EMJ EUROPEAN MEDICAL JOURNAL

INNOVATIONS

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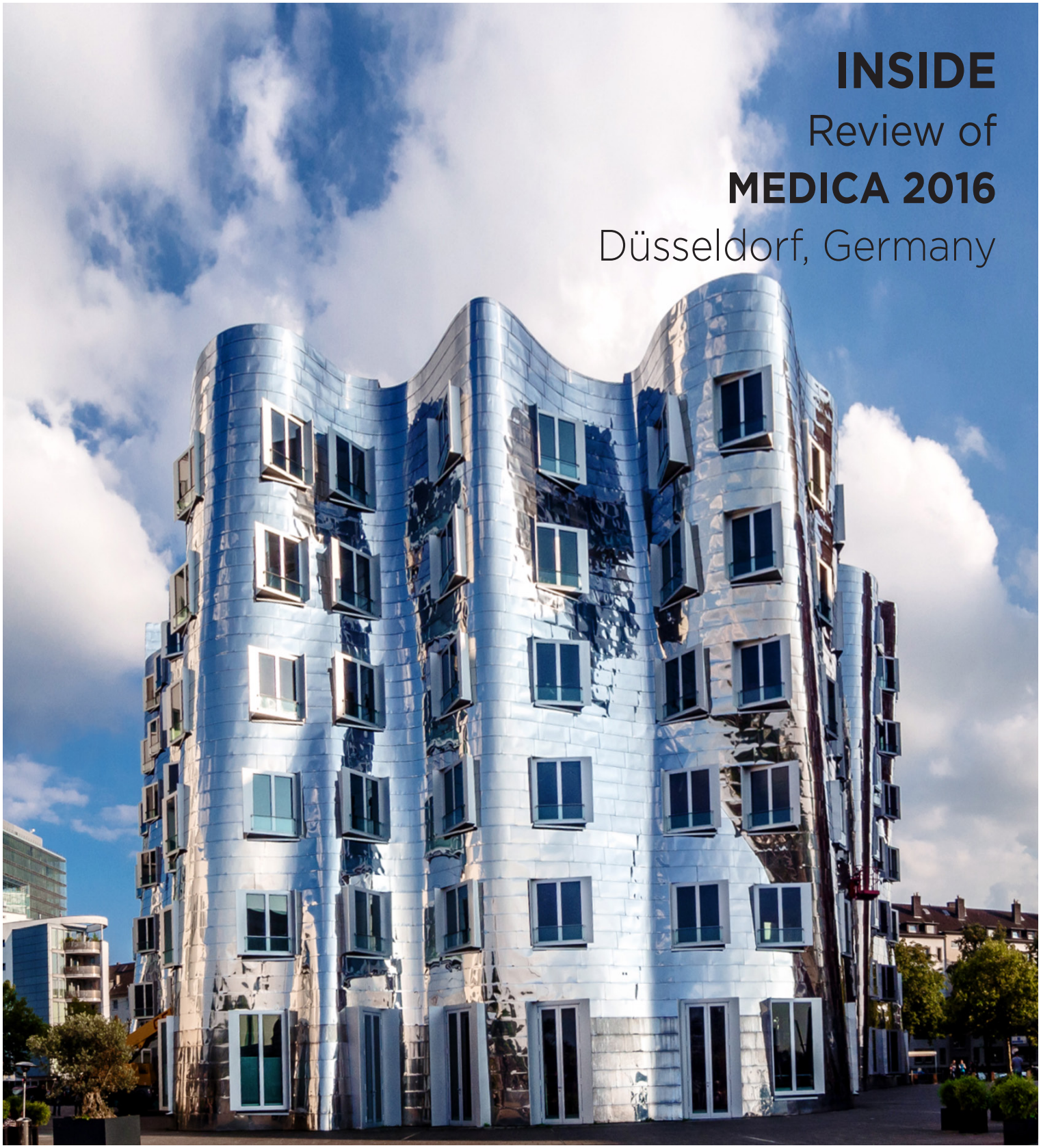

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MEDICA 2016

Düsseldorf, Germany

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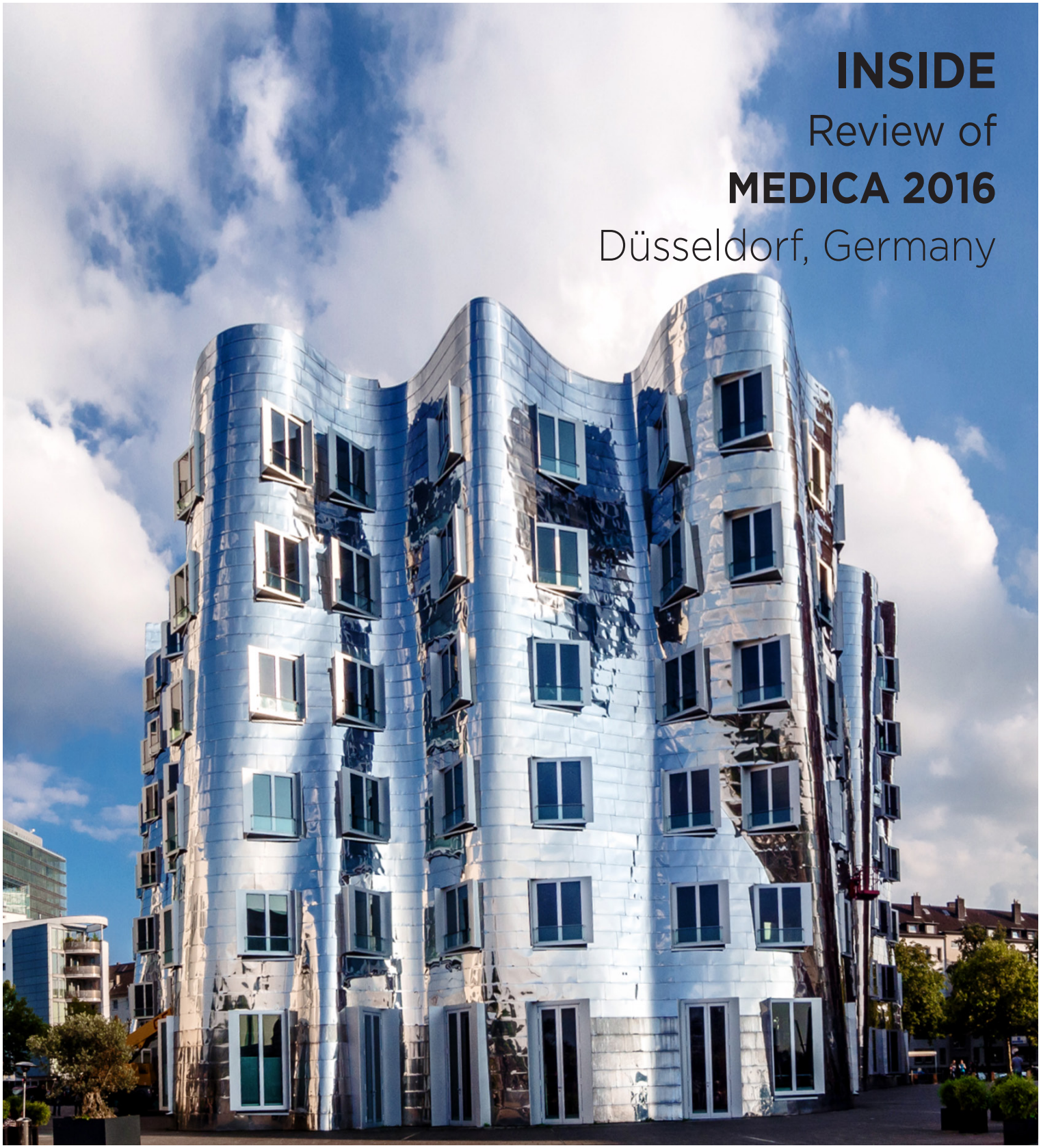

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INNOVATIONS

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Innovations

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Welcome

Hello and welcome to the inaugural edition of the *European Medical Journal Innovations* eJournal, a delve into notable developments of the last year and the eagerly anticipated technological advances of the near future. Complementing a review of MEDICA 2016, this publication presents an array of thought-provoking articles, including two features, and interviews with renowned professionals at the forefront of innovation in clinical practice.

MEDICA 2016 provided 4 days of key networking at the forefront of medical innovations, >5,000 exhibitors from >70 countries worldwide, and conferences aimed to update professionals on the growing concerns and progressions across medical practice and the ventures perused behind the scenes. Furthermore, interviews with our esteemed Editorial Board highlight the difficulties faced by both clinicians and patients, personal opinions, and future hopes and expectations regarding the ever-growing field of technology application and medical development.

The peer-reviewed articles selected for publication within include an in-depth review by Amann on the influence of eHealth technologies on patient participation figures, nominated as this year's Editor's Pick. Craig, Royal and Hedgpeth, and Kimble and Massoud present ideas on personalised medicine, flaws in medical school examinations and innovative solutions, and the concept of innovation within the field of healthcare, respectively. The topic of virtual reality-assisted surgery and mobile-monitored disease management are discussed by Vázquez et al. and Kelli et al., respectively, with the possibility of self-management advancement for epilepsy patients covered in detail by Hixson. Finally, we incorporate papers on thriving areas of research currently bringing about changes in pathogenesis and cellular interaction models systemically: the role of the microbiome in neuropsychiatric disorders by Evrensel and Ceylan and the utilisation of light sheet fluorescence microscopy in biomedical research by Bode et al.

Together with the above articles, this issue includes two feature articles illustrating the future for clinical innovation; Whittle explores the intricacies and peculiarities of technology and the presently unmet need for recognised guidance and directed strategy within the industry and Canhão et al. highlight the frequently overlooked role of patients and caregivers in innovation and their active contribution to their own therapeutic strategies.

These insights are guaranteed to draw the attention of those eager to embrace a new era of technological understanding and showcase the promise for further determination of molecular schematics for better therapy and drug development. We hope this first edition of *EMJ Innovations* provides food for thought and stimulating discussion.

Spencer Gore

Director, European Medical Journal

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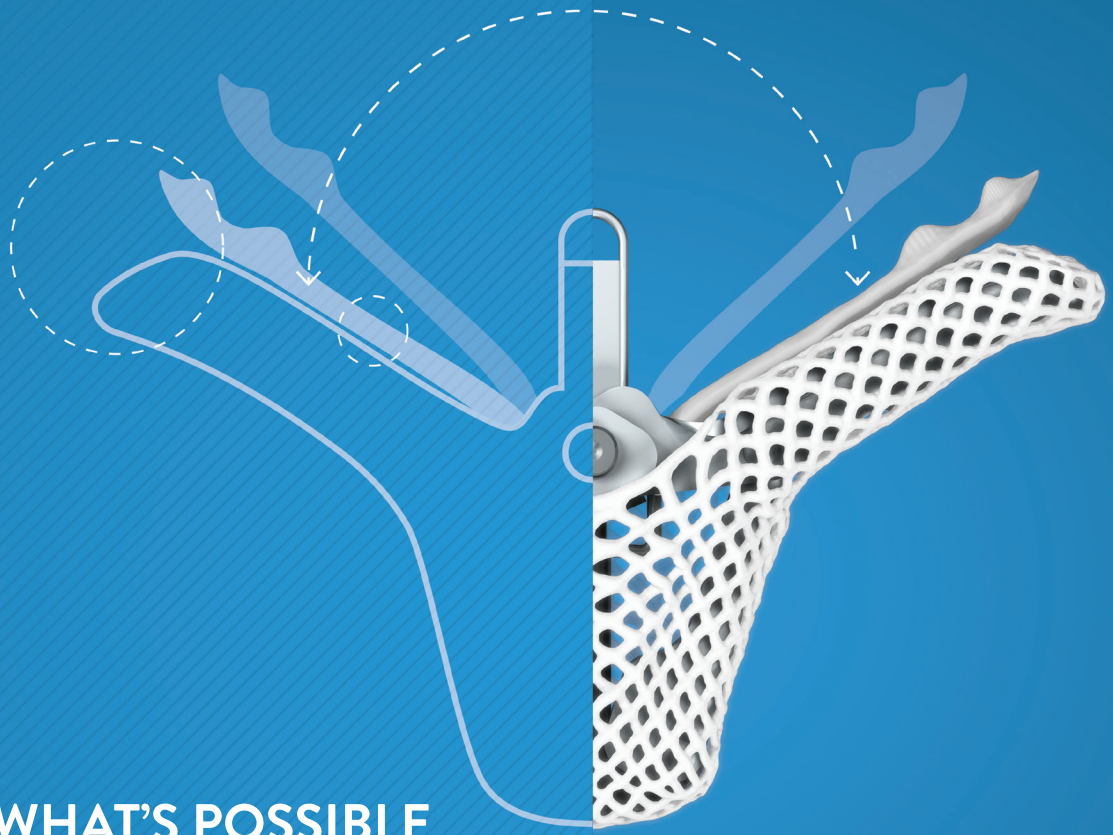

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Foreword

Dr Mike Bewick

Independent Health Consultant and Founder of IQ4U Consultants, London, UK.

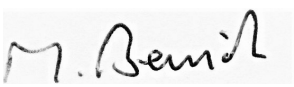
Welcome to your new online journal where we will bring you the latest and most relevant research from across Europe on innovation in healthcare. We have a vibrant and expanding research community whose fundamental aims are to improve the delivery of health and social care, addressing the gross health inequalities that pervade our systems. Enclosed, you will find a range of articles discussing cutting-edge research in mobile healthcare, virtual reality, and much more. Additionally, our coverage of the recent MEDICA 2016 which took place in Düsseldorf, Germany will provide you with everything you need to relive all of the excitement of the conference itself, or to catch up on anything you may have missed.

> "People working collaboratively with technology are far more effective than either people or technology alone.[1]"
>
> Robert Wachter

The availability of technologically enhanced care is increasing exponentially. Smart phone and tablet technologies support a growing move to telehealth-based systems. The number of apps supporting health is now >160,000 but we have little in the way of quality assurance or evaluation of these technologies. Within the UK there is a drive by policy makers and regulators such as the National Institute for Health and Care Excellence (NICE) to address this but it is likely that citizens will produce their own using social media to seek fellow users' views.

Care delivered at a distance, with the promotion of true 'patient-centred care' and 'self-care', is being realised. There is increasing momentum in delivering innovative healthcare through the application of technologies and improved clinical practice. This was reinforced at a meeting of the European Innovation Partnership on Active and Healthy Ageing (EIP-AHA) in Brussels, Belgium on the 6th–7th December 2016, where the European Commission received the completed blueprint for digital technologies supporting improved access to healthcare of the elderly population through technological innovation.

I hope that you will enjoy reading this inaugural edition of *EMJ Innovations*.



Mike Bewick

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MEDICA 2016

MESSE DÜSSELDORF,
DÜSSELDORF, GERMANY
14TH–17TH NOVEMBER 2016

Welcome to the *European Medical Journal* review of the Annual Meeting of MEDICA

Welcome to *European Medical Journal's* review of MEDICA 2016, the largest and most impactful medical trade fair globally, where decision makers and key stakeholders from across the global health industry met. This year's fair smashed records beyond predicted scope, with >5,000 exhibitors from 70 nations presenting.

Running alongside MEDICA 2016 was a diverse programme featuring the MEDICA Education Conference, a cutting-edge interdisciplinary training course which considers the link between medical technology and science, facilitating discussion and the mutual sharing of ideas between doctors and medical device designers. Conference president Prof Stefan Frantz, Director of the Policlinic for Internal Medicine III, Universitätsklinikum Halle, Halle, Germany, announced: "I am pleased that, for the third time in a row, we can offer national and international visitors to the conference a programme that is unique in its interdisciplinary and internationality." Prof Frantz went on to express that: "We will be delighted if many colleagues use this opportunity to broaden their horizons." The programme was scheduled in such a way as to allow participants to visit the MEDICA trade fair afterwards and view a huge range of medical innovations, perfectly complementing the conference.

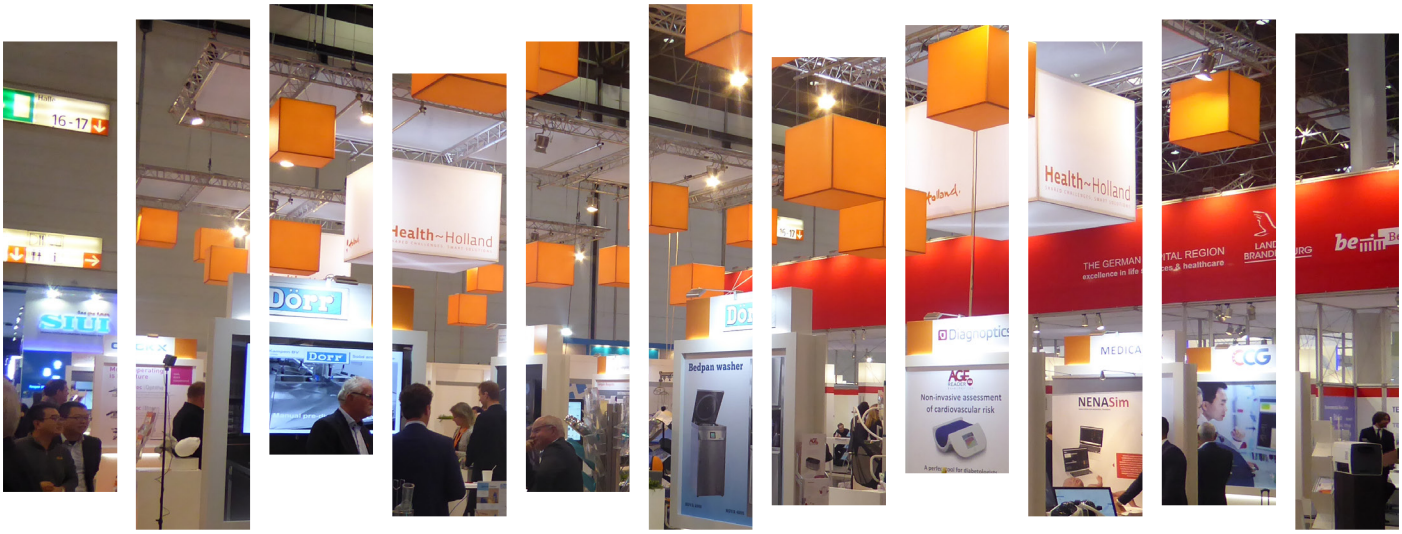
There was an excellent programme, with each day of the conference constructed around a chosen theme. Monday saw 'New Operative Techniques in Surgery' placed in the spotlight, covering the current standards of surgical methods, future possibilities, and innovations; Tuesday covered 'Imaging and Interventional Procedures' and Wednesday examined 'Future Technologies and Remote Patient Management', considering questions such as the impact of telemedicine on chronic diseases such as diabetes. Finally, Thursday highlighted 'Diagnostics in Internal Medicine, Laboratory Medicine, Toxicology and Hygiene'. In addition to symposia detailing technical innovations, medical training courses were provided to allow participants to equip themselves with the skills and know-how to utilise these innovations. Prof Frantz enthused: "In these courses, participants have the opportunity to become familiar with new medical technologies and to refresh their expertise in a practical and interactive manner."

As well as the MEDICA Education Conference, there were other complementary conferences targeting specific groups. For example, sports medical experts were catered for by the MEDICA Medicine and Sports Conference, which tackled the use of wearables for collecting data on vital signs and injury prevention. Additionally, this conference considered how physical and mental performance could be increased. Another tightly focussed event was the DiMiMed, which encompassed military and disaster medicine and saw military physicians unpack the latest medical technology findings related to war and crisis regions.

> “In these courses, participants have the opportunity to become familiar with new medical technologies and to refresh their expertise in a practical and interactive manner.”

Exhibitors at MEDICA showcased the latest trends and innovative developments, dovetailing perfectly with the accompanying programme. The products that were featured ranged from laboratory, physiotherapy, medical, and orthopaedic technology, to electrotherapy, health IT, and commodities and consumables. For instance, the Wearable Technologies Show hosted numerous devices, including a bracelet functioning as an early warning system for epileptics, a waistband clip that halts menstrual cramps, and a patch that allows the monitoring of asthma.

For the last 5 years, MEDICA has hosted the hotly contended MEDICA App COMPETITION, where teams go head-to-head to create the ‘Best Medical Mobile Solution’. This year’s competition was as tightly contested as ever, with the top honours and a €2,000 cash prize won by a development team from Israel, with ‘Up Right’, which combined an app and a wearable in order to optimise posture and stimulate movement. Utilising an accelerometer and a variety of sensors, the wearable device vibrates on the user’s back when they sit in a slouched position, encouraging them to develop improved posture. This app can already be purchased online and clinical trials are currently in progress.



Digitisation and Miniaturisation Key for New Technology

DIGITISATION of the healthcare sector has led to the development of a plethora of medical technology in recent years. In a MEDICA press release, Joachim Schäfer, Managing Director of the Messe Düsseldorf, the venue for this year's event, discussed the trend of smaller and lower-cost medical devices which are taking the market by storm.

> Automatic analysers, currently, are too specialised or, if this challenge is addressed with broad-spectrum analysers, too expensive.

Software innovation was a key player at this year's event; user interfaces and navigation are proving particularly important for new devices which must, increasingly, meet the specific needs of individual users. One development patrons seemed most interested in was a standardised operating method and control concepts for multiple devices, which allows greater accessibility for users who no longer need to learn a complex set of operating instructions for each new device. Innovations in this area could lead to greater efficiency in hospitals and laboratories as the machines become easier to use. Schäfer gave the example of analysing microscopy samples. He stated that automatic analysers, currently, are too specialised or, if this challenge is addressed with broad-spectrum analysers, too expensive. Using the results of recent trials, which demonstrated that diseased tissue emits and responds to light in different ways to healthy tissue, low-cost automatic scanning methods might be possible for a whole range of tests. Similarly, point-of-care devices for bedside use in hospitals could replace laboratories for simple blood tests, reducing both cost and time.

The miniaturisation and digitisation of medical technology could also benefit the world of minimally invasive surgery, for example in the case of microendoscopes. One such device, designed for examining the brain in patients with Alzheimer's disease, Parkinson's disease, or cancer, was presented at the COMPAMED congress; it is magnetic resonance imaging (MRI)-compatible, composed of part-plastic, part-ceramic materials, and also features ultrasound capabilities rendering it capable of destroying tumour cells. It is hoped that these new, ever-smaller devices will have a large impact on the healthcare industry.

Digital Initiatives to Improve Patient Care Discussed at the MEDICA HEALTH IT FORUM

DIGITISATION in the medical sector to improve patient care and efficiency was a major topic of discussion at MEDICA 2016. In Germany and elsewhere, there have recently been a number of such initiatives, and these were discussed during the MEDICA HEALTH IT FORUM according to a MEDICA press release.

One such innovation is the advent of 'x-Health', which is the necessary interoperable 'XChange' of location-independent digital services, a market that is growing internationally. In Denmark for example, patients can access their electronic health files, and the applications have since developed to allow people to add their own data. It is essential, however, that patients remain in complete control of their own records in such a system.

> "Legally and theoretically, patients are in sole control of their details, but in reality they are unable to view them or pass them on."

Another phenomenon that is attracting substantial interest in Germany is that of 'telemedicine'. This has been inspired by the shortage of doctors in rural communities, making the provision of good care difficult. Potentially, certain healthcare services could be provided via telemedicine, negating the need for patients to visit doctors. However, questions such as the extent to which these new technologies will reduce personal contact with physicians, and how secure the transfer of such data would be, still need to be answered.

Linked to the concept of telemedicine is the development of 'TeleVERAH', a project which was presented at the FORUM. In this system, a medical professional would attend to patients, instead of the general practitioner, to carry out various tests such as weighing. The data would then be transferred back to the practice. This would mean that travelling times would be eliminated for doctors, while maintaining good quality of care and interaction with patients.

According to Prof Britta Böckmann, Information Sciences and Medical Information Sciences, Dortmund University of Applied Sciences and Arts, Dortmund, Germany, such digitalisation of healthcare services cannot come quickly enough for patients: "Legally and theoretically, patients are in sole control of their details, but in reality they are unable to view them or pass them on." She added: "Patients are entitled to digitisation."

Treatment and Wearable Devices Displayed at MEDICA

A NUMBER of wearable devices were showcased at this year's MEDICA which took place on the 14th–17th November 2016 in Düsseldorf, Germany. Digital healthcare is considered an important aspect for both the treatment and prevention of certain diseases. Devices such as the 'Freestyle Libre', 'Smart Patches', 'Firstbeat Bodyguard', 'QardioArm', and 'QardioCore' were all discussed at this year's MEDICA Healthcare Forum according to a MEDICA press release.

Several digital devices to assist in the management of diabetes are already available on the market. The Freestyle Libre smart patch for example, assists in enabling the correct insulin dosage to be administered to the patient by determining blood sugar levels without the need for taking blood. Another smart patch solution involves the use of an Android™ smartphone to scan a sensor-incorporated arm patch in order to measure current glucose levels as well as additional values such as the patient's history over the last 8 hours. This device is considered particularly useful for paediatric diabetics as the scanner allows the parent or carer to assess glucose levels without having to wake the child should a dose of insulin not be necessary.

This device is considered particularly useful for paediatric diabetics as the scanner allows the parent or carer to assess glucose levels without having to wake the child should a dose of insulin not be necessary.

Devices to assist patients with the lifestyle management of diseases such as Type 2 diabetes mellitus are also being developed. The Firstbeat Bodyguard, usually worn for 72 hours, provides valuable information to physicians about fluctuating heart-rate, stress levels, and sleep quality, for example. Additionally, the QardioArm and QardioCore, which have been already approved by the US Food and Drug Administration (FDA), allow individuals to monitor blood pressure without Velcro straps or pumps, and body temperature, heart frequencies, and breathing without the need for cables and plasters, respectively.

Wearable devices are useful in helping patients manage their own treatment without the need of constant assistance from healthcare professionals. Companies are already investing in such schemes to allow patients to voluntarily obtain digital device incorporation within their healthcare plans.

Future Developments in Sports Technologies

DIGITAL innovations are fast becoming a key component within the field of sports medicine. The MEDICA MEDICINE + SPORTS CONFERENCE 2016, Düsseldorf, Germany, provided the ideal opportunity for multidisciplinary exchange between sports physicians, researchers, and professional athletes, as reported in a MEDICA press release.

The subject of 'Body Enhancement' was discussed on the opening day. While revolutionary progress has seen some athletes with prostheses required to prove they are not gaining an unfair advantage, further development of prostheses well-adapted for everyday life is required. Prof Robert Riener, Head of the Department of Health Sciences and Technology, ETH Zürich, Zürich, Switzerland, presented the world premiere of 'Cybathlons'. Individuals with disabilities partook in challenges designed to test the benefit of robot-assisted technologies to overcome everyday obstacles such as walking up the stairs.

> Physicians will not become redundant in future, they will rather continue to play a key role in the decisions about relevant diagnostics, the commencement of treatments, and in prevention.

Dr Christian Schneider, Head Physician for Sports Orthopaedics at the Schön Klinik München Harlaching, München, Germany, presented on the future of physicians, predicting that the automation of treatment aspects such as physiotherapy exercise accuracy, and regime adjustment could be just around the corner, meaning a stop to weekly hospital visits.

On its second day, MEDICA played host to a focussed conference on sports innovation ready for immediate implementation Prof Jürgen Scharhag, Team Physician for the under-21 German national team; Institute for Sports and Preventive Medicine, Saarland University, Saarbrücken, Germany, explained how those who participate in competitive sports are expected to live longer and that physicians are now able to utilise electrocardiography to discern between unwanted pathological effects and the physiological benefits of training. Development of wearable technologies to collect and collate physiological and biomechanical data is underway, such as the 'miLife' project, presented by Prof Björn Eskofier, Pattern Recognition Lab, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany.

"Physicians will not become redundant in future, they will rather continue to play a key role in the decisions about relevant diagnostics, the commencement of treatments, and in prevention," assured Dr Schneider. He is confident that innovation relays progress and that physician intervention will continue to run parallel to technological advance.

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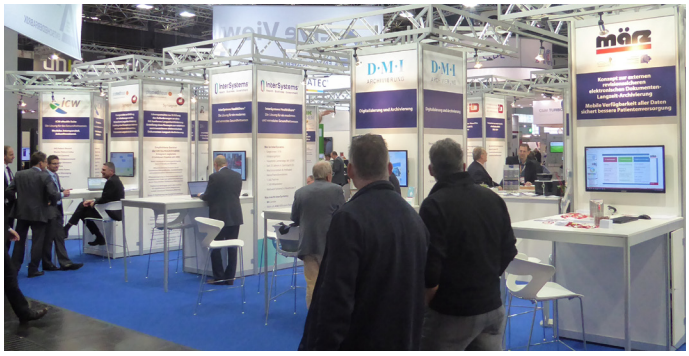
Running for more than 40 years



Computer-Generated Personalised Orthopaedic and Sports Insoles

COMPUTER-GENERATED orthopaedic and sports insoles are an innovation offered by one of the companies displaying their wares at MEDICA 2016, held in Düsseldorf, Germany according to a MEDICA press release.

