infrastructure)
- Reduced reagent consumption due to small volumes
- High reproducibility
- Reduced exposure to hazardous materials or infectious agents due to small volumes
- Minimal risk of sample contamination
- Convenient disposal
- Elimination of human error (you add the sample to the chip and the chip takes care of the rest)

Adapted from references (1-3).

![Diagram of biochemical steps in the chip](image)

**Figure 2.** Biochemical steps of the analysis in the chip. (A) Feces sample is applied to the chip and enters the sample well. Various types of bacteria in the sample are represented by different ovals. Different surface proteins on each type of bacteria are denoted by rectangles and triangles. (B) Antibodies specific to surface proteins on the bacteria of interest capture the bacteria in the chip. This example shows black colored bacteria captured in the upper chamber and grey colored bacteria in the lower chamber. Bacteria whose surface proteins are not bound by the antibodies are washed away. (C) Captured bacterial cells are lysed in buffer and bacterial DNA is purified on silica resin. (D) Purified bacterial DNA is eluted from the resin and enters the PCR amplification chamber. (E) A bacterial gene of interest is amplified using a standard molecular biology technique called PCR. Small DNA molecules (primers) specific for the gene of interest are found in this chamber. Primers are denoted as arrows in the diagram and are linked to a fluorophore (a fluorescent molecule) denoted by a star. (F) The gene of interest is amplified exponentially (there are many copies) and now contains fluorophores on each end. (G) Amplified bacterial DNA fluoresces when laser light is shone on the sample giving a readout, thus, leading to the diagnosis of the infection.
amperometry (measuring the flow of an electrical current) or conductimetry (measuring the conductance) of the sample. These values are then displayed on a screen. Different chips are used for different analytical applications and each chip is disposed of after one use. All the chips use the same handheld electromechanical read-out device.

We have only focused on two applications of lab-on-a-chip technology; however, there are numerous uses for this technology and many approaches to the miniaturization of biochemical, molecular biology and chemical assays for use on microchips. The miniaturization of medical technologies may very well revolutionize the delivery of medical care in the near future. Is your pocket ready for the lab-on-a-chip?

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An Interview with Dr. Ting-Yim Lee, PhD

Lauren Sham (Meds 2014), Abdul Naeem (Meds 2014), Joyce TW Cheung (Meds 2013)

Physicians are often limited by technology in their pursuit of patient wellbeing. Take for example a patient suffering from stroke among a myriad of other diseases. Having the capacity to measure blood flow to various organs and to specific regions within those organs – vital for proper bodily functions – can have prodigious implications on deciding which treatment plan to follow. Fortunately, measuring functional bodily processes with respect to hemodynamics has been a specialty of Dr. Ting-Yim Lee. Dr. Lee’s research on blood flow has contributed substantially in allowing physicians to appreciate a more comprehensive picture of some of the most severe diseases. But the journey there has not been easy.

Winston Churchill once said, "Continuous effort is the key to unlocking our potential." This quotation best exemplifies the driving force behind Dr. Ting-Yim Lee’s research endeavours. Having grown up in Hong Kong, Dr. Lee travelled to London University in England to pursue graduate degrees in Radiation Physics in the Department of Nuclear Medicine. To further his research interests, he immigrated to Canada in 1983. Dr. Lee exemplifies the qualities of a committed, ambitious scientist who manages to go above and beyond the typical protocol. He is hard working, humble and extremely knowledgeable in his research deriving functional and physiological information from contrast CT images. The University of Western Ontario has been fortunate enough to have him for well over two decades now. While at Western, Dr. Lee quickly emerged as a leader by developing a renowned functional CT imaging program. His aspirations are to study functional processes in the human body using CT imaging, specifically those with respect to hemodynamics. His hallmark is in pioneering a method of using x-ray dye and CT scanning to measure blood flow. This intricate research is making substantial contributions to several diseases including stroke, cancer and cardiac disease.

