EMJ EUROPEAN MEDICAL JOURNAL

INNOVATIONS

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EDITORIAL BOARD

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Front cover and contents photograph: Dusseldorf, Germany home of Medica 2017. © ewastudio / 123rf.com

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INNOVATIONS 2.1
JANUARY 2018

Welcome

A warm welcome to *EMJ Innovations 2.1*, the first European Medical Journal publication of 2018. Contained within is an independent review of MEDICA 2017 and peer-reviewed articles contributed by authors at the forefront of medical research and advancement, as well as fascinating interviews with some of the game-changing innovators that form the *EMJ Innovations* Editorial Board.

A total of 123,500 visitors attended the 4-day MEDICA trade fair held from 13th–16th November 2017. MEDICA hosted >5,000 exhibitors from 66 countries, and this ever-growing number of international exhibitors proves to be the winning formula used by MEDICA to communicate the importance of continued medical improvement. Alongside welcoming a range of medical innovations, MEDICA presented a variety of forums and seminars, including the first MEDICA Academy, which is dedicated to furthering the training of medical professionals from a plethora of specialities. Details of the key events that unfolded at MEDICA can be found in our extensive Congress Review section.

> *EMJ Innovations 2.1* is a perfect opportunity to discover the next phase of medical breakthroughs destined to change the way patients are treated.

Within the pages of *EMJ Innovations 2.1*, you will find four captivating interviews with members of the Editorial Board, including clinicians who implement and promote the latest inventions to improve patient outcomes, as well as former medical professionals turned full-time entrepreneurs and innovators. The use of innovative technologies for improving patient outcomes has proven to be an effective and thought-provoking approach to healthcare.

Furthermore, *EMJ Innovations 2.1* contains cutting-edge, peer-reviewed articles. The Editor's Pick for this issue is a review penned by Rygiel, which discusses the impact of cardiac remodelling following myocardial infarction, known to contribute to the progression of heart failure. The author outlines and evaluates the use of the injectable calcium alginate hydrogel, Algisyl®, to prevent adverse cardiac remodelling and discusses the new frontier of minimally invasive therapies that injectable biomaterials can offer. Additionally, a research paper by Sudbury-Riley focusses on the recent developments in eHealth technologies and details the importance of health innovations, while presenting an investigation into the eHealth literacy levels of baby boomers. The paper considers whether all populations are able to access life-saving eHealth technology.

EMJ Innovations 2.1 is a perfect opportunity to discover the next phase of medical breakthroughs destined to change the way patients are treated. With much more to discover inside, I hope that you find this issue of *EMJ Innovations* as fascinating and exciting as we do as we avidly count down the days to MEDICA 2018.

Spencer Gore

Chief Executive Officer, European Medical Group

Foreword

Prof Mike Bewick

University of Kent, UK.

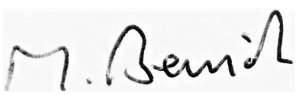
Welcome to the latest edition of *EMJ Innovations*, featuring a wide range of biotechnology-related research. The field of medical innovations continues to expand, building on the success of the 2017 MEDICA trade fair conference, held over 4 days in Dusseldorf, Germany, from 13th–16th November; the event attracted >120,000 professional visitors from across four continents. The trend of portable electronic monitoring of diseases, through wearables, continues, and progress in virtual reality technology and robotics is evident. The industry also strives to support the research and developments of essential new clinical entrepreneurs that drive future health systems.

This current issue contains a plethora of fascinating articles by authors at the forefront of biotechnological science. The breadth of topics covered is exciting, ranging from the impact of 'omics' in bridging the gap between clinical practice and public health by McGrath, through to the use of nanoparticles as diagnostic tools in liquid tumours, as reported by Matias et al. Sudbury-Riley discusses eHealth technologies, but I also wish to highlight the advances in the application to basic biology affecting our ability to regenerate failing organs or biological systems.

The paper by Rygiel is my Editor's Pick for this edition. The author discusses an injectable biomaterial-based therapy for patients with heart failure, Algisyl® implants, examined in the AUGMENT-HF clinical trial, and highlights the benefits and challenges of applying such novel therapies to supplement established pharmacological interventions. Heart failure has been a neglected chronic condition, causing significant morbidity and mortality. There is good evidence that specialist intervention improves clinically monitored outcomes and patient symptom scores. The modification of existing damaged myocardium through this injectable biomaterial-based therapy was shown to offer significant improvement at 6 and 12 months post intervention, superior to current established management. The results are exciting and signal a way forward, both in the long-term management of heart failure and towards the future of regenerative therapies.

Organ transplantation has, so far, offered the only alternative to end-stage organ failure; however, as we advance our knowledge of the very basics of biology and understand the complexity of proteomics, we can start to envision the use of minimally invasive technologies supporting organ failure, and one day reduce the burden on transplantation. As well as overcoming the ethical issues associated with organ transplantation, and the lack of donor organs available, it offers a potentially more economic model for the future. Herein, Rygiel illustrates the complexity of this approach, the challenges of its implementation and adoption, and the importance of quality of life for patients with heart failure.

I am sure you will enjoy and respond to the many fascinating articles in this year's *EMJ Innovations* publication, and I hope they stimulate you in your own research and practice.



Mike Bewick

Independent Healthcare Consultant and found of Iq4U Consulting; Honorary Professor, University of Kent, Canterbury, UK.

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Feature

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MEDICA 2017

MESSE DÜSSELDORF,
DÜSSELDORF, GERMANY
13TH–16TH NOVEMBER 2017

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

Citation: EMJ Innov. 2018;2[1]:12-25. Congress Review.

The Messe Düsseldorf once again opened its doors to attendees of the world's largest medical trade fair, MEDICA, from 13th–16th November 2017. Comprised of medical professionals from hospitals, research, practices, and of course industry, there was a total of 123,500 visitors from over 130 different countries during the 4-day event, showing the high regard in which this trade fair is held by the medical community. MEDICA took place alongside COMPAMED, the leading international market platform for suppliers to the medical technology industry, and continues to be recognised as the place where collaboration between suppliers and their customers begins.

In a statement, Joachim Schäfer, Managing Director, Messe Düsseldorf GmbH emphasised the trend of increasing numbers of exhibitors and visitors from the emerging economies of the world: "Besides the 'classic' target markets of Europe, North America, and Japan, suppliers are also increasingly focussing on emerging economies in spite of some uncertainties. This is because people's willingness to spend on health is increasing with rising incomes in these markets. More and more prosperity-related diseases and greater life expectancies in these countries are additionally driving up demand for medical products and modern treatments."

In total, there were >5,000 exhibitors from 66 countries present at MEDICA 2017. A plethora of cutting-edge developments was on show, including electromedicine and medical technology, laboratory technology and diagnostics, physiotherapy and orthopaedic technology, commodities and consumables, information and communication technology, and medical furniture and specialist furnishings for hospitals and practices. With such broad coverage, MEDICA had something to offer medical professionals of any background.

In addition to the vast range of innovative medical products, devices, and instruments on display throughout the many halls of the Messe Düsseldorf, there was a wide range of new conferences and forums for healthcare professionals to attend to allow them to keep abreast of current developments in key areas. Amongst these was the introduction of the MEDICA Academy, which enabled doctors from all therapeutic areas to undertake further training in imaging,

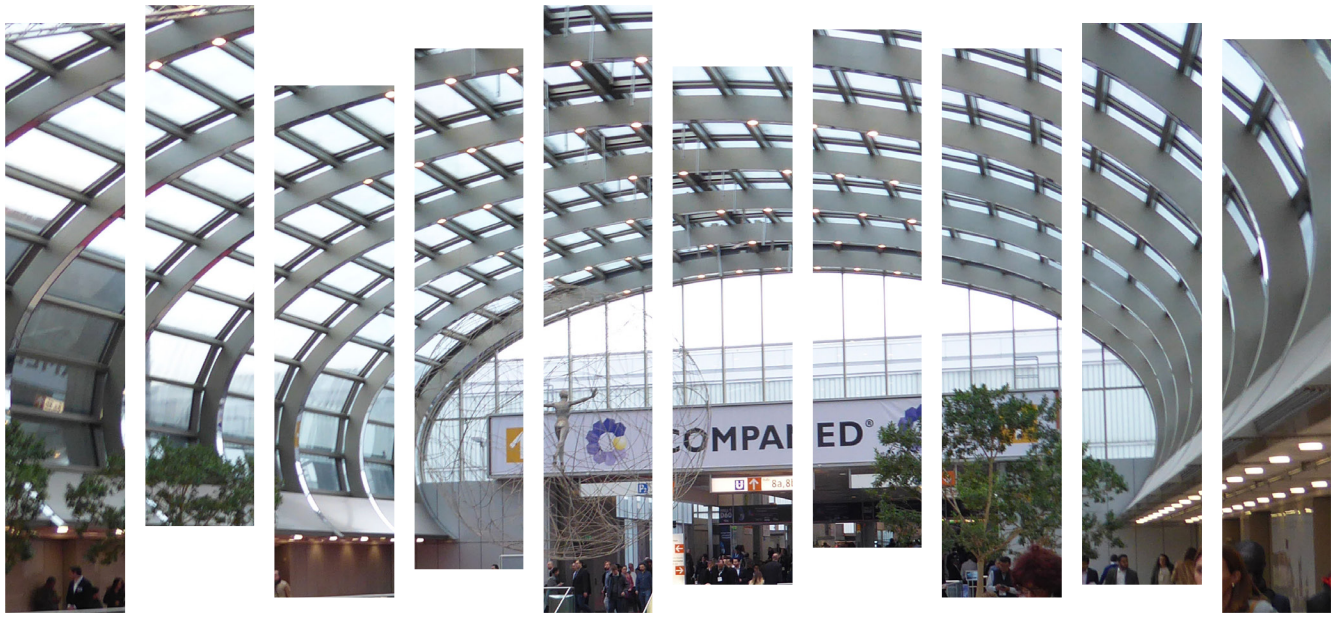
hygiene, and surgical procedures over the 4-day event. On Thursday 16th November, there was a whole day event entitled 'Update your infection prevention measures', focussing on the pressing issue of the spread of infection and increasing resistance to treatment. Presentations about the causes, scale, and strategies in place to attempt to tackle this growing problem also took place during one of the days of the brand new MEDICA Labmed Forum. This particular forum concentrated on the latest trends in laboratory medicine.

There was also great interest from attendees in forums that had continued from previous years, such as the MEDICA Health IT Forum, which included an emphasis on the hot topic of artificial intelligence, and the MEDICA MEDICINE + SPORTS CONFERENCE, focussing on prevention of injury and other developments in sports medicine.

> "Comprised of medical professionals from hospitals, research, practices, and of course industry, there was a total of 123,500 visitors from over 130 different countries during the 4-day event..."

Another new aspect of MEDICA 2017 was the MEDICA Start-up Park, which aimed to give founders of young companies in medical innovations the unique opportunity to network with potential business partners and investors. The MEDICA App competition was a particular highlight, in which the medical applications of 15 start-up companies battled it out to gain first prize. In a fast-paced format, each company representative was given just 3 minutes to make their pitch, before being quizzed for 2 minutes by the watching jury of experts. Following the pitches, the jury had a short period of deliberation before announcing the top three prize winners. A company called 'iSIKCure' won first place for the development of a mobile health exchange platform designed specifically for the health markets in Africa. Along with the prizes from MEDICA, sponsors, and media partners, the winners received substantial media coverage and international recognition, which should greatly enhance their opportunities for future growth.

The next edition of MEDICA will take place from 12th–15th November 2018, and we look forward to seeing even more medical innovations and developments throughout the following year!



The Growing Importance of Wearables in Modern Medicine

WEARABLES were very much at the forefront of the MEDICA 2017 congress, with dedicated sessions at the MEDICA CONNECTED HEALTHCARE FORUM, in addition to The Wearable Technologies Show, which focussed on the very latest developments in the field. Wearables represent a significant advancement in the field of healthcare and are a vital component of medicine's ongoing digital revolution. A MEDICA background article detailed some key areas of focus in the wearables sector.

> "Medical wearables are being increasingly developed in the form of smart patches and will so enable patients to use long-term monitoring products and even receive medication in such a way that is almost invisible to others."

The scope of wearable technology is massive, with >150 million wearables sold globally in 2017 a figure that is projected to rise in the future. Christian Stammel, CEO of WT Wearable Technologies Group, Munich, Germany, explained how wearables are much more ubiquitous today than might be realised, stating: "We define all electronic components that are worn on the body, close to the body, or in the body as wearables." Under this broad definition, it can be seen that the wearables revolution has been underway for a long time, through the use of devices such as pacemakers and hearing aids. Furthermore, there is still significant room for expansion of the wearables market. It is estimated that 400 million wearables will be sold in 2020 and that ≥50% of this figure will be medical wearables.

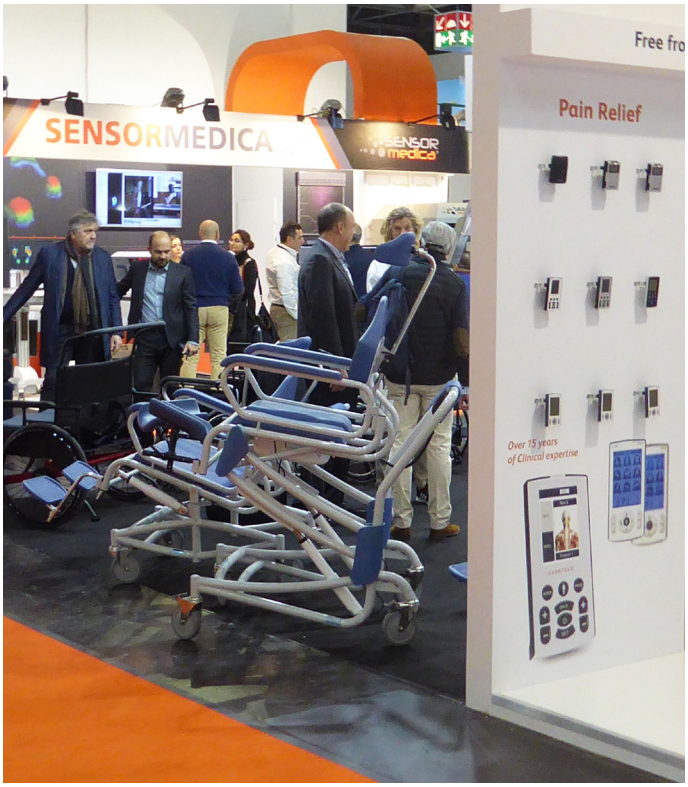
The vast scope offered by wearables is one of the main reasons why the market is predicted to have such significant growth. They provide new options in diagnosis, monitoring, and treatment across a huge range of medical specialities and are useful for rehabilitation, as well as inpatient and outpatient care. One of many wearable innovations on show at MEDICA was a training glove for patients recovering from debilitating stroke. This glove used robotic support and motion sensors to facilitate movements, such as grasping, and improving the perception of touch. Another key aspect of wearables is the ability they offer to monitor vital patient data, either at home or in the clinic. When combined with miniaturisation, this will change the paradigm of monitoring and treatment. Mr Stammel expanded on this, saying: "Medical wearables are being increasingly developed in the form of smart patches and will so enable patients to use long-term monitoring products and even receive medication in such a way that is almost invisible to others."

Looking to the future, there are a number of challenges that must be overcome in order to maximise the impact of wearables, including medical licensing, data protection, and data interoperability. Furthermore, Mr Stammel raised the interesting point that existing hospital and clinic infrastructure would impede the adoption of wearables in that domain, meaning initial benefits were more likely to be seen in the outpatient setting. Bearing in mind the sheer scale of the opportunities offered by wearables, as well as their associated challenges, Mr Stammel concluded: "It is up to the medical profession to openly explore the new opportunities that are being opened up by digital innovations and to indicate their interest to the established suppliers of medical infrastructure solutions for practices and clinics." Fortunately, MEDICA 2017 was the perfect opportunity to do so.

Augmented and Virtual Reality Glasses Benefit Both Surgeon and Patient

FUTURISTIC augmented and virtual reality eyewear was presented for the first time at the MEDICA 2017 conference. By aiding both the healthcare professional and the patient, these innovative technologies demonstrate numerous possibilities for application in the clinical setting, including increasing the accuracy and precision of surgery. Described in a MEDICA press release dated 12th November 2017, two leading wearable products were presented at the event.

> The MEDICA 2017 event highlighted the usefulness of augmented and virtual reality in helping healthcare professionals to improve patient quality of life by increasing accuracy, precision, and effectiveness of procedures and therapies.



Researchers investigated methods of enhancing the operating skill of oncology surgeons when determining the exact location of lymph node metastases to ensure successful removal of the node. A navigation tool, named 3D-ARILE, was developed using an augmented reality system to virtually pinpoint the position of the lymph node through data glasses worn by the surgeon. This innovative procedural aid should make it easier for surgeons to confidently remove the lymph node when preventing metastasis of a malignant tumour.

In addition, methodologies have also been developed that use augmented reality to enable accurate surgical procedures to be performed on the ears. As well as allowing precise intraoperative measurements for middle-ear prostheses, augmented reality has also been used for simplification of cartilage trimming during an operation to close the eardrum. The surface of interest in the situs is virtually marked under a microscope, which can then be displayed through the surgeon's binoculars using augmented reality when cutting the eardrum. Not only does the use of augmented reality in this setting assist the surgeons and increase accuracy, it may also reduce the risks associated with such invasive surgery.

Moving the focus towards the patient, an exercise training device for use in medical rehabilitation centres has been developed which combines simple exercises with virtual reality glasses. Used as a method to strengthen the back muscles, the patient moves on the device according to the virtual trajectory shown via their glasses, having a desirable effect on muscle group training. A similar technology was also shown to be possible using a massaging armchair and has the possibility of assisting and comforting patients with muscle pains.

The MEDICA 2017 event highlighted the usefulness of augmented and virtual reality in helping healthcare professionals to improve patient quality of life by increasing accuracy, precision, and effectiveness of procedures and therapies. Many companies are investing in such technology and virtual reality systems may soon be implemented into everyday clinical practice.

Innovative Technology Aids Detection and Diagnosis

INNOVATIVE wearable products and applications that can be used to diagnose and monitor health conditions were a topic of interest at the MEDICA 2017 event. According to a MEDICA 2017 press release dated 12th November 2017, there are many new products in the wearable technology sector, as well as a range of portable applications that can be used to efficiently assist patients and medical professionals.

Moving away from the common fitness-tracking applications, the wearable technology sector has evolved greatly in recent years and novel medical products are constantly being developed. For example, a glove has been created that uses sensors on the palm of the hand to predict seizures by consistently measuring data and transmitting the information to the patient's doctor. By recording indicators like skin conductivity, muscle tone, heart rate, blood pressure, and temperature, the gloves can be used by doctors to better assess symptoms and assist their diagnoses. Patients with other neurocognitive conditions can also benefit from wearable technology, including alleviation of depression by application of a small electrical shock via a headset; this technology is also being investigated in Alzheimer's disease patients.

One of the most important topics in the field of wearable technologies at MEDICA 2017 was the use of smart patches. Also known as intelligent patches, these wearable products can monitor vital signs when applied to a patient's skin. The patches have been used to measure the process of wound healing by recording temperature changes and communicating any irregular measurements to the patients or doctors via an app. Physical activity is also recorded by the device and, to encourage physical exercise, motivating messages were also directed to the patient's smartphone in response to changes in physical activity.

> By positively impacting therapy, prognosis, and hospital visit duration, wearables may have great benefits for patient survival, as well as health services around the world.

Other innovative applications include cloud-based voice services combined with health programmes. As well as answering personal health questions, the voice service can initiate actions that will aid the patient's everyday life and enhance their quality of life; for example, mattress pads can be connected to the software and heated on request. To assist diagnosis and treatment of potentially life-threatening cardiac conditions, app-based ultrasound technology has also been developed to enable physicians to perform sonography tests in any situation. The technology works by activating the corresponding app on a smartphone and connecting it to a USB probe, which contains the system hardware. The wide utility of this device makes it invaluable, particularly in a preclinical emergency setting. By positively impacting therapy, prognosis, and hospital visit duration, wearables may have great benefits for patient survival, as well as health services around the world.

Sports Medicine Racing Towards the Goal of Personalised Medicine

INDIVIDUALISED medicine was at the heart of a wide range of discussions held at the MEDICA MEDICINE + SPORTS CONFERENCE, an event celebrating its 5th anniversary as part of the MEDICA trade fair 2017, in Düsseldorf, Germany. In an increasingly digital age, the amount of individualised data available for analysis is unprecedented; a fact which, as the conference showed, the world of sports medicine is certainly using to its advantage.

A plethora of studies was presented as part of this event, with topics ranging from the latest in medical apps to the importance of sleep for tissue regeneration, injury prevention, and sporting performance. Prof Yannis Pitsiladis, University of Brighton, Brighton, UK, used this opportunity to showcase his work with the SUB2 Marathon Project, a programme he founded with the goal of supporting top athletes to complete a marathon in <2 hours. By taking an incredibly personalised approach to training, including the analysis of genetic data, transcriptomes, metabolites, proteomes, and epigenomes, Prof Pitsiladis hopes to push human sporting performance to new heights and promote 'clean running'.

How personalised medicine relates to injury recovery was also a pertinent subject of discussion. Dr Götz Welsch, the Team Doctor at Hamburger SV football club, discussed his methodology regarding when to allow players to 'return to activity', 'return to play', and finally 'return to competition'. This discussion was made all the more poignant in a following discussion by Prof Claus Reinsberger, Paderborn University, Paderborn, Germany regarding head injuries. The consequences of this form of injury are often underestimated in sport because the severity of head injuries often only becomes apparent the day after the damage was sustained. With sideline-diagnosis still largely dependent on pupil reflex tests, Prof Reinsberger introduced a safer diagnostic method in his presentation: 'Assessing Concussed Brains Between Clinic and Technology'.

> Ultimately, this conference sought to emphasise that exercise is itself a form of medicine, showing its remarkable benefits not only for mental health, but also for cardiovascular disease and even many forms of cancer.

Digital innovations were, naturally, at the forefront of this conference experience, with an enormous range of technology being showcased to supplement patients' sporting experience. Highlights here included a 'smart running coach', which operated based on biomechanical data, as well as devices for the real-time analysis of cardiac arrhythmias.

Ultimately, this conference sought to emphasise that exercise is itself a form of medicine, showing its remarkable benefits not only for mental health, but also for cardiovascular disease and even many forms of cancer. A growing dialogue between sports medical experts and healthcare professionals is paramount to ensuring a balanced, interdisciplinary approach to injury and disease.

Chatbot Allows Conversation-Like Communication for Young Women with Menstruation Questions

COMMUNICATION technology has changed radically in recent years, particularly in the last decade. With instant messaging across many different platforms becoming an integral part of everyday life, this platform presents an incredible opportunity for the medical field. A press release from this year's MEDICA congress highlights how an interactive chatbot is now being used by young women to quickly and easily answer questions about menstruation.

Izzy, an interactive chatbot accessed via Facebook messenger, allows young women to talk to 'her' about their menstrual cycle. This programme, specifically targeted at young women who are growing up in social environments where talking about pregnancy and menstrual cycles can be particularly difficult, is not designed to prevent pregnancies but to predict menstruation and ovulation cycles. By the end of August 2017, Izzy had received 750 comments and >1,000 shares on Facebook. This may seem like a bizarre way of communicating medical information, but by requiring only very little information and providing the comfort of not having to have the often-perceived embarrassing conversation with someone face-to-face, Izzy is meeting the needs of those unable, or too nervous, to seek answers to their questions in person.

> Izzy, an interactive chatbot accessed via Facebook messenger, allows young women to talk to 'her' about their menstrual cycle.

Interaction between the user and Izzy is said to be totally different to any other software currently available. Izzy differs from apps and other software in that there is no need for installation and communication takes the form of a real-time conversation rather than a questionnaire or flowchart.

Currently, Izzy is only English speaking, with the majority of users from the UK or USA, but in spite of this, there have also been a number of users in Germany. It is hoped by Izzy's creators that eventually this platform could be expanded to also be a marketplace for feminine healthcare products as described by Dr Hajnalka Hejja, CEO of Smart Health UG, Berlin, Germany: "Our plan is to develop specific services with companies whose target group is female."

The Digital Revolution Is Here!

THE DIGITALISATION craze in medicine is in full swing, according to a press release from this year's MEDICA congress. The implementation of information technology and precision medicine are examples of how the digitalisation of medicine is beginning to empower patients, as well as aiding medical professionals to carry out their jobs with increasing accuracy. Prof Erwin Böttinger, Chief Executive Officer of the Berlin Institute of Health, Berlin, Germany, presented a keynote speech at the MEDICA HEALTH IT FORUM as part of a panel discussion titled: 'The future is digital: How data and analytics will transform the healthcare market.' A summary of the discussion was presented in a press release from the congress.

The idea of a 'health cloud' was very much at the heart of the debate session, with the aim of collating all patient data onto one patient-controlled system, accessible anywhere at any time. It is hoped that the analysis of this patient data alongside clinical study information will allow for matchmaking between eligible patients and upcoming studies. This process would enable patients, with guidance from their doctors, to make informed decisions about which therapy path may be the most beneficial for them. The main obstacle highlighted was the transfer of data between sectors, which if not addressed, would hamper the progress of such a potentially national or international network.

The benefits of a system with detailed, genomic patient information have already been demonstrated in the USA. Clopidogrel, an anticoagulant prescribed to those having undergone coronary angioplasty, is inactive in one quarter of patients; as such, these

individuals are still at high risk of infarction, stroke, and other cardiovascular illnesses due to the beneficial effects of clopidogrel not being realised. However, an individual's resistance to clopidogrel can be determined by genetic testing. In the USA, software has been developed to allow a patient's genetic information to be screened almost instantly on a doctor's computer. Provided the genetic information is available, a doctor considering prescribing clopidogrel can utilise the patient's electronic file and instruct the programme to screen for a genetic predisposition to clopidogrel resistance. If the patient is resistant to the drug, a message will notify the doctor via their computer and an alternative solution will be suggested, preventing the prescription of a drug which will not help the patient.

> "This is truly an exciting time for medical innovation!"

Such comprehensive cloud-based data storage could cross many sectors of medicine and could even be managed by the patients themselves. In addition to the direct benefits to patient care, health services will also benefit from the significant reduction in expenditure previously incurred by the unnecessary use of ineffective drugs. This system will also help automate documentation and drug prescription, ultimately freeing up medical staff.

Analysing patient medical data, in combination with data collected from smartphones, fitness trackers, and smart watches, is hoped to be able to identify events which are likely to lead to undesirable outcomes. This use of big data is already being assessed in clinical trials for its reliability in diabetes; wearable technology collects data regarding the patient's normal daily routine and automatically identifies events that have a high probability of occurring in conjunction with hypoglycaemic events, such as long periods of sitting or a fall. If these events are detected, the patient will get a notification to eat something or a warning to see a doctor immediately. Not only does this technology provide early detection of potential medical incidences, it can also educate the patient on events that may occur because of changes in their disease status, allowing them to improve their own therapy or day-to-day activities to benefit their illness management.

The digital advances presented here represent just a snapshot of the effect this digital revolution may hold for both patients and medical professionals alike. This is truly an exciting time for medical innovation!

Novel Methods for Early Detection and Treatment of Cancer

NEW procedures for the early detection of cancer were discussed in Düsseldorf, Germany at the annual MEDICA trade fair. The presentation opened with the question: "Is it possible to diagnose cancer from blood?" introducing blood biomarkers of cancer as a 'hot topic' for oncology. Screening and early detection increases chances of identifying tumours at earlier stages of disease, when it is most likely to be curable, potentially even before symptoms become noticeable.

> "Circulating tumour cells, cell-free nucleic acids, and genetic and epigenetic changes to cell-free DNA and RNA may represent exciting new approaches for early tumour detection."

The latest developments in molecular and immunological treatment approaches have produced some impressive improvements in recent years, even benefitting patients whose disease is already at an advanced stage. One such development is the ability to detect molecular changes in DNA released by the tumour into the blood stream. Through continual patient monitoring during and after therapy, clinicians can determine the efficacy of treatments. "Some centres are already carrying out blood-based molecular trials during routine diagnostics," said Prof Stefan Holdenrieder, Director of the Institute for Laboratory Medicine at the German Heart Centre, Munich, Germany.

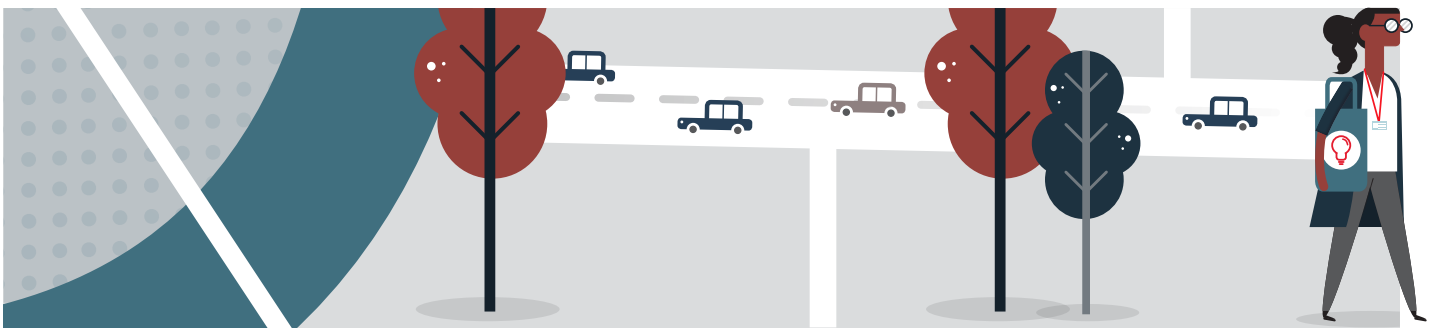
Prof Holdenrieder concluded by discussing biomarkers of future interest, and diagnostic tools that had not yet found their way into clinical application. Circulating tumour cells, cell-free nucleic acids, and genetic and epigenetic changes to cell-free DNA and RNA may represent exciting new approaches for early tumour detection. Moreover, circulating exosomes, small vesicles released by tumours, may constitute a compartment with tumour-enriched material in the blood, adding another method of early detection. Exciting novel research into the potential of these markers as cancer diagnostic tools is required.