The Orthema Group, Rotkreuz, Switzerland, have utilised a cutting-edge device with >500 sensors to capture a three-dimensional measurement analysis of an individual's foot. The device works with the help of an orthotic expert who uses the software to interpret these data and carry out a detailed analysis of the individual's weight-bearing and non-weight bearing gait, developing a personalised and unique solution. The orthotic expert determines the appropriate material to use, then connects a computer numerical controlled milling machine to the system producing an exact replica of the foot profile. These insoles have a variety of uses, with Marcel Herzog, the founder of Orthema, explaining: "I wanted to eliminate muscular pain by correcting gaits, but I was also looking for ways to optimise power transfer for elite athletes." While this device was originally intended to produce insoles for top athletes and the military to assist with injury recovery and power transfer, it quickly garnered attention from the orthopaedic industry who spotted its potential for treatment of issues such as overpronation, joint problems, plantar fasciitis, splayed feet, and other ailments. Currently, the German football team utilise this service for individualised insoles.

> I wanted to eliminate muscular pain by correcting gaits, but I was also looking for ways to optimise power transfer for elite athletes.

This method aims to be faster and more efficient than conventional methods of insole manufacturing, enabling increased production. It should be noted that it is crucial to have an operator trained in using the machine, otherwise a thorough analysis cannot be carried out. Hopefully in time, devices and methods such as this will be used on a larger scale to provide effective solutions to individual problems and reduce pain.

Demand for Emphasis on Healthy Lifestyle in Prevention Schemes

OBESITY needs to be recognised by global healthcare systems as a disease in its own right; this notion was emphasised in the run-up to this year's MEDICA Education Conference 2016, held in Düsseldorf, Germany, according to a MEDICA press release.

At present, data from the National Consumption Study reflects a startling reality: nearly 70% of men and >50% of women in Germany are classed as overweight, with a BMI of ≥25 kg/m^2. According to figures extrapolated by the World Health Organization (WHO), this could mean that >50% of German citizens will be categorised as clinically obese by 2040. Parallel to the rise in obesity, healthcare providers are also observing a marked increase in sufferers of related diseases, including but not limited to, metabolic, cardiovascular, and cancerous conditions. The rise in the associated complications is placing an increased burden, particularly economically, on an already overwhelmed healthcare system and therefore a lack of exercise or poor dietary choices can no longer be attributed primarily to effects on the individual.

> "We know today that a healthy lifestyle, including a balanced diet and regular exercise, can prevent diseases."

"According to our current findings, physical activity and sport is as important as a cancer drug," explained Prof Christian Löser, Head and Chief Physician of the Medical Clinic, the Red Cross Hospital, Kassel, Germany. "We know today that a healthy lifestyle, including a balanced diet and regular exercise, can prevent diseases."

Type 2 diabetes mellitus and metabolic syndrome comorbidities (e.g. coronary heart disease, stroke) are the most prevalent diseases suffered by individuals as a result of poor lifestyle regimens. Seemingly unbeknownst to many people, obesity and its BMI classification of ≥30 kg/m^2 has also been shown across large observational studies to correlate with specific cancers, particularly that of the colon. "Colon cancer is a typical prosperity disease," emphasised Prof Löser. "A healthy lifestyle can achieve a great deal in terms of prevention."

Telemedicine Early Warning System for Heart Failure Patients

EARLY warning of a deterioration in the condition of heart failure patients might now be possible thanks to the development of a telemedical system in Germany. The device, which monitors blood pressure, pulse, and body weight amongst other factors, could help doctors to treat a patient before complications occur.

In a MEDICA press release dated 6th November 2016, Prof Friedrich Köhler, Centre for Cardiovascular Telemedicine, Charité Medical University Berlin, Berlin, Germany, discussed how a fall in blood pressure, pulse acceleration, or water retention that is not immediately apparent to the patient, can signal an approaching deterioration in their condition: "If a diagnosis is made in the early stages, we are often able to take countermeasures to prevent deterioration or even premature death." He went on to discuss a trial currently underway in Germany named the Fontane study, testing a transmission

device to assess its efficacy as an early warning system for these symptoms. Half of the 1,500 chronic heart failure patients that have enrolled on the study have been provided with the device, which will transmit data on a daily basis to monitor the patients' condition. Prof Köhler explained: "The aim is to reduce the number of days lost by hospital stays or premature death." Initial results from this trial are expected in 2018.

> "If a diagnosis is made in the early stages, we are often able to take countermeasures to prevent deterioration or even premature death."

Telemedicine has been the subject of several trials in recent years with varying results regarding its efficacy. Both the CHAMPION and IN-TIME study showed favourable data regarding the improvement of quality of life for patients using a pressure gauge in the pulmonary artery and an implanted defibrillator, respectively. Contrastingly, MORE-Care and REM-HF suggested that data recordings from pacemakers and implanted defibrillators did not improve quality of life for patients.

Prof Köhler warned that telemedicine should only be used in conjunction with in-person appointments: "Treatment of a patient with chronic heart failure must be carried out personally by a specialist based on adequate information and in accordance with the medical confidentiality."

Fresh Perceptions into Cardiac Magnetic Resonance Imaging

MAGNETIC RESONANCE IMAGING (MRI) has long been used for diagnosis within different areas of the body including the head, abdomen, and locomotor system. Prof Michael Markl, Departments of Radiology and Biomedical Engineering, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA, presented fresh insights into cardiac MRI scans at this year's MEDICA Education Conference which took place from 14th–17th November 2016 in Düsseldorf, Germany.

Prof Markl explained in a MEDICA press release dated 15th November 2016: "Within a few years, the cardiac MRI has developed into an examination tool that can be used for diseases of the heart and blood vessels." In regard to the importance of the ability of being able to use cardiac MRI to assess blood flow he continued: "The dynamic propagation of the flow wave can be tracked in a quantitatively precise manner by monitoring the dynamic change of the flow profiles over the heart cycle."

> "The dynamic propagation of the flow wave can be tracked in a quantitatively precise manner by monitoring the dynamic change of the flow profiles over the heart cycle."

Prof Markl provided further information, explaining the importance of cardiac MRI in assessing the structure and function of the heart after injecting a contrasting agent into the vein, thus allowing doctors to assess which areas of the heart are and are not being supplied with blood: "After a heart attack, the cardiac MRI shows which parts of the heart muscles have died." Alongside this, a stress MRI can be carried out which examines "how the heart muscle responds to load," both of which are beneficial to monitor heart activity allowing doctors to assess patients' safety and enable them to react quickly should there be a problem.

Currently little is known about the interaction between heart activity and the elastic blood vessels and therefore the cardiac MRI can also be considered an important research tool. For instance, the heart requires a power of 1 W to pump almost 5 L of blood per minute through a tubular system with capillaries that are 0.01 mm thick. As Prof Markl noted: "This is much more efficient than any tubular system developed by humans."

Innovative Angiography System Benefits Both Patients and Surgeons

INNOVATIONS for surgical procedures proved to be some of the most eagerly anticipated developments at this year's MEDICA. Improvements to imaging methods and three-dimensional (3D) scanning are expected to improve the accuracy of diagnoses, efficacy of interventional surgery, and even reduce discomfort for patients. One such design was discussed in a MEDICA press release dated November 2016.

One of the new models presented during the congress was the Siemens Healthineers robot-supported ARTIS pheno angiography system. The new device boasts a plethora of features designed to address a range of challenges faced in minimally invasive surgery for multimorbid patients. Minimally invasive surgery can be challenging in patients who suffer from simultaneous health conditions, and in some cases, it may not even be possible to offer this type of intervention. This is especially pertinent in older patients, who can be at greater risk of complication during surgery due to chronic disease. By utilising a device that addresses challenges such as shorter scan times by using smaller amounts of contrast agent, surgeons can drastically improve the standard of care offered to patients. For instance, shorter scan times facilitate a reduction in the amount of iodinated contrast agent during 3D angiography in the thorax and abdomen by ≤15%. From a surgeon's point of view, devices such as this one could also improve patient care by removing the difficulties associated with extended surgery times. Being able to tilt the table to any angle means that imaging becomes easier and access to the operating area is not so limited.

> Shorter scan times facilitate a reduction in the amount of iodinated contrast agent during 3D angiography in the thorax and abdomen by ≤15%.

Hygiene in hospitals is another factor that needs to be addressed in the innovative new products being marketed. The ARTIS pheno for example, has been designed to allow constant hygiene via an antimicrobial coating to stop bacteria and viruses from reproducing. With such a huge range of innovative features, it is certainly exciting to ponder what might come next to revolutionise the healthcare industry.

Breakthrough in Light Therapy

LIGHT therapy in the form of organic light emitting diodes (OLEDs) is a potential means of accelerating the healing of wounds, particularly in chronic or infected cases. However, a major challenge in the use of the therapy is the inability to predict potential toxic effects of the materials used on patients. Now, for the first time, scientists at the Fraunhofer FEP in Dresden, Germany, have found a way to analyse the materials that might negatively impact patients, bringing the future of light therapy that much closer.

In an initial pilot study, discussed in a MEDICA messe newsletter, the team used samples of human skin cells (fibroblasts and keratinocytes) to assess the effects of green and cold-white OLED light. To obtain their results,

the team studied the vitality and mitochondrial membrane potential of the cells in question. They found that the green light had a positive effect on damaged cell cultures of the epidermal layer. If these results are supported by later trials, this could point towards future applications of therapy applicable for more patients.

> “Even after electrical operation and exposure to mechanical loading by bending, no toxic substances are able to alter cells diffused from the OLEDs.”

Additional studies have also delved further into the potential impact of toxic chemicals in OLED lights. They focussed on the possibility of these substances being released through the electrical operation or mechanical loading caused by bending of the lights, thus changing the shape, number, and metabolism of cells. These studies have, so far, not found any cytotoxicity in the lights that were investigated.

Dr Jessy Schönfelder, Head of Medical Applications Research Group, Fraunhofer FEP, Dresden, Germany, stated: “Even after electrical operation and exposure to mechanical loading by bending, no toxic substances are able to alter cells diffused from the OLEDs.” This breakthrough could mean that therapy using OLEDs can be offered to more patients thus improving quality of life by speeding up treatment times.

Transition Metal Oxide: Infection Control for Medical Devices?

BACTERIA colonising the surface of medical instruments could be killed by a novel, innovative product: a coating with transition metal acids. This invention has the potential to reduce the risk of hospital-acquired infections in patients occurring in the future.

The inventor, Prof Josef Peter Guggenbichler, a retired infectologist from the University of Erlangen-Nürnberg (FAU), Erlangen, Germany, was inspired by the natural protective acid mantle located on human skin, as discussed in a MEDICA press release dated 8th November 2016. Acids that reduce the pH to approximately 4.8 are produced by the sebaceous glands of the skin, forming a protective acid mantle that destroys many potential pathogens. Oxides or transition metals such as molybdenum or tungsten create a similar effect which, Prof Guggenbichler hypothesised, could remove pathogens from endoscopes, urological catheters, or electrocardiogram (ECG) lead sets, in addition to providing protection to room fixtures and furniture by a coloured coating to which only small amounts of the transition metal oxide must be added.

> “Bacteria are not only killed but the coating also prevents a biofilm from forming on the surface.”

A humidity of 25% is sufficient to provide enough water molecules for the reaction of water from the ambient forming acidic groups with the oxide particles on the surface of the coating, which adjust the pH to 4.5. These acids contain protons that attack the cell wall of many bacteria.

More than 5,100 exhibitors

"The protein envelope and fimbria that are used by the bacteria to adhere to surfaces are permanently denatured," explained Prof Guggenbichler. "Bacteria are not only killed but the coating also prevents a biofilm from forming on the surface."

Careful Planning Required for Modernisation of Operating Rooms

CAREFUL PLANNING when modernising operating rooms with high-tech equipment is necessary to avoid expensive mistakes, according to a press release from the MEDICA Education Conference 2016. Prof Clemens Bulitta, Director, Institute for Medical Technology, East Bavarian Technical University of Applied Sciences Amberg-Weiden, Amberg, Germany, who presented on this subject on the 17th November, stated: "Many hospitals think only of investment and operating costs but forget the qualification costs for the personnel."

This recommendation stems from the increased modernisation of operating rooms, to create 'hybrid ORs'; these enhance the operating environment with imaging techniques including computed tomography (CT) and angiography, and may also provide a robotic assistance system. These are of vital importance in performing minimally invasive procedures, such as heart surgeons repairing valves through a catheter in the inguinal artery. It is believed that >200 German hospitals have a hybrid operating room (OR) and due to financial constraints, in smaller hospitals, there is typically only one unit, meaning there is significant interdisciplinary use for the room. This makes it necessary to expend time and effort to consider the needs of all stakeholders and create a plan to ensure the hybrid OR meets the requirements of all users. Prof Bulitta elucidated: "We recommend a single 'master plan' that is orientated based on the hospital's workflow and considers all groups such as medical technology, technical building equipment, and building."

> "Many hospitals think only of investment and operating costs but forget the qualification costs for the personnel."

Furthermore, the huge investment cost of the hybrid OR can only be justified in a small hospital if it is optimally used. Prof Bulitta commented: "Personnel must know the basics of modern imaging and post-processing, the options for radiation protection, patient positioning, and how to organise ordering and storage of interventional materials." Prof Bulitta also noted that: "Due to the challenges in interdisciplinary co-operation, specific communication training also makes sense."

Failure to train personnel can have very negative consequences, with Prof Bulitta warning that: "In the worst case, the hybrid OR is filled with unused high-tech toys." The patient suffers from being denied access to optimal treatment and the hospital budget suffers as a result of spending a lot of money on equipment personnel are unable to operate.

MEDICA 2016: A World of Innovation

VISITORS to MEDICA 2016 were met with a fascinating array of innovative new technologies according to an official press release from the conference. From wearable technologies and apps for patients' use to enhanced surgical procedures, we summarise the very best that the exhibition had to offer within its range of specific foci including electromedicine, commodities and consumables, information and communication technology, and laboratory technology/diagnostics. The exhibitions spanned 4 days, offering solutions to healthcare professionals across the board.

...a fascinating array of innovative new technologies...

Wearable technologies in combination with smartphone apps for patient use are one of the most talked-about medical innovations at present. Cardiovascular disease, diabetes, and remote monitoring of therapies are just some of the areas where this technology has the potential to revolutionise patient care, with early estimates suggesting a very high level of uptake in the near future. Big data is also a key part of innovation research that is currently being developed, allowing researchers to compile findings on a mass scale regarding the effectiveness of therapy for certain diseases. This could pave the way for huge steps forward in our understanding of the causes and the most efficacious therapies for a plethora of health problems.

Innovations from a surgical point of view are also creating some exciting new developments. In great demand are calls for more sensitive imaging including medical imaging flows during surgery, allowing surgeons to view a more accurate picture of the procedure and thus ensuring that interventions are as precise as possible and avoid unnecessary discomfort for patients. Three-dimensional (3D) imaging systems are also eagerly anticipated which assist surgeons by producing a detailed, 3D picture using two image sensors carefully aligned on the tip of an endoscope. This not only makes diagnosis of conditions more accurate but could also reduce the likelihood of surgeons overlooking minute tissue alterations caused by a particular health condition.

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Kinan Muhammed

Wellcome Trust Clinical Research Fellow and NHS Clinical Entrepreneur Fellow, Nuffield Department of Clinical Neurosciences, Oxford University, Oxford, UK.

Q: In your personal work, you are particularly involved with understanding the mechanisms and consequences of apathy in patients with neurodegenerative disorders. To what extent are these notions currently understood, and how do you expect this understanding to develop in the next few years?

A: Motivational problems like apathy are very common in neurodegenerative disorders, but unfortunately, research in the area has been limited despite these problems having a large impact on patients and their caregivers. For example, we currently lack objective assessments for apathy that can be used in clinical practice, and we often group reduced motivation with depression even though they have different causes and treatments. Currently, we are still in the early stages of understanding the exact mechanisms of apathy but interest in the field is growing. More recent work suggests that problems in brain areas related to how patients perceive rewards and effort could be a contributory factor. For the future, I think more objective assessments using various physiological and behavioural measures of apathy will start to be able to tell us more accurately how motivated patients are and how that varies with time. This will allow us to quantify deficits in motivation in a more reliable and reproducible way as well as helping us to improve the quality of life of patients who suffer from apathy.

> “As new innovations in medicine emerge I think clinicians should play an active role in moderating their use appropriately and staying up-to-date with the practical and ethical consequences that can arise.”

Q: You are currently studying for your DPhil as well as working as a clinical fellow at the John Radcliffe Hospital, Oxford, UK. In what ways does your work intersect with innovative technology and concepts on a day-to-day basis?

A: I often combine my clinical work in neurology with my research interests as this allows me to continually evaluate our current understanding of diseases and challenge best practices. For example, within the clinical setting, we often assess patients with cognitive problems such as memory impairment or motivational deficits. This is usually carried out with a combination of clinical assessments and questionnaire-based interviews. However, this does not always lead to accurate results nor does it always inform us of the underlying mechanisms of the disease. Consequently, in partnership with my research colleagues, we develop novel experimental tasks that use technology in innovative ways to gain more insight into neurological conditions. For example, we recently carried out a study using infrared eye tracking to assess pupil dilation in response to rewarding stimuli like money. The way in which pupil size changed to rewards allowed us to gauge how motivated patients with Parkinson’s disease were, and greatly increased our understanding of the disease mechanisms while also providing a more objective assessment for apathy. Although these research tools are still in the early stages, they do provide promising uses of innovative technology in the clinical setting.

Q: How would you like to see this intersection expand and develop in the future?

A: I think many medical specialities would benefit from more personalised approaches to clinical assessments, particularly in cognitive neurology and psychiatry. Innovative technologies like eye

tracking, accelerometry, and decision-making computer tasks will increase our understanding of notoriously hard-to-measure diseases, including depression, apathy, and chronic fatigue to name a few. I would like to see new assessments that use various behavioural and physiological measures become incorporated further into the diagnosis and monitoring of medical conditions.

Q: What are the next challenges facing neurologists working both with neurodegenerative disorders and with other neurological conditions?

A: I think more and more we are appreciating the cognitive component associated with many neurological diseases. In neurodegenerative disorders like Parkinson's disease for example, we are now more aware of the importance of non-motor problems that can also occur like anxiety, depression, and apathy. In many cases, these issues can be more debilitating for the patient than their motor problem. The same is true for many other neurological conditions classically believed to spare cognitive function. I believe that the ability to recognise these problems and deal with them effectively will be a common challenge for both neurologists and the medical discipline in general, given the ever-ageing population.

Q: How important are conferences and meetings, such as MEDICA, for harnessing the power of innovation?

A: Conferences that facilitate discussion and dissemination of new concepts and innovation are hugely important to the field and tend to be incredibly engaging and motivating. Bringing people together from different disciplines and with different areas of expertise can often spark new collaborations and nurture new innovations, so I think any medium for stimulating conversation is going to be beneficial for future innovation.

Q: In the future, where do you expect that innovation will have the greatest value: in patient care, or disease prevention?

A: I think there is a place for innovation in all aspects of medicine. However, in terms of the biggest impact my opinion is that focussing our efforts more on disease prevention would likely result in the biggest benefits to the general population and reduce socioeconomic costs the most. Moving upstream of the consequences of chronic disease and dealing with root causes such as unhealthy lifestyle choices like smoking and diet, will mean that the burden on the health service and on patients in later life is reduced, freeing up valuable resources and prolonging health and quality of life.

Q: Digital innovations are bringing medical professionals together across the globe. Do you have any insights into this area of healthcare innovation?

A: Telemedicine is a rapidly expanding area ranging from general practitioner consultations on smart phones to robotic surgery delivered by surgeons remotely. My own experience in the field is with medical education, having co-developed an online service to teach medical students remotely in war-torn countries such as Syria. So, I see this area continuing to grow and with it will come its own set of benefits as well as new challenges which must be faced.

Q: Could you tell us a little about the importance of engaging in policy for doctors and innovators?

A: As new innovations in medicine emerge I think clinicians should play an active role in moderating their use appropriately and staying up-to-date with the practical and ethical consequences that can arise. Ultimately patient care and safety is paramount, so engaging in policies designed to keep new technology safe while not restricting its potential is important. There can often be a fine line between the benefits and the ethical implications of new innovations, so it is important for clinical staff and innovators to work closely together in order to ensure synergistic and safe partnerships.

Q: What would you say has been the single greatest accomplishment of your career to date?

A: Receiving a Wellcome Trust Clinical Research Fellowship has been one of my biggest career achievements. This has given me the opportunity to pursue my research interests in neurology

and allowed me to build and publish my work in numerous journals as well as present at conferences such as TEDxNHS.

Q: Finally, what advice would you give to any aspiring neurologists and innovators?

A: Being at the forefront of a clinical speciality like neurology has so much potential for innovation. Make use of all opportunities and learn from what patients actually need during your day-to-day practice. Many people can have great ideas, but it will always remain an idea unless it is acted upon and that is where the real hard work begins. In order to see an innovation through, you need commitment, real belief in your work, and resilience. So do not be disheartened and instead keep focussed, keep learning and adapting, and most importantly, enjoy the journey.

Julie Sanders

Director of Clinical Research, Quality and Innovation at St Bartholomew's Hospital, Barts Health NHS Trust, London, UK; Nursing and AHP Research Lead, Society of Cardiothoracic Surgery (SCTS) of Great Britain and Ireland.

Q: As Director of Clinical Research, Quality and Innovation at St Bartholomew's Hospital, London, UK, can you tell us a little about your role and responsibilities?

A: St Bartholomew's Hospital aims to be a leading and innovative nursing and allied health professional (AHP) centre committed to delivering evidence-based care and conducting high-quality research to drive improvement in clinical outcomes and outstanding patient experience. I have the privilege of leading this agenda, working with an incredible team of staff and patients to increase nursing and AHP research culture, capability, and capacity in aspects of care and experience; particularly those which matter most to patients, their carers, and our local community.

Q: What is it that drives your interest in this area of work?

A: Clinically and academically I have always been passionate about improving patient outcomes beyond just survival. The immediate recovery, the effect on short and long-term quality of life, and the care experience, often matters more to patients considering treatment options. My academic career has been guided almost exclusively by medics and I have been extremely fortunate to work with some inspiring and innovative medical academic leaders. However, as a nurse I feel strongly that nurses and AHPs should be given the same academic and clinical-academic career opportunities as our medical colleagues and the opportunity to conduct high quality research and develop innovations to drive improvements in our own disciplines. We know that research-active trusts have better patient outcomes, and while we are a very research-active institution, this is currently primarily medically led. Thus, cultivating a research-active culture among nurses and AHPs will be beneficial for both our staff and our patients.

Q: You previously worked at the National Institute for Cardiovascular Outcomes Research (NICOR). How important is this kind of data collection to improving healthcare for cardiovascular patients?

A: NICOR manages six national cardiovascular clinical audits and a number of health technology registries. As clinical audits assess practice against defined standards, involving the implementation of change to attain these standards to improve quality of care and patient outcomes, such data is extremely important. Transparency is key and publication of results is paramount for patient reassurance of standards, for patient choice, and for further driving improvements. Data from such large datasets also has extended use in terms of research and the new era of clinical trials includes

undertaking trials in registries. Trials in registries reduce the cost of conducting a trial, decrease the time to trial completion, increase participant inclusion (less-selected patient populations) and thus results can be published more timely.

Q: Innovation is percolating throughout clinical practice and academic research; is there scope for this to be translated across to nursing contexts?

A: Absolutely! Nurses have great process and product innovation ideas, so it is important that we develop innovation capacity and capability in nursing practice. While some amazing work is being done to drive innovation in nursing forward, further increased organisational culture, infrastructure, and resources to support and nurture both the innovator and the innovation in nursing is needed.

Q: What more could be done to improve the speed of uptake of innovative ideas at both bench and bedside?

A: Improving speed and uptake of innovation has been a focus in the National Health Service (NHS), particularly since the publication of the strategic report 'NHS Innovation, Health and Wealth accelerating adoption and diffusion in the NHS' in 2011. One example is the NHS Innovation Accelerator (NIA) programme, launched in 2015, where the NHS works in partnership with 15 Academic Health Science Networks across England to create the conditions for proven innovations to be adopted faster and more systematically through the NHS. Within the first year the programme achieved impressive results, winning 13 awards, with 389 additional NHS providers and commissioners using NIA innovations.

Q: Do you think patient-centred care is being adopted nationally and internationally? In what ways do you think it could be improved?

A: Many countries, both inside and outside of Europe, are committed to patient or person-centred care. Although their strategies for delivery are quite different, the challenges for delivery in terms of time, resources, and support available from other services are common. The World Health Organization (WHO) are launching a 10-year global strategy for people-centred healthcare (2016–2026) aimed at addressing these challenges and creating a true vision and strategy for achieving patient-centred care around the world by 2026.

Q: How important are clinical trials to the process of improving outcomes and what role do nurses play in this endeavour?

A: Clinical trials have revolutionised many areas of healthcare saving millions of lives across many disease areas. Although not a trialist, I am particularly passionate about the role of nurses working on clinical trials. Clinical trials rely on dedicated nurses experienced in planning and undertaking trials but who are often considered as 'data collectors for doctors'. Within the UK, the National Institute for Health Research (NIHR) has had a major role in the development of clinical research nurse roles and although there is still progress to be made, clinical research nursing is now beginning to be viewed as a viable and attractive career path.

Q: Throughout your career you have taken on a variety of roles in research leadership and innovation development. What project have you been most proud to be a part of and why?

A: This is difficult as I am proud of all the projects I have been involved in for different reasons. If I had to name one, at St Bartholomew's Hospital we have just completed the first nurse-led commercial study evaluating an innovative new device. This study required active involvement in the study by three intensive care nurses. I am particularly proud of how these nurses embraced this study, incorporating and conducting this research within their daily clinical work, and motivating others in the department to be engaged. This embodies the culture we aim to nurture at our hospital and I am proud of this team for leading the way.

> "Clinical trials have revolutionised many areas of healthcare saving millions of lives across many disease areas."

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REVOLUTIONISING HEALTHCARE BY EMPOWERING PATIENTS TO INNOVATE

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INTRODUCING A NEW PARADIGM OF HEALTHCARE INNOVATION

A growing stream of literature argues for a more active role for patients and caregivers in healthcare delivery, namely in:

- managing their disease, and becoming more active and empowered patients[1-3]
- participating in the decision-making process of their treatments[4,5]
- demanding free access to medical research papers, and organising research[6]
- demanding their illness data, and exchanging it with other patients[7]

However, this literature does not consider the innovation capacity of patients and caregivers, and their ability to develop new products and services. To attain the goal of truly patient-centric healthcare, it is necessary to also support and integrate the innovation-related activities of patients and caregivers into the current system.

In this article, we share a view of the paradigm shift in healthcare that is inspired by the work in the social sciences on users and user communities, and by the growing number of new initiatives that are propelling this shift in healthcare.

THE PATIENT INNOVATION RESEARCH STREAM

Many patients with chronic diseases and non-professional caregivers develop useful and innovative solutions to help them cope with their health disorders.[8-11] When we began studying this phenomenon, we first focussed on a set of rare and chronic diseases and looked at the solutions patients use to help them cope with their disease or health condition. We found that patients and caregivers have significant innovative capabilities and have developed various solutions, treatments, and medical aid devices for themselves (e.g. about 50% of the solutions for cystic fibrosis were developed by the patients). These solutions span from simple tools for everyday use, through to the discovery of previously unknown therapies and highly sophisticated solutions.[11]

Encouraged by these results, we decided to explore the phenomenon further, focussing on individuals, rather than the solutions. We administered a survey to a sample of 500 rare disease patients and caregivers and found that 40 respondents, i.e. 8% of our sample of patients and caregivers, had developed innovative solutions for themselves that were evaluated as novel by medical experts. If this fraction of innovators holds for the overall population, patient and/or non-professional caregivers represent a tremendous source of healthcare innovations.[9] Several other studies reported estimates of health-related innovation by ordinary citizens to be from 0.2–0.5% of a population.[12,13] If one considers the estimated fraction of the world's population afflicted by rare diseases to be around 6–8%, it is easy to conclude that the pattern is being repeatedly confirmed. The findings suggest that patients and caregivers around the globe may collectively offer a huge amount of information and knowledge on how to improve patient care in the medical setting.