In stroke, clots or injury to blood vessels can prevent proper delivery of oxygen and substrates (mainly glucose) to the brain. The standard treatment is thrombolysis. However, this must be done in a narrow time frame to meet current treatment criteria. Dr. Lee is developing tools to improve the time limitation criteria for treatment. He has developed software, which can measure functional aspects of blood flow to the brain (see Figures 1,2), including risk for hemorrhagic transformation. Taking into account ischemic brain changes after a stroke can lead to more inclusive treatment criteria for thrombolysis. As such, this could lead to reduced disability following stroke, therefore possibly mitigating other severe treatment complications.

Figure 1 – Patient #1 (A) admission non-contrast CT image, (B) cerebral blood flow map (scale 0-150 ml/min/100g), (C) cerebral blood volume map (scale 0-8 ml/100g) obtained 7 hours after stroke onset. Initial CT hypodensity corresponds to area of reduced CBF and CBV (solid arrow) while the dashed area shows an area of decreased CBF with normal/elevated CBV. Without recanalization, entire ischemic area at admission (CBF = 16.48, CBV = 1.81) progressed to infarction on the day 5 non-contrast CT (D). Subtle stripes of isodensity surrounded by the low density of infarction are typical for petechiae in cortex. Patient #2 (E) Admission non-contrast CT image, (F) cerebral blood flow map (scale 0-150 ml/min/100g), (G) cerebral blood volume map (scale 0-8 ml/100g) obtained 157 minutes after stroke onset. Large ischemic area on the admission CBF (dashed arrows) with an area of severely reduced CBV in the deep grey matter (solid arrow). Spontaneous recanalization occurred prior to the 24 hour follow-up CTA. (H) 5-day NCCT confirms infarct in the deep grey matter (matched decrease in CBF and CBV at admission) with progression of some surrounding tissue to infarction. A large portion of the mismatch area at admission (decreased CBF, normal/elevated CBV) recovered and did not show infarction on the 5-day non-contrast CT. Isodense region central within the low density infarction is typical for a hemorrhagic region.
to 7000 copies are currently in use, not only in North America, but also in Asia, Europe and Australia. He also has international collaborations as a result of his expertise in CT perfusion. One of these is with the American College of Radiology Imaging Network (ACRIN), an organization funded by the National Cancer Institute (US). One of his main research commitments was pushing through an application of imaging biomarkers in cancer management, looking at treatment efficacy, treatment response, and early detection. He is now involved with a trial using CT perfusion to look at ovarian cancer, which will hopefully be approved as the first major multi-centre trial of its kind with over 20 sites in the United States. Dr. Lee also constantly has informal collaborations occurring, from working with Italian researchers on analysis of their stroke patient data to getting his software into hospitals in China, though he confesses that that is going slowly. “Having the right contacts is very difficult,” he admits. “It seems as though it’s still not only what you know, but also whom you know.”

Finally and particularly, the golden question: how does he manage to do it all? Dr. Lee didn’t try to sugar coat it: it is always very stressful, and everyone who wants to do well in his or her profession will have this kind of stress. In the past, his strategy was to think: “If only I could get through this one crisis, I will be happy.” Unfortunately, he would have one crisis after another, and this became a problem. Recently he has come to the realization that “Happiness is a journey, not a destination.” This statement, which he now has taped to the wall in front of his desk, was a wakeup call for him. He realized that he could not constantly live from one crisis moment to the next. “You can’t really do this for long without burning out. You have to enjoy each step of the journey while you’re trying to get to your destination. Fortunately, being a scientist or a clinician, you can have this luxury.” He now approaches each day not only as a new problem, but a new learning experience, never having to repeat what he had to do before. He relishes his “Aha!” moments – those that he can reflect on to remind him of learning something new. Having this mindset allows him to enjoy his journey every step of the way, not just at the end.