The Impact of Migration on Infectious Diseases

'DANGEROUS travel companions' was the poignant theme for the final day of the MEDICA trade fair, Dusseldorf, Germany, 13th–16th November 2017. This theme introduced the growing problem of multi-resistant infectious diseases, such as tuberculosis and methicillin-resistant *Staphylococcus aureus* (MRSA), particularly with regard to those strains carried by tourists and herein lies the necessity for a new conception of 'migration medicine'.

Extrapolated data reveals that by 2050, the number of infection-related deaths will have increased more than 10-fold, with the prevalence of multi-resistant bacteria posing a serious threat. "Serious issues that will not be easy to deal with may soon develop if this problem is not brought to the public's attention more frequently", warned Dr Beniam Ghebremedhin, Helios University Hospital Wuppertal, Witten/Herdecke University, Witten, Germany.

> "Serious issues that will not be easy to deal with may soon develop if this problem is not brought to the public's attention more frequently..."



These potential problems are well-expressed in the example of Germany. Following increasing globalisation and an influx of refugees, Germany's healthcare system must now be prepared to battle an increasing incidence of tuberculosis, 3/4-multi-resistant Gram-negative bacteria infections, increasing scabies incidence, and parasitic infections such as malaria. Given the nature of refugee migration, it is likely that the majority of refugees will have either travelled from or through an area at high-risk of multi-resistant germs.

Reactivation of certain diseases in travellers also constitutes a risk, as Dr Ghebremedhin explained: "The greatest deficiency in the provision of care to migrants is the lack of support to help them deal with their psychosocial and physical stress they experienced during their migration, which means there is a risk of reactivation." This issue is exacerbated by the propensity to house migrants in close proximity with one another, thereby increasing the risk of an outbreak.

There is currently no affordable procedure for a simple, comprehensive screening for all the relevant multi-resistant Gram-negative bacteria, nor a way to detect the underlying molecular mechanisms of the bacteria using routine procedures. Subsequently, there is great unmet need for the optimisation of laboratory diagnostic tools with regard to economical screening for the migrated infections.

Hygiene: Improving Compliance to Hand Disinfection

BASIC HYGIENE is essential for prevention of transmissible diseases in healthcare environments; it acts to protect those receiving both inpatient and outpatient care, medical professionals, and visitors. The important issue of preventing nosocomial infection featured heavily at this year's MEDICA trade fair.

In the past, one of the most well-known, and effective, methods for infection prevention has been hand disinfection. The World Health Organization's (WHO) 'Clean Care is Safer Care' campaign has initiated an improvement in medical facilities providing in and outpatient care by implementing the Clean Hands Campaign (CHC).

In a MEDICA press release dated 15th September 2017, Dr Tobias Kramer, Institute of Hygiene and Medicine, Charité University Hospital, Berlin, Germany, who works on the CHC explained: "We still need to improve compliance with hand disinfection standards." To work as a long-term prevention strategy, these practices need to be supported by key stakeholders such as employees at management-level who have a direct influence over this environment.

> "...use of hand disinfection agents, reports on observations and compliance, sharing knowledge, memory aids, and optimised dispenser location and fitting, should be focussed on to improve hygiene conformity."

According to Dr Kramer, established methods included in the CHC, including the use of hand disinfection agents, reports on observations and compliance, sharing knowledge, memory aids, and optimised dispenser location and fitting, should be focussed on to improve hygiene conformity. Adding to this, focussing on employees at dispenser stations revealed evidence that when they established a disciplined commitment to hand disinfection standards, through methods such as setting targets, they produced a sustained improvement in compliance. "Many patients already check the medication that they are given by hospital staff and we want to encourage this same activity for hand disinfection," said Dr Kramer.

Both patients and staff can be unsure of procedures in respect to hand disinfection, therefore a further factor to improve medical professionals' compliance to hand disinfection relies on communicating this information effectively to patients, as well as their friends and relatives; in this way, these groups will be better informed of when and where disinfection is necessary and can ensure an equivalent level of hygiene from staff.

Challenges in Prevention Strategies: Infection and Antibiotics

THE GLOBAL spread of infection and the rising levels of antibiotic resistance requires effective translation of current knowledge from preventative strategies into hygiene measures. Methods of diagnosis, although fundamentally different to traditional hygiene measures, also play a key role in some cases of infection and antibiotic resistance, according to a MEDICA press release dated 15th September 2017.

Urinary tract infections are diagnosed through clinical presentation and microbiological reports. Dr Thomas Schwarz, Institute for Medical Microbiology and Hygiene, Johannes Gutenberg University of Mainz, Mainz, Germany, warned: "Both of these involve disturbance variables that can lead to a false diagnosis being given which in turn leads to non-indicated antibiotic exposure." Consequently, the development of optimised strategies in the future could help prevent urinary tract infections.

It should also be noted that, in some cases, 100% infection prevention cannot currently be achieved, in spite of the high level of prophylactic measures undertaken. This is the case for postoperative wound infections, where strategies have typically been erroneously based upon the notion that bacteria enter the operating wound from within the hospital environment, whilst in reality they are often carried in from the external environment. As Dr Roland Schulze-Röbbecke, Institute for Medical Microbiology and Hygiene, University Hospital Düsseldorf, Düsseldorf, Germany explains: "Most incidences of POWI [post-operative wound infection] are rather caused by bacteria that the patient brings into the theatre themselves and these can only be partly eliminated." As a result, recording data on this form of infection is of great importance, because its elimination cannot be achieved with the current level of data available. "This is because many of the significant risk factors cannot be influenced, for example severe primary disease, old age, obesity, and nicotine abuse," explained Dr Schulze-Röbbecke.

> "Most incidences of POWI [post-operative wound infection] are rather caused by bacteria that the patient brings into the theatre themselves and these can only be partly eliminated."

Furthermore, novel evidence shows how the 'Clean and Isolate' method of infection prevention in hospitals, used to combat antibiotic resistance, leads to poorer individual outcomes due to less contact with hospital staff. Dr Anna Eva Lauprecht, Essen-Mitte Clinic Group, Essen, Germany explained how this strategy is not sufficient to produce a reduction in hospital infections, but noted that: "*Clostridium difficile* infections can be drastically reduced by Antibiotic Stewardship and by restricting prescription of certain groups of antibiotics." Thus, if concretely implemented, antibiotic stewardship could provide a low rate of pathogen resistance to antibiotics; a crucial aspect in ensuring a safer improved quality of care.

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Thomas Oakley

NHS Clinical Entrepreneur Fellow, NHS England, London, UK.

Q: As a NHS Clinical Entrepreneur Fellow, what inspired you to move away from clinical practice and pursue an entrepreneurial pathway?

A: I have always had a creative streak. Problem solving is partly what attracted me to medicine in the first place and this has led directly to my interest in innovation. I soon realised that there were a number of areas that could be improved by some quite simple changes, and that there were many procedures that could be done differently to yield better results. This led me to look more widely at what was going on outside of medicine, and I soon realised that there was a whole world of invention taking place which had huge relevance to care delivery. Once I had looked up and seen what was happening elsewhere and what might be possible, I was hooked and realised I could not put my head back down and return to clinical practice full time. The problem is that being an entrepreneur is a full-time commitment, so I made the decision to step aside from clinical practice for a period in order to explore the possibilities of this exciting new world.

Q: How have you found the transition from daily life in the clinic to a more office-based role?

A: If anything, I am less office-based now than I was in the clinical setting. I have less administrative work than I did in the hospital environment and my work now involves constant travel and networking. The most important thing for an entrepreneur to do is to get out of the office and engage in the world around them, to source problems that need solving, identify customers, and to test their solutions. Constantly meeting new people with hugely diverse backgrounds, perspectives, and vested interests is really very stimulating. Being office bound is one of the things that kills entrepreneurship; you have to get out of the building and engage with the market.

Q: One of your focusses is the application of three-dimensional (3D) printing in medicine. What do you think are the key advantages of this relatively new technology and what can they bring to the medical world?

A: 3D printing represents an entirely new era of healthcare delivery. It enables truly personalised healthcare, from the use of 3D printed anatomical models to assist surgical planning, to tailoring surgery to the anatomy of the patient with patient specific cutting guides and patient specific implants. Currently, most implants are mass produced and the patient's anatomy is adapted to fit the implant, often traumatically; 3D printing designs implants from the patient's anatomy, creating a perfect tailored fit that results in better patient outcome, reduced complications, and subsequently reduced cost. 3D printing may also result in a move away from metal implants; these dense inflexible implants alter the natural biomechanics, often resulting in fractures and implant failures. Materials such as polyether ether ketone (PEEK) have biomechanical properties that more accurately reflect bone and may offer a better implant outcome. Some assume that this technology is expensive, but in many cases 3D printing can produce tailored solutions that are more cost effective than mass produced items. Most of the expenses come from proprietary costs of many printers, but as this technology's patents expire, the costs will fall dramatically. On the horizon, 3D printing holds the potential to unlock bio printing and the production of brand new organs derived from your own cells, in effect giving the potential to replace organs like car parts.

Q: As well as working to find new solutions to medical problems yourself, your work as a NHS entrepreneurial associate means you review NHS procurements; are there any projects currently in development that you are particularly excited by?

A: There is a growing focus on moving care delivery from hospitals to the community with a number of exciting technologies springing up in this space. Telemedicine providers are allowing remote access to clinicians, often at lower cost for both the patients and the clinical providers; wearable devices are enabling remote patient monitoring and subsequently earlier discharge from hospital; and digital pill management systems are allowing vulnerable groups, such as the elderly, to safely administer their medication at home, reducing admissions for medication errors and again enabling early discharge from hospital. There are two main areas that I am really pleased to see: the first is a move to make care especially inclusive of the elderly, with a view to making technology accessible to them; the second is a shift of focus away from pure treatment driven care delivery to enhancing quality of life and improving disease experience, especially where treatment is not possible. This particularly rings true for the area of prosthetics, especially paediatric prosthetics, where huge progress is being made in improving the acceptability and functionality of prosthetics, often through creative means such as dressing the prosthetic as an 'Iron Man' hand.

Q: How do you believe upcoming medical innovations, including those you have designed, will translate into the developing world?

A: Certainly, in the UK currently there is a strong driving force to provide more for less, and the market's price tolerance for new products means that innovations are having to become better value for money. In many ways, this should help products to translate into developing countries, where cost is obviously a key consideration. However, the needs of healthcare systems in developing countries are often different from those in our own and therefore the products being created for markets here are sometimes unable to directly translate to care providers in developing countries; this is further confounded by a lack of digital infrastructure in many of these settings. A number of innovations could hold real benefit in these economies, especially technologies that facilitate remote access to care and are capable of operating in rural settings. Many developing countries have large populations and represent sizeable potential markets for companies, but international expansion remains a challenge for small and medium-sized enterprises, which often struggle to find fertile land on home shores, let alone abroad. More work is needed to identify technologies with translatable benefits and to facilitate these companies selling to these large potential markets where they could hold real value for many people.

Q: What suggestions would you make to improve the way in which the NHS identifies and adopts new medical innovations?

A: Many healthcare providers, such as the NHS, have a very low risk tolerance and cannot be seen to spend money on things that might not work, which means that they are automatically at odds with innovation, where failure is a key component to success. Within these large organisations, funds are often siloed and pre-allocated, which results in an inability to release money easily or to use money to benefit the system as a whole, especially where the benefits are not felt by the silo that has to pay for it. Further to this, an innovation that helps the system overall may actually financially penalise the part that needs to pay for it. Take telemedicine, for example: telemedicine enables outpatient appointments to be held via phone calls, saving patients and clinicians time. In the NHS, the hospital would have to pay for the telemedicine service; however, the hospital is paid according to a tariff system, which only recognises and pays for face-to-face outpatient appointments. Therefore, if the hospital uses the telemedicine service it may increase patient throughput, which benefits the region's health economy as a whole, but it will cost the hospital money because they cannot claim against a tariff for the service. Greater budgetary oversight and cross silo flexibility and mobilisation, combined with a change of risk tolerance, is needed for the NHS to truly become receptive to innovation.

> "3D printing represents an entirely new era of healthcare delivery."

Q: You launched your first medical device whilst still studying at university. How have your experiences working within the NHS influenced your thought processes behind your latest projects?

A: I was lucky with my first medical invention because it ticked all the right boxes; it was cheaper for the same outcomes and took up less storage space than the then typically available kit. However, it sits in a saturated market with some large companies who effectively shut me out of the marketplace. This is an important point, because there are other barriers to market than just convincing a customer to buy your product. The public sector is particularly difficult, because many larger corporates enjoy a relatively protected market position that can be difficult to break through. My latest ventures have all been aimed at identifying emerging or new markets for which the NHS has allocated investment and in which there are not existing dominant market players. The advantage of start-ups is that they can move quickly and should be able to capitalise on emerging markets faster than larger corporates; the difficulty they continue to face is to be able to provide the evidence and assurance that larger companies can generate, because of the often excessive costs in doing so.

Q: You have graduated from medical school, worked within the NHS clinically and as an entrepreneurial associate, and performed a role as a company director; what do you believe is your greatest achievement to date?

A: My greatest achievement remains graduating from medical school; a lot of things have happened subsequently, but I am proud to have spent 6 years of my life training to join a profession that I still see very much as my calling. Although my interpretation of what being a doctor is, for me, different to many of my colleagues, it is an honour to belong to such a diverse body of professionals who are collectively working to enhance the human experience. I very much feel that our diverse approaches and how we identify with the profession is a hallmark of our many interests and is what, in part, gives medicine its great appeal. The thing that I am most proud of is to have had the courage to take that first step off the well-trodden path of clinical medicine and to allow myself to explore the possibilities within and outside medicine. I intend to practice medicine my own way, through entrepreneurship, and see my qualification as a charter and mandate to explore the possible in the name of human advancement.

Q: What advice would you give to young doctors looking to follow your lead and move away from clinical practice towards a career in business?

A: Entrepreneurship is not for everyone, you have to be okay with risk, with failure, and with the prospect that, at times, money will not be coming through the door. This is a hard thing for many doctors to do, as it goes against our training and our expectations of work. At the end of the day, clinical practice will always be there and if you are thinking about entrepreneurship chances are high that you are already looking for something more, and if you ignore it and keep doing the same thing then you will not find it. There is never a perfect time to do it and so my advice is that if you are thinking about it, then just do it; you will always be wondering 'what if' otherwise. Many will tell you, as they told me, to finish training first, and you should remember that this advice is based on their own experience and, although undoubtedly well-intentioned, may not be the right advice for you. Some may also feel that by leaving clinical practice that they are not doctors anymore, but that depends on your definition of being a doctor; remember there are many different types of doctor and being a consultant does not make you a better doctor, it just means you are better at doing certain things. Whereas many prefer to deliver care, some may choose to develop new mechanisms of care for others to deliver.

Q: Finally, what do you think the focus for future medical innovations should be?

A: I think that medicine is set to become increasingly patient-specific with the emergence of genomics, immunotherapy, and 3D printing manufacturing that will eventually convert most areas of clinical practice. There needs to be greater

alignment between innovation and clinical/service delivery need, rather than what we are seeing now which is a wave of unmatched, often reasonable, ideas crashing against an unprepared and unresponsive market. There should be a move away from the development of apps; the elderly population, who have the greatest healthcare needs, do not use app-enabled technology and younger generations, such as my own, have app fatigue and are deleting apps from their phones rather than adding new ones. Apps especially, but innovations more generally, must serve a purpose with measureable delivery benefits and be less about the technology and more about the improvement of care. Innovations should focus on improving quality of life and disease experience, especially where curative treatments are not possible, and digital technologies have the potential to minimise the impact of that disease on quality of life, so that people are able to be healthier and happier for longer.

Olusola M. Adeleke

NHS Clinical Entrepreneur Fellow & Clinical research fellow in Cancer Imaging, University College London, London, UK.

Q: You founded the company Aurora Medical Innovations, which helps match patients to suitable trials. What inspired you to set up such a company and what do you think the company's impact has been so far, and will be, on clinical trials?

A: I have been lucky enough to have worked on various kinds of cancer trials across different institutions and I have recently worked at the Phase I clinical trials unit at University College London (UCL), London, UK. I saw first-hand how many patients go from one hospital to the other frantically looking for trials; many of them die waiting to enrol on life-saving drugs. While some patients have a higher chance to access these trials just by virtue of their geographical location, there is not a single platform in place within the NHS that proactively matches cancer patients to clinical trials, especially using artificial intelligence. What Aurora Medical Innovations has done so far is create awareness across different stakeholders. For example, we are working with our technical partners to build a one-stop and robust matching platform and we recently gained approval from the research and development department to access a limited amount of data to run a pilot study at UCL Hospital as a proof-of-concept study.

Q: We understand one of the aims of setting up Aurora Medical Innovations was to cut the approval time of new drugs by 30–50%; do you think you are on track to do so? Also, why do you believe cutting the time for new drugs to be approved is so important?

A: In the USA alone, about 30,000 patients die annually waiting for drugs to be approved. It takes about 2–5 years to complete an average trial recruiting from 200–400 patients globally. If we can make trials accessible to more people, not only are we going to save lives in the process, but we will also save the healthcare costs and burden of looking after many unwell patients that could have died or been admitted to hospital if not for these new drugs. We are currently building a platform on this basis and developing collaborations and working agreements with different health organisations across the UK and Europe. We hope to start the first recruitment match by the summer of 2018.

> "If we can make trials accessible to more people, not only are we going to save lives in the process, but we will also save the healthcare costs and burden of looking after many unwell patients..."

Q: You are included on the NHS Clinical Entrepreneurs list; how do you think clinical innovations have helped progress healthcare? Do you think the NHS Clinical Entrepreneurs list helps to inspire new clinical specialists to push the boundaries and think outside the box in order to help advance the sector?

A: I think the NHS Clinical Entrepreneur programme, led by Prof Tony Young, has really motivated many doctors who have innovative ideas to help the health sector but do not have the business skills or support necessary to thrive. Many of my colleagues have had game-changing ideas that could have an impact on millions of people around the world. It has also put the UK at the forefront of innovation in healthcare across the world. There is nowhere else on the planet that has so many clinicians under one umbrella constantly striving to develop game-changing solutions.

Q: You are also a clinical research associate at UCL. Could you enlighten us on what your day-to-day duties and responsibilities are?

A: I am a clinical researcher at UCL developing new magnetic resonance imaging (MRI) techniques called hyperpolarised C13-pyruvate MRI and GlucoCEST MRI techniques. In terms of my day-to-day duties, I set up experiments, recruit patients, carry out imaging data acquisition along with my colleagues, and analyse the results.

Q: Your major research activity has been in the field of metabolic imaging; how much has this field advanced over the last 5 years and how do you think innovative processes have contributed to this progression?

A: The two new MRI metabolic imaging techniques in cancer mentioned previously have the potential to help diagnose cancer early and monitor disease both during and after treatment. Some of the techniques we are developing are so cutting-edge that they are only available in a handful of centres across the world. We scanned the first ever prostate cancer patient in Europe with the hyperpolariser technique in August 2017; this was quite exciting with some very promising results.

Q: Cancer metabolism is your more specific interest; how does metabolic imaging help in the diagnosis and treatment of cancers?

A: The most common way we currently diagnose or monitor cancer with imaging is by looking at macroscopic changes, i.e. what the eye can see on computed tomography (CT) scans and standard MRI. This is fraught with a lot of shortcomings and can sometimes lead to under or over-diagnosis depending on who is looking at the images. However, with metabolic images, we are able to detect biochemical changes in the tissue even before the cancer fully develops and becomes visible on conventional imaging. With this method we can detect disease early, before it spreads, and hence control the disease much better.

Q: You published a paper in 2016 on the use of next-generation sequencing in guiding patient selection for Phase I clinical trials. What are the take home messages of this paper and how do you think it has helped to advance both the oncology and clinical trial fields?

A: Next-generation sequencing is at the frontier of personalised medicine. We now know that two breast cancers or prostate cancers might not behave in the same way and might need different treatment approaches. Understanding this will help improve the successes of our treatment plans and even develop a bespoke treatment plan for patients. We still have a long way to go with genome sequencing because data from Muscato, Safir, and Matrix trials have all shown that we are still only able to match patients to specific trials or treatment only 15–20% of the time using genome sequencing data alone.

Q: Over the next 5 years, is there a specific sector you would like to look more closely at and which you feel will benefit from the advancement of the healthcare system?

A: I think artificial intelligence has the potential to change the way we practice medicine. If you look at medical imaging alone, we have petabytes of untapped imaging data siloed in various data centres around the world. These data could reveal a

lot of exciting new information that could be used to help advance personalised medicine. Robotics is another exciting area for me.

Q: Collaboration and debate are core to scientific progression. Do you believe that medical congresses provide an appropriate platform for such communication?

A: Absolutely, I consider medical congresses as opportunities not only to network but to get inspiration on how to solve burning medical problems, and to continue to improve quality of care across various health subsectors.

Cosima Gretton

School of Management, University College London, London, UK.

Q: To begin, why did you decide to specialise in health technology? Was there something or someone that piqued your interest in this area?

A: As a doctor, I found the parts of medical practice that both excited and frustrated me at the same time centred around technology. Technology can be both a fantastic enabler and a source of error, inefficiency, and frustration. I felt the greatest gains for clinical medicine were to be found in building better technologies to enhance the abilities of clinicians.

Q: Can you tell us a bit more about your role as a Health Technology Teaching Fellow at University College London? What are your principal responsibilities and duties in this role?

A: I run the Health Care Pathway on the Technology Entrepreneurship MSc at University College London with Dr Nasrin Hafezparast from Outcomes Based Healthcare, London. Together, we designed a program to guide entrepreneurs through the healthcare ecosystem. Innovating in healthcare presents very different challenges to consumer technology, and while the ground is well trodden in biotech, it is unfamiliar territory for most software-based start-ups.

Q: For those who are unfamiliar with the work of Karius, could you explain a little bit about how the start-up is revolutionising treatment of infectious diseases?

A: Karius is a life sciences company dedicated to transforming infectious disease diagnostics. We use next generation sequencing to detect cell-free microbial DNA in plasma, diagnosing infections that other tests cannot detect. This is known as agnostic sequencing; we have a curated database of >1,250 microbial genomes that we can detect. We launched in January 2017 and are now working with a number of institutions across the USA who find the test useful in patients with culture-negative sepsis or immune compromise.

Q: Can you explain the goals of AXNS Collective and why you decided to set up a public engagement programme connecting neuroscience to art?

A: The neuroscience of perception was one thing that has always interested me most about the brain and is also one of the greatest illusions of constancy in our subjective experience. I wanted to explore what happens when that is disrupted, and art is one of the most compelling ways of doing so. We started working in the visual arts because that was the founder's area of focus, but recently the team has moved into sound art as well.

Q: As the founder of AXNS Collective, which of your projects do you feel has been the most influential and can you briefly explain your hopes for the future of the programme?

A: I think one of the most influential ones was a recent sound art project in which I was not actually involved. The team obtained a set of electroencephalography data from an Imperial College London, UK, London study into LSD

and music, and brought together a group of data scientists and sound artists to create and record an album.

Q: You currently juggle many teaching, research, and corporate responsibilities and have achieved a lot in your career. What do you consider to be the biggest achievement in your ventures so far?

A: I guess AXNS would be that. The impact on people attending the exhibitions, and the personal satisfaction it brought me, makes it something of which I am very proud.

Q: We understand you are very active on Twitter and compose a regular blog for your website. How important do you believe the role of social media is in medicine, particularly healthcare technology?

A: It depends, in clinical practice social media does not play a particularly big part and since there are confidentiality issues, this makes sense. Figure 1 is an interesting social media application for clinical practice, where physicians can share and learn from each other's cases. For health technology and health policy, social media does play a big part; I think it can be effective in driving change or developing awareness of a new and better way of doing things. However, I do sometimes worry that we have our own healthcare echo chambers and end up preaching to the choir.

Q: In a recent blog post, you described the dangers of artificial intelligence in healthcare. Can you explain why it is necessary to track health outcomes from an episode of care and describe the role that value-based healthcare increasingly plays in this process?

A: The risk with artificial intelligence is that as it automates various human tasks, it risks fostering new errors due to automation bias. This is the propensity for the human operator to favour the decision made by a machine over their own internal judgement, or the presence of contradictory information. While we hope that artificial intelligence improves care, there is the risk that it may negatively impact outcomes through error. A healthcare system that systematically measures outcomes is better equipped to evaluate and monitor the impact of a new technology on patient care.

Q: What other risks may occur in the future as technology is implemented further into clinical practice and how should these risks be monitored?

A: It depends on the technology. I am particularly interested in intelligent clinical decision support. Automation of human tasks can lead to automation bias and complacency, two well-studied phenomena. These lead to errors of commission (the human agrees with an erroneous machine decision) and omission (the human fails to spot the machine's mistakes). The problem in healthcare is the lack of reliable feedback loops; when we make a mistake the impact often occurs later, when the clinician is not on shift or the patient is under another team's care. Decision-support in this context could easily foster an error that is not quickly detected.

Q: Looking to the future, what developments in healthcare technology do you predict we will see in the next 5 years?

A: I am really excited about brain-computer interfaces (BCI). There are two companies embarking on this long journey already. In many senses we already have task-specific BCI: cochlear implants and stimulation of the basal ganglia for Parkinson's disease. While the aim of these start-ups is to commercialise a general BCI, the stepping stones are likely to be creating new neural prosthetics for those with motor or perceptual impairments. There are huge challenges of course, and 5 years is a short time, but I would not be surprised if we see increased interest in the coming years.

> “Innovating in healthcare presents very different challenges to consumer technology, and while the ground is well trodden in biotech, it is unfamiliar territory for most software-based start-ups.”

Yoav Mintz

Center for Innovative Surgery, Minimally Invasive and Robotic Assisted Surgery, Hadassah Hebrew University Medical Center, Jerusalem, Israel.

Q: Firstly, can you tell us a little about what led you to pursue a role in innovative endoluminal surgery? What do you enjoy most about your role in this field of treatment?

A: To appreciate endoluminal surgery, one must first understand a little of the history of where we came from. Since minimally invasive surgery (MIS) was first introduced almost three decades ago, the approach has demonstrated significant advantages over standard open surgery. With significant reductions of postoperative pain, wound infections, and hernias to negligible numbers, in addition to a reduction in respiratory and thromboembolic complications, and significantly improved cosmetic outcome, patients stood to gain a lot with this new approach. In the last decade, efforts have been made to maximise the minimally invasive aspect to optimise the benefits of MIS, either by reducing the number or size of the already small incisions. Single incision surgery (SIS), also known as single port surgery (SPS), is the least invasive approach; however, it is not without its own issues, preventing it from being the preferred approach. If we take the idea of minimising the number of incisions to the extreme, we reach the point of endoluminal surgery, meaning performing surgery within the lumen of the intestine by accessing it through the mouth or anus. Natural orifice transluminal surgery (NOTES) is taking this concept one step further, perforating the intestinal lumen (usually the stomach or rectum) and therefore allowing for entry into the abdominal cavity. Once in this space, operations on abdominal organs, such as cholecystectomy, appendectomy, and sigmoidectomy, can be performed, leaving no indications of surgical intervention on the external body itself. These novel surgical techniques I have described (SIS, endo-luminal surgery, and NOTES), combined with the innovative drive necessitating the development of new instrumentation, are bringing surgeons into uncharted territory and it is this which led me to innovation in endoluminal surgery. The potential to shape the future of surgery and provide improved, optimised patient outcomes is what drives me forward.

Q: SPS is a brand-new technique performed in only a few specialised centres around the world by leading laparoscopic expert surgeons, including yourself. Could you briefly describe this technique and explain why it is such an important advancement for modern surgery?

A: Traditional laparotomy entails a large incision on the abdominal wall, including cutting muscles and nerves, with significant morbidity related to such incisions. In the late 1980s, video laparoscopy was introduced, significantly reducing morbidity. We already learned that having 4–6 small incisions, instead of one 20 cm long, reduces the body's metabolic response to trauma, thereby enhancing recovery. Abdominal incisions are just the means of entry to the abdominal cavity; with SPS, the thought was that if we could enter through a single incision, we might further reduce metabolic response, post-operative pain, and wound complications. SIS was a spinoff of NOTES that encountered technical and regulatory obstacles. We believed that if we can take out the gallbladder through the mouth or vagina as we do in NOTES, with a single incision it should be even easier through the navel.