INNOVATIVE SOLUTIONS DEVELOPED BY PATIENTS OR CAREGIVERS

There are many examples of innovations developed by patients and caregivers. The website

www.patient-innovation.com has >500 solutions, which have been collected, screened, and shared. Here, we will briefly mention solutions of varying complexity that we encountered during our research. Some of them are technically very simple, but nonetheless offer great value to patients and their families. The first of this group is the case of a daughter whose father had dementia and would take a long time to eat meals which proved a difficult time for all the family. He stared at the plate, hesitantly trying to pick up the food. One day, she realised that the colourful and illustrated dishes they used at home disturbed and distracted her father; he had trouble trying to find the food amongst the colourful illustrations. Once the daughter started using white plates, everything changed; the meals suddenly became much faster as the father could easily find the food on the plate.

Another case we identified in our research, is that of Michael Seres, who was diagnosed with Crohn's disease when he was 12 years old. After >20 surgeries, Michael underwent a transplant of the small bowel and started to use an intestinal bag. His own experience as an ostomy patient led Michael to design the Ostom-i Alert™ prototype, while recovering from the transplant. Ostom-i Alert helps warn patients when their ostomy bags are full so they can empty them without risking an overflow. Ostom-i Alert addresses a very relevant need for patients undergoing intestinal procedures that require them to wear colostomy bags, often for the rest of their lives.

The vast majority of the innovations in our sample were developed to increase patients' autonomy. For example, a patient with myasthenia gravis, an autoimmune neuromuscular junction disorder, reported designing several products, which were custom-built according to her specifications. She described the design of one of the tools, a metal two-hook aid that helps her button trousers without the assistance of others. Other reported solutions involved repeated experimentation with the design of elements commonly found in any household. This includes optimisation of the height and width of stairs to improve mobility, or design of tables and chairs with added features to produce safer solutions for hyperactive children with cognitive limitations.

Patients also develop very sophisticated solutions. For example, consider a footstep monitoring device named Sensastep® developed by Jon Christiansen, a sea captain with an amputated leg. When using an artificial leg, Jon experienced discomfort due to the absence of feedback from the ground, which led to the loss of balance, falls, and an increased cognitive effort spent on balancing. The device is small and relatively unnoticeable. The patient wears a conductive foam insole containing 13 embedded pressure sensors. As the heel or toe strikes the ground, a transmitter strapped to the ankle sends signals to a receiver that slips over the ear. The earpiece vibrates against the bone behind the ear, stimulating the cochlear nerve. Variations in the vibrations, which the patient perceives as audible tones, alert the brain as to what part of the foot has contacted the ground ensuring that Christiansen and other patients do not need to look down and watch every step they take to avoid falls.

Another example is Avi Yaron from Israel. After being diagnosed with a brain tumour, he realised that there were no three-dimensional cameras small enough to collect images in deep regions of the brain. He created a three-dimensional camera known as 'Insect Eye'; a scope that mimics the compound eye of a bee and is small enough to operate in the brain. The scope contains a miniature sensor with hundreds of thousands of micron-sized elements, each looking in slightly different directions and mapping the surgical field from many different points.

Although very sophisticated and complex solutions developed by patients do exist, the fact that the majority of these solutions are simple and easy to acquire may be their 'actual' advantage. Not only that, the externalised experience and knowledge in the form of solutions contributes to the stock of knowledge about the diseases and various ways to cope with them, it also adds to the variety of choices to address specific needs. An issue is that the general value of these solutions increases if the solutions diffuse, and several studies show that people who develop solutions to solve their needs rarely share them.[9,13]

THE LOW-DIFFUSION OF SOLUTIONS DEVELOPED BY PATIENTS AND CAREGIVERS

Innovation scholars suggest that, although millions of users develop or modify solutions (including solutions to medical care problems) to better fit their needs, very few of these solutions are shared.

In a study of user innovation in Finland, only 19% of the reported user innovations spread.[14] Among rare disease patients, 32% of those who self-developed a solution to cope with their disease shared information about it with others.[9] In both studies, for the majority of the solutions that were not shared, the developers believed that they could be valuable to the others;[14] the authors of the studies argued that the lack of sharing of valuable solutions is a type of market failure. Patients do not share the innovations due to several reasons: unlike businesses, they do not have the financial incentives, skills, or opportunities to enter the long process of approval and commercialisation; they solve their problem and keep the solution to themselves as they do not know about, or have access to, methods of sharing. An important question is: how do we help more people bring their solutions to a wider audience? One answer is to lower the cost of sharing. Technology and online platforms are one means of doing this. Primary care physicians, hospital specialists, and other health professionals may also serve in discovering and helping to spread new solutions by active solicitation of solutions in face-to-face and online meetings with their patients. Other crucial issues in the relationship between patients and doctors are the ethical aspects around the introduction of innovative therapies, the importance of informed consent, and open and transparent discussion with the patient, all of which are becoming increasingly necessary.[15]

MAIN IMPLICATIONS AND INTERVENTION (THE PATIENT INNOVATION PLATFORM)

Many patients and caregivers are not satisfied with the solutions currently available to help them cope with their needs. Technology improves an individual's ability to experiment with their ideas,[16] and it is likely that the innovative activity of patients and caregivers will increase because of technological advances. This activity may have important implications, in terms of improving both quality of life and health outcomes for many people, if we find a way to easily collect and compare these solutions. One way to intervene and reduce the cost of sharing and searching for existing solutions is to develop a centralised online inventory of patient or caregiver-developed solutions. With this in mind, we developed Patient Innovation, www.patient-innovation.com, a non-profit, international, and open platform designed to allow patients and caregivers to show and share the innovative solutions they have developed to cope with their diseases, as well as to foster collaboration among patients, caregivers, and others. This platform was launched in February 2014, and has a community of >36,000 users with >500 solutions curated and shared by the medical team, as of August 2016.

Platforms and other information and communication technologies facilitate participation and easy interaction amongst patients, caregivers, and health professionals. Health professionals may also learn more about patients' needs and the solutions they have developed to cope with problems in their daily lives, as well as having more options to offer patients in their jobs.

We are just at the beginning of understanding innovation by patients and caregivers, and learning to innovate with them. It is therefore important that all the stakeholders in the healthcare value chain increase their awareness of the phenomenon, and support the process of innovation by patients, caregivers, and other collaborators. Numerous challenges are associated with patients developing and sharing their health-related solutions. For example, how can we professionally assess them, determine their general value, and stimulate diffusion for broader long-term public health benefits. It is time to open our healthcare system to help patients help themselves and, in turn, many others.

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ABSTRACT

Last year in England alone there were approximately 57 million failed attempts to book general practitioner appointments. The following article outlines the spectrum of solutions being proposed and championed by National Health Service (NHS) organisations with a view to providing new models of care in a cost-effective fashion. The intricacies and peculiarities of technology as an enabler in healthcare are explored, with reference in particular to agile iteration as a key methodology in this space.

Keywords: Tech, National Health Service (NHS), MedTech, healthcare, NHS Digital, new models of care, Five Year Forward View, telemedicine.

INTRODUCTION: WHAT CHANGE IS NEEDED IN THE NATIONAL HEALTH SERVICE?

This is a question that has been asked hundreds of times and has hundreds, if not thousands, of truly valid answers. While some of these are more nebulous and conceptual than concrete and measurable, ultimately where we must look is to policy change that has come from service-wide consultation and information gathering.

In January of 2015, National Health Service (NHS) England announced a new programme, the New Models of Care Programme, to focus on the design and implementation of new models of care in health and wellbeing.[1] It set itself the task under Samantha Jones, Director of the New Models of Care Programme, UK, of achieving the rapid change that was recognised as necessary in the NHS Five Year Forward View.[2] While the Five Year Forward View set out a clear view on what change should look like in the NHS, it is 'on the ground' implementation processes that will drive this view to be realised.

The head of NHS England, Mr Simon Stevens, outlined the progress to date at the recent Liverpool NHS Annual Conference but also highlighted the need for further progress in urgent care: "We need to redesign the way our urgent care system works. The current system is confusing the public. We have to do a better job of joining it up. We need to simplify the urgent care spaghetti so we can manage the demands being placed on us." Mr Stevens urged parts of the country to step forward as urgent care vanguards. Organisations and partnerships were asked to come forward and help the NHS to innovate, and 50 were chosen as part of a rigorous process of selection. Each vanguard is taking a lead on developing new care models as a blueprint for the NHS moving forwards.[3] Many are in Primary Care, because evidence shows that healthcare systems with a greater focus on Primary Care help to keep people healthier for longer.[3]

While vanguards are a fantastic step in the right direction, their setup process prevents the smaller scale innovators from getting involved. Thankfully, vanguards are not the only solution being proposed and championed; there is a multi-pronged approach to the change that needs to occur to relieve pressure on our urgent care system. The following is a non-exhaustive list of current avenues:

Academic Health Science Networks

The goal of Academic Health Science Networks (AHSNs) is to translate research into practice,

through the alignment of innovation, training and education, clinical research, and healthcare delivery. Billed as 'systems integrators', AHSNs have been established as small autonomous enterprises with a specific 5-year NHS England commitment. Where they differ from traditional delivery vehicles is their focus on return on investment, in keeping with lean economic principles described later in this article.

NICE Implementation Collaborative

The National Institute for Clinical Excellence (NICE) Implementation Collaborative (NIC) is a partnership between NICE, the NHS, and multiple key health organisations and patient bodies. The goal is to drive improved access to NICE-approved medicines and technologies, and the key element is that it does this in a timely fashion. Having multiple large organisations increases friction and decreases agility; the NIC plays an important role in 'redrawing the landscape' by identifying barriers and allowing the right people to collaborate on practical solutions.

Innovation Connect and Portal

Anyone who has worked at any modern tech giant will tell you that opening up access to innovation support to everyone is a vital part of gathering an adequate spectrum of ideas. Innovation Connect supports innovators with ideas that have a clearly defined need and clinical support, while the Innovation Portal allows anyone to share ideas and meet other people with similar interests and experience. This comes down to scientific principles; the higher the 'N' value for a particular experiment, the more likely you are to get a statistically significant result.

Funding: Challenge Prizes and the Small Business Research Initiative

Arguably one of the world's most successful innovators, Elon Musk, whose founded companies include PayPal, Tesla Motors, and SpaceX, cites the basic psychology that has led to his success: "people respond to precedence, incentives, and superlatives." The NHS England Innovation Challenge Prize provides financial incentives to encourage, recognise, and reward key frontline ideas. The Small Business Research Initiative (SBRI), championed by the aforementioned AHSNs, provides another route of competition to address unmet health needs.

National Innovation Accelerator

The National Innovation Accelerator (NIA) is focussed on prevention, early intervention, and long-term condition management. Through support of Fellows to take innovations to NHS providers and commissioners, the NIA aims to deliver the commitments of the NHS Five Year Forward View.

Test Beds

Set up to help pioneer the use of interconnected devices for monitoring and data analysis, NHS test beds are allowing early evaluation of technologies in areas such as home monitoring, which many see as a key area for future development and potential cost-saving. The Internet of Things (IoT) element of this is particularly interesting; while the small agile nature of a test bed setup allows iteration on processes at the point of delivery, the NHS as a whole represents a key opportunity for scale where effective solutions are found.

Clinical Entrepreneur Programme

Involvement of frontline clinicians has long been seen as a key component to allowing the kind of problem-orientated solution testing that is needed. But, while allowing free rein on ideas and concepts for change allows a fast narrowing down of options, the true effect of each pain point is difficult to evaluate without a deep knowledge and experience of the multitude of processes involved. Doctors, who work in parallel process lines across specialties and rotate between trusts more frequently than many multidisciplinary team colleagues, see system after system and problem after problem. Recognising their role in problem identification is important but where the Clinical Entrepreneur Programme (CEnt) will make the biggest impact will be supporting doctors to implement and iterate their solutions to the wider health service.

HOW BIG IS THE PROBLEM?

In 2015 there were 57 million failed attempts to book general practitioner (GP) appointments in England alone.[4] The majority of these, on analysis of patient survey data, failed because of a lack of appointments on the day wanted and at the time requested.

Mr Stevens speaks of the "demands being placed on us"; his words echoed by the same patient survey data, which is the result of questions asked of nearly 1 million people each year showing a clear

rise in expectation of appointment immediacy year-on-year.[4] But even aside from the level of patient expectation, it is an objectively measurable numeric demand (more patients and more appointments per patient) that is increasing. The issue becomes more complicated when you look at factors such as administrative change and workforce alteration nationally.[5] But the effects of an overall increase in demand on GPs is clear to see, it was reported recently by the British Medical Association (BMA), relating particularly to the shortening appointment lengths as GPs try to cope with demand.[6] The BMA stated in no uncertain terms that the average 10 minutes per appointment that has become the norm is putting many complex patients in the UK at risk.[7]

HOW CAN TECHNOLOGY HELP?

Any communication system that still regularly uses faxes, in 2016, could benefit from today's technology. Unfortunately, this applies in both primary and secondary care settings across the country. And yet it is the fault of no individual when parts of a large organisation fall behind other industries in technology uptake; rather it is a function of in-agility and often resource focus in other areas. Healthcare, where the NHS has been at the forefront of increasing standards of clinical care inexorably since its inception, has its own 'unknown unknowns' such as new infectious disease outbreaks and avenues of costly treatment research. This is the reason management consultants have been called in to help manage trust-wide issues with MBA-style modelling.

But more than simple hardware upgrades, technology in this decade has brought with it a wave of logical thinking; where system design is widespread and iterations of architecture and protocol are commonplace. The agility of start-ups in the world-leading London tech scene is nothing new (after all, large corporations all generally began as small nimble companies) but their popularity and subsequent success is a testament to the 'lean' process that they nearly universally undergo to achieve success.

All of the above listed NHS England avenues for aiding urgent care point to lean processes as the optimum methodology. It is exactly for this reason that NHS England's Innovation team have set up the CEnt Fellowship, supporting front-line clinicians to take their ideas for innovation forwards, and iterate them to fit a marketplace that badly needs efficiency. Soon this fellowship will be extended to Allied Health Professionals, and ultimately to patients themselves. To paraphrase Sir Bruce Keogh, Medical Director of the NHS, at the CEnt opening event: in what other context would you make it difficult for your most involved and intelligent organisation members to innovate and lead change?

WHY THE UBER MODEL DOES NOT WORK FOR HEALTHCARE

As people see the 'uberification' of various industries, those on the fringes of healthcare begin to rub their hands and dream of the kinds of figures that healthcare generates in revenue. The next big tech unicorn, it is speculated, will come from digital health. Deloitte predicts 35% compound annual growth rate in what it calls 'mHealth' in the UK, while other industry onlookers predict even higher expansion. "What is not to like?" they ask. "Doctors on demand, to your door, whenever you need. How can it be a bad thing?"

There is of course much to be said for increased patient autonomy and using technology as an enabler for that is inherently a good thing for healthcare and patient empowerment. But when it comes down to extension of another industry's model, medicine is not the simple carriage of a person from one place to another, and doctors are not constantly circulating and simply in need of efficient redirection by a consumer-based service. Healthcare professionals as a whole already function in a relatively economical way in the community for face-to-face interactions; patients attend their surgeries (when well enough to do so) and the doctor sees far more patients this way than if he or she were forced to do house calls for all of those patients.

This is not to downplay the inefficiencies of a 'localised' system (immobile resource scaling and potential condition cross-contamination) where aspects could be delocalised. The above taxi driving analogy however would be more accurate if it were extended so that each person who wanted a taxi was unsure where they wanted to get it to, was unsure of the urgency, and in fact could only vaguely describe where they were presently located.

The solution, therefore, is not about shuttling doctors to their patients, on demand. It is about finding where it has been inefficient for a relatively fit and well patient to attend their GP, only to be

asked a few simple questions and sent on their way (occasionally clutching a signed piece of paper that will take a while to transform into treatment, normally at another institution altogether). It is about streamlining that interaction, such that GPs' time is opened up to dealing with those who need extensive history taking and examination; the elderly and those with chronic, poorly controlled conditions.

The NHS New Models of Care is about exactly that; the need for change has been recognised in the Five Year Forward View, and the various approaches outlined above are the lean methodologies for speeding up the process. Rather than being 'unfocussed', a widespread lean approach allows the kind of quantitative and qualitative testing and hypothesis acceptance and rejection that clinicians are very familiar with. The rapid iteration of these results is the part that needs to be focussed upon if we are to achieve significant change in such a large organisation; we should test safely until the optimum change is seen, and then provide evidence of safe, effective impact at scale.

The peculiarities of medicine that have kept it at a distance from innovators in the past are beginning to melt away. A decade ago, streamlining consultations based on likely clinical simplicity may have been perceived as too disruptive to be a working model. To extend the taxi analogy, it would be akin to trying to predict which taxi hailer is likely to want the shortest ride ahead of time. Now however, we have the technology provided by search engines and electronic patient records that gives demographic information and allows prediction to become a health-needs foresight.

CONCLUSION

In the 'big data' age, we are able to predict health outcomes in ways not thought possible in the past. The NHS New Models of Care, alongside complicit bodies like the Information Commissioner's Office (ICO) and the UK Department of Health, will allow innovation that safely keeps patient data under the watchful eye of appropriate informational and clinical governance. The 'crown jewel' of the welfare state has a unique standpoint on the health of a nation, just as Twitter (San Francisco, California, USA) has a unique standpoint of the security situation at the Olympics as it unfolds. The key is harnessing this in a safe and responsible manner. Our NHS, in this sense, represents a key opportunity to move human health forwards. The recognition of the need for guidance and directed strategy in this respect, from the very upper echelons of the world's fifth largest employer, is the first step on the road to bringing about the change that is needed. And in this author's humble opinion, it is just a matter of time before healthcare has its own 'Uber' model.

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EDITOR'S PICK

For my first Editor's Pick I have highlighted the paper 'The Role of eHealth technologies in driving patient participation'. As technology-assisted healthcare expands, we must ensure that those often left behind and disadvantaged are included and prioritised. To echo the views of Robert Wachter, as mentioned in my foreword, technology provides us with the tools for human endeavour, but does not yet replace it!

Dr Mike Bewick

DEMOCRATISING HEALTHCARE: THE ROLE OF eHEALTH TECHNOLOGIES IN DRIVING PATIENT PARTICIPATION

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ABSTRACT

Digital technologies are changing how we practice and experience healthcare. This review focusses on the role of eHealth technologies in facilitating patient participation within the healthcare process. The central claim of this paper is that interactive, web-based technologies allow individuals to become more active participants in the healthcare process, thereby opening up new perspectives and opportunities for improving healthcare.

By drawing on findings from recent research, the review seeks to highlight how the increasing availability of health information and individuals' ability to easily connect to others around the globe can facilitate knowledge exchange and collaboration between the general public, patients, healthcare professionals, and researchers. Acknowledging some of the potential challenges and pitfalls further shows how these new technologies, if used appropriately, can promote a new form of patient participation that goes beyond the individual level and as such, constitutes an invaluable resource for healthcare research and practice.

Keywords: Digital healthcare, eHealth, collaboration, innovation, patient participation, participatory research.

INTRODUCTION

Digital technologies such as artificial intelligence, nanotechnology, three-dimensional (3D) printing, augmented reality, social media, and wireless sensors are evolving at an ever increasing pace and are penetrating all areas of society including healthcare.[1] According to Goodall et al.,[2] the application of digital technologies in healthcare can be classified as measures targeting three broad areas: i) the improvement of healthcare practice by enabling better management of clinical records and patient information, and provider-to-provider communication; ii) the facilitation

of patient involvement in the care process; and iii) the increased availability of health information for patients and their families. As such, digital healthcare technologies are not only revolutionising the ways in which we collect, access, and share health data but also how we transform them into meaningful information and actionable knowledge.[1] This in turn leads to changes in traditional relationships, roles, and practices in healthcare.[3] It has been suggested that digital technologies have particularly contributed to strengthening the role of the patient by reducing the knowledge and power asymmetry prevalent in the healthcare setting.[4,5]

By reviewing the pertinent literature in the field, this paper aims to demonstrate how digital technologies are enabling individuals to become more active participants in the healthcare process thereby laying the foundations for the democratisation of healthcare. Moreover, it seeks to discuss some of the potential challenges and pitfalls these developments entail. In order to provide a concise and informative overview of relevant research in the field, a narrative review was conducted. PubMed was searched in August 2016 using search terms that were identified through key publications within the field.[4,6-10] To complement this search strategy, a hand-search was performed on Google Scholar and a reference list of the identified studies included.

PATIENT PARTICIPATION AND eHEALTH TECHNOLOGIES

As a part of the shift away from a top-down approach to care toward a more patient-centred perspective, the concept of patient participation has come into focus.[11] Traditionally, patient participation refers to the patient's active role in his or her own care process including aspects such as shared decision-making and self-management of chronic health conditions.[12] It emphasises the patient's right to choice and control over medical decisions concerning his or her own health[11] and has widely been recognised as a promising strategy to improving healthcare.[12]

An extensive body of literature covers topics related to patient participation in the context of web-based technologies that enable individuals to access health information and services online via their computer, smartphone, tablet, or smartwatch, including electronic health records,[13] health information websites,[14] interactive virtual patient networks,[15] smartphone applications,[16] and web-based decision support systems.[17] These technologies are commonly referred to as eHealth technologies[6] and are considered valuable tools for patient participation that can be utilised not only to promote the adoption of healthy behaviours and disease prevention but also to facilitate the early detection of emerging health issues.[7] Increasingly, they are also used to support patients in managing chronic health conditions.[18,19] In this context, wireless sensors and devices have gained increasing attention as a convenient way for individuals to track body functions, activities, and geolocation.[20] With their increasing accuracy and reliability, the data from these monitoring devices offers more transparency to patients and can facilitate the early detection of medical emergencies and diseases.[21] However, evidence on the impact and additional long-term benefits of eHealth technologies is not conclusive.[7,10,22,23]

eHEALTH TECHNOLOGIES: FOSTERING A NEW FORM OF PATIENT PARTICIPATION

Besides the debatable impact of digital technologies on long-term outcomes such as quality of care, health outcomes, or healthcare costs, it is evident that digital technologies have changed how health information and services are accessed and used by both patients and the general public. Findings indicate that web-based technologies can improve access to health information and services[24] which can in turn, foster a new form of patient participation that goes beyond the traditional understanding of patient participation, extending beyond the individual patient's health.

Indeed, more and more healthcare organisations have started to increase their online presence to provide their patients and the general public with high-quality medical information.[25] Some also use social media channels to promote behaviour change (e.g. smoking cessation)[26] or to communicate public health risks to the public (e.g. Ebola outbreak).[9] Moreover, as a result of the open access movement, patients have gained access to additional information resources, like medical journals and scientific publications, that were formerly only available to a selected audience of medical professionals and researchers.[27]

In contrast to traditional online health information resources, where the information flow is usually unidirectional in the form of patient education, the

emergence of peer-to-peer support networks allows for multidirectional information exchange among individuals.[28] This means that individuals can not only access health information and services online, but they themselves can become active information providers, health advocates, and collaborators.[8,29,30] As such, patients can assume new roles, tasks, and responsibilities that go far beyond the traditional concept of patient participation.[8]

NEW ROLES AND OPPORTUNITIES

Peer-to-Peer Support and Collaboration

More and more individuals are becoming active online to share health information and their personal experiences. Some of these efforts are directed at the general public, for example to promote a certain lifestyle (e.g. physical activity), while others are targeted at specific patient audiences with the purpose of sharing and discussing health condition specific topics, like diagnosis, treatments, or side effects.[31,32] Qualified by their lived experience, individuals can assume the role of health coaches that guide and motivate others to adopt certain behaviours or to engage in effective self-management practices for chronic health conditions.[33] The interactivity of social media channels enables individuals to use different types of media formats to provide clear and easy-to-follow instructions or recommendations. It also allows visual demonstration of the effects of different treatments or procedures for example, in the form of videos or before and after pictures. This sharing process helps to transform individuals' personal experiences into experiential evidence that can show the effectiveness or ineffectiveness of certain measures or treatments.[34] With an increasing number of individuals sharing their experiences, the value of this database of experiential evidence increases substantially. It can not only be an important resource for patients and their families but also for healthcare professionals and researchers.[31,34-36]

The increasing popularity of crowdsourcing platforms has further contributed to the distribution of power and information in healthcare. Broadly speaking, crowdsourcing, as the name suggests, refers to the outsourcing of a task. This assigns tasks usually left to specific individuals to a large, anonymous group of individuals, i.e. the crowd.[37] Crowdsourcing platforms allow individuals to engage in collaborative tasks, such as 'Question & Answer' sites or physician rating websites that are driven by the 'wisdom of the crowd'.[38] Crowdsourcing platforms can help individuals gather large amounts of information and may thereby support them in making informed decisions. Furthermore, web-based collaborative mapping has gained increasing importance in healthcare.[37] A prominent example of such a collaborative mapping project is Wheelmap, a service focussed on crowdsourced mapping of wheelchair accessible places to help individuals identify whether a certain location is accessible or not.[39]

More recently, in addition to sharing health-related information, individuals have also started to engage in innovation and co-creation activities by sharing their ideas on how to improve existing or develop entirely new technologies, tools, and devices to improve their health and/or quality of life.[30,40-42] This process of what is commonly referred to as patient-driven or patient-led innovation.[43,44] It is not merely a phenomenon of the online world however, digital technologies have certainly facilitated the exchange and dissemination of innovative ideas and practices among individuals. It has been suggested that the adoption of open source approaches that give all users the unrestricted right to study, modify, and distribute information, can indeed help to reduce costs and contribute to increasing the pace of innovation in healthcare, underlining also the role that patients can play in this process.[45]

An example of such a collaborative effort is the Nightscout initiative, a do-it-yourself mobile technology system for individuals with Type 1 diabetes mellitus that was created by patients, for patients, using open source software code. The Nightscout community continuously generates new personalised digital solutions that allow patients, their caregivers, and health professionals to better monitor, predict, and manage diabetes.[40] Being publicly available through open source, anyone can access, use, modify, and share the code to further improve or personalise existing solutions to better meet their needs. Another frequently mentioned example of collaborative co-creation is the Enabling the Future project, which has dedicated its efforts to providing disabled children with low-cost, personalised upper limb prosthesis. The e-NABLE community involves over 1,500 engineers, students, parents, healthcare professionals, and designers that interact via social media websites to exchange ideas for new designs or improvements of existing prosthesis, request help, or donate.[41] The availability of the required resources online

and the support from the community make the production of 3D-printable prosthetics affordable and simple. Some of the designs are in fact so simple to assemble that it can easily be done by children themselves.[41]

In this context, the concept of open source and crowdsourced health research will become increasingly important, as outlined by Swan. The author points to the emergence of self-run clinical trials and structured self-experimentation of patients, highlighting the potential of this new form of patient-led research to contribute to our understanding of rare health conditions that may not be prioritised by pharmaceutical companies and other funding bodies.[46]

Patient-Provider and Research Collaboration

Over the past decades, the understanding of the patient's role has changed dramatically.[46] Formerly perceived as a passive consumer of care, patients have evolved to become active decision makers and participants in relation to their own health, for example, by engaging in self-management activities. More recently, their role has extended beyond the individual level. Increasingly, patients are recognised as knowledgeable collaborators and partners both in healthcare research and practice.