Ultimately, what does he want in the end? “I just want to translate what is going on with my pencil and paper and animal research. It’s nice if something comes out of all the pipe dreams you have, if your methodology is adopted the world over. If you can see that the impact of what you’re doing means something in a clinical sense.” Dr. Lee chuckled as he shared that sometimes he finds he’s not even acknowledged in papers when his software is being used. “But I can’t complain because the product has been commercialized and this just means people are using it. When what you have toiled for bears fruit, if it is actually helping patients, it makes it easier to enjoy the journey.” Dr. Lee also has the quotation “Genius is only a great capacity for great patience” by Georges-Louis Leclere Buffon displayed on his desk. He explained that he was “a plodder, a late developer.” According to him, he was never someone who was a star upon graduating from his PhD program. Jokingly, he suggests that this Buffon quotation is something to remember in keeping yourself out of depression. But it is also important to keep in mind: perseverance really matters. That is something to keep in mind as we strive to achieve happiness during our own journeys.
Molecular genetics in clinical practice for the rapid identification of pathogenic organisms

Roman Shapiro (Meds 2014)
Faculty Reviewer: Dr. Caroline Hamm (Department of Oncology, Division of Medical Oncology)

A 50 year old male presents to the clinic with a history of fever and cough lasting a week. He has recently immigrated to Canada, and cannot communicate well. Upon examination, he is found to be hypotensive with an elevated heart rate. A chest x-ray is ordered, and it indicates pulmonary infiltrates. This finding, along with the clinical presentation, suggests that the patient has community-acquired pneumonia. He needs treatment, but what is the infection that brought about this episode? What should the clinician do when there is a limited amount of time to find the pathogen?

It is established that timely administration of antimicrobial therapy is critical for good patient outcome. Unless the clinical features and history are very suggestive of a particular causative agent, the therapy must be empiric. The recommendations in this case are to begin with broad-spectrum antibiotic therapy, and to adjust the treatment regimen once laboratory cultures identify the best antibiotics to use. This approach, although logical given the current potential of identifying the causative agent, is fraught with problems. For one, inappropriate initial empiric therapy is an independent risk factor for increased patient mortality and duration of hospitalization. Furthermore, the use of a variety of antibiotics may promote the development of antibiotic resistance among pathogenic organisms. Ideally, once the clinical picture is suggestive of an infectious crisis, rapid identification of the causative agent would allow for targeted therapy that optimizes outcome while minimizing the risk for the development of antibiotic resistance. While current medical technology does not have the rapid identification capacity in all cases of infections, it is progressing steadily towards this goal with the application of molecular genetics in the clinical environment.

**GENOTYPING**

The distinguishing characteristic of every organism must lie in its genes. Two pathogenic bacterial organisms may appear alike in presenting clinical symptoms, on gram stain, and in their growth characteristics, yet be distinctly different and require different treatment. The differences between these organisms that cannot be seen based on culturing and staining alone will be reflected in their genetic makeup. Gene sequencing, therefore, is an excellent approach for the identification of a particular infectious organism from a slew of possibilities. As sequencing technology becomes more efficient, the approach will not only be highly sensitive and specific, it will be rapid and inexpensive. Before this can happen, however, hurdles must be overcome. One is specificity – there must be an identifying genetic sequence for every pathogenic organism. This is no easy task given the large variety of known pathogenic species as well as newly evolving ones. But the automation of gene sequencing coupled with computer processing power allows for the alignment of whole genomes from different pathogenic species in order to identify key differences that can be used to distinguish one infection from another. As these genetic differences are identified, it remains for highly sensitive tools to be developed that can assay for the differences in clinical specimens.

Let us return to the patient with pneumonia symptoms. He is recently immigrated, meaning the infection could have been picked up at his place of origin. One of the most common global human infections is with members of the family Mycobacteriaceae. They can be missed as causes of community-acquired pneumonia because of the absence of readily available rapid diagnostic tests. Recent technological advances have made progress in rectifying this problem. In identifying a mycobacterial causative agent, it would be important to distinguish tuberculous mycobacteria from non-tuberculous mycobacteria (NTM). Furthermore, it would be important to determine the particular subspecies as this can be critical in identifying the source of the infection. Taking advantage of known genomic data for the mycobacterial organisms, multiplex PCR is one assay that can be used.

