EMJ INNOVATIONS

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"Publication day, as always, is a special celebration of the hard work carried out by the contributors for this journal"

Spencer Gore, CEO

Editorial Board

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Aims and Scope

The European Medical Journal (EMJ) is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

EMJ also publishes 16 therapeutic area journals, which provide concise coverage of salient developments at the leading European congresses. These are published annually, approximately 6 weeks after the relevant congress. Further details can be found on our website: www.emjreviews.com

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EMJ is supported by various levels of expertise:

- Guidance from an Editorial Board consisting of leading authorities from a wide variety of disciplines.
- Invited contributors are recognised authorities from their respective fields.
- Peer review, which is conducted by EMJ's Peer Review Panel as well as other experts appointed due to their knowledge of a specific topic.
- An experienced team of editors and technical editors.

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All peer review is double blind.

Following review, papers are either accepted without modification, returned to the author(s) to incorporate required changes, or rejected.

Editorial staff have final discretion over any proposed amendments.

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We welcome contributions from professionals, consultants, academics, and industry leaders on relevant and topical subjects.

We seek papers with the most current, interesting, and relevant information in each therapeutic area and accept original research, review articles, case reports, and features.

We are always keen to hear from healthcare professionals wishing to discuss potential submissions, please email: editorial.assistant@emjreviews.com

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Innovations 4.1

EMJ 4.4

A celebration of triumphant advancements throughout an outstanding year.

VIEW ALL JOURNALS ←

Welcome

Happy new year and welcome to EMJ's first publication of the new decade. Taking you straight to the biggest stories, I present to you *EMJ Innovations*, offering an in-depth interview, features, and much-anticipated peer-reviewed articles. Stay up to date with the latest advances in medical research, including our exclusive coverage of the debate titled "The Quest for the Perfect Human...? A Debate on the Implications of Human Genome Editing" held by The Royal Society in partnership with Bristows in London, UK.

Within this eJournal you will discover more about the era of immersive health technology in the paper by Bremner et al., which highlights the journey technology has taken in the medical industry, from visionary to a part of day-to-day life. Other articles for recommended reading include the paper by Dr Jatinder Bali and Dr Ojasvini Bali on 'Artificial Intelligence Applications in Medicine: A Rapid Overview of Current Paradigms' and the review by Dr Maheswari Mukherjee entitled 'E-learning in Pathology Education: A Narrative Review and Personal Perspective.'

Our editorial team also had the pleasure of interviewing the pioneering medical expert Lara Mott, CEO and Co-founder of the junior doctor feedback app ImproveWell. Lara spoke to us about her career in the healthcare industry and the ability of her ImproveWell system to prioritise listening to healthcare staff to unite the international healthcare workforce in the future.

Publication day, as always, is a special celebration of the hard work carried out by the contributors for this journal, but this one feels especially profound as we anticipate the forthcoming year, which is to be our largest ever in terms of publications. With brand new journals to bring you the latest advances in microbiology, infectious diseases, and radiology, as well as the launch of our new American journals in haematology, dermatology, cardiology, oncology, diabetes, and rheumatology, we hope you will share our excitement for the release of these publications and for all that they will achieve.

Best wishes,

Spencer Gore

Chief Executive Officer, EMG-Health

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Contribute your ideas on current healthcare conversations: submit your blog today.

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Foreword

Dear colleagues

Welcome to the newest edition of the *EMJ Innovations* eJournal. Innovations in healthcare continues to encompass a range of ground-breaking developments across many therapeutic areas, from advancements in day-to-day practice to artificial intelligence. My editor's pick in this edition is Bremner et al.'s review paper "The Era of Immersive Health Technology," which looks at how immersive health is revolutionising many aspects of healthcare, including techniques and research. Within the paper, Bremner and his co-authors consider four main areas of immersive health technology: artificial intelligence, machine learning, augmented reality, and virtual reality.

Within healthcare innovation, E-learning is a growing realm that cannot be ignored, and it is being used to transform education in healthcare through internet programmes. Mukherjee delves into this topic in the paper "E-learning in Pathology Education: A Narrative Review and Personal Perspective." For this paper, Mukherjee reviewed literature on E-learning in pathology education and found that usage is widespread, but there was call for more studies on impact on pre and post-test scores, as well as the cost-effectiveness of this game-changing technology.

Social media is integrated into every part of our lives, and healthcare is not exempt from this. In the feature "Social Media for Clinical Trial Recruitment: How Real is the Potential?," Reuter considers the challenge of clinical trial recruitment and how this can be improved with the adoption of social media. She goes on to consider the barriers to implementing social media-based recruitment, such as the suitability of the method for all demographics and conditions. A challenge is also posed when usage of social media across different countries is reviewed, and it is clear that rates differ around the world.

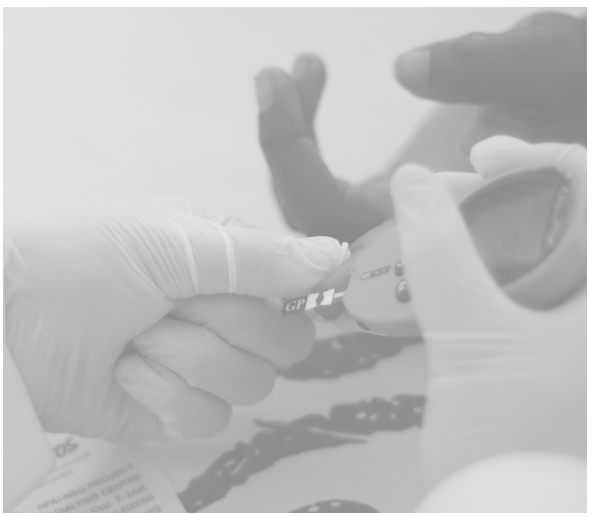
As always, I hope you will enjoy the thought-provoking articles provided in this new edition of *EMJ Innovations* and look forward, as much as we do, to seeing how innovation changes healthcare even more in 2020.

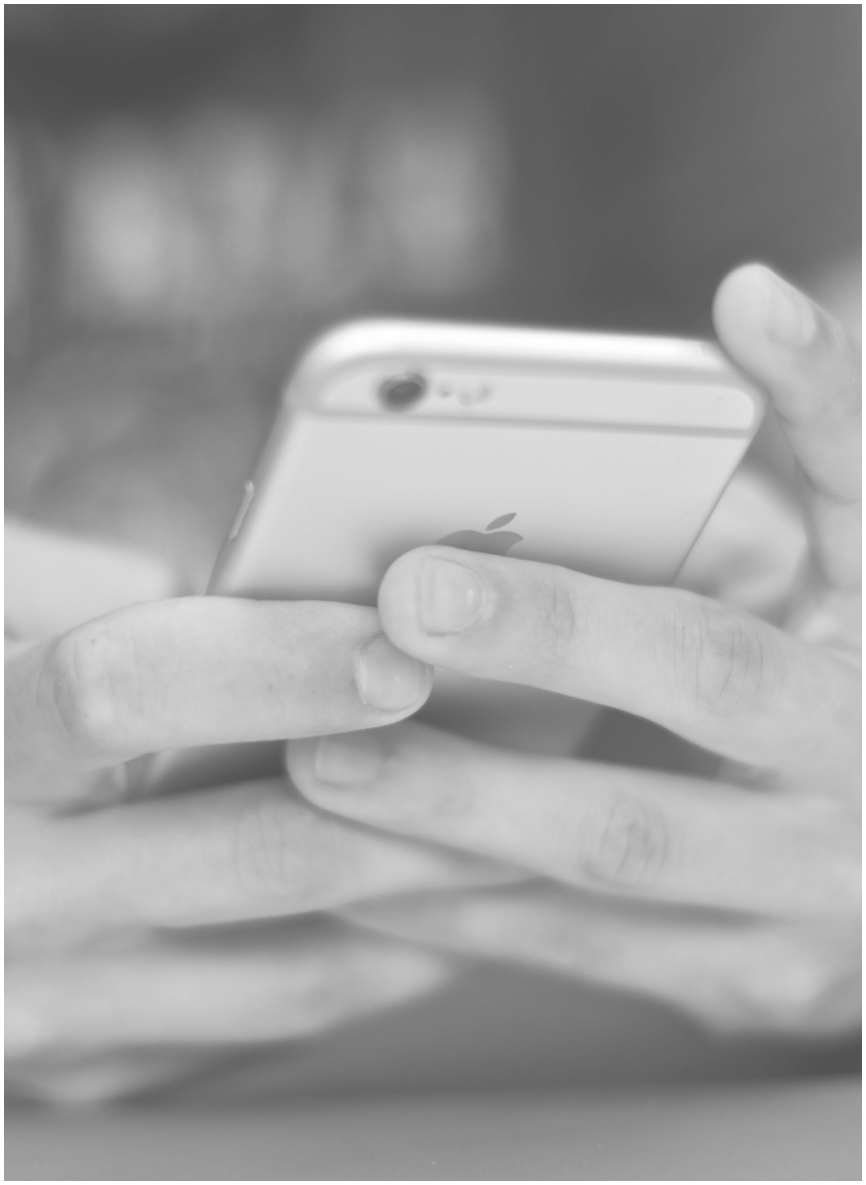
Best wishes,

Prof Mike Bewick
IQ4U Consulting, UK

The Year in Innovations

A series of feature articles written by our in-house editorial team reviewing some of the year's most exciting developments in this burgeoning field of study.





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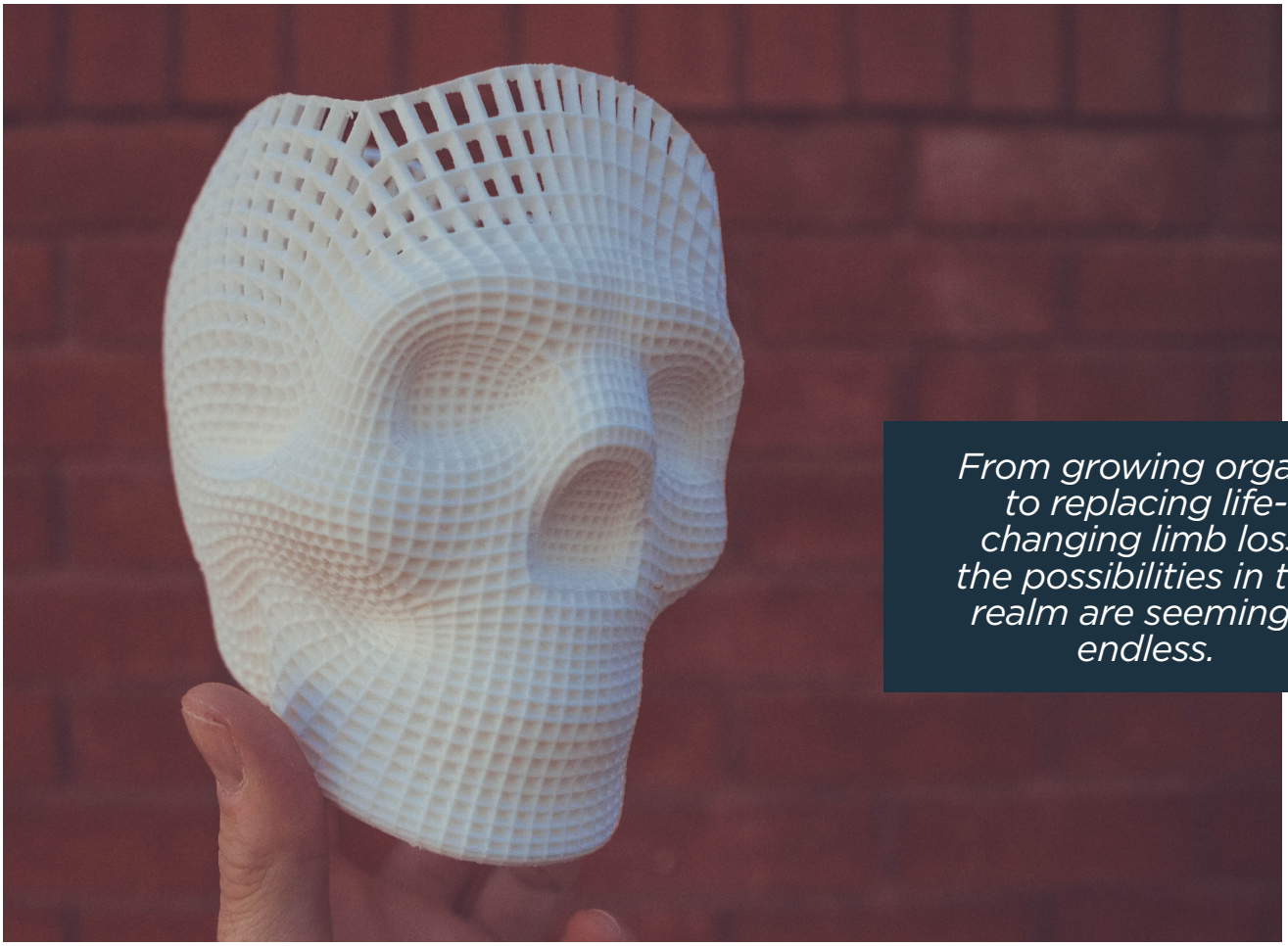

From growing organs to replacing life-changing limb loss, the possibilities in this realm are seemingly endless.

The Era of Three-Dimensional Printing

Kirstie Turner
Editorial Assistant

Introduction

Amongst the plethora of ground-breaking innovations in healthcare, one standout feat of engineering is addressing an abundance of conditions: three-dimensional (3D) printing. In the >35 years since Chuck Hall produced the first 3D printer, and with it the world's first printed item, an eye wash cup, 3D printing has come a long way in many industries, from a working gun to an acoustic guitar. And now? The technology is being harnessed for fertility preservation, healing burn victims' skin, and individualised prosthetics, amongst many more areas in healthcare.

Fertility Preservation: Ovary Printing

It is just 2 years since researchers first used a 3D printer to produce a viable ovary that was implanted in mice, who went on to produce offspring.[1] Gelatine ink was used to print exact patterns until a 3D model is constructed, designed to replicate a natural ovary. Ovary follicles were then placed into the printer model; these contain eggs and hormone-secreting cells. When implanted into mice, their blood vessels began attaching to the ovaries, which were then able to function.

The eventual goal is to replicate this in humans, providing an option for women who have undergone treatments that cause sterility, such as chemotherapy. While fertility preservation options have been improved by the advent of ovarian tissue freezing before treatments, this has considerable limitations, such as a time limit. For human application, ovary follicles would be

removed from females prior to chemotherapy. Once the scaffolding has been printed, this tissue could be added, before implanting the 3D ovary structure into the patient post-chemotherapy.

Skin Grafts for Burn Victims

In the realm of dermatology, a team in the USA has developed a printer that could take over from skin grafts in the healing process of burn wounds. This technique involves scanning the wound to assess the size and depth; then, this data is processed to create skin cells that are printed to cover the burn.[2] The printer, similarly to the ovary device, uses ink to structure the skin, which in this case is made from the patient's own cells.[3] This reduces the chance of the new skin being rejected. A biopsy is taken, harvesting fibroblast and keratinocyte cells. This sample is then used to grow more cells which go on to form the ink.

Technologies such as this could remove the need for skin grafts, which can often result in a traumatic healing process and substantial scarring, and can be hindered by a lack of healthy skin on the patient's body to harvest the graft. This research, again completed in mice, is now destined for human trials, with the eventual goal of treating burn wounds, amongst other complicated wounds that are difficult to heal.

Prosthetic Limbs

Natural materials, such as cells and gelatine, are not the only materials being sourced for 3D printing; technology that uses man-made materials is also being used in areas such as prosthetics. This is not only offering a quicker turnaround time on creation of prosthetics but can considerably reduce the cost of the traditionally expensive prosthetic options. Printing can also offer a completely customised option, increasing comfort and usability for the patient.[4]

Some 3D printer options are innovating this even further, such as Limbitless Solutions[5] who are trialling prosthetic arms which have muscle-flexing built in, allowing guided movement in the arm. The arms are created from acrylonitrile Butadiene Styrene plastic, offering a lower production cost, increasing their potential reach. They even personalise the arms they create for each child so that it is completely individual and helps them to feel more confident.

Conclusion

These are just a handful of examples from the ever-growing world of 3D printing within healthcare, which is offering innovative solutions across many therapeutic areas. While much of the research is still at the stage of animal trials, there are some promising results in humans as well. From growing organs to replacing life-changing limb loss, the possibilities in this realm are seemingly endless.

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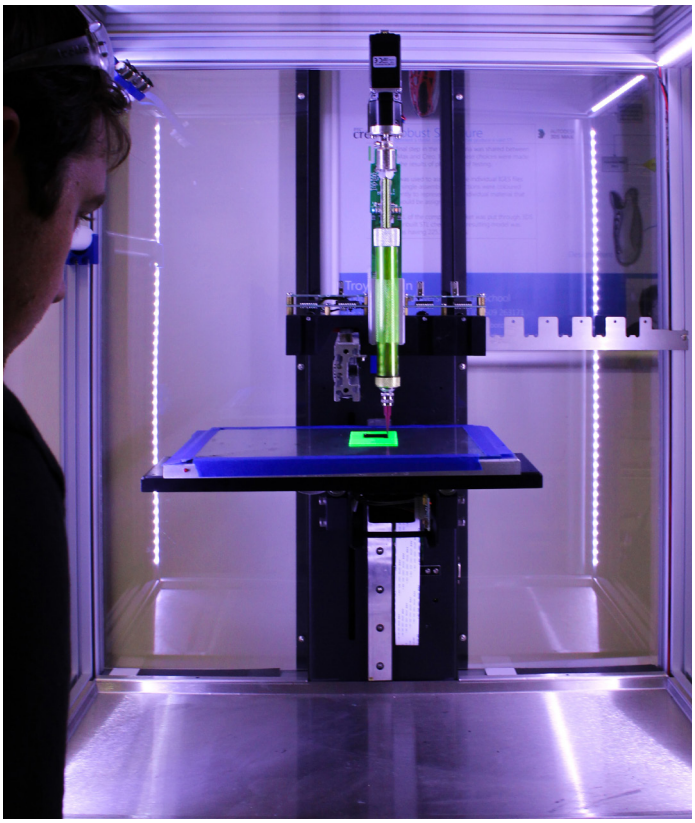


Intellectualising the Artificial Pancreas

Lenos Archer-Diaby
Editorial Assistant

Introduction

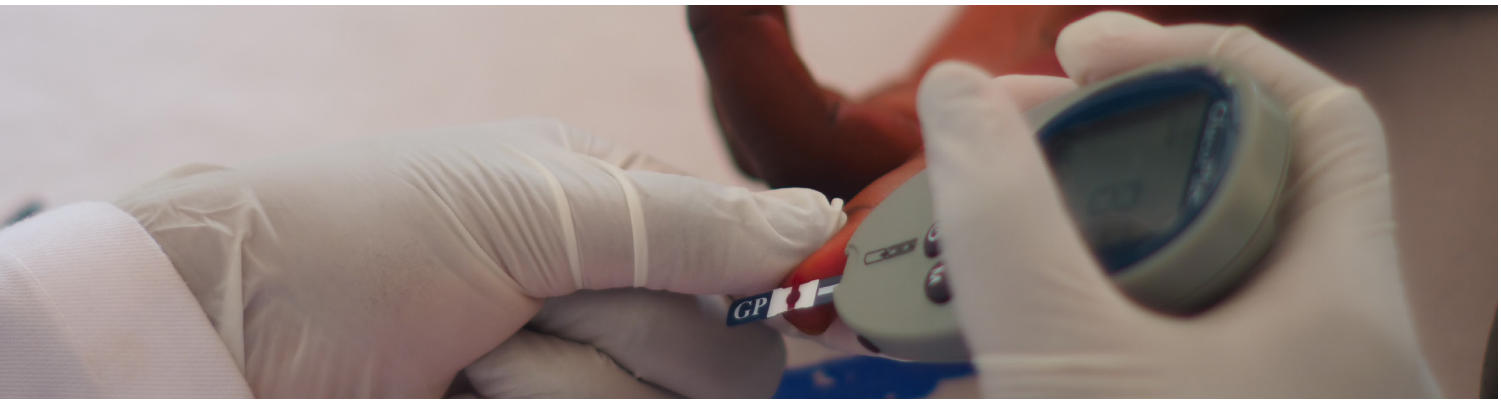
In 1500 BC, clinical features similar to diabetes were described by the ancient Egyptians.[1] True understanding of diabetes however, including the role of the liver in glycogenesis and the concept of the disease being causative of excess glucose production, only came to light in the early 19th century. In 1889, professors Josef von Mering and Oskar Minkowski identified the pancreas as the causative organ,[1] prompting various animal experiments which resulted in the extraction of insulin in 1921.[2] The discovery of insulin and its appliance has saved the lives of millions of patients, and the drug is now available in various forms including ultra-rapid and ultra-long acting. Additionally, insulin can be administered using pens and pumps, allowing patients to take autonomy over their condition management.

Despite these trailblazing discoveries and innovative methods of appliance, diabetes is still a major global health problem. Current International Diabetes Federation (IDF) statistics indicate that every 8 seconds someone is estimated to die from diabetes or its complications, with 50% of those deaths occurring in individuals under the age of 60 years.[3] Combined with the fact that diabetes is a major cause of blindness, kidney failure, heart attacks, stroke, and lower limb amputation,[4] these harsh statistics unearth the global burden of the disease and highlight the importance of improving diabetes awareness, diagnosis, and treatment. However, considering that >425 million people worldwide are currently affected by diabetes,[5] a greater emphasis needs to be placed on the development of novel treatment approaches.

The chronic autoimmune disease Type 1 diabetes mellitus (T1DM) is characterised by insulin deficiency as a result of T-cell mediated pancreatic β-cell destruction[6] and its treatment requires consistent doses of insulin through multiple daily injections or continues subcutaneous insulin infusion using a pump. Management of the disease places a heavy burden on the patient, requiring constant adherence to self-care behaviours, including scheduling meals, counting carbohydrates, and monitoring blood glucose levels.[7] Optimism does exist for the future however, in that artificial intelligence (AI) is a promising and rapidly growing field posing great potential in its application to diabetes research.

The Artificial Pancreas

Research teams around the globe have been working on replicating the pancreas function for years. Patients with diabetes are now presented with a continuous glucose monitor, a small sensor inserted under the skin which monitors the accumulation or deficit of the simple sugar. Coupled with an insulin pump, which can continuously provide insulin to the patient through a catheter that sits under the skin, this system is known as an 'artificial pancreas'. Equipped with a controller that can be embedded into one of the devices or to a smartphone, the patient is able to control insulin secretion levels using this 'open loop' system; however, this system still requires the patient to announce meals and calculate required insulin doses. The newest artificial pancreas systems are considered 'closed loop', rendering self-management by the patient obsolete and



enabling software to receive and interpret signals from the monitor, determining the required amount of insulin, and instructing the pump to administer. One might believe that all hurdles have been overcome with this system; however, running a closed loop artificial pancreas has proven challenging such as the fact that meals cause a faster response in blood glucose concentrations than insulin delivered causing a lag in the reading.

Meal Detection Technology

Taking a further step forward, researchers at Stevens Institute of Technology, Hoboken, New Jersey, USA, have developed a system capable of detecting when a patient is eating and calculating the amount of consumed carbohydrates with unprecedented accuracy and speed. This allows patients with continuous glucose monitoring systems to be administered the correct insulin dose closer to the time it is needed, reducing the chances of dangerous fluctuations of blood glucose levels. Samantha Kleinberg, Associate Professor at Stevens Institute of Technology, stated: "This brings us a step closer to the holy grail – an 'artificial pancreas' that can quickly detect glucose changes, and correct them with an insulin pump, without the user having to do anything."

The Always Learning Artificial Pancreas

The way individuals respond to changing levels of carbohydrates and their response to insulin is complicated, difficult to model accurately, and differs greatly from person to person. Rather than trying to explicitly understand the exact model for how bodies react to insulin and carbohydrates, and incorporate an 'all-for-one' approach, AI and machine learning may hold the keys to a different type of solution. Provided that enough data is available, machine learning is able to establish patterns within the date and make predictions from these. Continuous glucose monitors generate robust quantities of data and present an ideal symbiosis. The data from various patients with diabetes can be used to train the AI algorithms which can then be further implemented into the closed-loop artificial pancreas system. Because the system will continue to generate more individualised data, it can continue to learn, and each patient's artificial pancreas can customise itself to the patient's particular reactions over time. Only when this has been accomplished can we truly refer to it as an artificial pancreas.

Conclusion

Creating a continually improving self-regulating system is ideal, yet it is important to consider its safety. How can we ensure no errors have snuck themselves into the algorithm? As it stands, these systems will likely require careful monitoring by patients, doctors, and potentially the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). Furthermore, because AI cannot be listed as a medical device, would FDA jurisdiction be feasible? If an accident occurs, who is to take blame, the device manufacturer or the AI manufacturer? A key attribute of AI is its potential to analyse data, interpret it, and make decisions based of it, while continually learning from every intermission. On the downside, understanding the basis on which AI makes decisions will prove challenging because we would have to analyse the trained algorithm data which will not be straightforward and will be hard to interpret. On top of this, companies currently do not share their algorithms to allow for competitive advantage, which is counterproductive for a system that learns from its previous errors. Implementing AI into the artificial pancreas, akin to precision medicine, would provide a patient-tailored strategy and prevent the issues caused by patient noncompliance. Insulin appliance methods have made great advances since the extraction of the hormone in 1921, and it will be interesting to see how it will be used in the future, and if AI will be able to deliver an artificial pancreas worthy of the title.

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The Revolutionary Catheter

Anaya Malik
Editorial Assistant

Urinary catheterisation is necessary in 25% of all hospitalised patients, as well as in those who are bedbound in hospices or in nursing homes.[1] Accidental urinary catheter extraction occurs in 11–17% of all cases of urinary catheterisation and 5% of all urological catheters are traumatically dislodged.[1] It is common practice for inpatients to accidentally remove the catheter in an unconscious state or when the presence of the catheter is intolerable; consequently, patients cause themselves pain, further injury, and increase the risk of irreversible damage[1] to the bladder and urethra which may lead to serious infection.[2]

There are many examples in history for which the initial idea was born from a deep friendship and care

FoleySafe is a product developed by CATHETRIX (Tel Aviv, Israel) to actively prevent significant damage caused by accidental catheter dislodgement. The first catheter of its kind to avoid dislodgement in this manner,[2] the FoleySafe improves quality of life in catheterised patients and reduces the risk of catheter-associated urinary tract infection (CAUTI).[2] CAUTI is commonly observed among urinary catheter patients and increases the length of hospital stay and healthcare costs.[3]

The U.S. Food and Drug Administration (FDA)-approved[4] securement device has attracted much attention thus far following its presentation at MEDICA 2019. The Director of Marketing from CATHETRIX, Robert Baum, Tel Aviv, Israel, spoke to EMJ about the ways CATHETRIX intends to maintain this momentum and explained how the organisation will ensure they achieve their desired outreach and goals. "Although the patients are the final customers, doctors and nurses make the decision about whether or not to use the device in hospitals. There are two ways to approach these

decision-makers: medical expositions and better instructions to distributors on how to present the huge advantages of the FoleySafe when approaching hospital staff."

By cutting the sterile fluid tube following a vigorous pull on the catheter, the FoleySafe allows the retention balloon to deflate and the catheter slides out, minimising pain and damage to the bladder and urethra.[4] With regards to the impact of the FoleySafe since its development in August 2019, Baum drew upon the initial rudimentary success of the lifesaving airbag for comparison: "...after only 4 months, one could not yet reflect on its future benefit." The prevalence of the FoleySafe in hospital care is intended to become more significant, as Baum explains: "The CATHETRIX engineering team is working hard on continued improvement of the existing device and developing the next generation of the securement device to be applied in all types of catheter." Baum also set forth prospects and intentions for the progression of the device, "In the future, when the catheter is disturbed for any reason, the device will send an audio alarm to the nurse's room or any other control centre." Ambition and staggering development such as this will surely shape an age of medical innovation across the globe.