As patient-helpers, patients are recognised as an important resource for other patients and as allies for healthcare professionals. They are not in competition with physicians, but rather complement existing healthcare services.[8] Indeed, the value of peer-led self-management support and its potential to improve health literacy and foster patient empowerment have been demonstrated repeatedly within the offline setting.[47] A prominent example is the Stanford Chronic Disease Self-Management Program which includes small, patient-led group interventions. Patients leading these self-management workshops assume a role model function and are trained in a structured way on how to lead the workshops.[48]

Similarly, patients are also becoming more and more involved in research activities.[49] While traditionally patients were subjects of research (e.g. randomised controlled trials), participatory research approaches, where patients join research projects as equal partners, have gained increasing attention.[50-52] In this context, patients have been described as essential components of healthcare research, including medical conferences[53] and publishing.[54] It has been suggested that patient participation in these traditionally closed communities can indeed provide researchers and healthcare professionals with a better understanding of the actual needs and problems of patients, fostering collaboration between the different stakeholders.[53,55]

eHealth technologies can help to facilitate this collaboration process.[49,56-58] The digital aggregation of experiential evidence by patients can not only help to track and predict disease trends but can also provide new insights into comorbidities and treatments.[36,59,60] In this context, Riley and Gagnier[61] underlined the potential of combining case reports produced by practitioners with patient reports, referring to organisations such as Cancer Commons, Patients Like Me who are promoting a more active form of patient participation within healthcare research. Other examples of web-based collaborative efforts include the CureTogether, MedHelp, and Inspire platforms (for more examples see Swan[46]). Moreover, it has been shown that patient online communities can provide healthcare professionals with valuable insights into patients' needs and perceptions which can in turn be used to anticipate patients' questions or fears, to identify and address topics of public concern, to advocate for the introduction or change of policies, or to prioritise certain areas of research and funding.[34,35]

One of the key benefits of this novel form of online collaboration between patients, healthcare professionals, and researchers is that findings are disseminated more efficiently, offering immediate clinical utility for patients.[49,62] Indeed, it has been highlighted how the use of personally controlled health records can foster patient participation as a driving force in the healthcare process. Contrary to electronic health records that grant patients better access and control over their health information, these are entirely controlled by the patient, who decides who can read, write, or modify their personal records.[57]

CHALLENGES

As outlined above, eHealth technologies provide individuals with the possibility to assume a more active role in the healthcare process that is, by no means limited to, taking charge of their own health. However, these developments do not come without risks and potential pitfalls, most of which are related to the lack of control over the quality

of online health information, poor health and/or digital literacy skills, privacy and data protection, and the impact of the use of these new technologies on the doctor-patient relationship.[63]

As highlighted by Wald et al.,[63] the lack of control over the quality, quantity, and access to online health information constitutes a major public health concern. Inadequate utilisation of eHealth technologies may for example, result in patients' inappropriate use of health services, unnecessary anxiety, or adverse events.[63-66] This in turn may have a significant impact on healthcare systems. Research further suggests that patients' use of online resources to gather information may be perceived as a threat to medical authority, thereby putting a strain not only on the doctor-patient relationship but on the healthcare system.[67,68] Some authors have even attributed the lack of proven success of eHealth initiatives to resistance in adoption. It has been suggested that current adoption and acceptance rates are not yet high enough for eHealth technologies to reach their full potential and that there is a need for healthcare professionals to adapt their practice to the changing healthcare environment.[46,69] However, findings indicate that healthcare professionals in particular, who are the driving force in promoting eHealth initiatives and patient participation, are concerned with issues related to the performance of eHealth technologies as well as the effort needed to implement and sustain them.[12,69] Strict policies and regulations present in the healthcare sector may further decelerate progress with respect to eHealth initiatives.[70]

Moreover, despite increasing coverage, there are still parts of the population lacking adequate access to, or knowledge of, modern eHealth technologies. Authors have noted that these technologies may in fact contribute to reinforcing existing health inequalities within the population and that more research is needed to better understand the use of eHealth technologies by medically underserved and disadvantaged social groups.[71-73] Findings indicate that particularly people belonging to disadvantaged social groups may lack access, knowledge, and confidence in using eHealth technologies.[71,73,74] This can in turn intensify existing social inequities and disparities, leading to poor health outcomes in disadvantaged populations, like ethnic minorities, the elderly population, or individuals with low socio-economic status.[71] In this context, some authors have also pointed to the risks of victim-blaming that may result from the adoption of eHealth technologies that 'nudge' individuals to engage in self-management in their own interests.[75] By implementing interventions focussed on changing individual behaviours and beliefs rather than addressing overarching social factors responsible for particular health conditions, the responsibility is shifted from the state to the individual.[76]

Another imminent issue related to the adoption of eHealth technologies arises from ethical concerns regarding the privacy and protection of individuals' personal health information.[77,78] In some instances, this information is willingly generated by individuals themselves, while in others it is the result of imposed data surveillance.[71] The latter in particular raises important questions related to individuals' rights to their own health information: Who has the rights to access, manipulate, or analyse individuals' publicly shared information? Who has the right to draw conclusions from individuals' search queries or information shared on a message board? And can these rights be revoked? These questions become even more critical with the entry of more and more commercial entities, like pharmaceutical or insurance companies, into digital healthcare, as they may have conflicts of interest.[79] By limiting access to records through patient consent, some of these ethical-legal concerns over data protection and privacy may be attenuated.[57]

CONCLUSION

Digital technologies are breaking down traditional hierarchies, barriers, and power dynamics in healthcare contributing to a democratisation of healthcare. Once dependent on healthcare professionals as the sole source of information, digital technologies in general and the internet in particular, have opened up new opportunities for patient participation that extend beyond the individual level. As patient-helpers and research collaborators, patients can actively contribute to shaping and improving healthcare research and practice by sharing not only their health information but also their insights and experiences.

However, it needs to be kept in mind that all of these technological developments entail certain risks and ethical concerns related to the dissemination and adoption of potentially harmful information that may not only put a strain on healthcare systems and professionals but may indeed jeopardise individuals' health. In this

context, special attention should also be paid to disadvantaged social groups who may lack access, knowledge, or confidence in using the available technologies. This is why the active involvement of healthcare professionals, researchers, and policy makers is essential to the success of patient participation.

The adoption of a more inclusive and collaborative approach to care, that combines medical and experiential knowledge, has the potential to improve healthcare by ensuring that efforts are aligned and tailored to the actual needs of those affected by a particular health condition. Recognising the challenges this entails requires healthcare institutions and policy makers to develop adequate strategies and incentives to foster this new form of patient participation in healthcare.

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PERSONALISED MEDICINE WITH COMPANION DIAGNOSTICS: THE INTERCEPT OF MEDICINES AND MEDICAL DEVICES IN THE REGULATORY LANDSCAPE

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ABSTRACT

Personalised medicine, with the aid of companion diagnostics, is a burgeoning field. The potential benefits of personalised medicine with regard to improved patient outcomes and reducing healthcare burden are recognised, but there remains obstacles that may limit growth in this area. Limitations include the current regulatory framework in many areas, in which the pharmaceutical is identified as a medicine, whilst the companion diagnostics are identified as a medical device; thus the two components may be governed and assessed by differing bodies and processes. This in turn results in disparity in approval times, patent and intellectual property claims, and reimbursement. Regulatory agencies are working together with industry and academia towards bridging these gaps, with significant inroads seen across the globe.

Keywords: *In vitro* diagnostics (IVDs), regulatory agencies, biomarkers, genetic tests.

INTRODUCTION

In recent times, the development of personalised medicine has been amongst the most significant outcomes of the acceleration in genomic science.[1] This development has deepened our understanding and ability to predict both the process of disease evolution and the mechanisms of action through which potential therapies can interrupt or arrest this evolution.[2] The concept of personalised medicine, or precision medicine, is to tailor a treatment regime for the individual to achieve optimal results, based on a detailed understanding of the molecular and genetic basis of diseases. This has a number of advantages, including: avoiding unnecessary treatment that would be of little to no benefit and a closer understanding of the risk-to-benefit ratio for a patient, thus ensuring that the risk of adverse drug reactions in that particular patient are likely to be outweighed by the benefits.

Two broad categories of diagnostics have emerged with the advent of personalised medicine: complementary and companion diagnostics (CDxs). Complementary diagnostics are generally identified as assays that inform on the potential benefit of a therapeutic for an individual, but do not require a regulatory link to a specific pharmaceutical at the time of development. In contrast, CDxs are directly linked to a specific pharmaceutical during and post-regulatory approval.[3] CDxs identify those individuals with expression of specific genetic biomarkers that identify a disease or the likelihood of response to a therapy, as well as tools to optimise and monitor therapeutic doses. The potential benefits of this type of treatment regime are numerous, including the optimisation of treatment, decreasing healthcare costs by treating only those patients that will benefit from the therapy, which is associated with a reduction in waiting times for treatments; reduction to treatment delay with a second-tier treatment that may be of greater benefit to a patient than the primary treatment; and focussed clinical development of the therapeutic, enhancing the risk-to-benefit profile, which is advantageous for patients, industry,

and for regulatory approvals and compliance.[4] However, there are also a number of stumbling blocks and disappointments, as is the case with most new paradigms, including patient and societal expectations, which may be unrealistic in terms of both improved efficacy of the treatment and increased ability to treat a greater number of disorders, costs, and resources associated with undertaking CDxs,[5] patent associated issues resulting in the reluctance of companies to invest in research and development of the CDx,[6,7] differential reimbursement/payment schemes for the pharmaceutical and the CDx,[8] and traversing the regulatory landscape whilst it is under development to accommodate the interplay between pharmaceutical and CDx.

The development of CDxs is ideally concomitant with a pharmaceutical, thus enabling appropriate evidence collection to demonstrate and evaluate the risk-benefit profile of particular patient cohorts. Previous research has identified the need for the development of new models of research and development to address the area of CDxs.[9] However, it is also essential to consider the emerging challenges for both industry and regulators in the co-ordinated approval and post-market monitoring of these medicines and medical devices.

CURRENT STATUS OF APPROVED COMPANION DIAGNOSTICS

The CDx is, in essence, similar to any other *in vitro* diagnostic (IVD) device in regard to the purpose of detecting the presence of an analyte or genetic sequence to inform on the potential susceptibility to a disease, potential efficacy of a therapeutic, or in monitoring the effectiveness of a treatment regime. Similarly, the evidence supporting the intended purpose of the device is similar to that of other medical devices. The differentiator for a CDx from other IVD assays is the association specified within the approved labelling of a particular pharmaceutical. Examples include the 26 CDxs currently cleared or approved by the US Food and Drug Administration (FDA), in which the intended use specifies the associated treatment (Table 1).

Interestingly, some of these pharmaceuticals have benefited with the advent of CDxs. Iressa® (gefitinib) and Herceptin® (trastuzumab) are examples of pharmaceuticals that were not considered cost-effective or sufficiently efficacious in cancer treatment prior to being coupled with a CDx. In the case of gefitinib, in 2005, following failure to demonstrate significant benefit in Phase III clinical trials, use was restricted in the USA market and the marketing authorisation application was withdrawn in Europe. However, an additional Phase III trial identified that the patient cohort with an epidermal growth factor receptor gene *(EGFR)* mutation had a greater favourable outcome when treated with gefitinib, resulting in the European Medicines Agency (EMA) approving treatment of gefitinib, with the CDxs for EGFR-tyrosine mutation, in non-small cell lung cancer (NSCLC).[10]

Similarly, when trastuzumab was assessed for the treatment of advanced gastric cancer by the National Institute for Health and Clinical Evidence (NICE), an independent body which provides guidance to the UK National Health Service (NHS) on the clinical and cost-effectiveness of health technologies, it was initially not recommended on the basis of the latter. However, following a resubmission of health economic data with the patient subset of HER2 overexpression being defined, the outcome was positive.[11] This example not only highlights the importance of defining the optimal patient population for the therapeutic, but also the benefit of health economic reviews where the cost and value of the CDxs and pharmaceutical are jointly assessed to clearly demonstrate the cost-effectiveness.

Additional benefits of understanding the disease process and drug mechanistics, and thus in turn the effect on different patient subpopulations, are reflected in terms of decreased development times and improved approval process for new pharmaceuticals. For example, the development and approval of Zykadia® (ceritinib) in the treatment of NSCLC was based on small open-labelled non-randomised Phase I/II studies in patients with anaplastic lymphoma kinase rearrangement who had developed resistance to Xalkori® (crizotinib). The patient cohort with the specific genetic marker and CDxs had already been indentified with the development and approval of crizotinib.[12,13]

CHALLENGES FOR REGULATORY APPROVAL

Regulatory agencies, in many first-world jurisdictions, identify a CDx as a medical device and a pharmaceutical therapeutic as a medicine. This in turn requires separate applications through two separate regulatory frameworks. The differing requirements of these two regulatory systems may result in a delay in the approval of one component.

Table 1: Companion diagnostic devices cleared or approved by the US Food and Drug Administration (FDA).[14]

Device trade name	Device type	Biomarker	Disease	Associated drug trade name (generic name)
cobas® EGFR Mutation Test (two models)	Real-time PCR	Mutations in *EGFR*	NSCLC	Tarceva® (erlotinib), Tagrisso™ (osimertinib)
therascreen® EGFR RGQ PCR Kit	Real-time PCR	Mutations in *EGFR*	NSCLC	Gilotrif® (afatinib), Iressa® (gefitinib)
PD-L1 IHC 22C3 pharmDx	IHC	PD-L1	NSCLC	Keytruda® (pembrolizumab)
VENTANA ALK (D5F3) CDx Assay	IHC	Anaplastic lymphoma kinase (ALK)	NSCLC	Xalkori® (crizotinib)
DAKO EGFR PharmDx Kit	IHC	*EGFR* expression	Colorectal cancer	Erbitux® (cetuximab), Vectibix® (panitumumab)
cobas® KRAS Mutation Test v2	Real-time PCR	Mutations in *KRAS*	Colorectal cancer	Erbitux® (cetuximab), Vectibix® (panitumumab)
therascreen® KRAS RGQ PCR Kit	Real-time PCR	Mutations in *KRAS*	Colorectal cancer	Erbitux® (cetuximab), Vectibix® (panitumumab)
DAKO c-Kit pharmDX	IHC	c-kit protein/CD117 antigen	Gastrointestinal stromal tumours	Gleevec® (imatinib mesylate)
BRACAnalysis CDx™	PCR and sequencing	Mutations in *BRCA1* and *BRCA2* sequences	Ovarian cancer	Lynparza™ (olaparib)
Vysis CLL FISH Probe Kit	FISH	Deletion of LSI TP53	B-cell chronic lymphocytic leukemia	Venclexta® (venetoclax)
PDGFRB FISH	FISH	*PDGFRB* gene rearrangement; 5q31-33	Myelodysplastic syndrome/ myeloproliferative disease (MDS/MPD)	Gleevec® (imatinib mesylate)
KIT D816V Mutation Detection	PCR	*KIT* D816V mutation	Aggressive systemic mastocytosis	Gleevec® (imatinib mesylate)
Ferriscan	R2-MRI	Liver iron concentration	Thalassaemia	Exjade® (deferasirox)
Inform HER-2/neu	FISH	*HER2/neu* amplification	Breast cancer	Herceptin® (trastuzumab)
Inform Her2 dual ISH DNA probe cocktail	CISH	*HER2*	Breast cancer	Herceptin® (trastuzumab)
PathVysion HER-2 DNA probe kit	FISH	*HER2/neu*	Breast cancer	Herceptin® (trastuzumab)
Pathway Her2	IHC	c-erbB-2 antigen	Breast cancer	Herceptin® (trastuzumab)
InSite Her-2/Neu	IHC	c-erbB-2 antigen	Breast cancer	Herceptin® (trastuzumab)
Spot-light HER2 CISH	CISH	*HER2/neu* gene amplification	Breast cancer	Herceptin® (trastuzumab)
Bond Oracle Her2	IHC	*HER2*	Breast cancer	Herceptin® (trastuzumab)
Her2 CISH PharmDx	CISH	*HER2*	Breast cancer	Herceptin® (trastuzumab)
Hercep Test	IHC	HER2 protein expression	Breast and gastric cancer	Herceptin® (trastuzumab); Perjeta® (pertuzumab); Kadcyla® (ado-trastuzumab emtansine)

Table 1 continued.

Device trade name	Device type	Biomarker	Disease	Associated drug trade name (generic name)
HER2 IQFISH pharmDx	FISH	*HER2* amplification	Breast cancer, metastatic gastric or gastroesophageal junction adenocarcinoma	Herceptin® (trastuzumab); Perjeta® (pertuzumab); Kadcyla® (ado-trastuzumab emtansine)
THxID BRAF kit	Real-time PCR	BRAF V600E and V600K mutations	Melanoma	Mekinist® (tramatenib); Tafinlar® (dabrafenib)
Cobas 4800 BRAF V600 mutation	Real-time PCR	BRAF V600E	Melanoma	Zelboraf® (vemurafenib)

EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; NSCLC: non-small cell lung cancer; PCR: polymerase chain reaction; IHC: immunohistochemistry; MRI: magnetic resonance imaging; CISH: chromogenic *in situ* hybridisation; FISH: fluouresence *in situ* hybridisation.

The outcome may be a pharmaceutical that cannot be prescribed, despite the benefit identified, as the CDx lacks approval, resulting in a delay in patient treatment. Conversely, a diagnostic tool may be approved prior to the medicine, resulting in a CDx that has no purpose, as the associated pharmaceutical has not been approved. Whilst the latter may not appear to be of significant consequence clinically, it does have a substantial financial impact for the manufacturer of the CDx who has invested extensively in the development and validation of the tool. In addition, the early release of a CDx may result in 'fast-follower' devices being brought to market without the same investment, in part due to the inability of developers to patent these types of devices.[4,6] This in turn has an impact on the willingness of industry to invest in this area, which may lead to stagnation of innovation and an impediment to the development of personalised medicine.

Additional challenges that may be faced when seeking regulatory approval of personalised medicines include the difficulty in undertaking clinical trials of sufficient size when the patient cohort is relatively small. This issue is further compounded when the therapy is highly personalised, such as RNA-based pharmacotherapies.[15] Consideration must also be given to the regulatory requirements relating to the inclusion of biomarker-negative patients in clinical trials, with exclusion and inclusion criteria differing across regulatory agencies. Moreover, there are challenges and uncertainties with the introduction of alternate biomarkers, and therefore a new CDx, which may also alter the patient apparent designation as either biomarker-negative or positive, dependent upon the marker.[16]

Other challenges arise from the differences in international dossier requirements for the submission of a medicine and medical device and involvement of different bodies within countries reviewing each dossier. For example, in Europe a medical device dossier may be reviewed by a notified body, whereas a pharmaceutical dossier may be reviewed by the EMA. From a regulatory perspective, attention must also be given to potential loop-holes in regulatory frameworks. Previous research has documented issues with the utilisation of laboratory-based diagnostic tools that do not undergo equivalent scrutiny as a CDx.[17,18] This raises concern for both the consistency of approval and the ability to ensure post-market safety of both the medical device and its accompanying pharmaceutical agent.

Despite all the challenges, there are examples where the co-ordinated approval of both the CDx and the pharmaceutical has occurred concurrently, and furthermore, approval has been expedited. For example, under the US FDA's priority review programme, the approval of Zelboraf®, in conjunction with the cobas 4800 BRAF V600 mutation CDx, was expedited for the treatment of metastatic or unresectable melanoma.[19] Both manufacturers and regulatory agencies should reflect upon exemplars such as this to better inform policy and practice.

Table 2: Exemplar regulatory guidance documents.

Regulatory agency	Documents
China Food and Drug Administration (CFDA)	Provision for In-vitro Diagnostic Reagent Registration[21]
European Union (EU)	Proposal for a Regulation of the European Parliament and the Council on in vitro diagnostic medical devices[22]
Health Canada	Draft Guidance Document: Guidance for Risk-based Classification System for *In Vitro* Diagnostic Devices Draft Guidance Document - Guidance on supporting evidence to be provided for Class III and IV in vitro diagnostic device licence applications and amendments[23]
Health Sciences Authority, Singapore	Guidance on the Risk Classification of *In Vitro* Diagnostic Medical Devices[24]
Medicines and Healthcare products Regulatory Agency (MHRA), UK	In vitro diagnostic medical devices: guidance on legislation[25]
Pharmaceutical and Medical Devices Agency (PMDA), Japan	Technical Guidance on Development of In Vitro Companion Diagnostics and Corresponding Therapeutic Products[26]
Therapeutic Goods Administration (TGA), Australia	Draft: Australian regulatory guidelines for medical devices;[27] Medicines and medical devices regulation review - consultations[28]
US Food and Drug Administration (FDA)	In Vitro Companion Diagnostic Devices. Guidance for Industry and Food and Drug Administration Staff[29]

The development of guidance documents or amendments to legislation to keep up with health innovations, such as companion diagnostics, is varied across the globe.

CHALLENGES FOR POST-MARKET MONITORING AND REGULATION

Once approved, manufacturers, sponsors, and regulatory agencies must then employ appropriate post-market monitoring of both the pharmaceutical and medical device. This also raises challenges, for example: integration of pharmacovigilance data into the quality management system of a medical device, integration of device vigilance data into pharmacovigilance tools such as a periodic safety update report, and combined reporting of medicine and medical device adverse events.

Furthermore, the ability to adequately implement regulatory actions, such as recalls and safety alerts for a companion medical device must be considered. This can have a significant impact on the ability to administer and monitor the accompanying pharmaceutical, including the potential impact of delayed or interrupted therapy cycles. Appropriate systems to communicate and manage the risk of post-market problems with either the medicine or medical device component must be considered and documented.

NAVIGATING THE CHALLENGE: EMERGING PATHWAYS

To overcome issues with disparity between the pre-existing regulatory processes of medical devices and medicines, regulatory agencies have been consulting with academia, industry, and other international regulatory agencies, to explore a streamlined approach to regulating medicines with their CDx.[16] Despite many regulatory agencies still having separate approval and post-market vigilance areas for medicines and medical devices, with no evidence of an integrated approach being implemented, guidance documentation, draft regulations, and legislative proposals are now becoming available that reference personalised medicine (Table 2). In addition, there are initiatives being implemented with the aim of bridging the gaps between the separate regulatory areas, including proposals such as the central Medical Device Coordination Group (MDCG) proposed in Europe. The working group is proposed to consist of experts in medical and IVD devices, to assess high-risk and CDx devices, working in conjunction with designated reference laboratories, notified bodies, and the EMA.[20] Whilst many regulatory

agencies recognise the benefit of personalised medicine, as well as the challenges, countries such as Japan and the USA appear to be leading the way in terms of pre-market approval processes.

CONCLUSION

The benefit of personalised medicine is clearly evident, not only to the patients, but also to the healthcare system and pharmaceutical companies both pre and post-regulatory approval. The need for CDxs, which are appropriately sensitive, specific, and accurate, is similarly evident. It is in the regulatory space, and some would argue the reimbursement and patent areas also, where there is still work to be done to provide legislation and guidelines that meld the approval systems for the medicine and CDx, which will ultimately benefit not only the manufacturer, but also patients and regulatory bodies. However, this does not necessarily equate to faster process times of applications, nor a relaxation in the scrutiny of review that is undertaken, but rather a way to streamline applications and bring together regulatory oversight of the medicine and medical device, in both the pre and post-market arena.

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SELF-MANAGEMENT IN EPILEPSY CARE: BACKGROUND, BARRIERS, AND SOLUTIONS

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ABSTRACT

Self-management programmes for epilepsy have been developed and studied for several decades but have proven difficult to implement and sustain in clinical practice settings. The most advanced work on the concept of self-management has occurred in academic centres with a focus on the theoretical underpinnings of patient and caregiver learning and social support, and the validation of outcome metrics. Although limited by trial design and real-world implementation, many programmes for epilepsy self-management have been successfully demonstrated to provide some benefits. Very few of these programmes however have been successfully sustained and scaled beyond the academic world. Known barriers include logistics and staff resource limitation, patient/caregiver travel, lack of an incentive structure, and limited healthcare promotion. New digital methods of presenting self-management educational content and services may address many of these barriers, even if the experience is less controlled. These online and mobile services permit 'on-demand' availability of content that can be tailored to individual needs. However, the epilepsy community must continue to actively promote and sponsor the concept of self-management as a whole.

Keywords: Epilepsy, self-management, self-efficacy, patient engagement, digital health, remote monitoring, patient education.

INTRODUCTION

Epilepsy is a chronic neurological condition defined by a predisposition to recurrent seizures that are not provoked by some environmental or reversible trigger. Approximately 1% of the USA population has been diagnosed with epilepsy and an even greater percentage of the world's population suffers from seizures.[1] Fortunately, many anti-epileptic medications are available and are very effective for the treatment of seizures. In fact, ~65% of patients with a diagnosis of epilepsy can achieve seizure-freedom with singular but daily medication.[2] Although the remaining patients often deal with resistant seizures, relief can be provided to many using approaches such as: advanced medication combinations, surgical approaches, and innovative devices.

In addition to standard therapeutic options, patients are also urged to engage in epilepsy self-management. The concept of self-management for epilepsy has existed for decades, supported primarily by a theory of robust patient education for increasing disease knowledge and improving decision-making.[3,4] Multiple formal self-management programmes have been developed and academically tested for epilepsy patients, and in its 2012 report, the Institute of Occupational Medicine (IOM) highlights the importance of self-management research on behavioural interventions on health outcomes and quality of life for people with epilepsy. The IOM report also recommends improved and expanded educational opportunities for people with epilepsy.[5] Despite this emphasis, self-management programmes have not found traction in clinical use. A recent Cochrane review found it challenging to demonstrate a high volume of evidence supporting self-management strategies;[6] it has been challenging for investigators to demonstrate substantive and quantitative outcomes from these programmes in comparison to traditional clinical trials. Additionally, most of these programmes

are relatively labour and time-intensive, requiring substantial investment from the clinical centres choosing to support them.

Nonetheless, healthcare providers should become familiar with and consider the potential value of self-management programmes for epilepsy. As the field evolves and more evidence is generated, these approaches will become more readily available and thus, practitioners should be knowledgeable about the concept of disease self-management. This article will provide an overview of traditional and digital self-management interventions, with a focus on the evidence base supporting the use of these programmes, the current barriers preventing adoption, and new digital approaches and solutions that may lower the barriers to implementation.

CONCEPT OF SELF-MANAGEMENT

Health-related self-management is largely rooted in patient education, awareness, and engagement. For epilepsy patients, a lack of patient education about their condition is a widespread problem.[7,8] One of the most common reasons for 'breakthrough' seizures is simple medication non-adherence.[9,10] Unlike some other chronic medical conditions, for which missing several doses of medications may have little or no effect, even a single missed dose for an epilepsy patient can result in a seizure. For well-controlled patients, this event can be a disabling setback. Additionally, a basic understanding of lifestyle decisions, the importance of adequate sleep, and first aid approaches is often lacking in epilepsy patients and their family members, friends, and caregivers. This is partially due to an over-reliance on the 'pill' as a prescription and a lack of incentivisation for basic patient education and longitudinal chronic disease support.

The concepts of patient education and self-management have been studied in academic circles for several decades, but have failed to penetrate the routine practice of medical clinics. This may be because patients have not been prioritised as active and engaged participants in their own healthcare. Multiple research streams have now begun to build on the concept of critical social theory, seeking to educate through patient empowerment, often with an emphasis on social connections and learning through context.[11] In recent years, there appears to have been a renewed emphasis and attention on the possibilities of patient self-management, with multiple studies[12-16] and even a new, validated instrument.[17] This trend may be a reflection of a natural increase in patient activation through better information-gathering on the internet and a flourishing of online communities. There may also be recognition of the limitations of traditional treatment algorithms and the opportunity presented by alternative financial models within the USA healthcare system in particular.

Table 1: Self-management programmes with an educational focus and randomised study design.

Name of programme	Type of intervention	Study design	Outcomes measured	Setting of intervention
Sepulveda Epilepsy Education (SEE)[21]	2-day in-person educational programme	Randomised control trial with waitlist control group (N=38)	Proprietary questionnaires about depression, anxiety, seizures, and coping	In-person only
Modular Service Package Epilepsy (MOSES)[22]	2-day in-person educational programme	Randomised control trial with waitlist control group (N=242)	Proprietary questionnaires about disease knowledge, coping skills, seizure frequency, depression	In-person only
WebEase[20]	6-week modular education programme using online tools	Randomised control trial with waitlist control group (N=192)	Validated questionnaires on self-management and self-efficacy: adherence, stress, sleep quality, quality of life	Online (with in-person option)
Aliasgharpour et al. (2013)[12]	1 month of four in-person small group educational sessions	Randomised control trial (N=66)	Validated questionnaire on self-management: seizure control, medications taken	In-person only
Program of Active Consumer Engagement in Self-Management (PACES)[13]	8 weeks of weekly in-person, small group educational sessions	Randomised control trial (N=83)	Validated questionnaires on self-management: self-efficacy, quality of life, and anxiety	In-person only (with possible telephone and internet-based options)

Epilepsy self-management is formally defined as: 'The sum total of steps taken and processes used by a person to control seizures and manage the effects of a seizure disorder'[18] and this has been found to be important for the related concept of self-efficacy.[19] Self-efficacy has been defined as: 'The beliefs in one's capabilities to organise and execute the courses of action required to produce given attainments.'[19] Patients who successfully improve their self-efficacy have been demonstrated to successfully complete self-care tasks, such as taking medications and engaging in other healthy behaviours.[19] Thus, although related, these two concepts reflect slightly different patient traits that are important for improving health; while self-efficacy represents a patient's belief or confidence in making favourable health decisions, self-management reflects the actual steps or behaviours that are adopted. Appropriately, standardised and validated metrics for both these concepts exist and have been used in the existing literature on epilepsy management programmes.[20]

The majority of the historical self-management programmes for epilepsy have focussed on in-person educational sessions and peer support groups (Table 1).[12-14,20-22] Most of these programmes focus on specific educational sessions (either in person or digital), but a number of other services exist that may augment the ability of a patient with epilepsy to perform better self-care. These include a growing number of digital and mobile applications for tracking condition-specific data points, such as seizures, side effects, and medication adherence. Streamlining data capture (either through passive techniques or via brief notification requests) and presenting this back to the patient as feedback is increasingly popular. Additionally, the importance of peer support and online communities is well recognised, and these continue to grow. Peer networks are finding their way to mobile platforms, with an increasing amount of 'matching' sophistication.