**MULTIPLICITY PCR**

The principle of the polymerase chain reaction (PCR) is to specifically amplify a target DNA sequence using thermostable enzymes such as Taq polymerase or Pfu. The sequence to be amplified is localized between two DNA primers that hybridize to the target DNA. The major advantage of this technique in clinical diagnosis is that it requires very little starting material for amplification. For infections with mycobacteria, this could allow for identification without the culturing step that is so time-consuming. Unlike traditional PCR techniques whereby a single target sequence is amplified, multiplex PCR is able to specifically amplify several target sequences in one reaction. This poses several technical challenges because every sequence in the reaction requires an optimal temperature and buffer for amplification. Furthermore, once the reaction conditions are optimized it is unnecessary to distinguish one amplified sequence from another. When these challenges are overcome, it is possible to amplify several species-specific genetic sequences, including testing for the presence of antibiotic-resistance genes.

In the case of mycobacterial infections, multiplex PCR can distinguish between M. tuberculosis complex (MTC) and NTM based on known genetic differences. These have been tested on clinical specimens, yielding high sensitivity and specificity. Other multiplex PCR assays exist that can distinguish between the NTM subspecies, in particular those of the Mycobacterium avium complex.

The major advantage of all of these assays is the sensitivity and rapidity of PCR, allowing for very small amounts of DNA sequences to be detected within several hours. However, results must be interpreted with caution, as the possibility of false negatives is considerable when running several PCR amplification reactions at
once. In addition, PCR may be prone to false positive results since very minute amounts of DNA may be amplified considerably.22-25

SPOLIGOTYPING

Whereas multiplex PCR has found a use in distinguishing MTC from NTM and identifying subspecies of the NTM group, spoligotyping is a method that has been developed and used to identify and genotype strains of bacteria in the MTC group.26-28 The method is based on the presence of conserved direct repeat (DR) sequences separated by non-repeating spacer regions in the genomes of these bacteria. Different strains vary in the number of such DRs as well as the length and sequence of the spacer regions.22 By designing oligonucleotide primers that hybridize to conserved regions within the DRs, it is possible to run a PCR reaction that yields a large variety of amplified DNA sequences of different sizes (Figure 1A). The pattern of these amplified DNA sequences is characteristic of a strain of MTC bacteria (Figure 1B).22

![Figure 1. The basic principles involved in spoligotyping. A Two juxtaposed blue rectangles indicate a conserved direct repeat (DR) in the genome of a particular strain of Mycobacterium tuberculosis complex. Only a subset of DRs are shown for clarity, whereas there would be many more in the actual organism. PCR primers are designed to hybridize at particular locations within the DRs as shown by the arrows. An arrow pointing to the right is a forward primer, while one pointing to the left is a reverse primer. The primers may hybridize at any of the DRs, and the resulting possible PCR products are indicated. The red square indicates a specific sequence in the first spacer region, while the yellow rectangle indicates a specific sequence in the second spacer region. B The PCR products from A are hybridized to an array containing immobilized oligonucleotides whose sequences correspond to a spacer region. Examples of this are demonstrated with the red square and yellow rectangle from A, whereby the sequence in each of the coloured rectangles is recognized by a specific oligonucleotide probe on the array. Hybridization between a PCR product and the array is indicated by a blank circle on the spoligotype. Each row on the array corresponds to hybridization signals from a single strain.](image)

Spoligotyping has been applied to clinical specimens.23,24 It is a rapid assay because it relies on PCR, and studies have shown that it is sensitive and specific to MTC infections.22,25 It has the additional advantage of being able to distinguish strains of M. bovis from those of M. tuberculosis, a difficult task with traditional techniques.22 Much of the use of spoligotyping has involved contact tracing in instances of suspected MTC infections so as to limit the spread of infection.22,25 Further studies are undergoing to definitively determine its use in clinical diagnosis and genotyping of MTC infections.

REAL-TIME PCR (rtPCR) WITH HIGH-RESOLUTION MELTING ANALYSIS (HRM)

A spoligotype performed on clinical isolates from the pneumonia patient revealed a pattern consistent with a highly virulent species of Mycobacterium belonging to the Beijing lineage.26 This lineage is known to be highly transmissible and often drug-resistant, requiring specific treatment regimens that differ from other mycobacterial infections.27 For the purposes of rapidly confirming an infection with this pathogen, one assay that can be used is rtPCR with HRM analysis. This assay relies on the presence of a single-nucleotide polymorphism (SNP) corresponding specifically to the Beijing lineage that was identified using methods such as spoligotyping and resulted in nearly 100% sensitivity and specificity as long as there was a sufficient load of bacterial organisms in the sputum.26 It has the additional advantages of being very rapid and relatively inexpensive to perform.29 When clinical isolates from the patient with pneumonia symptoms were subjected to the assay, the presence of the Beijing lineage of M. tuberculosis was confirmed.