Developments that repeatedly further the field of medical innovations can be attributed to the fundamental building blocks and reason for innovation in any capacity: care. Baum explains, "There are many examples in history for which the initial idea was born from a deep friendship and care." He considered the work of the scientist, Dr Frederick Banting, who pursued a career in medicine and co-discovered insulin[5] after he witnessed his good friend suffering from diabetes. Baum then reflected on the development of the FoleySafe, "...the initiative was born after our chief engineer lost a dear friend following the traumatic extraction of a urinary catheter and the consequences which followed. He decided to find a solution that would ease the lives of other patients, this is how the FoleySafe was born. This was the starting point, representing the first step in our long adventure of bringing together top experts in different fields to develop additional solutions that will improve patients' quality of life." The importance of continued development of novel devices by companies such as CATHETRIX is abundantly clear, with duty of care at the forefront of the idea.

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m(y)Health – Handing Disease Ownership Back to the Patients

Layla Southcombe
Editorial Assistant

Introduction

Many industries are capitalising on the increased use of smartphones, and the healthcare industry is no exception. With a predicted growth of 15% over the next year to reach a staggering worth of $31 billion, mobile health (mHealth) apps are one of the fastest growing categories in the app market.[1] The use of mHealth apps have the potential to improve many aspects of a troubled healthcare system, impacting factors such as the number of visits to a healthcare centre, which will therefore improve patient health and free up more time for the clinician: a win-win situation. Many apps are now available in multiple languages, meaning that mHealth applications may be the key to facilitating the shift of disease control and responsibility from the clinician to the patient worldwide. Innovative apps influence numerous therapeutic areas, potentially improving patient care and health for a myriad of diseases.

Asthma and Chronic Obstructive Pulmonary Disease

Three-fifths of asthma patients in the UK do not receive a basic level of care, which can have a substantial impact on the patient in the form of emergency hospital admittance and the risk of death. The Digital Health Passport, a digital version of the personalised Asthma Action Plan, is just one example of how a smartphone app can make this basic level of care accessible to patients.[2] Patients can acquire information relating to management of their asthma, how to perfect their inhaler technique, and can track their medication use. Users can even record their symptoms so that they can report these back to their healthcare professional. This could be a simple step to improve patient health, as proven by the fact that patients who use an asthma action plan are four times less likely to be admitted to hospital because of their asthma.[2]

Despite constant efforts to increase adherence to treatment, which is one of the driving factors in poor asthma control, no sufficient improvements have been seen.[3] Apps that simply make inhaler use more fun for children by transforming it into a game have been developed, addressing this pressing issue in the younger population. A recent U.S. Food and Drug Administration (FDA)-approved technology is taking the use of apps one step further, by using a sensor that attaches to inhalers to better understand the patient and their disease. The technology, Proppeller, sends information regarding time and location of inhaler use to the app. Use of the technology can result in a reduction of up to 79% of asthma attacks and an increase of up to 50% more doses taken on schedule and 50% more symptom-free days.[4]

An important aspect of chronic obstructive pulmonary disease (COPD) care is breathing exercises, which strengthen the muscles required for breathing, resulting in the patient using less effort to breathe, while receiving more oxygen with each breath. Apps such as myCOPD can provide a vital platform that hosts educational videos from world experts and a complete online pulmonary rehabilitation class, reducing the need to travel to clinics and potentially risking infection and respiratory health decline, in addition to the general ease of being able to perform these exercises from the comfort of their home or work.[5] In 2017, a randomised controlled trial showed that myCOPD was non-inferior to gold standard class-based programmes at improving 6-minute walk test and COPD assessment test (CAT) scores, confirming that the app can be beneficial to COPD patients.[6]

Food Allergies

One of the biggest challenges for someone with food allergies can be gaining the confidence to eat out and trust the ingredients listed by the restaurant. Apps such as Biteappy allow you to search for allergy-friendly and diet-specific restaurants in your area, and even around the world for those who are concerned about eating out abroad.[7] When seated in the restaurant, patients can even enlist the help of a portable allergen-detecting device that can sense any allergen in your meal, this data is then sent to its partner app via Bluetooth and the results are displayed, identifying any hidden allergens.[7]

Eating at home can also be made easier with the use of apps that are able to scan barcodes and detail the full list of ingredients in packaged foods. If the patient is at the early stage of their diagnosis, then a diary and tracker to identify the triggers and potential allergens can be life changing. All of these examples provide people with food allergies with information to make a more informed decision on the food that they eat, ensuring that there will not be any adverse events if it is eaten.

Mental Health Disorders and Dementia

Taking into consideration the statistic that mental health disorders affect 1 in 5 adolescents, the fact that there are hundreds of apps dedicated to the improvement of mental health should not come as a shock.[8] These apps tackle a number of disorders by using an assortment of techniques. Those wishing to ameliorate symptoms of depression, anxiety, or fear can take advantage of apps that provide cognitive behaviour therapy. Apps that are clinically approved can be 'prescribed' to patients, especially to those who are fearful of, or are not ready to attend, group therapy, or for those who cannot afford private therapy and therefore can act as a stepping stone in the path to recovery. One of the hardest steps for an individual to initiate treatment is seeking help from others, so the ability to download a simple app and access treatment and advice at one's own discretion can help to eliminate this.

Dementia is a disease that, in addition to the patient, significantly affects the individual's family and loved ones. The emotion that accompanies not being recognised by a loved one or them moving further away from who you once knew can be traumatic. Therefore, the ability to bring back moments of memory and joy benefits not only the patient but the family too. Carers or family members can use the smartphone apps that are dedicated to this mission to improve the individual's quality of life. The apps work by stimulating memories by showing images and playing sounds that may evoke a memory for the patient. Families can now upload their own pictures to the app, a new additional feature to this already enlightening app.

With a predicted growth of 15% over the next year to reach a staggering worth of $31 billion, mobile health (mHealth) apps are one of the fastest growing categories in the app market

Skin Cancer and Eczema

A staggering 2–3 million non-melanoma and 132,000 melanoma skin cancers occur annually worldwide;[9] therefore, it is no surprise that mobile apps have been developed to reduce the morbidity and mortality associated with the diseases. By using artificial intelligence and clinically proven algorithms, some apps can analyse an image and provide a probable diagnosis and advice; however, this should be

confirmed by a dermatologist, something that can be achieved by the app itself in some instances. Dermatologists can use the app and provide diagnoses and advice for potential skin cancers, in addition to a multitude of dermatological diseases. Apps can even feature the addition of an integrated GPS tracking system to provide real-time ultraviolet (UV) radiation levels using the UV Index, as well as locating the nearest dermatologist.[10]

Use of the technology can result in a reduction of up to 79% of asthma attacks and an increase of up to 50% more doses taken on schedule and 50% more symptom-free days

Eczema is among a collection of chronic, dermatological diseases, and fluctuations in severity can be expected over time. The ability to identify triggers that may contribute to or initiate flares is crucial to any patient with a chronic illness. Apps can provide the platform to monitor pollen, mould, temperature, humidity, UV levels, medication use, and food intake in one central location, facilitating the user to be able to pinpoint triggers, of which they can then avoid to assist disease control.[10] Numerous apps with this approach exist and are improving patient awareness of their own disease.

Contraception and Fertility

One of the most commonly used hormone-based methods of female contraception, the pill is taken by nearly 16% of women aged 15–44 years in the USA.[11] This approach is >99% effective, but is accompanied by some potentially serious, long-term side effects such as migraine, heart attack, stroke, blood clots, and even various cancers.[11,12] There now exists an abundance of smartphone apps that are replacing these traditional methods of contraception, providing women with an alternative and more control over their future health. Smartphone apps such as Natural Cycles use clinically proven algorithms compounded with data from the user and hundreds of thousands of women, including menstruation dates and fluctuations in body temperature, to reliably predict ovulation. According to clinical studies, this particular app is 93% effective in the average user, but it becomes more effective the more data that is inputted, and can be 99% effective if it is used perfectly.[13] Natural Cycles is currently the only mobile app that is cleared for marketing as a certified contraception in Europe, and was also cleared by the FDA last year.

On the flip side to this, there also exists numerous apps that use a similar algorithm to pinpoint the times when a woman it at her most fertile point in her menstrual cycle to assist conception. For those who may not be able to afford the cost of fertility treatment, these apps can provide advice and a service of which would normally be out of reach. These easily accessible products must be used with caution however; numerous studies have indicated that the apps are not as accurate as they are marketed to be, with the results from a study presented at Fertility Society of Australia (FSA) Annual Conference 2019 even indicating that <50% are able to accurately predict ovulation (unpublished data). Despite this, the potential of such apps is undeniable and, with further tweaking and fine tuning, will more than likely be a welcome addition to reproductive technology.

Conclusion

It is undisputable that the surge of mHealth applications are empowering patients to gain control over their disease. It can be argued that standardisation of the market and European Medicines Agency (EMA) and FDA-approved apps would be beneficial to patients, as opposed to hundreds of unproved and potentially inaccurate alternatives. The overwhelming choice may leave patients choosing the app that is not best for them; this has led to organisations, such as the NHS, to compile a list of their recommended apps.[14] Despite the popularity of mHealth applications being undeniable, how these are going to be integrated into the existing healthcare is far from clear and is going to be a long-term challenge and a potential hinderance to the expected huge growth of the market. The future is bright, and both patients and healthcare professionals appear to stand to benefit from their implementation into the healthcare structure.

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Great Power, Greater Responsibility.

Ethical Implications on the Genome Editing Frontier

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In 1993, responding to the continually emerging and prospective possibilities of genome editing in the field of agricultural modification, social theorist Jeremy Rifkin proclaimed: "The devil is already at the door, cleverly disguised as an engineer."[1] Whilst Riskin's assessment of the genomic revolution that would erupt in the following 27 years and expand to patient therapy perhaps skewed negatively, the social theorist's concerns were by no means unfounded. In fact, Riskin's scepticism foregrounded one of the most serious ethical debates to grip the scientific community in recent memory. As technological capacity advances in the genomic field and aspirations for therapeutic application grow more optimistic, so too do important conversations need to be had regarding the proper use of such applied science. One such conversation captivated the intellectual curiosity of a London, UK, audience when The Royal Society, in partnership with Bristows, hosted an event in November of 2019 titled "The Quest for the Perfect Human..? A Debate on the Implications of Human Genome Editing." The discussion broached the increasingly apparent ethical responsibilities of the scientific community, with panellists and audience members discussing how we got to where we are, what we can do, what we can't do, and what we should do.

Dr Helen O'Neill, lecturer in reproductive and molecular genetics at University College London, London, opened proceedings with the difficult task of briefly summarising an intricate technology under scrutiny: CRISPR-Cas9. She began by acknowledging that while genetic editing attempts exist dating back 50 years, CRISPR has been used as an inherent and natural mechanism within bacteria for an estimated 3.5 billion years. In this model, CRISPR works through

the acquisition and assimilation of foreign genetic material into the bacterial genome as a means to confer immunity in the organism. To alternatively utilise this function as means to introduce sequence-specific edits in gene therapy approaches remains one of the most innovative bacterial-derived applications to date.

Realisation of the fact that this system can be exploited in such a way for genetic engineering,[2] as well as the benefits relating to its ease of use, adaptability, and affordability, led to the attention of the scientific community being assuredly piqued: "Since the acronym was coined in 2002, there are now 19 million hits on google for CRISPR," highlighted Dr O'Neill, who also noted that since 2012 there have been an estimated 5,000 related-publications and at least 2 babies born through the technology's assistance. "This is nothing short of a nucleotidal wave." Be it incorporation into immunotherapeutic regimens for cancer, to the correction of congenital defects in embryos, CRISPR appears to be growing from strength-to-strength. Despite, or perhaps because, of this increasing applicability, Dr O'Neill eluded to a range of ethical and regulatory questions that remain unanswered.

"I think it's generally implicit that as long as you are doing good, it's ok; the question is, are we doing good?"

Dr Nessa Carey was next to address the audience. A visiting Professor from Imperial College London, London, Dr Carey highlighted one of the most important distinctions to be acknowledged in the gene editing debate. Generally, this technology is referenced in application to either the soma or the germ line. In the former, localised and disease-tailored editing can be administered in an individual to ameliorate symptoms and potentially cure conditions, as seen successfully in cystic fibrosis[3] and muscular dystrophy.[4] Not unlike other pharmaceutical therapies, these treatments go through rigorous development pipelines subject to strict regulatory guidelines. However, a key difference exists in that these interventions cannot be withdrawn. Once a patient's DNA has been edited, the change is permanent notwithstanding further CRISPR utility. Such permanence emphasises the significance of DNA tampering, yet the technology is employed precisely for this kind of longstanding effect. "During almost all drug discovery, one of the major things we try to do is prevent changes to the DNA of the patient; with this technology, we're actually trying to change the DNA," reflected Dr Carey.

Often, however, it is the application of gene editing to the germ line that attracts the most controversy. Germ line editing entails the use of this technology in embryos at an early stage of development to remove deleterious alleles. This means that during the subsequent mitotic and differentiative processes each cell will inherit the edit. Far further down the developmental cascade into maturity, this also permits the possibility of the edited individual's offspring inheriting a haploid copy of the alteration. As a consequence, CRISPR has the potential to influence individual characteristics and variance on a population-wide scale. Dr Carey noted that although such technology would initially be rolled out to a very small number of cases, the ethical questions remain just as important; not only are these embryos incapable of giving consent, but the justification of the edit can be brought into question when considering the morbidity of the 'disease' being met. Take the example of congenital deafness: can we really consider this condition life limiting? Furthermore, does widespread application of gene editing to eliminate congenital deafness lead to marginalisation of present-day deaf communities, in which better-suited help could be provided through societal change? Dr Carey argued that an appreciation of medical and social models of disability is central to the genetic engineering debate.

Ethical considerations regarding gene editing are not the only concerns held by the scientific community, a message delivered by Prof Robin Lovell-Badge, senior group leader and head of the laboratory of stem cell biology and developmental genetics at the Francis Crick Institute in London, UK. The regulation of such powerful technology is highly complex, partly due to the aforementioned distinction between somatic and germ line modification, but also because of the undeniable risks associated: "I think it's generally implicit that as long as you are doing good, it's ok; the question is, are we

doing good?" Today's headlines are replete with shining stories of success related to advances made in genetic engineering. Despite these studies working well in a lab environment, however, translation to the clinic is far-away yet. The potential for undesirable effects on the target loci being modified,[5] or indeed off-target effects altogether,[6] means that currently the risks are simply too great to allow germline editing with CRISPR to be readily adopted into clinics worldwide. Yet the promise of this technology is alluring enough to consider a gentle push on the brakes as opposed to an emergency stop.

Prof Lovell-Badge informed the audience of the concentrated efforts being made by the World Health Organization (WHO) to help regulation in preparation for this future, in which a select committee has been formed to aid with this technology's governance. Considering the vast legislative, financial, and sociocultural differences between countries, a blanket set of regulatory rules for germline editing is unlikely to be effective; instead, this committee are in the process of formulating a framework to offer guidance to countries in an individualised manner. This is a complicated process, but it is encouraging to see preparatory steps being taken towards an eventuality where genome editing is globally accessible.

Offering a different perspective to the debate, Dr Rodger Novak, co-founder and president of CRISPR Therapeutics©, reflected on his involvement with genetic engineering on a commercial platform. Recognising the perceived immaturity, and indeed complexity, of this technology back in 2012, Dr Novak and his associates first highlighted the prime capabilities of CRISPR editing in an attempt to delineate a business model to pursue: genetic knock-down through non-homologous end joining,[7] insertions of exogenous DNA templates into the double helix,[8] and epigenetic regulation of gene expression using a deactivated form of the excision machinery.[9] Believing foremost in CRISPR's natural function, a focus on developing scalable knock-down strategies was chosen, all facilitated *ex vivo* to best optimise these therapies before reintroduction to the patient.

"This is nothing short of a nucleotidal wave."

Fast-forward to the present day, and CRISPR Therapeutics are currently involved in three active clinical trials: two investigating the haemoglobinopathies sickle cell anaemia and β-thalassaemia, and another investigating T-cell editing for allogenic therapy. Early results from the β-thalassaemia trial have already shown that a patient treated with the gene-editing machinery is now transfusion-independent:[10] a landmark achievement in haematological research. Assuming that CRISPR gene editing becomes further implemented in the clinical trials of various therapeutic disciplines, Dr Novak considered the need for new economic models that place patient outcomes at the centre of the pricing decision-making process. This model of pricing will undoubtedly bring its own challenges: the true 'success' of genome-editing therapy would need to be determined over an extensive time period, and the emergence of unexpected side-effects at later dates may also complicate matters. Much like the individuality of the therapy itself, however, pricing must surely adopt a patient-centric consideration.

As the debate was opened up to the audience in attendance, further vital arguments were brought to light. Following one question, in which a member of the audience asked how the public can develop trust in the regulatory bodies towards the proper use of such powerful technology, Prof Lovell-Badge emphasised the importance of appropriate public engagement from the earliest stages of regulation. He spoke of the concerns that members of the scientific and wider communities had regarding the lax regulatory approach of certain countries, referencing 'rogue' stem cell clinics that have arisen which are offering therapies to patients in desperate need of help. Such unregulated practice is often dangerous and lacking in actual clinical benefit, with the prospect of similar conduct with gene editing not a comfortable one. To this effect, the dissemination of accurate information to societies across the globe is of the utmost importance. Dr Novak concurred, speaking of the need to communicate with these countries in which disreputable practice is rife as well as to those who are, arguably, introducing CRISPR too readily into the clinic.

One audience member raised the possibility of using germline editing to completely eliminate genetic disease in three generations' time, and what this reality could look like. The speakers were unanimous in agreeing that this is likely impossible; Dr Carey pointed out that although this could feasibly be achieved temporally in one family, the occurrence of *de novo* disease-causing mutations in individuals, along with the fact that many diseases manifest through the homozygous coupling of recessive mutations over generations, means that genetic diseases are somewhat inevitable in their appearance in the population. Dr O'Neill agreed with this sentiment, adding that the reality of *de novo* mutagenesis means that despite the fact preimplantation genetic screening and diagnosis have been used in clinics for some 30 years, genetic disease is nowhere close to being eliminated.

Another impassioned attendee decried the lack of apparent objection to the use of genome editing during the debate, particularly in regard to germline alteration. Highlighting the current climate of social inequality and authoritarianism, they expressed deep concerns of CRISPR misuse to further eugenics movements. Dr Carey countered this point with referral to a case report she had discussed with her students involving a family tree afflicted with Huntington's disease. The hopeful mother who carried the deleterious allele carried out preimplantation genetic screening of the limited amount of eggs she could produce to find a disease-free candidate. A concession of 10 embryos were terminated, an emotionally devastating ordeal for the family that Dr Carey argued had the potential to have been prevented with CRISPR: "We need to flip the question from what right do we have to intervene, to what right do we have to withhold this from a family who are really desperate for it?" Both Dr Novak and Prof Lovell-Badge agreed in emphasising the potential application of this technology in patient or family-centric scenarios, purely for the prevention of disease burden as opposed to characteristic correction.

A resonant question to conclude the debate came from another member of the audience in referral to the title of the event: what does the perfect human look like? Dr O'Neill was steadfast in her dismissal of such an entity, proclaiming that we are erroneous in our making and being; even if the technology was to be perfected to the point of no off-target effects or risk, scientists would still be working with the most flawed biological model in human reproduction and biology. Dr Carey took this sentiment further, stating: "The idea of a perfect human is biologically irreverent and ethically disastrous." Indeed, this perception of perfection often lies in the eyes of the beholder, which, in the instance of implementing powerful technology, can be corrupted by the dominant socioeconomic bias. Perhaps, however, this line of thinking will, in time, become obsolete. Arguably, a re-emphasis of the intended therapeutic application of genome editing to the general public is sorely needed, especially in a time when over-sensationalised fears of 'designer babies' complicate efforts being made to meet the existing hurdles of regulatory implementation and ethical acceptance. At least for this night, these burning issues were put to rest to allow reflection on the inspired points made, but a debate of this magnitude will most certainly continue to rage for years to come.

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"Does innovation have to involve grand gestures, hefty price tags, and shiny new toys, or could it be something even smarter?"

A Revolution in Healthcare Innovation

Katie Earl
Assistant Editor

Introduction

Asked to name the first thing that came into their heads when thinking about innovation, the editorial team members at EMG-Health thought carefully before listing words such as data, machinery, nanobiology, lightbulb, new, and technology. Of course, each of these things has an important place in healthcare innovation: the advancement in technology has impacted every sector for the better in most cases, medical devices have revolutionised the way both complex and everyday procedures are performed, and the collection and processing of data allows more patients than ever to contribute to the results of clinical trials. But are these definitions confusing innovation with the narrower phenomenon of technological advancement? Does innovation have to involve grand gestures, hefty price tags, and shiny new toys, or could it be something even smarter?

We've all read the stories about artificial intelligence encroaching on our lives and big data being collected by wearable technology and bots. These daunting concepts tower over us in our everyday lives, not just in healthcare. The problem is that these technologies take time and money to implement, and, as healthcare professionals, payers, and patients can attest to, innovation is needed now.

And if one looks closely enough, they'll find that innovation really is happening right now, but not in the way you might think. In fact, it's happening in patients' backyards, on public transport, and in the back offices and meeting rooms of sectors far removed from healthcare altogether. They might not be high-tech, they might not even be U.S. Food and Drug Administration (FDA)-approved (yet), but they certainly are making a difference to patients every day.

Cocoon

The Cocoon is Uma Smith's invention to address the very pressing need for wider public understanding of epileptic seizures and how to support someone who experiences a seizure. After being diagnosed with the condition aged 11, Uma found that the public were underprepared to help, meaning that having a seizure in a public place was dangerous and unpredictable.

"Smith invented Cocoon to give patients a portable device that would allow them to have a safe space within which to allow the seizure to pass"

Smith invented Cocoon to give patients a portable device that would allow them to have a safe space within which to allow the seizure to pass, while also informing the public via written messages about how to help and support them. When the patient notices visual cues that they are about to experience a seizure (such as aura), they can wrap the device around the top of their head to cushion. The device contains a chip that will automatically alert the ambulance service if a seizure lasts for >3 minutes. As well as being functional, the design of the equipment was inspired by sportswear to help users feel reassured and empowered without it being associated with disability.

The device has been awarded the James Dyson Award, and Smith hopes to refine the device through further testing and prototyping to achieve FDA approval in the future.

Mastectomy-Friendly Bra

Healthcare and fashion might not be the most obvious of bedfellows, but when underwear-brand CEO Fran Dunaway found herself struggling to find a well-fitting bra after her mastectomy, she decided to take matters into her own hands. Her brand, TomboyX, has since launched the Ruched Bralette with Removeable Inserts, allowing wearers to mix and match inserts and breast forms to suit their lifestyle and wishes, whether this is post-mastectomy patients, transition patients, or anyone else who feels they would benefit from the feature. Patients are therefore empowered to feel comfortable in their bodies following these life-altering procedures, while being enabled to see reconstructive surgery as a choice, rather than the only option available.

Liftware

Tremors are a complication of a number of neurodegenerative diseases, impacting almost every facet of everyday life for patients and their carers. When engineering student Anupam Pathak graduated his studies developing new technology to stabilise camera and recording equipment, he began to look at other applications for the technology that would enhance standard of living for patients with disabilities. Liftware was born: a series of handles that attach to kitchen and dining utensils, keeping them steady in spite of hand tremors and allowing patients to be independent when eating meals. Since being set up in 2012, Liftware has now been acquired by Verily and their range of products continues to expand.

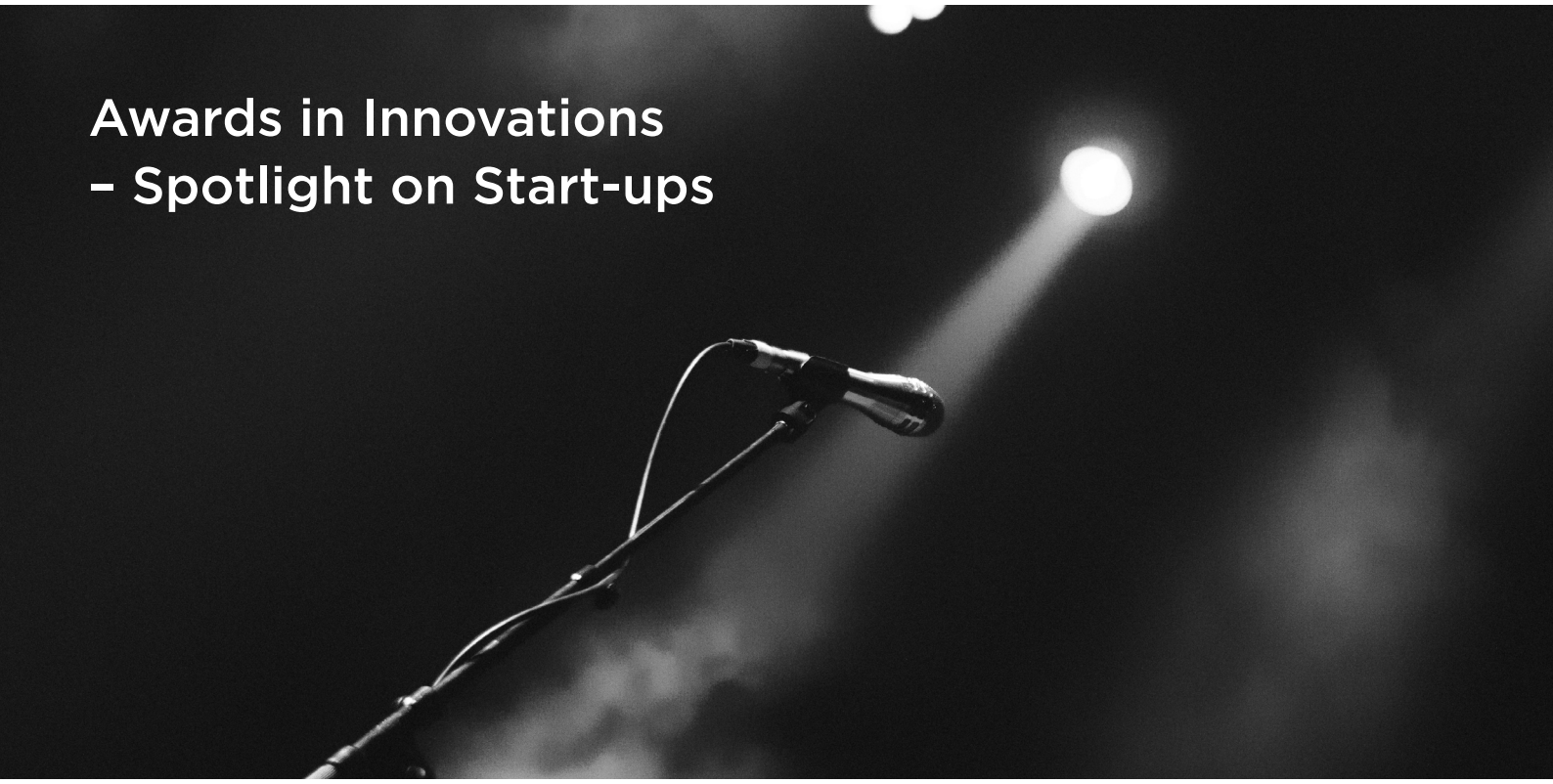
Kids Kicking Cancer

Kids Kicking Cancer is a programme which was founded by Rabbi Elimelech Goldberg in 1999 after he witnessed his daughter's painful battle with leukaemia. Their mission is to ease the pain of very sick children, while empowering them to heal physically, spiritually, and emotionally using martial arts and meditation to give young patients coping mechanisms for the painful or uncomfortable procedures accompanying cancer treatment. Since its conception, Kids Kicking Cancer has expanded to 5 countries and 48 hospitals, and only continues to grow. In 2018, they also launched an app, "Breathe Brake®," connecting the children who are part of the programme to adults across the world, giving them the opportunity to become teachers themselves, empowering them and giving them a sense of control over their lives. The app also allows adults to leave messages of support for the children.

"Kids Kicking Cancer demonstrates how innovation need not be a high-tech solution to patient support and welfare"

Kids Kicking Cancer demonstrates how innovation need not be a high-tech solution to patient support and welfare. Their work has been acknowledged on a plethora of media networks and Rabbi Elimelech Goldberg has been awarded the Robert Wood Johnson, Community Health Leaders Award in Washington D.C., USA, and was featured in People Magazine as a Hero for his work with Kids Kicking Cancer.