In SIS, we enter the abdominal cavity using a single 2.5 cm incision as opposed to standard laparoscopy in which we make a few 5–12 mm incisions. Although this incision is twice as large, to allow all the instrumentation to pass through a single keyhole incision, the resultant improved cosmesis (as the scar is hidden within the navel, which is usually tucked in and hidden), is highly

attractive to patients. In SIS, however, new ergonomic problems arise due to the nature of working with multiple instruments through a single small hole, bestowing it the nickname 'chopsticks surgery'. Despite these problems, SIS operative results are comparable to standard laparoscopy; hence, the process of overcoming the inherent technical difficulties of SIS will eventually pave the pathway to incisionless, scarless surgery with minimal post-operative pain and wound morbidities. One can imagine a cholecystectomy in stealth mode, like Navy SEALs, where the surgeons enter, grab the gallbladder, and take it out without leaving any trace. This is what we do in SIS and medical centres that can provide this option are highly sought after by patients around the globe. The reason that SIS has not yet become the standard of laparoscopic surgery is due to the technical difficulties encountered and the need for new instruments to facilitate such operations. Over the past 5 years, new dedicated robotic platforms have emerged, specifically targeting SIS and enabling complex operations using only one small incision. These robotic platforms are undergoing clinical trials that will hopefully result in a successful market release.

Q: NOTES is another new technique improving surgery of the oesophagus. What are the main advantages of this technique?

A: NOTES is a surgical approach using a flexible endoscope entering the gastrointestinal tract and abdominal cavity through a natural orifice like the mouth, anus, or vagina. This concept was first described in 2003 by Anthony Kalloo and Sergey Kantsevoy from Johns Hopkins Hospital, Baltimore, Maryland, USA. Since its inception, a lot of research and development has been carried out in this area, with hundreds of millions of US dollars invested in developing this technique. If you think about it, it is the ultimate way to perform surgery. There are no incisions on the abdominal wall, eliminating the post-operative pain associated with abdominal wall incisions, as well as significantly reducing morbidity such as wound infections, haematomas, seromas, hernias, and scarring. Despite these advantages, NOTES did not succeed in overcoming its inherent barriers, including a lack of rigidity in flexible endoscopes, difficulties with visual orientation, instruments that are too small in size, and the lack of assisting instruments. Currently, NOTES is performed in a hybrid approach, where some minimal laparoscopic assistance is used concurrently.

Experience and data is being gathered towards the final goal of a pure NOTES operation. In addition, the funding, research, and development of NOTES encountered a significant blockade when U.S. Food and Drug Administration (FDA) officials did not approve novel instrumentation. For now, research and development is limited to a smaller scale until the next breakthrough in innovation for NOTES emerges. In the meantime, surgeons have learned to appreciate the beauty and advantages of the flexible endoscope which are used daily by gastroenterologists. Progress and innovation continues in the areas where FDA approvals are not necessary, as such operations within the GI tract using flexible endoscopes are thriving. One great example of this is per oral endoscopic myotomy (POEM) for the treatment of achalasia. In achalasia, the lower oesophageal sphincter is continuously held closed by the circular muscles of the oesophagus. The goal of surgical treatment is to release this strangling effect of the muscle rings, opening the passage from the oesophagus to the stomach, thereby enabling the patients to eat without vomiting.

The gold standard surgical approach is a laparoscopic Heller myotomy, where the muscular rings are incised, releasing the strangulating effect of the lower oesophagus, allowing food to pass freely into the stomach. However, this is not a simple task. Oesophageal surgery is sometimes referred to as the surgical Tibet; it is a hard to reach, hostile, and unforgiving territory. The oesophagus is hidden in the chest behind the heart, between the lungs and the aorta. In a laparoscopic Heller myotomy, the first part of the operation is dedicated to providing access to the oesophagus. The surgeon needs to release the oesophagus from its surrounding structures and then start cutting through the overlying longitudinal

oesophageal muscles to finally reach the circular muscles. In contrast, in endoluminal surgery, using a flexible endoscope, all of the delicate and risky dissection is avoided. The only thing separating the circular muscles from the endoscopic knife is a 2 mm thick mucosal lining. Performing surgery from inside of the oesophagus is straight forward, without the need to dissect tissue and disrupt anatomy to reach the area of interest. Additionally, patients have little to no post-operative pain, with return to daily activities even earlier than those patients having undergone laparoscopic surgery. POEM is a new technique gaining worldwide acceptance for the treatment of achalasia due to the many advantages of this truly minimally invasive surgery and is leading the way for surgery being more flexible.

Q: Your surgery team implemented a da Vinci robot-assisted surgery system in 2009 and you were the first surgeon in Israel to perform robotic-assisted surgery. How has your clinical practice improved with the use of the robot?

A: Our hospital was indeed the first medical centre in Israel to acquire the da Vinci robot. It was not an easy task to convince the administration to authorise the purchase of such an expensive medical device, especially in light of the fact that there is no reimbursement for a robotic surgery here. Using the robot increases the cost of each operation, resulting in a financial loss, not profit, per surgery performed. After deliberations, the decision was made to purchase the robot not based on financial opportunity, but based on the hospital's objective to serve as a leading institute in Israel, both in clinical care and in research and development. Following the purchase of the da Vinci robot, the robotic programme came to fruition, with operations being performed by several departments, including general surgery, urology, gynaecology, and otolaryngology.

Personally, I cannot say that robotic surgery, as it is today, improves patient outcome; however, for us it served as a driving force to move our surgical specialities from open surgery to MIS. Surgeries like oesophagectomy and complex hepatobiliary operations previously performed only via open surgery are now being performed via MIS. The robot enhances performance of these complex operations by enabling delicate and small space suturing. The strikingly noticeable changes in the immediate post-operative course following robotic surgery was the reduction of pain, earlier return to ambulation, and reduced post-operative complications. Being the first to use this platform, we established our position as pioneers in the field of robotic surgery and, a year after our purchase, other hospitals jumped on the band wagon, purchasing the robot as well. Today in Israel, a country a mere 8,500 square miles, with a population of 8 million, there are 10 hospitals with the da Vinci robot performing robotic surgeries.

Q: Some patients may be worried about the use of robotics in their surgical procedure. What would you say to reassure a sceptical individual who is uncertain about undergoing a new surgical technique using robots?

A: When educating patients about any surgery, a detailed explanation of what the surgery entails is provided. With robotic surgery it is important for patients to comprehend what exactly robotic assisted surgery means. The term robot is actually misleading. A robot, by definition, is a machine capable of carrying out a complex series of actions automatically and repetitively with ultimate precision. The da Vinci robot is none of the above; it is a master-slave tele-manipulator with no automatic function and no repetition. Basically, it is just a machine which replicates the surgeon's (master) movements inside the patient's body. There are many advantages of the robotic system that make them attractive to surgeons, the most important being 1) articulating instruments with seven degrees of freedom that facilitate and enhance the surgeon's dissection capabilities; 2) three-dimensional (3D) view (as opposed to the two-dimensional visualisation in standard laparoscopy), which gives the surgeon better depth perception and better spatial orientation, not only increasing the speed of the task performance but providing better precision; 3) in standard laparoscopy, moving the surgical

instruments is counter-intuitive, whilst in robotic surgery the movements are very intuitive, hence the name of the manufacturing company of the da Vinci robot, Intuitive Surgical, Inc. (Sunnyvale, California, USA); 4) Software between the surgeon and the patient enhances the surgeon's performance, making all movements more refined, resulting in improved precision; and 5) with robotic surgery, the surgeon performing the surgery sits on a comfortable chair at a console, places their forehead on an ergonomically correct headrest, where they are provided a 3D image, while resting their arms on an armrest. This position combined with more comfortable instrument manipulation is the most ergonomically correct and comfortable for the surgeon. The result is a physician with improved concentration, who is less fatigued during and after surgery. All of the aforementioned factors contribute to what is called 'immersion technology', meaning the surgeon is totally immersed in the patient's body, whilst making the environment and instrument control more user-friendly to achieve a smoother and better operation. Following giving this explanation to a patient concerned about a robot operating on them, there is a great sense of relief and gratitude that their surgeon will be assisted by such a sophisticated system that will aid the surgeon to perform at their best.

In the 21st century, technologies can make life easier; in medicine in particular it can simplify and improve the delivery of medical treatment. Surgeons, more so than other medical specialities, embrace new technologies, as we feel the impact immediately in the operating room. Operating room technology today is not an obstacle for improvement and success, rather a field of opportunity. The only limitation is the human mind, which needs to think of novel ways of implementing available technology to further improve the delivery of medical treatment, both for patient outcome and for the actual delivery of care.

> "Personally, I cannot say that robotic surgery, as it is today, improves patient outcome..."

Q: Do you think there will ever be a time when human surgeons are completely replaced by robots?

A: This is a philosophical question that will be determined by humanity itself, although I can compare this question to the use of genetic engineering. Science today can repair defective genes and determine the sex and hair colour of a fetus. I believe the decision whether or not to use this technology will be a social decision and not a medical one. Undergoing a surgical operation performed by a non-human platform is not simply an issue of technical competence; throughout surgical procedures, there is continuous decision making, sometimes including life or death decisions. While technology is on the verge of enabling automatic functions, such as instrument movement, grasping and displacing tissue and organs, and even suturing the intestine, the decision-making process itself is a skill currently lacking but eventually will be provided by artificial intelligence (AI). I am a strong proponent of AI and I am certain that once we master both technologies a true robotic surgery will not only be feasible but will be faster, safer, and better.

The path to this goal, however, is not so straightforward. We are surrounded by AI every day; for example, commercial airplanes today fly thousands of people every day while AI controls most of the flight. Pilots of the new generation of planes, like the Boeing and Airbus, state that the planes operate themselves, with only 7 minutes of actual human flight control, on average, per flight. Automatic cars are already driving on our streets, potentially lowering motor vehicle accident rates to the bare minimum in the future and making vehicular transportation safer than ever before.

Taking this experience and knowledge of decision making by AI from other areas and implementing it to the medical field, specifically into the operating room, is being developed. It is just a matter of time until AI will analyse movements and address unplanned events, making the appropriate decision of action and reactions, just like the AI driven cars on the streets. Moreover, this kind of AI will be able to make such decisions based on a

vast database of operations, much more than any human surgeon would ever be exposed to during their training, allowing for flawless execution of decisions, instantly. No doubt these capabilities will one day exceed human abilities and patient outcomes will rise to a different level.

Q: You are the head of the Surgical Technology and Innovation Laboratory at the Hadassah Medical Center, Jerusalem, Israel. Can you briefly detail your current research focus and your aspirations for the future of surgical technology?

A: I am fortunate to be involved in many surgical innovations. Living in the start-up nation and having developed a Center for Innovation capable of developing the future of surgery puts me in the perfect intersection where many ideas come to fruition. There are many projects that are currently being developed here; the common thread with all the projects is best described as novel innovations. Novel techniques and devices which further minimise the invasiveness of surgical procedures, achieving safer and faster surgery with reproducible results. Projects like a wireless miniature camera for MIS, a novel approach to prevent adhesions to surgical meshes for herniorrhaphy, a new endoluminal technique for prevention of gastric reflux, an endoluminal approach for the resolution of Type 2 diabetes mellitus (T2DM), targeted delivery of treatment for tumour cells with magnetic nanoparticles, as well as several novel surgical devices. The dream is to develop Star Trek like devices, such as those used by Dr McCoy to diagnose pathology instantly, and to cure them effortlessly as Dr Crusher does, healing wounds with a laser beam. Although we are not there yet, and the handheld Star Trek tricorder is currently a room size CT scanner, we are definitely on the right track.

Q: What are you most proud of during your time as head of the Surgical Technology and Innovation Laboratory?

A: For me, innovation and being the head of the lab is not about taking pride in specific projects, it is about the process itself. Every project I take under my wing is like a child waiting to be born. Once the seed flourishes into a breathing baby, it is nourished and perfected until it is ready for use. I enjoy the process of development as much as the end results. I am most proud of the projects that began with very raw and naïve ideas coming from non-medical professionals. My expertise is to take these kinds of ideas, extract their essence, and turn them into a feasible and necessary project, resulting in a novel surgical instrument or technique. Such innovative connections are the result of the extensive experience I have acquired, providing me with the tools to think outside the box.

Q: As well as many other great achievements, you have developed a potential cure for adult-onset T2DM using two magnets. Could you briefly explain this technique and what implications it may have for the future?

A: The idea of creating a gastric bypass using magnets came to mind after witnessing the quick resolution of T2DM in diabetic patients following bariatric surgery. A staggering 300 million diabetic patients are receiving treatment for T2DM symptoms and preventative therapies, but the disease itself is not being cured. While we do have surgical options to cure T2DM, most patients consider gastric bypass surgery too complex, and a significant risk that they are not willing to take. Keeping this in mind, using an endoluminal non-invasive approach we have developed a method using magnets placed endoscopically into the stomach and duodenum to create a compression anastomosis between the stomach and the intestine, just like with surgery but with less risk. Following anastomosis formation, the natural passage between the stomach and duodenum is plugged, so that food bypasses the duodenum.

This new innovative approach has potential implications which are significant, by treating what is thought to be a medical problem with a surgical non-invasive approach. In the USA, only 1% of eligible morbid obese patients undergo bariatric surgery due to the lack of certified surgeons, high cost, and low availability of operating rooms. This novel technique will enable the procedure to be performed not in the operating room, but in an

endo-suite, potentially as an out-patient same-day surgery procedure. This type of innovation can potentially reduce medical costs in many ways: saving money that would have been spent on a lifetime supply of drugs, saving money spent on hospitalisations secondary to complications from diabetes, not to mention the reduction of morbidities and their costs as related to diabetes. As we move forward with clinical trials of this novel technique, I am very excited at the potential it has to actually treat patients in the future and cure T2DM.

Q: Lastly, what advice would you give to a budding surgeon hoping to follow in your footsteps and make a large impact on modern surgery?

A: Gandhi once said: "Be the change you wish to see in the world." This not something you would typically hear a surgeon quote; surgeons are usually very conservative. It is a profession learned by watching your mentor and surviving as an apprentice until you reach proficiency, before being released to continue this circle of learning. This is the reason why, as an independent surgeon, one rarely tries to change the practice of what they learned from their mentor. Whatever worked for 100 years will work again and rarely does one dare to challenge or change it; the old adage of tried and tested invariably rings true. Although the main concepts of surgery and biology should still be respected, new technologies enable us to perform surgery with better devices than the progenitors of modern surgery used. This is why I believe that first one should always ask themselves why they are doing what they do, and if there is a better way to do it. Thinking out of the box is the key to this process, because as an apprentice we were taught to do exactly as our mentors.

When I was a resident, my chairman and mentor always told me that the oesophagus is a non-forgiving organ with limited healing capabilities: "You can operate only once and you had better do a good job the first time, because there is no going back". Damaging the oesophagus during stomach or oesophageal surgery was a feared known complication. Today, during POEM surgery, I deliberately incise the oesophageal mucosa only to reach the abdomen, the complete opposite from what was inundated into me. So, question everything, try to find novel techniques out of the box, collaborate with complimentary disciplines, and never give up. If you fail, try again until you succeed. If you believe there is a different, better way, it is just a matter of time and hard work until you find it. Like Thomas Edison said: "Many of life's failures are people who did not realise how close they were to success when they gave up."

> "So, question everything, try to find novel techniques out of the box, collaborate with complimentary disciplines, and never give up."

PATIENT–PHYSICIAN INTERACTION ON SOCIAL MEDIA: THE PHYSICIAN'S POINT OF VIEW

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ABSTRACT

The use of social media (SM) in healthcare has provided a novel means of communication in line with a more modernised approach to care. For physicians, SM provides opportunities for enhancing professional development, networking, public health, and organisational promotion, among others. For patients, SM provides potential for taking a more active role in health, sharing information, and building virtual communities, especially in the case of chronic and/or rare diseases. SM has the potential to bring patients and physicians closer together, beyond the walls of clinics; however, the interaction between physicians and patients on SM has received mixed feelings, especially from the physicians' perspective. On the one hand, the potential for a more enhanced, albeit remote, communication has been viewed positively, especially in an era where digital technologies are fast expanding. Conversely, concerns around breaches in professional boundaries and ethical conduct, such as mishandling of patient-sensitive information on these platforms, have fuelled heavy criticism around its use. From this viewpoint, issues arising from the use of SM in healthcare, with a focus on the patient–physician interaction, discussing the potential benefits and pitfalls are covered in this article.

Keywords: Facebook, online communication, patient–physician interaction, social media (SM), Twitter.

SOCIAL MEDIA USE IN HEALTHCARE

Recent times have witnessed a true revolution in the use of social media (SM), enabling human communication and interaction to take place in ways that go beyond traditional face-to-face interactions. In healthcare in particular, SM has been increasingly used by both professionals and patients as a way to bridge gaps in communication, providing new methods and opportunities for interaction. The 'traditional' patient–physician relationship as known from the Hippocratic times[1] has shifted through the years, revamping roles and attitudes. Once, patients were passive recipients of health-related information from the physician, whereas the current expectation is that they are active participants in their care. The emphasis on having more holistic consultations in a patient-focussed manner has further enhanced this shift. Parallel to this, evolving digital technologies have shed light into new avenues for delivering care in a more modern way, such as the use of virtual consultations and wards, connecting remote places and people through web cameras and other online technologies.

Reflecting on the two communities separately, physicians on one hand and patients on the other, undoubtedly SM has played a crucial role in how the two parties interact, both personally and professionally.[2] For physicians, SM interaction provides opportunities for enhancing professional networking, opinion-sharing, organisational promotion, public health promotion, and education.[3] For example, the use of SM platforms, like Twitter and Facebook, to raise disease awareness and contribute to public health are only

a few examples of the current common uses of SM. In a survey of young urologists (N=316), 99% reported using SM in a personal and/or professional way, with YouTube and LinkedIn being the most frequently used platforms for professional use.[4] This study highlighted the value of SM in urologic education. In the rheumatology community, approximately half of the rheumatologists and basic scientists have reported using SM for clinical and research updates, with other professional uses including the expansion of professional networks and the learning of new skills.[5] Beyond education and professional interaction, SM has proved to have a role in pharmacovigilance, enabling monitoring for adverse drug reactions; more specifically, there seems to be increasing interest in the utilisation of vast amounts of available SM data for adverse drug reaction monitoring, from both health-related and also general SM data.[6]

Patients are becoming increasingly more 'present' on SM, particularly those with chronic conditions.[7,8] In other words, an increasing number of patients are seen interacting with others on SM platforms, such as online forums, Twitter, and Facebook, showing a remote presence on these platforms. These 'modern' patients seek out SM to connect with others, sharing experiences and exchanging health information.[9] The formation of virtual online communities not only prevents people from suffering in silence, but often inspires and instils positive energy, even in those less motivated to take a more active role in their care and become advocates of their own health.[3] As a result, SM can help improve self-management of chronic diseases, including rheumatic musculoskeletal diseases, although the benefits seem to be particularly evident in the psychosocial management of disease via fostering support and information sharing and less so for physical condition management.[10] Furthermore, SM can help enhance the quality and the implementation of recommendations for the management of diseases.[11] Finally, from a research perspective, SM is empowering patients in several other ways, including influencing the way clinical research is undertaken as well as patient recruitment into clinical trials.[12]

The exchange of information on SM can therefore inform, educate, and inspire; the expectation, of course, is that the information provided is accurate and valid. It is not always possible, however, to know and identify who the SM users are, whether who and what they claim to be is real, or whether the information they share is accurate. The freedom of speech on SM, with the potential to reach out to millions of people across the globe, is not without its problems. The possibility to use SM for sharing any kind of information online poses important risks to the health community; the background, knowledge, and intention of the sender can conflict with the understanding and perception of the receiver.

From a physician's point of view, sitting in clinic listening to long lists of information brought in by patients following an online search either on their condition, treatment, or prognosis, is a recurring scenario. The question relating to this is how much detail can a physician go into, especially during time-restricted consultations, in clarifying, answering, correcting, and relaying information retrieved from the web? Is this feasible and sustainable in routine clinical practice? On the other hand, imagine the scenario of a newly diagnosed rheumatoid arthritis patient who needs to start disease-modifying treatment and who attends the clinic fully aware of the condition, its course and prognosis, and the need for and type of treatment to control it, following their online search. The two scenarios are obviously very different and potentially have a very different approach, impact, and outcome of the patient–physician interaction.

Taking a step further and considering patient–physician interaction on SM platforms and communication beyond the walls of a clinic raises even greater concerns. Violations of professional boundaries and patient confidentiality, with consequent disciplinary actions, have already been reported.[11] Compromising patient-sensitive information can lead to social stigmatisation and employment discrimination, among other potential harms.[13] The damage can be irreversible. However, whereas building a relationship with your patient in clinic can be strong and deeply personal, continuing to grow this relationship online has been described as: "...less personal than an office visit but more personal than having no contact until the next visit."[3] However, not all patients will have the necessary background and skills for using SM-related technology, and a challenge in this respect is to educate and give the opportunity for this kind of interaction to those less familiar with these technologies (e.g., the elderly, those with no internet access, or with difficulty in reading or writing, etc.). Often, it is this group of patients that is the most vulnerable one in terms of their health.

It is important to maintain clear boundaries between personal and professional relationships and expectations. Reflecting on a study of trainee doctors in France, the need to protect one's personal information and photographs seems to outweigh the fear of embarrassing the patient or losing their confidence in the context of accepting a friend request from a patient.[14] Another study revealed that physician-disclosed personal information in the setting of a face-to-face consultation was unhelpful, and focussed more on the physician's needs rather than the patient's.[15] This raises the suspicion that physician self-disclosure is likely to be equally unhelpful in online interactions, which, in this setting, typically involve informal chatting that can be intensified by photographs and other highly personal content.[14]

The realisation that unprofessional use of SM takes place among medical students, ranging from violations of patient confidentiality through to profanity, discriminatory language, depiction of intoxication, and sexually suggestive material,[16] highlights the need for education in professionalism beginning at the start of the medical school. It could be argued that professionalism cannot be taught, but at least key principles can, including professional and patient-related boundaries that need to be firmly adhered to, eliminating threats to patient privacy and confidentiality.

Overall, and reflecting on the aforementioned, the authors believe that, if properly used, SM can strengthen patient–physician interaction and keep it in line with modern medical practice. There are certainly ways to remain professional in the digital world, starting from careful review of privacy setting on SM profiles and accounts through to practicing safe SM use and protecting sensitive patient data.[17] Despite potential risks, there are positive applications that should not be ignored, especially when it comes to educating and raising awareness on important public health issues; however, lack of awareness on how to use SM seems to be an important reason for not using them[4] and it is also likely to be one of the reasons for inappropriate use of SM. Furthermore, online friendships between patients and physicians need to be cautiously considered with existing SM use guidelines and privacy settings in mind.[14]

CONCLUSION

Despite potential hazards of SM use among healthcare professionals and patients raising concerns around professional boundaries and ethical conduct, SM has largely augmented communication and interaction. In addition, SM has been a strong influence in providing care in a more modern and engaging way. The lack of clear boundaries on the use of SM between patients and physicians poses significant threats to patient confidentiality and invasion of privacy for both parties. Finding a balance in this delicate matter is challenging, but not impossible, and a clear understanding of the rules, at the very least, is necessary.

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EDITOR'S PICK

Rygiel describes an exciting development in the improvement of heart failure management, but also signals early evidence of regenerative therapies. The author illustrates the complexity of Algisyl® injections, the challenges of implementation and adoption, and the importance of quality of life for patients with heart failure.

Mike Bewick

ALGISYL® INJECTIONS: AN INNOVATIVE STRATEGY FOR PATIENTS WITH ADVANCED HEART FAILURE

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ABSTRACT

The remodelling of the heart that occurs after myocardial infarction independently contributes to heart failure (HF) progression. In a rapidly growing patient population with chronic HF, new, safe, and effective therapeutic strategies are needed. Recently, injectable biomaterial-based therapies have been gaining interest, especially for patients post myocardial infarction who have had complications due to advanced HF. One such intervention, based on Algisyl® (LoneStar Heart Inc., Irvine, California, USA) injections, has been examined in the recent prospective, randomised, controlled AUGMENT-HF clinical trial. This paper briefly presents characteristics of Algisyl, an injectable calcium alginate hydrogel; describes a minimally invasive myoplasty procedure for the insertion of Algisyl implants; and provides a concise overview of the design, methods, and results of the AUGMENT-HF study. This paper focusses on the promising findings that Algisyl, in addition to standard medical therapy, was more effective than the standard medical therapy alone for providing sustained 6-month and 1-year benefits in exercise capacity and symptomatic improvement among patients with advanced HF. In addition, this report discusses some implications and challenges relevant to the AUGMENT-HF trial, and addresses the importance of a blind study design for further studies in this field. Moreover, this paper highlights future perspectives for examining the Algisyl implants, aimed at functional clinical outcomes, quality of life, and safety issues, prior to a possible implementation of this strategy into clinical practice.

Keywords: Algisyl®, clinical symptoms, functional capacity, heart failure (HF), safety.

INTRODUCTION

Remodelling of the heart is the term often used in the context of cardiac architectural changes (hypertrophy and dilatation) after myocardial infarction (MI), and in heart failure (HF).[1] At present, pharmacotherapy, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics, and aldosterone antagonists, alongside revascularisation procedures, such as the percutaneous coronary intervention, with a stent implantation performed after MI, have given rise to a substantial reduction in left ventricular (LV) aneurysms, as well as an improvement in clinical outcomes.[2,3] Nevertheless, in many post MI patients, a loss of contraction by the anterior wall

and septum occurs, and the resulting LV dysfunction often leads to chronic HF.[1,4] Over the past few decades, there have been various surgical attempts to reverse cardiac remodelling; however, some were unsuccessful.[5] Therefore, to fulfil the unmet needs of a growing patient population with chronic post-MI HF, new, safe, and effective strategies are needed. One such intervention, based on a calcium alginate hydrogel, Algisyl® (LoneStar Heart Inc., Irvine, California, USA), was examined in a recent AUGMENT-HF clinical study.[6,7]

UNIQUE CHARACTERISTICS OF ALGINATE-HYDROGEL BIOMATERIAL

Algisyl alginate, originating from brown seaweed, is a proprietary calcium-alginate-hydrogel that consists of two components: a sodium ion alginate component, supplied as a sterile aqueous solution with 4.6% mannitol, and a calcium ion-alginate component, consisting of water-insoluble particles suspended in a sterile 4.6% mannitol solution. These two components are mixed immediately before use, and then combined in one syringe for delivery as intramyocardial injections. When mixed, the Algisyl forms a solid hydrogel in the ventricle. This permanent implant, which is directly injected into the LV muscle, plays the role of a prosthetic scaffold that modifies the shape and size of the LV.[6,7] It should be noted that alginate, which is known to be a safe biomaterial, has been used for many years in preclinical studies as a biologically inert filler substance.[8] Moreover, it has been reported that the alginate hydrogel curtailed LV remodelling after MI in animal models.[8,9]

ALGISYL IMPLANTS: A MINIMALLY INVASIVE MYOPLASTY PROCEDURE

In the AUGMENT-HF trial, the Algisyl implants, which were inserted through a ministernotomy, negating the use of the much more invasive coronary artery bypass grafting surgery, were then injected directly into the heart muscle.[6,7]

Table 1: Synopsis of the AUGMENT-HF trial.[6,7]

AUGMENT-HF study design	Prospective, RCT, parallel, open-label, multicentre, international.
Study hypothesis	Algisyl® (injectable calcium alginate hydrogel) is superior to standard medical therapy for improving functional capacity and clinical outcomes in patients with advanced HF.
Baseline characteristics of the study population	Number enrolled: 78 (40 alginate-hydrogel group, 38 controls); mean age: 62 years±10; men: 85%; women: 15%; diabetics: 39%; mean LVEF: 26%.
SMT for HF	Diuretics, beta-blockers, ARB/ACEI, mineralocorticoid receptor antagonists, anti-thrombotics or anti-platelet agents, anti-platelet aggregation agents, anti-coagulants, lipid lowering agents.
Inclusion criteria	Moderate-to-severe HF on SMT, LVEF: ≤35%, peak VO_2: 9.0–14.5 mL/kg/min, LV end-diastolic dimension index: 30–40 mm/m^2.
Exclusion criteria	Renal or liver disease, LV wall thickness: <8 mm.
Intervention group (Algisyl with SMT)	Algisyl implants administered during a surgical procedure. n=35 (modified intention to treat).
Control group (SMT alone)	Active comparator: SMT n=38
Duration of follow-up	6 months 12 months
Summary of 12-month study outcomes (mean difference for Algisyl versus control group)	Peak VO_2: 2.1 mL/kg/min (**p<0.001**) Total exercise time: 1.5 minutes (**p=0.002**) 6-minute walk distance: 101 m (**p<0.001**)
Serious adverse events at 6 months	40.0% for Algisyl versus 26.3% for control (p=0.063)
Serious adverse events at 12 months	53% for Algisyl versus 47% for control (p=0.19)
Deaths at 12 months	9 (22.5%) for Algisyl versus 4 (10.5%) for control

Data are presented as means±SD. p values in bold are considered statistically significant.
ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; HF: heart failure; LV: left ventricular; LVEF: left ventricular ejection fraction; RCT: randomised controlled trial; SD: standard deviation; SMT: standard medical therapy; VO_2: maximal oxygen consumption.