CONCLUSION

The assays mentioned here in the context of a possible infection with a member of the family Mycobacteriaceae are intended to demonstrate the utility of the gene sequence in rapid clinical diagnosis. Improvements in the efficiency of gene sequencing as well as bioinformatics analysis are generating a large amount of data regarding specific genetic targets for each pathogenic organism that could be assayed by techniques based on PCR. Some of these techniques, including multiplex PCR, spoligotyping, and rtPCR with HRM demonstrate that assays can be designed and implemented in a clinical setting to identify particular infectious organisms. As these assays become less expensive and standard in all microbiological laboratories, their rapidity will allow for the use of appropriate targeted therapy in order to optimize patient health while minimizing the risk of the development of antibiotic resistance.
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The application of three dimensional laser surface scanning and imaging in a case of total nasal reconstruction

Michal Brichacek (Meds 2013)
Faculty Reviewer: Dr. Douglas C. Ross, MD MEd FRCSC (Department of Plastic Surgery)

The earliest reports of reconstructive surgery are presented in an ancient Egyptian medical text dating back to 1600 B.C. that describes the treatment of nose, ear, lip, and chin injuries. However, it was Indian surgeons who are credited with employing the first definitive plastic surgery techniques, with specific reports describing Sushruta performing the first rhinoplasty in 500 B.C.

Plastic surgery developed at a time when there was a tremendous need for reconstructive correction of catastrophic deformities after World War I. Never before had surgeons been presented with such extensive injuries that required complex and innovative reconstructive procedures. The Greek work plastikon, meaning to be capable of being molded, would become used to describe a field where surgeons molded those devastated by the injuries of war.

As technological advances have improved protective gear and medical advances have improved advanced trauma care, the proportion of soldiers dying in combat as a result of their injuries has markedly decreased. Soldiers are currently surviving injuries that would have killed them in any previous conflict, but as a result they are surviving with massive facial and cranial injuries that require complex reconstruction.

PATIENT PRESENTATION
M.F. is a 21-year-old African American war veteran who sustained significant facial and body trauma in Iraq. He was involved in a situation where a vehicle exploded and he ultimately received multiple soft tissue injuries and facial fractures. This resulted in amputation of his left arm and left him with an extremely flattened nose. He presented to Johns Hopkins Hospital seeking nasal reconstruction.

Nasal reconstruction would have to be performed through a midline forehead flap, where a large flap of skin is taken from the middle of the forehead, rotated, and folded down to create a new nose. Due to the lack of underlying cartilage to provide support for the nose, rib cartilage would have to be harvested and a nasal subsurface would have to be recreated. Additionally, a radial forearm free tissue transfer would need to be performed to provide a vascularized internal skin lining for the distal half of the nose.

However, the patient was informed that he was not a good candidate for this procedure due to the need for multiple stages and his elevated risk for failure. Due to his significant facial soft tissue injuries, it is unlikely that the blood supply to this flap would still be intact, which means there was a significant chance of it failing and becoming necrotic.

Despite these risks, the patient felt very strongly opposed to a nasal prosthesis and expresses his desire for surgical reconstruction. Being aware of the significant risk of complications and the need for multiple stages, the patient elected to proceed with surgical reconstruction.

TECHNOLOGICAL PLANNING
The nose is a complex three-dimensional object that must be in harmony with the remainder of the face. The challenge with this case was to create a new nose from nothing. Extensive facial soft tissue injuries the surgeon can use the remnants of the nose as a guide in order to create a new nose. In this case, even the cartilage, which serves as a framework for the nose and could act as a guide, was absent.

It was decided that technology could help with this problem by providing the surgeon with two types of guides to aid him in the reconstruction: a two-dimensional template showing the complex area of skin that must be taken as a flap from the forehead, and a three-dimensional plastic mold showing the final shape that the surgeon should strive to achieve during the creation of the subsurface framework of the nose.