Awards in Innovations – Spotlight on Start-ups



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We've all heard of the Silicon Valley start-ups who have revolutionised the modern world. They've produced the likes of Apple, Google, Facebook, and Uber. But as more and more entrepreneurs leave the Californian business haven, more money is being invested elsewhere, especially in healthcare start-ups; Business Insider crowned healthcare as the top industry for artificial intelligence (AI) start-up funding in 2019.[1] We take a look at this year's most successful, creative, and undeniably lifesaving start-ups which have been commended for their forward-thinking and outside-the-box ideas to revolutionise global healthcare systems.

UK and Ireland

The 2019 Univants of Healthcare Excellence Awards[2] by Abbott Diagnostics were initially started to recognise teams within the healthcare industry who have collaborated across disciplines to transform patients' lives. Commended this year was a team from the University of Dundee, Dundee, UK, who came together to create an intelligent liver function test (iLFT) for the early detection of liver disease.[3] Prof John Dillon of the University of Dundee, and his team noticed that: "All too often we were seeing patients dying of liver failure who had an abnormal LFT recorded years before when something could have been done."[4] The intelligent part of the new test involves inputting LFT results into software that can detect the early warning signs of not just liver disease, but autoimmune liver diseases, hepatitis C, and metabolic diseases.

UK start-ups are also attracting interest from the rest of Europe, with start-up DNAnexus[5] being awarded the Clinical Research News European Innovation Award[6] in September for their biospecimen and data resource cloud platform of >500,000 individuals. Already, DNAnexus has accelerated discovery with pharmaceutical companies, healthcare organisations, and academics alike using the software, which can now boast citations in >170 publications.

Italy

The unofficial home of healthcare start-ups Italy scooped a total of 7 of the 15 available grants, each worth €50,000, at the 2019 European Institute of Innovation and Technology (EIT) Health Headstart Awards.[7] Biomedicallab,[8] who created the Parkinson's Disease Watch, was one such award recipient. The wearable device can access the therapeutic effects of the current treatment by monitoring patient motor symptoms, with the aim of finding the best treatment option possible

and acting as a form of personalised medicine. Another awardee was smartDONOR,[9] which offers a space for communication between blood donors and operators to ultimately increase efficiency by promoting a community of blood donors and informing volunteers on the real-time donation needs of their city. From a mental health perspective, Mindlenses Professional[10] provides a web platform divided into four areas: medical records, neuropsychological evaluation, rehabilitation, and report. The project began with Prof Massimiliano Oliveri, previously of Harvard University, Cambridge, Massachusetts, USA, and now a cognitive neuroscience specialist at the University of Palermo, Palermo, Italy. Accessible from any device, personalised treatment plans can be created for patients through digital rehabilitation, making use of the latest research from the laboratory.

Portugal

Staying in western Europe, Portugal has recently generated several innovative companies worthy of an EIT InnoStar Award.[11] First up we have B-CULTURE:[12] a novel start-up that designs 4D *in vitro* human tissue models for drug testing in pharmaceutical and cosmetic industries. This is an extremely topical subject, especially with increasing pressure on research institutes to reduce testing on animals and the creation of institutes such as the National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs). However, the UK Home Office published statistics in 2018 revealing that despite the availability of predictive, non-animal computer models, the UK are still using >3.5 million mice, cats, and rabbits every year for research.[13] On the theme of urology, Portuguese start-up HydrUStent[14] have developed a portable, minimally invasive ureteral stent that eliminates bacterial infections and allows long-term continuous monitoring. The team's focus is on healthcare systems that lower medical costs and decrease environmental impact; the HydrUStent reduces costs by 60% as it lessens the need for second surgery and produces zero waste as it is biodegradable. In the same playing field, is TimeUp,[15] who are also an InnoStar Awardee for their medical device: a urine monitor for the detection of bacteria, indicative of a urinary tract infection. Placed between the catheter and urine bag, continuously auditing patient's urine, it is hoped that it may minimise the €84 million spent annually in Portugal on cases of urinary tract infection.

Romania

Travelling across to Cluj-Napoca in Romania, the recent StartUp Europe Awards[16] recognised the start-ups making the most impact in the world of social healthcare innovation. Winner of the Best Female-led Start-up category was OKRA Technologies,[17] founded by Dr Loubna Bouarfa. OKRA is an AI system with the power to predict and make suggestions across the life sciences field. By ensuring the right drug is given to the right patient at the right time, OKRA has revolutionised clinical medicine by predicting surgical error preoperatively and in real time. Dr Bouarfa of St John's Innovation Centre, Cambridge, UK, is a member of the European Union's (EU) High-Level Expert Group and has recently called on data companies to collaborate to progress healthcare innovations to the levels needed for us to tackle the most prevalent global diseases. She spoke passionately to data companies at the EFPIA Oncology Data Summit, stating: "If we look back at recent significant, scientific breakthroughs in cancer treatment, they are all driven by data."[18] She also sought to crease out the misconceptions surrounding AI, stressing that it can be used to "support physicians with mundane tasks and decision making."[18]

"If we look back at recent significant, scientific breakthroughs in cancer treatment, they are all driven by data."

Poland

Crossing the borders of eastern Europe to Poland, we are back at the EIT Health HeadStart Awards, in which Polish start-up BrainScan[19] is revolutionising data set handling. The AI system searches a database of CT and MRI scans for similar cases to aid doctors in their diagnosis. The EIT InnoStars Awards also highlighted Poland's innovative advances, with UVera[20] receiving the €25,000 funding to continue their work on skin protection against the entire spectrum of ultraviolet sun radiation. With a particular focus on minimising the ecological impact of sunscreen lotions which are harming marine water, their ultraviolet protector is harvested from cyanobacteria and is therefore harmless to wildlife.

What's Next for Healthcare Start-Ups?

If you are curious about where to look next for start-up innovations, EU-Startups have put together a list[21] of the most exciting and eagerly anticipated technologies to watch out for in the not-too-distant future. First up we have FindMeCure,[22] a tool for patients and their families to search for on-going clinical trials in their surrounding area. Such a platform could provide newfound hope for those diagnosed with rare or difficult to treat conditions. Other companies include German based Mecuris,[23] who are using 3D printing technology to personalise prosthetics and orthotics to give a 100% customised fit, whilst also lowering production times by 75%. Also in the sphere of rehabilitation technology are ABLE Human Motion,[24] who are producing an exoskeleton for spinal cord injury patients so that they might regain their capacity to walk intuitively. The firm recognise the debilitating effects of paralysis socially and psychologically, and therefore it is their aim to reach the market by next year. By the looks of things, we could be on track for an even bigger year for healthcare start-ups in 2020 than we have had in 2019.

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Interview

Lara Mott

CEO and Co-founder, ImproveWell LTD

What first inspired you to pursue a career in the healthcare industry?

I loved chemistry and biology at school and had always imagined pursuing a career in medicine. Instead, I chose to read pharmacology at university, which combined elements of my two favourite subjects. During my studies I had the opportunity to visit Pfizer which I will never forget: their walls of charts and data scribbled all over them and, of course, the labs. Being introduced to the world of drug development and design ultimately sparked an interest for my future career, working with biotechnology companies in particular.

As co-founder and CEO of ImproveWell, the quality improvement platform for health professionals, can you tell us about what inspired the concept behind the company?

My co-founder, Dr Na'eem Ahmed, and I went to school together 25 years ago and have both pursued careers in healthcare. As an NHS frontline clinician, he came with the original concept of a 'Junior Doctor Feedback App' to capture those day-to-day micro-improvements and innovations, which are otherwise lost at the point of care. Since then, in collaborating with pioneering NHS partner organisations and developing three core feedback systems, ImproveWell is now a digital solution which empowers the frontline to drive change. Anyone, from the ward to the board, can get involved in improving their workplace.

ImproveWell uses collective intelligence to improve quality in health by empowering frontline healthcare staff to communicate ideas for improving healthcare directly to senior management. What are the biggest challenges you face in executing this mission?

Our digital solution helps organisations to capture real-time data from a highly skilled workforce to inform improvement initiatives. Technology is an incredible enabler, but there is no substitute for the internal commitment to fostering a culture of continuous improvement. We work with organisations at varying stages of their improvement journeys, and therefore our biggest challenge is helping our customers to identify the most effective strategies to maximise spread and adoption across their organisations.

The technology is already being used in multiple NHS Trusts across the UK. What are your long-term goals for ImproveWell?

ImproveWell has been designed by the NHS, for the NHS. Our founding vision is to harness the

innovation across a workforce of 1.7 million in the NHS to improve the way care is delivered. With healthcare organisations globally under increasing pressure to deliver better care, at a lower cost, our long-term goal is to unite the international healthcare workforce. Not only can organisations unlock innovation from their own workforce, they can also benefit from the aggregated data insights from similar organisations. This, in turn, will maximise the impact of collective intelligence on a local, national, and international scale.

Did your background in pharmacology, along with your experience across healthcare investment, biopharmaceuticals and life sciences consulting, aid you in your ability to recognise the need for quality improvement in the NHS?

My co-founder and I bring a complementary skillset to ImproveWell. As a frontline clinician in the NHS, he has deep domain knowledge and ensures that we remain clinically focussed on our own journey of innovation. The entrepreneurial spirit of the biopharmaceutical industry certainly resonated with me and I have been privileged to work with exceptional people throughout my career. Collective intelligence is the key to innovation, and my background helps me to recognise the need for collaboration in quality improvement in the NHS. Collaboration is at the heart of everything we do at ImproveWell.

"ImproveWell is now a digital solution which empowers the frontline to drive change"

Looking to the future, what role do you expect frontline staff to play in healthcare innovation over the next few years?

Following the Institute for Healthcare Improvement's Framework for Improving Joy in Work, published in 2017, healthcare delivery organisations are prioritising listening to their workforce and understanding what matters. Frontline staff have the answers on how to improve day-to-day operations and service delivery, so they should play the leading role in healthcare innovation. Finding ways to give everyone a voice will foster a culture of continuous improvement which, in turn, will lead to breakthroughs in healthcare innovation, a happier workforce, and better patient care.

You have been named rising star amongst the top 50 female leaders in UK healthcare. What are your views on the suggestion that women are driving innovation in healthcare?

It is fantastic to see so many talented women in healthcare, especially the inspirational efforts of those helping the NHS such as Tara Donnelly, the Chief Executive of the Health Innovation Network, working with tech companies to encourage the spread and adoption of innovation to improve patient care. These women will, as they always have, make a significant contribution to improving the healthcare landscape across the globe. Our healthcare system is universal; it treats all people regardless of race, sex, or background, and it is important that this extraordinary diversity is also reflected in the healthcare workforce. This melting pot of different experiences, opinions, and expertise will drive innovation forward, which is why fostering a culture of diversity and inclusion is so important within the healthcare sector.

Looking back at your career pushing innovation in the healthcare sector, what is your proudest achievement so far?

One of our trailblazer NHS organisations, Royal Cornwall Hospitals NHS Trust (RCHT), managed to capture the attention of South West Academic Health Science Network who commissioned an independent evaluation of the use of ImproveWell to listen and act on staff ideas for improvement. The report concluded that the ImproveWell solution is an effective tool to empower staff to make positive changes that benefit staff morale, create resource efficiencies, and improve patient safety and experience. The external validation of the solution was a major milestone for both the ImproveWell team and the pioneering staff at RCHT. We are passionate about empowering frontline healthcare staff to drive change, and doing our part to help them improve patient care, so to be able to see that in black and white was extremely gratifying for us all.

Social Media for Clinical Trial Recruitment: How Real is the Potential?

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INTRODUCTION

Research teams increasingly use social media to supplement nondigital methods for recruiting research participants. This trend is likely to grow as recruitment continues to pose a major challenge to clinical trials and other forms of human subject research. The European Patients' Academy (EUPATI) defines clinical trials as research studies involving people (healthy volunteers or patients) that test the safety and efficacy of a new medical treatment, device, surgical procedure, or medical test. Without these volunteers, this type of research and medical progress would be impossible; however, research participants can be hard to recruit. A recent systematic review found that 76.1% (131/172) of randomised clinical trials were discontinued due to poor recruitment.[1]

Social media provides a new gateway for connecting larger and hard-to-reach groups of the population with research opportunities. Social media includes widely accessible web-based and mobile information tools which allow users to view, create, and share information with others online.[2] The ability to build a network, i.e., social networking, makes social media unique and distinguishes these platforms from other interactive websites such as Craigslist (Craigslist, Inc., San Francisco, California, USA) or Wikipedia, (Wikimedia, San Francisco, California, USA) for example. While 56% of Europeans were using social media in 2018,[3] the use of this media varies across European countries and globally, as shown in Figure 1 and Table 1. The most popular platforms among Europeans include Facebook (Facebook Inc., Menlo Park, California, USA), Pinterest (Pinterest, Inc., San Francisco, California, USA), Twitter (San Francisco, California, USA), YouTube (Google, San Bruno, California, United States), Instagram (Facebook Inc., Menlo Park, California, USA), Tumblr (Verizon Media, New York City, New York, USA).

The ability to target segments of the population based on their demographic characteristics, interests, and previous online activities differentiates digital media, such as social media, from other more traditional recruitment approaches via printed flyers or mailed postcards, community talks, billboards, newspapers, TV, or radio advertisements (ads). Through paid ads, social media platforms, such as Facebook, allow the targeting of users with specific characteristics, e.g., age, sex, location, language, race and ethnicity, interests, and behaviours. Trial recruitment messages are presented to these audiences over a couple of days to reach a certain number of impressions, i.e., times a post is displayed to users regardless of whether the post is clicked or not, and to ultimately get users to click on the message link, view a webpage,

and take action. In addition to paid ads, social media also allows users to send nonpaid, organic messages that may be seen by followers of an account or people who are online at the same time or interested in the same topic. Paid and organic messages provide the link to the study page. On a clinical study webpage, users might be asked to complete a prescreening survey, contact the study team, or provide consent and download a mobile health intervention. However, not every social media platform permits paid advertising of clinical trials; it is prohibited on Twitter and Pinterest, and requires prior authorisation on other platforms such as Facebook, Instagram, YouTube, and Reddit (Advance Publications, San Francisco, California, USA). Despite these restrictions, social media provides new opportunities for identifying and engaging with potential clinical trial participants including previously under-represented groups,

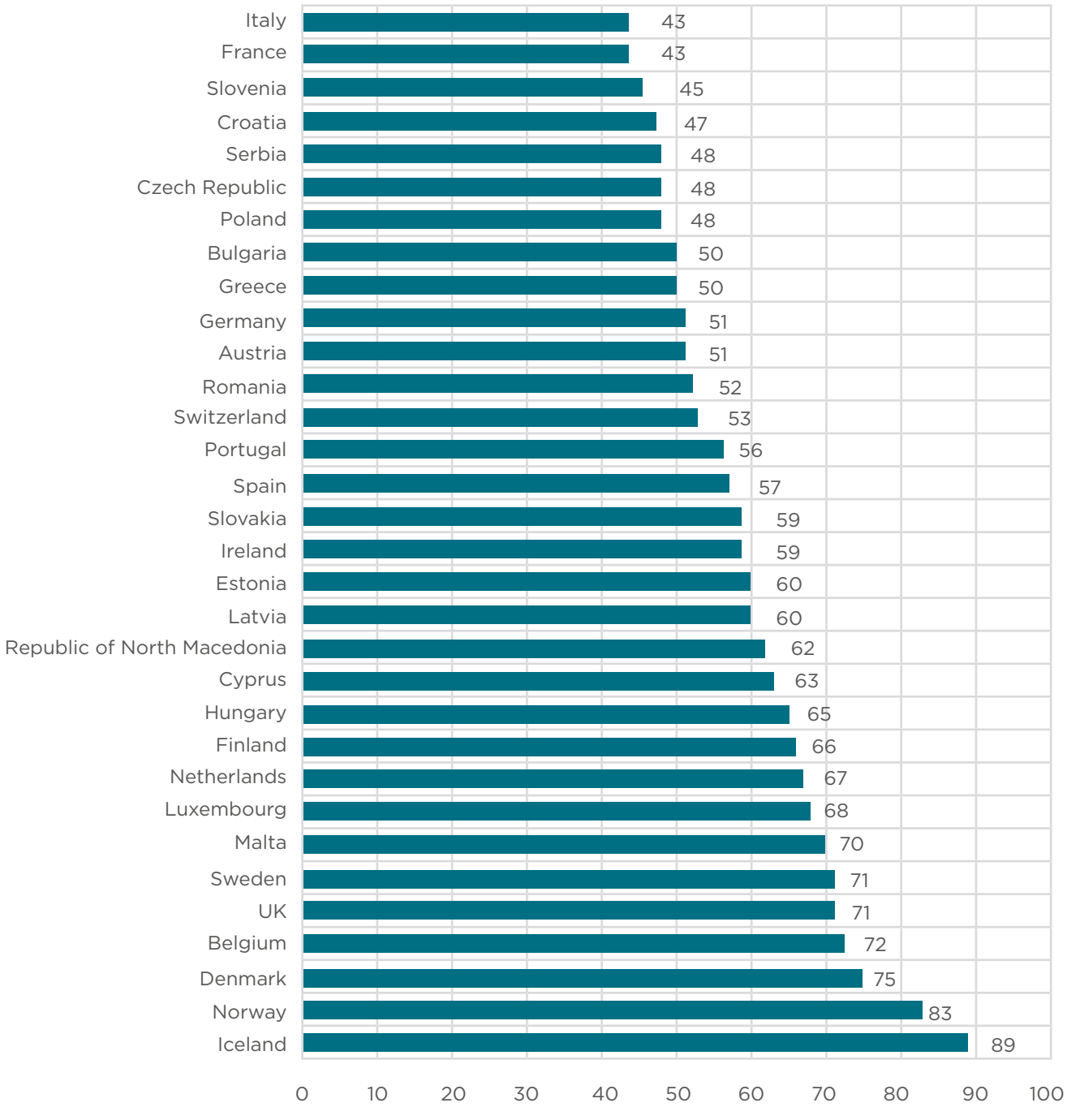

Figure 1: Social media use among adults in European countries in 2017.

Adapted from StatCounter Global Stats.[3]

Table 1: Use of social media in Europe, North America, South America, and Asia for May 2019.

Social media	Europe	North America	South America	Asia	Africa
Facebook	76.30%	54.64%	78.79%	79.72%	72.43%
Pinterest	11.55%	24.54%	8.00%	4.27%	6.55%
Twitter	4.66%	7.22%	4.30%	6.67%	3.63%
YouTube	2.83%	1.89%	5.77%	6.43%	16.32%
Instagram	2.56%	1.73%	2.64%	1.90%	0.73%
Reddit	-	8.79%	-	-	0.11%
Tumblr	0.98%	-	0.33%	-	-
VKontakte	-	-	-	0.59%	-

The table only includes the top eight social media platforms used. Social media are ranked according to the amount of traffic they refer to other websites indicating usage.

Adapted from StatCounter Global Stats.[3]

such as women and some minorities. So, is it worthwhile for research teams to invest limited time and resources in social media-based recruitment?

CAN SOCIAL MEDIA-ENABLED RECRUITMENT MOVE THE NEEDLE?

Although researchers have reported mixed results after using social media for research participant recruitment, there is some initial evidence of its efficiency and effectiveness,[4,5] i.e., the European Physical Activity through Sustainable Transport Approaches (PASTA) project.[6] The study team concluded that Facebook and Twitter served as "time-efficient" venues to recruit 17.39% (1,859/10,691) participants from seven European cities in a longitudinal, web-based survey. In some cases, social media offered an even more cost-effective solution. Guthrie et al.[7] used Facebook to recruit postmenopausal women, aged 45–70 years, with bothersome vulvovaginal symptoms within 20 miles of the study sites in Minneapolis, Minnesota, or Seattle, Washington, USA, for a randomised, double-blind, placebo-controlled trial. Over 28 days, they enrolled 8.3% (25/302) of their trial participants via Facebook at the cost of $14,813, compared to 277 women who they recruited via 277,000 direct recruitment mailings at the expense of $98,682.

For the most part, social media has complemented, rather than replaced, traditional recruitment efforts, but it has the potential to accelerate the timeline toward achieving the accrual target. For example, in a randomised controlled trial in the UK to assess the effectiveness of a behavioural intervention and prevent weight gain over the Christmas holiday period, the study team used social media to recruit 11% (35/311) of their adult participants aged 18 years and older with a BMI ≥20.[8] However, other recruitment methods were equally important and included word-of-mouth, recruitment at workplaces, community events, and schools.

It may be less of a surprise that social media has shown to be a useful tool to connect research opportunities with younger audiences as reported by Wisk et al.[9] The team used Facebook, Twitter, and Instagram to recruit college students aged 17–25 years with Type 1 diabetes mellitus onto an online longitudinal intervention trial. They achieved a retention rate of 88.4%. What about mid-life and older patients in the population, however? There are also encouraging reports of success. Langbaum et al.[10] were able to enrol 75,351 cognitively healthy adults aged 55–75 years in USA into a registry (GeneMatch) of Alzheimer's disease prevention studies online, over half of whom (60%) joined the registry based on social media ads. A second study by Nash et al.[11] reported dwindling participant

recruitment at 20 months and showed a significant increase in recruitment of middle-to-older-aged people into a blood pressure randomised controlled trial after implementing a 4-month Facebook ad campaign. The team was able to increase the average number of recruited study participants from 1.8 per month using conventional recruitment to 7.3 per month using Facebook ($p<0.05$).

Finally, one might believe that it is harder to recruit healthy research volunteers, i.e., as a control group, because they have no vested interest in research outcomes related to a specific disease. However, recruitment of healthy elderly participants aged ≥60 years for a Phase I clinical trial on Facebook showed, within a reasonably short period of 8 weeks, that a total of 621 people responded to Facebook ads of whom 45 (7.25%) enrolled.[12]

Box 1: Examples of barriers to the broader application and assessment of social media-enabled recruitment, and potential solutions.

Barriers	Description and potential solutions
Lack of reporting standards	Despite the promise of social media, there is currently a lack of accurate, complete, and consistent reporting standards of social media-based recruitment methods and results. Social media-enabled recruitment should be reported transparently so that readers can follow what was planned, what was done, what was achieved, and what conclusions were drawn. Reporting standards and guidelines will be the basis for moving toward evidence-based recruitment strategies enabling research teams to implement more tailored recruitment strategies that meet their specific recruitment goals.
Lack of ethical and regulatory guidelines	The lack of consistent ethical and regulatory guidelines challenges the broad application of social media-enabled recruitment, especially for multi-site trials within and across European countries. Challenges include questions related to assessing the risks to participants prior to collecting the data, protecting participants anonymity by not using direct text quotes in publications or shared data, complying with local and European Union (EU) laws such as the General Data Protection Regulation (GDPR) on data protection and privacy for all individual citizens of the EU and the European Economic Area (EEA). Gelinas et al.[16] were among the first to offer actionable advice. They suggested applying the nonexceptionalist methodology for assessing social media recruitment and proposed "normalising social media recruitment techniques while remaining sensitive to their potentially novel aspects." Their approach is unique in that it looks at "whether social media recruitment differs from offline recruitment in ways that warrant further review." The authors provided compelling use cases and checklists. A second group recommended incorporating a Privacy-by-Design (PbD) framework in online recruitment efforts, a globally recognised standard for privacy protection that uses clear privacy notices and disclaimers.[17]
Lack of verifiable information	Social media offers limited options to verify demographic information such as age, e.g., adults versus minors, sex, ethnicity, and race. However, the collection and verification of self-reported information can be built into downstream processes using closed and secure digital data collection environments.
Sample representativeness	Some study teams have reported sample representativeness issues such as the decrease in the age of participants as a result of social media-based recruitment.[11] However, studies have also demonstrated the utility of social media to recruit diverse participants with respect to race and ethnicity, education, and employment.[13] Recruiting across multiple social media platforms is recommended to optimise sample diversity.
Research needs	Further research is required to examine factors that may influence the effectiveness of social media-based recruitment as well as individual determinants that may affect who is likely to respond to a recruitment ad and enrol in a clinical trial, e.g., study disease type, study requirements, target audience, eligibility criteria, ad content (text and image or video), frequency of ads (saturation), and ad budget.
Managing trial participants	Participants may share information about a trial and their experiences on social media. New approaches and best practices are needed to manage trial participant's social media activities during trial participation, e.g., approaches to follow them on social media, to track their activities, or to contact them regularly and help them understand the implications of sharing information about ongoing trials.
Lack of training and resources	Social media is a rapidly evolving technology. Research teams often lack the time, training, and resources to budget for and successfully implement social media-based clinical trial recruitment. More training opportunities could be beneficial to build capacity as well as centralised support services for researchers at larger academic centres.

These examples demonstrate the potential of social media that is already being harnessed to support clinical study recruitment. While most study teams report the use of paid social media ads, primarily on Facebook, some groups were also successful in recruiting participants using nonpaid organic social media-based approaches. Adrian et al.[13] used 'friend requests' on Facebook to recruit 66.7% (212/318) young adults who were previously involved in health research into a new mental health study. Another experimental approach that is being tested consists of monitoring public Twitter conversations for targeted recruitment.[14] The idea is to engage and recruit those patients in clinical trials who have already discussed their disease experience on Twitter. However, most studies reported the use of social media for study recruitment outside Europe with the USA, Canada, and Australia among the leading countries. Hence, a unique opportunity presents itself to better the understanding of social media as a tool for enhancing clinical trial recruitment within and across different countries and populations in Europe.

BARRIERS THAT AFFECT THE BROADER APPLICATION AND ASSESSMENT OF SOCIAL MEDIA-ENABLED RECRUITMENT

While some studies offer early signs of promise supporting the use of social media as a cost-effective recruitment method, more research is required to determine how best to use social media for research recruitment. For example, is social media better suited for the recruitment of study participants from certain demographic groups or groups with specific health conditions? What are the characteristics of effective messaging approaches? What are social media users' attitudes on different platforms toward using social media data and digital ad techniques for clinical trial recruitment, or how does the type of research question affect the suitability for social media-based recruitment?

Additionally, some barriers prevent the broader use and thorough assessment of social media-based recruitment in clinical and human subjects research (Box 1), e.g., digital media offers us the possibility to measure recruitment efforts in much more robust ways. However, the collection and reporting of data about digital forms of recruitment are still in its infancy. Guidelines for reporting the design, implementation, and results of social media-enabled recruitment methods are needed to allow the learning from existing recruitment strategies and the development of better ones. The lack thereof hampers the development of evidence-based recruitment methods and the ability to reliably compare the effectiveness of recruitment efforts across different social media platforms, disease trials, and populations. Another challenge is posed by the lack of clear guidance to assist researchers and institutional review board members with the use of social media in human subject research in general and clinical research participant recruitment, which affects both investigator-initiated or sponsored research. Concerns may include how to engage with patients on social media directly, how to manage and respond to user comments, how to track and report adverse events shared by users on social media, or how to avoid introducing potential biases within a study. The lack of consistent regulatory guidelines makes it especially challenging to leverage social media-based recruitment for multi-site trials.

Notably, the use of social media targeting capabilities based on users' previous behaviour, e.g., what they searched for, liked, or mentioned on social media, raises new types of user and data privacy issues and may be perceived as "creepiness"[16] by members of the institutional review board, researchers, and social media users alike. While this is an area that requires more research, Gelinas et al.[16] were among the first to offer actionable advice in this regard. As they put it: "it is doubtful that the mere perception of creepiness has intrinsic ethical weight or would demand greater protection for social media users." Instead, they suggested applying the nonexceptionalist methodology for normalising social media-based recruitment techniques while remaining sensitive to new aspects. More practically, this means comparing social media with commonly used, more traditional approaches. In the case of social media-based targeting, one could question whether targeting individual women with young infants via customised ads on Facebook gives rise to greater research and privacy risks compared with the targeting of women with young infants generally

at a paediatric office. After all, the personal information on which digital ads are based is usually not available to research teams; it is part of a proprietary algorithm owned by the website or ad company. That said, researchers have the obligation to familiarise themselves with the privacy policy and terms of use of social media to assess whether the proposed research adheres to a website's terms of service and to ensure that the site will not use the data it collects, from tracking responses to recruitment ads, in ways that violate ethical norms and regulations. Finally, social media is only the first step toward enrolling study participants. If the enrolment rate is considered one of the primary outcomes for assessing the effectiveness of social media-based recruitment, it is vital to pay equal attention to improving downstream recruitment and retention processes such as follow-up, screening, consent, treatment adherence, and data collection. Such steps in the clinical research recruitment funnel need to be optimised, i.e., through chat bots, also known as conversational agents, and artificial intelligence-driven software programs designed to interact with potential study participants or media-rich electronic consent forms and teleconsent[15] that reduce the complexity and inaccessibility of common consent forms. Box 1 lists additional barriers that may hinder the application and assessment of social media-based recruitment and possible solutions.