Table 2: Comparison of clinical outcomes between intervention group (Algisyl® injections) and control group (standard medical therapy) in the AUGMENT-HF trial.[6]

Study endpoints	Intervention group baseline	Intervention group 6-month	Control group baseline	Control group 6-month	p value between groups
LVEF (%) LV mass (g) LVESD (cm) LVEDD (cm)	25±5 296±59 5.5±0.52 6.3±0.40	28±5 275±63 5.2±0.65 6.0±0.42	26±5 317±59 5.7±0.56 6.4±0.50	28±6 300±56 5.4±0.59 6.2±0.47	0.61 0.44 0.091 0.17
Peak VO_2 (mL/kg/min)	12.1	13.5 increase in mean peak VO_2 =1.24	12.2	unchanged	**0.014**
6MWT distance (m)	275±86	increase in median 6MWT=141	310±80	unchanged or declined	**0.001**
NYHA functional class (mean)	2.9±0.4	84% of Pts with NYHA Class I or II	2.8±0.5	26% of Pts improved by 1 NYHA class	**<0.001**
Quality of life: PGA self-reported	low	>55% of Pts improved	low	28% of Pts improved	**0.019**

Data are presented as means±SD. p values in bold are considered statistically significant.
HF: heart failure; LV: left ventricular; LVEF: left ventricular ejection fraction; LVEDD: LV end-diastolic diameter; LVESD: LV end-systolic diameter; 6MWT: 6-minute walk test; NYHA: New York Heart Association; PGA: patient global assessment; Pts: patients; SD: standard deviation; VO_2: maximal oxygen consumption.

At present, a limited left thoracotomy is required with a subsequent identification of the mid-wall of the beating heart. This is followed by a series of 0.3 cc Algisyl injections performed circumferentially at the LV mid-ventricular level with an average of 15 implants per ventricle, roughly 1 cm apart. This procedure takes about 80 minutes and, depending on the patient's overall condition, the length of hospitalisation varies from approximately 3 days to a few weeks. It should be noted that some of these patients have to face a very difficult decision on whether to implant an LV assist device or whether to undergo heart transplantation. In this context, the potential therapeutic option of injecting Algisyl would be less invasive than the above two options. In the future, when the percutaneous device will be available to inject Algisyl endocardially, it is conceivable that this procedure could also be performed by invasive cardiologists.

AUGMENT-HF TRIAL: A BRIEF OVERVIEW

AUGMENT-HF[10] (Table 1) is a randomised controlled trial, prospectively comparing Algisyl injections (intervention group) with the standard medical therapy (SMT) alone (control group) to determine the impact of Algisyl on functional capacity and clinical outcomes in patients with advanced, chronic HF.[6,7] The primary endpoint of AUGMENT-HF included the change in peak maximal oxygen consumption (VO_2) (from baseline to 6 months), measured during cardiopulmonary exercise testing. The secondary endpoints included changes in the 6-minute walk test (6MWT) distance and in the New York Heart Association (NYHA) functional class (Table 2).[6,7] In addition, the assessments of safety (e.g., serious adverse events [SAE] and postoperative cardiovascular [CV] mortality) were conducted (Table 1).[6,7] It has been shown that 35 patients in a modified intention-to-treat population from the intervention group were successfully treated with the alginate-hydrogel injections, administered through a limited left thoracotomy approach. These patients achieved an improved peak VO_2 of 1.24 mL/kg/min from baseline to 6 months compared with the control group (Table 2).[6] Similarly, after 6 months, patients in the intervention group improved by a mean of 84.7 m on the 6MWT compared with baseline; in contrast, the patients in the control group deteriorated, with an average of 15.4 m or less on the 6MWT, compared with baseline. The NYHA class was also reduced by one in the intervention group, while it remained the same in the control group.[6,7]

Overall, the alginate-hydrogel was more effective than SMT alone for improving exercise capacity and decreasing HF symptoms.[6,7] There was no significant difference in the number of SAE at 6 and 12 months between the intervention and control groups.[6,7] The results of the AUGMENT-HF trial provided a proof of concept for possible LV reconstruction with Algisyl injections as a potential therapy for patients with advanced HF.[6,7] However, the trial findings are far from conclusive; it is expected that future studies will explore the potential long-term benefits, as well as safety issues, for this innovative therapy.

CLINICAL IMPLICATIONS AND CHALLENGES RELEVANT TO RESEARCH ON ALGISYL

The recent report of the AUGMENT-HF study is the first step towards a more comprehensive treatment using injectable biomaterials for patients with advanced HF. It should be emphasised that the HF research focussed on early phase trials of novel interventions faces a big challenge, since such studies are usually underpowered to demonstrate the improvement in evidence-based clinical outcomes, including hospitalisation, SAE, and CV mortality.[11] For this reason, such trials have to rely on other clinically relevant endpoints, including surrogate endpoints, for example, physiological parameters intended to predict outcome benefits, which are considered in larger trials.[11] Since beneficial changes in the LV remodelling have been associated with improved clinical outcomes in larger studies, the AUGMENT-HF trial may offer some hope that, in the future, the intervention with Algisyl implants, aimed at the reshaping of failing LV, can really improve functional status of patients suffering from advanced HF.[12]

In the meantime, however, different issues, such as biological response to the Algisyl implant, beyond the mechanical benefits that could possibly result in alterations of myocardial structure or function, need to be explored.[6,7] There is also concern surrounding an unblinded study population; for instance, the intervention group had a limited median sternotomy and surgical insertion of the Algisyl implant and as such these patients were aware of the therapeutic procedure. In contrast, the patients in the control group did not have this procedure. Under these non-blind circumstances, when the 6MWT was analysed, both the study patients and physicians knew who received an intervention. In this setting, it was possible that some expectations with regard to the outcome among patients in the intervention group might have some positive impact on the test results; the patients, who were aware of receiving the real intervention, could have performed slightly better on the 6MWT than the ones in the control group.[6,7] However, the VO_2 was an objective parameter of their functional capacity, which was measured by blinded adjudicators.[6,7] In the future, randomised controlled trial designs need to address with caution the issue of blinding to avoid a potential bias.

FUTURE PERSPECTIVES: AUGMENT-HF II

As a follow-up of AUGMENT-HF, the AUGMENT-HF II trial has recently been approved by the U.S. Food and Drug Administration (FDA). This trial will enrol >250 patients and will use a similar design, including patient randomisation to the intervention group, which will receive the Algisyl implants versus the control group, which will receive SMT for HF. The study endpoints include peak VO_2, hospitalisations due to HF, and CV mortality. In addition, the AUGMENT-HF II will focus on measurements of the quality of life.[7]

ALGISYL IN CONTEXT OF OTHER BIOMATERIALS CONSIDERED FOR MYOCARDIAL INJECTION POST MYOCARDIAL INFARCTION

Several approaches using specific biomaterials exist to help injured myocardium post MI. They include scaffolds (from natural or synthetic biomaterials), decellularised extracellular matrix (which can be applied to create cardiac patches), techniques to vascularise scaffolds, and injectable biomaterials (designed for endogenous or exogenous repair, or to maintain ventricular architecture after MI).[12] In particular, the hydrogels class of biomaterials designed for direct injection into the heart can be divided into three main groups. Firstly, hydrogels for prevention of adverse remodelling and for recruitment of endogenous cells for repair; secondly, a temporary matrix for cell transplantation and exogenous repair; and thirdly, a support to the failing LV, by maintaining ventricular architecture after MI and promoting functional LV improvement.[12,13]

Currently, the injectable biomaterials are the focus of translational research, and they include:

- The first group, which contains naturally derived compounds, such as alginate, collagen, hyaluronic acid, fibrin, keratin, chitosan, and decellularised extracellular matrix.
- The second group, in which the main representatives include synthetic hydrogels; for example, self-assembling peptide or polymer-based materials that can augment stem cell survival or retention *in vivo*, enhance the release of growth factors, or even enhance endogenous tissue regeneration.[12]

Injectable hydrogels were initially investigated to augment cell retention and survival associated with cell transplantation in the heart. According to current knowledge, the injected cells act via paracrine mechanisms. Therefore, the main purpose of introducing a biomaterial scaffold is to augment their survival by providing the cells with an extracellular matrix that will enhance the beneficial paracrine signals.[12] It has been shown that the cell retention was significantly improved after a direct epicardial injection of bone marrow-derived mononuclear cells in self-assembling peptide nanofibres in a large animal MI model (resembling a human MI model). The cell injection within the nanofibres contributed to better LV haemodynamic functions (both systolic and diastolic) as well as an increased capillary density.[14]

In recent years, some preclinical studies have explored the release of growth factors, therapeutic agents, and biologics from injectable scaffolds, in order to prevent negative LV remodelling. For instance, it has been found that the vascular endothelial growth factor release can be sustained for 2 weeks from self-assembling peptide nanofibers *in vivo*. Overall, in a large animal MI model, the nanofiber-vascular endothelial growth factor system improved angiogenesis and decreased infarct size after a direct epicardial delivery.[15] Likewise, in another experimental MI model, it was shown that the myocardial extracellular matrix hydrogel, delivered via a transendocardial approach, improved the LV end-diastolic and systolic volumes, left ventricular ejection fraction, and global wall motion index. Overall, it has been shown that the hydrogel improved LV architecture and ability to contract.[13] Although some preclinical studies appear promising, the exact therapeutic potential of biomaterials for HF has yet to be determined, based on large scale clinical trials. The translation of these therapeutic strategies into clinical practice faces several challenges that are mostly relevant to the manufacturing processes, methods of delivery, quality control, and complex regulatory and financial issues.[12,16]

Alginate biomaterial has been explored for potential applications in cardiac tissue engineering and regeneration due to its biocompatibility and non-thrombogenic nature.[16] Biomedical applications of alginate range from its supportive use in patients after acute MI to its possible use as a vehicle for stem cell delivery, and for the controlled delivery and presentation of multiple bioactive molecules and regenerative factors into the heart.[16] In conclusion, it should be noted that some properties of alginate, when taken separately, are not unique; however, the fact that the alginate combines all of these properties makes it a remarkable material that could be helpful to many patients suffering from severe myocardial damage after MI.

SUMMARY

Post-MI remodelling of the heart independently contributes to HF progression and, thus, there is a great interest in innovative approaches to attenuate and reverse LV remodelling. The AUGMENT-HF trial revealed that Algisyl, as a permanent implant designed to reduce the LV wall stress, is feasible, safe, and translatable into improvement of functional capacity. For example, improvements to peak VO_2 and 6MWT have been sustained in 1-year follow-up in patients with MI and advanced HF. Further studies, including the AUGMENT-HF II trial, examining the Algisyl implants will focus on functional, clinical outcomes, quality of life, and safety issues such as SAE and CV mortality, among HF patients. Unquestionably, larger multicentre randomised, blinded studies are essential for evaluation and conclusion of clinical efficacy of this innovative therapeutic strategy.

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THE INFLUENCE OF 'OMICS' IN SHAPING PRECISION MEDICINE

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ABSTRACT

Precision medicine is quickly emerging as an exciting new medical model in which patient information is extracted from their lifestyle, environmental, and genetic data. These data will be used to augment and refine traditional medical data to provide a higher level of specificity for disease prevention and patient care. Of the three pillars supporting precision medicine, this paper takes a deeper look at the genetic and genomic pillar; in particular, investigating the role the field of 'omics' has played in helping to develop precision medicine. The term omics is used to describe the collective research efforts of molecular biology for various subdomains (e.g., genomics, proteomics, metabolomics). While this paper is not exhaustive in scope, cases where omics has impacted both clinical practice and public health are highlighted, as well as a discussion of where omics has yet to bridge the gap between these two areas of medicine. The aim of this manuscript is to provide the reader with insight on the particular challenges and benefits of pursuing precision medicine.

Keywords: Molecular biology, precision medicine, public health.

INTRODUCTION

Precision medicine is a medical model in which an individual's genes, environment, and lifestyle are used as additional layers of patient data in disease treatment and prevention plans (Figure 1).[1] Diagnostic clustering and categorisation of patients via parameters such as genetics, biomarkers, phenotypes, and psychosocial characteristics will enhance the level of care physicians will be able to provide.[2] This concept is not new and, in fact, the model has already obtained several monikers, like personalised and individualised medicine.[3,4] Linking an individual's environmental exposure to the associated health impact has given rise to the study of the exposome[5] and the field of molecular pathological epidemiology (MPE).[6] The depth and breadth of the exposome and MPE studies eclipse many aspects of the other two pillars. For example, MPE research probes the complex network of macroenvironments with tissue microenvironments, and the unique profile creates multiple factors, such as microbiomes, transcriptomes, and interactomes, to name only a few.[7] This paper explores the genomic pillar of precision medicine to help gauge the model's overall progress; however, this should not be taken as emphasis of its importance over the environmental and lifestyle components, which are equally valuable.

Announced in 2015, the USA-based Precision Medicine Initiative (PMI) established $215 million to help actualise precision medicine.[8] To help drive this research initiative, the National Institutes of Health (NIH) aims to build a voluntary research cohort of ≥1 million people.[9] A wide range of data types will be collected from each participant in this cohort, including genes and microbiome sequencing, lifestyle data, metabolites, and wearable sensor data. As of June 2017, beta testing for this programme, now known as 'All of Us', has begun.[10]

How close is precision medicine to reality? Is it merely years, or closer to decades, away? This paper investigates some of the impact human genome, proteome, and metabolome research has

had on clinical practice. These fields of research are colloquially known as the 'omics', designated as such for the suffix used to identify the biology research focus (e.g., genomics, proteomics, metabolomics). How do we maximise efforts in these areas? This paper aims to leave the reader with a greater understanding of how omics is shaping precision medicine, the promise it provides, and an appreciation for the amount of effort still required. Cases of omics impacting either clinical practice or public health, in addition to conditions which omics has yet to bridge the final gap from clinical practice to public health, are highlighted.

The PMI aims to: "Pioneer a new model of patient-powered research that promises to accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients."[11] To provide an accurate overview of what has been achieved by omics and what is still a work in progress, two different cases of omics use are examined. The first case reviews the enhancements omics have provided to health surveillance systems and the second case inspects cancer research, which was included as a major target of the PMI, as a part of the Cancer Moonshot initiative.

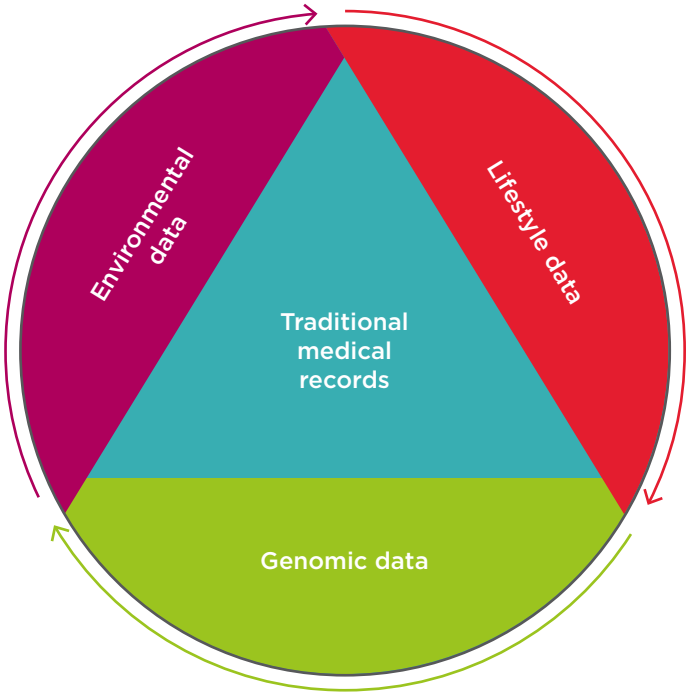

Figure 1: Precision medicine adds three additional data sets to existing traditional patient medical records: data about the patient's environmental exposures, their lifestyle, and their genomic data.

Health surveillance using genetic sequencing for pathogens has direct applications for both fields, whereas omics and cancer is just starting to yield results in clinical practice but remains largely on the drawing board for public health.

HEALTH SURVEILLANCE SYSTEMS

A powerful tool for public health has been surveillance systems enhancements. These systems incorporate biomedical data to provide continuous analysis and interpretation in a systematic way. The Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) both operate surveillance systems that help to watch for pathogens with the potential of becoming widespread epidemics. DNA sequencing has had a profound impact on global public health surveillance efforts; sequencing is not just a tool that is effective in identifying pathogens, but it is useful in efforts to trace an infectious agent's origins and provide insight on how best to combat the pathogen. These discoveries can then be sent back to the 'front lines' of clinics, hospitals, or triage centres in the event of an actual outbreak. In 2009, sequencing was a major component in tracing lineages of the A(H1N1) influenza virus, also known as swine flu. By performing analysis of A(H1N1), previously unrecognised molecular determinants were detected and were suspected to be involved with the increased virility of the pathogen.[12] Similar techniques were repeated for the Ebola virus (EBOV) in 2014. A cohort of 78 patients from Sierra Leone provided 99 EBOV genomes for sequencing; this method identified that the West African variant of EBOV most likely diverged from a central African lineage in 2004.[13] This new subtype then spread from Guinea to Sierra Leone in May 2014.[13] This information helped to shape the efforts of vaccine development, therapies, and diagnostics occurring in the field and these techniques have also been deployed against the Zika virus (ZIKV).[14] Efforts for sequencing ZIKV have been staged by collecting amniotic fluid samples from patients with fetuses diagnosed with microcephaly.[15] Sequencing of 110 ZIKV genomes was recently used to track the evolution and spread of the virus from Brazil into Central America and into the USA.[16] Work on ZIKV is still developing, but it provides a good example of how deeply embedded omics techniques have become for public health and how the knowledge gained is transferred to clinical practice.

DEVELOPMENT OF PERSONALISED CANCER TREATMENTS

Personal cancer therapy strategies provide a strong illustration of omics in action, from the targeting of *BCR-ABL* mutations with imatinib for patients suffering from chronic myeloid leukaemia,[17] and the use of crizotinib to assist lung cancer cases where the patient has the *EML4-ALK* fusion gene.[18] One can also look at the Icahn School of Medicine at Mount Sinai's Institute for Genomics and Multiscale Biology personalised cancer treatment programme. In 2013, they transplanted tumour cells from a colon cancer patient into fruit flies.[19] The use of this fly model allowed for rapid propagation of the cancer cells thanks to the accelerated lifecycle of the flies. By taking this approach, a multitude of cancer drugs could be tested quickly against the cells from the flies to find the most efficacious drug for targeting the patient's tumour cells.[19] In an additional cancer study, the researchers opted to not use genome-wide association studies (GWAS) and instead performed whole exome sequencing (WES); WES is a more focussed method in comparison to GWAS, targeting only protein coding sections (exons) and skipping the non-coding sections (introns). This method also reduces costs and allows for comparison across a large population. WES was performed for 46 patients and samples were genotyped using single nucleotide polymorphism microarrays for both tumour and patient-matched normal tissue.[20] RNA sequencing was performed to find somatic (tumour-specific) mutations, copy number alterations, gene expression changes, gene fusions, and germline variants.[20] The results of this study showed 17.3 cancer-related somatic mutations per patient.[20] To benchmark results, samples were also run against Ion AmpliSeq™ Cancer Hotspot Panel v2 (CHPv2) (Thermo Fisher Scientific, Waltham, Massachusetts, USA), a sequencing assay used to find somatic mutations.[21] Results were also compared to other somatic mutation detection tools, Oncomine® Cancer Research Panel (OCP) (Thermo Fisher Scientific)[22] and FoundationOne® (Foundation Medicine, Cambridge, Massachusetts, USA),[23] and the results were found to be 13.3-fold, 6.9-fold, and 4.7-fold improvements, respectively, against the other somatic tests. This investigation was able to identify genetic drivers and helped determine the best-fit therapeutic options. Medically actionable options were identified in 91% of the patients, even with a wide range of cancers being surveyed (colorectal, breast, thyroid, multiple primaries, and unknown primary), and 28% of the cancers had already metastasised. These results are very promising, and the study led to adjustments to the treatment plans for four of the participants.

GENOME-WIDE ASSOCIATION STUDIES IN PUBLIC HEALTH INFORMATICS

Next-generation sequencing is providing the means to perform whole genome sequencing, which has been a paradigm shift for how we can address complex diseases.[24] This provides a new depth of insight for individuals, but for public health informatics, the interest in populations over patients changes a few parameters. Public health informatics uses GWAS as a screening tool for helping to find medically actionable results, and Berg et al.[25] explored this topic in a 2011 commentary paper. Due to prohibitive costs of running GWAS for large populations, asymptomatic individuals who have family members who have developed a disease should be targeted. This achieves two goals: it helps to screen individuals of interest and builds sample cases of potential disease-causing variants. The screening for public health purposes also allows for a modification of protocol that is not practical with personalised cancer therapy. Any statistically driven test must balance sensitivity and specificity to avoid false-positives. For individual cancer treatment, approaches must have a high sensitivity; however, when performing these tests for public benefit, the scan can maximise specificity and minimise false-positive results, all at the expense of sensitivity. This will generate large numbers of variants, but these should all be approached with caution as the results have an increased likelihood of being a false-positive. This establishes a clearer picture of the breadth of possible variants for the disease.

The challenge then arises as to whether these increased findings should be acted upon, keeping in mind that many variants may be false-positives. To solve this, Berg et al.[25] proposed removing incidental findings from these screenings. Three primary bins based upon the clinical implications of the finding would be established: Bin 1 would contain variants with known clinical use, like *BRCA1/2* mutations, where there is a clinically actionable option available; Bin 2 would contain variants where there is clinical validity, but no strong clinically actionable options. Examples here would be prion diseases, Huntington's disease,

amyotrophic lateral sclerosis, and *APOE* gene polymorphisms. Bin 2 would also be subdivided into three subcategories of low, medium, and high risk for incidental information based on the patient's preference. This allows people to opt-in for receiving fatal, degenerative disease results like amyotrophic lateral sclerosis or Huntington's disease. Bin 3 is designed as a 'catch all' for findings with unknown clinical implications. However, it should be kept in mind that this is a proposed method for using GWAS as a public health tool and is not in actual practice. By being at the opposite end of the translational medicine curve, public health takes the longest to integrate the innovation developed by bioinformatics, so the fact that GWAS adoption is still in the discussion phase is not surprising.

DISCUSSION

The omics influence on clinical practice is at a point of transition and the surveillance sequencing work is an example of when it has been easily integrated into public health and clinical practice. There are also scenarios where efforts are just beginning, as explored with the cancer studies that use GWAS. Therefore, is it prudent to start performing genomic sequencing for individuals to identify potential health hazards? Doing so would allow identification of genetic variants that increase a patient's chances of developing common diseases or cancers. Interventions could begin earlier, helping reduce risk through behaviour modification (healthier diet or increased exercise) or leading to placement of patients on drug therapies. On the surface, it appears that this additional layer of information would have similar healthcare cost savings as the practice of preventative medicine. If it is possible to prevent or delay the onset of serious disease, major medical expenditures can be avoided. GWAS and WES are some of the most effective tools we have that allow implementation of this, but there are downsides to consider, prompting the question: is it prudent to deploy these strategies at a population level?

There are four major criteria that should be considered before deploying a genetic screening programme to identify disease risk for a population. The first consideration should be: is the information captured from the genetic screening better at predicting the disease than traditional phenotypic methods? The second criterion is that a cost-effective intervention needs to be currently available for the disease with an increased risk profile. Benefits are drastically reduced if there are little-to-no options available to the patient. Also, does simply being aware of the risk automatically justify the cost of the screening test? Cost is a central point for the third criterion, namely, are these genetic screening methods more cost-effective than other population-level interventions? Deploying strategies like adding 'sin taxes' to fizzy drinks and cigarettes or creating national advertising campaigns may be more cost-effective than screening tests. The final consideration is: does the knowledge of genetic risk enhance behaviour change? If an individual is aware of an increased risk of diabetes, will they start exercising more and improve their diet? As it stands now, there is a lack of screening tests that can meet all four of these criteria.[26]

GWAS have helped advance our understanding of the genome in many ways, but as far as identifying variants with increase odds ratios for predicting disease, results have not been encouraging. Most odds ratios for disease uncovered through GWAS have been in the range of 1.1–1.6.[25,27,28] It can be difficult to find novel loci with GWAS, as major variants in the genome that have significant odds ratios have often already been found through other methods, as seen in some studies on *BRCA* mutations.[29,30] GWAS have been effective at identifying minor influences, but less successful in finding the major drivers for disease. When contrasting GWAS results and the traditional medical practice of focussing on family history and environmental factors, results are a marginal improvement at best. Looking at genetic variants for Type 2 diabetes mellitus was only a slight improvement in predictive power over other variables like age, BMI, and sex.[31] In other studies, genetic variant tests proved less predictive for coronary heart disease than traditional predictive factors of age, blood pressure, cholesterol, triglycerides, cigarette use, and diabetes.[32] Therefore, the first major criterion listed for consideration to deploy widescale genome screening has not been cleared yet.

The second criterion is more of a case-by-case scenario, but it follows previously established ethical standards for conducting the screening test to begin with.[33] Take for example prostate-specific antigen screening. Identifying the presence of prostate-specific antigen indicates an odds ratio of 0.52–0.67 for developing prostate cancer;[34] however, it would involve screening 1,500 males

to prevent a single death, and would result in 80 out of those 1,500 having to undergo unnecessary major surgery.[35]

How well does knowledge of genetic predisposition to disease drive behaviour change? The resulting behaviour changes seen so far have been small and lack staying power.[36] When informed of increased genetic risk for lung cancer, cigarette smokers did reduce the number of cigarettes smoked per day, but this effect did not last >6 months.[37] There is also a concern about ensuring clear communication about genetic risks. Miscommunicating genetic risks can have a deleterious effect on an individual's belief that they have the capacity to change behaviours.[38] The effectiveness of helping people quit smoking by informing them of genetic risks has a very long way to go to match the success of other behavioural modification techniques. It has been documented that these population-based strategies operate at more efficient margins than high-risk strategies,[39] as taken by predictive genomic medicine. The high-risk strategy approach is seeking out those who are at greatest risk of developing a disease for treatment; these individuals are found towards the end of a normal distribution curve, so focussing on the higher numbers closer to the top of the curve can have a larger impact overall.

From a population standpoint, involving omics-derived data may not be the best use of our resources at present. Hall et al.[26] also make the astute point that with the lack of major cost-effectiveness of population genomic screening, the message may be subverted by industry. This has occurred in the past when the tobacco industry tried to promote genetic causes of disease to exonerate smoking as a cause;[40] however, the same barriers are not present when viewed at the individual level. The Mount Sinai study[19] demonstrated that the burden of cost-effectiveness is reduced when working with patients rather than populations. This is not to suggest that these interventions are cheap, as they remain very expensive, and the cost is prohibitive for the vast majority of people; continued innovation from bioinformatics and industry will help to reduce the cost over time. Improved understanding and filtering of results from GWAS, or a future iteration of the technology, may help to reach the point where population genomic screening will be achievable, but it still eludes our grasp for now. The intersection of omics and precision medicine in the future will rely on several components, including advanced bioinformatics, the merger of multi-omics technologies, big health data, and deep machine learning to extract novel insights.

CONCLUSION

Public health surveillance work spotlights the potential of omics-driven innovations. However, with other areas like cancer, it is either just being developed or the ethics and methods are still being debated. While omics-based methodologies have not yet been implemented into widespread practice, that time is quickly approaching. A constant theme with genomics has been learning about increasing levels of complexity. Before the completion of the Human Genome Project, non-coding sections of DNA were thought to simply be 'junk DNA', implying these sections were not important or worthy of investigation. However, now the name has become a misnomer due to the discovery of features like transcription factors among these sections. Such is the nature of genomics, and, in turn, precision medicine; for every discovery that helps to simplify our understanding, there will be many more that add layers of complexity. The process of precision medicine has been akin to solving one Gordian knot sealing a box, only to find another potentially more complex one inside. These omics-derived tools, in concert with others, can help researchers and clinicians tease apart the next layer in that knot, by which progress is made. It is this progress that may, one day, deliver on the promise of precision medicine.

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eHEALTH TECHNOLOGIES: THE FASTER WE GO, THE MORE WE LEAVE BEHIND?

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ABSTRACT

The importance of health literacy is well recognised. Health literacy has a strong impact on health status and is crucial for empowering patients to pursue a more active role in their own healthcare. Health information is one of the most frequently searched topics on the internet, and in the current networked environment, electronic health resources are becoming increasingly vital in improving overall health literacy. New technologies that allow a myriad of eHealth applications and communication channels are revolutionising the ways in which health information is accessed and used by both providers and patients. Hence, the concept of eHealth literacy, which is an individual's ability to find, evaluate, and apply health information from electronic sources, is a crucial area of study to understand and enhance the ways in which patients access and use eHealth information. This study examines eHealth literacy levels among a group of UK baby boomers (individuals born between 1946 and 1964) (N=407) who had recently used the internet to search for health information. The results suggest that even among this group of internet users, there are skill gaps that need to be addressed before the full potential of these electronic resources in empowering patients to play an active role in their own healthcare can be reached.

Keywords: Ageing population, baby boomers, digital health, eHealth, health literacy, health technologies, online health.

INTRODUCTION

A woman, named Bernadette, collapses in a store and an ambulance is called. She does not regain consciousness until she is in hospital, where she becomes increasingly distressed. Hospitals and doctors terrify her. How will she cope in this alien environment, with forms to fill in, signs to read, and questions to answer? She cannot read or write very well; she left school aged 14 years because she fell pregnant, but had not attended much before that because she was looking after her younger siblings. She is worried about her husband's reaction, too; they have been together for 50 years, how will he cope without her? It does not take long before the patient is diagnosed with ulcerating metastatic breast cancer and she dies a few weeks later, aged 64 years, having never sought any treatment prior to the day she collapsed in the store.