The Art as Applied to Medicine division at Johns Hopkins began by taking a plaster mold of the existing condition of the patient’s face. Using this and photographs provided by the patient’s family, a wax model was created of the patient’s nose before his injury. This wax model was then sent to Direct Dimensions Inc. (Owings Mills, Maryland) for surface scanning and digital manipulation of the resulting 3-dimensional model.

The mold is scanned using a laser surface scanner (Perceptron Laser Scanning Systems, Plymouth, Michigan) that creates a three-dimensional point cloud of data that is converted into a resulting three-dimensional computer model using PolyWorks software (Innovmetric Software Inc, Quebec City, Quebec, Canada). In the same manner, the patient’s existing face was then laser surface scanned and created into a three-dimensional computer model (Figure 1).

Figure 1. Three-dimensional laser scanning is used to create a digital model of the patient’s face in the original condition.
DISCUSSION

More recently, the implementation of three-dimensional object scanning and visualization has been applied in the medical field to provide great benefit to both surgeons and patients alike. By applying this technology, a radiation shield was created to protect adjacent tissues in the treatment of head and neck cancers. 6 The creation of three-dimensional breast models through imaging has become possible in order to help guide surgical management. 7 In more of a mainstream application, surgeons can show patients expected results after surgery in a dynamic three-dimensional view using imaging systems such as the Canfield Vectra M3 (Canfield Scientific Inc, Fairfield, New Jersey) or the Axis Three XS200 (Axis Three Inc, Boston, Massachusetts).

The patient in this case presented with an extremely challenging defect due to a combination of significant facial soft tissue trauma, multiple facial fractures, as well as the absence any subsurface nasal framework. Cases of total or subtotal nasal reconstruction are particularly challenging as the reconstructed structure must be vascular in order to heal predictably, stable in order to withstand the scar contracture and maintain symmetry, yet at the same time be functional enough to be acceptable to the patient’s lifestyle. 8

The construction of an abstract three-dimensional object such as the nose from a flat segment of tissue is extremely difficult in the absence of a subsurface framework. By using novel technological innovations involving three-dimensional laser surface scanning and imaging, the likelihood of achieving a favorable result is potentially increased. The creation of a custom made translucent template for use during the procedure is achieved by the combined efforts of the patient, the anaplastologist, and the surgeon. 9 The template is created such that it anticipates the thickness of the skin that will be provided by the forehead flap and serves as a surgical guide for the surgeon in the creation of the subsurface framework of the nose.

The application of three-dimensional laser surface scanning and modeling is a powerful tool that can be utilized in order to aid in the visualization of challenging defects as help in the surgical reconstruction of these defects. Although still in its infancy, as this technology evolves and its full potential becomes realized, it will surely find many more applications in medicine and particularly in the field of reconstructive plastic surgery.

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The three-dimensional model of the pre-injury nose was then superimposed into the proper position on the patient’s injured face, showing a three-dimensional rendition of what the ideal reconstruction would achieve. From this combined model engineers were able to determine the dimensions of a three-dimensional model molded in clear plastic to be used as a surgical guide, and using complex mathematical simulations engineers were able to unroll the complex shape of the three-dimensional pre-injury nose onto a flat two-dimensional surface. (Figure 2) This served as a guide to the surgeon during the procedure for both the shape and size of the flap of tissue to be harvested from the forehead.

Ultimately, the patient required six separate procedures to complete his reconstruction. His recovery was complicated by an MRSA infection as well as a small degree of distal flap necrosis. Fortunately, total flap necrosis did not occur and the remainder of the flap was salvaged. The patient was extremely pleased with the result and was extremely satisfied that he was able to have both the form and function of his nose restored (Figure 3).

Figure 2. A three-dimensional translucent plastic model served as a guide for the nasal structure during the procedure, while the two-dimensional shaped served as a guide for harvesting of the flap from the forehead.