EVIDENCE BASE SUPPORTING SELF MANAGEMENT

Many epilepsy self-management programmes have been developed and tested over the past several decades. A recent Cochrane review identified 16 separate interventions focussed on alternative care delivery and self-management strategies for epilepsy patients.[6] Of these 16 programmes, the authors determined that four clinical trials were of sufficient quality to be assessed specifically for their focus on self-management (Table 1).[12,20-22] Of these, three utilised in-person multi-day educational programming;[12,21,22] the work by Dilorio et al.[20] utilised the WebEase platform consisting of digital educational modules. The authors of the review concluded that only programmes including a specialised epilepsy nurse and dedicated self-management education showed evidence of benefit. Although the quality of evidence in this area remains quite limited, it is suggested that "...innovative service models could improve identified problems in epilepsy care by improving the knowledge and awareness of epilepsy amongst clinicians and patients..."[6] Based on the small numbers of high-quality studies in the review, the Cochrane authors could not "...advocate any single model of service provision." The review however did provide growing evidence of the importance of dedicated self-management education strategies and highlighted the need for more comprehensive research studies in this area to create a compelling body of supportive evidence.

One of the programmes included in the Cochrane review is the MOSES (Modular Service Package Epilepsy) educational platform, which was tested in a randomised trial in Europe.[22] This programme was interactive and tailored, consisting of nine specific modules that highlight different elements of epilepsy care. In the study, the modules were offered as a part of a 2-day course, with 22 epilepsy centres participating in recruitment. The study outcome measures included both epilepsy-specific and generic questionnaires, assessing quality of life, self-esteem, mood, restrictions in daily life, stigma, epilepsy knowledge, and self-reported seizure frequency.[22] A total of 242 patients participated in the trial which used a waitlist controlled approach, and questionnaire responses were assessed before the course and after 6 months. The results demonstrated significant improvement in some metrics, such as epilepsy knowledge and coping with epilepsy. Additionally, participants self-reported improved seizure control and more overall satisfaction with their treatment (tolerability). The authors concluded that this study provides clear evidence of a need for improved epilepsy patient education.[22]

In the 1990s, Dilorio et al.[20] developed and validated quantitative questionnaires for assessing both epilepsy self-management and self-efficacy. This created an academic mechanism for demonstrating the value of different programmes

focussed on improving self-management. One of the more prominent internet-based self-management programmes is the WebEase effort, developed by Dilorio et al.[20] This programme is a primarily internet-based programme, consisting of three learning modules focussing on medication management, emotional stress management, and sleep management. The original programme has its underpinnings in several theoretical learning constructs, including social cognitive theory.[11] The WebEase programme is relatively unique in that it is primarily internet-based, and is largely patient-driven. The academic study employed a randomised approach, with half of the study population falling into a waitlist control group for comparative purposes. All participants spent 6 weeks in the trial, spending 2 weeks on each of the three educational modules. Participants were encouraged with email reminders at the beginning and throughout the entirety of the study, and completers were compensated with a gift card. The final study results demonstrated that patients in the treatment group reported higher levels of medication adherence than those in the waitlist control group. Furthermore, patients who completed at least some of the modules achieved higher levels of self-efficacy at the end of the study period.[20] Later commentary from the same research group confirmed that social support was a critical component of self-management behaviours in the WebEase study population, although this support was not linked to the online aspect of the programme.[23]

Since 2007, the WebEase platform and other self-management interventions have been supported in the USA through the Managing Epilepsy Well (MEW) Network which is co-ordinated by the Centers for Disease Control and Prevention (CDC) Epilepsy Program.[24] The purpose of this venture is to provide an evidence-based portfolio of digital tools for patients, families, and caregivers to increase awareness and improve self-management opportunities. In a series of formative studies prior to the establishment of the MEW Network, researchers highlighted data suggesting that patient input and needs assessments should be included in any new self-management strategy. Interestingly, although the potential for digital tools was noted, some patients also reported a preference for in-person tools and services. This observation highlights the fact that a variety of interventions will be necessary to adequately target different patient categories. However, in terms of scalability and dissemination, the digital platforms remain highly promising solutions.

Completed after the recent Cochrane review, another self-management programme worth mentioning is the Program of Active Consumer Engagement in Self-Management (PACES) in Epilepsy. This effort builds on prior self-management programmes, which were largely developed by expert opinion, by using patient needs assessments to build the educational content. This platform was studied in an intensive randomised controlled trial, involving weekly in-person meetings over an 8-week period. The study demonstrated robust improvements in validated measures of epilepsy self-management, epilepsy self-efficacy, and quality of life.[13] Additionally, the work showed evidence of a durable effect at 6 months for self-management and reported a relatively low rate of attrition in comparison with other intensive educational programmes.

Finally, international medical bodies, including the World Health Organization (WHO) and the IOM, have recently recognised the importance and potential for epilepsy self-management by issuing formal recommendations. In its 2012 report, the IOM prioritised research on behavioural interventions on health outcomes and quality of life for people with epilepsy, and formally recommended improved and expanded educational opportunities for people with epilepsy.[5] In 2015, the World Health Assembly (WHA) formally adopted a sweeping international resolution to better address the global impact of epilepsy. One of the formal recommendations included a reference to self-management programmes directly endorsing: "...empowering people with epilepsy and their carers for greater use of specified self and home care programmes..."[25]

BARRIERS TO IMPLEMENTATION

Despite the wealth of academic evidence supporting epilepsy self-management programmes, these services have unfortunately failed to gain a foothold in most clinical programmes in the USA and worldwide. The projects in active use are either supported through research funding operations or through philanthropic efforts, preventing widespread implementation. Furthermore, the logistical planning, staffing requirements, and patient travel often present a significant barrier for ongoing success.[26] In our own anecdotal experiences, in-person support group attendance tends to be highest at the beginning

of a programme, then suffers significant attrition with time.

Additionally, the lack of an incentive structure supporting these self-management programmes is another barrier, particularly in the USA. The historical reimbursement system, now perpetuated through systemic inertia, provides few financial drivers to improve epilepsy self-management. Although medication and some procedural interventions should remain the mainstay for active epilepsy treatments, an ideal payment system would support a comprehensive treatment approach, including self-management services. For instance, in conjunction with a new medication prescription, patients should be provided with access to better education and tools for tracking early side effects and improving pill adherence. New alternative payment models are beginning to explore these approaches however widespread implementation remains a challenge.

Under different healthcare models in Europe, more success has been achieved with self-management programmes for other chronic diseases such as diabetes[27,28] and asthma.[29] Despite facing similar barriers related to resource and logistical support, particularly in some lesser-developed countries, some European nations have initiated and sustained momentum for formal chronic disease self-management programmes. These success stories have largely depended upon official policy statements prioritising patient education services, such as the National Service Framework (NSF) which has been issued in the UK since 2002.[27] Consensus-based guidelines are an important first step towards driving research interest towards self-management programmes including outcomes focussed on clinically meaningful metrics and economic impact. From an epilepsy perspective, the WHO and IOM reports are particularly relevant, although these resolutions have only been recently issued.[5,25]

More specifically, Rogers et al.[28] noted that while "European countries are increasingly adopting systems of self-care support for long-term conditions…" there remains significant barriers and disparities due to a variety of country-specific practices. The authors additionally concluded that the "…infrastructure and culture for supporting behavioural change and living well with a long term condition is driven to a significant extent by political decision-makers, the socio-economic and policy [of the] environment and the ethos and delivery of chronic illness management in health care systems."[28] They identified three main areas for targeted outreach: social environmental influences, the reluctance of policy makers to regulate, and a gap in biomedical research focussed on self-management strategies. Focussing on the policy-related barrier, the authors noted that vested interests of other stakeholders within the healthcare ecosystem can impede progress in this arena.[28] In Europe, formal guidelines for some chronic diseases, such as diabetes, have succeeded in furthering the pressure to adopt self-management programmes but the inertial force continues to slow the pace of adoption.[27,28]

In recognition of the need to directly address historical disincentives to implementation, the USA-based Chronic Disease Self-Management Program (CDSMP) has recently been evaluated for its impact on healthcare costs and utilisation.[30,31] The CDSMP is a generic self-management education programme utilising a small focus group structure to engage patients and improve their health behaviours. In 2013, a study of the impact of the CDSMP on healthcare savings demonstrated a reduction in both emergency room visits and hospitalisations.[30] This was followed in 2015 by the release of a savings 'estimator tool' that could be used to determine the overall cost savings that the CDSMP could provide for patients with certain chronic diseases.[31] Moving beyond assessments of education and engagement improvements, these types of studies are important to add to the body of evidence justifying an investment in self-management strategies. However, it must be noted that none of these programmes have specifically investigated the impact on epilepsy patients.

Even when the implementation effort is seemingly straightforward, most clinics do not invest heavily in patient education or self-management. This is usually not due to a lack of interest from healthcare providers, many of whom would welcome more resources and time to conduct comprehensive patient and caregiver education. However, even in healthcare systems where economic considerations do not disincentivise these types of programmes, the required intensity of commitment from both the healthcare team and patients often limits long-term participation. However, in a constantly evolving digital age, new approaches to patient education and engagement should be actively sought out and promoted by epilepsy clinics. Methods of simple promotion, such as pamphlets or business cards with website addresses, should be attempted.

NEW DIGITAL APPROACHES TO SELF-MANAGEMENT

The digital and mobile health movement offers an opportunity to dramatically impact the barriers affecting self-management programmes. By offering traditional self-management resources through digital 'on-demand' means, the challenges of logistics, travel, and staff resource support are substantially lessened.[20] Patients can access resources and engage asynchronously (and anonymously if desired) at their own time and convenience; this offers the promise of expanding access to many patients who previously would have been marginalised. Although some research suggests that patients with epilepsy may use internet-based health tools less than their non-epilepsy counterparts,[32,33] the absolute magnitude of usage is still significant (>50%). Furthermore, our own research demonstrates that historically resistant patient populations may be growing more comfortable with technological interventions[34] and that real-world online platforms can provide similar self-management benefits to the formal education programmes described earlier.[15,35] However, it is important to recognise that online and mobile self-management programmes (particularly those that are patient-driven) are more difficult to study in a controlled trial due to a lack of a consistent setting and a fluid patient experience.

In addition to educational programmes, a medley of mobile diaries and wearable devices are emerging and could eventually further empower patients with data to better manage their epilepsy. Electronic seizure diaries with optimised mobile interfaces are enabling better tracking of seizure details, side effects, and medication adherence.[36,37] Furthermore, new wearable technologies can capture a variety of biometric data points that may more accurately quantify seizure burden and severity.[38] Although these devices are still investigational, rapid progress is being made and it is likely that some of these approaches will become clinically meaningful in the coming years. More compellingly, these mobile diaries and devices will serve as adjunctive tools for producing meaningful clinical information that may be integrated into the existing online self-management platforms.

CONCLUSIONS

With an ever-increasing amount of evidence supporting the use of self-management programmes for epilepsy, the clinical community should embrace this concept and begin directly addressing the current barriers to implementation. Many academically supported self-management programmes now exist, with various focusses for tailoring to individual patient needs. Although some may critique the magnitude of 'real-world' impact of these solutions, many patients are desperately seeking these types of resources and support. Furthermore, the risks associated with these programmes are low, and in the case of self-guided, digital solutions, the logistical support and cost are also low. Thus, with a concerted effort across the clinical epilepsy community, self-management for epilepsy can become a new standard of care for all.

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THE PREVALENCE OF ITEM CONSTRUCTION FLAWS IN MEDICAL SCHOOL EXAMINATIONS AND INNOVATIVE RECOMMENDATIONS FOR IMPROVEMENT

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ABSTRACT

The purpose of this study was to calculate the prevalence and nature of item construction flaws within one large medical school and to identify several innovative approaches that may serve as potential remedies for these problems. Results indicated that approximately one in five items contained a construction flaw, with the overwhelming majority of flaws involving poor quality distractors. A series of innovative recommendations are presented, including modern psychometric analytical techniques to more thoroughly inspect data, item manipulation techniques, and the use of innovative item types that may alleviate the need for distractors altogether.

Keywords: Multiple-choice questions (MCQs), item writing, item quality, assessment, medical education, educational measurement, psychometrics, testing, innovative items.

INTRODUCTION

Multiple-choice questions (MCQs) continue to be the preferred method of assessment in medical education due to the ease of administration and scoring, especially with large class sizes. Teaching faculty members are typically tasked with the challenge of developing items for classroom assessments. However, because the stakes associated with these assessments typically are moderate-to-high in nature, the need for quality items, particularly in terms of their construction, is paramount because items with construction flaws introduce measurement errors that threaten the validity of students' performance measures. Fortunately, item construction flaws can largely be mitigated with careful attention, by following best practice guidelines, and by making use of innovative item types. To that end, we sought to: i) calculate the prevalence of construction flaws at one medical school, ii) characterise the nature of these flaws, and iii) identify some innovative approaches that would likely mitigate many, if not most, of these flaws.

BACKGROUND

MCQs are the most commonly utilised assessment method used in medical education classroom assessments. This largely is due to the ease of administration, more objective and transparent scoring processes, and increased defensibility of scores. Many credentialing organisations, such as the United States Medical Licensing Examination® (USMLE), and various subspecialty boards comprising the American Board of Medical Specialties (ABMS), largely depend on MCQs for assessing their future and current workforce. Given the prevalence of testing with MCQs in medical education, it is important that item authors be aware of the major principles of sound item construction.[1] Considering that assessment comprises a significant amount of educators' time,[2] the teaching faculty should be provided with the opportunity to learn the principles of item writing.

Jozefowicz et al.[3] reported that teaching faculty are not routinely trained on how to develop quality

MCQs. As a result, items that are authored by teaching faculty do not always meet the recommended item writing criteria that have been established and widely circulated by experts in the field.[1,4-7] More specifically, items that contain technical flaws may contaminate examinees' scores with errors that interfere with both the accuracy and the valid interpretation of exam results.[8-11] It is imperative to evaluate the degree to which item flaws exist in a medical school's pooled item bank because inferences made about score results typically carry moderate-to-high stake implications for students (they are used to determine class rank and promotion to the next programme year and to identify suitable candidates for a residency programme, for example).

At a large public medical school in the southeast of the USA that offers Doctor of Medicine degrees, considerable resources are devoted to the pursuit of quality exam items. A team of assessment and testing experts, with significant experience in academia and the professional medical certification industry, work to ensure that faculty-generated items are sound in terms of both their technical quality and their psychometric properties (desirable reliability estimates and adequate discrimination indices, for example). All items appearing on exams are reviewed by this team and items flagged with technical flaws are reported to the faculty for potential revision. Furthermore, the assessment team routinely conducts workshops to educate the faculty regarding item writing, psychometric indicators, modern validity conceptualisations, and a host of other assessment-related issues. Given that so many resources and efforts are devoted to improving classroom assessments, it would be expected that the item bank at this institution would be particularly robust.

METHOD

Instrumentation

A systematic review of all preclinical (Year 1 and 2) MCQs presented on midterm and final exams was performed using an unpublished instrument developed by the late Prof Linnea Hauge (Table 1) and adapted from Haladyna et al.[1] who provided guidelines (as opposed to 'hard and fast' rules) intended to maximise item clarity and minimise validity threats stemming from various sources of error (an examinee's 'testwiseness' skills, construct irrelevance variance, for example).

All items were reviewed by two assessment experts. The instrument essentially collapsed the most prevalent item construction errors into one of eight flaw types and provided assessors with the ability to easily tally the number of flawed items. The two assessors worked together to read, review, and classify items as containing an item construction flaw(s) or as meeting the item writing standards of Haladyna et al.[1] Flawed items were identified as any item in which the item writer ignored one or more of the principles of quality item development. While each item may have had more than one technical flaw, for the purpose of scoring items in this study, the experts coded only one flaw per item; this was the flaw that, in their agreed opinions, was the most severe violation of the set standards. In these instances, secondary flaws were noted in the comments section of the scoring rubric. Items not containing a construction error were considered to have met recommended item writing principles.

Rating Process

A total of 2,204 items were carefully read, discussed, and classified according to the wording of each item by two assessment experts. Instances in which the experts disagreed on the type of flaw were flagged and the item was reviewed again by both experts individually; each expert noted the reasoning based upon Haladyna et al.'s[1] recommendations. The experts then discussed their individual decisions and worked to find a consensus opinion. All disagreements by experts were due to items having more than one identified technical flaw. The number of items with construction flaws versus the number of items that met the guidelines were calculated.

Examination and Item Characteristics

All items appearing on mid-term and final exams from the first 2 years of the pre-clinical, undergraduate medical school curriculum during the 2012–2013 academic year were investigated. The disciplines assessed by these exams covered basic science courses (microbiology, anatomy, physiology, and immunology) in the first year (MS1) and the major organ systems (cardiovascular, respiratory, gastrointestinal, renal-urinary, endocrine, reproductive-genetics, brain, and musculoskeletal) in the second year (MS2). One to three weeks of instruction were covered on each of the exams analysed, depending on the length of the overall course, exam items were authored by multiple

faculty staff who taught in each course and were considered content experts for their respective subject area. Each course may have had a dozen or more lecturers, all of whom may have contributed exam items. Most exam items were of the single best answer format with either four or five answer options.

The number of items appearing on these exams ranged from 28–100. There were 182 students enrolled in the MS1 cohort, and 175 students enrolled in the MS2 cohort. The MS1 data set consisted of 17 exams, with each exam assigned a score depending on the percentage of items meeting the established and widely recognised guidelines for sound item construction.[1,4-7]

Table 1: Types of item construction flaws.

- Items written in the negative (e.g. "Which of the following are not true?" or "All the following are correct except:")
- Items that included the use of 'none of the above', 'all of the above', or that used combinations of answer options within the distractors (e.g. K-Type questions)
- Items that were unfocussed (e.g. did not ask a direct question or required the examinee to read all answer options before being able to answer)
- Items that had answer options that were not homogenous, not of equal length, or the correct answer repeated elements included within other options
- Items that included the use of extreme language (e.g. always or never)
- Items that were tricky (e.g. extraneous reading in the answer options that was not required, making the item unnecessarily complicated)
- Items that were not formatted properly (e.g. vocabulary was not appropriate, punctuation was not correct, or item formatted horizontally instead of vertically)
- Items whose distractors included the use of humour or were not plausible

Instrument adapted from unpublished data from Prof Linnea Hauge.

Table 2: First and second year exam descriptive statistics.

	MS1 mean (SD)	MS2 mean (SD)
Number of items used	56.72 (13.02)	57.20 (20.40)
Lowest exam score	59.32 (4.03)	58.57 (8.17)
Highest exam score	98.85 (1.15)	99.72 (0.57)
Exam score	84.08 (2.76)	85.09 (2.51)
Exam SD	7.69 (0.59)	7.97 (1.30)
Exam reliability (KR-20)	0.66 (0.08)	0.67 (0.10)
Standard error of measurement	2.45 (0.38)	2.41 (0.48)

MS1: first year; MS2: second year; SD: standard deviation; KR-20: Kuder–Richardson Formula 20.

Table 3: Frequency and type of flawed items by programme year.

Technical flaws	MS1 exams (n=1,034)	MS2 exams (n=1,170)	Total flaws (n)
Negatives used in stem or distracters (e.g. except, not true, least likely)	27	61	88
None of the above/all of the above, K-type, true-false	93	36	129
Unfocussed stem	97	25	122
Length of distracters is unequal, not in logical order	60	50	110
Grammatical structure and/or extreme language	4	2	6
'Tricky'	0	1	1
Inappropriate vocabulary and/or language	2	2	4
Distractors that are not plausible, use of humour	2	1	3

MS1: first year; MS2: second year.

The MS2 data set consisted of 20 exams, with each exam assigned a score regarding the percentage of items meeting these same recommended guidelines. Table 2 presents descriptive statistics for MS1 and MS2 exams. All exams were administered via a standardised web-based assessment system with a secure browser to mitigate sources of error stemming from conditions of administration.[9] Students were allotted approximately 1 minute and 40 seconds per question on average.

RESULTS

The percentage of exam items meeting guidelines for the MS1 courses was found to be 72.43%, and 84.79% for MS2 courses. Of the 2,204 total items administered to students during the 2012–13 academic year, 463 (21.01%) items contained flaws (Table 3). The most frequent item writing flaws found across both MS1 and MS2 courses was 'none of the above/all of the above', combinations of answer options (K-type), or true/false formats (n=129), followed by unfocussed stems (n=122), uneven formats of answer options where the correct answer was the longest option (n=110), and the use of negatives in item stems or distracters (n=88). Other types of flaws, such as grammatical structure, inappropriate language, implausible distracters and the use of humour, and tricky items were far less frequent, with 14 collective occurrences.

DISCUSSION

Substantive Results

The exam items reviewed were representative of all faculty-authored items administered during the first two preclinical programme years at the medical school. Results indicated approximately 79%, or about 1 in 5, of all items administered met the recommended guidelines for construction quality, while 21% did not. Given all the expert personnel, resources, and meticulous reviewing efforts provided to the faculty, we believe these values serve as a reasonable and potentially best case estimate for item construction flaws appearing on medical school classroom examinations.

On the surface, this finding is quite alarming as it suggests that about one in five items contain a source of error that could otherwise be mitigated with more careful discernment on the part of the faculty item writers.[8-9,11] It is important to note however, that there was considerable variation across course year. MS1 courses focussing on the basic sciences contained considerably more flaws (27.56%), with approximately 1 in every 3.62 items containing a technical flaw, whereas MS2 courses focussing on the clinical sciences contained considerably fewer flaws (15.21%), with approximately 1 in 6.57 items containing a technical flaw.

It is important to note that while the institution devotes considerable resources and training to help faculty generate items that are technically sound in construction, it is unknown exactly how many faculty staff take part in training exercises and/or use the resources made available to them. While it would be ideal to train every faculty member who contributes to the medical education enterprise, this simply is not realistic given the enormous number of medical school faculty members, often in the hundreds, and the many competing demands of the faculty, for whom education is often a lower priority.

Furthermore, it remains unknown how many faculty members take part in instruction and/or contribute items to exams. Given course directors often have different styles for managing courses therefore any answers given are likely to be highly variable. Of course, it is hoped that responsible course directors will ensure continual efforts are made each year to improve items and over time, this should result in a significantly improved item bank. However, we are fearful that such continuous improvements may not be entirely realistic. For example, a best practice in testing recommends faculty staff alter their exams each year as a preventative measure to combat cheating, as students often share information about items appearing on exams.[12] When items are replaced with new ones, it is unlikely that the new items are any better in terms of construction quality, especially if the items were generated as last minute substitutes which faculty staff acknowledge is often the case. Of course, the extent to which faculty staff heed recommendations about improving their exams also remains unknown. We suspect this practice is also highly variable and likely depends on many factors, not the least of which is the depth of one's item bank and one's true commitment to conducting objective assessments.

With respect to the consequences that may result for students, this also remains largely unknown. On the one hand, it may be argued that students

significantly benefit from construction errors such as choosing the longest response option as this 'testwiseness' strategy is widely taught to students as a cued-guessing strategy when the answer is unknown. In such instances, students' performance measures will be inflated and an overestimate of what students truly know (or can do) will be obtained. On the other hand, some item construction flaws may work to the detriment of students. For example, a question that asks students to identify the response option that is 'not true' or 'least likely' may cause some students who truly understand the concept(s) in question to render an incorrect response. In such cases, students' performance measures will be deflated and underestimate what students truly know (or can do). In any instance, the mismeasurement stemming from these sources of error no doubt results in some students appearing more/less knowledgeable (or capable) than they actually are. From an assessment perspective, this is most unfortunate because the errors stemming from item construction are largely preventable by following the well-recognised guidelines for quality item construction and properly acting upon the findings generated from a review of psychometric (statistical) indicators.

Recommendations for Improvement

Several clever and easy-to-implement techniques exist to help item writers improve traditional MCQ items. For example, team item writing by way of leveraging the expertise of peers, residents, and interns can help generate additional plausible distractors. Another technique is 'nudging' and 'shoving'[13] where distractors are easily manipulated to alter an item's difficulty level. Some research also suggests that moving from the traditional four or five option responses to three options might alleviate the challenges of generating more than two plausible distractors without affecting student performance measures.[14] Options also exist with respect to scoring. For example, Rasch measurement models have proven to be very robust for medical education examinations.[15] These models investigate an examinee's response pattern relative to an expected structure based on a given set of items with varying degrees of difficulty. These analyses can provide useful insights regarding aberrant responses, problematic items, potential for guessing, etc.

If item writers administer electronic exams, then several innovative options noted recently in the psychometrics literature are possible (audio items provide one possibility, for example). Although research on the use of audio exams is currently sparse, the concept seems promising in some situations. Psychology research indicates that sounds are processed differently by the brain than visual information,[16] so it is possible that audio items may unlock improved measurements of students' knowledge, skills, and abilities. Advantageously, audio items are essentially a higher level of simulation compared with written MCQs (low fidelity simulation). For example, imagine a cardiovascular and/or respiratory item that presents the examinee with an audio file of the pertinent findings (e.g. heart arrhythmia, murmur, abnormal breathing associated with bronchitis, etc.) and asks the examinee to diagnose it. One challenge to this approach would be that exam administrators must stringently vet headphone/laptop activity for exam security purposes.[12]

'Hotspot' items provide another powerful option. These item types provide a graphic and allow examinees one click on the image to indicate the correct answer.[17] This item type alleviates the need to generate written distractors, as a click on any area outside the designated correct zone (on the graph) is incorrect. An example might include asking examinees to identify with one mouse click a particular vessel on an anatomy exam. 'Drag and drop' items are particularly helpful for mid-level simulation activities. For example, in a typical anatomical practical exam the student is asked to identify body parts by placing a flag on a specific location. The drag and drop electronic format could closely resemble this procedure and remove many of the challenges associated with practical exams (scheduling, time commitment, and cadavers, for example).

'Figural structured response'[17] items essentially ask students to move around pieces on a graphic to demonstrate their knowledge. An example might include asking students to click on nerves that are responsible for movement of the bicep or testing reflexes. 'Alternate choice' items display several images and ask examinees to identify the most appropriate/best option.[18] For example, an examinee must evaluate four different cell/tissue/organ stains and determine which one would most likely be the microscopic finding that corresponds to the symptoms of a given disease. Again, this item does not require generating names of other diseases to use as potential distractors and it focusses the examinee on the problem to be solved

without generating hypothetical distractors that might be implausible if presented in written form. This format more closely resembles actual practice.

CONCLUSION

Findings resulting from a systematic review of medical school exam items revealed that approximately one in five items contain an item construction flaw and the overwhelming majority involve ineffective distractors or unfocussed stems. The aforementioned innovative item types present a number of potential remedies, as they would largely mitigate the use of distractors, and help item authors to focus questions on clinical reasoning skills (as opposed to recall of knowledge) while potentially providing a more accurate measure of knowledge, skills, and abilities, minimise 'testwiseness' strategies (detecting cues in how the item or its distractors are presented and sequencing cues where the response to one item can trigger a response to a previously administered item, for example), as well as better simulating medical practice. At present, innovative item types have not yet been thoroughly explored in medical education, thus future research should explore the benefits and challenges associated with these promising item types.

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LIGHT SHEET FLUORESCENCE MICROSCOPY COMBINED WITH OPTICAL CLEARING METHODS AS A NOVEL IMAGING TOOL IN BIOMEDICAL RESEARCH

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ABSTRACT

In the past decade, imaging has advanced to become a crucial tool in fundamental and biomedical research and it has become increasingly important to be able to image whole organs with single cell resolution. Light sheet fluorescence microscopy, also called selective plane illumination microscopy or ultramicroscopy, provides a high resolution in transparent and intact whole organs. By the application of a thin light sheet, only a defined slice of the specimen is illuminated and the fluorescence signal is detected by an objective perpendicular to the specimen. By moving the specimen vertically through the laser, a z-stack is acquired which corresponds to an optical sectioning without physical disruption of the specimen. The data can further be reconstructed to a three-dimensional volume and analysed in its entire complexity in micrometre resolution.

This article reviews the prerequisites for successful light sheet fluorescence microscopy, in terms of tissue preparation and optical clearing, and highlights recent advances and applications in the context of basic and biomedical research, with special focus on the central nervous system of rodents.

Keywords: Light sheet fluorescence microscopy (LSFM), ultramicroscopy, biomedical research, optical clearing.

INTRODUCTION TO LIGHT SHEET FLUORESCENCE MICROSCOPY AND ESTABLISHED *IN VIVO* TOOLS

In biomedical research, as well as during the preclinical development of novel drugs and treatment regimens, *in vivo* and *ex vivo* imaging techniques have advanced to become major research tools used to address many important questions. A high spatial resolution is needed to investigate morphological changes and interactions at the cellular level, especially in preclinical disease models of the central nervous system (CNS), such as brain tumours, Alzheimer's disease, or multiple sclerosis. Classical non-invasive *in vivo* imaging tools such as computed tomography (CT), magnetic resonance imaging (MRI),[1,2] positron emission tomography, or single-photon computed tomography (SPECT),[3] provide a spatial resolution in the sub-millimetre to millimetre range in living specimens. Yet, this resolution is not high enough to study single cells involved in disease pathology. *In vitro* and post mortem *ex vivo* microscopy techniques such as confocal or two-photon microscopy, which can also be applied *in vivo*, achieve a resolution of a few micrometres but involve the deterioration of the investigated sample required to be cut into thin slices prior to the imaging procedures.[4] In the case of *in vivo* two-photon microscopy, a method that involves laborious sample preparations, clear subcellular resolutions of living organisms can be achieved.