Bernadette's story is true, but is not one that happened many years ago, or in a remote village in a developing country, it happened in one of the biggest cities in the UK in 2015. Bernadette's story, though extreme, is not an isolated incident. Writing for NHS England, Berry[1] tells of a woman who thought her 'positive' cancer diagnosis was a good thing; a man who, despite being directed to the radiology department many times, could not find the X-ray department, so went home; and a group of young women who did not know the location of the cervix in the body. These examples all have one thing in common: low levels of health literacy. Health literacy, defined as "the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand, and use information in ways which promote and maintain good health",[2] goes beyond being able to read labels or pamphlets, or make appointments; it incorporates tasks such as completing complex health forms, sharing medical history, seeking preventative healthcare, understanding the links between behaviour and health, and managing

chronic health conditions.[3,4] Health literacy is crucial to enabling people to actively improve and manage their own health. A body of research demonstrates that health literacy is a strong determinant of health status, with clear evidence that low health literacy is associated with poor health outcomes, including higher rates of hospitalisations and visits to doctors, lower rates of immunisations, and lower levels of health knowledge and understanding of health information.[5,6]

Vast amounts of health information and resources are available, and these are extremely valuable to those people who are health literate. Additionally, in today's digital and networked environment, electronic health (eHealth) resources are revolutionising many aspects of healthcare and health promotion for both patients and providers. The World Health Organization (WHO) defines eHealth as "the cost-effective and secure use of information communication technologies (ICT) in support of health and health-related fields, including healthcare services, health surveillance, health literature, and health education, knowledge, and research."[7] Hence, there is now an additional dimension to overall health literacy: the concept of eHealth literacy, which is defined as "the ability to seek, find, understand, and appraise health information from electronic sources and apply the knowledge gained to addressing or solving a health problem."[8] While overall health literacy has been investigated extensively, the relatively new concept of eHealth literacy remains understudied.[9]

This paper considers the levels of self-perceived eHealth literacy among a group of UK baby boomers (individuals born between 1946 and 1964) who were relatively health literate insofar as they had used the internet to search for health information in the previous 6 months. The paper begins with a brief overview of eHealth, before moving on to outline the importance of the baby boomer cohort from an eHealth literacy perspective. The details of the empirical study undertaken are described, before discussing the implications of the results for providers of eHealth resources.

eHEALTH

In many countries across the world, eHealth strategies are in various stages of planning and implementation. New technologies have delivered imaginative ideas, such as eHealth records, telehealth initiatives, mobile health-promoting applications, interactive health-related social media, and a myriad of online health information websites. Patients can now use electronic resources to book and change appointments, order prescriptions, access healthcare records, and interact with healthcare providers or other patients. There is also a vast array of health and wellbeing information on the internet, with websites providing details from general wellbeing facts to detailed information about diseases, treatments, and procedures. eHealth applications are often suggested as solutions to the consequences of ageing populations and the increasing prevalence of chronic diseases, combined with rising healthcare costs.[10] Other promised benefits include enhanced quality of care[11] and patient participation and empowerment, marking a shift as patients convert from passive recipients to active consumers of healthcare.[12,13]

The internet is a major source of health information,[14] and over half of UK adults who use the internet have searched online for health information.[15] However, it is difficult to imagine Bernadette, or people like her, searching various websites for insights about health issues. Bernadette was among many people who have insufficient levels of health literacy; nearly half of all Europeans have health literacy levels described as inadequate or problematic.[16,17] In the UK, the available health information is too complex for 43% of working-age adults, a figure that rises to 61% if the information contains numbers,[18] and the levels of inadequate eHealth literacy may be even greater. In 2017, almost 1 in 10 UK adults had never used the internet, and it has been shown that internet usage differs between sexes, with men displaying greater usage levels, and between regions, with London having higher internet usage than the rest of the UK. Notably, 22% of disabled people have never used the internet[19] and, hence, a lot of health information is not useful for and/or not available among some groups in society.

Baby Boomers: Health and eHealth

Globally, life expectancy has increased by almost 20 years over five decades, leading the United Nations (UN) to describe population ageing as one of the greatest social, economic, and political transformations of all time.[20] Ageing populations impact healthcare provision, and age-related diseases, such as cardiovascular disease, arthritis, osteoporosis, Type 2 diabetes mellitus, and dementia, place greater demands on healthcare providers. Indeed, while life expectancy has increased, overall morbidity rates have not changed;

heart and respiratory disease, musculoskeletal problems, sensory impairment, diabetes (incorporating Type 1 and 2 diabetes mellitus), and depressive disorders remain the leading causes of morbidity in this cohort. Forty-five percent of the disease burden among baby boomers is attributable to lifestyle choices, such as poor diet, smoking, or being overweight.[21]

Nevertheless, many baby boomers are technologically skilled and increasingly taking a greater role in their own healthcare.[22] Internet adoption is high among this cohort, with 90% of 55–64-year-olds and 78% of 65–74-year-olds having used the internet in the first 3 months of 2017. Notably, of those in the 55–64 year age cohort, half of individuals searched for health-related information;[19] however, what is not fully understood is how fruitful these health-related information searches were. If eHealth resources are to reach their full potential, it is important to understand the levels of eHealth literacy among middle-aged adults, since this baby boomer cohort comprises the elderly of tomorrow, and, among older generations, low health literacy is associated with lower levels of health status, lower quality of life, and higher mortality.[6,18]

THE STUDY

Sample

Research Now Group, Inc., Plano, Texas, USA, a global leader in digital research data, was commissioned to administer an online questionnaire to a sample of baby boomers (born between 1946 and 1964). The questionnaire was sent to 3,000 randomly selected baby boomers and eligibility to participate in the study was dependent on having used the internet to search for health information in the last 6 months. The prospective respondents were informed of the questionnaire's purpose (a research project studying the use of the internet to search for and share health information), academic nature, how the data would be stored (password-protected secure university files) and for how long, and the length of the survey, which typically took 20 minutes to complete. Since approximately half of the baby boomers used the internet to search for health information, the sample comprised early adopters of eHealth and the early majority[23] in terms of acceptance of these technologies, and, as such, was expected to demonstrate relatively high levels of eHealth literacy compared to those who do not use the internet at all or those who do not use it for health-related information. The survey was open for 24 hours.

Health Literacy Measure

In addition to a range of questions pertaining to health and the eHealth resources used, the updated version[24] of the eHealth Literacy Scale (eHEALS)[8] was used to ascertain the levels of eHealth literacy among this sample of baby boomers. The scale has been used extensively in eHealth literacy studies around the world,[25] and the objectives were defined as to "measure consumers' combined knowledge, comfort, and perceived skills at finding, evaluating, and applying eHealth information to health problems".[8]

Table 1: eHealth Literacy Scale (eHEALS) measure.

eHealth facet	Item number	Scale items
Awareness of online health resources	1	I know what health resources and information are available on the internet.
	2	I know where to find helpful health resources and information on the internet.
Skills needed to find and use online health resources	3	I know how to find helpful health resources and information on the internet.
	4	I know how to use the internet to answer my questions about health.
	5	I know how to use the health information I find on the internet to help me.
Ability to effectively evaluate online health resources	6	I have the skills I need to evaluate the health resources and information I find on the internet.
	7	I can tell high-quality health resources and information from low-quality health resources and information on the internet.
	8	I feel confident in using information from the internet to make health decisions.

eHealth: electronic health.

The measure comprises eight items that together examine three distinct facets of eHealth literacy.[24] The first facet measures the levels of awareness of what health resources and information are available on the internet; the second pertains to the skills and ability needed to find and use these health-related online resources; and the third reflects the individual's self-belief and confidence that he or she can evaluate the different resources to use them effectively. These dimensions and the individual scale items are shown in Table 1.

RESULTS AND DISCUSSION

A total of 407 responses were received. The mean age of the sample was 59.6 years and comprised 47% males and 53% females, with a variety of work statuses (for example, 48% were employed, 32% retired, 9% homemakers, and 9% unemployed), and levels of educational attainment (for example, 38.5% were educated to secondary school level, 36.5% to college, technical, or occupational level, and 24% had a degree).

Respondents reported an assortment of chronic health conditions, with over one-quarter of individuals suffering from hypertension and high cholesterol, almost 1 in 5 suffering arthritis, and around 15% reporting neural or mental issues, lung problems, or diabetes. One-third of the sample reported other chronic health conditions, with cancer, stroke, heart disease, fibromyalgia, and osteoporosis among the most common. When comparing the prevalence of chronic health conditions in this sample with the figures available in the public health domain,[21] the sample of baby boomers investigated in this study are healthier than the wider population of baby boomers. Nevertheless, significant numbers are living with at least one chronic condition and many of these conditions, such as hypertension and high cholesterol, are often associated with unhealthy lifestyles.[26] The economic burden resulting from such chronic diseases in these large numbers cannot be ignored, and preventative measures need to be given priority in healthcare.[27]

As shown in Figure 1, government-run specialist websites, such as NHS Choices, are the preferred choice for baby boomers when searching for online health information, with 45% using such sites regularly and a further 32% accessing them sometimes. Only 16% used general information sites, such as Wikipedia, on a regular basis, with over one-third turning to them occasionally. Online support groups and forums (such as cancer support and chronic obstructive pulmonary disease [COPD] support) were used at least occasionally by 38% and 23%, respectively, while other sources, such as blogs, electronic newsletters, and social media, were used less frequently and, for the vast majority of respondents, were never used. Therefore, the potential benefits of interactive social media, such as enabling individuals to become health advocates and collaborators,[12] have some way to go before being recognised.

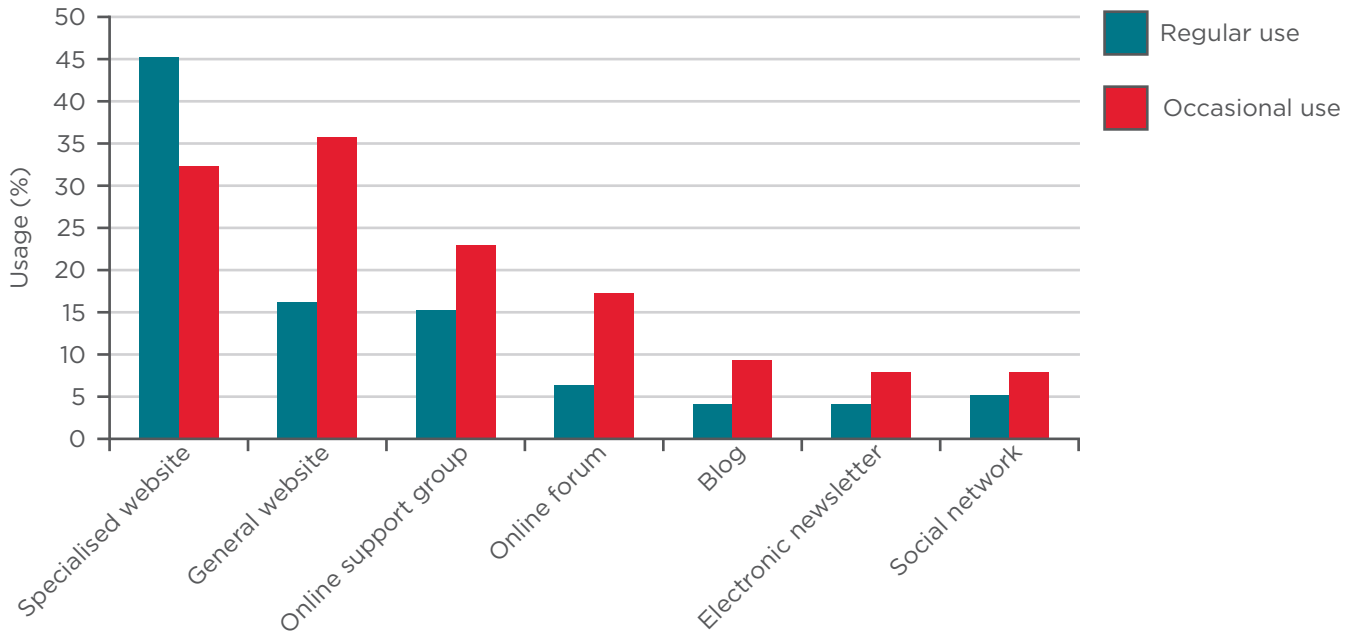

Figure 1: Sources of electronic health resources.

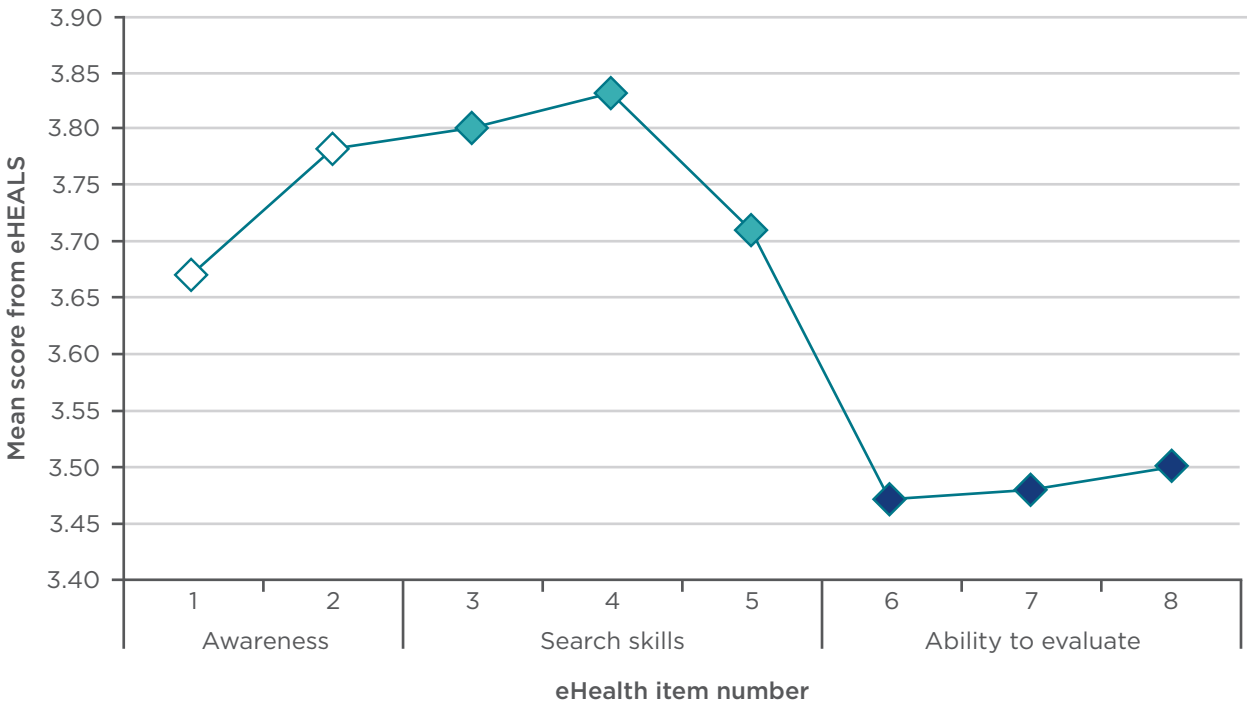

Figure 2: Electronic health literacy.
eHEALS assesses self-perceptions of three important and distinct (though inter-related) elements of eHealth literacy: Awareness of internet health resources (items 1 and 2), the skills needed to access them (items 3–5), and the self-belief that one can effectively evaluate them (items 6–8).[24] See **Table 1**.
eHEALS: eHealth literacy scale; eHealth: electronic health.

Despite increasing adoption rates among older adults, young people are still the most likely to use social media,[28] and, hence, these results may be less pronounced among younger samples. Nevertheless, these findings reflect results from earlier studies which report that, in comparison to using other internet health resources, the use of social media is lacking.[29] Extensive research into social media with a health focus is still needed, and this is a topic for future research.[30]

Even at this stage in the lives of the study participants, there is the potential for intervention to reduce modifiable risk factors.[21,26] While the major information sources depicted in Figure 1 currently offer lifestyle information on diet and exercise, there is an opportunity for these key information providers to better stress preventative measures and the need for lifestyle changes. Perhaps the baby boomers who do not access such online resources are more important to consider and target education to. There is a very real risk of a 'digital divide',[31,32] where health inequalities may be intensified as increasing numbers of health systems and health information rely on technology.

Turning to eHealth literacy, Figure 2 demonstrates the three elements and the average score for each of the eight items. The study sample comprised baby boomers who had used the internet to search for health information in the previous 6 months. Hence, the sample is drawn from the upper level of the cohort in terms of those who use the internet for eHealth purposes. There are still some discrepancies, however, in the levels of awareness of exactly what eHealth resources are available online (items 1 and 2). Given the nature of the sample, these baby boomers demonstrated relatively high levels of internet searching skills and, therefore, the majority felt confident that they knew how to find eHealth online resources (items 3 and 4). However, although the sample participants were relatively confident in terms of eHealth awareness and internet search skills, they were far less confident in their ability to effectively evaluate online health resources (item 6) (Figure 2). They also experienced difficulties in determining high-quality health resources and information from low-quality health resources and information on the internet (item 7) and did not feel particularly confident in using the online information they found to make

health decisions (item 8). Concerns relating to the lack of control over the quality of some online health resources have previously been raised,[12] and the fact that there are such high levels of evaluation problems, even among those who do use the internet for health information, is a major issue that needs to be addressed.

Analysis was then used to examine differences within the sample. An independent t-test revealed highly significant differences between sexes (t=-5.508; degrees of freedom=405; p<0.001), with males demonstrating higher levels of eHealth literacy than females. There were no significant differences between those who worked and those who were retired or homemakers. However, the small number of unemployed individuals in this sample demonstrated significantly poorer eHealth skills than the rest of the sample ($F_{(3,392)}$=1.778; p<0.05). Finally, a significant positive correlation was found between educational attainment and eHealth literacy (r=0.162; N=407; p=0.001). Most of these findings reflect the patterns identified in studies of inequalities among older people and overall health literacy. There is powerful evidence of gender inequalities in financial security in later life,[33] and it is well established that people with limited resources, both financial and social, and low educational attainment are more likely to have restricted health literacy.[34] The results found here suggest that eHealth literacy follows a similar trajectory. The one unexpected finding is the lack of significant differences between workers, retirees, and homemakers; however, it should be kept in mind that the term homemaker incorporates both traditional housewives, who are often female, as well as a growing number of older males who, for various reasons, are not actively seeking work and therefore not classified as unemployed.[35] More research is needed in this area.

Clearly, even among these adopters of eHealth online resources, there is still a great deal of variance in the knowledge about the resources that are available, and there are particular skill gaps in the ability to evaluate and use this information to make informed health decisions. There are also differences within this sample, with lower levels of eHealth literacy found among women and less educated individuals. Therefore, there is a need to pinpoint the precise skill gaps and underlying reasons to allow effective design of training programmes to ensure that the vast array of online health resources are accessible and of value to this important cohort.

Perhaps what is even more important are those baby boomers who did not meet the criteria for inclusion in this sample. It is currently estimated that almost 90% of baby boomers use the internet, and half of these do so for health purposes.[19] Clearly, this leaves 1 in 10 who do not have any access to these resources, and half of those baby boomers who do have internet access choose not to use online health resources. The vast amounts of online health information and lifestyle advice is failing to reach the majority of baby boomers.

This study is not without its limitations. First, it is a cross-sectional study, relying on a single-age cohort, and results may differ if a wider age range was used. Second, the study focusses solely on eHEALS, the most extensively used self-perceived measure of eHealth literacy,[24] and does not include any objective measures. There are two previous studies that examined the relationship of eHEALS with actual eHealth literacy. In the first, 88 participants completed a variety of health-related performance tests to measure their internet skills.[36] Results revealed no correlation between performance and self-perceived eHealth literacy as measured by the eHEALS scale. Therefore, this outcome cast some doubt on the validity of the eHEALS scale. A more recent study, however, finding this result "somewhat surprising", used 15 computerised simulation tasks and compared the performance on these tasks to the scores on the eHEALS scale.[37] In this second study, a correlation between self-perceived and actual eHealth literacy was found, though to a moderate degree, leading the authors to conclude that people make a reasonable evaluation of their eHealth literacy level, although not always accurately. More research needs to be conducted into the validity of the eHEALS scale as a measure of eHealth literacy.

CONCLUSION

Baby boomers are the elderly population of tomorrow and are forecast to place significant financial burden on healthcare systems.[38,39] This sample was drawn from those boomers who use the internet for health purposes and so the participants were expected to demonstrate much more competent eHealth literacy skills than those boomers, currently >50% of this cohort, who do not use the internet for health purposes. Yet, even among this sample, there are skill gaps, particularly around evaluation and use of online health

resources, and significant differences based on sex, work status, and educational attainment. Greater skill gaps could be expected within other samples of baby boomers and, hence, there is a need to address these gaps. Practical intervention and training in eHealth is crucial because eHealth has the potential to assist patients with chronic health conditions in self-management,[40] which could significantly reduce the burden on healthcare provision. Improvements in competence levels of eHealth literacy will also have associated benefits in terms of confidence in using other eHealth resources, including eHealth records, patient portals, and self-management tools.[41] Therefore, an understanding of the current skill levels and training gaps is needed for policy makers and healthcare providers to develop targeted interventions and training for different sectors of the population. This study suggests progression is needed before eHealth technologies can reach their full potential in empowering patients to play an active role in their own healthcare.

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PRECISION ONCOLOGY WITH ELECTRONIC MEDICAL RECORDS

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ABSTRACT

Electronic medical record (EMR)-based precision oncology is a vision that is so far limited to a few pilot and basket studies, with the goal being the design of a proper treatment for cancer patients in real time, based on the panomics knowledge of the patient, and that of similar types of patients. It aims to deliver better treatment outcomes through the design of rational drug combinations, a lower number of futile therapies, reduced patient discomfort, and a healthy human society with a reduced risk of cancer. The concept of precision oncology began with a few cancer awareness programmes and preventative screenings almost a decade ago. However, the technique took an astronomical leap with the start of the Precision Medicine Initiative Cohort Program and Cancer Moonshot programme very recently. Both projects have invested heavily towards several goals, including the merging of cancer registries and EMR to find the best treatment options for a cancer patient, an idea which, if extended globally, will generate unprecedented possibilities for precision oncology. EMR serve as a broad platform merging a variety of patient information and expert advice to facilitate co-ordinated cancer care. In this article, a summary of the recent EMR-based precision oncology practices for prevention, diagnosis, prognosis, prediction, and their associated concerns and limitations is presented. Though the path of precision oncology is unchartered, the usefulness of real-time information derived from EMR or electronic health records will lead to better precision decision-based oncotherapies.

Keywords: Electronic health records (EHR), electronic medical record (EMR), individualised medicine, panomics, precision cancer medicine, precision decision, stratified medicine.

INTRODUCTION

Cancer is a universal phenomenon, yet each cancer type differs from the other variants. In addition, individual human beings differ from one another by a genome difference of approximately 1%. This tiny difference in the genome sequence, in turn, causes a huge discordance in cancer treatment and drug resistance. The dimensionality of cancer networks is much higher compared to other disease systems; cancer is a genomic disease, harbouring a number of mutated oncogenes and tumour suppressor genes that specify the molecular pathways for tumour growth, sustenance, and progression. The network function depends on the individual patient, external factors, and the ability of the network to overcome treatment mechanisms. The treatment of cancer requires a combined effort among a varied team of experts, including counsellors, medical doctors, caregivers, pathologists, radiologists, surgeons, and others. Irrespective of best efforts, a complex disease like cancer is often unmanageable due to the involvement of genetic, lifestyle, and environmental factors. However, with the use of precision medicine, the situation is improving, albeit slowly. Even though a definitive cure for cancer has not been found, the life expectancy of certain cancer patients has certainly increased.

Predictive, preventative, personalised, and participatory (known as P4) treatment of each individual patient, often coupled with population perspective,[1-3] is one of the definitions of precision

medicine,[4] also known as stratified medicine;[5] it tries to impart proper treatment to a patient in real time.[6,7] Identification, risk assessment, and targeted therapy for cancer patients by considering resources like the genomic sequence, the prevalence of rare mutations, and proteomic profile, among others, is known as precision cancer medicine or precision oncology.[8]

In simpler words, precision oncology can be defined as diagnosis, prognosis, prevention, treatment, and follow-up that are tailored specifically to an individual patient based on their genetic profile and supported by the genetic profiles of similar types of patients;[9,10] it is an emerging approach for disease treatment and prevention that takes into account the genetic variability, environment, and lifestyle-related habits of each person.[11]

DISCUSSION

Precision oncology is applicable to various aspects of human health, for example, identification of presymptomatic individuals, detection of disease, patient-specific therapy, the study of disease evolution, the design of effective surveillance, and management techniques, among others; altogether, it focusses on providing a uniform platform for human health management.[8] Traditional evidence-based medical practice along with precision medicine will pave the way for the achievement of such ambitious goals.

The idea of precision oncology gained momentum after a few 'fit for all' solutions, i.e., molecularly driven therapies that have been devised for certain types of cancers. At present, imatinib has dramatically improved the survival of chronic myeloid leukaemia patients[12,13] and HER2-targeted therapies have improved survival rates of women with metastatic HER2-positive breast cancer.[14,15] More detailed applications of precision oncology have been reported by Hyman et al.[16] Precision oncology aims to reduce morbidity and mortality, along with improving clinical outcomes of cancer patients, as each patient and cancer type is unique, and so must be the precision decision for each treatment.

Catalogue maintenance and curation of cancer sequence variants are crucial for precision oncology and have immense clinical relevance.[17] Profiling the somatic mutations of genes may predict tumour evolution, prognostics, and treatment. In this context, Tsang et al.[18] reviewed various functional annotation resources and tools to interpret variants in precision genomic oncology. OncoPaD,[19] a web-based tool, has been developed for the rational design of cancer next-generation sequencing (NGS) panels based on mutational data.[20] Based on 7,298 cancer cases from 29 cancer types, it estimates the cost-effectiveness of the designed panel on a cohort of tumours and provides reports on the importance of individual mutations for oncogenesis and therapy. The tool helps in addressing many translational and basic research questions, including those regarding precision oncology. The advent of this NGS technique has a crucial role in precision cancer therapy, a subject that cannot be covered in the present article's scope, but is well described elsewhere.[21]

However, the idea of large-scale precision oncology is burdened by many hurdles, for example, acquired resistance of tumours, cost-benefit analysis, clinical evaluation, clinical trial design, drug resistance, genetic and genomic analyses of tumours of patients, informatics methods to evaluate genetic variants, liquid biopsy data-related issues, target prioritisation, molecularly targeted drug effectiveness, and tumour heterogeneity, among others.[22,23] Improvement is needed in the areas of genome sequencing of cancer patients, identification of targets, better access to clinical studies, and design of therapies. In addition, involvement of appropriate parties and stakeholders at every step is crucial for progress in precision oncology, starting from the patient, clinician, physician, caregiver, and third-party insurance providers. These issues should be properly addressed before precision oncology becomes a universal phenomenon for cancer treatment.

In this context, electronic medical records (EMR), the digital version of patient health records, play a crucial role in providing a means by which a patient's previous health history or health history of patients with similar cancer types can be studied and used for real-time treatment. EMR serve as a broad platform that merges a variety of patient information and expert advice to facilitate co-ordinated cancer care.[24] They aid in personalised cancer risk management and treatment by taking into account the behavioural and social contexts.[5] An EMR-adapted healthcare system efficiently streamlines day-to-day hospital procedures, along with internal quality control checks, and facilitates easy access to patient data from anywhere around

the globe following proper authentication from a user. EMR are changing the current practice of medicine, as expected almost a decade ago.[11,25,26]

Interestingly, the basket studies into the use of patient EMR for precision oncology[12-15,21-23,26-35] have provided meaningful observations for better clinical outcomes. New knowledge developed from the large range of EMR data, with help from predictive models, has generated confidence for precision oncology-based decisions. Precision oncology is a nascent area of therapy but, gradually, with help from information technology and more EMR data, it will take shape from the variety of heterogeneous cancer-related patient data. Precision medicine alongside patient EMR will aid prevention, diagnosis, prognosis, and prediction of cancer types, often one form of assistance combined with others, for the improvement of cancer treatment. Here, we discuss the research developments, or rather the lack of them, in these specified areas.

Preventive Approach

There is currently little scope for adding any cancer prevention measures to a patient's EMR, as hardly any such measures exist. Mostly, the preventive measures are limited to small cohort screenings[22] but, as a Pre-Cancer Genome Atlas (PCGA)[36] is being developed, it will be important to add information on preventative measures into EMR to help in individualised cancer care. For example, programmes like the Million Veterans Program[37] and the Precision Medicine Initiative Cohort Program[38] are adding EMR data into their repositories as part of their quest for cancer prevention. Similarly, there are many existing cancer data and knowledge-bases (Table 1) that will be necessary to include for the development of preventative, diagnostic, and prognostic approaches for cancer.

Cancer Diagnosis

To date, the conventional method for cancer diagnosis is mostly based on histopathological reports and radiographic findings. However, the essential role of genomics in the form of biomarkers, molecular signatures, and the molecular profiling reports to detect cancer types cannot be negated. This information is now being stored in the EMR of cancer patients and, in the future, can be used for fast cancer categorisation. Precision cancer diagnostics extend beyond the conventional methods of gene expression profiling and EMR-based decisions. In this respect, we herein discuss some innovations that generate standardised onco-data for inclusion in EMR or electronic health records (EHR).

Pyradiomics[39] is a Python programming language-based open-source radiomic quantification platform to extract radiomic features from computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) images. It establishes a reference standard for radiomic analyses with immense significance that will reflect in cancer diagnosis.[40] The Health Level Seven® (HL7) Clinical Genomics group[41] is working towards the standardisation of genome data and harmonisation with EMR. LesionTracker[42] is a web-based open-source image assessment and tracking platform for oncology clinical trial workflows. Tumor Map[43] is an integrated portal for exploration and interrogation of cancer genomics data by using Google's map technology. It can also facilitate identification of cancer subtypes in silico based on common molecular activities in a set of tumour samples.[44] The inclusion of such data with EMR or EHR will be beneficial for further analyses at a later stage for diagnostic purposes.