CONCLUSION

The potential in social media for enhancing clinical trial recruitment is real. However, are we harnessing its full potential? The answer is no. More proactive and collective research efforts by European countries to address some of the concerns and barriers could help to leverage the full potential of social media for clinical trial recruitment. The question is also not solely if social media is more effective or cost-efficient than traditional recruitment methods. It will require a combination of the best traditional and digital recruitment methods to address the clinical trial recruitment challenge in new ways.

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The Era of Immersive Health Technology

EDITOR'S PICK

My editor's pick for this edition is Bremner et al.'s review of the four main areas of immersive health technology: artificial intelligence, machine learning, augmented reality, and virtual reality. Bremner and his colleagues explore how these technologies, which were once idealistic future plans, are now integrated into many aspects of healthcare.

Prof Mike Bewick

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Abstract

Immersive health technologies are revolutionising the delivery of frontline healthcare, therapeutic techniques, and research. They also offer great potential to improve the training of healthcare professionals through reality-simulation training. This review paper summarises the current developments and uses of four types of immersive health technology: augmented reality, virtual reality, machine learning, and artificial intelligence. Current examples of their use in healthcare, opportunities and pitfalls, and how the use of these technologies could be improved further in the future are highlighted. How technology that once appeared to be only visionary is now part of day-to-day life for many patients and consumers is also addressed.

IMMERSIVE HEALTH

Immersive health is a term that encompasses technologies that interact with, or leverage, the neuroscience of the human brain. Within healthcare, immersive technologies have the potential to disrupt every medical specialty and collectively can also be thought of as 'digital therapeutics'. These technologies allow health workers to treat or manage a medical condition more optimally than would be possible in traditional healthcare. A broad definition is proposed by the Digital Therapeutics Alliance (DTA): "Digital therapeutics deliver evidence-based therapeutic interventions to patients that are driven by high quality software programs to prevent, manage, or treat a medical disorder or disease. They are used independently or in concert with medications, devices, or other therapies to optimise patient care and health outcomes."[1] There are four main immersive modalities:

Virtual reality (VR): the computer-generated simulation of a three-dimensional image or environment that can be interacted with in a

seemingly real or physical way by a person using special electronic equipment, such as a helmet with a screen inside or gloves fitted with sensors.[2,3]

Augmented reality (AR): an interactive experience of a real-world environment where the objects that reside in the real-world are 'augmented' by computer-generated perceptual information, sometimes across multiple sensory modalities, including visual, auditory, haptic, somatosensory, and olfactory.[4]

Machine learning (ML): a process leveraging the computing power of modern architecture to learn relationships from data, with its emphasis on efficient computing algorithms and pattern recognition. ML algorithms build a mathematical model based on sample data, known as 'training data', in order to make predictions or decisions without being explicitly programmed to perform the task.[5]

Artificial intelligence (AI): the theory and development of computer systems able to perform tasks normally requiring human intelligence such as visual perception, learning, reasoning, and action-taking.[4,6]

One of the first uses of immersive health technology was in the mid-1990s, when the Oregon Research Institute Eugene, Oregon, USA, used VR to train mobility-impaired children on how to control their motorised wheelchairs.[7] VR devices have evolved exponentially since initially being extremely cumbersome, expensive, and having issues including inducing motion sickness. In recent years, the use of immersive technologies has become mainstream, whether via voice recognition in systems such as Amazon's virtual assistant Alexa™ (Amazon, Seattle, Washington, USA), or in video gaming in Pokémon Go™ (Niantic, Inc., San Francisco, California, USA), where players compete to collect VR animals overlaid on a real-world environment. Immersive technologies have become widely accepted by consumers for recreational use and accepted in part of their daily lives, consciously or not; however, their use in healthcare is currently not exploited to its full potential.

VIRTUAL MEDICINE TODAY

Today, the furthest that telehealth extends to in mainstream use is that of programmes like Simple Telehealth run by NHS Highland. This is a programmed protocol of text messages for patients with chronic, long-term conditions in the community, offering advice, tips, reminders, and questions for the patients to send in medical observations such as heart rate, blood pressure, and peak flow from home.[8] Clinicians can log into the website to see readings and edit messages. A review in 2018 of multiple disease protocols found that patients felt less isolated, clinicians were better able to remotely monitor patients, and improved adherence by patients resulted from reinforcement of health advice.[9]

New mobile technologies are bringing the diagnosis to the patient enabled by AI analytics. Kardia's AliveCor™ device (AliveCor Inc., Mountain View, California, USA) is one of the best known. AliveCor is a small device, half the size of a one-dollar bill, purchasable on the internet, and able to connect with a mobile phone in order to analyse whether the patient's heart rhythm is irregular and indicative of atrial fibrillation (AF). Analysis of the rhythm is by AI within the application downloaded onto a mobile phone. Given that ≤50% of patients with AF are asymptomatic, and yet ≤25% of cardioembolic strokes can be attributed to AF, the positive benefits to healthcare systems are easily seen.[10] In a review of 1 screening event of 954 people who had a basic AliveCor electrocardiography, 54 (5.6%) had an abnormality.[11] Even without specialists on-site, detection of paroxysmal AF is enabled by the ability to email aberrant detections which patients can take as and when they have symptoms.

In the UK, the health-delivery company Babylon™ (London, UK) is expanding and now operates a remote service. This enables virtual consultations with doctors, nurses, and therapists by text and video messaging on a mobile application. They suggest that the majority of core primary care consultations are best managed at least initially by a video consultation, reducing human transport and movements.[12] Telehealth also means that tests can be ordered and prescriptions dispensed without patients having to visit a general practice surgery.

The above technologies are all in current use and represent the apogee of healthcare delivery today. There has been little change to the way healthcare professionals are trained for decades, but immersive health technologies offer a chance to change that. By utilising immersive technologies, it is possible to deliver healthcare diagnosis and investigation remotely, with all the subsequent benefits to cost, outcomes, and compliance.

VIRTUAL REALITY AND AUGMENTED REALITY: "I KNOW IT'S NOT REAL, BUT IT FEELS REAL."

Training Healthcare Professions

Training any healthcare professional is time and capital-intensive. To train the doctors of the future using traditional methods, which are partly implicated in the exponential growth in the societal cost of delivering healthcare, is an unrealistic expectation.[13] Could immersive health technologies be a path both to cheaper and better training? VR training is not new; it has been used frequently in commercial applications for decades, from flight simulators in training air force pilots to Formula 1™ car racing, reducing both training duration and costs.[14,15] This power has positioned VR and AR as vital teaching and research tool in multiple fields, including aviation, oil, shipping, and the military.[16] The aviation industry credits immersive simulation education as a major contributor to the approximate 50% reduction in human error-related airline crashes since the 1970s. It has provided a safe space to place pilots in rare but critical situations, with enough immersion to replicate the physiological manifestations of stress that results in the error in real life scenarios, but which are not replicated in ordinary simulation.

In health education, learning involves multifaceted physiological systems, developed adaptive expertise, and the acquisition of collaborative skills. Learning in the medical domain is often situated in a real-life context yet training in this real-life context is not always possible. To truly achieve simulation-training that replicates medical environments, there needs to be not only analogous mental challenges, but also analogous physiological responses. To replicate and train for human factors in clinical decision making to date has been difficult to achieve, but the immersive nature of VR now provides the necessary tools.

A systematic review and meta-analysis of 31 studies by Khaw et al.[17] found positive benefits for VR-trained groups with greater knowledge of a subject compared to traditional online or offline learning methods. They also identified improvements in healthcare professionals' cognitive skills.[17] However, these studies focussed heavily on the healthcare professional and none of the studies reported any patient-related outcomes or adverse effects, and cost-effectiveness was not addressed. VR has also been reviewed in improving nontechnical skills such as teamwork, situational awareness, and communication. A systematic review by Bracq et al.[18] however, highlighted that there have been minimal measures of the outcome of the use of VR on nontechnical skills. Other studies have highlighted the potential for VR to supplement clinical training, especially set against increasing restrictions on the number of hours trainees are permitted to work, and the ability for observed review of VR practice. VR training compared to video training in laparoscopic surgery was reported by Gurusamy et al.[19] as being at least equally effective as video training. In participants with limited laparoscopic experience, VR training resulted in a greater reduction in operating time, error, and unnecessary movements.

VR can also enhance learning performance in medical simulation.[20] The sense of presence offered by immersive VR leads to much better learning from experience.[21] "Virtual reality simulations can bridge the gap between theory and practice by immersing the learner in a realistic, dynamic, complex setting."[22] Both VR and AR solutions can teach clinicians complex procedures,[23] are effective in CPR training,[24] can improve communication skills,[25] may enhance critical thinking,[26] and have been shown to improve clinical decision making.[27] They have also been shown to reduce cost and improve safety in advanced life support training.[28]

Advances in medical imaging over the last few decades have been exponential, from ultrasound to complex cross-sectional imaging using MRI. Yet the way the images are displayed has not changed. Imaging is still usually on a flat computer

screen and requires skill, imagination, and lengthy training to convert this to an understanding that allows surgeons to operate on the patient in front of them. Research in the USA is working to prototype AR applications in medicine such that a surgeon using an AR headset would be able to see digital images and other data directly overlaid on their field of view.[29] This has the potential to reduce intraoperative time, complications, and cost, ultimately leading to increased patient survival.

A systematic review by Munzer et al.[30] on the use of AR on the training and delivery of care in the field of emergency medicine evaluated the outcomes of 24 papers across 3 themes; the user-environment interface, telemedicine and prehospital care, and education and training. Most of these studies were observational and had small cohorts but had a wide range of participants including nursing students, critical care doctors, and multiple specialties of surgeons. Overall positive effects were noted on improved practitioner engagement with training, reduced practitioner distraction, and cognitive load during procedures. However, issues including equipment cost and sterility were noted. All of the studies reviewed were in training only and none were carried out in the live patient environment.

Treating Patients

Off-the-shelf VR technology using simple headsets has promise for the prevention and treatment of health conditions, particularly in psychological care. The immersive and potentially entertaining nature of VR means that rehabilitation medicine has also been posited as an area which could benefit from VR technologies. In prevention, VR has been used by the military as part of predeployment training with the aim of reducing the incidence of post-traumatic stress disorder (PTSD). VR has been tested in real-life deployments of American soldiers to Afghanistan and Iraq as part of the Stress Resilience in Virtual Environments (STRIVE) project.[31] Using VR headsets, soldiers are embedded in challenging combat contexts. The prevalence of PTSD in returning military personnel in the USA is estimated at 16.6%, substantially higher than the background lifetime population prevalence of 6.8%.[32] The lifetime costs of PTSD are higher than other standalone mental health disorders and if predeployment resilience training using VR can reduce this, it is likely to be cost-effective.[33]

A systematic review of 50 studies by Valmaggia et al.[34] demonstrated that VR offers a valuable method of assessing symptoms and the potential to facilitate learning new emotional and behavioural responses. One example of this can be found in a study in which 23 patients with arachnophobia were encouraged to gradually approach a virtual spider with increasing degrees of proximity. By the end, 83% of participants showed significant improvement in how they dealt with spiders, with some so desensitised they could approach real spiders without experiencing anxiety.[35] Of equal relevance and despite the challenge of having to face their fears, there were no dropouts. Similar progress has been reported with the use of VR in tackling the fear of heights. A study of 100 subjects allocated participants between VR therapy and no treatment. All VR participants experienced a reduction in their fear of heights, with an average of 68% reduction in fears according to the Heights Interpretation Questionnaire (HIQ).[36] More than 50% of participants experienced a 75% or greater reduction in their fears. This is comparable to, or better than, the best psychological intervention delivered face-to-face.[36]

Just as pertinently, while exposing those who have anxiety or post-traumatic disorders to powerful stimuli causing physiological response, therapists can be present alongside to guide, coach and, re-assure patients *in situ*. The effect or realism with VR allows a therapeutic window because scenarios can be repeated. The thought of facing a situation that triggers real physiological anxiety is never a pleasant one. The thought of facing it with support alongside, in what is recognised as a virtual scenario, is far more surmountable than it would be in real life.

The benefits of VR can be seen outside psychological therapy. In rehabilitation medicine, a study by Ho et al.[37] in patients post-acute stroke showed that the use of VR in combination with conventional therapy improved outcomes compared with conventional therapy alone. The group of 100 case-matched patients receiving VR and conventional therapy had better functional independence at discharge and reduced medical costs. A 2018 study by Hanna et al.[38] demonstrated

the use of VR in remote supervision and annotation, and real-time pathology-radiology correlation during autopsy and examination of pathological specimens. VR has also been shown to enhance the enjoyment and intensity of physical activity, and by using omni-directional treadmills, potentially increase the activity of participants.[39]

ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING

AI is the "theory and development of computer systems able to perform tasks normally requiring human intelligence."[40] It is necessary to understand exactly how AI and ML are individually defined. Deo defined ML in a 2015 paper as "the scientific discipline that focuses on how computers learn from data." ML can be either supervised learning, which focusses on classification (e.g., sorting pictures into those with cats in and those with dogs in from a large set of images), and unsupervised learning. Unsupervised ML has no set outputs. The 'machine' seeks to find patterns or groupings within unsorted data.[5] AI is the broader umbrella under which ML lies, and which encompasses the use of technology to perform tasks that would usually require human intervention including sensing, learning, reasoning, and taking action.[6]

The cumulative effects of Moore's Law mean that we now have computational power in the palm of our hand which dwarfs that used to put mankind on the moon. This immense ability to perform billions of calculations a second allows the use of decades old mathematical tools to perform unique and highly accurate pattern recognition and analysis. In health data, this is allowing the ability to reveal associations and anomalies from previously thought random health data sets. Furthermore, the ability to create artificial neural networks and allow them to learn by trial and error, billions of times, creates software that evolves to solve complex problems in a nature akin to a child learning.

ML is already widely used in the consumer market, from recommendations by online film companies as to what film to watch next, to fraud detection and action. Self-teaching game-playing algorithms using re-enforcement learning can defeat the currently best-known chess playing program without any human intervention.[41] AI and ML have an excellent performance in tasks involving image interpretation, suggesting that medical specialties such as dermatology and radiology are one of the most promising applications of the technologies.[42] In dermatology, skin cancer is the most common human malignancy increasing in both incidence and prevalence. Current clinical reviews of simple skin lesions such as basal cell carcinomas and follow-up after a melanoma diagnosis require frequent follow-up in person. A convolutional neural network application demonstrated performance on par with all tested board-certified experts in classifying skin cancer.[43]

In radiology, it is expensive and time consuming to train radiologists, so radiographic image recognition is held to be one of the areas of AI 'witness to the greatest gains'. In one study at Cornell University, Ithaca, New York, USA, a deep convolutional neural network was capable of automatically filtering CT head images and reporting with an error rate well below that for board-certified radiologists.[44] A 2019 publication by Annarumma et al.[45] found that AI systems can reduce the time needed for the most common radiological investigation, the chest radiograph, to be reviewed. Researchers collaborating with Guy's and St Thomas' NHS Foundation Trust, London, UK, used a data set of almost 500,000 anonymised adult chest radiographs to train an AI system to recognise abnormalities and then triage images for formal reporting, cutting the average delay in reporting from 11 days to 3 days. Normal chest radiographs were detected with a positive predicted value of 73% and a negative predicted value of 99%, and with a speed that meant abnormal radiographs could be prioritised to receive expert human opinion sooner. This is important in two ways: it recognises that AI systems presently have their limits and still require expert human input, and also that the use of AI can dramatically improve the service provided to patients.

A snapshot survey by the Royal College of Radiologists, London, UK, in 2015 estimated that at any one time in the UK, it is estimated >330,000 patients waited >30 days for their imaging to be reported.[46] The situation has worsened with only 2% of radiology departments in UK hospitals in 2018 meeting their reporting requirements compared to 8% in 2014. Approximately half of departments reported leaving images auto-reported or unreported altogether, raising the

spectre of potential delayed or missed diagnoses.[47] An AI system capable of prioritising could make a significant contribution to improving the situation and reducing risk.

Moorfield's Eye Hospital is an ophthalmological hospital based in London, UK. Clinicians at this hospital collaborated with DeepMind (London, UK) in using a deep learning architecture to interpret three-dimensional optical CT scans, reaching a performance level that met or exceeded that of experts after training on only 14,884 images.[48] The next proposed step is to assess whether the same type of deep learning architecture would be able to diagnose conditions in advance of when a human expert would be able to, offering the option to assess the risk of complications before they formally present and stratify resources accordingly.[49] The same team note that "volume and complexity of diagnostic imaging is increasing at a pace faster than the availability of human expertise to interpret it."[48] Saria et al.[6] note that this is particularly true of low resource settings. The use of AI in this way offers a force multiplier for a limited workforce of clinicians.

In cardiology, there is increasing demand for imaging services such as echocardiography for the surveillance of heart function and valvular abnormalities. Commercial echocardiography software vendors have started incorporating automation to improve accuracy of images and to recognise required views.[50] Deep learning has been tested at the initial step of evaluating imaging views, as well as for diagnosis in deliberately challenging images. The deep learning program was superior in terms of accuracy.[51] Ultromics is a UK company spun out from the University of Oxford, Oxford, UK, which has developed AI capable of achieving better-than-human accuracy in interpretation of stress echocardiograms, at approximately 90% versus the 80% achieved with human interpretation.[52] This has significant potential to reduce unnecessary investigations (initial interpretations are more accurate) and to reduce clinician time taken for interpretation of complex scans.

Beyond image analysis, there are ML algorithms in development to analyse physiological data and make predictions on when the patient may clinically deteriorate. These have proved to be extremely valuable and indeed picked up hitherto unknown patterns in patients' physiology.[53] One of the most recent applications of AI was in predicting early deterioration in renal function in patients developing acute kidney injury. Tomašev et al.[54] used a data set from >700,000 patients in Veterans' Affairs hospitals to develop an AI program capable of predicting 55.8% of all inpatient episodes of kidney injury, and 90.2% episodes which subsequently required dialysis. This was a retrospective study however, and the same program has not yet been validated in a live patient population.

Nonetheless, combining this approach with the exploding field of smart devices and the 'always on' connected world could reap enormous benefits in both health outcomes and resource efficiency. The ever-increasing volume of data in health, from key symptoms picked up in consultation, to blood test results and radiology investigations, are rich pickings for ML to assist with, including monitoring prognosis to suggesting possible diagnoses and treatments.

Patient monitoring is another application for AI. Oxehealth™, Oxford, UK, have created a medical device in Europe intended to perform spot observations of pulse and respiratory rate 'contact free' via optical and infrared sensors with no staff involvement. Its novelty means no published academic papers are available, but an audited case study of its use on an acute psychiatric ward showed improved in speed of observation collection and in the patient experience as they did not have to be woken to have their observations taken.[55] Being woken to have observations taken can contribute to patients' sleep deprivation and a poor patient experience.[56]

CONCLUSIONS

The technological advances of recent years have given us new tools and technologies to transform how we deliver healthcare. We can now educate and examine healthcare professionals with high fidelity immersive simulations at low cost and to a higher level of training. We can perform training and testing in human factors, tackling clinical errors not currently targeted effectively but that are associated with an almost ubiquitous element of bad outcomes. In healthcare delivery, no longer will the approach be central-down and population-based, but instead the patient becomes the centre of everything and the source of real-time data. The patient has the opportunity to become their own data controller, to contribute to their health analytics, and to leverage the power

of smart devices. ML and AI algorithms can aid in prediction and diagnosis of disease, and for us as clinicians, enable the delivery of personalised healthcare in the home remotely using AR, with innovative VR treatments. In a world with a patient-centric record, data contributed comes from a wide variety of sources, forming part of our cultural heritage to improve health outcomes. The obstacles are no longer technical, but cultural and organisational. The era of immersive health is upon us.

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E-learning in Pathology Education: A Narrative Review and Personal Perspective

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Abstract

In recent years, E-learning, also known as web-based learning, online learning, computer-assisted instruction, or internet-based learning, has been used frequently in healthcare education programmes. E-Learning has played a significant role in the author's cytotechnology programme by providing online distance education to multiple sites nationally, and soon internationally.

Although many papers currently exist regarding E-learning, the literature lacks review papers on E-learning in pathology education. The objectives of this paper, therefore, are to provide a narrative review of the approaches used in incorporating E-learning in pathology education, and to provide a faculty member's perspective of experiences, lessons learned in developing E-learning modules, and suggestions to future faculty developers of E-learning modules.

For the purpose of this review, PubMed and Google Scholar search engines were used to search articles published between the years 2008 and 2018. Any review articles and articles from proceedings were not selected for this review. The search resulted in 17 articles that met the criteria for further review. The reviewed literature showed that E-learning has been widely used in pathology education. There is, however, a lack of studies evaluating pre and post-test scores and the cost effectiveness of E-learning technologies.

INTRODUCTION

In recent years, E-learning, also known as web-based learning, online learning, computer-assisted instruction, or internet-based learning, has been used frequently to train healthcare practitioners, including those in nursing and radiology.[1,2] E-Learning has played a significant role in the author's cytotechnology (CT) programme by providing online distance education to multiple sites nationally, with plans for international implementation as well. This CT programme is a post-baccalaureate certificate programme with a 12-month curriculum that provides students with entry-level competencies as cytotechnologists. The class size ranges from 4 to 12 participants, and is currently the only programme in the nation that offers synchronous distance education, serving 4 satellite sites.

This CT programme has incorporated E-learning slowly and steadily for the past few years,

with the significant step of incorporation of a virtual microscopy (VM) system. E-learning started with the building of a VM database of cytopathology digital images scanned using iScan Coreo Au scanner (Ventana, Arizona, USA) in mScope software (Aurora Interactive, Montreal, Quebec, Canada). Currently, the author has >3,000 digitised images that are used to create annotated teaching images, unannotated daily screening practice images, and screening test images. The digitised images are also used to create virtual scope session videos to mimic multihead microscope sessions. These videos are made available to the students on the course management system.

After it was determined that the students were able to learn cytomorphology using VM and apply their learning to screening glass slides with a microscope,[3] the author aimed to reduce or eliminate the need for additional in-person training in the cytology laboratory by adding E-learning modules to the current online curriculum. With internal funding received from the author's institution, the digitised images were used to develop E-learning modules. At this time, nine E-learning modules have been developed using Articulate 360 (Articulate Global, Inc., New York City, New York, USA) software. The E-learning modules include the title, specific objectives, video clips of the content, and interactive self-assessment questions with feedback. The perceptions of the CT students were assessed regarding the content of the E-learning modules and the perceived influence of the E-learning modules on their performance during clinical rotations. Students responded positively to the statements regarding the quality of the video and audio, duration, navigation, and the materials presented. Most of the students also responded positively, stating that the E-learning modules better prepared them for their role during clinical rotations and recommended developing more E-learning modules for cytology courses in the future.[4] With the positive results received from the students, more E-learning modules are currently being developed. The programme, however, is yet to evaluate the objective outcomes of students' learning influenced by E-learning modules. It is crucial to determine the role of E-learning modules in students' education, which can be measured by comparing the pre and post-test scores. The author's long-term goal is to statistically prove the effectiveness of E-learning modules in students' education in this CT programme. The short duration as well as small class size of the programme, however, makes it difficult to statistically measure the objective outcomes.

Although many research papers have been published regarding E-learning in the training of healthcare professionals in sectors such as radiology, pharmacy, and nursing, the literature lacks review papers regarding the effectiveness of E-learning in specific healthcare professional educational training. As a faculty member who has had positive as well as challenging experiences in developing E-learning modules, the current paper was the result of the author's own personal curiosity to know how other educational programmes have used E-learning for pathology education. The primary objective of this review was to identify the approaches to measure the objective outcomes of students' learning influenced by E-learning modules in pathology education. The secondary objectives were to provide a narrative review of the approaches used to incorporate E-learning in pathology education, with a particular interest in describing the purpose of that incorporation, how E-learning has been incorporated, what types of outcome measures have been used to evaluate the effect of E-learning in pathology education, and a faculty member's perspective of experiences and lessons learned in developing E-learning modules with suggestions for future development of E-learning modules.

METHODS

For the purpose of this review, PubMed and Google Scholar search engines were used to search articles published between the years 2008 and 2018. The keywords used to search the articles were "E-Learning", "E-learning", "eLearning", "e-learning", "Web-based", "online", and "pathology". This search resulted in 26 articles. Seven articles, however, did not report E-learning in pathology education, one article was a proceeding, and another article was a review article and therefore all nine articles were excluded from the analysis for this study. The title or the abstract of the articles that contained at least one of the six keywords mentioned

above and the words "pathology/pathologist", "training", and/or "education" were included for the analysis of this study.

RESULTS

The search resulted in 17 articles that met the criteria for further review for this paper.[5-21] Review of the literature led to the arrangement of 3 categories: 1) purpose of incorporating E-learning in pathology education; 2) how E-learning has been incorporated; and 3) outcome measures that were used to evaluate the effects of E-learning in pathology education. The main information gathered from the 17 articles reviewed in this study are summarised in Table 1.

Table 1: A summary of the main information gathered from the 17 articles reviewed in this study.

Author, year	Purpose of the study	Type of E-learning	Findings
Ariana et al.,[5] 2016	To determine if blended learning combining E-learning with traditional learning methods of lectures and tutorials would improve students' scores and satisfaction over those who experienced traditional learning alone.	Online practical and lecture notes, digitised slides images interactive microscopy section for the students to review materials and conduct self-evaluation.	E-learning tools for delivering pathology instruction can be an effective supplement for developing dental students' competence, confidence, and satisfaction.
Klatt,[6] 2014	To analyse the usage and results of web-based pathology practice examinations that were developed to assist students using formative assessments of their knowledge.	Website that provides pathology images with text descriptions, along with examination questions. The questions provided feedback for each answer chosen by the user. The website also contained timed examinations to mimic real testing environment.	A cohort of serious users fully completing the exams had sufficient preparation to use them to support their pathology education.
Hosseini et al.,[7] 2014	To examine the efficiency of using educational software in practical oral pathology scores of dentistry students.	Software (CD-ROM) that had images of pathology samples put in appropriate arrangements.	The mean scores of the students in the new group were higher than the traditional group; however, this difference was not statistically significant. The scores of the practical pathology in dentistry may be enhanced if the traditional method is conducted along with supplementary multimedia software.
Sivamalai et al.,[8] 2011	To investigate undergraduate medical students' perceptions of the benefits and challenges when digital microscopy software is combined with classroom management software to deliver online practical pathology teaching sessions in rurally orientated medical school.	Digital-online website.	Nearly all medical students welcomed learning pathology via online digital technology.
Samulski et al.,[9] 2018	To investigate the effectiveness of adaptive online modules in teaching cervical cytopathology.	Adaptive E-Learning modules (developed using the platform developed by Smart Sparrow) that consisted of still images, basic informative texts, educational diagrams, and assessments that guided students to next learning concepts or to remedial didactics.	Learners demonstrated improvement in their knowledge after the use of adaptive E-Learning modules compared to traditional methods. The modules were viewed positively by participants.

Table 1 continued.