Figure 3: The patient shown from a side-view preoperatively (a) and postoperatively (b).
Candles to computers: the story of minimally invasive procedures

Pencilla Lang (Meds 2011)
Faculty Reviewer: Dr. Terry Peters, PhD (Department of Medical Imaging, Medical Biophysics, and Biomedical Engineering)

For many people, the words “minimally invasive surgery” conjure up visions of medical robots, MRI machines and nanotechnology. Although we frequently herald minimally invasive procedures as the future of surgery, the concept is much older than most of the technology it is associated with. It is an ancient vision enabled by many technological developments unrelated to medicine—the introduction of electricity, digital video, video game graphics, and industrial robots have all played major roles in shaping the way surgery is practiced today.

WORKING IN THE DARK

The first documented attempt to “look inside” the internal organs was described by Hippocrates (460-375 BCE) in a passage referring to a rectal speculum (Figure 1). Roman medicine also describes similar instruments, including a three-bladed vaginal speculum from the ruins of Pompeii. The initial attempts to make a diagnosis by examining internal body orifices all faced the same problem: inadequate lighting. Almost all of the early tools were designed to maximize the amount of external ambient light available for direct visualization of internal structures.

Figure 1. Example of a rectal speculum similar to the one described by Hippocrates. Image courtesy of the Historical Collections & Services of the Health Science Library, University of Virginia.

The first attempt to design a tool specifically guiding light to the target was an instrument called the “Lichtleiter” designed in 1806 by Phillip Bozzini (1773-1809), a young obstetrician (Figure 2). This device was an elongated thin funnel that could be passed into an orifice. The end of this device was a stand carrying a candle for lighting. Reflectors directed candlelight down the funnel. Many funnels of different sizes could be used, and it could help examine the bladder, rectum, vagina and nasopharynx. Although Bozzini is now credited with creating the first endoscope, the device was poorly received. The candle produced heat and smoke leading to burns, the device could be painful to introduce, and lighting was still inadequate. In the following years, attempts were made to improve the design by many people including Pierre Segalas (1792 – 1874), John D. Fisher (1798 – 1850), and Antonin J. Desormeaux (1815 – 1894). Desormeaux was the first to use an endoscopic instrument for therapeutic purposes when he used his endoscope to remove a papilloma from the urethra. Eventually, it was realized that “to light up a room one must carry the lamp inside”, and the idea of the endoscope itself as a light source was born.

Figure 2. Construction drawings of the “Bozuniform Lichtleiter”. Images courtesy of the Medical University of Vienna, Department of History of Medicine.

With the invention of the incandescent light bulb by Thomas Edison (1847-1931), endoscopy began to be taken more seriously by medical practitioners. There were simultaneous developments of cystoscopy, thoracoscopy, and gastroscopy. Many modifications and improvements were made to endoscope designs in the 20th century, including the use of insufflation by Georg Kelling, and the development of flexible fibre-optic instruments, pioneered by Basil Hirschowitz (1925).

FROM DIAGNOSIS TO TREATMENT

While therapeutic applications of laparoscopy began in the 1930s, the development of the computer chip television camera was a key piece of enabling technology for the use of endoscopy to guide surgery and therapy in addition to diagnostic uses. Video-endoscopy allowed endoscopic surgeons to stand upright and use both hands to carry out the procedure. In addition, the entire operating team was able to view the magnified image on a monitor. In the 1980s, CCD cameras became small enough that it became possible to integrate them into tools. In conjunction with these changes was the development of specialized tools for endoscopic procedures. These typically had a form similar to traditional tools, but with a long straight shaft allowing insertion into the body cavity.
SEEING “WITHIN”

While endoscopes allowed surgeons to see inside body cavities, their vision was still limited to the outer surfaces of organs. Frequently tumours and other abnormal tissues were buried under a layer of normal tissue. Physicians had to “hunt” around for their targets, usually in a trial-and-error process that could result in the removal of large sections of normal tissue. The discovery of X-rays in 1895 by William Roentgen allowed physicians to see inside tissues for the first time. X-rays were immediately used for diagnostic purposes, and early images could possible.8

The key developments of video-endoscopy and interventional fluoroscopy as these technologies were applied to a range of different problems. While these modalities continue form the mainstay of intra-operative procedures. Some examples include:

- intra-operative MRI for brain tumour removal9, epilepsy surgery10, catheter-based aortic valve placement11, catheterizations12, and stenting of aortic co-arctation13
- intra-operative CT for brain lesion and sinus surgery14
- ultrasound-guided breast surgery15

Cost, acquisition speed and difficulty in making the imaging systems OR compatible remain barriers to intra-operative CT and MRI guidance of surgical procedures. As real-time imaging has grown in popularity, it has become increasingly important to develop new surgical tools that do not introduce artifacts into the images. This requires changes in both the mechanical design and the materials used.