Prognostic Approach

Nowadays, a few rapid learning health systems[45-48] are in practice for sourcing prognostic and associative factors from text-based cancer EMR. Text-based Exploratory Pattern Analyser for Prognosticator and Associator discovery (TEPAPA)[45] is a feature learning pipeline for identifying disease-associated factors from unstructured EMR narratives. It has already been applied to a cohort of 82 head and neck squamous cell carcinoma patients' EMR for phenotyping. CancerLinQ™,[46] a cancer decision support system, uses more than a million EMR for any kind of precision decision; it stores data from any format including EMR, provides real-time clinical decision support, measures clinical performance, and generates hypotheses from clinical data to provide lessons learned about technical and logistical challenges. Cancer Commons[49] is a non-profit network of patients, physicians, and scientists who help in identifying the best options for treating an individual's cancer. It facilitates rapid learning for precision oncology by gathering panomic and clinical data about individual patients from the Donate Your Data (DYD) registry.

Furthermore, the Melanoma Rapid Learning Utility (MRLU)[47] is an analytical engine and user interface that provides clinical decision support for

melanoma treatment by identifying and analysing cohorts from a database of 237 metastatic melanoma patients. Precision Oncology 3.0[48] advocates the analysis of panomic data to hypothesise the patient-specific cancer molecular pathways and their personalised treatments by combining the targeted therapies, and Watson,[50] an IBM developed machine learning system, recommends trials and individualised therapies based on cancer patient data obtained from various sources, including EMR. The Electronic Medical Records and Genomics (eMERGE) Network[51] is also helping to develop the EMR-guided cancer genomic studies and associated decisions.

In addition, cancer-associated research often reflects important information for the oncology community based on EMR data, a few of which are discussed. Gregg et al.[27] performed a study of 2,352 prostate cancer patients' EMR to automate the determination of risk strata according to the D'Amico Risk Classification, in which prostate cancer patients can be labelled as low, intermediate, or high-risk. The natural language processing (NLP) algorithms developed by Gregg et al.[27] had 91% raw agreement with manual risk categorisation, with a recall of 78% (N=1,833). With proper standardisation, such automating procedures for collecting risk characteristics will reduce the time and effort taken, while integrating the information into the respective EHR or disease registries.

Symmans et al.[28] have assessed the long-term prognostic risk of breast cancer patients by analysing 1,158 patients' EMR belonging to five cohorts after neoadjuvant chemotherapy alone or in conjunction with HER-2-targeted treatment. Patient-specific age, classification of primary cancer (whether multifocal or multicentric), clinical and radiologic characteristics of primary cancer, clinical stage of cancer before treatment, diabetic status (present or absent), follow-up for relapse or death, height, and weight data have been considered from the respective EMR for the prognostic study. The study indicates long-term survival after neoadjuvant chemotherapy in all the considered phenotypic subsets of breast cancer, albeit with a need for further external validation.

Heo et al.[30] performed a study of 44 advanced biliary tract cancer patients' EMR to investigate the significance of the clinical impact of overexpression of the proto-oncogene *c-MET*. Various patient-specific details have been taken from EMR and expression of the c-MET protein has been generated from tumour samples of metastatic patients for this study. In approximately one-third of the patient population, overexpression of c-MET was found, but it cannot be significantly correlated with the other associated variables, generating a need for further studies.

A research study of 99 smokers' EHR performed by Begnaud et al.[22] reflected a randomised electronic promotion of lung cancer screening and Afghahi et al.[47] found the differential use of chemotherapy associated with sociodemographic characteristics by a study of EMR, cancer registry, and genomic data belonging to 293 breast cancer patients. In addition, Rioth et al.[52] created an automated, real-time database of annotated tumour variants of cancer patients to gather data generated during cancer care for secondary use during the precision decision. Schwaederle et al.[33] generated a study using NGS of 439 diverse cancer patients where they integrated the NGS data with age, cancer histology, sex, stage of metastasis at diagnosis (if any), metastatic disease at the time of the biopsy (if any), and race extracted from electronic medical charts, among others, to find actionable aberrations in patients. Lastly, Servant et al.[53] developed a knowledge data interface that facilitates data integration and tracks the processing of individual samples for precision decision in real-time.

As EMR and/or EHR are being considered as a global data source for cancer prognosis, their completeness in accumulating all kinds of patient-related data is necessary. At present, there are many cancer resources (Table 1) and their inclusion or association with the EMR will ensure a more detailed cancer prognosis.

Predicting Cancer Risk

EMR, the data flat files for cancer patients, can be subjected to standard statistical analysis techniques.[22,28,30,47] Symmans et al.[28] used the Kaplan–Meier estimator with 95% confidence intervals estimated using the Greenwood formula with log-log transformation for determination of survival probability. In addition, Heo et al.[30] used the t-test, Fisher's exact test, or one-way analysis of variance, as appropriate, to analyse correlations between expression of the proto-oncogene *c-MET* and the associated clinicopathologic variables. They used the Kaplan–Meier estimator for the analysis of all time-to-event variables.[30]

Table 1: Examples of existing cancer data and knowledge-bases.

Name	URL	Remarks
Cancer Genome Interpreter	https://www.cancergenomeinterpreter.org/home Last accessed: 14 December 2017.	Relies on existing knowledge for the identification of alterations in a cancer and detection of therapeutically actionable alterations.
Cancer Moonshot	www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative Last accessed: 14 December 2017.	The government of the USA has plans for authorising $1.8 billion in funding for the Cancer Moonshot programme over 7 years, starting from 2017. The project is aimed at vaccine development for cancer types.
Cancer Driver Log (CanDL)	https://candl.osu.edu/ Last accessed: 14 December 2017.	An expert-curated database that lists all possible nucleotide positions for each amino acid change along with their associated literature reference and the chromosome locations.
cBIOPortal	http://www.cbioportal.org/ Last accessed: 14 December 2017.	Large-scale cancer genomics data sets can be visualised, analysed, and downloaded from this source.
Clinical Interpretations of Variations in Cancer (CIViC)	https://civic.genome.wustl.edu/ Last accessed: 14 December 2017.	A cost-free source for variant information and cancer-related mutations.
ClinVar	https://www.ncbi.nlm.nih.gov/clinvar/ Last accessed: 14 December 2017.	Human variations and their associated phenotypes are listed in this database.
Genomics Evidence Neoplasia Information Exchange (GENIE)	http://www.aacr.org/Research/Research/Pages/aacr-project-genie.aspx#.WZWgm1EjHIV Last accessed: 14 December 2017.	This project aggregates and links clinical-grade cancer genomic data with clinical outcomes from tens of thousands of cancer patients treated at multiple international institutions.
Georgetown Database of Cancer (G-DOC)	https://gdoc.georgetown.edu/gdoc/ Last accessed: 14 December 2017.	A precision medicine platform containing molecular and clinical data from thousands of patients and cell lines, along with tools for analysis and data visualisation.
International Cancer Genome Consortium (ICGC)	http://icgc.org/ Last accessed: 14 December 2017.	With 89 committed projects, the goal of the ICGC is to obtain a comprehensive description of genomic, transcriptomic, and epigenomic changes for different tumour types, which has great importance across the globe.
My Cancer Genome	https://www.mycancergenome.org/ Last accessed: 14 December 2017.	A tool that matches tumour mutations to therapies, making information accessible and convenient for clinicians.
National Cancer Institute (NCI)'s Molecular Analysis for Therapy Choice (MATCH)	https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match Last accessed: 14 December 2017.	A precision medicine cancer treatment clinical trial for cancer patients with tumours with specific genetic changes.
OncoKB	http://oncokb.org/#/ Last accessed: 14 December 2017.	A precision oncology knowledge base listing 476 genes, 3,701 variants, 65 tumour types, and 97 drugs.
Personalised cancer therapy	https://pct.mdanderson.org/ Last accessed: 14 December 2017.	An integrated research and clinical trials strategy for implementing personalised cancer therapy and improving patient outcomes.
The Cancer Genome Atlas (TCGA)	https://cancergenome.nih.gov/ Last accessed: 14 December 2017.	Maps of the key genomic changes in 33 types of cancer have been generated and stored in this database.
TCGA Pan-Cancer Compendium	http://bioinformatics.mdanderson.org/TCGA/NGCHMPortal/ Last accessed: 14 December 2017.	Stores next-generation clustered heat maps (NG-CHM) covering multiple tumour and data types profiled by TCGA.
Cistrome Cancer	http://cistrome.org/CistromeCancer/CancerTarget/ Last accessed: 14 December 2017.	Predicted transcription factor targets and enhancer profiles in cancers have been collated from TCGA expression and public ChIP-seq profiles and stored in this resource.

Statistical analysis by Begnaud et al.[22] included the Wilcoxon rank sum test for quantitative characteristics and Fisher's exact test for categorical items, and the multivariable logistic regression technique was used by Afghahi et al.[47]

EMR data can also be subjected to advanced machine learning techniques for better retrieval of insightful information.[27,52] Gregg et al.[27] used natural language processing to achieve >90% accuracy for low, intermediate, and high-risk stratification of localised prostate cancer patients. A naïve Bayes classifier was used by Rioth et al.[52] to categorise cancer patient care data into 18 separate clinical groups with 99.37% accuracy, and Schwaederle et al.[33] used linear or binary logistic regression analyses and Spearman's rho coefficients. However, application of these statistical and machine learning techniques in one or more cancer resources (Table 1) is yet to be attempted.

Limitations

Precision oncology has many limitations at the preventive, diagnostic, prognostic, and predictive stages.[54] Molecular profiling of tumours is not yet used for all types of cancer and many of the molecular alterations observed in patients do not respond to drugs; therefore, more research is required regarding the complete characterisation of viable target biomolecules. Diversity also exists among the types of clinical molecular tests and opinions vary among clinical oncologists regarding the interpretation of genomic test results. These inconsistencies will be reflected in the EHR and will diminish confidence in precision oncology-associated therapies.

Most often, DNA-based alterations, such as mutations and gene duplications, among others, are found to be responsible for the development of a typical subtype of cancer in a patient. A large proportion of EMR lack DNA alteration data of cancer patients, since third-party payers rarely reimburse for mutational analysis, and so forms a major bottleneck for progress in precision oncology. Even when the mutations are available, a great diversity arises when EMR for all patients of a population are referred to as a background study. How to overcome such diversity and reach a consensus for treating a real-time patient is a dilemma for many oncologists.[55]

Furthermore, EMR are often erroneous or have incomplete data. Knowledge derived from such error-prone or partial data either misleads the oncologists or prevents the achievement of a consensual opinion regarding cancer treatment in general. Even if the EMR are correct, various protocols and sometimes unbalanced treatments across the globe contribute a lot of variation, and a small sample size and heterogeneous patient population may create more confusion. Automated data collection from EMR cannot guarantee the precision level of manual data extraction by experts and the allowable level of precision in automated data collection is a big debate. However, >90% precision is generally considered high. Overfitting of data must be avoided while aiming for higher levels of precision.[27]

An EMR is a single record of disease instance and, for better cancer care, a properly monitored EHR should be established for a patient. An EHR is an accumulation of multiple EMR over a time period listing the relapse of cancer and retreatment, where applicable; it should list the patient history, family histories, detailed social histories, the testing and imaging results, treatment details, and genomic information to be considered as an ideal cancer EHR.[24] However, there is no universal guideline for criteria of an EHR, except a definition of minimum requirement from the World Health Organization (WHO)[56] for structuring EMR or EHR.

Moreover, searching for a common factor across related EHR may be a daunting and large task due to a lack of interconnections, mutual compatibility, and interoperability.[5] If similar types of EHR cannot be analysed in real time, finding a common clue for a disease will prove difficult. To date, no uniform approach to address all the above-mentioned issues is in place. Altogether, the lack of completeness, consistency, homogeneity, and accuracy of cancer EMR or EHR will reflect in precision oncology-based decisions. Hence, a robust universal format and clear regulations should exist for patient EMR to avoid these caveats and to ensure reliability and efficiency.[57,58]

In developed countries, maintenance of the EHR is a must for the free centralised government healthcare; a report regarding this has been penned by Ben-Assuli.[59] However, in developing and under-developed countries, the maintenance of EHR is performed by third parties, particularly for insurance purposes of the wealthier population who can afford private healthcare facilities. It is often pursued in a very incomplete and sporadic manner. As precision oncotherapies are heavily dependent on population or cohort-based details, EHR data

of developed countries may not help for precision oncology-based treatments in other geographic populations. A lack of proper EHR data will delay and hamper the scope of precision oncology in these countries.

EMR-based precision oncology has provided a large amount of introspection and garnered a lot of focus; however, whether it has generated enough confidence for the decisions to be adopted for clinical and therapeutic purposes is doubtful. A selection of scientists and researchers have already expressed their concerns regarding the performance of precision oncology[60,61] and there are doubts regarding clinical usefulness of targeted therapies derived from EMR.[62] According to these professionals, current precision oncology practices are too simple an approach for a complex disease like cancer. However, there is also another cohort of professionals who strongly believe in it due to a few clinically useful, although unexpected, advances.[63,64] Often, the same researchers are found to sway between feeling hope, optimism, and/or concern regarding precision oncology. Whether the concept of precision oncology will be the next groundbreaking landmark innovation of science, or result in a pseudo-innovation, is not clear.[65-67] However, the authors' opinions favour pragmatic optimism with the advent of the new cloud-based software platforms,[68,69] novel ways for phenotypic representation[70] and stratification,[71] multiomics data analytics platforms,[72] and big data infrastructures[73] for advancement of precision oncology.

CONCLUSION

In this paper, the authors have introduced the emerging area of electronic record (EMR/EHR)-based advances for the improvement of cancer treatment. Moreover, this paper has summarised a few of the recent EMR-based precision oncology practices for prevention, diagnosis, prognosis, prediction, and their associated concerns and limitations.

A cancer patient experiences many emotional and physical hurdles, starting from the initial confirmation and acceptance of their diagnosis. The associated stress, stigma, and sickness looms like a black cloud over the patient. Irrespective of any kind of curative or palliative care, a cancer patient's life expectancy certainly decreases following diagnosis; some patients have a few days of life or a few years, while others live longer, but always with a fear of tumour recurrence. In these scenarios, even a few scientific details derived from EMR and some unexpected advances that aid in oncotherapy become a baton of hope and belief.

The idea of EMR data-derived precision oncology is novel and the path for achieving this idea is unchartered, while the limitations are many. With the increase of lifestyle addictions and disorders coupled with the genetic and environmental factors, cancer is becoming the second leading cause of global death,[74] with 75% of deaths occurring in low and middle-income countries. However, the unbeatable human desire for cancer-free, longer, and healthier lifespans also exists and EMR/EHR will lead the way towards this through precision oncology-based therapies.

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A TRANSITION FROM DISEASE-CENTRED TO GOAL-DIRECTED INDIVIDUALISED CARE OF PATIENTS WITH MULTIPLE MORBIDITIES: A JOURNEY TO GOAL-ORIENTATED PATIENT HEALTHCARE

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ABSTRACT

Goal-orientated healthcare is multi-level strategic planning of medical care in which the patient's goals are set first and, thereafter, their operationalisation is implemented into clinical practice. This is a novel approach to the management of patients with multiple morbidities. In this care model, the patients are treated as partners participating in a therapy process that is focussed on improving quality of life and health outcomes. This approach also facilitates the achievement of individually desired therapeutic targets by patients, their families, and/or their caregivers. The aim of this review is to present the concept of goal-orientated care based on current research from the medical literature and to describe some serious concerns related to the disease-centred model commonly used for patients with complex medical and/or mental conditions, such as the elderly. To illustrate the advantages and limitations of the goal-orientated patient care model, two exemplary cases of patients often seen in practice, such as primary care, cardiology, or geriatrics, are briefly described. The principles of goal-orientated patient care and available solutions to common problems should be useful to both the medical practitioners and their patients, in many contexts of multidisciplinary collaboration.

Keywords: Care team, goal-orientated, multidisciplinary, multiple chronic conditions, patient activation, patient-centred care, patient engagement.

INTRODUCTION

A goal-directed healthcare system involves multi-level strategic planning for medical care. Within this approach, the patient's goals are set first, and then their operationalisation is implemented into clinical practice. This is particularly important for patients with multiple chronic conditions, or those with short life expectancies, for whom the standard outcome measures may not be as relevant.[1] To explore some challenges related to goal-orientated care and propose solutions to commonly encountered clinical problems, two virtual patient cases that are often seen in clinical practice, for example primary or speciality care, are presented hereafter.

Case Study One

The first patient is a 78-year-old man who presents with decreased appetite, weakness, sadness, and insomnia. He has been diagnosed by his physicians with chronic diseases, including arterial hypertension (HTN), congestive heart failure, Type 2 diabetes mellitus (T2DM), and depression; he receives treatment prescribed by different specialists according to the recent state-of-the-art guidelines. For example, to achieve a better blood pressure control, his cardiologist increased the dose of beta-blockers and diuretics. In addition, to optimise his glycaemic control, his diabetologist increased the dose of blood glucose-lowering medication. Furthermore, his psychiatrist is concerned that the adjustment to the patient's cardiac medications could potentially aggravate

his depression, and, therefore, he advised discontinuation of the beta-blocker therapy and starting a new antidepressant therapy. A primary care physician, knowing that the patient lives alone, recommended a nursing home placement since his care would be easier to manage in the in-patient setting. Overall, and strictly based on medical evidence, the therapeutic choices that were made by these physicians were appropriate. In reality, however, these recommendations were not helpful to the patient, since he still feels fatigued and wishes to stay at home.

Case Study Two

The second patient is an 86-year-old woman with medical history positive for coronary heart disease, a myocardial infarction 20 years ago, HTN, T2DM, thyroid insufficiency, dyslipidaemia, and mild dementia. The patient lives with her family and is cared for by her cardiologist, endocrinologist, neurologist, psychiatrist, and primary care physician. She takes nine prescription medications, as well as a few dietary supplements, amounting to approximately 18 tablets daily. Her physicians strive to achieve target therapeutic goals; however, when a social worker interviewed the patient, she discovered that the patient's goals were different to those of the physicians and included taking a smaller number of daily medications so as to avoid confusion and minimise potential medication errors. Furthermore, both the patient and her family desired to decrease the number of hospitalisations, since the visits are extremely stressful. At this point, simplification of the therapeutic regimen and honouring the patient's wish to remain at home for as long as possible should be the main objectives, especially when the life expectancy of the patient is limited.

Discussion of Case Studies

It should be noted that, in both cases, the physicians appropriately followed evidence-based guidelines based on target values for blood pressure and glycaemic control, and adjusted the pharmacotherapy based on separate disease-related goals.[2,3] However, there is a discrepancy between the disease-focussed recommendations (strictly followed by these physicians) and the goal-directed treatment approach, which considers the individual patient goals and preferences. Recently, patient goal-orientated care has gained more interest. In practical terms, this means that, instead of fragmented care, where different diseases are treated without the necessary co-ordination, the patient's goals should be identified as early as possible, as a key element of the interdisciplinary therapeutic management.[1,4] This new approach will consequently lead to the eradication of unnecessary medications or an adjustment of treatment doses, subsequently eliminating some related dietary restrictions. It will also motivate patients to participate in exercise programmes and community support groups.[1,4] Communication between the treating physicians, both primary care and consulting specialists, is needed to determine what interventions work best for every individual patient, and which professional should be considered as a medical partner 'in charge' of the patient's health.[1,4]

DISADVANTAGES OF THE DISEASE-CENTRED APPROACH

Common disadvantages of the traditional, fragmented approach of focussing on individual diseases, for example, in elderly patients with multiple comorbidities, include the treatment burden, relevant to often contradictory recommendations for different conditions (e.g., treatments that are beneficial for one disease can worsen the condition of another).[5,6] In addition, many treatments do not favour the patients' wishes. Therefore, expensive medical care often does not translate to the desired outcomes of the patients, their families, and/or their caregivers. This is frustrating for both the patients and medical personnel. Furthermore, when a group of medical professionals is treating many individual diseases in the same patient, it is often unclear who is responsible for prescribing certain medications or making decisions. In this situation, patients aged >70 years who are prescribed ≥5 medications are most vulnerable to medical errors.[5,6]

ADDRESSING THE PATIENTS' GOALS AND PREFERENCES

In a recent study survey, a group of primary care physicians who had experience with caring for the elderly population were asked how they approached treatment decision-making in patients with multiple medical conditions, taking many medications, as compared to younger patients without multiple medical conditions. In addition, the doctors were asked to consider how the clinical guidelines should be applied to these elderly patients and whether the patient's condition influenced the patient's decision-making.[7]

According to the survey results, the physicians needed much more information on the risk and benefit ratios for treatments of common comorbid diseases. In addition, they understood theoretically that the patients' goals and preferences needed to be acknowledged by the treatment team; however, they had received no adequate practical training focussed on these issues. Furthermore, incorporating the patients' goals and preferences into the management process would require relevant guidelines and quality measures for the patient-centred metrics, rather than for the individual diseases. Compensation for the time spent on precise communications regarding the patient's goals of care and skilful integration of the medical and personal needs would also be necessary. It is expected that the goal-orientated model will be cost-effective in the long-term, compared to ordering expensive tests and therapies that are often unnecessary or incompatible with the patient's wishes.[8]

Table 1: The main barriers to goal-directed patient care from the physician's and patient's perspective.

The barriers for physicians[18]	**Possible strategies for solutions or potential clinical implications**	**Practical tools or methodologies to accomplish goals**
Insufficient time during routine visits, a busy work schedule, and brief contact and superficial communication with patients.	Acquiring skills to communicate clearly and efficiently, and learning how to delegate some additional duties to other members of the treatment team.	Building professional relationships with patients and using available technology to communicate with patients.[11,14,19] Create an algorithm: how to delegate certain tasks to nurses, therapists, secretaries, or social workers.[16]
Medical school or residency training is mostly directed at diagnosing and treating diseases.	Teaching practical communication skills as a part of the medical school curriculum.	Practical training in patient and physician communication through role playing, focussed on various therapeutic scenarios or options (from both the patient's and the physician's point of view).[10-12]
Lack of skills to identify individual patient goals or needs.	Incorporating input from patients and considering it when scheduling speciality consultations, diagnostics, and therapeutic procedures.	Documentation and update of the patients' goals and preferences in their medical records.[10-12]
Reductionism: different specialists giving unco-ordinated or conflicting recommendations for the same patient.	Improving the flow of information between various speciality consultants and co-ordinating referrals and procedures. Finding a proper balance between the medical necessity and the patient preferences, and introducing simple methods to facilitate collaboration between primary and speciality care.	Determining who is in charge of managing which diseases and deciding ahead of time. This involves documenting when and how the discrepancies between the medical advice and the patient wishes will be addressed. In addition, indicating specific reasons for the speciality referrals (for example, adding the patient's individual goals to the medical diagnosis, such as to avoid unnecessary hospitalisations or to reduce a number of daily medications).[8-11]
The barriers for patients	**Possible strategies for solutions or potential clinical implications**	**Practical tools or methodologies to accomplish goals**
Difficulties articulating their own needs, goals, and wishes.	Creating opportunities for patients to express their goals, which is crucial for making healthcare decisions.	Scheduling visits with social workers or nurses to receive direct input from patients, such as health-related goals and preferences.[12,16]
The common stereotype that patients are only passive recipients of the medical care.	Transforming patients to active partners, who participate in decision-making throughout the therapy process. Reinforcing the patient's adherence to medical recommendations.	Ongoing patient education, self-monitoring, and self-management. Support groups for patients, families, and caregivers, and regular medication utilisation reviews and follow-up calls from medical staff.[10,11,14,15]
A lack of concept of the physician–patient partnership in the traditional healthcare model.	Encouraging patients to work with their medical providers to accomplish the individual health-orientated goals, in line with medical advice.	Resources from the American Geriatrics Society (AGS) to empower patients to play an active role in the management of their health conditions.[10-12]

A TRANSITION FROM DISEASE-CENTRED CARE TO A GOAL-DIRECTED MODEL OF PATIENT CARE

In most circumstances, the optimal time to transition to the goal-directed model of care is when the standard treatment becomes a burden or when it is more likely to cause harm than benefit for the patient. The transition should also be considered when there is a growing discrepancy between the provided medical care and the patient's own healthcare priorities.[8,9] At this point, identification of the most appropriate type of care is required, particularly for patients with multiple chronic conditions.[8,9] In practical terms, it is necessary to focus on the patient's functional outcomes, such as important daily activities. It is also useful to incorporate information about patient functionality into medical records so that the information is easily accessible and easily transmissible to all treatment team members. Moreover, medication reconciliation helps facilitate the goal-directed care for an individual patient since it can verify whether the medications prescribed by different specialists are appropriate, not only for medical reasons but also for achieving the patient's goals and maintaining quality of life.[8,9] However, it should be kept in mind that this approach is not free from potential problems; for example, it may be difficult to operationalise what an individual patient goal could be for personal autonomy. In additon, many patients are concerned about being a burden to their families.

It should be highlighted that disease-based goals are vital to some patients since they are disease-specific and often include specific signs and symptoms, such as dyspnoea, chest pain, or other acute medical problems, and functional or health-related quality of life outcomes (e.g., specific measures for quality of life relevant to arthritis and other chronic conditions) that can be effectively managed. On the other hand, personalised goals are particularly important for patients with multiple chronic conditions or limited life expectancy, for whom the traditional outcome measures may be insufficient; these patients are often interested in their comfort, autonomy, and independence, while their caregivers commonly focus on safety issues.[8,9] In summary, both the disease-centred model and the goal-directed model have advantages and disadvantages, and, therefore, physicians should balance these two approaches according to the requirements of the individual patient.

ADVANTAGES AND BARRIERS TO GOAL-DIRECTED, PATIENT-CENTRED CARE

The goal-directed healthcare approach simplifies decision-making for patients with multiple chronic conditions.[10,11] It also prompts patients to express what they want from their healthcare, and creates a common, mutually agreed upon path for both the patient and medical provider with regard to the next steps in the medical care.[11] There are also many obstacles regarding goal-directed care related to the patients; for example, difficulties in articulating personal health-related goals, literacy, and cultural issues, and to the physicians, such as limited time for appointments, lack of adequate training, and/or insufficient infrastructure (Table 1).[10,11] Furthermore, one of the largest barriers to goal-directed care is reductionism between the various specialists, many of whom have different beliefs about what type of specialised tests, procedures, or medications should be applied.[11,12] Therefore, it is crucial to determine who is in charge of managing inter-related comorbidities (e.g., malignancy and cardiovascular diseases), or what happens when the recommendations from different specialists conflict. It is possible that many practising physicians may not be prepared for goal-directed care due to a range of factors, including a lack of inclusion in core curriculums and time constraints. Furthermore, the patient's goals can be transient; for example, after a myocardial infarction and subsequent reduced ejection fraction, the functional goals need to be re-established. The goals can also be unrealistic; for example, a patient who suffered a stroke followed by hemiplegia who wants to drive a car. Medical practitioners need to be prepared for such dynamically changing scenarios and react in a professional manner, whilst also having a supportive and emphatic attitude.

POTENTIAL STRATEGIES TO ACCOMPLISH FUNCTIONAL GOALS OF INDIVIDUAL PATIENTS

One of the potential solutions to achieving patient functional goals is the Informatics Corporation of America (ICA) CareAlign® project, which aligns primary and speciality care to focus on priorities that matter most to patients with multiple chronic conditions, based on their medical preferences and goals.[13] The project involves primary care and speciality physicians, patients, caregivers, healthcare

experts, and organisations. The main goal is to design a flexible healthcare system that is focussed on achieving safe and effective care for better individualised outcomes, in the most economical way. In particular, CareAlign targets the gaps between primary and speciality care, and the discrepancy between addressing standard medical needs and fulfilling individual patient needs, for example, a reduction of disease symptoms, improvement of function, and/or independence.[13] In essence, this means that while treating arterial HTN or heart failure for instance, the main purpose of the treatment is to meet the functional goals of the individual patient rather than to strictly manage their laboratory parameters.[13]

INTEGRATING INPUT FROM INDIVIDUAL PATIENTS WITH THEIR MULTIDISCIPLINARY CARE

The first step in integrating patient input into their multidisciplinary care is to document and regularly update the patients' goals, which may be subject to change. Therefore, it is necessary to create opportunities for patients to express their goals, which will be crucial for making healthcare decisions. Physicians who have established professional relationships with their patients and are therefore familiar with their patients' condition and prognosis, should use this relationship to come to a mutual decision, rather than an individual decision, with regard to the recommended therapy as well as other available treatment options, including the associated benefits and risks to the patient.[14]

Traditionally, for a patient with multiple chronic diseases, several decisions must be made during the short visit to their physician. Since this is usually not feasible and unsatisfactory to physicians and patients, there is a growing need to create a more efficient, shared decision-making model in which the patient, or the designated family member or caregiver, sets the goals, and the treating physicians, or other members of the medical team, estimate the probability that the available therapies can help the patient to achieve these goals.[15] Subsequently, a shared care plan should be formulated, in which input from patients is considered when arranging referrals to speciality care (Table 1). Another critical task is to transform the patients from passive treatment recipients to active partners in their healthcare, where they will participate in the decision-making process throughout their therapy. This requires ongoing patient education, self-monitoring, adherence to recommendations, and self-management. Furthermore, since both primary care and specialist physicians do not have sufficient time to address many of these issues, it is essential for them to acquire skills on how to communicate efficiently and delegate some duties to other members of the treatment team for example, nurses, therapists, or social workers (Table 1).[15,16]

It should be noted that the roles and responsibilities of the team members need to be well established and then flexibly adjusted according to dynamically changing demands. Also, transmitting medical information, including preliminary decisions agreed upon by all team members, to the patients and their caregivers as promptly as possible is of utmost importance. Furthermore, when moving from disease-specific to goal-directed referrals, co-ordination of various medical tasks and optimising interactions between members of multidisciplinary teams are essential. For instance, including not only the patient's medical diagnosis but also their goals in speciality referrals would not only facilitate collaboration between medical practitioners but also help ensure high-quality care for the patient (Table 1).[17]

PATIENT ENGAGEMENT AND ACTIVATION

Patient engagement is the willingness and practical knowledge that is necessary for a patient to take a major part in his or her own healthcare. For medical personnel, patient engagement means that the patient is playing the role of the responsible partner, so that the treatment team can best achieve mutually agreed upon goals.[18] In this partnership collaboration, the patients are encouraged to develop skills to accomplish their individual health-orientated goals. According to the Society for Participatory Medicine (SPM), engaged patients are not only well educated but also empowered as they move from being passive 'passengers' to active 'drivers' of their health conditions. Patient activation includes four levels: a) a belief that the physician is completely in charge of the health condition, b) an opinion that, in addition to the physician's care or guidance, making lifestyle changes will result in better outcomes, c) the patient has a participatory role in the healthcare team, and d) the patient has a driver position and is in control of making healthcare decisions.[18]

Some patients actively search for healthcare providers who will consider them as partners in their own care.