Author, year	Purpose of the study	Type of E-learning	Findings
Kerfoot et al.,[10] 2010	To compare knowledge transfer and retention between bolus web-based teaching modules and online spaced education, a novel email-based method of online education founded on the spacing effect.	Web-based teaching module containing series of MCQ containing a clinical scenario and histopathology image.	Online spaced education generates transfer of histopathology diagnostic skills and substantially improves their long-term retention.
Lee et al.,[11] 2015	1) To evaluate the usefulness of an internet-based system for the training students in dermatopathology using skin diseases with different prevalence and complications; and 2) to evaluate the use of this system by experts who are already familiar with reading conventional dermatopathological slides.	iSlide, web-based interface that contained clinical histories, digitised skin images (scanned using Aperio digital slide scanning system) and interactive dermatopathology.	iSlide system was found to be a useful tool for learning dermatopathology.
Peacock and Grande,[12] 2016	To explore the use of Google (Alphabet Inc., Mountain View, California, USA)-based online app platform in a 1-year pathology course at Mayo Clinic Alix School of Medicine, Rochester, Minnesota, USA.	Google Apps on which the lecture PowerPoints, videos, pathology slides, collaborative group learning presentations, course syllabus, assessments, and grades can be accessed.	Students found that the app platform was helpful in establishing a collaborative, online classroom environment.
IJspeert et al.,[13] 2017	To assess the effect of an E-learning module on interlaboratory consistency.	Interactive E-learning module that had histopathological images.	Variability decreased after implementation of the E-learning module.
Ho et al.,[14] 2014	To assess the benefits of online testable concept maps for learning in pathology by volunteer junior medical students.	Online testable pathogenesis maps are scaffolded concept maps relating to disease processes. They are preconstructed and key concepts or linking phrases are removed so that they can be 'dragged and dropped'.	Online testable pathogenesis maps are well accepted and can improve learning of concepts in pathology by medical students.
Huang et al.,[15] 2015	1) To design automatic classifiers based on integrated genetic algorithm and support vector machine to cluster 4 different types of cells and to discriminate dysplasia from normal cells; 2) To implement a web-based cytopathology training and testing system to increase learning efficiency of cytopathologic education.	A web-based cytopathological training and testing that has question bank management, test management, and online testing operation functions.	Most of the users agreed the operation interface is friendly and easy to use. Users expressed strong behaviour intention to further adopt the system.

Table 1 continued.

Author, year	Purpose of the study	Type of E-learning	Findings
Van Dijken et al.,[16] 2008	1) To describe the patient-based, web-based learning programme that the authors created to help students to better understand and interpret the clinical and laboratory findings associated with disorders in fluid, electrolyte, and acid-base homeostasis; 2) to comment the feedback of students obtained on the online, interactive support of traditional teaching; 3) to share the positive experience with this pedagogical set up and make freely available the software developed for all teachers who would like to use it.	A web-based learning that contained clinical history of patients.	Complementing traditional lectures with online case-based studies and interactive group discussions represents therefore, a simple means to promote the learning and the understanding of complex pathophysiological mechanisms.
Desai et al.,[17] 2011	To report the preliminary results of learner satisfaction using an online nephropathology teaching site.	Website that had digitised kidney biopsy specimen with a description of key pathological findings and final diagnosis.	Nephrology on-demand histopathology is a well-received teaching tool to learners of all training levels.
Abdollahi et al.,[18] 2014	To assess the effect of a web-based educational course on the concordance rate among the Gleason Score reports of pathologists from selected hospitals of Tehran University of Medical Sciences, Tehran, Iran.	Web-based course with photos and course materials.	Through web-based education, pathologists can exchange views and contribute to the rise in the level of reproducibility. Such training courses are strongly recommended for significant pathological issues including the grading of prostate adenocarcinoma.
Bijol et al.,[19] 2015	To assess the difference in final exam performances on quizzed and non-quizzed materials as well as differences in performances between students who did and did not use the quizzes.	Website: Articulate Quizmaker 13. Interactive features such as hot spots, MCQ, drag and drop, and mix and match. Feedback explanation of the answers to the questions.	Adding interactive online formative assessments improved students' learning experience overall.
Jurjus et al.,[20] 2018	To develop and pilot MAPA and to test the hypothesis that principles of E-learning, applied to an integrated microanatomy and pathology laboratory in a modular based curriculum would improve medical student satisfaction and perceived learning of the material.	Online, self-directed learning.	MAPA has been perceived by medical students as a helpful, web-based, and self-selected adjunct for learning.

Table 1 continued.

Author, year	Purpose of the study	Type of E-learning	Findings
Engelberg et al.,[21] 2015	To document and reduce interobserver variation of ER, PR, Ki-67, and HER2 scores among the pathologists participating in the Athena pathology harmonisation projects; 2) to document how pathologists perform on biomarker scoring and assessing 'Score the Core' as a training tool; 3) to improve the precision and accuracy of assessing breast cancer biomarkers: ER, PR, Ki-67, and HER2 (IHC4).	Online training tool with digitised whole slide images.	The online training tool can serve as an important component of ongoing quality assessment and can improve the accuracy of breast cancer prognostic biomarkers.

ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; IHC4: immunohistochemical 4; MAPA: Microanatomy and Pathology Atlas; MCQ: multiple choice questions; PR: progesterone receptor.

Purpose of Incorporating E-Learning in Pathology Education

Current evidence indicates that E-learning has been incorporated in pathology education in both classroom and clinical settings. In dental, medical, and resident classroom settings, E-learning has been used to determine the effectiveness of blended learning (combining E-learning with traditional learning methods) compared to traditional learning in histopathology education;[5] examine the efficiency of using educational software in practical oral pathology scores;[7] evaluate the usefulness of an internet-based system in learning dermatopathology;[11] explore the use of Google (Alphabet Inc., Mountain View, California, USA)-based online app platform in teaching pathology course;[12] evaluate both the qualitative and quantitative impact of online testable pathogenesis maps on learning pathology;[14] explore the educational value of web-based formative assessment tool for renal pathology, and develop and pilot an Microanatomy and Pathology Atlas (MAPA) for medical students;[20] investigate perceptions of digital microscopy software when combined with classroom management software to deliver online practical pathology teaching sessions;[8] compare the knowledge transfer and retention between bolus web-based teaching modules and online spaced education;[10] investigate the effectiveness of adaptive online modules in teaching cervical cytopathology;[9] and collect students' feedback on an online, interactive support of traditional teaching of pathophysiology.[16]

In clinical settings, E-learning has been used to assess the intra and interobserver concordance rates in the Gleason scoring of prostatic adenocarcinoma, before and after a web-based educational course among the pathologists;[18] evaluate the performances of pathologists on using a web-based pathologist training tool;[21] implement a web-based cytopathology training and testing system;[15] and assess the interlaboratory consistency in the histopathological diagnosis.[13] In addition, E-learning has been used to analyse the usage of web-based pathology practice examinations[6] and gather learner satisfaction of web-based teaching modules in nephropathology education.[17]

Incorporation of E-Learning in Pathology Education

In the articles reviewed, E-learning has been incorporated as a) quizzes on the website, such

as a series of multiple choice questions (MCQ) containing a clinical scenario and histopathology image;[10] b) course materials with photos on websites;[18] c) digitised images on websites and pathological findings and diagnosis;[8,21,17] d) digitised images with text descriptions, clinical histories, and self-assessments with feedback on websites;[11,6] e) course materials with online practical and lecture notes, and digitised slide images with interactive microscopy section for the students to review materials and self-evaluate on the website;[5] f) CD-ROM with images of pathology samples put in appropriate arrangements;[7] g) Google apps through which the lecture PowerPoints, videos, pathology slides, collaborative group learning presentations, course syllabus, assessments, and grades can be accessed;[12] h) E-learning modules developed using special software that consist of images, informative texts, educational diagrams, assessments that guide students to the next learning concepts or to remedial didactics, interactive features such as hot spots, MCQ, drag and drop, mix and match, and feedback explanations of the answers to the questions; and finally,[9,13,19] i) online testable pathogenesis maps that are scaffolded concept maps relating to disease processes.[14]

Outcome Measures

In the reviewed articles, the outcome measures that were used to evaluate the effects of E-learning in pathology education were retention skills, long-term learning efficiencies of online educational methodologies, resident performances on spaced education versus web-based teaching, student perceptions, pre versus post-scores, and only post-scores.[5-21]

In general, from the studies reviewed, students welcomed the addition of learning pathology via digital technology.[8] They found the app platform helpful in establishing a collaborative, online classroom environment.[12] They favoured online testable pathogenesis maps,[14] supported further adoption of the online system because it was useful in cytopathology diagnosis and training,[15] and they found that online quizzes improved learning experience.[19] Very few studies that compared the pre and post-scores showed that post-scores improved after using E-learning tools.[9,13,21] Studies that focussed on only the post-scores found that the scores of the students who used the E-learning tools were higher than the students who did not use the E-learning tools.[5,7,14,19]

The following common survey statement topics received positive responses in the reviewed articles: helpful annotations, easy access from anywhere, more convenient for learning, faster than using microscopes, allows self-paced learning, everyone sees the same image, better for group learning, better technology, feedback received was helpful in reinforcing concepts, module was effective in presenting the content and concepts, more engaging than the lecture and texts, online learning was a worthwhile adjunct to training, recommend to my classmates, collaborative capabilities to create joint-projects were helpful, enhanced learning, and improved understanding and identification of the differences between normal tissues and those with pathologies.[8,9,11,14,20] Some difficulties participants indicated when using the online methods of learning included a lack of practice with a microscope, less interaction with the teacher while on rural placement, problems with the internet connection, technical problems with online technology, user needs of computer skills, among others.[8] In the open comments, students also indicated that they found the interactive aspects of E-learning very interesting and engaging: it yielded more impact than just reading about a topic; it could be done at the student's own pace and they could start and stop at will;[9] it was easier to visualise; and was clearly organised and labelled.[20] Students also suggested some improvements to future E-learning modules, such as user interface; more information; integration with other disciplines; more quiz features, pictures, tissue samples, and short explanations; consistency in the presentation of the material; comprehensive test features; and magnification features.[14,20]

DISCUSSION

The primary objective of this paper was to identify the approaches to measure the objective outcomes of students' learning influenced by E-learning modules in pathology education.

Out of 17 articles reviewed, this study identified 2 articles that used pre versus post-scores to measure the participants' performance in clinical settings, and 1 article in an educational

setting.[9] The study, which was conducted in an educational setting using a randomised, mixed methods, crossover design, reported improved post-test scores of the participants. Even though this method would be an ideal approach to measure the objective outcomes of the CT students, unlike this study which had a total of 36 participants, the present author's CT programme has 4–12 students per year. Therefore, it is always a challenge to show statistically significant results with fewer student participants. A collaborative approach with other CT programmes to increase the sample size would help measure the students' objective outcomes and achieve significance.

The secondary objectives of this study were to provide a narrative review of the approaches used in incorporating E-learning in pathology education and to provide a faculty member's perspective of experiences and lessons learned in developing E-learning modules and suggestions for future faculty developers of E-learning modules.

Based on the reviewed articles, it is evident that E-learning has been incorporated and evaluated successfully in pathology for variety of purposes. Students' perception surveys predominated as an outcome measure than the cost effectiveness of the E-learning modules or the test scores, particularly, the pre versus post-test scores.

Many of the articles reviewed used either digitised whole slide images or pathology images with quiz materials as E-learning tools. A limited number of studies used E-learning as a module that included lecture materials, videos, pathology images, and interactive features such as hot spots, MCQ, drag and drop, and mix and match, with feedback explanation of the answers to the questions. In the author's experience in cytopathology education, students enjoyed and benefited from similar E-learning modules with videos that had voiceover descriptions and interactive self-assessment features.[4] Additionally, the reviewed articles lacked detailed explanation in regard to the time and cost involved in developing the E-learning modules. In the author's experience, time and cost are critical issues to consider for the faculty members in developing E-learning modules.

The anticipated faculty time commitment exceeded 50% when the author developed their first E-learning module (12 minutes 23 seconds in length) in their programme. This was primarily to learn the various E-learning technologies and software available and to choose those that best fit the objective. By the time the optimal option was chosen, affordable software that fit the objective of the module, and learned to develop the E-learning module, updated software programmes were already available to consider for the next E-learning modules. Therefore, faculty members need to be aware of the constant changes and updates in the technologies and the software and plan to spend considerable time to learn these technologies.

Updating educational material is a critical process in training healthcare professionals. A faculty member needs to be aware of the considerable amount of time spent in this process to make the most of the E-learning modules for education. From a faculty point of view, the author found updating E-learning modules initially challenging, particularly videos that contained digital images and voiceover audio descriptions. For example, when a description in an existing video portion of the E-learning module needed to be included, the whole video then had to be reshot, edited, inserted in the module, and republished to acquire the URL. This led to the rearrangement of the whole E-learning module.

A time-saving strategy identified through experience in developing E-learning modules was to involve the students. The author's institution provided yearly funding opportunities for faculty-led E-learning projects, in which the students help the faculty members develop these modules. From this experience, working with students also helped the author to understand what they would like to see and how they would use the module. Their innovative ideas made the modules more creative and interactive. All of the E-learning modules were developed through internal funding mechanisms. As the process unfolded, unanticipated costs were identified. For the initial E-learning modules developed in the programme, the biggest expenditure was a professional videographer, voiceover recording, and editing of the videoclips. For the later modules, the author's institution created an E-learning Lab that provided high quality video cameras in addition to a soundproof booth in which the audio recording could be done for the E-learning modules. This reduced expenses considerably.

A limitation of this study was the small number of articles reviewed. A more systematic approach on searching and selection of articles to review could have identified more information on using E-learning modules in pathology education.

In summary, the task of developing and evaluating E-learning modules may seem difficult; however, with proper planning and commitment it is achievable. As a faculty member who developed and evaluated E-learning modules in this CT programme, it gives the author great satisfaction and encouragement to observe students enjoy and benefit from these modules. Therefore, the author highly recommends that faculty members of other educational programmes who have never had the opportunity develop this valuable resource to enhance their training in their educational programme. One way to sustain the inclusion of E-learning in pathology is to collaborate with other educational programmes to develop E-learning modules so they can be shared among programmes. Through this, the time and manpower can be shared and the content of the modules can be standardised. Involving students, residents, or fellows in the development of E-learning modules with the faculty members to capture students and faculty members perspectives can also be considered to improve the quality of E-learning modules.

CONCLUSIONS

E-learning has been widely used in pathology education. There is still, however, a lack of studies that evaluate the cost effectiveness of the E-learning technologies, and pre and post-test scores of the participants.

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A Step Ahead for Difficult Airway Management Using GlideScope®: A Prospective, Randomised, Comparative Study

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Abstract

Background and Aim: Different techniques have been developed in order to optimise the practice of intubation with GlideScope® (Verathon Inc, Bothell, Washington, USA) video-assisted laryngoscope. This study aimed to demonstrate the use of a new, safe, and effective technique by inserting both the video-assisted laryngoscope blade and endotracheal tube (ETT) together.

Methods: A prospective, randomised study was conducted with 50 patients who were anticipated as difficult for endotracheal intubation, aged 18–90 years, with an American Society of Anesthesiologists' (ASA) classification of Grades I–IV, and who presented for elective surgery. The patients were divided into 2 groups of 25 participants: an intubation with traditional GlideScope (TG) technique group, and combined GlideScope (CG) and ETT simultaneous insertion group. The optimal glottic view and the time-to-intubation were recorded. Postintubation airway trauma and both practitioners' and patients' satisfaction were documented. The categorical data are presented as a number and percentage and were subjected to Fisher's exact or Chi-square test for analysis. The statistical significance was $p \leq 0.05$.

Results: The optimal glottic view was 64% in TG and 72% in CG ($p=0.216$); intubation was achieved within ≤15 secs in 22 patients in TG and all patients in CG ($p=0.077$); and 88% of patients in TG showed high satisfaction scores compared to 92% in CG ($p=0.646$). The practitioners' satisfaction was 76% in TG and 96% in CG ($p=0.042$).

Conclusion: Simultaneous insertion of both the GlideScope blade and ETT could provide fast, effective, and safe endotracheal intubation.

INTRODUCTION

Airway management is a fundamental anaesthetic practice. Delay in securing an airway could be extremely serious in certain conditions. Therefore, many techniques and a lot of equipment are used to manage the problem. Anaesthetists must have the skills, different tools, and techniques of airway management. GlideScope® video-assisted laryngoscope (GVAL) has been a revolution in difficult airway intubation since its introduction in 2003. Recent studies have proposed the GVAL as the first choice for intubation in a difficult airway.[1-6] Practitioners could encounter up to three problems when intubating with the hyperangulated blades of GVAL: the laryngoscope may be too close to the glottic opening, the practitioner may not direct the tip of the endotracheal tube (ETT) to enter the vocal cord opening, or they may be unable to advance the tip via the glottic opening.[6,7] It was hypothesised that combined insertion of both the GVAL blade and ETT provides a fast, safe, and effective alternative to the traditional GlideScope technique. In this study, the authors aimed to adopt a new combined GlideScope technique to achieve improvement in these parameters during endotracheal intubation. The secondary objective was to optimise, if possible, the use of GlideScope and to reduce the risks and complications related to its use.

METHODS AND MATERIALS

This prospective, randomised, comparative study was conducted during the period from March 2017 to August 2018. Ethical approval was obtained from the Hospital Ethical Committee. Informed written consent from all patients was taken. A total of 50 patients aged 18–90 years with an American Society of Anesthesiologists' (ASA) classification of Grade I–IV, anticipated difficulty in airway intubation, and who presented for elective surgery under general anaesthesia were enrolled in the study. Exclusion criteria included patients with unanticipated difficult intubation, airway trauma, airway pathology, bleeding tendency, emergency procedure, pregnancy, full stomach, or need for rapid sequence intubation. Additionally, patients unwilling to participate were excluded. All patients were informed about the study and written consent was obtained. Routine preoperative evaluation including medical history and physical examination was performed. Proper airway assessment and evaluation was carried out by an experienced consultant anaesthetist. All patients fulfilled the criteria of anticipated difficult intubation. Every patient had at least two criteria out of the history of difficult intubation, Mallampati Score III/IV, thyromental distance <6 cm, and neck circumference >40 cm. All patients were premedicated with ondansetron 4 mg and dexamethasone 8 mg intravenously. All patients received intravenous midazolam, at a dosage of 0.5–2.0 mg, in the holding area before moving to the operating room.

Patients were randomly selected and assigned to 1 of the 2 groups with 25 patients in each (TG and CG) using a computer-generated block randomisation program. The results of the allocation were kept in an opaque envelope in the operating room and were picked randomly by a designated person per patient. TG consisted of the patients who were intubated with GlideScope; the blade was inserted, followed by optimisation of the glottic opening, and finally ETT insertion via the mouth for tracheal intubation. In CG both the GlideScope and ETT were inserted at the same time, and the glottic opening was optimised for tracheal intubation.

After tracheal intubation the stylet was removed and ETT placement was confirmed by lung auscultation and end-tidal carbon dioxide and secured into place. The intubation procedure was performed by consultant anaesthetists with sufficient experience in using GlideScope (>10 years). The optimum view of the glottis (based on Cormack–Lehane [CL] system classification); the time-to-intubation (TTI), defined as the time needed from blade insertion to ETT placement; postintubation airway trauma; and practitioner and patient satisfaction were all assessed and evaluated. The primary outcome of the study was based on the TTI (divided into 3 categories: ≤15, 15–30, and >30 seconds) and CL classification (scored as excellent [CL=1], good [CL=2/3], and bad [CL>3]). The intubation time category was selected based on the observation that most complete GlideScope intubations could be performed in >30 sec, and the time was recorded by the assigned anaesthetic technician. The secondary objectives were postintubation

airway trauma and satisfaction of the patients and practitioners. The satisfaction of the patients and practitioners performing the procedure was assessed using a 1–10 satisfaction score. Construction of a pilot questionnaire was carried out for both patients and practitioners to validate the scores.

Data entry and analysis using the Statistical Package for Social Sciences 21.0 (IBM, Armonk, New York, USA) was performed. For the purpose of sample size calculation, TTI was used as the primary outcome of this study. More than one trial for intubation was excluded from the study. No previous studies have compared this technique for the GlideScope with the traditional method; however, some studies compared the GlideScope with the conventional laryngoscope, using 25 patients per group. Assuming the same, a 2-sided Type 1 error of 0.05%, power of 80%, and sample size of 25 for each group was required to detect a significant difference. A total of 58 patients were enrolled and randomised in the study, however, 4 patients were excluded from each group, therefore, 50 patients were included in the study, with 25 in each group (Figure 1). The categorical data are presented as a number and percentage and were subjected to Fisher's exact or Chi-square test for analysis. The statistical significance was considered at $p \leq 0.05$.

RESULTS

There were no significant differences between the two groups regarding the criteria of anticipated difficult intubation (Table 1).

The field of view and optimum access for intubation obtained during the procedure was assessed in both groups. It was divided into three categories: excellent, good, and poor view, based on glottic opening, centralisation, and epiglottic view. A total of 16 patients in TG (64%) showed an excellent field view compared to 18 patients (72%) in CG. The good field view was demonstrated in 8 patients (32%) in TG compared to 6 patients (24%) in CG. The differences between both groups regarding the excellent and good field view were not significant. In the study, 2 patients, 1 from each group, showed bad field view; however, the intubation was successful (Table 2).

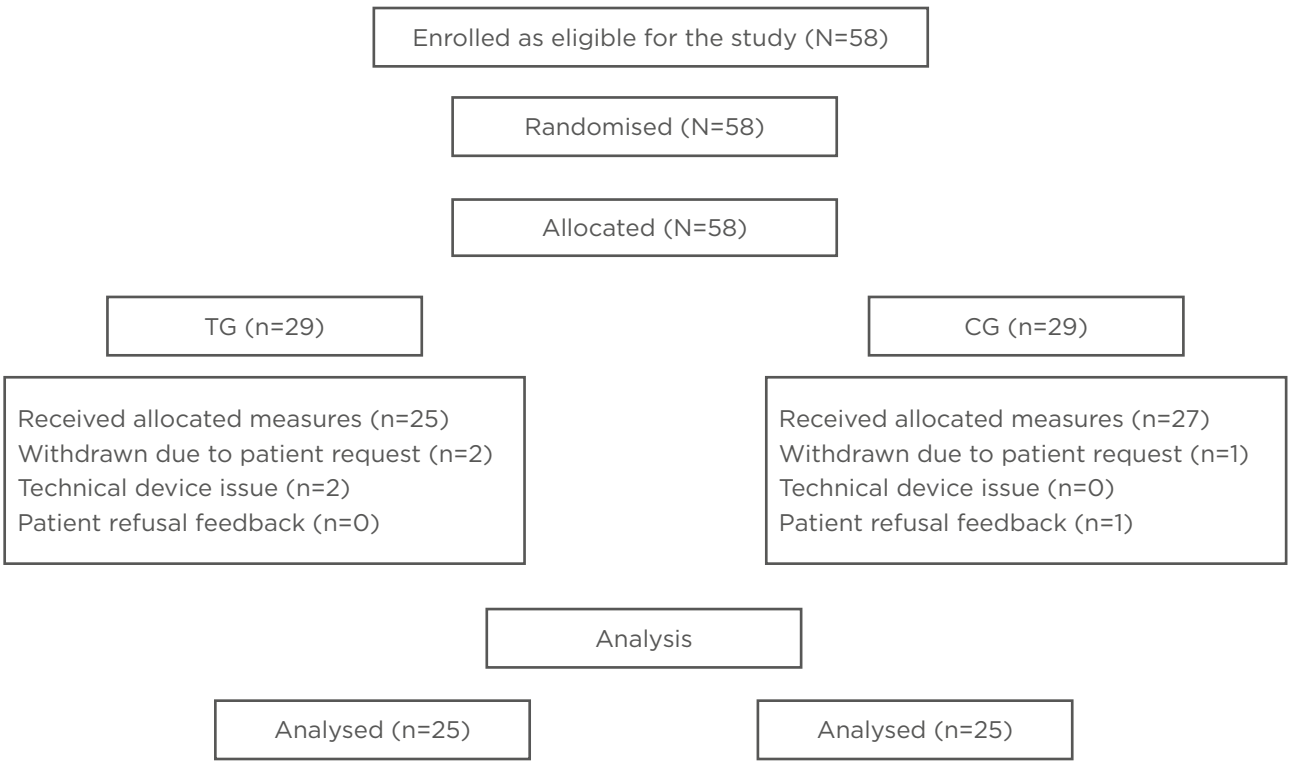

Figure 1: Diagram for sample size of the study.

CG: combined GlideScope®; TG: traditional GlideScope.

Table 1: Age, sex, airway parameters, and history of difficult intubation distribution.

Characters	Group A n=25	%	Group B n=25	%	p value
Age					
18–30 years	3	12%	5	20%	0.450
30–60 years	14	56%	13	52%	0.782
≥60 years	8	32%	7	28%	0.763
Sex					
Male	14	56%	12	48%	0.580
Female	11	44%	13	52%	0.310
Mallampati score					
I and II	11	44%	9	36%	0.573
III and IV	14	56%	16	64%	0.573
Neck circumference					
≤40 cm	12	48%	10	40%	0.578
≥40 cm	13	52%	15	60%	0.578
Thyromental distance					
≥6 cm	17	68%	16	64%	0.771
≤6 cm	8	32%	9	36%	0.771
History of difficult intubation					
No	20	80%	22	88%	0.230
Yes	5	20%	3	12%	0.451

The TTI from the beginning of the blade insertion to tube placement was assessed and divided into three categories: <15, 15–30, and >30 seconds (when more than one attempt was used). Most patients in the TG group (n=22) were successfully intubated within <15 seconds compared to all patients in CG. No significant differences were found (p=0.0767). Postintubation airway trauma was also evaluated. One patient in the study, from the TG group, experienced minor airway trauma because of upper lip injury, which only needed patient reassurance. There were no significant differences (p=0.322) (Table 2).

The satisfaction of the patients and practitioners performing the procedure is shown in Table 2. A satisfaction score of 1–10 was used. A score of 8–10, 4–7, and 0–3 were considered as high, fair, and bad satisfaction, respectively, <3 was also considered as a bad satisfaction score. The number of patients in the TG and CG groups who reflected a high satisfaction score was 22 (88%) and 23 (92%), respectively, with no significant statistical difference (p=0.646). Additionally, 76% of the practitioners reported a high satisfaction score during the procedures in TG compared to 96% in CG (p=0.042).

DISCUSSION

To the authors' knowledge, this is the first study to evaluate this new technique for intubation with GVAL. It is crucial to consider laryngoscopy and intubation as two separate steps in airway management, because there is a possibility of facing difficulty in either step. Although GlideScope provided a good or excellent view of the glottis, the intubation was not always straightforward. Many types of stylets and ETT are used to increase successful intubation with GlideScope; however, there are numerous reports of airway trauma during intubation attempts.[1,2] The good-to-excellent glottic view offered by GlideScope has markedly increased its popularity over recent years compared to direct laryngoscopy.[3] Different studies performed in emergency departments have shown intubation using GlideScope requires significantly more time. The rates of successful intubation on first attempt are not significantly different between GlideScope and direct laryngoscopy.[4]

Table 2: Field view, time from start to intubation, postintubation airway trauma, and satisfaction.

Characters	Group A n=25	%	Group B n=25	%	p value
Field view and optimisation					
Excellent (C–L: 1)	16	64%	20	72%	0.216
Good (C–L: 2 or 3)	8	32%	4	24%	0.533
Poor (C–L: >3)	1	4%	1	4%	1.000
Time from start to intubation					
≤15 sec	22	88%	25	100%	0.077
15–30 sec	3	12%	0	0%	0.077
≥30 sec	0	0%	0	0%	
Postintubation airway trauma					
Yes	1	4%	0	0%	0.323
Patient's satisfaction					
8-10	22	88%	23	92%	0.646
4-7	3	12%	2	8%	0.646
≤3	0	0%	0	0%	
Doctor's satisfaction					
8-10	19	76%	24	96%	0.042
4-7	6	24%	1	4%	0.042
≤3	0	0%	0	0%	

C–L: Cormack–Lehane.

Successful ETT placement is usually best achieved by using a stylet formed in the shape of a hockey stick with a 90° bend. Once the tube enters the glottis the stylet is withdrawn by approximately 3 cm, followed by advancing of the tube slightly in order to prevent hitting the tracheal wall.[5,6]

The authors found that the differences between the TG and CG groups regarding the excellent and good field view were not significant. Only two patients in the study, one from each group, showed a poor field view, despite successful intubation. Evaluation of TTI, starting from the beginning of blade insertion up to ETT placement, revealed no significant difference. All the patients were intubated within 30 seconds in both groups. Postintubation airway trauma was also evaluated. One patient in the study, from the TG group, experienced minor airway trauma due to upper lip injury, which only required patient reassurance. This difference was not significant.