Figure 1: A schematic description of a commonly used ultramicroscopy-setup showing the bidirectional laser excitation of the sample.

Different filter settings can be used for the excitation of the sample (A). The objective enters the cuvette and detects the emitted fluorescence perpendicular to the sample (B and C). With this setting, strong fluorescence signals from the specimen, in this case from the mouse brain (C), are clearly detectable.

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However, the penetration depth is limited to ~200 µm (*in vivo*) to 500 µm (*ex vivo*), restricting the volume of investigation to the surface of the organ.[5,6] Furthermore, problems of confocal and two-photon microscopy for *in vitro* and *in vivo* imaging are photobleaching and phototoxicity; optical clearing of organs allows for deeper penetration depths and when investigating cleared organs using light sheet fluorescence microscopy (LSFM), photobleaching and phototoxicity are of no concern.

In the past decade, LSFM has evolved to become the new imaging method of choice in biomedical research as it overcomes the issues of poor spatial resolution and limited penetration depth combined with the retained integrity of the specimen.[7] In LSFM, the sample is illuminated by a thin light sheet perpendicular to the direction of observation. Moving the sample through the light sheet results in a stack of two-dimensional images; this can be referred to as optical sectioning. Importantly, the laser only illuminates the tiny sheet of a given specimen presently in focus. Therefore, the surrounding areas cannot outshine the imaged area and out of focus regions do not cause stray light.[8] For the illumination of larger organs, such as whole mouse brains, two opposite lasers are commonly used for imaging. By using two light sheets, the sample can be uniformly illuminated without loss of light that would cause insufficient illumination and loss of information. Observation of samples often takes place in a liquid or gas environment. In ultramicroscopy (UM), whole organs can be used, ranging from several millimetres to centimetres in size. For a three-dimensional (3D) reconstruction of an organ or tissue using UM, hundreds or thousands of single images are collected in one measurement and create a picture of the whole specimen.[9]

The fundamental technique of LSFM was originally developed under the designation of UM by Richard Adolf Zsigmondy and Henry Siedentopf a century ago; it was awarded the Nobel Prize in 1925.[10] The constant development of LSFM from the 1960s up until today's powerful tool was comprehensively reviewed by Peter A. Santi.[11] However, two major contributions were made by the groups of Ernst Stelzer,[7] who invented the selective plane illumination microscopy (SPIM),[12] and Dodt et al.,[13] who applied optical clearing of specimens, paving the way for present applications. Today, this advanced technique represents a powerful tool to image total organs, whole animals (e.g. mouse embryos) or tissues and investigate the volume of interest in 3D reconstruction which allows for optical sectioning.[14,15] The technique can also be used for *in vivo* applications in transparent specimens like fruit fly embryos or zebrafish. Other applications for LSFM are live imaging of 3D cell cultures, e.g. cellular spheroids, epithelial sub-organs, or stem cell organoids.[14,16,17] Figure 1 illustrates a schematic description of a commonly used UM setup, showing the bidirectional laser excitation of the sample. Different filter settings can be applied for the excitation of the sample (Figure 1A). In this particular example derived from LaVision BioTec`s

UltraMicroscope II, six filters can be incorporated into the microscope in order to measure different fluorescent signals in parallel. The objective enters the cuvette and detects the emitted fluorescence perpendicular to the sample (Figures 1B and C). With this setting, strong fluorescence signals from specimens of interest, in this case mouse brains (Figure 1C), are clearly detectable.

Here, we will focus on the application of LSFM in biomedical research with optically cleared specimens. A recently published article by Pan et al.[18] shows a newly developed clearing method allowing for imaging of entire adult mouse bodies.

OPTICAL SAMPLE CLEARING METHODS FOR LIGHT SHEET FLUORESCENCE MICROSCOPY APPLICATIONS

Optical clearing was initially invented by Werner Spalteholz in 1914, who adjusted the refractive index of the surrounding medium to the proteins of the specimen and obtained a transparent sample from that which was previously opaque.[19] By adjusting the refractive index of the sample to the imaging solution, scattering of the laser is minimised and the light can cross the specimen with very little diffraction. During the last decade, several optical clearing methods were developed and improved. Becker et al.[8,20-24] invented a multi-purpose clearing protocol for Drosophila, mouse embryos, mouse brains, and isolated mouse brain hippocampi. Today, various clearing methods with significant differences based on the solvents applied are used for tissue preparation, amongst others: ScaleA2,[25] 3DISCO,[26] iDISCO,[27] uDISCO,[18] ClearT2,[28] SeeDB,[29] CLARITY,[30,31] CUBIC,[32] and FluoClearBABB.[33] The common denominator of the clearing methods mentioned is to preserve endogenous fluorescence of proteins such as green or yellow fluorescent protein (GFP or YFP), red fluorescent protein from *Discosoma sp.* (DsRed) or mCherry expressed in the cells and organs of interest. In general, optical clearing of tissue by organic solvents is applied to match the refractive index of a tissue sample to a surrounding solvent. The first step of clearing involves the dehydration of the tissue since water has a lower refractive index than cellular structures like proteins and lipids.[26] Afterwards the dehydrated tissue is impregnated with an optical clearing agent of the same refractive index. The tissue turns transparent and its composition is firmer than before.

Imaging of solvent cleared organs in 3D (3DISCO) and its successor techniques, whole-mount immunostaining and volume imaging (iDISCO) and ultimate DISCO (uDISCO), are frequently used clearing techniques to image neuronal connections in the nervous system.[18,26,27] In order to get better clearing results of myelinated tissues in the adult CNS, 3DISCO was invented. Screening for a new chemical lead to the development of a new clearing protocol using dibenzyl ether, with the protocol for optical clearing of a mouse brain taking only 4–5 days.[26]

iDISCO is a simple, rapid, scalable, and inexpensive method for volume-imaging of whole-mount immunolabelled deep tissue structures. Existing whole-mount immunolabelling methods were tested and modified to achieve the deepest tissue penetration possible. Nearly 30 antibodies were shown to work well in immunohistochemistry and iDISCO.[34] Glycine and heparin treatment was identified as a good option to reduce immunolabelling background in whole mouse embryos, whole adult mouse brains, kidneys, and other organs.[27] The newly published uDISCO protocol is an improvement of 3DISCO to circumvent the disadvantage of quenching of endogenously expressed fluorescence signals. uDISCO uses diphenyl ether, an organic solvent with a refractive index of 1.579 in order to clear samples. In addition, Vitamin E is used to scavenge peroxides and tert-butanol, a dehydrating reagent that is more stable than the tetrahydrofuran used before in 3DISCO.[18]

The DISCO protocols enable high resolution imaging of neuronal connections within entire organs and even within an entire mouse without physical sectioning. The protocols for clearing are straightforward and can be performed in a relatively short time span of several days, depending on the size and tissue composition of the specimen. Subsequent imaging of the cleared specimen can be executed within several minutes to hours, depending on the scan region and scan protocol. However, a major drawback of the 3DISCO clearing protocol is the rapid loss of fluorescence. Hence, cleared samples need to be immediately scanned within 24 hours post-clearing. Due to the loss of fluorescence of 3DISCO-cleared samples, multiple scans of a region of particular interest can be challenging.[26]

The very recently published uDISCO method enabled imaging of whole adult rodents by taking

advantage of the solvent-dependent shrinkage of tissue. The application of organic solvents for clearing causes a shrinkage of up to 65% of the original volume of the sample, which allows for imaging of undissected cleared adult mouse bodies. Importantly, the shrinkage does not affect microscopic or macroscopic scales.[18]

Another recently published clearing method, especially suited for imaging of whole adult mouse brains, is FluoClearBABB. Samples are initially dehydrated with an ascending series of butanols and the protocol requires 6 days for whole mouse brains. Afterwards, this method applies a mixture of benzyl alcohol and benzyl benzoate (BABB), in combination with an adjusted basic pH, which allows for whole brain clearing while reducing the optical distortion to a minimum.[33] The majority of fluorescence is preserved for years with almost no photobleaching, enabling multiple repeated scans of the cleared specimens.

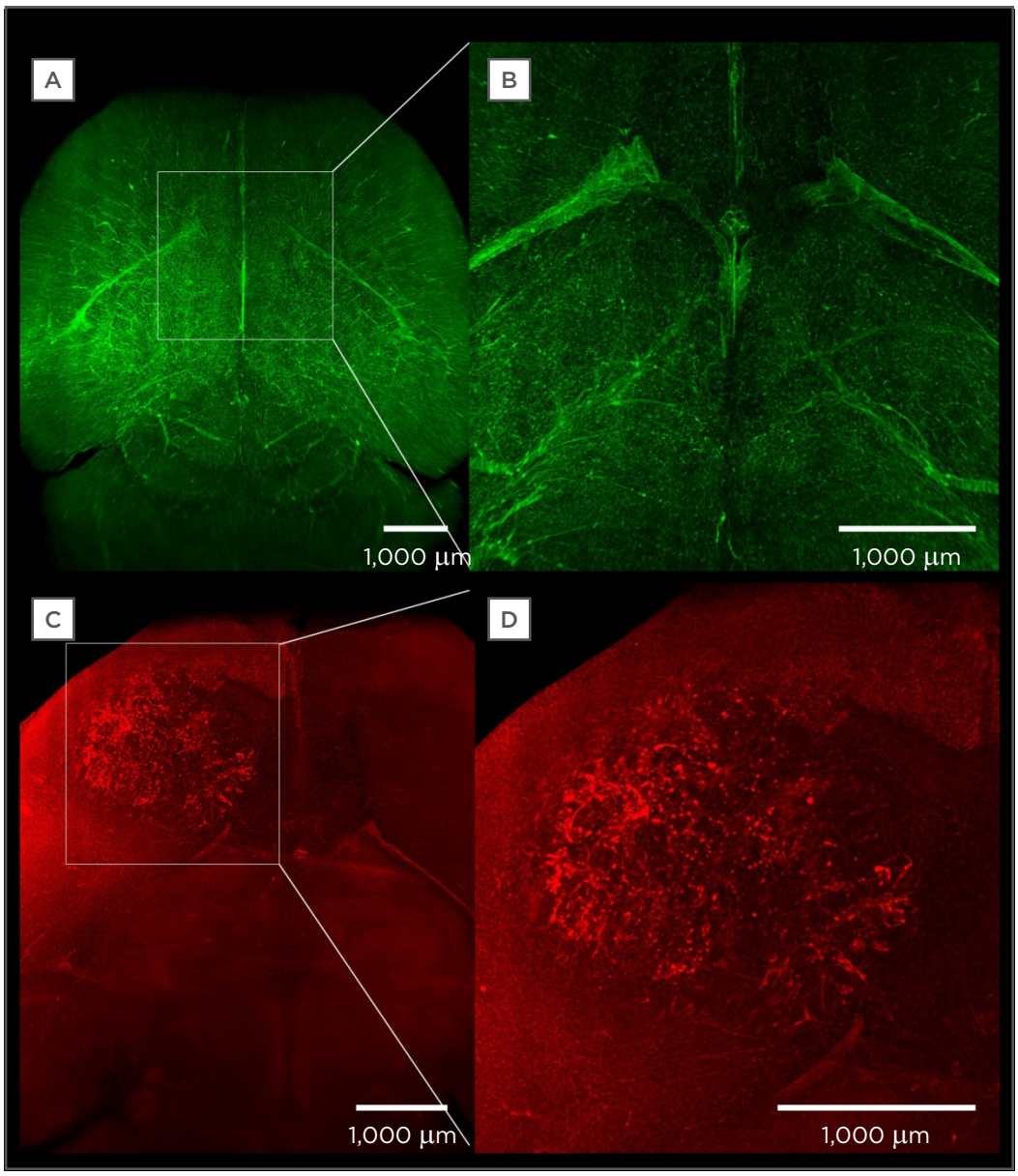

Figure 2: The injection of fluorescently-labelled tracers to visualise anatomical and subanatomical structures.

A) A maximum intensity projection of the vasculature of a healthy brain after intraveneous injection of fluorescently labelled lectin (12 mg/kg body weight) in the tail vein of a mouse; B) a magnification of A; C) a maximum intensity projection of the vasculature of a mouse brain with a 3-week-old human U87 glioblastoma; D) a magnification of the tumour.

(Bode and Krüwel, unpublished data).

The CLARITY protocol, developed by the group led by Karl Deisseroth, is very different to the previously described clearing protocols.[30,31,35,36] The method is based on an incubation of the tissue in a hydrogel matrix combined with an electrophoretical removal of lipids, a procedure that renders the specimen transparent. The CLARITY protocol was already used for the clearing of whole rodent brains and spinal cords,[37,38] parts of the human brain,[39] several other non-CNS organs from rodents, and also for clearing of embryos.[40] This protocol preserves the structure of the cells, along with nucleic acids and proteins, and enables the localisation of RNA within the 3D specimen. However, the CLARITY protocol is very laborious and requires significantly longer time frames of weeks to months for the clearing procedure.

Another solution suitable for the clearing of whole brains, combined with preserved fluorescence, is the clear, unobstructed brain imaging cocktail (CUBIC) that achieves transparency of brains by the use of aminoalcohols.[32] The CUBIC protocol is especially useful if the imaging of multiple fluorophores is desired.

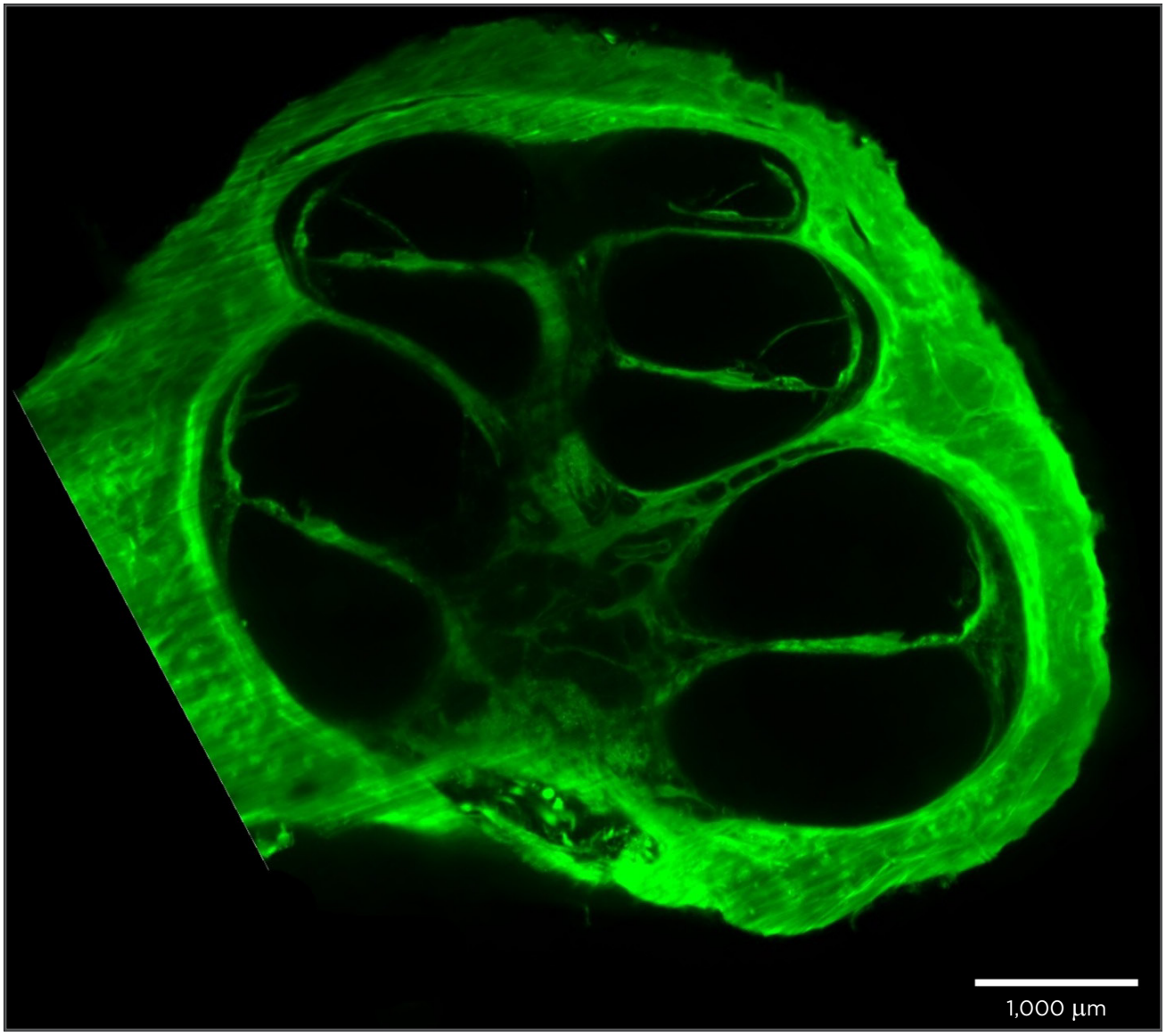

Figure 3: A preparation of a human cochlea.
The cochlea was decalcified and cleared using FluoClearBABB. Autofluorescence of the cochlea was then imaged using LSFM.
LSFM: light sheet fluorescence microscopy.
The sample was provided by Prof Dr M. Praetorius and M. Gestewitz, University Heidelberg, Heidelberg, Germany; sample preparation and imaging were performed by J. Bode and T. Krüwel.

LIGHT SHEET FLUORESCENCE MICROSCOPY APPLICATIONS IN BIOMEDICAL RESEARCH

Optical clearing can be applied to tissues or organs of any species, however, for imaging with LSFM the size of the specimen is restricted to several centimetres due to the design of the microscope. This limits its application mainly to mice and rats, if the investigation of whole organs is desired. A prerequisite for LSFM is the presence of fluorescence, either as protein or fluorophore, which labels the cell/region of interest. This can be done in various ways by the application of transgenic mice or xenografting of modified cells that express fluorescent proteins. Furthermore, the injection of fluorescently-labelled specific tracers, such as antibodies or proteins in general, ligands, or nanoparticles, is a frequently used method to visualise anatomical and subanatomical structures of interest, i.e. by the injection of fluorescently-labelled lectin that binds to endothelial cells to visualise the vasculature (Figure 2; Bode and Krüwel, unpublished data). Additional anatomical information can also be obtained by tissue-inherent autofluorescence. Figure 3 shows the utilisation of autofluorescence for LSFM imaging of a human cochlea. The sample was decalcified and cleared using FluoClearBABB. As already mentioned above, it is possible to stain dissected tissue post mortem with fluorescently-labelled antibodies to validate results.

LSFM is a versatile technique for medical research. In basic research, the high resolution on a single cell level, in combination with the fact that the imaged specimens are intact and undissected, enabled novel insights into neuronal and vascular development patterns. Hägerling et al.[41] applied LSFM on whole-mount immunostained mid-gestation mouse embryos to shed light on the development of the lymphatic system by precisely describing the morphogenetic events during the separation of the lymphatic from the venous endothelium. Belle et al.[42] used LSFM to study axonal connectivity in transgenic mouse embryos and analysed axon guidance defects in the development of the neuronal system. Other studies have applied LSFM to investigate axonal regeneration and interaction of axons and scar-forming cells,[43] or assessed the regeneration of optic nerves after injury, combined with the analysis of axonal trajectories.[44] A very recent study described a workflow for the rapid acquisition of brain activity at cellular resolution by profiling immediate early gene expression, which highlighted the use of LSFM as a powerful platform for developmental biology.[45] Additionally, LSFM was applied using a quantitative hydrogel-based technology to correlate activity in cells reporting on behavioural experience with measures for brain-wide wiring and regarding molecular phenotype.[46] Stefaniuk et al.[47] created a novel transgenic rat harbouring fluorescent reporter GFP expression under control of a neuronal gene promoter. This study is the first reference to a cleared rat brain, which exceeds the size of a mouse brain by far. The authors stated that FluoClearBABB clearing was found superior over passive CLARITY and CUBIC methods.

Besides these applications in developmental and behavioural biology, LSFM was extensively utilised for the investigation of diseases, especially those of the CNS, such as Alzheimer's disease or brain tumours.[48] In the case of Alzheimer's disease, LSFM was used to assess the formation of amyloid plaques in whole mouse brains and in a part of the human brain.[49] Surprisingly, the authors reported a higher complexity of the plaques of the human compared to the mouse brain. In translational biomedical research, LSFM helped to solve many different questions. Our group recently used LSFM to investigate the tropism and efficiency of adeno-associated viruses as transport vehicles for gene therapy of neuronal diseases.[48] The use of undissected adult mouse brains allowed for a rapid 3D analysis of the viral transduction pattern of neuronal cells deep inside the brain. The high resolution of the microscope enabled the detection of single cells expressing the fluorescent proteins transduced by the viruses and proved the usability of this microscopic setup for higher throughput analysis. In glioblastoma, our group has investigated the role and modification of the vasculature during tumour progression and the effects of antiangiogenic treatments.[50] Dobosz et al.[9] and Weber et al.[51] assessed the penetration of therapeutic antibodies in subcutaneous tumours and glioblastoma xenografts by LSFM.

THE EVOLUTION OF LIGHT SHEET FLUORESCENCE MICROSCOPY TO BECOME A POWERFUL TOOL IN BIOMEDICAL RESEARCH

A limitation of the method is the fact that only optically cleared tissue can be used for imaging and, thus, in non-transparent model systems, only

ex vivo imaging is possible. By solely applying LSFM, dynamic monitoring of disease progression is laborious and involves a high number of animals. Therefore, our group and others combined LSFM with classical lower resolution *in vivo* imaging modalities, such as MRI and CT, to overcome this problem.[50,52] By applying functional MRI (fMRI), the progression of glioblastoma models could be spatiotemporally monitored and the obtained data were registered to the high-resolution post mortem LSFM data.

An issue that needs to be solved in the future is the handling of the huge amount of data output obtained; one image is often >10 MB. Hence, full 3D image stacks easily exceed sizes of 10 GB. Therefore, better compression of these high-resolution images is desperately needed.

In this review, we presented LSFM as a novel and powerful imaging tool for basic and biomedical research and provided an overview of recent applications and requirements for imaging. If the interaction of single cells is the focus of research, LSFM is superior to all other microscopy techniques in terms of acquisition speed, imaging depth, sample size, photobleaching, and phototoxicity. The possibility to acquire a complete stack of images of an organ of interest without physical fragmentation will improve and accelerate biomedical research within the next few years.

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VIRTUAL REALITY ASSISTED ANAESTHESIA DURING UPPER GASTROINTESTINAL ENDOSCOPY: REPORT OF 115 CASES

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ABSTRACT

Objective: The utility of virtual reality (VR) pain management to reduce visceral or autonomic responses is presented in 115 cases during diagnostic upper gastrointestinal (GI) endoscopy.

Methodology: 115 patients with peptic disease and gastro-oesophageal reflux were given an upper GI endoscopy with local anaesthesia. They were divided into two groups, 56 treated with VR and 59 without VR during procedures. A 10-point Visual Analogue Scale (VAS) for pain was administered to patients and the physician rated level of stress on a 3-point scale.

Results: Overall, visceral responses during oesophageal, stomach, and duodenum endoscopy were reduced using VR. Overall pain was significantly lower in the VR group than the control group with a moderate effect size. Physician stress was also reduced in the VR group, allowing greater accuracy and a shorter procedure time. A total of 115 satisfactory GI endoscopy procedures were carried out with no complications.

Conclusions: VR therapy considerably reduces the need for medication, effectively lowering costs for public health institutions and decreasing patient complications and recovery time.

Keywords: Panendoscopy, anaesthesia, virtual reality (VR), pain distraction, gastrointestinal (GI) endoscopy, surgery.

INTRODUCTION

An endoscopy is an examination of the interior of a canal or hollow viscus by means of a special instrument, such as an endoscope and often calls for analgesics.[1] Oesophagogastroduodenoscopy (OGD), or panendoscopy, is a diagnostic endoscopic procedure that visualises the upper part of the gastrointestinal (GI) tract up to the duodenum. OGD is also called an upper endoscopy, gastroscopy, or simply endoscopy. A gastrointestinal endoscopy aims to explore gastrointestinal structures such as the oesophagus, stomach, duodenum, biliary, and pancreatic tract. Over 1 million upper gastrointestinal endoscopies are performed each year in the USA, accounting for a significant portion of healthcare services.[2] However, there are only approximately 10,000 GI physicians in the USA and that number is decreasing annually.[2,3] Thus, increasing efficient and effective practices is integral to continued success and availability of GI procedures.

In the present study, we explored the oesophagus, stomach, and duodenum for diagnostic and therapeutic purposes following clinical examination and assessment. In an upper GI endoscopy

there are two types of anaesthesia that may be administered to a patient depending on their preoperational condition, local anaesthesia and intravenous medication (fentanyl, midazolam).[4-18] In this study, endoscopic procedures were carried out under local anaesthesia. As with many medical procedures, pain management is an essential aspect to the quality and comfort of a patient during an operation. Intravenous anaesthesia is often used to prevent pain during a procedure and reduce recall. However, with the use of local anaesthesia, a patient remains awake and cognisant of their surrounding environment, thereby enhancing their awareness of happenings and potentially increasing their risk of experiencing autonomic distress. They are however, able to co-operate during the procedure if necessary. Therefore, the introduction of pain management techniques is essential to maintaining patient comfort. Past studies and procedures underscore successful pain distraction techniques for reducing anxiety.[19-27] For example, Hudson et al.[22] found that when allocated distraction techniques during venous surgery, such as listening to music or watching a DVD, patients' intraoperative anxiety ratings were significantly reduced and their overall experiences were satisfactorily improved. Additionally, Umezawa et al.[23] found the application of visual distraction (watching a silent movie) worked to improve patient satisfaction and decrease both anxiety and pain while undergoing a colonoscopy. Such research highlights the successful use of pain distraction during invasive surgeries. As a result, the development and implementation of new, innovative, efficient, and effective technological pain distraction techniques is pertinent to enhancing patient comfort, reducing negative effects, and improving overall wellbeing during medical procedures.

Table 1: Published studies using handheld devices in pain management.

Author	Description	Methods	Results
Miller et al.[39]	This easy to use, handheld interactive device uses customised programmes designed to inform the child about the procedure he/she is about to experience and to distract the child during dressing changes.	A prospective randomised controlled trial was completed in a paediatric tertiary hospital, Burns Outpatient Clinic. Eighty participants were recruited and studied over their first three dressing changes. Pain was assessed using validated child report, caregiver report, nursing observation, and physiological measures.	MMD distraction and MMD procedural preparation (MMD-PP) were both shown to relieve reported pain significantly ($p \leq 0.05$) and reduce the time taken for dressings ($p \leq 0.05$) compared to standard distraction and video game. The positive effects of both MMD-D and MMD-PP were sustained with subsequent dressing changes.
Stinson et al.[40]	Our research group has developed a native iPhone app called Pain Squad to tackle the problem of poorly managed pain in the adolescent with cancer group. The app functions as an electronic pain diary and is unique in its ability to collect data on pain intensity, duration, location, and the impact pain has on an a adolescent's life (e.g. relationships, school work, sleep, mood). It also evaluates medications and other physical and psychological pain management strategies used. Users are prompted twice daily at configurable times to complete 20 questions characterising their pain and the app transmits results to a database for aggregate reporting through a Web interface.	We used both low and high fidelity qualitative usability testing with qualitative semi-structured, audiotaped interviews and iterative cycles to design and refine the iPhone based Pain Squad app. Qualitative thematic analysis of interviews using constant comparative methodology captured emergent themes related to app usability. Content validity was assessed using question importance rating surveys completed by participants. Compliance and satisfaction data were collected following a 2-week feasibility trial where users were asked to record their pain twice daily on the app.	Thematic analysis of usability interviews showed the app to be appealing overall to adolescents. Analyses of both low and high fidelity testing resulted in minor revisions to the app to refine the theme and improve its usability. Adolescents resoundingly endorsed the game-based nature of the app and its virtual reward system. The importance of app pain diary questions was established by content validity analysis. Compliance with the app, assessed during feasibility testing, was high (mean 81%, standard distraction 22%), and adolescents from this phase of the study found the app likeable, easy to use, and not bothersome to complete.

Table 1 continued.