BENEFITS OF THE PARTICIPATORY MEDICINE MODEL

Patient engagement and active participation in medical care makes a significant difference for both the health of patients and the work of physicians. For instance, in some specialities, like cardiology, oncology, palliative care, or geriatrics, there should be particularly close communication with patients, since there is no single right answer to their complex levels of care. From a physician's perspective, it is more likely that certain clinical goals will be achieved when the goals have been previously discussed with the patients. Therefore, inviting patients to participate in the care process is superior to solely prescribing medications.[19] Moreover, many patients can provide invaluable feedback that will guide further therapeutic choices.[20] Participatory medicine has practical implications, especially in the management of chronic diseases, such as T2DM, HTN, coronary heart disease, or congestive heart failure. According to a recent study, a higher patient activation was associated with a reduction of glycated haemoglobin levels.[21]

CONCLUSION

In summary, implementation of goal-directed healthcare should facilitate the achievement of specific goals that matter most to the individual patients, their families, and their caregivers, and improve their functional outcomes and quality of life. This involves articulating, recording, and forwarding these goals to the entire medical team so that goal-based shared decisions can be made accordingly. Subsequently, integration of patients' goals with medical recommendations, as well as co-ordination of care between various physicians and medical settings, needs to be well documented and maintained. The two aforementioned virtual patient case studies are commonly encountered in a daily practice setting, and they illustrate how individual situations could be improved using goal-directed therapies. It is possible that certain patients would benefit more from the goal-directed care than the disease-centred care; however, at present, there are not sufficient outcome measures available to evidence this (e.g., patient satisfaction data). To conclude, patient engagement and activation have become a major focus of healthcare, both in clinical and research medicine. Therefore, further studies in patients with multiple chronic conditions, especially older patients, aimed at person-centred care, are definitely warranted.

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NANOPARTICLES AS EMERGING DIAGNOSTIC TOOLS IN LIQUID TUMOURS

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ABSTRACT

Nanotechnology has become an important approach to improving the diagnosis and treatment of cancer; advances in this area have made it possible to use various materials to detect cancers in the early stages. Materials at the nanoscale have unique physical, optical, and electrical properties that are useful for cancer detection. Nanoparticles, alongside the discovery of several biomarkers, made it possible to reduce the detection limit of cancer biomarkers and this breakthrough provided the possibility of new methodologies for diagnosis with simple and non-invasive approaches. Haematological malignancies such as leukaemia and lymphoma represent a specific class of cancer that attract special attention in this area of diagnoses. The aim of this review is to elucidate the applications of nanotechnology for these types of cancer and the potentialities of nanotechnology for the diagnosis of haematological malignancies. When combined onto a single nanomaterial (an approach known as nanotheranostics), these platforms may revolutionise the way we tackle liquid tumours, as well as providing innovative tools for precision oncology, diagnostics, and follow-up therapy and disease management.

Keywords: Circulating tumour cells, circulating tumour DNA (ctDNA), exosomes, leukaemia, liquid tumours, lymphoma, nanomedicine, nanoparticles.

INTRODUCTION

Nanotechnology offers multiple solutions for cancer diagnostics and therapy, as it is capable of detecting even a single cancerous cell, as well as acting as a vehicle of drug delivery to the cell. Nanodiagnostic strategies are being developed to meet the requirements of clinical practice, providing increased sensitivity for early detection of disease biomarkers. Nanoparticles play a central role in the development of the new generation of platforms for cancer biomarkers detection, which is essential for precise treatment regimes. The versatile structural and functional properties of nanoparticles, which are incomparable to bulk materials, pave the way for the development of rapid, specific, and sensitive diagnostics, opening the door for decentralised assessments and/or ambulatory follow-ups.[1]

Despite their significant impact, haematological disorders have been rather neglected where nanotechnology platforms are concerned; the majority of these techniques have been directed at solid tumours. Nevertheless, haematological disorders are very good candidates for this approach, since the molecular basis of each sub-group of patients is well-defined by typified molecular alteration that may easily be integrated to develop suitable diagnostic schemes. Additionally, when retrieving a patient's blood sample (liquid biopsy), one is gathering information on the patient's full tumour profile via a less invasive routine.

BASICS OF LIQUID TUMOURS

Haematological malignancies comprise several different disorders, such as leukaemia, lymphoma, and myeloma, which affect the bone marrow, lymphatic system, and blood cells, respectively. In fact, haematological malignancies are the most frequent cancer type in children and young adults.[2] Haematopoietic differentiation provides multiple occasions for mutations and other disruptive events to occur, resulting in distinct tumour subtypes and varying clinical presentations.[3] The tremendous heterogeneity of haematopoietic and lymphoid tumours presents unique challenges for diagnosis and treatment.[4-6] In the following section, we detail some of these differences and highlight the relevant biomarkers of disease.

Leukaemia

Leukaemia is a clonal disorder originating in the bone marrow during haematopoiesis, characterised by unregulated proliferation of poorly differentiated white blood cells (blasts). Disease classification is based on the affected cell type (myeloid or lymphoid) and the degree of cell proliferation (acute or chronic).[3] Acute myeloid leukaemia (AML) is most common in adults, while acute lymphocytic leukaemia (ALL) is more prevalent in children.[2] Chronic myeloid leukaemia (CML) is a myeloproliferative disorder with an annual incidence of 1–2 cases per 100,000 adults, accounting for 15–20% of newly diagnosed adult cases of leukaemia.[2,7]

Table 1: Common genetic abnormalities associated to haematological disorders.[11,13]

Disorder	Subtype	Frequent genetic biomarkers
Leukaemia	AML	• t(8;21)(q22;q22); *RUNX1-RUNX1T1* • inv(16)(p13;q22) or t(16;16)(p13;q22); *CBFB-MYH11* • t(15;17)(q22;q12); *PML-RARA* • t(9;11)(p21;q23); *MLLT3-KMT2A* • t(6;9)(p23;q34); *DEK-NUP214* • inv(3)(q21;q26) or t(3;3)(q21;q26); *RPN-EVI1*, *GATA2*, *MECOM* • t(1;22)(p13;q13); *RBM15-MKL1* • t(9;22)(q34;q11); *BCR-ABL1* • *CEBPA*, *NPM1*, and *FLT3* mutations (predict response to chemotherapy for cytogenetically normal AML patients)
	CML	• t(9;22)(q34;q11); *BCR-ABL1*
	B cell ALL	• t(9;22)(q34;q11); *BCR-ABL1* • t(v;11q23); *KMT2A* • t(12;21)(p13;q22); *ETV6-RUNX1* • t(5;14)(q31;q32); *IL3-IGH* • t(1;19)(q23;p13); *TCF3-PBX1* • Hyperdiploidy • Hypodiploidy
	T cell ALL	• *TAL1* gene rearrangements (1p32) • *TLX1* gene rearrangements (10q24) • *LMO2* gene rearrangements (11p13) • t(5;14)(q35;q32); *TLX3- BCL11B* • t(10;11)(p12;q14); *PICALM- MLLT10* • *NUP214- ABL1* fusion and amplification • *KMT2A* gene rearrangements (11q23)
Lymphoma	B cell lymphoma	• t(8;14)(q24;q32) or t(2;8)(p12;q24) or t(8;22)(q24;q11); *MYC* (Burkitt lymphoma) • t(14;18)(q32;q21) or t(3;14)(q27;q32) or t(2;3)(p12;q27) or t(3;22)(q27;q11) or t(3;v)(q27;v); *BCL2*, *BCL6* (Diffuse large B cell lymphoma) • t(14;18)(q32;q21); *IGH-BCL2* (Follicular lymphoma) • t(11;14)(q13;q32); *IGH-BCL1* (Mantle cell lymphoma) • t(11;18)(q21;q21) or t(14;18)(q32;q21) or t(1;14)(p22;q32) or t(3;14)(p14;q32); *MALT1*, *IGH* (Marginal zone B cell lymphoma) • t(9;14)(p13;q32); *IGH-PAX5* (Lymphoplasmacytic lymphoma) • del(13q), trisomy 12, del(11q)/*ATM*, and del(17p)/*TP53* (SLL/CLL)
	T cell lymphoma	• t(2;5) (p23;q35); *ALK*

ALL: acute lymphocytic leukaemia; AML: acute myeloid leukaemia; CLL: chronic lymphocytic leukaemia; CML: chronic myeloid leukaemia; SLL: small lymphocytic leukaemia.

Lymphoma

Lymphoma originates in the lymph nodes, where the lymphoid lineage of haematopoiesis differentiates into B, T, or natural killer cells. Several abnormal events may be observed in lymphoma, such as extensive cell proliferation, somatic mutations, and antibody class switching, that ultimately impair the immune system, particularly its adaptive capabilities.[8] It is the most common haematological cancer in more developed countries, mostly associated with the formation of aberrant B cells.[8] Lymphomas and lymphoid leukaemia, both included in the lymphoid neoplasm category, are closely related; in fact, chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) are essentially the same disease, the only difference being the location of the primary occurrence of cancer. In CLL, a significant number of the anomalous lymphocytes are found in the blood, bone marrow, and lymphoid tissue; in SLL, the bulk of the disease is in the lymph nodes, bone marrow, and other lymphoid tissues, but is rarely detected in peripheral blood. Both conditions are tackled in the same way, using immunomodulating agents, monoclonal antibodies, or kinase inhibitors.[9]

Molecular Characterisation

The laboratory diagnosis for haematological malignancies usually follows clinical depiction and includes morphological and immunophenotypic (via flow cytometry or immunocytochemistry) characterisation.[10] Genetics play an important role for the classification of these disorders, since they originate from common chromosomal abnormalities that cause fusion of genes, a critical step in cancer progression (Table 1). Moreover, identification of mutations in specific genes allow for risk stratification, from poor to favourable prognosis.[11] These distinguishing genomic alterations and associated chimeric genes are easily detectable via cytogenetics (karyotype or fluorescence *in situ* hybridisation [FISH]). At the molecular level, quantification of fusion gene expression via polymerase chain reaction (PCR) is mandatory and point mutations are typically identified via Sanger sequencing.[12] In haematopathology, the use of molecular markers is key to integrated diagnostics, prognostics, and therapeutics. CML is a prime example of how haematological diseases have greatly benefited from the advance of cytogenetic and molecular methodologies. It was progress in this field that led, for the first time, to the identification of a unique chromosomal abnormality that was directly related to cancer onset: t(9;22)(q34;q11), forming what is known as the Philadelphia chromosome (Ph), and the associated *BCR-ABL1* fusion gene, providing a specific target for disease treatment.[1] In fact, tyrosine kinase inhibitors target the fusion protein encoded by *BCR-ABL1* so as to block the dysregulated kinase activity.

LIQUID BIOPSIES IN LEUKAEMIA AND LYMPHOMA

The diagnosis and molecular management of cancer, including follow-up and companion diagnostics, are mainly performed on tissue biopsies that provide material for histological characterisation of the tumour and genetic assessment. These biopsies then facilitate the characterisation of the cancer subtype, indicating the appropriate therapy and, eventually, predicting therapeutic response.[14,15] When one refers to solid tumours, biopsies are only a small portion of the neoplasm, not representing the existing heterogeneity. Usually performed at a specific time-point, the tumour dynamics and mutation patterns are neither assessed nor represent the whole cancer. Taking multiple biopsies from patients is not feasible, mainly due to the invasiveness of the procedure, the considerable risk, and, above all, the tremendous discomfort suffered by the patient, along with the considerable costs.

In myeloid and/or lymphoid neoplasms, conventional diagnostics consist of blood counts and biomarker evaluation on peripheral blood cells, complemented by morphologic examination of tumour tissues, which includes a collection of a substantial core biopsy of the bone marrow using a fine needle, or an excisional biopsy of lymph node or extranodal sites.[16] Follow-up relies on peripheral blood assessments every 3 months for morphological, cytogenetic, or molecular marker evaluation. Since there is a good correlation between blood and core biopsies in haematological disorders, whether bone marrow or lymph node, biopsies are still necessary.[17,18]

The discovery of circulation tumour cells (CTC) and circulating cell-free DNA (cfDNA) presents clinicians with the opportunity for non-invasive disease monitoring techniques, i.e., liquid biopsies.[15,19,20] Nowadays, from a peripheral blood sample it is possible to screen CTC, DNA, and other circulating biomarkers, such as microRNA (miRNA) and vesicles, capable of retrieving valuable information before and during treatment.[20-22]

Circulation Tumour Cells as Biomarkers

CTC can provide valuable information about tumour composition, invasiveness, drug susceptibility, and resistance to therapy, which in turn, through its isolation and further molecular and cellular characterisation, can allow a personalised approach to treatment, guiding chemotherapy and targeted therapy approaches.[23,24] CTC can be passively or actively released to the bloodstream from the tumour site; however, most of them are accidental, since they are pushed by external forces (e.g., tumour growth). Dead tumour cells may passively release DNA or RNA into the circulation, or do so actively when cells release nucleic acids spontaneously.[21]

Circulating-Free DNA as a Biomarker

cfDNA and lymphocyte DNA are two types of DNA present in blood.[25] cfDNA comes from rapidly dividing tissues, such as bone marrow, intestinal epithelium, or the fetus during pregnancy, and serum specimens from lymphoid neoplasms patients feature higher levels of cfDNA.[20,25] Only a small percentage of cfDNA actually corresponds to circulating tumour DNA (ctDNA), which is less stable and displays different cytosine and guanine composition than that of DNA from non-tumour cells.[20] Since ctDNA levels are higher in the later stages of disease, screening cfDNA allows a correlation to be made between molecular heterogeneity and therapy response.[20,26] For example, in one study, at diagnosis, lymphoma patients had a cfDNA median concentration of 24.1 ng/mL, twice as much as the healthy controls; after 2 years of follow-up within patients with complete response to therapy, nearly 90% showed a significant decrease in cfDNA levels.[20] Assessing ctDNA levels to monitor cancer rather than solely for diagnosis has been proposed, where the search for the characteristic *BCL2-IGH* translocation also allows identification of minimal residual follicular lymphoma.[24] Another example is monitorisation of the diffuse large B cell lymphoma disease status, where ctDNA screening identified risk of recurrence before clinical evidence, resulting in further reduced disease burden at relapse.[27] Additionally, cfDNA is detectable in 96% of diffuse large B cell lymphoma patients and may be used to detect somatic variants in this type of tumour.[28]

Exosomes and Vesicles as Biomarkers

Exosomes play an important role in cell communication, being able to induce transformations in receptor cells, including activation, proliferation, differentiation, or apoptosis.[29,30] Exosomes are small vesicles (30–100 nm) that transport proteins, messenger RNA (mRNA), and miRNA, whose overall composition depends on the cell type or tissue that they are released from, as well as the cell's physiological condition.[31] In addition to CTC and cfDNA, since tumour cells release exosomes at a higher rate, exosomes present growing interest in oncology.[20] Cancer-derived exosomes present characteristic cargo that may provide not only information about the pathophysiological status of cancer patients, but also disease detection and monitoring. Particularly, their RNA content displays several advantages when compared to DNA, such as information on coding mRNA that might indicate which particular genes were transcribed and expressed as proteins; or the analysis of small noncoding miRNA, indicating the presence of particular types of cancer. Although there is a high ribonuclease (RNase) activity in blood, which would render free-RNA useless, encapsulation of this RNA into exosomes allows their retrieval and use as valuable biomarkers.[32]

Despite considerable knowledge of the exosome role in solid tumours, their role in haematological tumours is not well-studied.[30,33] As for cfDNA levels, higher levels of exosomes are found in cancer patients. For instance, concentration of exosomes in plasma increased along with AML development, and decreased after a conventional therapy regimen with parallel reduction of blasts in bone marrow.[30,34] Exosome reduction is also associated with a quantitative change of exosome-derived proteins. In this case, studies propose that the tumour growth factor β1 levels were higher upon AML diagnosis compared to normal controls, and these levels were significantly reduced following chemotherapy.[33] Exosome miRNA has also been proposed as an early biomarker for AML.[30] In CML-derived exosomes, a specific expression pattern of miRNA was unveiled, which may be further explored for future use as disease biomarkers.[33] In fact, higher concentrations of exosomes are found in the sera of AML, CML, and CLL patients, with abundant expression of surface proteins according to their cell of origin that is rarely observed in exosomes of healthy individuals. Together, this supports the use of exosomes as cancer biomarkers.

Liquid biopsies are associated with circulating material, mainly CTC, nucleic acids, and exosomes. However, this is dependent on which liquid tumours

are concerned, since a direct sample of tumour cells may be retrieved from a peripheral blood collection. As a result, besides the usual counting of leukocytes, haemoglobin, lymphocytes, and platelet levels, new prognostic markers should be addressed as far as disease outcome and clinical decision-making are concerned.[35] This also allows for detection of molecular markers, such as point mutations and chromosomic aberrations related with each lymphoid neoplasm subtype. Gomes et al.[35] observed significant changes for phospho-p38 and Mcl-1 proteins in CLL patients when compared to the control group. Mcl-1 protein, an anti-apoptotic protein of the Bcl-2 family, was associated with malignant cell survival, worse prognosis, and chemoresistance in CLL. Low levels of phospho-p38 also endorse apoptosis resistance, since p38 is a protein of MAPK family with a pro-apoptotic role. Circulating miRNA in the plasma of AML patients showed upregulation of let-7b and miR-523 and downregulation of let-7d, miR-150, miR-339, and miR-342, independent of patient sex.[36]

NANOPARTICLE APPLICATIONS IN LIQUID TUMOURS

The progressive field of nanotechnology has had a tremendous impact on biomedicine, now known as nanomedicine. Cancer nanomedicine has raised the stakes towards the improvement of detection limitations for cancer biomarkers, but therapeutics could also benefit from these new strategies, which are more target-driven than traditional chemotherapeutics. Among the plethora of different nanoscale devices applied to cancer diagnostics and therapeutics, here we will focus on nanoparticles, which are synthesised in the range of 1–100 nm and feature unique optical, electronic, and catalytic properties, very different from those of the bulk material.[37,38] Concerning liquid tumour diagnostics, different approaches using nanoparticles have been proposed towards better diagnostics, imaging, and treatment.

Nanodiagnostics in Liquid Tumours

Traditionally, leukaemia and lymphoma cells are detected through morphological analysis, immunohistochemistry, microarray of antibodies, flow cytometry, FISH, PCR, and DNA sequencing. These techniques are costly and time consuming, requiring sophisticated instrumentation and multi-step processing, and are not suitable for rapid routine testing.[39] To overcome these shortfalls, several efforts have been directed at using nanoparticles for liquid tumour testing and assessment. These platforms may be used to detect biomarkers at lower concentrations more quickly than a non-invasive approach. One of the major problems in diagnostics in lymphoid neoplasms is the limit of detection of immature white blood cells, because their abundance is very low at such an early stage. Since these cancer types are extremely common and aggressive, an effective treatment largely depends on the accuracy and sensitivity of diagnosis.[40] Signal amplification coupled with nanoparticles can be a viable approach for an earlier detection, leading to fluorescent quantum dots and nanometre semi-conductors, which have superior fluorescent features, being applied in the diagnostic field. In addition to fluorescent enhancement, metal nanoparticles feature other unique physicochemical properties, including their localised surface plasmon resonance, as well as photoluminescence or superparamagnetic properties, which turn them into extremely good candidates for imaging and diagnostics.[41] Some of these platforms are close to the clinics, but still need to provide convincing performance data in the diagnostics lab (Table 2).

For acute leukaemia diagnostics, an anti-leukaemia thiolated aptamer (such as sgc8c) is used to specifically recognise protein tyrosine kinase 7, an overexpressed transmembrane receptor in human T cell ALL cells.[39,40,52] Aptamers feature a high affinity and selectivity towards their targets, as well as being extremely sensitive, allowing an accurate detection of cancer cells. Aptamers are also inexpensive, easier to produce and modify, have more stability, and less immunogenicity or toxicity than antibodies.[40,52]

Concerning CML, since it is associated to a unique chromosomal abnormality, the Ph chromosome and the corresponding *BCR-ABL1* gene, this specific target is used as a diagnostic approach. Between the existent strategies using nanoparticles, we can only find examples with gold nanoparticles.[43,56] Both examples are based on the optical properties of gold nanoparticles. The former relies on a colorimetric differentiation upon salt-induced aggregation, where a positive test reveals a red colour; whereas in a negative test, the gold nanoparticles aggregate, yielding a blue colour solution. Gold nanoparticles are functionalised with oligonucleotides that specifically hybridise to the target, in this case the *BCR-ABL1* gene.[43,57]

Table 2: Nanoparticles for molecular diagnostics in liquid tumours.

Type of NP	Target	Detection	Stage
Silica NP[42]	Melanoma	Imaging	Phase I
AuNP functionalised with oligonucleotides[43]	*BCR-ABL1* fusion transcript	Colorimetric	Clinical samples
Aptamer-conjugated NP[44]	Acute leukaemic cells on blood	Microscopy	Preclinical
AuNP functionalised with oligonucleotides[45]	Chronic lymphocytic leukaemia	Electrochemical	Preclinical
Chitosan-PEG-coated iron oxide NP[46]	B cell lymphoma	Microscopy	Preclinical
Antibodies coupled with iron oxide NP[47]	Leukaemic cells in the bone marrow	Microscopy/magnetometry	Clinical samples
Silver NP functionalised with antibody[48]	B cell lymphoma (CD20)	Surface-enhanced Raman spectroscopy	Preclinical
Magnetic NP functionalised with antibody[49]	B cell lymphoma (CD20)	Microscopy and flow cytometry	Preclinical
Gadolinium-labelled dendrimer[50]	Lymph nodes	MRI	Preclinical
Hyaluronic acid-coated magnetic NP[51]	Acute lymphoblastic leukaemia	Quartz crystal microbalance	Preclinical
Aptamer-conjugated gold-coated magnetic[52]	Acute lymphoblastic leukaemia	Nitrogen-doped graphene modified electrode	Preclinical
AuNP functionalised with antibody[53]	T47D breast cancer cell	Photoacoustic flowmetry	Preclinical
AuNP functionalised with antibody[54]	Prostate-specific antigen	Fluorescence immunoassay	Preclinical
Carbon NP[55]	Lymph nodes in advanced gastric cancer	Colorimetric	Phase III

AuNP: gold nanoparticles; MRI: magnetic resonance imaging; NP: nanoparticles; PEG: polyethylene glycol.

Gold nanoparticles are also known to modulate the fluorescence of nearby fluorophores, which have been used for a multitude of sensing approaches for DNA and RNA. One example is the BioCode approach, a spectral coding approach using fluorescence energy transfer for the distinction of *e14a2* and *e13a2* transcript fusions in CML. In this approach, a complementary sequence to the loop portion of hairpin-functionalised gold nanoparticles allowed for fluorophore emission. Then a second (revealing) fluorescent oligo hybridises to the palindrome part of the hairpin promoting fluorescence energy transfer between the fluorophores and a specific spectral signature.[1]

The remaining targets for both leukaemia and lymphoma diagnostics are antigens, such as CD20, which are overexpressed by malignant B cells.[58] In this case, CD20 antibody (rituximab) has been applied to lymphoma treatment, but is also suitable for lymphoid neoplasms diagnosis.[49] Besides CD20, CD45 and CD19 are the two most common surface proteins expressed by B cells, and are used in diagnostic immunophenotyping.[59] Based on these molecular differences, it is possible to diagnose, image, and isolate malignant B cells via gold nanoparticles and surface-enhanced Raman scattering, magnetic nanoparticles, and polymeric-fluorophore-labelled nanoparticles, respectively.[49,59,60]

FUTURE PERSPECTIVE ON HAEMATOLOGICAL MALIGNANCIES

Many features of nanoparticles have been described in this review that are particularly attractive for biomarker detection. This versatility makes them suitable candidates for nanotheranostics, a central approach in precision oncology, since it allows the integration of diagnostics and therapeutics onto a single material. When designing nanotheranostics for haematological malignancies, one should take into consideration the following parameters: a) choice of the most suitable nanocarrier for effective delivery

and cell internalisation; b) the effector molecule, usually conventional drugs or nucleic acids; c) ensure controlled release of effector molecule; d) an imaging component that allows for real-time monitoring of the nanoconjugate location and effect on targeted aberrant cells; e) an active targeting agent, typically a cell-surface marker or an oligonucleotide that maximises specificity of the vector and minimises damages to healthy cells, whether in peripheral blood or when targeting the bone marrow or lymphoid tissues.

Because most of these liquid tumours are closely linked to specific molecular events, novel nanoparticle-based detection schemes could be easily implemented both for diagnostics and, above all, for follow-up therapy and disease management. Several nanoformulations have also been proposed for improving therapeutics by means of smart nanoparticle designs capable of searching for and destroying malignant cells.

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AUTOMATED ITEM GENERATION: THE FUTURE OF MEDICAL EDUCATION ASSESSMENT?

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ABSTRACT

A major innovation in psychometric science, termed automated item generation (AIG), holds the potential to revolutionise assessment in medical education. In short, AIG involves leveraging the expertise of content specialists, item templates, and computer algorithms to create a variety of item permutations, often resulting in hundreds or thousands of new items based on a single item model. AIG may significantly improve item writing capabilities, reduce human error, streamline efficiencies, and reduce costs for individuals in the medical and health professions. Thus, the purpose of this work is to provide readers with a current overview of AIG and discuss its potential advantages, future possibilities, and current limitations.

Keywords: Assessment, automated item generation (AIG), educational measurement, innovation, item writing, medical education, multiple-choice questions (MCQ), psychometrics, testing.

AUTOMATED ITEM GENERATION: THE FUTURE OF MEDICAL EDUCATION ASSESSMENT?

Despite many decades of use, multiple-choice questions (MCQ) remain the most commonly used assessment method in medical education. At the undergraduate level, MCQ are routinely administered in classroom assessments due in part to the enormous amount of information students are responsible for learning and the large class sizes that make other assessment methods implausible. At the graduate and postgraduate levels (e.g., medical residency, licensure, and certification), MCQ are regularly used to assess both breadth and depth of ability within a particular medical specialty. General advantages of MCQ are well-documented and include factors such as greater objectivity (scoring is free of judge inconsistencies and bias); greater efficiency (examinee responses can be captured quickly); increased quantity of items (more questions result in smaller error estimates and more reliable scores); increased range of content (broad representation of content provides a more accurate estimate of ability); and a variety of item statistics that help discern the psychometric quality of the items.

Despite these important advantages, MCQ often present several major implementation challenges, namely time, difficulty, expense, and security. Constructing MCQ is time-consuming; the process typically involves constructing each item by hand, reviewing the item, editing the item, and entering the item into a computer.[1] Constructing MCQ is also difficult and research has noted that item writers often have difficulty generating plausible distractors,[2] writing items to a specified difficulty level,[1] and are subject to committing item writing flaws.[3] In fact, one study investigating the quality of items administered at a major medical school in the USA found as many as one in five items contained an item construction flaw.[4]

Stem:

[Situation] [Symptoms] [Physical Findings] [Laboratory Testing] [Question prompt] or a combination of these

Elements 1

Situation (Text): 1: A [AGE]-year-old [GENDER] came to the office with the complaint of [INITIAL PATIENT SYMPTOM 1] and [INITIAL PATIENT SYMPTOM 2]. 2: A patient presents to the office with the complaint of [INITIAL PATIENT SYMPTOM 1] and of [INITIAL PATIENT SYMPTOM 2]. The patient is a [AGE]-year old [GENDER].

Symptoms (Text): 1: Upon further questioning, the physician learns the patient has [PATIENT REPORTS 1]. 2: Through the physician interview it becomes clear the patient has [PATIENT REPORTS 1]. 3: The patient reports having [PATIENT REPORTS 1]. 4: The patient reports having [PATIENT REPORTS 1] and further questioning reveals [PATIENT REPORTS 2].

Physical Findings (Text): 1: On physical examination, the patient is found to have [PHYSICAL FINDINGS 1], [PHYICAL FINDINGS 2], and [PHYSICAL FINDINGS 3].