The satisfaction of the patients and practitioners performing the procedure was assessed using a 1–10 satisfaction score. There were no significant differences in patients' satisfaction; however, the practitioners showed higher satisfaction in the CG group compared to the TG group (p=0.042). To improve ETT insertion through the mouth, Bacon et al.[7] recommended GlideScope blade insertion to the left of the mouth midline. They also recommended ascending the scope to improve the laryngeal view and holding of the tube at the level of the connector to improve the manoeuvrability.[7] Kramer et al.[8] used the technique of ETT insertion through the mouth in a horizontal plane to GlideScope, and once the tube had passed the flange of the GlideScope, they rotated it to the vertical position. Cho et al.[9] found that the insertion of the blade of the GlideScope nearer to the left corner of the mouth resulted in a larger space for ETT insertion. With this manoeuvre, Cho et al.[9] noticed a potential avoidance of oropharyngeal mucosal injury. They also showed that introduction of ETT into the mouth prior to the insertion of the GlideScope may result in airway trauma.

Walls et al.[10] reported a case in which, despite Grade 1 laryngeal view, they encountered difficulty in ETT insertion via the vocal cord to

the trachea due to a steep posterior angle of the trachea with the laryngeal/glottic axis. They successfully completed ETT insertion using a sharply curved malleable stylet. Once the ETT entered the glottis it was then rotated 180° clockwise to enable passage down the trachea.[10] A similar manoeuvre was used in another reported case by Xue et al.,[11] after the failure of 90° rotation and relaxation of the tilt angle of the GlideScope. However, in reply to Walls et al.,[10] Sharma et al.[12] considered their manoeuvre during tube insertion and removal of the stylet as traumatic and suggested the use of another manoeuvre. Dow et al.[13] used a reverse loading technique by loading the tube on the lubricated curved stylet as usual (inherent memory of the tube), followed by bending the distal stylet in the opposite direction to the inherent memory of the ETT, the tube was loaded and bent backwards against its natural curve.

A successful GVAL tracheal intubation has been performed by Bader et al.[14] in 12 patients consecutively, with strict cervical stabilisation using a J-shaped tube. Direction of the ETT via the vocal cord could also be achieved by using a gum-elastic bougie or a long, semi-rigid catheter with a controllable tip.[15,16] Dupanovic et al.[17] adopted a gear stick technique by bending the proximal end of the stylet 90° to the right to form a handle, in addition to 90° curving of the distal tube anteriorly. They had held the handle like an automobile gear lever. They inserted the tip of the ETT via the right corner of the mouth.[17] Corda et al.[18] found that a jaw thrust manoeuvre was often helpful in improving the glottic view when the GlideScope is used; however, cricoid pressure showed no significant improvement. They recommend the use of jaw thrust as a first line manoeuvre to aid glottic visualisation and tracheal intubation during GVAL.[18]

The limitations of this study included the lack of blinding in the intubation methods, the need for sufficient experience in handling both GlideScope and ETT, and the need for sufficient mouth opening to cope with both the GlideScope blade and ETT.

CONCLUSION

Combined GlideScope techniques reduces the incidence of lost glottic view, reduces time to complete intubation, and reduces trauma as the ETT passed under vision with the blade. However, training is needed to synchronise the handling of GlideScope and ETT at the same time.

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Utility of Perioperative Warming for the Prevention of Surgical Site Infection and Patient Rehabilitative Complications: A Systematic Review

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Abstract

Overview: Surgical site infection (SSI) is a leading cause of postoperative complication, rehospitalisation, and patient mortality after invasive clinical interventions. Surgical risks compounded by SSI introduce greater medical, economic, and quality-of-life challenges for both patients and providers alike, and to better inform clinical practice, empirical evaluation of modern surgical warming techniques is relevant. This systematic review and meta-analysis qualitatively examined the efficacy of both active and passive perioperative warming interventions upon SSI presentation versus standardised (i.e., non-warming) care.

Methods: This review analysed available literature on active and passive warming application across general anaesthesia procedures, containing longitudinal data on patient outcomes and SSI. The primary outcome studied was occurrence of post-surgical SSI; secondary outcomes included rehabilitative length of stay, attributable SSI-related mortality, and incidence of re-admittance.

Results: Meta-analysis demonstrated a significantly reduced risk ratio for SSI in patients receiving any surgical warming intervention (odds ratio: 0.36; 95% confidence interval: 0.18–0.87; $p<0.01$) compared to individuals treated under standard care conditions, with limited further data supporting improved active warming effect in contrast with passive implementation. Secondary postoperative outcomes, including length of rehabilitative stay or wound healing score (ASEPSIS), correspondingly demonstrated greater outcomes for surgical patients receiving perioperative warming. Introduction of warming interventions consistently correlated with reduced patient-reported pain experiences ($p<0.05$) and downstream care expenditures ($p<0.01$).

Conclusion: The present review identified evidence supporting a statistically significant correlation between both active and passive perioperative warming interventions to SSI prevention. These findings strongly support the recommendation of standardised perioperative warming implementation with continued investigation of relative efficacy contrasting active and passive methodologies, and across more diverse and substantial patient population sizes.

INTRODUCTION

In modern surgical procedures, a consistent risk is the development of surgical site infection (SSI) postoperatively, projected to be affecting approximately 1–3% of all American and European patients[1] and associated with $4.25 billion in preventable costs.[2] SSI are defined by the World Health Organization (WHO) and U.S. Centers for Disease Control and Prevention (CDC) as infections occurring within the physiological locale of preceding surgical intervention, typically within 30 days of operation.[3] Clinical definition may include physical manifestation of discharge or swab with $>1.0x10^6$ colony forming units per mm^3 tissue, associated with at least 1 symptomology of pain, inflammation, oedema, redness, or elevated dermal temperature.[4] Traditionally established risk factors for SSI presentation include the scale and scope of intervention, comorbidities, patient demographics, immunocompromisation, and diabetes;[5] however, increasing recognition is becoming directed toward the role of perioperative temperature regulation (approximate euthermia 36.5–37.5 °C) in maintaining patient SSI-protective immunohomeostasis.[5] During surgeries, heat loss is often most significant in relation to anaesthesia introduction and general patient environmental exposure, which, in turn, downregulates immune function and instigates risk for coagulopathy, decreased basal metabolic rate, lower oxygen consumption, and immunosuppression.[5-7]

Operative hypothermia (core temperature <36.5 °C) is exceedingly common however, because of the dynamic nature of operating conditions and external factors which must be controlled for during invasive procedures.[8] Literature has demonstrated that many prevalent surgical complications encompassing excessive bleeding, cardiac arrest and myocardial infarction, musculoskeletal ischaemia, and increases in all-cause rehabilitative hospital stay, as well as total expenditures for both patient and care organisations,[9,10] link strongly to the persistence of surgical hypothermia. Methodologies aiming to maintain ideal patient temperatures intraoperatively have therefore become increasingly implemented, ranging from active devices, such as forced warm airflow, to passive introduction, such as heat-retaining blankets. In isolation, these techniques have been established as efficacious for reducing intraoperative hypothermia across environmental conditions of the operating theatre.[11,12] As a result, considerable assumptions regarding their intuitively protective influences against the risks of both SSI and their complications are made.[13,14] In practice, however, the proposed degree of secondary generalisability amongst surgical warming-reduced normothermia and SSI reduction remains in need of robust empirical support.

Alongside relatively lacking clinical literature relating warming interventions directly against SSI presentation and related patient recovery measures, existing studies have also yielded conflicting conclusions. Most recently in 2015, Ousey et al.[15] concluded that while both active and passive perisurgical warming conferred significant benefits toward some reduction in short-term inpatient SSI recordings, follow-up tracking data suggested that these benefits disappeared when evaluated by more longitudinal factors such as SSI-related hospitalisations, further acute exacerbation, or long-term morbidity and mortality of attributable cause. Contemporary research from paediatric spine procedures indicate that surgical warming interventions significantly reduce postoperative bleeding and blood transfusion volume but generally fail to produce meaningful decreases in patient-centred results, including SSI severity and length of admittance.[16] Critics of these and comparable studies have argued that small sample size, narrow surgical specialisation patient populations, and lack of effective mid-to-long-term follow-up measurements (beyond 1 year post surgery) often leaves negative or inconclusive findings underdeveloped.[17-19] Other studies have attributed unexpectedly differing postoperative outcomes to individual factors such as patient health status[20] or adherence to perioperative instruction.[21] Nonetheless, they recommend that warming methods be clinically standardised to work towards reduction of SSI-related complications by way of normothermia assurance. Throughout a seemingly contradictory assembly of conclusions on the proposed overall inter-relationship between warming, thermal conditions, and SSI development status, investigators have consistently noted potential differences between specific warming intervention methods and outcomes. Of

particular interest is the operational divide between active and passive intervention, with some evidence to suggest that the former may confer greater effect; this debate remains actively investigated.[22] At present, consultants routinely cite insufficient evidence-based findings as explanation for a widespread lack of agreement upon differential application of any or either perioperative warming approach.[23-26]

The present review is therefore particularly relevant for quality-of-care improvement efforts, in that quantitative evaluation of available data, associating various pathways of warming intervention with outcome variables, will inform the strongest candidates for efficacious SSI prevention. Occurrence of SSI rehospitalisation and significant postoperative complications remains a singular source of medico-economic burden, with remediation a foremost priority. Findings derived from the present study may prove especially productive for eventual construction of specialty-selective groundwork for adaptable and patient-personalised care guidelines, which may govern warming intervention within traditionally hazardous surgical theatres.

METHODS

This systematic review examines emerging clinical dissonance upon whether intraoperative clinical warming implementation, in addition to component divisions upon passive or active methodology, confer measurable benefit towards the prevention of downstream patient SSI development through alleviation of perioperative hypothermic states. Design and implementation of this study was collectively modelled upon the most recently updated version of the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) framework, with direct fulfilment of the standardised 27-item checklist.[27] This encompassing generalisable review and meta-analysis examines study formation (i.e., incorporation of clear inclusion and exclusion eligibility criteria) to practical application (i.e., funding disclosures).

Consequently, all included studies obtained via a comprehensive, sequential-scope, and keyword-based online literature search of PubMed/Medline/EuropePMC, ScienceDirect, and Google Scholar were screened initially by title and abstract for eligibility. Keyword-driven search parameters proceeded with increasing specificity, from generalised papers covering perioperative normothermia, to noted trends in SSI incidence, warming intervention introduction and variation, and measurable patient-specific rehabilitative indicators. Keyword implementation and database-output filtering was achieved primarily by dynamic boolean operators, followed by manual inspection of produced literature for specificity and validity. After eliminating abstracts not matching PRISMA guideline-driven selection criteria, a full-text review highlighted nine papers suitable for in-depth analyses (see Table 1 for detailed review summation).

A most recent (2018) version of the Critical Appraisal Skills Program (CASP) framework was used as the foundational guideline for determining selected studies' quality, relevance to the present review, and rigour of extracted data. In addition to CASP, specific risk of bias in selected studies were also subjected to a peer Cochrane Collaboration tool for bias assessment; this dual and apparent overlapping usage of review guidelines derives from its previously demonstrated success for increasing descriptive detail and source selection standardisation.[28] Independent sensitivity testing for potential meta-analysis results confounded source material language-of-publication (consideration of non-English materials), study analysis by an alternative fixed-effects statistical model, and subjective review of related case-report and case-series literature (individual patients, or small and homogenous patient populations). All sensitivity analyses failed to significantly alter the present review's quantitative findings or ensuing qualitative discussion emphases, and therefore the overall methodology and recorded outcomes of the study are suggested as being robust (collective changes in empirical outcomes: $p>0.68$).

Data Analysis

Intra-study effect size between warming intervention, both actively and passively delineated, and standard non-warming care upon SSI prevalence were the primary outcomes examined. Across selected literature, standardised units of measurement were the

recorded downstream patient occurrence SSI presentations by both raw constituency within total population (cases per total patients), as well as percentage composition. Secondary outcome measures such as morbidity and mortality are discussed by empirical proportion, and subjectively as needed.

Results

Nine studies met all the criteria and were selected for analysis in this review. The data from some 3,627 demographically diverse patients across the included literature were aggregated for systematic analysis. Individual study scope and population sizes of these studies ranged from 38[29,30] to 1,824 patients.[31,32]

Evaluation of Outcomes

All studies reported favourable effects of warming intervention after introduction of perioperative hypothermia prevention, and literature that separated active versus passive warming preliminarily identified active means as being somewhat more efficacious in the clinic.[30,31] Eight of nine examined studies significantly associated warming procedures with reduced SSI occurrence, with the lone dissenting study exhibiting marginally insignificant strength of association between said factors (p>0.05; Lista et al.[25] descriptive following). Publication-specific secondary outcomes varied between literature and encompassed a range of factors such as patient reintervention and readmittance rates, attributable mortality, and recovery length-of-stay. These admittedly more limited indicators generally confirmed hypothesised patient post-surgical outcome improvements concurrent with implementation of perioperative warming intervention.

Mason et al.[33] found in a cohort of cancer patients (N=246; aged 20–87; mean BMI: 28) that aeriated active CO_2 normothermia regulation significantly decreased incidence of postoperative hypothermia (odds ratio [OR]: 0.10; 95% confidence interval [CI]: 0.04–0.23) alongside amplified SSI risks for patients experiencing perioperative hypothermia (OR: 4.0; 95% CI: 1.25–12.90), relative to standard care control. With humidification of active CO_2 warming, recipient patients' relative SSI risk decreased by approximately 66% in contrast to control non-warming care (p=0.04). SSI prevention-related cost-effectiveness analysis estimated net downstream healthcare savings from intraoperative warming at £155 per patient through preventable SSI-related follow-up. A post-investigative incremental cost-effectiveness ratio was concurrently negative, indicating an overall dominant cost-effective determination of SSI-prevention through intraoperative warming.[33]

Table 1: Selection criteria.

Inclusion criteria	Exclusion criteria (by design)	Exclusion criteria (de facto)
Quantitative design (randomised controlled trials preferred), clinical cohort studies also included	Qualitative and non-empirical studies	Not available in Medline/ PubMed, Google Scholar, or ScienceDirect
English language	Non-English language publications	Published
Surgical site infection as outcome measure	Did not explicitly measure surgical site infection outcome	Relatively recent (to be available and/or cited electronically)
Warming interventions as independent variable	Did not use warming interventions as independent factor(s)	
Meets established literature/results quality standards (see results)	Does not meet data/study quality criteria	
Studies reference primary patient data	Secondary patient data and/or reviews	
Passes author conflict of interest checks	Author conflict of interest noted	
Involved general anaesthetic surgical procedures	Non-surgical and/or localised anaesthesia	

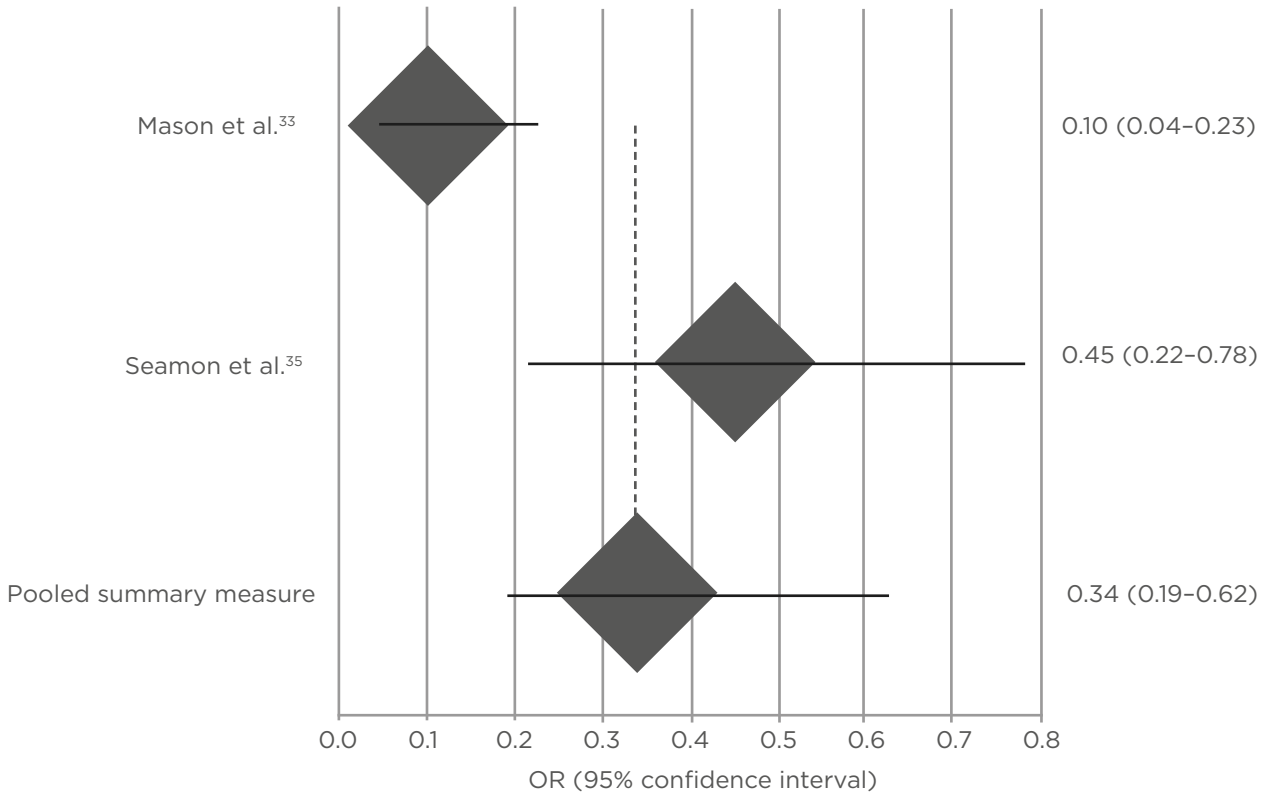

Figure 1: Meta-analysis of warming intervention and operative hypothermia by Forest plot.

Odds ratio of surgical site infection development and perioperative hypothermia [95% confidence interval]. Odds ratio below 1.0 indicates relative risk reduction in surgical site infection for patients with warming intervention compared to standard, non-warming care.

OR: odds ratio.

Conclusive findings by Mason et al.[32] compare favourably to the study of elective open colorectal surgery, wherein 18/96 patients examined experienced SSI under hypothermic surgical conditions (34.7±0.6 °C; 19%) contrasted to 6/104 patients under passive-intervention normothermia (36.6±0.5 °C; 6%).[21] This statistically significant finding (p=0.009) was supported by numerous secondary outcomes: faster time to suture removal for normothermia patients (p=0.002) and decreased postoperative hospitalisation timeframe (2.6 days or roughly 20%; p=0.01) compared to hypothermic condition patients. Multivariate analysis additionally identified commonly-associated risk factors of tobacco use (OR: 10.5; 95% CI: 3.2–34.1) and patient age (OR: 1.6; 95% CI: 1.0–2.4) as significant positive correlates in consequent SSI prevalence. On a much wider scale, Liau et al.[32] quantified reduction in incidence of SSI from 3.1% to 0.5% among non-warming standard operative care and targeted surgical warming intervention (p<0.001), a relative 84.0% decrease. Corresponding SSI prevention-associated savings were tabulated at approximately USD$ 147,967.[32]

Melling et al.[34] performed intention-to-treat analysis and identified SSI in 19/139 non-warmed hernia surgery patients (14%) compared to 13/277 patients receiving active warming intervention (5%; p=0.001). ASEPSIS wound score severity likewise significantly decreased between warmed and control procedures (p=0.007). Corresponding to reduced SSI risk for patients receiving intervention, necessity of antibiotics post-surgically was diminished relative to control (p=0.002). No added significant differences were established for measurements of haematoma and seroma presentation. Follow-up in 2006 factoring in ASEPSIS standardised wound categorisation in hernia surgery again confirmed significant improvement in patients operated

with active perioperative warming (p<0.05) relative to non-warmed control, with statistically significant differences in subjective patient pain scores (p<0.05), for both short (2 hours) and longer-term (7 days postoperatively) warming versus baseline.[35] Similarly strong associations between warming, hypothermia reduction, and SSI prevention were shown by Wong et al.[36] in generalised abdominal surgery (N=103). Patients operated with passive warming (n=47) exhibited markedly lower SSI complication rates (32% versus 54% control; p=0.027) and blood loss (50% median quantity decrease; p=0.011) in contrast to non-warmed individuals. Anecdotally for review, this study individually reported perioperative mortality which was two amongst controls against one for within warmed patients; no relevant conclusions were drawn from this extremely incomplete dataset for warming correlation to intra-surgery mortality.

Clinical cohort analyses by Seamon et al.[37] demonstrated more significant associations between intraoperative hypothermia presentation and SSI development. Within non-warmed individuals SSI risk increased 221% per degree below 35 °C, a common clinical benchmark for perioperative hypothermic states (OR: 2.21; 95% CI: 1.24–3.92; p=0.007). In comparison were complementary results from Lista et al.[25] demonstrating significantly reduced postoperative length of stay and recovery rate over passive warming intervention (p=0.001), alongside lower perioperative analgesia administration requirement (p=0.042). Of note is the fact that Lista et al.[25] proved the only selected study in this review that failed to identify a meaningful association between warming intervention and postoperative SSI complication incidence (p>0.05). Guarded findings were observed by Smith et al.[29,30] in the field of gynaecological surgery; data indicated active warming resulted in more effective perioperative hypothermia prevention than either passive normothermia maintenance or non-warming standard surgical care, as evaluated by immediate measures and resulting occurrence of SSI (both p<0.05). Longitudinal patient outcomes (SSI, morbidity, and mortality) failed to exhibit meaningful consensus. This divergence, however, was attributed to difficulties in attrition and follow-up.

Meta-Analysis

Whereas the association between warming intervention and perioperative hypothermia prevention has been assumed at times and therefore inconsistently studied in literature, currently hypothesised clinical relationships between warming intervention implementation and SSI reduction nonetheless constitutively derive from this foundation. Mason et al.[33] and Seamon et al.[37] determined an OR of 0.34 (95% CI: 0.19–0.62; Figure 1), supporting intuitive expectations that both active and passive perioperative warming confers significant control over, and effect upon, normothermia retention. Kurz et al.[21] (p=0.009) and Seamon et al.[37] (p=0.007) similarly indicated strong temperature regulation improvements by active warming techniques contrasted to passive, and further validated the foundational warming-to-normothermia relationship by significance stratification of SSI risk across approaches. Meta-analysis of SSI development was OR-dependent, and the warming intervention demonstrated compatibly significant reductions in patient SSI post-normothermia surgeries, in contrast to procedures within which either hypothermic patient conditions were empirically identified (OR: 0.36; 95% CI: 0.18–0.87; p<0.01; Figure 2). Three selected studies in this review did not quantify SSI prevalence and warming intervention by OR measure, but nonetheless demonstrated significance between objectively-measured operative normothermia and reduced SSI presentation by counterpart risk ratio (RR) and maximum likelihood estimation (p<0.001; p=0.001; p<0.05; by Liau et al.,[32] Lista et al.,[25] and Smith et al.,[29] respectively).

Secondary outcome measures as reported by evaluated literature collectively indicated broad concurrence of perioperative improvement to SSI prevention, as well as normothermia guarantee. Relevant significant findings included time to suture removal (Kurz et al.:[21] p=0.002), differences in postoperative inpatient hospitalisation time (Kurz et al.:[21] p=0.01; Wong et al.:[36] p<0.05; Seamon et al.:[37] p=0.001), ASEPSIS wound score (Melling et al.:[34] p=0.007; Melling and Leaper:[35] p<0.05), patient-reported pain score (Melling and Leaper:[35] p<0.05), median blood loss (Wong et al.:[36] p=0.01), and perioperative analgesia use (Lista et al.:[25] p=0.04). A solitary, nonsignificant

secondary outcome indicator, as consecutively recorded by Melling et al.[34] and Lista et al.,[25] involved SSI-complicating haematoma and seroma frequency across surgical specialty, evaluated by both severity occurrence between warmed and non-warmed patients, whereupon interventions failed to show effective alleviation.[35]

DISCUSSION AND IMPLICATIONS

Against control care of non-warming operative treatments only, active warming methodologies consistently demonstrated a statistically significant effect for prevention of SSI (OR: 0.36; 95% CI: 0.18–0.87; p<0.01) as well as improving a host of related secondary outcome measures. In comparison of active to passive implementations of warming intervention, quantifiably contrasting data was more lacking. Although, the studies that did juxtapose both approaches consistently rated active means as having magnified relevant patient warming effects, both empirically (e.g., normothermia stability, primary SSI occurrence) and subjectively (quality-of-life estimation).[21,30,31,37]

Applications of surgical warming intervention investigations remain far-reaching across efforts to improve clinical outcomes and constituent patient experiences. Recorded postoperative microbial infection cases in the USA in 2019 have outpaced procedurally related rehabilitative complications by many magnitudes.[38] Having already been strongly correlated by prevalence with consequent SSI,[39] perioperative hypothermia prevention represents a promising clinical alternative to hazardous, resource-intensive reactive therapies. Furthermore, literature strongly suggests additional medical benefit outside of simple infection-rate reduction, such as accelerated physiological neogenesis.[40] Whilst no studies included for meta-analysis presently examined expectation for side-effect profiles via treatment with warming methodologies, some presentations have been noted; these include case reports of sustained burns from active forced-air warming[30] owing to improper implementation, alongside ongoing debate over potential methicillin-resistant *Staphylococcus aureus* bacterial infection exposure risks derived.[41]

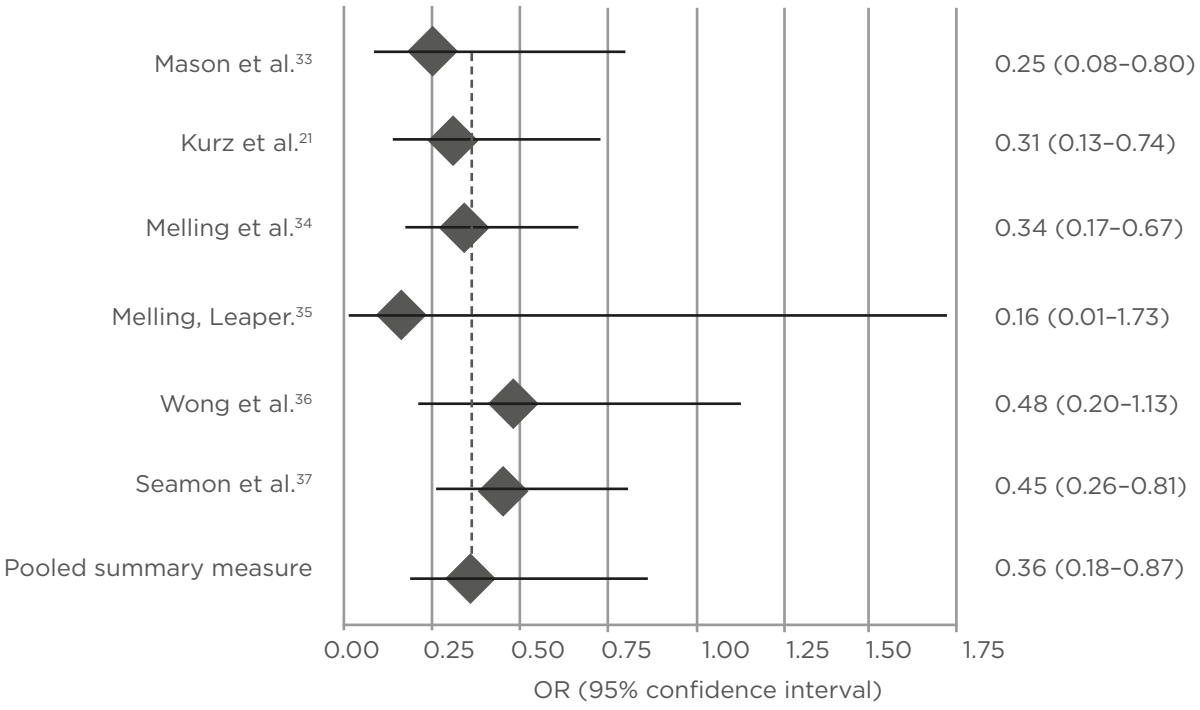

Figure 2: Meta-analysis of perioperative warming intervention and SSI risk by Forest plot.