Author	Description	Methods	Results
Spyridonis et al.[41]	In this paper, we present an Android application (PainDroid) that has enhanced VR technology for the purpose of improving the management of pain.	-	Our evaluation with a group of wheelchair users revealed that PainDroid demonstrated high usability among this population, and it is foreseen that it can make an important contribution in research on the assessment and management of joint pain.
Mosso et al.[19]	When undergoing ambulatory surgical operations, the majority of patients experience high levels of anxiety. Different experimental studies have shown that distraction techniques are effective in reducing pain and related anxiety. VR has been demonstrated to be a good distraction technique, it has been repeatedly used in hospital contexts for reducing pain in burn patients, but it has never been used during surgical operations.	With the present randomised controlled study, we intended to verify the effectiveness of VR in reducing anxiety in patients undergoing ambulatory operations under local or regional anaesthesia. In particular, we measured the degree to which anxiety associated with surgical intervention was reduced by distracting patients with immersive VR provide through a mobile phone connected to a HMD compared to a no-distraction control condition.	A significant reduction of anxiety was obtained after 45 minutes of operation in the VR group but not in the control group, and, after 90 minutes, the reduction was larger in the experimental group than in the control group.

VR: virtual reality; MMD: multi-modal distraction; MMD-PP: multi-modal distraction procedural preparation; app: application; HMD: headmounted display.
Adapted from Wiederhold et al.[42]

Virtual reality (VR) as an established and effective tool in reducing autonomic response pain has been demonstrated in uterine cervical procedures (conisations, cone biopsies, etc.) and even in peritoneum manipulation in certain cases. Furthermore, VR reduces somatic pain in soft tissues of the abdominal wall, legs, arms, neck or head in outpatient surgeries. The utility of VR in decreasing pain has been demonstrated in psychology, dentistry, rehabilitation, and many other fields of medicine (Table 1).[23-31] As an example, Czub and Piskorz,[32] and Mühlberger et al.[33] conducted studies measuring variance of pain intensity thresholds of subjects immersed in VR. Ultimately, the experiments produced higher pain thresholds for those immersed in a virtual environment. Additionally, augmented reality, a blend of physical and virtual worlds, has been applied to alleviate pain adjunctively with pharmacological analgesia in children undergoing dressing changes following burn injuries.[34] In another application, Wiederhold et al.[35] demonstrated the effectiveness of VR pain distraction during dental procedures. VR pain distraction has also been applied for a wide range of surgeries, including cardiac procedures.[36,37] There are many applications of VR in healthcare, especially for pain management.[38] Overall, the application of VR as a state management tool for medical procedures is increasingly recognised as an effective application to manage patient pain all the while costing less and being more accessible than many other analgesia options. The clinically validated capability of VR to manage pain points to a number of possible VR applications in surgery. In an attempt to expand the existing body of research, the present study explored the application of VR as an assistive anaesthetic during upper gastrointestinal endoscopy procedures. We aimed to elaborate on previous methods by examining the analgesic effects of VR in a large sample of patients. In addition, our approach to understanding the representations of pain will offer additional insight into the most effective behavioural and medical applications of VR technology.

METHODS

Participants

This study took place at the Endoscopy Service at the Pisanty Clinic of the Institute for Social Security

and Services for State Workers (ISSSTE) in Mexico City, Mexico. A total of 115 outpatients participated with full informed consent. There were 34 male and 81 female participants, all without cardiorespiratory disease who took part. The control group (n=59) received local anaesthesia, while the treatment group ('VR distraction') (n=56) received local anaesthesia and an immersive VR relaxation environment. Patients were not randomised. The average age of the control and VR groups was 53.2 and 47.6 years old, respectively. In the control group, the age range was 27–81 years (mean [M]=53.2).

Stimulus

The virtual scenarios used were: 'Enchanted Forest', 'Cliff', 'Castle', and 'Beach', all developed at the Virtual Reality Medical Center, La Jolla, San Diego, California, USA (Figure 1). Each of these four environments are clinically validated relaxation worlds to reduce autonomic stress responses and reduce pain.

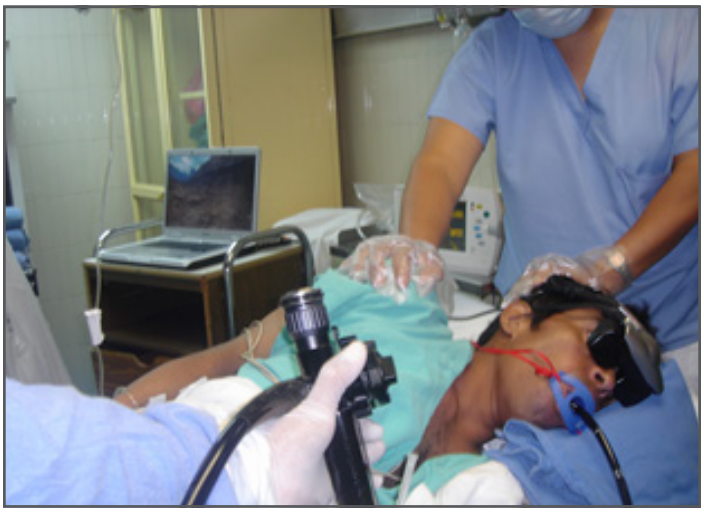
Materials

The equipment necessary for an endoscopic procedure includes optic fibre to transmit the image to a monitor, a light source for illuminating the inside of the cavities, and insufflation to distend the virtual spaces of organs. Additionally, instruments inserted through the endoscope are used to take samples for cytological and histological examinations (biopsy forceps), and to cauterise, infiltrate, dissect, cut, and remove superficial injuries. Heart rate and additional sensors were used to measure each patient's vitals. Gauzes were also used to measure oral secretion. We will report the findings on physiological measurement in an upcoming publication.

The VR scenarios were presented through an eMagin Headmounted Display (HMD) that displayed three-dimensional (3D) stereoscopic colour images with a resolution of 1,024x768 pixels. The auditory effects were delivered through binaural headphones. The computer was a Pentium IV, 3 GHz, 2 GB Ram, NVIDIA QuadroFX 4500 512 MB DDR3 Graphics card. Virtual scenarios were modelled and animated using 3D StudioMax, Adobe Photoshop, and Maya. Navigation was conducted with a Logitech Joypad.

Procedures

In this study, we performed diagnostic OGD and biopsies. All patients were referred to the clinic with benign diagnoses of peptic ulcer disease, gastritis, oesophageal reflux, upper bleeding, duodenogastric reflux, oesophageal varix, and human immunodeficiency virus (HIV) amongst others (Table 2). To become accustomed to the intervention, the VR group was trained how to navigate the relaxation environment prior to the procedure. Each patient's vital signs were measured before, during, and after the endoscopy, as were their subjective perceptions of pain, measured via self-report on the Visual Analogue Scale (VAS). With the patient seated, initial vital signs and patient pain were recorded. Endoscopic procedures were done under local anaesthesia; the physician sprayed five doses of xylocaine into the oral cavity before beginning the procedure.



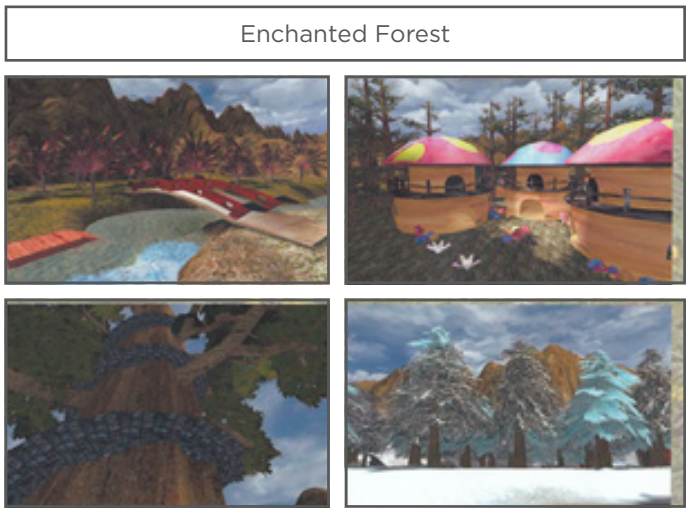


Figure 1: Virtual reality headmounted display and one of four virtual environments displayed to patients.

With the patient lying on their left side decubitus with an oral protector (nozzle), the physician set up the HMD linked to a laptop in order to present one of the four virtual environments (Figure 1). The physician then inserted the endoscope through the oral cavity into the larynx. Next, the patient was instructed to swallow in order to insert the endoscope into the upper oesophagus. The VR headset and environment was then turned on and the patient began navigation. Continuing to explore the stomach and gastric antrum, the endoscopist performed a retrovision manoeuvre. The bending of an endoscope can cause pain and distention and because of this it was decided that this was the optimal time to record the in-procedure vital signs. This data was recorded as 'face', or pain, 'during'. If necessary, the endoscopist took biopsy samples from the fundus, body, or antrum. We continued with the exploration of the first and second portion of duodenum where vital signs were again measured. The procedure ended and the endoscope was removed. After the endoscope was extracted, gauzes were analysed. These oral secretion measurements served as indicators of stress levels during the procedure. Patients in the VR group continued immersion in the virtual environment for 10 minutes after the conclusion of the procedure while the endoscopist cleaned the equipment. At this time, the last vital signs, pain ratings, and gauze scores were recorded.

Measures

Subjective vital signs were recorded before, during, and after the procedure via the pain VAS. This Likert-type scale instructed patients to rate pain on a scale of 0–10 (0=no pain, 10=maximum pain). Physician stress was measured on a self-report scale of 1–3 (1=no stress, 2=some stress, 3=much stress). The length of the procedure was also recorded.

Table 2: Frequency of diagnosis: Comparison between virtual reality and control groups.

Diagnosis	Frequency with VR (n=56)	Percentage with VR (n=56)	Frequency with no VR (n=59)	Percentage with no VR (n=59)
Normal	10	17.8%	12	20.33%
Peptic ulcer disease	12	21.42%	8	13.55%
Gastritis	4	7.14%	1	1.69%
Hiatal hernia	26	46.42%	26	44.06%
Gastroesophageal reflux	3	5.3%	5	8.47%
Oesophagitis	3	5.3%	12	20.33%
Human immunodeficiency virus	2	3.57%	0	0%
Oesophageal varix	3	5.3%	1	1.69%
Upper bleeding	1	1.78%	0	0%
Duodenogastric reflux	0	0%	4	6.77%

VR: virtual reality.

Table 3: Pain distraction during endoscopic surgery. Comparison between virtual reality and control groups on perceived pain, physician stress, and length of procedure.

	VR	No VR	p(α=0 .05)
Pain during (0=no pain, 10=maximum pain)	4.536	5.814	0.016*
Physician stress	1.429	1.644	0.077**
Length of procedure (minutes)	5.35	7.08	0.186**

*p<0.05, **clinically significant.
VR: virtual reality.

Statistical Analysis

For the assessment of differences in measurements of perceived pain between the VR and control groups, multiple one-way analyses of variance (ANOVA) were run. Cohen's d tests were run to assess effect size. Statistical significance was set at $p \leq 0.05$. All data analysis was conducted using Microsoft Excel.

RESULTS

Table 3 presents mean values and significance levels of the differences between the VR and control group during upper gastrointestinal surgery with local anaesthesia. First, overall pain, as measured on the VAS scale (0=no pain, 10=maximum pain) was 31% lower for patients in the VR group (M=4.536, standard deviation [SD]=2.662) than the control group (M=5.814, SD=2.921), ($F [1, 113]=5.991$, $p=0.016$, $d=0.469$). While statistically non-significant, the average time per procedure with VR was 30% faster than without, a clinically significant difference between groups. The VR group averaged 5.17 minutes per procedure (SD=1.523) while the control group averaged 5.97 minutes per procedure (SD=3.279) and d=0.29, suggesting that VR has a small effect on reducing time per procedure ($F [1, 111]=2.33$, $p=0.13$). Comparisons of physician stress also produced clinically significant differences. The physician rated his stress level lower when operating on the VR group (M=1.43, SD=0.599) than the control (M=1.64, SD=0.689) ($F [1, 113]=3.19$, $p=0.077$ $d=0.34$). No complications were presented in this study.

DISCUSSION

This study adds to the current body of research regarding the efficacy of immersive VR distraction for invasive medical procedures and highlights specific ways in which this technology can be successfully applied. VR was shown to reduce pain during medical procedures in this group of 115 patients. The results were statistically significant. VR has a small effect on reducing the time per procedure. In addition, analyses indicate that patient stress positively correlates with physician stress, suggesting that as a patient exhibits physiological signs of discomfort, the physician too reflects higher stress levels. Moreover, due to the moderate effect size of VR on physician stress, we suspect that VR can be an important tool to help physicians relax as well. We have shown in a number of clinical studies that levels of immersion are important for an effective VR experience. Because our VR worlds are highly engaging and interactive, patients were able to become immersed, which was supported by much lower subjective pain ratings. Overall, we conclude that the ability of the VR intervention to produce statistically significant lower levels of pain underlines its capability as an effective tool in managing physiological responses.

CONCLUSION

As virtual distraction gains traction and is used in conjunction with pharmacological analgesia, there is potential for lower costs in medication and hospitalisation. Aside from lowering costs, VR as a technique of pain distraction can lower medical risks associated with pharmacological analgesia in both public and private health institutions. VR is a non-invasive technology and has the advantage of being easy to use. With VR distraction, practitioners avoid risk factors associated with pharmacological agents such as over-sedation, hypoventilation, and vasovagal episodes. Currently, rapid technological improvements in mobile phones and other mobile devices are facilitating the replacement of bulky, hard-to-handle HMDs with low-cost, easily accessible products. VR scenarios are becoming widely available on today's smart mobile phones and allow patients to easily navigate virtual worlds. Subsequently, the low cost of VR equipment makes it readily available to more institutions interested in using this technology for additional treatments. Overall, this study and the body of research before it contributes to the conversation about the impending ubiquity of VR and both its known and undiscovered benefits across medical settings.

Future research may complement this study by exploring, in greater depth, more reliable physiological and subjective measurements of pain. Our study reveals the effectiveness of VR pain distraction in clinical settings (i.e. the operating room) while a patient is sedated or under some form of pharmacological agent. Nonetheless, it is important that subsequent research be conducted to explore societal applications of VR as an analgesic alternative to pharmacological agents.

VR-assisted analgesia is an effective adjunct to pharmacological agents and is trending toward being a low-cost, highly effective, and widely accessible tool for pain management. Continually

evolving research and development on such technologies suggests that VR holds a promising position in the future of healthcare.

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MICROBIOME: THE MISSING LINK IN NEUROPSYCHIATRIC DISORDERS

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ABSTRACT

The relationship between intestinal microbiota and the brain has been the focus of attention of the scientific world in recent years; >90% of the articles discussing the microbiome have been published only recently.[1] There is a strong and bidirectional relationship between the brain and the gut. Gut bacteria communicate with the intestinal epithelium and the immune system cells, with this communication causing many autoimmune, metabolic, and neuropsychiatric diseases. New horizons have been opened in the understanding and treatment of neuropsychiatry disorders. Microbiota dysbiosis can be restored with faecal microbiota transplantation, dietary arrangements, and probiotics. The efficacy of faecal microbiota transplantation in neuropsychiatric disorders is being investigated currently, and through the manipulation of the composition of intestinal bacteria in a conscious way, the treatment of neuropsychiatric disorders may be performed in a cheaper, easier, and natural way in the near future. Searching through the relevant literature on PubMed, EMBASE, and Google Scholar electronic databases, this is one of the first articles to discuss faecal microbiota transplantation in neuropsychiatric disorders in detail.

Keywords: Gut, microbiota, brain, psychiatry, faecal microbiota transplantation (FMT).

THE HISTORY OF THE MICROBIOME

The term 'microbiome' is used to denote all organisms living in the body and their genetic material; the term 'microbiota' is used to denote populations of micro-organisms in the different floras of the body (e.g. intestinal microbiota, vaginal microbiota).[1] A total of 380 trillion micro-organisms live in the gut. This number is >10-times the total number of human cells.[2] Furthermore, these micro-organisms contain approximately 150-times more genes than in the human genome.[3] Élie Metchnikoff was the first to realise the importance of the microbiome to human health, with the Nobel Prize in Physiology or Medicine 1908 awarded to Metchnikoff for his contribution to the understanding of cellular and humoral immunity.[4] Two years later, the first article concerning how probiotic bacteria can be used in the treatment of depression was published by Phillips.[5] However, interest in this subject only lasted for a short time. Throughout the following years, the relationship between intestinal microbiota and the brain was not studied.

Old Friends

The idea that micro-organisms may not all necessarily be harmful has been remembered again nearly 80 years after publication of Phillips' article. Strachan[6] has argued that there may be a relationship between hygiene (increased use of antibiotics, disinfectant cleaning products, modern lifestyle, and urbanisation) and the increase in the incidence of allergic diseases. Rook[7] has looked at the human-microbiota relationship from a broader perspective. He has argued that *Homo sapiens* have evolved along with 'the old friends' in the body, namely micro-organisms, for millions of years.[7]

The Leaky Gut

The surface of the intestinal mucosa is about 260–300 m^2 (almost the size of a tennis court).[8] More than 7,000 bacteria subspecies live in this vast area.[3] Intestinal bacteria produce active

metabolites (neurotrophins and antigens) that affect human cells.[9] The mucosa is in constant contact with bacteria and metabolites and the intestinal epithelium and mucus layer act as a physical barrier to bacteria and antigens.[10] If microbiota change because of the influence of alcohol and nutrition (dysbiosis), the intestinal epithelial wall will be destroyed; this causes increased epithelial permeability and 'leaky gut' occurs. Antigen bacterial metabolites leak into the bloodstream from the weak intestinal epithelium and an immune reaction occurs.[11] In addition to leaky gut, subepithelial dendritic cells produce exosome-containing bacterial material. Exosomes reach the brain through the blood and lymph.[12]

MICROBIOTA–GUT–BRAIN AXIS

Another method of interaction between bacteria and the human body is direct communication. Intestinal bacteria interact with the first step of the cytokine production pathway, the intestinal mucosal cells' toll-like receptors (TLRs). TLRs are also widely available in neurons.[13] Therefore, if the gastrointestinal system is referred to as the largest immune organ,[14] the intestinal microbiota is the forgotten organ.[15] The vagus nerve is another way of communicating between the gut and brain; any change in the gut is transmitted to the brain by the vagus nerve.[16] The possible mechanisms of the effect of the microbiota on the central nervous system are as follows:

- Microbiota dysbiosis[17]
- Antigen bacterial metabolites[10]
- Neuroactive bacterial metabolites (e.g. brain-derived neurotrophic factor, synaptophysin, postsynaptic density protein-95 [PSD-95])[18,19]
- Immune system activation[20]
- Vagus nerve-mediated effects[16,21,22]

Microbiota studies in neuropsychiatric disorders have revealed surprising results. It is useful to review these studies in detail.

Schizophrenia

Several studies on immune system problems in schizophrenia have been performed. The incidence of rheumatoid arthritis has been found to be low in patients with schizophrenia;[14] inflammatory cytokine interleukin (IL)-1 receptor antagonist levels in patients with schizophrenia are high, an occurrence thought to protect the patient from developing rheumatoid arthritis.[23]

It has been shown that anti-gliadin antibodies and gluten sensitivity are increased in patients with schizophrenia;[24] there is also a relationship between non-coeliac gluten sensitivity and diseases such as autism and schizophrenia.[25] Casein antibodies are increased in patients with schizophrenia and those positive for casein immunoglobulin G antibody have an 18% greater risk of schizophrenia (positive casein immunoglobulin G is a predictor for schizophrenia).[26]

Neuroinflammation is considered the starting point for pathogenesis of schizophrenia.[27] In germ-free (GF) mice, production of brain-derived neurotrophic factor and N-methyl-D-aspartate (NMDA) 2a decreases.[28] Changes in microbiota composition may cause NMDA dysfunction in schizophrenia.[29] Minocycline (a second-generation tetracycline) shows an antipsychotic-like effect in rats,[30] and is also effective in the treatment of negative symptoms of schizophrenia.[31] The positive effect of minocycline in the treatment of schizophrenia may happen through a change in the bacterial composition of the microbiota. In a study comparing serological immune markers between schizophrenia, bipolar disorder, and control groups, it was found that microbial products in the systemic circulation caused immune disorders in the schizophrenia group.[32] Through probiotic therapy, inflammation subsides in patients with chronic schizophrenia.[33]

An interesting experiment with olanzapine (an antipsychotic drug) has been performed. One of two groups of GF mice was given a high fat diet only and the other received olanzapine in addition. At the end of the experiment, no differences were detected in terms of weight gain between the two groups. Olanzapine-related weight gain was not realised due to the lack of intestinal bacteria. In the second phase of the experiment, it was found that olanzapine had an antibiotic-like effect on the bacterial flora.[34]

Anxiety and Depression

In patients with depression, a chronic and mild inflammation is found. The source of this inflammation may be the leaky gut.[35] The relation between the microbiota and mood has been investigated, mostly in animal experiments. *Campylobacter jejuni* given orally leads to anxiety-like behaviour in mice,[36] whereas *Bifidobacterium infantis* has reduced depressive symptoms in GF mice;[37] *B. infantis* is called a psychobiotic

because of its antidepressant effect.[38] Probiotic drugs include copious amounts of this bacterium.

The anxiety scores of rats given *Bifidobacteria longum* and *Lactobacillus helveticus* have been found to decrease,[39] while *Lactobacillus farciminis* decreases the hypothalamic–pituitary–adrenal axis response to stress in mice.[40] In an experiment by Bravo et al.,[41] the anxiety and depression scores of mice given *Lactobacillus rhamnosus* for 28 days decreased. In another experiment, anxiety-like behaviour declined after 21 days of *L. helveticus* usage. When the same implementation was performed in IL-10 (an immunoregulatory cytokine) knockout mice, anxiety levels did not change.[42] This finding shows the influence of the immune system on the gut–brain axis.

Probiotic bacteria increase IL-10 levels in GF mice;[43] in experimental animals given *Lactobacillus* GG, an increase in plasma IL-10 levels was found.[44] Antidepressants create an anti-inflammatory effect via IL-10[45] and treat depression by acting on monoamines and the immune system. In a double-blind placebo-controlled study with healthy volunteers, the first group was given *B. longum* and *L. helveticus* R0052, and the other group received a placebo; urinary-free cortisol levels and anxiety/depression scores decreased in subjects who received probiotic bacteria.[46] The positive effects of probiotics in emotional tasks have also been shown through functional magnetic resonance imaging (MRI).[47] Microbiota may additionally play a key role in linking an unhealthy diet and depression.[48]

Autism

Autism is one of the diseases where the gut–brain axis is mostly studied.[49] In autistic mice, increased neuroinflammatory markers have been found,[50] while in another experiment, autistic behaviours returned with *Bacteroides fragilis*; this bacterium has been shown to repair intestinal permeability disorder through cytokine production and tight junction expression. Also, 4-ethylphenyl sulphate (a bacterial metabolite) has been found to result in elevated serum levels in autistic mice. When this metabolite has been given to normal rats, the emergence of autistic behaviours has been observed.[51,52] In autistic children, decreased *Bifidobacterium* species, increased *Lactobacillus* species,[53] and increased *Bacteroides* species[54] have been found. It has also been argued that a high carbohydrate diet increases the production of short-chain fatty acids in the gut, and their release into the systemic circulation leads to autistic behaviour.[55]

Alcohol Addiction

By weakening the wall of the intestinal mucosa, alcohol eases the release of bacterial antigens into the systemic circulation. These substances induce the secretion of proinflammatory cytokines (IL-1β, IL-8, and IL-18) by binding to TLR-4 and TLR-2 receptors of mononuclear cells in peripheral blood. Few studies have investigated links between microbiota and alcohol abuse, although in a study by Leclercq et al.,[56] 63 alcohol addicts were investigated. It was found that chronic alcohol consumption increased the levels of IL by activating inflammatory processes. A correlation was found between IL levels and the levels of alcohol consumption and craving.[56] In a second study by the same investigators, the role of intestinal permeability in alcohol addiction was examined. Intestinal permeability was found to be commensurate with the severity of alcohol dependence.[57]

REGULATION OF INTESTINAL MICROBIOTA

There are several ways to treat intestinal microbiota dysbiosis. These are prebiotic drugs, probiotic drugs, activated charcoal, and faecal microbiota transplantation.[9,58] A prebiotic enables an intestinal bacterium to become more dominant than other ones. A probiotic gets a special kind of bacteria into the body orally or rectally.[1] In a single year, >$1 billion is spent on probiotic drugs in the USA.[59] Activated charcoal is used in the treatment of poisoning that occurs after usage of high-dose medication as it prevents absorption from the intestines by binding to toxins. Tablets and capsules are used in reducing complaints of diarrhoea, indigestion, and bloating; these may help to relieve the gastrointestinal system and neuropsychiatric symptoms by binding to toxins secreted by microbiota.[9]

FAECAL MICROBIOTA TRANSPLANTATION: A RISING STAR IN NEUROPSYCHIATRIC DISORDERS

Stool was used for the first time for treatment purposes in China in the 4th Century,[60] and has been applied orally under the name of 'golden syrup' or 'yellow soup' in the treatment of diarrhoea.[58]

Interestingly, this technique was forgotten over the centuries and was recalled in 1958. Eiseman et al.[61] treated a pseudomembranous enterocolitis case with antibiotic-associated severe diarrhoea through faecal microbiota transplantation (FMT), however nowadays, a very high percentage of publications on FMT are regarding *Clostridium difficile* infection (*CDI*) and its treatment. This method has started to be used in the treatment of neuropsychiatric disorders in recent years.[58]

Preparation and Usage of Faecal Microbiota Transplantation

It is recommended to provide faecal material from a stool bank for transfer.[62] If this is not possible, health screening of a donor candidate should be performed.[63] The stool should be ≥150 g and fresh.[63] The receiver should be given a mild laxative a night before the application and the transplanted stool should stay for ≥4 hours within the patient's gut. An antidiarrhoeal drug (loperamide) should be given an hour before FMT.[58] The preparation of the stool material is as follows: the stool is diluted with water, milk, or saline and it is then mixed with a blender. This stool suspension is filtered with a filter or gauze to separate solid particles and the faecal suspension taken up into syringes.[63,64] The stool suspension can be sent to the duodenum through oesophagogastroduodenoscopy and can be applied to the colon through a colonoscopy or enema.[63] In three-quarters of cases, colonoscopy or enema has been used. In one-quarter of cases endoscopy has been used.[65]

Faecal Microbiota Transplantation in Neuropsychiatric Disorders

Information on the application of FMT in major psychiatric disorders is insufficient. In the following neuropsychiatric disorders, the effectiveness of FMT has been examined.

FMT can be an effective therapeutic technique for irritable bowel syndrome,[66] with the remission rates of irritable bowel syndrome case series ranging from 36–89%.[58] The neurological complaints of three multiple sclerosis patients have disappeared after FMT, and their quality of life has improved.[67] It has been reported that autistic children have benefited from FMT and their symptoms have regressed.[65] Any Parkinson's disease cases treated with FMT have not been reported yet. However, the chronic constipation of a patient with Parkinson's disease has been treated with antibiotic treatment; the patient's neurological symptoms completely disappeared after antibiotherapy.[68]

FMT is a reliable, easy, and cost-effective treatment[69] and its side effects are usually mild. In some cases, diarrhoea presented a day after FMT application, and only a few cases have reported constipation, gas, and abdominal discomfort.[63] In a recently published comprehensive review article, the serious side effect rate was determined to be 2%.[70] In this study, FMT was applied to all cases of *CDI*. In *CDI* cases, serious side effects such as infection, sepsis, and bowel perforation are more likely to occur, therefore this study does not reflect the neuropsychiatric sample. It can be said that FMT is a much more reliable treatment in cases with a neuropsychiatric disorder however the information obtained from the neuropsychiatric patient sample is composed of a small literary anthology (there were not any randomised controlled trials included). There is a need for more evidence and testing in terms of the effectiveness and reliability of FMT.

FMT is often viewed as an undesirable treatment,[64] therefore, some patients respond negatively. Women and young people are more reluctant than men and the elderly to try FMT and 33% of patients are unwilling to pay for FMT.[71] As an alternative to FMT, oral capsule treatment has been tried. After centrifuging and placing the stool in swallowable capsules, it is frozen at -80°C. Fifteen frozen capsules per day are taken orally.[72]

CONCLUSIONS

The impact of bacteria that live in the intestines on human health and especially on neuropsychiatric functions has been the centre of interest in the scientific world over the past 5 years. Studies on the microbiome–brain axis comprise mainly GF mouse experiments and due to the large number of bacteria in the human intestinal microbiota, it is difficult to carry out randomised controlled trials. Scientists uncover new treasures from this 'gold mine' every day. The beneficial effects of probiotics have been shown many times in experiments with mice however any positive effect of the probiotic bacteria *L. rhamnosus* on psychological parameters in healthy volunteers has not been found.[73] The micro-organism-immune system–diet–brain relationship will be revealed gradually and in the near future, psychomicrobiotics will be used in the treatment

of neuropsychiatric disorders. Additionally, FMT, being a cheap, easy, and reliable treatment method will be used commonly. The gut–brain axis seems to be the missing link that will provide a full understanding for the treatment of neuropsychiatric disorders.