Laboratory Testing (Text): 1: Laboratory testing found that [LABORATORY RESULTS 1], [LABORATORY RESULTS 2] and [LABORATORY RESULTS 3]. 2: Laboratory testing found that [LABORATORY RESULTS 1] and [LABORATORY RESULTS 2] 3: Laboratory testing found that [LABORATORY RESULTS 1].

Question prompt (Text): 1: What is the next best step in management? 2: Which of the following is the best diagnosis? 3: Given this information, what is the best course of action? 4: Which of the following is the most likely diagnosis? 5: These findings are most consistent with which one of the following diagnoses? 6: Given this information, what is the most likely diagnosis?

Elements 2

AGE (Integer): From 18.0 to 70.0, by increments of 1.0

GENDER (String): 1: female 2: male

INITIAL PATIENT SYMPTOMS (String): 1: dry skin 2: elevated blood cholesterol level 3: slow heart rate 4: depression 5: slower thinking 6: needing to sleep more than 8-9 hours per night 7: hoarseness 8: generalized fatigue/exhaustion 9: fatigue 10: unexplained weight gain of 20 lbs over the past year 11: of increased sensitivity to cold, even in the summer months 12: neck pain 13: irregular menstrual periods 14: pain, stiffness or swelling in joints 15: muscle aches and pains 16: muscle weakness

PATIENT REPORTS (String): 1: thinning hair 2: constipation 3: been sleeping for more than 8 hours per night 4: been suffering from forgetfulness 5: a spouse who had remarked about recent changes in voice 6: difficulty swallowing and has a feeling as if there were a lump in the throat 7: a family history of thyroid disease 8: a history of other autoimmune disease 9: periods that have become irregular and seem lighter than usual (female) 10: periods that have become heavier than normal (female) 11: had trouble maintaining an erection (male)

PHYSICAL FINDINGS (String): 1: dry skin 2: coarse hair 3: fragile skin 4: brittle and broken nails 5: alopecia 6: bradycardia (from pulse rate on vital signs) 7: delayed relaxation phase of reflexes 8: periorbital edema 9: no thyroid enlargement or pain 10: a firm, non-tender goiter of irregular shape 11: a deep voice

LABORATORY RESULTS (String): 1: Serum thyroid-stimulating hormone (TSH) levels were elevated at 12 U/ml (normal <4). 2: TSH levels were found to be normal (<4). 3: Total serum thyroxine was low. 4: Antibodies to thyroid peroxidase were present at a high titer. 5: Antibodies to thyroid peroxidase were not present. 6: Free T4 levels were high. 7: Free T4 levels were low. 8: Free T3 levels were high. 9: Free T3 levels were high/low. 10: Reverse T3 levels were normal/high/low. 11: Thyroglobulin antibodies (TgAb) were present. 12: Thyroglobulin antibodies (TgAb) were not present. 13: A radioactive iodine uptake test was performed and results indicated an increase in iodine uptake. 14: A radioactive iodine uptake test was performed and results indicated a decrease in iodine uptake.

ANSWER OPTIONS: 1: Iron deficiency anemia 2: Lymphoma (endocrine, mesenchymal, and other rare tumors of the mediastinum), 3: Hypocholesterolemia 4: Addison's disease (adrenal insufficiency) 5: Primary adrenal insufficiency 6: Alzheimer dementia 7: Pituitary adenoma 8: Depression 9: Sleep disorder 10: Acute thyroiditis (microbial inflammatory) 11: De Quervain's thyroiditis (granulomatous) 12: Grave's disease 13: Hashimoto's thyroiditis (Chronic lymphocytic thyroiditis, or Autoimmune thyroid disease, or Primary autoimmune hypothyroidism) 14: Hypothyroidism 15: Hypothermia 16: Microbial inflammatory thyroiditis 17: Riedel's thyroiditis (invasive fibrous) 18: Iodine deficiency 19: Subacute granulomatous thyroiditis 20: Subacute lymphocytic thyroiditis (postpartum thyroiditis) 21: Ovarian insufficiency 22: Pregnancy 23: Male infertility 24: Chronic fatigue syndrome 25: Fibromyalgia

Figure 1: Sample automated item generation criteria.

Costs associated with constructing MCQ are also quite severe. In addition to time and opportunity costs, Rudner[5] estimates the monetary cost associated with a single item approximates from $1,500–2,500. Finally, given the high stakes associated with medical education assessments and the pressures to perform well, some unscrupulous individuals will attempt to harvest items, thus rendering them ineffective for all future examinations.[6,7]

Each of the aforementioned limitations, coupled with increased demands for new and more numerous items for both high-stakes examinations and practice tests, have made it difficult for the field of medical education to keep pace with current demands. Fortunately, a major breakthrough in psychometric science, called automated item generation (AIG), holds the potential to overcome many of the weaknesses and challenges associated with MCQ. Thus, the purpose of this work is to provide an overview of AIG and discuss its potential implications for the field of medical education.

OVERVIEW OF AUTOMATED ITEM GENERATION

Broadly defined, AIG is the process of using item models to create examination items with the assistance of computer technology.[8] Unlike the typical item generation process in which a content specialist constructs each item individually, AIG involves leveraging the expertise of content specialists, item templates, and computer algorithms to create a variety of item permutations, often resulting in hundreds or thousands of new items based on a single item model.[9] AIG is considered both an art and a science, as developing an examination requires human judgment and expertise (art) and computing technology systematically combines large amounts of information to generate new items (science).

Automated Item Generation Process

The AIG process involves three steps: first, content experts create a cognitive map by identifying the content necessary for inclusion in an examination item; second, content experts develop an item model (or template) for the content; finally, a computer algorithm combines various elements of content to generate items. New items can be classified as either a 'clone' or a 'variant', where cloned items appear very similar and will possess only subtle differences with comparable psychometric properties, whereas a variant will vary in some more discernible way and likely possess different psychometric characteristics (Figure 1).

Sample Items Generated to Assess One's Ability to Diagnose Hypothyroidism

Using the criteria in Figure 1, we have used AIG to generate four sample items to assess one's ability to diagnose hypothyroidism.

#1: A 30-year-old female came to the office with the complaint of unexplained weight gain of 20 lbs over the past year and of increased sensitivity to cold, even in the summer months. Upon further questioning, the physician learns the patient has periods that have become irregular and seem lighter than usual. On physical examination, the patient is found to have dry skin, delayed relaxation phase of reflexes, and a firm, non-tender goiter of irregular shape. Given this information, what is the most likely diagnosis?

A. Adrenal insufficiency
B. Depression
C. Hypothyroidism*
D. Iron deficiency anemia

*Correct answer option

#2: A 36-year-old female came to the office with the complaint of dry skin and fatigue. The patient reports that her spouse had remarked about recent changes in her voice and further questioning reveals a family history of thyroid disease. On physical examination, the patient is found to have coarse hair, bradycardia, and delayed relaxation phase of reflexes. Laboratory testing found that TSH levels were elevated at 12 U/ml (normal < 4), total serum thyroxine was low, and antibodies to thyroid peroxidase were present at a high titer.

Which of the following is the most likely diagnosis?

A. Acute thyroiditis
B. Hashimoto's thyroiditis*
C. Iodine deficiency
D. Pituitary adenoma

*Correct answer option

#3: A 28-year-old female came to the office with the complaint of generalised fatigue/exhaustion and irregular menstrual periods. The patient reports having difficulty swallowing and has a feeling as if there were a lump in the throat. On physical examination, the patient is found

to have fragile skin, brittle and broken nails, and no thyroid enlargement or pain. Given this information, what is the most likely diagnosis?

A. Adrenal insufficiency
B. Fibromyalgia
C. Hypothyroidism*
D. Ovarian insufficiency

*Correct answer option

#4: A patient presents to the office with the complaint of needing to sleep more than 8-9 hours per night and fatigue. The patient is a 35-year-old female. The patient reports having constipation. On physical examination, the patient is found to have bradycardia, delayed relaxation phase of reflexes, and periorbital oedema. Given this information, what is the most likely diagnosis?

A. Adrenal insufficiency
B. Depression
C. Hypothyroidism*
D. Sleep disorder

*Correct answer option

ADVANTAGES OF AUTOMATED ITEM GENERATION

Perhaps the most obvious advantage of AIG is its ability to quickly produce thousands of new items. This strength is particularly advantageous in scenarios such as medical licensure and certification, in which the organisation must maintain thousands of updated, high-quality items at all times. A common problem for most organisations, including medical schools, is that item banks often possess shallow pools in certain content areas. AIG can be particularly helpful in this situation by populating notoriously sparse content areas.

Another major advantage of AIG is that items can be targeted based on known difficulty estimates and reproduced with 'clones' to generate new, yet different, items.[10] Similarly, if an examination developer discovers an examination contains too many easy or difficult items, AIG can help populate the item bank with 'variants' to improve item targeting (e.g., ensuring items are appropriately easy or difficult relative to the ability of the collective sample frame).

In the context of medical licensure and certification, it is common practice for examination committees to construct new items, review others' items, and enter items into the item bank for operational use. The use of AIG can help examination committees shift their focus from creating new items to evaluating new items and providing quality assurance efforts. This change in functional duties could result in the exponential increase of high-quality items produced in the same amount of time.

In the context of medical schools, most faculty members have little to no formal training in item construction, yet are expected to produce their own high-quality items. AIG could also prove invaluable for these individuals. Research[4] has also noted that the most common item construction flaws involve poor item formatting and structures (e.g., unequal distractor length, unfocussed stem, use of negative statements, etc.). Because AIG use standardised templates for constructing each item, it could help the faculty avoid these common mistakes and result in more standardised and robust items for students.

FUTURE POSSIBILITIES

The medical and health professions offer numerous opportunities for AIG to be applied and evaluated. For example, there are numerous types of assessment beyond MCQ, such as objectively structured clinical examinations, simulations, live-patient examinations, oral examinations, mannequin examinations, and more. Furthermore, there are multiple levels of medical education, including undergraduate, graduate, postgraduate, and continuing medical education. At present, we are unaware of anyone who has used AIG in any assessment context beyond MCQ, but such use is certainly possible. We are also only aware of <5 organisations in medical licensure and certification that have trialled AIG, thus further evidencing the room for growth and development of AIG.

While none of the authors of this paper claim to have any prognosticating abilities, we can envision several ways in which AIG may be used in both medical education and clinical medicine. First, licensing and certification boards spend a large sum of money training physicians to write high quality MCQ. Even after physicians are trained and items developed, professional editors must still review the newly generated items to identify any flaws and ensure standardisation in format. It is possible that AIG can mitigate many editorial duties for both physicians and professional editors and significantly improve efficiencies by having

content experts focus almost entirely on content creation and review.

Secondly, there is currently a significant focus on maintenance of certification (MOC) and medical recertification. Most MOC efforts require physicians to complete a battery of practise cases for ongoing professional development purposes. Given MOC cases and practise items are similarly expensive to produce, AIG could significantly reduce costs and promote efficiencies. In the context of medical school training, perhaps even greater possibilities exist.

For academic staff, item writing flaws could significantly reduce resulting in items that are more likely to yield accurate estimates of what students know or can do. Furthermore, if the staff desire to have more clinically based items in their item bank, AIG can help with its use of a standardised template. Faculty members could then spend more time reviewing and editing items, as opposed to generating new items from scratch. With respect to classifying items into content domains, AIG can likely also improve this process.

Through the use of an established model, such as Bloom's taxonomy, the faculty could create a variety of templates to assess learning from a variety of cognitive approaches. For example, Bloom's taxonomy identifies the following domains: Know, Comprehend, Apply, Analyze, Synthesize, and Evaluate. Staff could structure item templates to address each of these domains and provide greater balance in domain assessment should they choose.

Students also have much to gain from AIG, as a virtually unlimited item bank could provide students with endless opportunities to learn and self-assess. Automated items could also be provided to students as part of virtually any course for continuous and long-term study extending months or even years later. Additionally, AIG has the potential to revolutionise the post-examination review process. Several assessment experts have noted that reviewing secured examination items during post-examination review sessions could increase the odds of items being leaked, thus affecting the validity of future scores. If students were presented unsecured items on related content, it could achieve the goal of reviewing substantive content without sacrificing potential item loss.

CURRENT LIMITATIONS

Perhaps the greatest limitation of AIG today is that it remains a budding, albeit potentially revolutionary, science. Before a paradigm can become an established science, it must be scrutinised, thoroughly tested, and become well understood. Although scholars have worked on the foundations of AIG for decades, the AIG paradigm has yet to take hold in most areas of research and practice. While there are many potential reasons for this, perhaps the greatest is the limited availability of software and a reluctance to share it from those who do have access. Clearly, AIG science cannot grow and be tested if others cannot test AIG for themselves and contribute toward new discoveries. Assuming the scientific community fully embraces AIG, the next challenge will be to extend AIG into everyday practice in a variety of settings. It is likely, however, that the field of medicine will be among the many potential first adopters of AIG, given the need for continuous, rigorous assessment of students and practicing healthcare professionals alike.

One major limitation of AIG involves ill-structured problems.[11] AIG appears to work effectively with well-structured problems, such as clinical vignettes in which there are multiple replacement characteristics to generate a variety of vignettes and a single correct answer. However, an instance in which a problem is ill-structured becomes much more problematic. For example, a problem may be inadequately defined, have many correct answers, lack background information, or its scope may be broader than a single item can capably assess.[8] In these instances, AIG will suffer from the same limitations as ill-structured items prepared by traditional means.

Another potential limitation pertains to distractor quality. AIG selects potential distractors based upon information entered into an algorithm, thus there is a strong possibility that many of the newly generated distractors may be problematic. For example, many distractors may be implausible, irrelevant, and/or factually incorrect. Depending upon the information used to generate distractors, some output may be entirely unintelligible. Furthermore, because of the manner in which items are generated, there is a risk that item quality may be highly variable. While it is true that AIG may produce hundreds of items based on a single case or scenario, it remains unclear what proportion of newly generated items and

distractors are typically of sufficient quality or worthy of use. As noted previously, the need for human discernment is an inescapable element of AIG, thus any benefit gained from producing additional items will be at the costs of additional time spent conducting quality assurance activities. Naturally, all automated items will still need to undergo review for substance, clarity, and appropriateness to minimise item flaws.

Finally, the cost-benefit economics of AIG technology have not yet been thoroughly evaluated or reported. In theory, AIG has the potential to save exorbitant amounts of time for item writers, which may include subject matter experts who provide items for board examinations and medical school departments charged with the task of teaching and assessing students' learning. Increased time savings could allow item writers to focus their energies in other areas and potentially result in greater achievement of outcomes, such as student learning.

It remains unclear how steep any learning curves may be for item writers to use AIG technology. It is unknown how difficult the typical subject matter expert will find the process of writing cases and preparing content to fit a structured item model. It is also unknown how subject matter experts will respond to AIG software, particularly if it is something they can do themselves or if it will require the assistance of an information technology specialist.

CONCLUSION

The purpose of this review aimed to familiarise readers with AIG and promote interest in this exciting, and potentially revolutionary, innovation in medical education. Although much is currently unknown about AIG in practice, extant research from those who have used it is assuring. While the future of AIG is sure to encounter some turbulence as early adopters become acquainted with this new science and explore its possibilities, its long-term prospects for improving the way in which students are assessed is very bright.

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In-Hospital iPad Case Reduces Risk of Infection Spread

RISK of infection is a significant concern for patients when prolonged hospital stays are required. Therefore, personal belongings allowed in hospital bays are limited in attempt to minimise healthcare-associated infection risk, which can make the experience for the patient uncomfortable, particularly for children. However, developers from FutureNova, Chelmsford, UK, have created an iPad case, named the FlipPad™, that allows patients, visitors, and clinicians to use an iPad in hospital without increasing the risk of infection spread.

The FlipPad is built with an antimicrobial glass screen, which limits the spread of infection, and is made from a durable material so it can withstand cleaning with infection control products without causing damage to the iPad itself. The glass screen can also be used when the operator is wearing surgical gloves, meaning clinicians will be able to use the iPad in sterile environments without the risk of infection spread.

This enhanced protection from the spread of pathogens means that patients are safely able to use the iPad while requiring inpatient care, providing a more comfortable hospital stay and enabling the opportunity for research on the condition during consultations with clinicians. Patients and family members can use the iPad to learn more about the patient's condition, allowing them to gain a greater understanding of the treatment regime.

Discussing the importance of their iPad case in clinical environments, Mike Casey, CEO of FutureNova, said: "Using the iPad gives patients and their families more information about the patient's stay in the hospital and engages them in their care. FlipPad removes any issues of infection control as it can be cleaned using standard infection control sprays."

The FlipPad is already being used in Texas Children's Hospital, Houston, Texas, USA, with great success. This came about after a set of missions created by the Association of British Healthcare Industries (ABHI), London, UK, which aims to improve relationships between Texas and the UK. Use of the FlipPad should effectively reduce the risk of infection, as well as improve patient experiences during a hospital stay.

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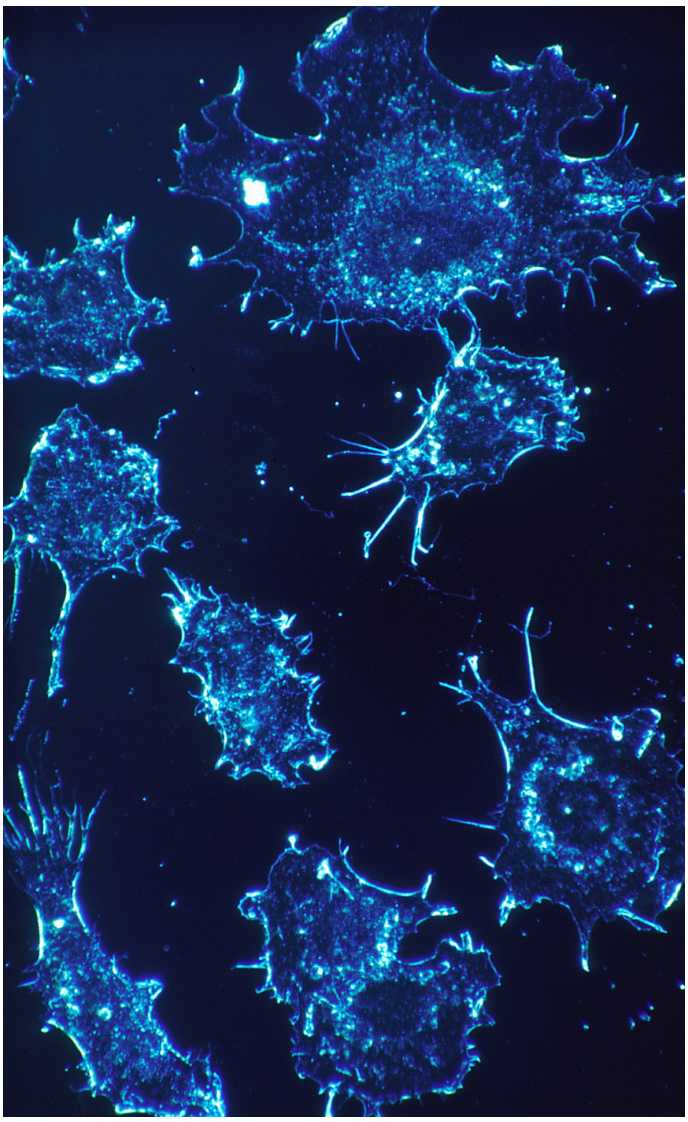
Nanoparticle Therapeutics for Preventing Cancer Recurrence

STEM CELLS are unique, unspecialised cells that are capable of differentiation into any cell type. This provides fantastic opportunities for prospective cures for many diseases; however, cancer stem cells have the potential to differentiate into cells that form tumours. Even years after the original tumours have been treated, cancer stem cells can remain within tissues, resulting in disease recurrence.



Researchers from the University of Illinois, Champaign, Illinois, USA, have developed a new therapeutic technique in which a nanoparticle capable of specifically targeting cancer stem cells transports a drug that is able to switch off genes that allow the unlimited differentiation ability of stem cells, hence preventing cancer recurrence.

The mechanism by which the nanoparticle–drug combination works is one that the researchers believe to be unique. The nanoparticle locates cancer stem cells by targeting the cell surface protein CD44 and delivers the drug niclosamide, which is already used worldwide for treating tapeworm infections. The drug deactivates STAT3, which participates in cellular processes such as growth, division, movement, and death. Through targeting and switching off genes that are downstream of STAT3, the researchers have discovered a way of deactivating cancer stem cells, reducing the occurrence of cancer relapse and metastasis. When tested in both cell cultures and mouse models, it was found that cancer cell growth was also reduced.

As niclosamide is already used in healthcare regimes worldwide, the researchers hope their novel technique will be a cost-effective and accessible method of treatment. Prof Dipanjan Pan, University of Illinois, explained: "We purposely used an extremely inexpensive drug. It is generic, and we can mass produce it on a very large scale. The nanoparticles are a polymer that we can make on a large scale; it is highly defined and consistent, so we know exactly what we are delivering. The rest of the process is just self-assembly."

> "...the researchers have discovered a way of deactivating cancer stem cells, reducing the occurrence of cancer relapse and metastasis."

World AIDS Day 2017 Reflects on Significant Medical Advances

'WORLD AIDS DAY', held on 1st December 2017, marked a day during which researchers, clinicians, and patients could contemplate and review the most significant advances in treatment and preventative medicine for HIV over the last 30 years. AIDS results from the symptoms of prolonged, uncontrolled HIV infection; the associated loss of immune cell function enables the intrusion of several infectious pathogens which the patient cannot mount an effective immune response against, subsequently leading to the acquisition of diseases and resulting in the gradual deterioration of the patient's health.

> "...patients infected with HIV who take their antiretroviral therapy daily, as prescribed, now attain an undetectable viral load; therefore, the risk of passing the infection on to their partners is significantly reduced to almost no risk."

The main points to reflect on from the day included the fantastic medical advances facilitated by biopharmaceutical companies, which have resulted in an 88% reduction in HIV/AIDS death rates since the 1990s, as well as an 18% reduction in annual HIV infections between 2008 and 2014. These figures mean that the average life expectancy of patients with HIV/AIDS who began antiretroviral therapy between 2008 and 2010 has increased to approximately equal that of an unaffected individual. One study, pursued by the Antiretroviral Therapy Cohort Collaboration (ART-CC), University of Bristol, Bristol, UK, discovered these results when looking at HIV patients throughout Europe and North America treated with ≥3 antiretroviral therapy drugs. Pre-exposure prophylaxis is also an effective method of preventing the spread of infection, as highlighted on the day.

It is now an established fact worldwide that patients infected with HIV who take their antiretroviral therapy daily, as prescribed, now attain an undetectable viral load; therefore, the risk of passing the infection on to their partners is significantly reduced to almost no risk. Research efforts are continuously ongoing, including into new treatments, preventative medicines, and a cure for HIV infection, with the aim of achieving an AIDS-free generation.

Cell Reprogramming Boosted by Two Single Molecules

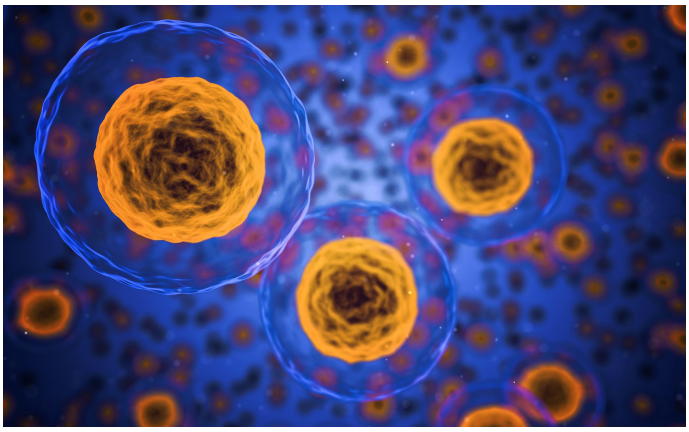
PRODUCTION of cells in a laboratory could become a much quicker process according to researchers at the MRC Centre for Regenerative Medicine, Edinburgh, UK. Their research has led to the elucidation of the role of two molecules, SMAD2 and SMAD3, play in reprogramming different cell types.

Reprogramming cells involves transforming one cell type into another, for example, keratinocytes to neural cells. SMAD2 and SMAD3 have been shown to speed up this reprogramming process, as well as improve the efficiency of transforming mature cells into pluripotent stem cells, which are cells that are capable of differentiating into any cell type.

The addition of either SMAD2 or SMAD3 to cell culture dishes was shown to halve the time taken to convert skin cells to brain cells, from 50 days to 25 days. The researchers hope that this discovery will aid the study of degenerative diseases, such as Parkinson's disease and multiple sclerosis, through accelerating cell production in the laboratory, enabling further tests to be pursued.

Dr Rob Buckle, Chief Science Officer at the MRC Centre for Regenerative Medicine, said: "Regenerative medicine is one of the most promising fields in biomedicine and a priority for the MRC. Pluripotent stem cells offer great potential for developing new treatments for a wide range of currently untreatable diseases, so the discovery of the role these two molecules can play in improving the way we can make these cells, and how they can enhance the direct conversion of one mature cell type to another of quite different function, represents real progress for the field."

Discoveries such as this could revolutionise modern research, allowing quicker and more efficient investigations and leading to improved treatment and management techniques for many different disease types. "We have shown it is possible to boost reprogramming of diverse cell types using a single molecule," said Prof Keisuke Kaji, MRC Senior Fellow, University of Edinburgh, Edinburgh, UK. The researchers hope that these discoveries will inspire others to seek more molecules with similar or improved abilities in reprogramming cells.



"...the discovery of the role these two molecules can play in improving the way we can make these cells, and how they can enhance the direct conversion of one mature cell type to another of quite different function, represents real progress for the field."

What's New Feature

If you have enjoyed this, be sure to subscribe to our newsletter by clicking here and receive even more great content in the future.

UPCOMING EVENTS

16th Medical Innovations Summit

14th April 2018

London, UK

The 16th Medical Innovations Summit, hosted by The Royal Society of Medicine, brings together medical innovators from across the globe. This world-class meeting is a fantastic networking opportunity to share and test out ideas; in recent years the summit has given rise to Nobel Prize-winning inventors and a range of world-leading experts and innovators. Videos of presenters are also shared online, so, wherever you are, you can make the most of the event.

Medtec Europe

17th–19th April 2018

Stuttgart, Germany

Over 6,000 attendees were recorded at Medtec 2017, a hub of European medical innovations, and even more are expected in 2018. Medtec boasts a myriad of exhibitors from a range of countries, bringing together a cornucopia of technology suppliers, engineers, and researchers, showcasing the current state of medical innovation. Medtec offers a range of services for companies of all sizes, including a specialised START-UP academy. With the opportunity to book a stand still available, what are you waiting for?

Annual World Medical Innovation Forum: Artificial Intelligence

23rd–25th April 2018

Boston, Massachusetts, USA

This year, the 2018 World Medical Forum is dedicated to the use of artificial intelligence in medicine. Home to the world-famous Massachusetts Institute of Technology, Boston is the ideal location for discussions on the use of artificial intelligence in medicine, led by experts in the field. The event also offers a podium for new research presentations during the 'First Looks' session, in which 10-minute presentations will be given on cutting-edge discoveries and insights.

Med-Tech Innovation Expo

25th–26th April 2018

Coventry, UK

The leading medical trade fair in the UK and Ireland, Med-Tech plays host to an industry worth £27 billion. The action-packed 2-day event will be home to >200 exhibitors representing a wide variety of approaches to medical innovations, from advanced technologies and medical solutions to new materials. In addition, informative live demonstrations and presentations will take place across two stages. The Med-Tech Innovation Expo promises to be a fascinating event that should not be missed!

13th World Congress on Healthcare & Technologies

14th–15th June 2018

Dublin, Ireland

The 13th World Congress on Healthcare & Technologies will this year be held in Dublin, Ireland. With discussions led by world-leading industry experts, this year's congress will focus on a myriad of hot topics ranging from healthcare and global economics to technology, innovations, and informatics in healthcare. The congress not only focusses on the development of new technologies but also how healthcare systems can constantly be improved upon.

Innovation in Medicine 2018

25th–26th June 2018

London, UK

This annual event pushes the boundaries of medicine and 2018 marks the 500th anniversary of the Royal College of Physicians. Innovation in Medicine 2018, hosted here at home in London, UK, boasts researchers and inventors at the forefront of creativity, alongside speeches from world-leading experts. One such presentation will be led by Prof John Wass, the college's special advisor on obesity. Prof Wass' presentation will focus on the use of bariatric surgery in obesity management.

30th Conference of the Society for Medical Innovations and Technology (SMIT)

8th–10th November 2018

Seoul, South Korea

The 30th Conference of the Society for Medical Innovations and Technology (SMIT) this year moves to Seoul, South Korea's capital city. The city has an esteemed reputation for technological developments and is an ideal setting for the annual SMIT congress. The 3-day event will be chaired by world-leading experts and cover a range of topics, including artificial intelligence in medicine, the use of robotics, image-guided surgery, and nanotechnology.

MEDICA

12th–15th November 2018

Düsseldorf, Germany

Billed as the largest congress dedicated to medical innovations, the MEDICA trade fair, which is held in Düsseldorf, Germany, has been at the forefront of changing the way physicians can treat, diagnose, and aid the rehabilitation of their patients for >40 years. Alongside >5,000 expected exhibitors, the MEDICA trade fair is home to world-leading MEDICA forums in which experts and innovators discuss and debate important medical innovation issues. The EMJ team look forward to seeing you there!