Odds ratio of surgical site infection post-perioperative warming intervention. Odds ratio below 1.0 indicates relative risk reduction in surgical site infection for patients with warming intervention compared to standard, non-warming care.

OR: odds ratio; SSI: surgical site infection.

Hypothesised from inherent disturbance of operating suite sterility from requisite warming techniques ranging from normothermic fluid administration to forced airflow, the validity and strength of proposed warming side-effect profiles remain actively researched.[42,43]

Relevant Limitation and Biases

Important secondary measures complementary to empirical postoperative SSI presentation rates are consistently less well-tracked in literature. Given the clinically-oriented nature of perioperative care, this presents difficulty in accurately constructing a sufficient understanding of patient postoperative outcomes in context, especially in consideration of attrition and continuity of care confounds; a greater quantity of analysable supporting measures would prove extremely valuable for confident generalisation of currently available literary findings. Procedurally, of note is some persistent, although minor, variation of institutional definition for perioperative hypothermia. Concerningly, lower normothermic boundaries varied up to 1.0 °C (35.0–36.0 °C) between studies.[11] Follow-up elucidation on the relevance of this dissociation and greater evidence-based operative climate benchmarks are frequently discussed in literature, yet have not been extensively investigated to date.[44-46] In the present review, a slightly divergent bottom-array border differentiation between hypo and normothermic states similarly constrained confidence to generalise. Targeted research, aimed at continually elucidating patient-oriented outcome differences between hospital-determined acceptable operating suite standards, remains highly relevant for greater elucidation.

Largely inherent demographic and medical factors could have induced a degree of differential normothermia intervention, for example the complexity of surgical procedures. Prevailing clinical issues, such as morbidity and mortality, among patients' postoperative discharge due to disease state (or adherence to medical therapy, among other factors) could alter measured SSI strengths of association. Practically, extensive ethical and procedural challenges of blinding clinically-based research inevitably reduce internal validity of examined studies.[47,48] Slight procedural bias could arise from this review's literature selection, as no grey literature, hand searches, or non-English sources were considered (Table 1); although, sensitivity analyses of these factors would suggest negligible collective influences upon the overall findings. Macroscopic lack of a major multicentre, prospectively randomised controlled trials constrained the availability of high-quality data. Despite such, this review remains the most updated within a modest pool of literature examining effects of perioperative warming for SSI prevention and patient rehabilitation.

CONCLUSION

Guarantee of absolute perioperative normothermia remains among the most pressing of surgical challenges. Studies across numerous surgical subspecialties suggest that important protective effects exist between perioperative hypothermia prevention and downstream reduction in SSI or related complications incidence. The current systematic review and meta-analysis empirically confirmed numerous predicted fundamental associations between warming intervention and perioperative normothermia, with significant differences in both SSI occurrence across warming and non-warming perioperative conditions, as well as some improved secondary outcome measures. However, not enough data is presently available in literature to comprehensively analyse pair-wise associations of active versus passive warming with definitive ascertainment of relative patient-safety efficacy between modalities. It should be noted that preliminary findings discussed in this review nonetheless strongly suggest that magnified active warming benefits require greater adaptability and surgical staff influence.[49] The expectation therefore remains that with greater literature availability, further co-operative relationships between active surgical normothermia and SSI prevention may be strengthened across specialty and patient characterisations. Prospective investigation therein remains critical given that existing evidence is merely sufficient to endorse by clinical experience the implementation of active patient warming in the absence of exceptional patient or situational risk factors.[50-52]

Observed and common limitations in clinical outcomes literature, such as limited secondary

patient-oriented postoperative rehabilitative indicators[53-55] in combination with SSI occurrence, remain highly relevant and require additional subspecialty field and patient-population specific studies to elucidate for wider generalisability. Elucidation of effect size for warming interventions across wider operating methodologies, particularly in light of emerging minimally invasive surgical techniques, concurrently represent newly pressing directions of inquiry. Within retrospectively oriented research common in the clinical realm, particularly imperative is artificial elevation of Type-I error likelihood by means of structural course-of-treatment evaluation biases.[56-58] Across surgical interventions in the current review, interplays between SSI prevention from novel perioperative warming relative to variations in traditional antibiotic prescriptions proved difficult to unambiguously isolate; a fine scrutiny further complicated by existing concerns on clinical prescription pattern biases regarding situational or patient characteristics that influence type or quality of care.[34,35,59,60]

Considering the increasing availability of data regarding warming interventions and sustained interest in improving patient surgical outcomes, the expectation that normothermia regulation will play increasingly prominent roles across surgery is viewed as highly practical. As a largely inexpensive and easily implementable measure in modernised clinics, perioperative surgical warming should presently be routinely subscribed across surgical procedures with moderate-to-strong strength of recommendation[61] in the absence of contradictory clinical findings.

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Artificial Intelligence Applications in Medicine: A Rapid Overview of Current Paradigms

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Abstract

Artificial intelligence (AI) is defined as "the ability of a digital machine or computer to accomplish tasks that traditionally have required human intelligence." Simply put, these are machines that can think and learn. AI has become ubiquitous and is now being applied in healthcare. It uses concepts from statistics, computer science, and data science. An increased understanding of the tools is essential for medical practitioners and medical researchers so that they can contribute meaningfully to the development of the technology, instead of being mere data providers or data labellers. AI has been employed in the finance, marketing, and travel industries for a considerable length of time, but its application in medicine is only gaining acceptance now. Practical office tools based on the AI technologies appear to still be some time away, but these AI-based applications have the potential to benefit all stakeholders in the healthcare industry. This article briefly overviews the current paradigms of AI in medicine.

INTRODUCTION

The Merriam-Webster dictionary defines artificial intelligence (AI) as "a branch of computer science dealing with the simulation of intelligent behavior in computers" or "the capability of a machine to imitate intelligent human behavior." The layman may think of AI as mere algorithms and programs; however, there is a distinct difference from the usual programs which are task-specific and written to perform repetitive tasks. Machine learning (ML) refers to a computing machine or system's ability to teach or improve itself using experience without explicit programming for each improvement, using methods of forward chaining of algorithms derived from backward chaining of algorithm deduction from data. Deep learning is a subsection within ML focussed on using artificial neural networks to address highly abstract problems;[1] however, this is still a primitive form of AI. When fully developed, it will be capable of sentient and recursive or iterative self-improvement.

Classification

AI and AI-enabled machines can be classified depending on the emulation of the human mind. Technically, AI can be differentiated into three broad types: artificial narrow intelligence (ANI), artificial general intelligence (AGI), and artificial super intelligence.

AGI describes machinery that can work like the human brain and has the capacity to understand

or learn any intellectual task that a human can and to transfer this knowledge to other related domains. AGI is also referred to as strong AI, full AI, or as having the ability to perform 'general intelligent action'.[2,3] This is differently viewed by some authors who feel that strong AI is one that is capable of experiencing consciousness;[3] however, this is a powerful feat that we are some way away from yet.

ANI, also known as narrow-AI or weak-AI, is the only AI in existence at the present time. It possesses a narrow range of abilities and is focussed on a single, narrow task. Most people are aware of machine intelligence using natural-language-processing (NLP) such as Siri, Cortana, Google Assistant, Google Translate, and Alexa. Some AI systems in medicine diagnose and treat cancers and other illnesses using human-like reason and cognition, and as such are further examples of ANI.

Futuristic artificial super intelligence could in time surpass humans in certain domains because it can not only be applicable on a programmable level, but also in artistic creativity, emotional relationships, and decisions. Although these are strictly human domains, even today the population can struggle at managing emotional relationships.[2,3]

Current Sources of Data

The main areas in which AI is being applied in healthcare include mass screening, diagnostic imaging, laboratory data, electrodiagnosis, genetic diagnosis, clinical data, operation notes, electronic health records, and records from wearable devices.

Until recently, the most commonly used data in healthcare transactions and research were relational and heterogeneous databases. With the continual integration of the internet of things and advent of wearable technologies, the volume of data available for analysis is increasing and the techniques will also undergo paradigm shifts. This article focusses on the current paradigms and leaves the future direction of AI open to scientific advancements. Formerly, AI techniques used for structured data were ML methods such as classical support vector machines and neural network use, whereas for unstructured data, modern deep learning and NLP were commonly used. Various tools used in oncology, neurology, radiology, ophthalmology, and cardiology have become available.[4] Early detection, diagnosis, treatment, prognosis evaluation, and outcome prediction have all benefitted from AI systems, for example, IBM Watson.[5]

Currently, the use of IBM's Watson Oncology computer system at the Memorial Sloan Kettering Cancer Center, Manhattan, New York, USA, and the Cleveland Clinic, Cleveland, Ohio, USA, has identified drugs for the treatment of cancer patients with equal or better efficiency than human experts. It can also analyse journal articles for insights on drug development in addition to tailoring therapy.[5] At the Oregon Health & Science University (OHSU) Knight Cancer Institute, Portland, Oregon, USA, Microsoft's Hanover Project has analysed medical research and has predicted the most effective cancer drug treatment option tailored to individual patients with equal efficiency as a human expert.[6] The UK NHS has been using Google's DeepMind platform to detect certain health risks by analysing data that was collected using a mobile phone app. It also analyses medical images collected from NHS patients with the aim to generate computer vision algorithms to detect cancerous cells.[7] At Stanford University, Stanford, California, USA, the radiology algorithm performed better than human radiologists in identifying pneumonia, while for meeting the challenges of diabetic retinopathy (DR) management, the computer was as good as the expert ophthalmologists in making a referral decision. In addition, these computers could be on duty all year round, day and night, unlike the human experts.[8]

MACHINE LEARNING, DEEP LEARNING, AND NATURAL LANGUAGE PROCESSING

AI uses the ML component for handling structured data (images, electrophysiology [EP] data, genetic data) and the NLP component for mining unstructured texts. The algorithms are then trained using healthcare data, meaning the computers can aid physicians with disease diagnosis and treatment suggestions. The IBM Watson system is a pioneering system that has ML and NLP modules, and its application in the oncology field has received much praise.

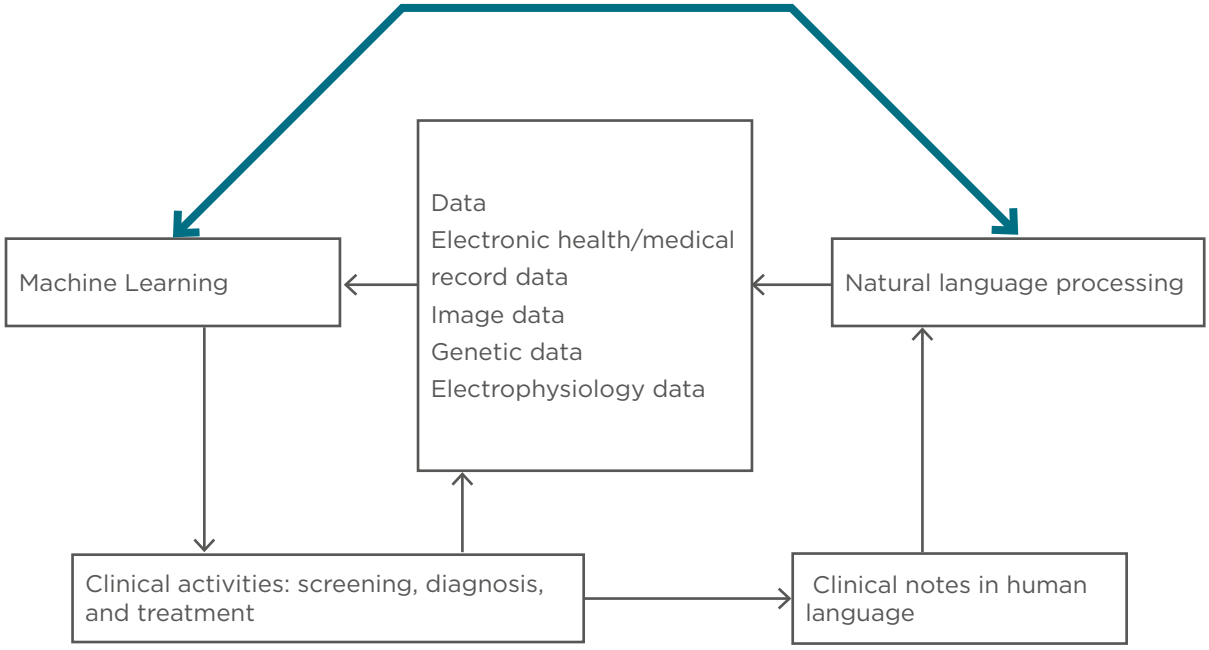

Figure 1: Schematic diagram of clinical decision making using clinical data cues with natural language processing and machine learning analysis.

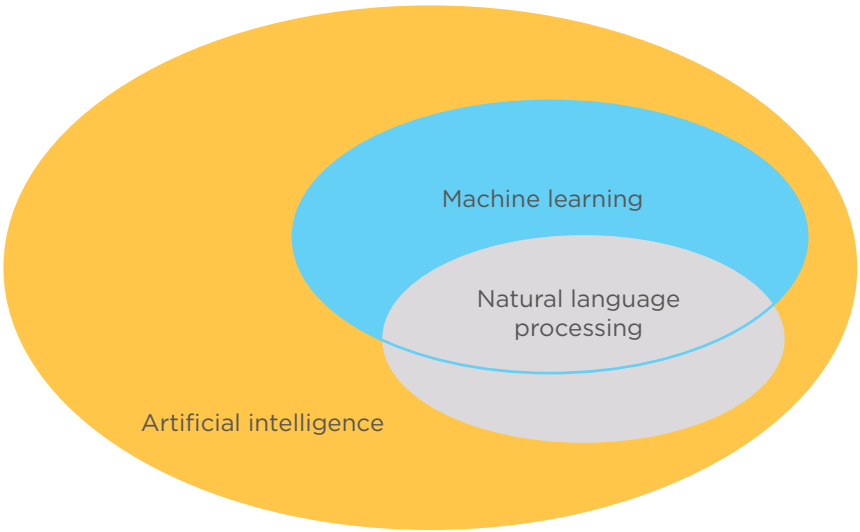

Figure 2: Schematic representation of the relationship between machine learning and natural language processing.

From Watson cancer treatment recommendations, 99% have correlated with decisions of the treating physician.[5,9] Watson in collaboration with Quest Diagnostics offer AI genetic diagnostic analysis.[10] By analysing genetic data, Watson has successfully identified the rare secondary leukaemia caused by myelodysplastic syndromes in Japan.[10]

For this discussion, AI devices are divided into two categories: ML techniques, which analyse structured data such as imaging, genetics, and EP data, and NLP methods, which extract information from unstructured data including clinical notes, medical journals, and other sources (Figure 1).[4,11]

ML procedures aid in clustering traits or attributes of patients and integrate the information to determine the probability of different disease outcomes. NLP procedures convert text to machine-readable structured data that can then be analysed using ML techniques (Figure 2).[11]

In the entity-attribute relationship, the patient is an entity and the attributes or traits include data such as age, gender, clinical symptoms, past history, diagnosis, biochemical parameters, diagnostic imaging, EP tests, physical examination results, medication, genetic testing, and follow up. Prognostic outcomes are also important in the analysis. Disease markers, disease indicators, quantitative disease levels such as tumour sizes and tumour marker levels, and 5 or 10-year survival rates are also important factors collated in records today.

UNSUPERVISED, SUPERVISED, AND REINFORCEMENT LEARNING

The ML algorithms can be broadly divided into unsupervised learning, supervised learning, and reinforcement learning. Unsupervised learning helps in feature extraction, while supervised learning is used for predictive modelling. Prediction elucidates the relationship between a patient trait and the outcome of interest, which is then used outside the training dataset. The reinforcement learning mode aims at 'strategic sequencing of rewards and punishments'. Semi-supervised learning is a hybrid system used for scenarios in which the outcome is missing for certain subjects.[12,13]

Unsupervised Learning Methods

Among the unsupervised learning methods, clustering and principal component analysis (PCA) are used to cluster subjects with similar traits together. Clustering algorithms provides cluster labels for patients, maximising similarity of patients within clusters and minimising similarity of patients between different ones. Hierarchical clustering, k-means clustering, and Gaussian mixture clustering are the most common clustering algorithms used in medicine. PCA is the mainstay of dimension reduction to represent the trait in some important dimensions and ignore background noise from noncontributing dimensions when the trait is recorded in a large number of dimensions. This analysis can be understood as the effort to project the trait in fewer principal component directions, such as the number of genes in a genome-wide association study;[12-15] however, when too many dimensions are used in the analysis the random effects interfere with one another and cause significant issues.[13,14]

Supervised Learning Methods

In supervised learning, the outcomes of the subjects are studied depending on their traits using a particular 'training process' to determine a function or an algorithm that correlates or associates outputs with the traits that are closest to the outcomes. Supervised learning has been used to study and provide information about clinically relevant results and therefore is one of the most commonly used AI techniques in medicine.[16] Unsupervised learning is often used in the preprocessing step for dimensionality reduction or cluster recognition to make supervised learning more data-efficient. Once a more powerful AI becomes available, this step will be automatically transferred from one dimension to another whether related or unrelated. In the present day, many are conversant around the techniques used for medical applications, including linear regression, logistic regression, naïve Bayes, decision tree, nearest neighbour, random forest, discriminant analysis, support vector machine (SVM), and neural network.[16]

Support Vector Machine

SVM and neural networks are the most popular techniques used because most of the work is related to image, genetic, and EP analysis. SVM and neural networks have been extensively used in oncological, neurological, and cardiovascular diseases.[16] SVM has been used for early detection of Alzheimer's disease, identification of imaging biomarkers for neurological and psychiatric diseases, and diagnosis of cancer. Model parameter determination, a convex optimisation problem, is always the global optimum in SVM. Mathematically, SVM is a discriminative classifier defining a separating hyperplane between two or more groups. It is a form of supervised learning using labelled training data where the algorithm creates an optimal hyperplane. In a two-dimensional space, the hyperplane can be represented by a line dividing the plane into

two parts with different classes on either side of the line.[15,17]

SVM is therefore extensively employed in medical research. It classifies the subjects into two or more groups; the outcome Yi is a classifier. It operates on the assumption of mutually exclusive groups, meaning that subjects can be separated into two or more groups through decision boundaries defined by the traits. A weighting is applied to the trait depending on its relative importance on affecting the outcome. The sum total of all weights should ideally add up to 1.0 or 100.0%. The goal of this training is to determine the optimal weight so that the outcomes are explained as much as possible in the resulting classification by the traits. The ideal goal is to minimise the error of classifying a patient to the wrong group based on outcome (Yi), also called misclassification error. The outcome is Yi and the tuning parameters are used to draw a plane that separates the groups in nonprobabilistic space. This can be done using many methods, but the most common ones still retain minimisation of quadratic loss function or ordinary least squares.[15] The main tuning parameters used are kernel, regularisation, gamma, and margin. The learning of the hyperplane in linear SVM involves transformation of the problem using a linear equation. For linear kernel, the equation for prediction for a new input using the dot product between the input vector (x) and each support vector (xi) is calculated by f(x)= B(0) + sum[ai* (x,xi)].

This equation involves the calculation of inner products of a new input vector (x) with all support vectors from the training data incorporated. Coefficients B0 and ai need to be calculated for each input from the training data by the learning algorithm. The polynomial kernel is calculated by K(x,xi)= 1 + sum(x*xi)^d and exponential as K(x,xi)= exp(-gamma*sum((x — xi^2)). Regularisation or C parameters reflect the effort to avoid misclassifying each training example. Larger values of C will choose a hyperplane that will be better at getting all the training points classified correctly even if that line or plane has to curve repeatedly. A small C value makes the optimiser define a larger margin separating the hyperplane at the cost of misclassifying more points. A margin is a separation of line from the closest class points; a good margin is one where this separation is larger for both the classes. Gamma parameter shows how far the influence of a single training example reaches. A low gamma reflects 'far' points, away from the plausible separation line that is considered in the calculation, and high values mean 'close' points; therefore, points close to the plausible separation line are considered. SVM has been used in the diagnosis of cancer imaging biomarkers[18] of neurological and psychiatric disease.[17,19]

Neural Network

Neural network is a technique in which the association between the input variables and the outcome are represented by multiple hidden layer combinations of prespecified functions. The goal of the equation is to estimate the weights through input and outcome data so that the average error between the outcome and their predictions is minimised. Neural networks have been used to diagnose stroke, to diagnose cancer from 6,567 genes,[20] to predict breast cancer using texture information from mammographic images,[21] and to diagnose Parkinson's disease from motor and nonmotor symptoms and neuroimages.[22]

DEEP LEARNING

Deep learning is a neural network with multiple hidden layers and is capable of exploring complex nonlinear data patterns and high volumes of data. Increased data volumes and complexities have ensured the increasing popularity of deep learning. In 2016, deep learning achieved a 100% year on year increase in the field of medical research. Deep learning is extensively used in imaging analysis because the images are complex and the number of pixels generated is high. Commonly used deep learning algorithms in medicine include recurrent neural network, deep belief network, deep neural network, and convolution neural network (CNN), of which remains the most popular.[15,23]

Classical ML algorithms have failed to handle high-dimensionality data with large numbers of traits. The images contained thousands of pixels as traits and hence increased dimensionality. Initial solutions depended on dimension reduction by using a subset of pixels as features and later performing the ML algorithms, but information

loss in images can be substantial with such handling. Unsupervised learning techniques like PCA or clustering have been used for data driven dimension reduction.[15,23] Training datasets with experts performing heuristic analysis was an alternative approach used in radiology and ophthalmology, with CNN being used for high-dimensional image analysis.[24] Normalised pixel values were used from images and weighted in convolution layers with iterative sampling in the subsampling layers. A recursive function of weighted input values gave the final outputs. The weights were optimised to minimise the average error between outcomes and predictions[24] and the popular software packages Caffe, TensorFlow, and Cognitive Toolkit provided CNN support.[25-27]

CNN has been used for disease diagnosis in congenital cataract disease using the ocular images,[28] in diagnosing skin cancer from clinical images,[29] and for detecting referable DR through the retinal fundus photographs.[30] The sensitivity and specificity of the algorithms were >90%, and the CNN performance was comparable to experienced physicians in the accuracy for classifying both normal and disease cases. In 2009, Retinopathy Online Challenge used competition fundus photographic sets from 17,877 patients with diabetes who had not previously been diagnosed with DR, consisting of two fundus images from each eye. It is universally agreed that a combination of blood vessel parameters, microaneurysm detection, exudates, texture, and distance between the exudates and fovea are among the most important features to detect the different stages of DR.[31] Nayak et al.[32] used the area of the exudates, blood vessels, and texture parameters, analysed through neural networks, to classify the fundus image into normal, nonproliferative DR, and proliferative DR. A detection accuracy of 93% with a sensitivity of 90% and a specificity of 100% were reported. SVM classified fundus images into normal, mild, moderate, severe, and prolific DR classes, with a detection accuracy of 82%, sensitivity of 82%, and specificity of 88%. Lee et al.[33] described a software to grade the severity of haemorrhages and microaneurysms, hard exudates, and cotton-wool spots of DR as a means to classify the disease.[33]

Clinical information in narrative text, physical examination, clinical signs, laboratory reports, operative notes, and discharge summaries are unstructured and not understood by computer programs. NLP is important in such situations because it parses the narrative text to extract information to assist the clinician in decision making.[14] The NLP pipeline has text processing and classification components. Using text processing, a series of disease-relevant keywords are identified in the clinical notes in databases. A subset of the keywords, through domain reduction, are selected and validated to analyse the structured data to aid clinicians in the decision-making process.[12,13]

The NLP pipelines have been used to read chest X-ray reports to alert physicians regarding the need for anti-infective therapy,[34] to monitor laboratory-based adverse effects[35] and variables associated with cerebral aneurysms disease,[36] and to extract cases of peripheral vascular disease from narrative clinical notes[37] with a high degree of accuracy.

Real-life implementation of AI technologies is still in nascent stages in medicine. It is facing hurdles including regulation, the interoperability of information algorithms, and availability of data for algorithms especially for validation after the training is over. Lack of standards to assess the safety and efficacy of AI systems has resulted in a proliferation of proprietary algorithms which do not crosstalk. The U.S. Food and Drug Administration (FDA) has recently advised classifying AI systems as 'general wellness products' putting them under loose regulation. Furthermore, rules for adaptive design in clinical trials were formulated for the assessment of operating characteristics of AI systems.[38]

There are no explicit laws covering data transfer for processing in many countries. Extraordinarily large amounts of data can be processed by an indirect third-party by service providers, recoding data according to USA laws, such as the deal between Google DeepMind and the Royal Free London NHS Foundation Trust which lead to debate in 2017. That agreement was criticised on the grounds of violating the Caldicott principles by transferring more data than necessary and blurring the line between the data controllers and data processors. Direct care providers need to be careful when sharing data with third-parties who are not in a direct care relationship with

the patient in question. If explicit consent and notice have not been given then all deidentified data, whether labelled or unlabelled, should come into public domain and be published by a statutory body. This will keep a check on illegal proprietary exploitation of the data and force the data processor to seek limited amounts of data for exchange.[39] Since, in the absence of consent, such deidentified datasets should be considered community resource, there is logic in placing it in the hands of the community, thereby enabling policing of these data exchanges is an extremely important issue that the governments across the world must consider seriously. With transfer learning and AGI, humans may not even be able to understand how the machine handled the data in the AI tools employed by them. Therefore, there is an extreme need to ensure the formulation of and adherence to principles of computational bioethics.[39] Once the AI system is deployed there should be a lack of continued data supply for the development and improvement of the system, and after initial training with historical data, little fine tuning and further algorithm development should be done. Additionally, no incentives for sharing data among users of the system should be made (Figure 3).

WHO PAYS FOR FINANCING THESE SYSTEMS?

Tax incentives have been offered, and the more recent emergence of the insurance companies as primary payers has started to shift the paradigm from 'payments based on treatment volume' to 'payments based on the treatment outcomes and fiscal efficiency'. Thus, the treating physicians, pharmaceutical companies, and patients have greater incentives to compile and exchange information.[40]

Development of complex algorithms is laborious and requires skilled resources. Once developed, they can be used in simple devices with standard hardware, similar to how face recognition was implemented on mobile phones. These algorithms can bring down the costs of the screening programmes immensely. Though in its nascent stages, the potential of this deep learning for use in DR screening programmes has been recognised and the latest results from Google's recent attempt are very encouraging.[39]

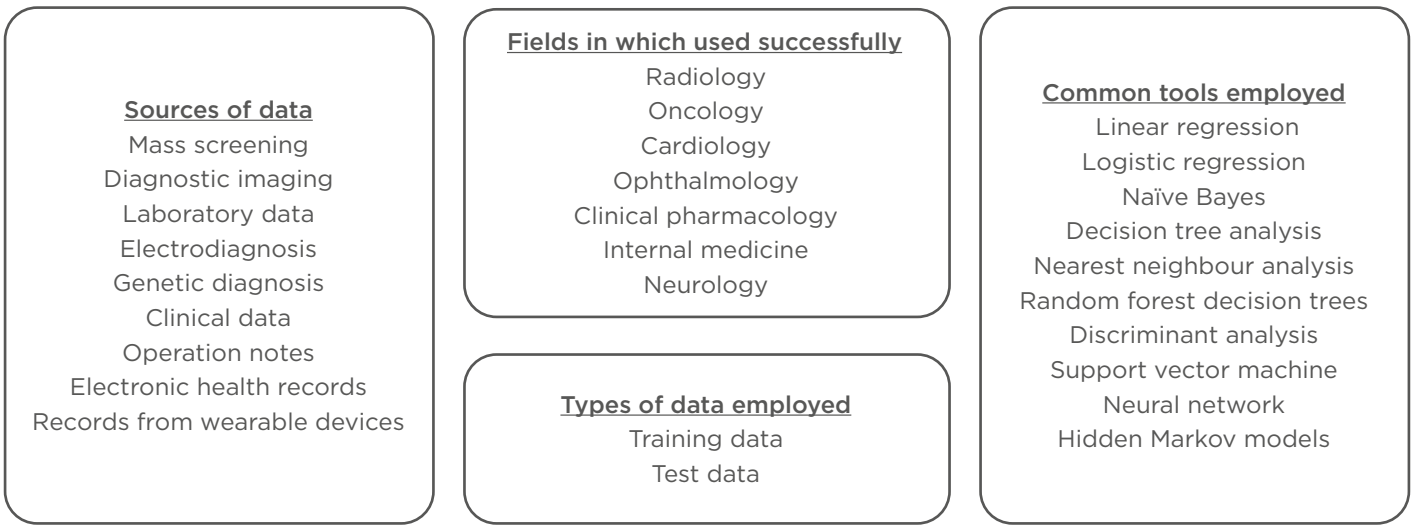

Figure 3: Overview of artificial intelligence in healthcare and challenges in obtaining and using data.