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WHAT DO WE MEAN BY INNOVATION IN HEALTHCARE?

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ABSTRACT

Just as in other modern industries, the term 'innovation' in healthcare has become associated with new developments in the field that allow for improvements in solving problems, in this instance, healthcare problems. This paper seeks to clarify what the term truly means. To address this issue, we first define innovation as a general term, then define what innovation means in the context of the healthcare industry. To better understand what may be considered 'innovative' in healthcare, we suggest criteria for innovation and identify potential challenges to newly introduced innovations in the field.

INTRODUCTION

'Innovation' denotes new, better, more effective ways of solving problems. Adopted from the business, technology, and marketing industries, the term has been used to describe policies, systems, technologies, ideas, services, and products that provide solutions to existing healthcare problems. With many dynamic methods and approaches available, the word 'innovative' has been coined as a buzzword in the field of healthcare. What has been absent from discussions around innovation is a clear, common understanding of what the term means. A clear definition is necessary because lack of consensus acts as a barrier to bringing innovation to clinical practice. Due to a lack of clarity and consistency, the term 'innovation' has been frequently used inappropriately to describe different developments within healthcare.

This paper explores what it means to be innovative, how innovation can be understood in the context of healthcare, and how 'health innovation' affects our understanding of developments in the field, particularly in improving healthcare. By defining what innovation is and what it is not, this paper will help clarify the notion of innovation in healthcare.

INNOVATION IN HEALTHCARE: A GENERAL DEFINITION

Innovation itself is not a new concept. The term has made its way into healthcare as a concept adopted from other fields, with a similar definition to those used in business, technology, and marketing. The dictionary definition of innovation is: i) "a new idea, device, or method" and ii) "the act or process of introducing new ideas, devices, or methods."[1] Innovations in healthcare fall under the broader umbrella of social innovations, which aim to solve social issues.[2] Social innovation encourages new approaches to tackle issues of poverty, education, health, and other human development problems by making system-level changes.[3] The World Health Organization (WHO) explains that 'health innovation' improves the efficiency, effectiveness, quality, sustainability, safety, and/or affordability of healthcare. This definition includes 'new or improved' health policies, practices, systems, products and technologies, services, and delivery methods that result in improved healthcare.[4,5] Improvements in research, patient satisfaction, education, and access to care are additional factors to keep in mind. Simply put, the ultimate goal of health innovation is to improve our ability

to meet public and personal healthcare needs and demands by optimising the performance of the health system.[6] In theory, innovations in healthcare should yield scalable solutions and improvements in health policies, systems, products, technologies, services, and delivery methods, in order to improve treatment, diagnosis, education, outreach, prevention, research quality and delivery, and access to healthcare.

'NEW OR SIGNIFICANTLY DIFFERENT': WHAT IS INNOVATION? WHAT IS NOT?

To break down the concept of innovation in healthcare, we must ask: in healthcare, what is an innovation, and what is not? To answer these questions, we must consider that: i) problems in healthcare have resulted in solutions to problems of efficiency, effectiveness, quality, sustainability, safety, and/or affordability of healthcare; ii) solutions that have resulted from problems in healthcare may be considered an innovation because they have solved a problem by introducing a new or significantly different approach, concept, idea, service, process, technology, or product; and iii) not all solutions are innovations, and not all innovations are solutions. Some solutions to problems in healthcare are merely developments within the field.

Just as technological advancements (e.g. email, mobile phone, GPS, etc.) find solutions to the world's communication problems, developments in healthcare seek to address issues in the field. Healthcare is continuously changing and adapting. In order for a solution to a healthcare problem to be an innovation, it must introduce something that is new or significantly different from other solutions in the field. The use of innovation as a general term has led to the dilution of its meaning and how it is understood in healthcare. Without clarity on what innovation truly is, the term is loosely adopted and applied. On one hand, a general definition allows for praise and recognition of positive developments and new ideas, methods, and products in the field of healthcare. On the other hand, without a concrete understanding of what innovation is, we are unable to develop and properly identify new innovations in healthcare.

Omachonu and Einspruch[7] provide a synopsis and explanation of what innovation is, as applied to the field of healthcare. Based on technological innovations, developments in technologies allow for opportunities for product and process innovation. Omachonu and Einspruch's description of product innovation involves the new goods and services within the market. Process innovation, on the other hand, involves the enhancement of the production of goods and services.[7] In healthcare, developments in technologies and practices are evidence-based.[8,9]

ADOPTING AND IMPLEMENTING INNOVATIONS: STAKEHOLDER CONSIDERATIONS AND BARRIERS TO UPTAKE

The three components of innovation, as suggested by Länsisalmi et al.,[10] are that innovation is i) a novelty, ii) an application component, and iii) an intended benefit. An 'intended benefit' should be centred around the receiver of care, the patient, although stakeholder considerations must also be considered. Stakeholder considerations are particularly important in regard to the adaption and adoption of innovations.[10] With these components in mind, the 'innovation process' can be understood by analysing the needs, wants, and expectations of stakeholder groups. With patients at the forefront, other stakeholders to consider include physicians and other care givers, organisations, innovator companies, and regulatory agencies. When health innovation takes place successfully, it addresses three key areas: i) how the patient is seen, ii) how the patient is heard, and iii) how the patient's needs are met.

Even if the criteria are met, barriers remain for the recognition and uptake of innovations in healthcare. The process of diffusion is social and interactive and therefore requires collaboration, communication, and knowledge exchange between those involved within the system.[11] As such, adoption and implementation in healthcare involves multiple individuals, constraints, and factors that are specific to the social, political, policy, economic, institutional, and cultural context of a particular system.[3,8,12,13] The Harvard Business Review explains that innovation in healthcare, while complex, can be understood based on three categories: i) consumer focus, ii) technology, and iii) business models. Within these three categories, the factors that affect uptake and diffusion in healthcare include: stakeholders and their interests, funding and cost, policy and government regulations, competition and other developments that affect uptake in healthcare technologies, consumer views and opinions, and accountability.[11,14]

Each of these factors affects not only whether or not something is considered to be an innovation, but whether or not it is accepted and adopted in the field of healthcare. In other words, uptake requires that stakeholders see a relative advantage in adopting and implementing the innovation. However, relative advantage on its own does not guarantee adoption and implementation.[5] Other considerations include capacity, compatibility, complexity, trialability, observability, reinvention, and risk. Stakeholders are more likely to adopt an innovation if they have the individual and organisational capacity to do so, it is compatible with their interests, simple enough to adopt easily, can be tested on a small scale, it is observable, can be refined to suit their needs, and requires minimal risk.[5,15]

CONCLUSION

The first step in solving a problem is to create a plan for change. In preparation for change within healthcare, there is often an anticipation that change will result in an improvement or solution for an existing problem. In reality, not all changes result in a solution or improvement, much less an innovation. Change may in fact produce little to no improvement or benefit, and in some cases, may unexpectedly yield negative results or outcomes. For this reason, introducing a change, whether big or small, cannot be considered innately 'innovative'. Observing the effects of change, whether it results in failure or success, is one of the keys to improvements and developments in healthcare. When the change is something new, or involves the process of introducing something new, and results in a benefit of improvement in the field of healthcare, the criteria for innovation in health has been met.

Beyond satisfying these criteria, newly introduced ideas, methods, products, and/or the process of introducing something new in healthcare, face the additional burden of being accepted within the field. An innovation must be something truly new or at least significantly different, applicable to healthcare, and provide a benefit to the field, with patients at the centre. In addition to these hurdles, external demands of stakeholders, funders, regulators, competitors, consumers, and general accountability must be met. Innovation in healthcare is complex, constantly changing, and exclusive of a large interwoven network of factors and considerations. Allowing a flexible or broad application of the term provides an overly inclusive terminology and restricts the exploration of new thinking and adoption of true innovations. By understanding what is innovative and what is not, as well as the barriers to adoption and implementation, we are better able to conceptualise what is needed in the field to bring about long-lasting and large-scale developments for increased efficiency and effectiveness in healthcare.

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THE FUTURE OF MOBILE HEALTH APPLICATIONS AND DEVICES IN CARDIOVASCULAR HEALTH

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ABSTRACT

Mobile health (mHealth) is the utilisation of mobile technologies in healthcare and has particular relevance in improving lifestyle behaviours which may ultimately reduce cardiovascular disease risk. Various intervention studies for example integrate self-monitoring of diet and physical activity with text messaging systems to improve intermediate outcomes. Currently the future progress of mHealth technologies in formal diagnostic and therapeutic roles is pending and includes the need to validate and standardise accelerometer and heart rate data from various devices. Data also needs to be integrated from such devices into the medical record system to facilitate communication between providers and patients. Although short-term behaviour changes have been found with technologies such as Fitbit® (Fitbit, Inc., San Francisco, California, USA), whether such technologies/interventions lead to sustained behaviour change and reduced risk of myocardial infarction and death remains to be seen.

Keywords: Mobile health (mHealth), cardiovascular disease, prevention, behaviour modification, health technology.

INTRODUCTION

Cardiovascular disease is the leading cause of death and disability among men and women in the world and the number of deaths per year caused by the disease is expected to rise to 22.2 million by 2030.[1] Identification of modifiable risk factors is essential in the prevention of cardiovascular disease. Mobile health (mHealth), the use of mobile computing technologies in healthcare mostly through smartphone applications (apps) and wearable devices, is a rapidly growing field with many apps focussed on cardiovascular disease prevention through behaviour modification.[1,2] Most apps focus on three major topics including: dietary management, physical activity promotion, and smoking cessation. The purpose of this review is to examine the current state of mHealth smartphone apps and wearables in the context of improving the cardiovascular behaviours suggested by the American Heart Association's (AHA), 'Life's Simple 7', which are: blood pressure control, cholesterol management, blood sugar management, smoking cessation, weight control, physical activity promotion, and healthy eating.[3] All of the Simple 7 are amenable to modification through mHealth interventions by varying degrees; diet, activity, and smoking cessation have an impact on weight, cholesterol, blood sugar management, and blood pressure.[2,4-6]

We searched PubMed, MEDLINE, Web of Science, and the World Wide Web from inception to January 2016. We selected studies and articles

relevant to the topic of mHealth in relation to physical activity, dietary management, and smoking cessation. New trends in mHealth were also evaluated. Studies that did not include smartphones or wristband devices were excluded. This review was restricted to certain validated studies and randomised controlled trials focussed on using new mHealth technologies with a sustainable impact. We focussed on a selection of manuscripts that were considered the highest impact based on the three authors' reviews. The authors undertook an iterative process to screen articles and select papers with the highest impact. Table 1 presents a summary of the selected articles discussed.

CHANGES IN PREVALENCE OF MOBILE HEALTH TECHNOLOGY USE OVER TIME

Smartphone access and utilisation of health apps are quickly rising. According to the Pew Research Center based in Washington DC, USA, approximately 64% of adults possess a smartphone in the USA and 68% of these access the internet through their devices. An estimated 62% of smartphone owners utilise their phone to access health information and obtain education about diseases and health conditions, while 57% utilise their phone to perform online banking.[7] Approximately 100,000 mHealth apps on iTunes® (Apple Inc., Cupertino, California, USA) and Google Play™ (Google Inc., Mountain View, California, USA) are available, as well as ≥400 wearable activity monitors.[8] These figures are expected to further increase as technologies advance.[9,10]

MOBILE HEALTH INTERVENTIONS TO INCREASE PHYSICAL ACTIVITY

According to a recent study, only half of American adults met the physical activity guidelines promoted by the AHA.[1] Physical activity has many benefits in reducing low density lipoprotein cholesterol, blood pressure, and fasting glucose while maintaining weight loss and psychological wellbeing.[11] mHealth apps can engage participants to encourage physical activity through reminders and goal-setting. In a recent meta-analysis, pedometers were found to increase physical activity by 27% compared with baseline; pedometer users also experienced slight decreases in BMI (0.4 kg/m^2) and 4 mmHg decreases in systolic blood pressure. These decreases are similar to those seen in studies evaluating blood pressure-lowering drugs.[12] Clinical trials use interventions of varying sophistication, ranging from a smartphone app to wristband or waistband accelerometers and sophisticated health coaching programmes. An example of a low-resource study was the SMART MOVE trial; a randomised, open label trial of 78 Android™ smartphone users who were assigned to either lifestyle improvement education versus education and smartphone app (Accupedo-Pro Pedometer) which gave automated feedback on daily step counts and facilitated goal-setting. After 8 weeks, those who were assigned to the intervention group (the smartphone app group), walked approximately 1,000 more steps per day than the group who did not receive the app.[13] Although the cost was low because it did not involve investment in a separate pedometer, it was limited to smartphone users with the Android operating system. On the other hand, the mActive study was more sophisticated because it provided 42 participants with wristband pedometers (which did not provide step counts) and randomised them to automated smart-texts (versus none) that delivered physician-written, theory-based texts 3-times per day based on 16 personal factors and real-time data to encourage daily physical activity.[10] The results were more impressive, with an increase of 3,300 step counts documented in the intervention group versus blinded controls. Overall, it appears that more aggressive, personalised interventions may have a larger effect size on promoting physical activity, although this remains to be proven in a large, adequately powered study.

The introduction of wearable devices such as Fitbit and Apple Watch® provide further opportunities in physical activity tracking and promotion. However, there are limited studies that show the sustainable impact on improving physical activity over time. A study of 67 adults suggested improved physical activity at 6-week follow-up after utilisation of Fitbit device for instant feedback on performance.[14] Another trial of postmenopausal overweight women also showed similar findings; those in the intervention group with a Fitbit demonstrated increased physical activity and adherence to their steps goal after a limited period of time.[15]

DIETARY MANAGEMENT USING MOBILE HEALTH TECHNOLOGIES

Although physical activity can facilitate weight loss, such programmes by themselves have not proven particularly successful at leading to weight loss.

Table 1: Selected studies on the impact of mobile health on physical activity, dietary management, and smoking cessation.

Mobile health and physical activity			
Authors	**Design**	**Sample and condition**	**Findings**
Turner-McGrievy et al. 2013[21]	Longitudinal cohort	N=96, overweight adults	Lower BMI at 6 months after using app for self-monitoring of physical activity
Glynn et al. 2014[13]	Randomised controlled trial	N=139, in primary care setting. Utilisation of smartphone app	Increased physical activity over 8 weeks
Martin et al. 2015[10]	Randomised controlled trial	N=48, in ambulatory cardiology centre. Utilisation of pedometer and text messages	Increased physical activity with automated tracking–texting intervention
Chow et al. 2015[9]	Randomised controlled trial	N=710, patients with coronary artery disease	Lifestyle-focussed text messaging improved physical activity and reduction in smoking
Wang et al. 2015[14]	Randomised controlled trial	N=67, overweight and obese adults	Utilisation of Fitbit increased physical activity after 6 weeks
Cadmus-Bertram et al. 2015[15]	Randomised controlled trial	N=25	Wearable device encouraged improvement in physical activity adherence
Mobile health and dietary management			
Authors	**Design**	**Sample and condition**	**Findings**
Burke et al. 2012[20]	Randomised controlled trial	N=210, overweight/obese adults recruited from community	Weight loss and adherence to self-monitoring at 24 months after utilisation of tracking device with feedback
Wharton et al. 2014[22]	Longitudinal cohort	N=57, weight-stable adults from a campus community	Smartphone app improved dietary self-monitoring
Jospe et al. 2015[19]	Cross-sectional survey	N=180, from sports dietitians. Utilisation of diet apps	One-third of sports dietitians utilise smartphone diet apps for nutrient practice
Mobile health and smoking cessation			
Authors	**Design**	**Sample and condition**	**Findings**
Free et al. 2011[25]	Randomised controlled trial	N=5,800, smokers	Automated text messaging improved smoking cessation rates at 6 months

A cornerstone of weight management is restriction of caloric consumption; mHealth apps may for example help with this endeavour by providing electronic diaries that facilitate calorie counting with integrated food databases.[16,17] Many studies have focussed on the impact of dietary self-monitoring and have found a significant association with weight loss.[18]

A cross-sectional online survey reported 33% of sport dietitians used diet apps to assess and track dietary intake, and smartphone apps were rated better than traditional assessment methods by 47% of participants.[19] The SMART trial presented promising results of weight loss at 24 months by utilising a personal digital assistant with a feedback system focussed on self-monitoring and recording food intake.[20] Another randomised study among overweight subjects reported decreased energy consumption in subjects using a dietary monitoring app.[21] Weight loss was documented at 8 weeks after monitoring dietary intake through the mobile app 'Lose It' (FitNow, Inc., Boston, Massachusetts, USA) in another small study.[22]

Current apps may benefit from additional scientific rigour: one study concluded that most apps only included 19% of the 20 behavioural strategies in evidence-based interventions.[23] It is unclear if isolated dietary apps or interventions have a sustainable impact on weight loss. Although validation studies are needed, the combination of dietary and physical activity self-monitoring with individualised behavioural modification plans may hold the most promise in not only helping to lose weight, but also sustaining the weight loss.

SMOKING CESSATION

Smoking cessation is another risk reduction behaviour that mHealth strategies have been used to promote.[24,25] According to the World Health Organization (WHO), tobacco use is the leading cause of preventable and premature death worldwide. Smoking cessation is associated with reduction in cardiovascular mortality by approximately one-third.[11] Smartphone apps have a lower barrier to entry, available at minimal cost to those who already use smartphones, and are preferable for many individuals compared to a smoking cessation hotline.[26] Many mHealth studies focus on SMS text-based smoking cessation services with tailored reminders and messages as well as telephone counselling.[27] The txt2stop smoking cessation study randomised 5,800 subjects either to a mobile phone smoking cessation programme with motivational messages and behaviour change support or to a control group that received text messages unrelated to quitting. The intervention more than doubled the chance of biochemically-verified continuous abstinence at 6 months in experimental groups compared with control (10.7% versus 4.9%).[25] The long-term impact of the intervention however was not studied. Despite the promise of such apps to help the success of smoking cessation with little cost, they rarely adhere to established evidence-based tactics, and therefore may be underachieving.[28] A combination of various lifestyle interventions may work together in synergy. Several studies have shown a significant increase in smoking cessation success by adding exercise as an additional intervention. These combination programmes have demonstrated success at ≥1 year.[29,30] Other arenas of mHealth integration and synergy include incorporation of social media and wearable devices into tobacco control programmes.[31]

NEW TRENDS IN MOBILE HEALTH TECHNOLOGIES

The growing field of mHealth creates a platform for innovation and new trends in capturing patient health data, providing new ways to promote healthy lifestyle. Several major technology companies including Apple Inc., Google Inc., and Samsung Group (SAMSUNG, Suwon, South Korea) have integrated new approaches for health activity tracking in the design of their smartphones.[32,33] Apple's HealthKit™ platform is a central portal that organises physical activity data from the phone's accelerometer as well as other health information from associated apps, such as various blood pressure monitors and scales. Large scale electronic medical record systems such as Epic and Cerner are also working with Apple to integrate with HealthKit.[34] Physical activity quantification is expanding beyond steps; for example, companies like FocusMotion (Focus Ventures, Inc., Los Angeles, California, USA) are expanding the portfolio of activities to include weight lifting and yoga. Heart rate is increasingly being offered on several popular wristband devices to measure performance and caloric consumption although such data have not been validated in peer-reviewed literature. A new paradigm of 'smart clothing' allows for continuous data collection from the chest during work-outs and typically yields more accuracy than wrist-based devices during physical activity in detecting heart rate.

As accelerometers become more versatile and heart rate sensors become increasingly accurate and available, the apps of these data streams also increase beyond fitness into prediction algorithms. To manage such data, companies such as Validic (Motivation Science, Inc., Durham, North Carolina, USA), Human API (Human API, Redwood City, California, USA), and Open mHealth (San Francisco, California, USA) can facilitate the aggregation of cloud-based mHealth data for apps in various analytic models. To further expand the possibilities of such data to improve health outcomes, these services would need to integrate with electronic medical record systems. Patient providers may also benefit.[35,36] For example, it may lead to feedback systems which objectively quantify behaviour data from mHealth devices to inform providers how to best treat their patients with a personalised wellness approach.[36]

THE POTENTIAL TRANSFORMATION OF MOBILE HEALTH FROM CONSUMER GRADE DEVICES TO MEDICAL GRADE INTERVENTIONS

mHealth technologies are increasingly being utilised in translational healthcare research settings, for example to provide early warning signs for seizures by monitoring the autonomic nervous system in real-time.[37] This potential however, needs to be matched with infrastructure changes that allow such data to sync with the electronic medical record and healthcare system as a whole.[33] This integration will require continued validation of

current technologies, standardisation of data outputs, and integration of mHealth data streams into the clinical decision-making processes.[38,39]

Future research should be aimed at evaluating consumer wearables and smartphones for medical use, given their ubiquity and potential utilisation in the clinical setting.[40] It naturally follows that not everyone will have the exact same device or smartphone, therefore future research efforts are needed to standardise the outputs obtained from multiple devices in order to achieve generalisable recommendations for digital health interventions. Ultimately such efforts will help clinician assessments of health and disease, as well as allow them to recommend specific programmes or apps for patients needing lifestyle changes to improve cardiovascular health.

In addition to healthcare integration, more clinical trials are needed to confirm findings from smaller studies at various centres and demonstrate generalisability.[25,41-43] In addition to the studies already mentioned, a recent success has been the TEXT ME trial which implemented a simple one-way (no interaction) text-messaging reminder system of individualised messages to motivate certain lifestyle changes based on patient need. The study included 710 patients with coronary heart disease randomised to text messages versus usual care, followed over 6 months, and showed significant reductions in low-density lipoprotein cholesterol and blood pressure.[9] While this and other similar studies hold promise, the duration of benefit and translation of outcomes remain in question. Nonetheless, costs are minimal when considering this type of fully automated, one-way intervention, and could be easily integrated into a healthcare framework.

mHealth programmes represent the next wave of biotechnologies after medical devices to benefit from industry and academic partnerships. Such partnerships can help to ensure that validation studies are conducted with appropriate design and validation of hardware against the gold standard. For example, devices such as the Fitbit Charge HR have yet to provide any validation data on the accuracy of their heart rate monitor; as such the heart rate data cannot be used in a medically meaningful way until this occurs.

There are several limitations of this article. It is a narrative review focussed on highlighting the relevant studies discussing the use of mHealth technology in behaviour change and cardiovascular risk reduction. As such, the review is not a comprehensive analysis of all such studies; certain studies that were not deemed high enough impact by the authors were excluded. mHealth technologies and devices are rapidly changing which limits reproducibility and quality control. Novel interventions with clinical impact may, to a certain extent, lose relevance over time as newer smartphones, wristbands, etc. are released and older versions are phased out.

CONCLUSION

mHealth technologies offer promise with regard to the management and prevention of cardiovascular disease via risk factor modification. Various studies have been published to demonstrate efficacy in promoting small but substantial behaviour changes and improvements in health status. Despite this, the potential is scattered amongst myriad consumer-grade devices which do not have validation, and although large-scale buy-in from payers is possible, it has not yet occurred. The next steps include improved analytics, evaluation, and advancement of newer sensors such as heart rate monitors, and larger clinical trials. Private and academic partnerships will be vital to the future of the field, and the potential public health benefit is very large given the ubiquity of such devices in the world.

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New Breast Screening Method Shows Promise

TOMOSYNTHESIS, a new method of screening for breast cancer, has shown promise following approval of its use from the US Food and Drug Administration (FDA). The novel technology, which produces three-dimensional (3D) mammograms to screen for breast cancer, has reduced the rate of patients requiring further testing by 30–40% in the USA.

Mortality rates from breast cancer have decreased in recent decades; it is believed that early detection through screening and improved treatments are largely responsible for this. The early detection of breast cancer before it has spread to neighbouring tissues makes the disease far easier to treat, with a greater likelihood of avoiding mastectomy or chemotherapy. Mammograms enable the detection of tumours in the breast tissue before they are big enough to be felt or seen.

Tomosynthesis uses similar technology to regular mammograms to render a 3D image of the breast. The image is produced by an X-ray tube that takes about 11 separate images of thin slices of breast in the space of roughly 7 seconds, moving in an arc. The images are then spliced together using a computer. The 3D images that are created could help to overcome the challenges faced when using regular mammograms which only take two X-rays: one facing from top to bottom, the second from one side to the other. Assembling images from these X-rays can cause problems, as overlapping breast tissue can be misinterpreted as a lump or mass.

Although tomosynthesis seems to be proving a positive step forward in breast cancer screening, it is not yet clear whether the 3D representations are more accurate than two-dimensional (2D) mammograms as no quality studies have been undertaken. The advantages found so far relate to clearer representation of the data, allowing clinicians to more easily see whether there are tumours present, and if there are more than one. Disadvantages include the higher cost of the equipment, which is currently only available in a very limited number of hospitals, and the increased radiation dose when combined with a 2D mammogram.

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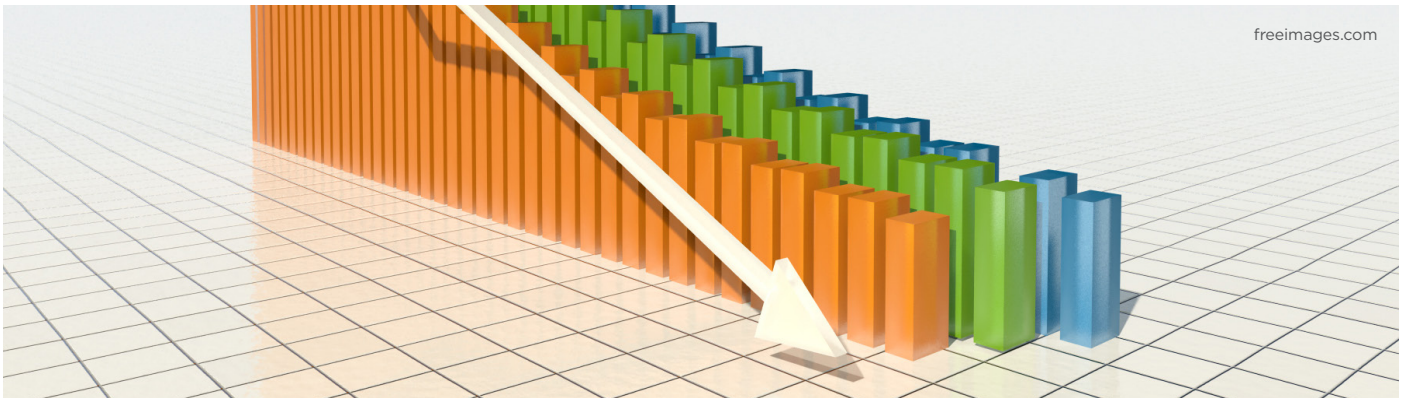

Efficacy of Light Therapy for Prostate Cancer Patients Indicated

LIGHT therapy could provide an effective, non-surgical treatment for localised prostate cancer patients. According to the results of a recent trial, the procedure was shown to destroy prostate cancer cells without causing damage to healthy surrounding tissue.

Currently, active surveillance with prostate specific antigen tests, digital rectal exams, or prostate biopsies is utilised for men with localised prostate cancer. If the cancer does become more severe, it may be treated through radiation therapy or prostatectomy, both of which can cause significant adverse effects including urinary incontinence.

The researchers, led by Prof Mark Emberton, University College London, London, UK, undertook a Phase III trial to test vascular-targeted photodynamic (VTP) therapy in localised prostate cancer patients. During this procedure, a light-sensitive bacteria-derived drug named WST11 is injected into the bloodstream. The drug then releases free radicals, following its activation by laser, which kill cancer cells in the prostate.

In the study, 413 men diagnosed with localised prostate cancer and under active surveillance were recruited from 47 treatment sites in 10 European countries. The patients were separated into two groups: 206 were randomised to receive VTP while 207 remained under active surveillance. The patients were followed-up for 2 years, with prostate specific antigen (PSA) testing and assessment of urinary and erectile functions undertaken at 3-month intervals, and prostate biopsies at 12 and 24 months.

Subsequent to this follow-up period, it was found that 49% of VTP-treated patients entered complete remission, whereas this outcome was only observed in 13.5% of those under active surveillance. Furthermore, while radical therapy was necessary in 30% of the active surveillance group, just 6% received such treatment amongst the VTP-treated patients. Additionally, patients in the VTP group had double the time-to-progression (from 14 to 28 months), and were 3-times less likely to see the cancer progress. No significant side effects were present in the VTP-treated patients after 2 years.

"These results are excellent news for men with early localised prostate cancer, offering a treatment that can kill cancer without removing or destroying the prostate," stated Prof Emberton. "This is truly a huge leap forward for prostate cancer treatment, which has previously lagged decades behind other solid cancers such as breast cancer."

> "These results are excellent news for men with early localised prostate cancer, offering a treatment that can kill cancer without removing or destroying the prostate."