ROADMAPS

There were also early attempts at minimally invasive surgery without the use of any real-time imaging to locate internal structures. In lieu of direct visualization, a model was used to help the physician estimate the location of internal structures. A paper published by Horsley and Clark (1908) described a stereotactic device that could be affixed to a subject’s head and aligned using external landmarks such as the auditory canals and orbital rims (Figure 3).16 This alignment device provided a coordinate system that could be used to guide the introduction of electrodes into the skull. This was the first time an attempt was made to correlate a model of the internal anatomy with the patient in physical space. Horsley and Clark assumed that brains possessed a constant structure and that every brain is the same as another, and that specific internal structures could be targeted by simple coordinates. Although this assumption is incorrect, the design of the stereotactic frame was a major breakthrough that would later allow pre-operative images to be aligned with the patient for procedure guidance (The invention of stereotactic frames actually preceded the invention of CT and MRI).

The ability to bring models and images into the patient’s coordinate system was an important step in allowing models to be used for planning and guidance of procedures. With the invention of CT scanners in 1973 (Hounsfield, 1919 – 2004), CT stereotactic surgery became possible. The use of pre-operative images to guide interventions is a current area of research of research and growth (Figure 4). Examples of clinically used systems include the Carto XP EP Navigation System (merges CT or MRI with electroanatomical information for catheter ablations) and the Medtronic Stealth Station (merges pre-operative CT and MRI images with tracked surgical tools and intra-operative images).17,18

An explosion of new techniques and procedures followed the key developments of video-endoscopy and interventional fluoroscopy as these technologies were applied to a range of different problems. While these modalities continue form the mainstay of intra-operative procedures, recent years have seen the exploration of many other modalities for the guidance of intra-operative procedures. Some examples include:

Figure 4. Example of multimodality imaging showing overlay of CT and US images of the aortic root.

MOTION AT A DISTANCE

With minimally invasive access to internal structures through small ports, tools became more difficult to control and navigate. In response to these challenges surgical robots were developed. Adapted from industrial designs, the first medical robots were designed to hold a fixture at a specific location in space.19 The first robot used in surgery was an industrial robot called the PUMA 560 that held a fixture next to a patient’s head to locate a biopsy tool in neurosurgery (Figure 5).20 However, shortly after this initial breakthrough, the company that manufactured the PUMA 560, Unimation Limited, was sold to Westinghouse Limited, which refused to allow the robot to be used for surgical purposes on the basis that it was unsafe.21 Soon
companies began developing robotic systems specifically for medical applications. The first to be tried on human patients was developed at IBM and called the Robodoc. It was used to hold a rotating cutter that reamed out the proximal femur to take a prosthetic implant.\(^{22}\) Today, medical robots are used routinely for many procedures, including coronary artery bypass grafting and transpubic radical prostatectomy.

Surgical robots can provide many advantages, including the ability to move in predefined 3D paths, the ability to hold tools for long periods of time rigidly and without tremor, the ability to make precise micromotions and the ability for tele-operation. However, surgical robots can also be bulky, expensive, and difficult to navigate. Today it is still unclear whether surgical robots provide clinical advantages over computer aided surgery, in which navigation and placement of surgical tools are aided by images and measurements provided on a computer, but the tools remain manually controlled by the surgeon.

**LOOKING FORWARD**

Since the 1980s there has been an explosive interest in minimally invasive procedures and the technology behind it. As physicians become more comfortable and confident with the new technology, they are attempting increasingly complex procedures minimally invasively—spurring on the engineering of new devices and systems. Meanwhile, the study of interactions between surgeons and these tools has developed into a research area of its own. What does the future hold? Multimodality imaging platforms, steerable robots, nanobots and augmented reality?

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