Artificial intelligence systems require continuous training using data from clinical studies.
The data employed can broadly be classified into training data and test data.[13,14]

FUTURE CONCERNS AND COMPENSATION OF THE CONTRIBUTORS

It must be remembered that these algorithms are being developed using resources from the communities at large and these communities must be suitably compensated. The ownership of the pooled data also needs to be looked at more carefully, especially with the increased use of wearable technologies. The proprietary platforms and lack of data interexchange, as well as absence of crosstalk, was a major inhibiting factor in the development of such technologies. The medical personnel need to become guides in the development of bioethics-based rules. It is important that adequate care is given to address all these bioethical concerns, because these rules will form the basis for all future developments and documentation. The supremacy of the human will should not become subservient to AI, even after it subjectively becomes increasingly more intelligent than the human beings. Clinical research, with the use of emerging tools, expanding volumes of data, structured databases, and rich information is now answering ever more complicated clinical questions and allowing forward chaining to real-life clinical questions. Prevention, diagnosis, treatment, and prognosis are becoming better defined with AI techniques, but the onus of ensuring that the machines do not run amok in the future lies with the clinicians and society at large.

CONCLUSIONS AND RECOMMENDATIONS

AI applications in healthcare have tremendous potential for being useful; however, success is dependent on clean, high-quality healthcare data, which requires impeccable planning and execution. Data capture, storing, preparation, and mining are critical steps and a standardised clinical vocabulary and the sharing of data across platforms is required. Bioethical standards in collecting and using data cannot be overemphasised. The authors hope that this paper makes the stakeholders realise their responsibility, contributes to AI in healthcare literature, and guides the development of tools to be employed for practice.

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The Role of Telemedicine in Infectious Diseases

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Abstract

The use of telemedicine has been described for various medical conditions. Telemedicine can improve access to care, reduce geographic barriers, and optimise healthcare for patients. The role of telemedicine has been described in antimicrobial stewardship programmes for the management of both acute and chronic infectious diseases, including HIV and hepatitis. The goal of this review is to provide data on the implementation of synchronous telemedicine programmes to provide infectious disease management.

INTRODUCTION

The continuous advancement of technology provides opportunities to create, improve, and expand access to healthcare in varying populations using telehealth and telemedicine. The World Health Organization (WHO) defines telemedicine as "the delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment, and prevention of disease and injuries, research and evaluation, and for the continuing education of healthcare providers, all in the interests of advancing the health of individuals and their communities."[1] Although the terms 'telehealth' and 'telemedicine' are often used interchangeably, telehealth refers to 'a broad scope of remote healthcare services', while telemedicine refers specifically to the provision of remote clinical services.[2] Numerous benefits have been realised through the practice of telemedicine because of wider availability and acceptance by both patients and medical practitioners in this growing clinical practice. Clinical and educational benefits have led to increased availability and affordability of equipment, changes to Medicare and Medicaid reimbursement, and increased billing parity laws. In addition, the potential for cost savings to not only the patient, but also healthcare systems, has led to additional interest in this mode of providing healthcare.

The use of telemedicine in infectious diseases is an expanding clinical practice with the goal of optimising clinical outcomes and improving access to care. It provides a link to healthcare that patients with acute infectious diseases and chronic infections, such as HIV and hepatitis C virus (HCV), and those who live in rural or isolated populations, may not have access

to otherwise. In addition, telehealth may provide improvement to access in cases like pre-exposure prophylaxis (PrEP) to assist in preventing HIV. Despite the expanding practice of telemedicine in infectious diseases, the Infectious Diseases Society of America (IDSA) is the only infectious diseases organisation that has a formal position statement on the use of telehealth and telemedicine. The purpose of this position statement is to educate members of IDSA on the use of telehealth and telemedicine technologies, as well as promote IDSA's position on the use of such technologies, specifically in the field of infectious diseases.[2] This literature review will evaluate and focus on the growing number of telemedicine programmes for use in the evaluation and treatment of infectious diseases.

SOURCES AND SELECTION OF CRITERIA

Articles pertaining to the role of telemedicine in infectious diseases between 1st January 2015 and 13th March 2019 were identified through EMBASE, PubMed/Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Google Scholar databases. Additional literature was identified through bibliography review from articles obtained through search databases. "Telemedicine", "telehealth", "infectious diseases", "HIV", "hepatitis C", "PrEP", and "antimicrobial stewardship" were key terms included in the literature search. While international articles were searched through EMBASE, CINAHL, and Google Scholar, only English language articles were included.

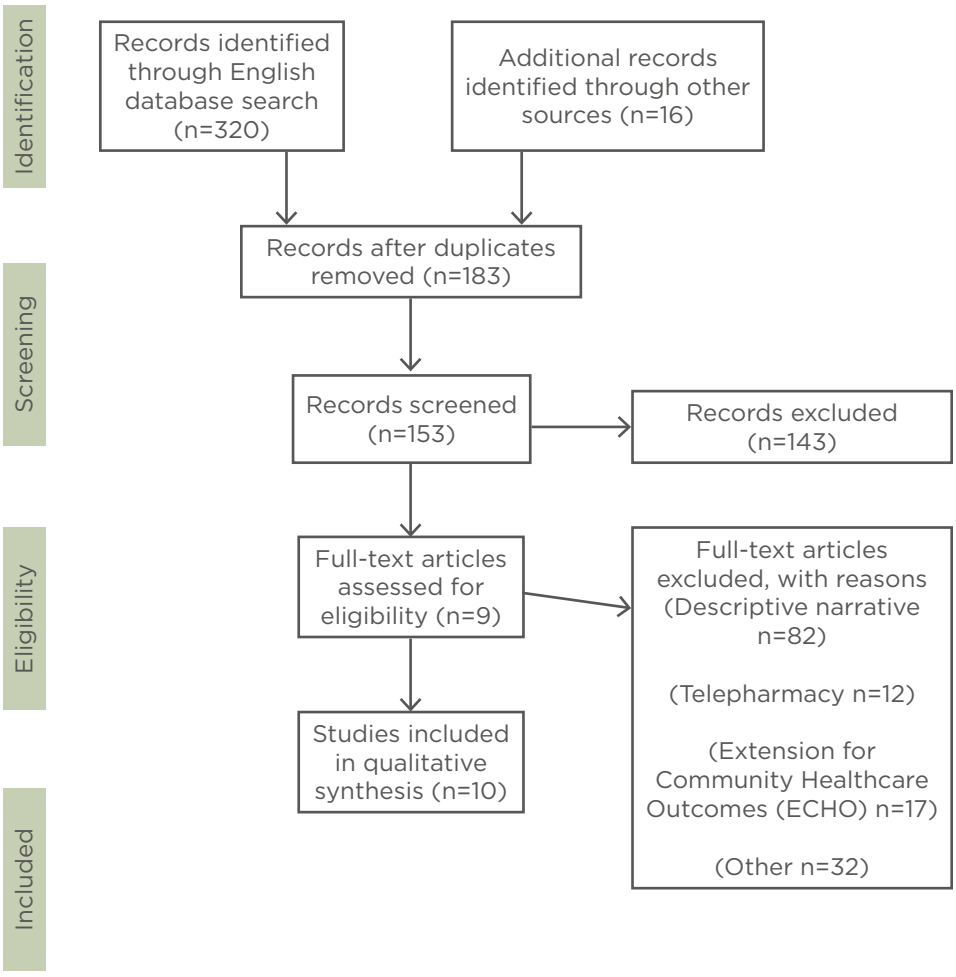

Figure 1: PRISMA flow diagram of the selection process of the studied literature.

Because a previous review on the use of telemedicine in the specialty of infectious diseases was previously published in 2014,[3] the authors limited their search to studies after this period to avoid any redundancy in the literature. For the purpose of this review, articles involving infectious diseases programmes with synchronous telemedicine (two-way video conferencing) and programme evaluation (outcome data and/or patient satisfaction) were included. Articles pertaining to telepharmacy, descriptive site narratives, and Extension for Community Healthcare Outcomes (ECHO) were excluded to focus on synchronous telemedicine programmes with documented clinical outcomes (Figure 1).

RESULTS

Antimicrobial Stewardship

Telemedicine in antimicrobial stewardship provides additional opportunities to address concerns of growing antimicrobial resistance. In southern Brazil, a 220-bed hospital designed a web-based platform to facilitate immediate post-prescription review of clinical data and provide feedback to physicians from remote infectious diseases specialists.[4] After data collection on its use, the programme increased the rate of appropriate antimicrobial prescribing from 51.4% to 81.4% (Table 1).[3] In Italy, a highly specialised paediatric cardiac hospital developed and implemented a remote infectious diseases consulting stewardship program via telemedicine.[5] This remote stewardship programme consisted of bi-weekly virtual meetings of all inpatient clinical cases facilitated through real-time online discussions. A high-definition camera, microphones, real-time sharing of files, desktop sharing, and radiographic images were available to the medical team. The hospital performed a 'before and after' study comparing the time before the programme implementation and 1 year after. They found a trend in the reduction of nosocomial infections, overall antibiotic cost, and average antibiotic prescriptions used per admission (Table 1).[5]

Acute Infectious Diseases

In rural or isolated populations, infectious diseases can often be mismanaged when there is a lack of access to health services and care by medical personnel whose expertise lies in infectious diseases. In addition, the IDSA supports the use of telemedicine to provide timely access to those in need of infectious disease care.[2]

A study evaluating the effect of telemedicine (three times per week) versus on-site infectious disease consultation (standard of care [SOC]) in the management of *Staphylococcus aureus* bacteraemia [SAB]) was performed. This retrospective cohort analysis of adult patients included 163 patients in the telemedicine intervention compared to 583 in the SOC group, and found no difference in SAB bundle adherence, 30-day mortality, 30-day SAB-related readmission, persistent bacteraemia, or time-to-culture clearance between groups.[6]

The 32 First Nations communities in the Sioux Lookout region in Ontario, Canada, is afflicted by a high incidence and rate of infectious diseases, such as tuberculosis, acute rheumatic fever, and skin and soft tissue infections, compared to the rest of Canada.[7] In 2014, a telemedicine-based consultation programme was developed between the Sioux Lookout Meno Ya Win Health Centre, the Sioux Lookout regional hospital, and the Division of Infectious Diseases at The Ottawa Hospital in Ontario, Canada.[7] During the data collection period between July 2014 and July 2015, patient satisfaction surveys for the provision of telemedicine were conducted after each patient's initial video-consultation, with an overall patient satisfaction rate of 98% (Table 1).[7]

In North Carolina, USA, the Division of Infectious Diseases at the Carolinas Healthcare System (now Atrium Health) developed a virtual face-to-face inpatient infectious diseases consultation service for an outlying community hospital.[8] Infectious diseases consultations, most commonly regarding bacteraemia, skin and soft tissue infection, osteomyelitis, prosthetic joint infection, and urinary tract infections, were provided for 312 patients in the 175-bed hospital from January 2015 to December 2015; during that period, there were only 13 patients who required transfer to a tertiary facility, with a 20% 30-day readmission rate for all patients.[8]

Table 1

Type	Reference	Study design	Results/outcomes
Antimicrobial stewardship	Dos Santos et al.,[4] 2018	- Quasi-experimental study in a 220-bed hospital in southern Brazil. - Web-based platform designed to facilitate review of clinical data and provision of feedback to physicians.	- Appropriate antimicrobial prescribing increased from 51.4% at baseline to 81.4%. - Significant reduction in consumption of fluoroquinolones (level change, β=-0.80; p< 0.01; trend change, β=-0.01; p=0.98), first-generation, cephalosporins (level change, β=-0.91; p< 0.01; trend change, β=+0.01; p=0.96), vancomycin (level change, β=-0.47; p=0.04; trend change, β=+0.17; p=0.66), and polymyxins (level change, β=-0.15; p=0.56; trend change, β=-1.75; p<0.01). - Significant reduction in the rate of carbapenem-resistant *Acinetobacter* spp. isolation (level change, β=+0.66; p=0.01; trend change, β=-1.26; p<0.01).
Antimicrobial stewardship	Ceradini et al.,[5] 2017	-A 'before - after' study compared the period immediately before programme initiation and 1 year after. -Evaluated the impact of a remote stewardship. programme based on a) appropriateness of antibiotic prescribing, b) incidence of multi-resistant infection, and c) cost.	- A trend in the reduction of nosocomial infections (9.5 vs 6.5 per 1,000 person-days). - A reduction in the overall antibiotic cost (25,000 vs 15,000 EUR) and in the average antibiotics packages/prescriptions used per admission (9.0 vs 6.7 packages/prescriptions). - A significant reduction in multi-drug resistant isolation rate was observed (104 vs 79 per 1,000 person-days, p=0.01).
Acute/general infectious diseases	Isip et al.,[6] 2018	-Retrospective, cohort analysis compared inpatient adults with *Staphylococcus aureus* bacteremia (SAB) between September 2016 and December 2017 to compare outcomes of ID consultation received through telemedicine or on-site consultation on clinical outcomes.	- No difference was observed between groups on the basis of adherence to SAB bundle, mortality, readmission, or culture clearance.
Acute/general infectious diseases	Mashru et al.,[7] 2017	- Patient satisfaction surveys were conducted following each patient's initial consultation. Each survey evaluated the patient experience related to technical components and physician–patient interaction through telemedicine over a 1 year period.	- Overall patient satisfaction was 98% in the nine questions asked of each patient. 1) Patient understood the nurse's explanation of how their session would run. 2) Help was available if problems were to arise. 3) Able to hear specialist comfortably. 4) Satisfied with picture quality of specialist. 5) Privacy was respected. 6) Would use telemedicine again. 7) Would recommend to family/friends. 8) Overall satisfied with appointment. 9) Number of team members was not overwhelming.

Table 1 continued.

Type	Reference	Study design	Results/outcomes
Acute/general infectious diseases	McCurdy et al.,[8] 2016	- Retrospective review of a virtual on-call ID consulation service evaluated diagnosis, transfer, 30-day readmission, and ambulatory care follow-up.	- Remote ID consultation performed for 312 patients. - 13 patients required transfer to a tertiary facility with the majority transferred for surgical evaluation. - 91 patients (29%) were prescribed outpatient parenteral antibiotic therapy written by ID physician. - 30-day readmission rate for all patients was 20% with only 14 (4%) patients readmitted for ID-related complications.
Hepatitis C	Cooper et al.,[10] 2017	- A cohort database analysis was performed on patients following at the Ottawa Hospital and Regional Viral Hepatitis Program between January 2012 and August 2016 - Compared patient characteristics, fibrosis work-up, and antiviral treatment outcomes in TM (n=157) and non-TM (n=1,130) patients.	- SVR rates with interferon-free, DAA regimens were 94.7% and 94.8% in TM and non-TM groups (p=0.99), respectively.
Hepatitis C	McPherson et al.,[11] 2018	- To review results of the implementation of universal offer of blood borne virus testing in Durham Prison and the impact of the introduction of Telemedicine HCV treatment clinics in Northumberland Prison.	- 57 (71%) of prisoners commenced anti-HCV treatment while receiving consultant-led TM clinic visits compared to the preceding year prior to implementation where only six patients received HCV treatment. - Overall, patient satisfaction using TM in the prison setting was very high (80% good or excellent). - Additionally, this intervention was cost effective and reduced the cost of prisoner movement (~£500/hospital visit).
Hepatitis C	Lepage et al.,[12] 2018	- The Ottawa Hospital Viral Hepatitis Program was evaluated for patients entering HCV care from January 1, 2012 until December 31, 2016.	- Per protocol SVR for TM, OPC, and MD patients with DAA- based treatments were 100% (26/26), 93% (440/472), and 94% (44/47), respectively. - Interferon - DAA treatment regimens, SVR rates were 100% (1/1) for TM, 92% (76/83) for OPC, and 100% (3/3) for MD patients. - Interferon-based treatments, SVR rates for OPC and MD patients were 64% (134/211) and 80% (4/5), respectively. - SVR rates, when controlled for treatment allocation, were similar by care-delivery method (p=0.93).
HIV	Baguley et al.,[14] 2018	- Attend Anywhere consultations as part of medical care for people living with HIV and in remote areas where care is received. - Patients visit their primary provider for blood tests at a time convenient for them. Afterwards, a teleconsultation from home using the Attend Anywhere app can be performed.	- Despite small enrollment, the service is popular with patients who have used it. - Authors noted that the majority of people will be required to attend follow-up appointments in person due to their symptoms or testing requirements.

Table 1 continued.

Type	Reference	Study design	Results/outcomes
PrEP	Refugio et al.,[15] 2019	- PrEPTECH is a pilot study that enrolled 25 HIV-negative young men who have sex with men to participate in TM visits and receive cost-free PrEP delivered to their home. - Patients had to participate in two laboratory visits at baseline and 90 days post PrEP initiation.	- No HIV infections detected during the intervention period. - Rates of sexually transmitted infections were 20% at baseline and 19% at 90 days.

DAA: direct-acting antiviral; HCV: hepatitis C virus; ID: infectious diseases; MD: mixed deliver; OPC: outpatient clinic; PrEP: pre-exposure prophylaxis; SAB: Staphylococcus aureus bacteraemia; SVR: sustained virologic response; TM: telemedicine.

To assist with the increasing infectious diseases burden, telemedicine programmes have the ability to connect patients in those populations with multidisciplinary infectious diseases specialised teams who can provide them with the necessary treatment and care to optimise clinical outcomes.

Hepatitis

Telemedicine programmes can play a vital role in addressing WHO's objectives of increasing access to care and promoting health services geared toward the treatment of hepatitis. According to the WHO, hepatitis B and C currently affect approximately 325 million people worldwide.[9] The organisation aims to achieve global elimination of viral hepatitis by the year 2030 by increasing hepatitis prevention, testing, treatment, and care services, promoting universal health coverage of hepatitis services, and improving partnerships and funding in the fight against hepatitis.[9]

In Canada, data analysis was performed on patients followed at The Ottawa Hospital and Regional Viral Hepatitis Program from January 2012 to August 2016 comparing sustained virologic response (SVR) between patients in the multidisciplinary telemedicine programme and patients in a nontelemedicine programme seen at the Ottawa Hospital Viral Hepatitis Outpatient Clinic.[10] This programme was created as part of an effort to engage and retain rural and remote populations that lacked access to HCV subspecialty care. Patients in the telemedicine group had an SVR rate of 94.7% and patients in the nontelemedicine group had an SVR rate of 94.8% (Table 1).[10]

In prisons in the North-East of England, UK, a universal offer of blood borne virus testing was offered and prison telemedicine clinics to increase HCV treatment rates.[11] In one of the prisons, 80 patients were seen in the telemedicine clinic between August 2015 and October 2017.[11] Prior to the introduction of the telemedicine clinic, only six patients received access to treatment for HCV. Post-implementation of the HCV programme, anti-HCV treatment was increased to 57 of the 80 patients seen in clinic.[11] The prisoners in the telemedicine clinic reported a high satisfaction rate (80% good or excellent) and a reduced cost of prisoner movement (estimated £500 per hospital visit) with the programme.[11]

The Ottawa Hospital Viral Hepatitis Program evaluated patients in HCV care from January 2012 to December 2016 and compared SVR between patients enrolled in telemedicine clinic, outpatient clinic, and mixed-delivery.[12] The study found that telemedicine-delivered, direct-acting antiviral-treated patients achieved higher SVR outcomes: the per protocol SVR rates for telemedicine, outpatient, and mixed-delivery with direct acting antiviral treatments were 100% (26/26), 93% (440/472), and 94% (44/47), respectively.[12]

With increased access to HCV treatment made possible with telemedicine and the availability of direct acting antivirals, along with their safety and efficacy, viral eradication of HCV by 2030 may turn into a reality.

Human Immunodeficiency Virus

While advancements in HIV medications have provided patients with options to prevent and treat HIV, it remains a serious health issue for many worldwide. The Centers for Disease Control and Prevention (CDC) estimated that in 2016 there were 36.7 million people living with HIV, only 19.5 million people of which were receiving treatment.[13] Rural and isolated populations may lack access to HIV specialised care and treatment. The National Health Services (NHS) Grampian in Scotland provides HIV care to patients from the Orkney and Shetland islands by flying patients into Aberdeen for lab tests and consultations.[14] In 2017, the NHS Scotland implemented the 'Attend Anywhere' application, a platform in which patients would receive secure video consultation from home after completing blood work at their own convenience at a general medical practice on their island.[14] By implementing the programme, the NHS provided patients living with HIV in remote areas with a wider range of health services and care.

Telemedicine programmes provide and promote access to specialised HIV care for patients who might not have otherwise received treatment. With the advent of safer and simpler antiretroviral regimens and the expansion of telemedicine to manage this chronic disease, reduced transmission of HIV may be possible because of improved virologic suppression.

Pre-exposure Prophylaxis

Numerous barriers to PrEP access and continued use have been reported in patients receiving the treatment. For instance, stigma, cost, and adherence to the medication, as well as medical appointments, are often cited as hurdles for patients to access treatment. A study in 25 young men who have sex with men aged 18–25 performed in San Francisco, California, USA, evaluated the use of cost-free PrEP through telehealth services. This telemedicine model provided home delivery of PrEP at no cost to the participant, as well as sexually transmitted infection kit testing. Two physical lab visits were required at baseline and 90-days after initiation of PrEP for HIV and associated tests. Participants were followed longitudinally over 180 days. Twenty-one participants completed the study with no cases of HIV detected, yet rates of sexually transmitted infection remained the same. At least 75% of participants reported the intervention to be confidential, fast, convenient, and easy to use. Less than 15% of participants reported PrEP stigma.[15]

DISCUSSION

Increased access to testing, health services and care, cost-effectiveness, and decrease of inappropriate antimicrobial prescriptions are some of the many benefits that have come from the aforementioned telemedicine programmes. While there has been an upward trend of telemedicine programs since the early 2000s, the growth of these programmes has somewhat plateaued. Infectious diseases, acute or chronic, often require treatment and care from providers who have the training and expertise; however, access to these providers is limited for many populations. Programmes, such as the Ottawa Hospital Viral Hepatitis telemedicine clinic that resulted in patients with high SVR rates and the Brazilian Hospital remote consultation that increased appropriate antimicrobial prescriptions, demonstrate that telemedicine can provide some of the same benefits as face-to-face consultation while reducing geographic barriers to care and improving healthcare access and treatment.

While the programmes highlight the benefits of telemedicine use, there are some limitations in how these programmes were studied. Some of the programmes used patient satisfaction questionnaires instead of clinical assessments or laboratory measures to evaluate their outcomes, which may not be reliable measurement on the efficacy of telemedicine clinics. Another limitation was the settings of the studies. Most of the programmes were developed and implemented in developed countries and may not reflect generalisability for use in areas that do not have access to the technology necessary to apply telemedicine. Laboratory testing for safety and efficacy of treatment or intervention may be another limitation of telemedicine because

patients still have to go to a testing site to have labs drawn. Many of these programmes had small sample sizes and warrant further studies with larger sample sizes to better determine the cost-effectiveness of these programmes as well as demonstrate the clinical benefits of telemedicine. Furthermore, the available data is rather heterogeneous, with little ability to compare across studies.

CONCLUSION

As the usage of and advancements in technology continue to grow, telemedicine is a viable option to provide health services, treatment for acute and chronic infectious diseases, and prevention of HIV. This review demonstrates the value of implementing telemedicine for the use of infectious diseases and the need for continuous development of such programmes to expand access to healthcare.

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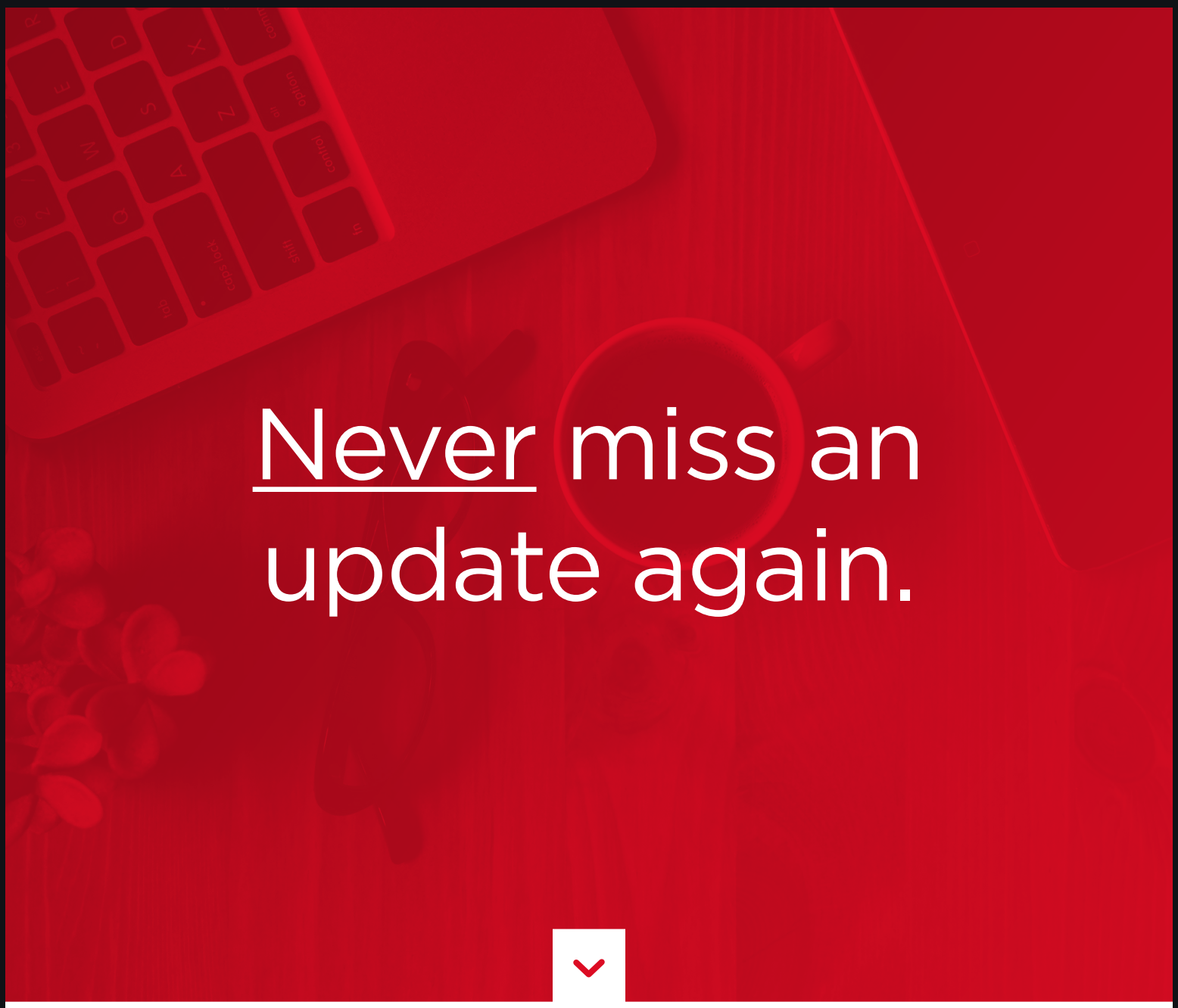

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