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INNOVATIONS

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INSIDE

Review of

MEDICA 2018

Düsseldorf, Germany

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"MEDICA is the most prominent event for the decision-makers of the international healthcare industry, presenting attendees with insights into the complete process chain of medical innovations..."

Spencer Gore, CEO

Editorial Board

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Aims and Scope

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

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

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

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- Guidance from an Editorial Board consisting of leading authorities from a wide variety of disciplines.
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Front cover and contents photograph: Düsseldorf, Germany, home of the MEDICA 2018. © Olena Kachmar / 123rf.com

EMJ Innov.

European Medical Journal 3.3

Hello and welcome. It is my great pleasure to introduce to you the third edition of the European Medical Journal for 2018: *EMJ 3.3*. As always, our flagship journal melds articles...

VIEW ALL JOURNALS ←

Welcome

Starting 2019 as we mean to go on, I am proud to welcome you to EMJ's first publication of the year: *EMJ Innovations 3.1*. Our prestigious authors and Editorial Board members have assisted greatly in the production of this new edition, so sit back and relax with this collection of innovative peer-reviewed articles alongside highlights from the 2018 MEDICA Trade Fair.

MEDICA is the most prominent event for the decision-makers of the international healthcare industry, presenting attendees with insights into the complete process chain of medical innovations, from medical devices and instruments to high-tech solutions. We are therefore pleased to have created our unique and informative summary of the event for the third year in a row. With the exhibition halls filled with advances set to transform the healthcare industry, including digital technologies, artificial intelligence, and big data, the Congress Review section will transport you directly to Düsseldorf, Germany to relive those special moments. Reflecting the focus on start-up innovators at MEDICA 2018, this edition also contains our signature summary of the growth of med-tech companies across the globe.

Our independent review of MEDICA is supplemented by a range of high-quality articles describing the latest innovations from a variety of therapeutic areas. For those of you interested in regenerative medicine, the Editor's Pick for this issue explores the mechanisms and applications of four-dimensional bioprinting, provoking creative thinking and the enhancement of modern-day medical techniques. Timely reviews on the reporting of medical device incidents and the use of nano-interventions in atopic dermatitis, providing all readers with the opportunity to delve into some of the latest issues and solutions in healthcare, can also be found within. Last but not least, we have included a small selection of upcoming events and news updates from the field of medical innovations, making *EMJ Innovations 3.1* your go-to place to remain at the forefront of the healthcare industry.

I would like to take this opportunity to thank all of the contributors for this journal, without whom the fascinating and insightful content would not be available, and I hope all readers find the issue as interesting as we do. With many more EMJ eJournals to be published in 2019, containing more updates and advances from the medical world, here's to the beginning of a fantastic year.

Best wishes,

Spencer Gore

Chief Executive Officer, European Medical Group

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Foreword

Welcome to the latest edition of the *EMJ Innovations* eJournal. We continue to see rapid developments in healthcare-based technologies, with a myriad of innovations available to patients and their clinicians, improving health outcomes. Advances in restorative and regenerative medicine offer the real possibility of not just reproducing tissues but whole organs. My Editor's Pick for this edition, 'Four-dimensional bioprinting for regenerative medicine: Mechanisms to induce shape variation and potential applications' by Morouço and Gil, offers an almost philosophical view of how this particular aspect of medical technology will advance.

Many of the new biotechnologies are focussed on rare diseases or malignancies; however, two papers included herein focus on more common conditions. The paper by Kakkar et al. provides an overview of atopic dermatitis and nanointerventions; it explores the importance of delivery models of active management for this prevalent illness and how new technologies are supporting often neglected areas of clinical medicine. In addition, the article by Haider and Custovic on asthma pathways is a timely reminder of the importance of how integrated care adds value to the longitudinal care of patients with respiratory conditions. The focus on heterogeneity of the condition and tailored management based on the understanding of different pathophysiological processes is poignant, as new pharmacological developments assist us in improving care.

I also want to highlight the paper in this edition by Craig et al. entitled 'The need for greater reporting of medical device incidents'. The introduction of pharmacovigilance, defined as the reporting of adverse events, often post-licensing of a new technology, brings to light potentially longer-term or novel adverse events, through an effective incident reporting system. This has reduced the incidence of major catastrophes, such as the use of thalidomide and its teratogenic effects in the 1960s. It is important that we monitor the safety of any new intervention and an international adverse incident reporting process is appropriate. The recent case of failed robotic heart surgery and subsequent death of a patient in the UK highlights the serious consequences of ill-prepared systems implementing new technologies. The latter is an extreme and unusual case but all interventions have the potential for harm and, therefore, it is timely to raise this important issue.

I am sure you will enjoy all the stimulating articles in this new edition and I hope you will learn from the innovations that, in our view, are leading-edge and transformational.

Best wishes,

Prof Mike Bewick
Iq4U Consulting, UK

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Congress Review

Review of MEDICA 2018

Location: Düsseldorf, Germany – Messe Düsseldorf

Date: 12.11.18–15.11.18

Citation: EMJ Innov. 2019;3[1]:12-23. Congress Review.

Known as the most prominent event for decision-makers of the international healthcare industry, MEDICA 2018 welcomed around 120,000 visitors and >5,000 exhibitors to the jam-packed halls of the Messe Düsseldorf during 4 autumnal days in Düsseldorf, Germany. "Nowhere else in the world will you find the entire process chain of innovations for the development, manufacture, and marketing of medical devices, products, instruments, and high-tech solutions presented in such a seamless manner," commented Wolfram Diener, CEO of Messe Düsseldorf. From laboratory products to modern treatment solutions concerning many areas of healthcare, MEDICA 2018 had something for everyone to explore and learn from. Excitement filled the exhibition halls from Day 1 of the event, not only for the innovative solutions about to be presented to transform the healthcare industry, but also for the attendance of the German Federal Minister of Health, Jens Spahn, who opened MEDICA 2018 and the 41st German Hospital Conference, which took place in parallel this year.

With the choice of themes available to attendees being as wide as ever, one of the most prominent topics of interest at this year's event was digital transformation, known to be shaping the healthcare industry worldwide and changing both processes and business models for the better. Around 1,000 presentations were related to the digitalisation of healthcare, with a particular focus on benefits to doctors and patients. "Benefits for patients are a more efficient use of medical personnel on the one hand and easier access to specialist know-how on the other, for example, when experts from neighbouring university hospitals or even from abroad are called in virtually," elucidated Horst Giesen, Global Portfolio Director Health & Medical Technologies at Messe Düsseldorf. MEDICA 2018 also saw the presentation of the study on Healthcare 4.0, highlighting the huge potential of digital healthcare in Germany in particular.

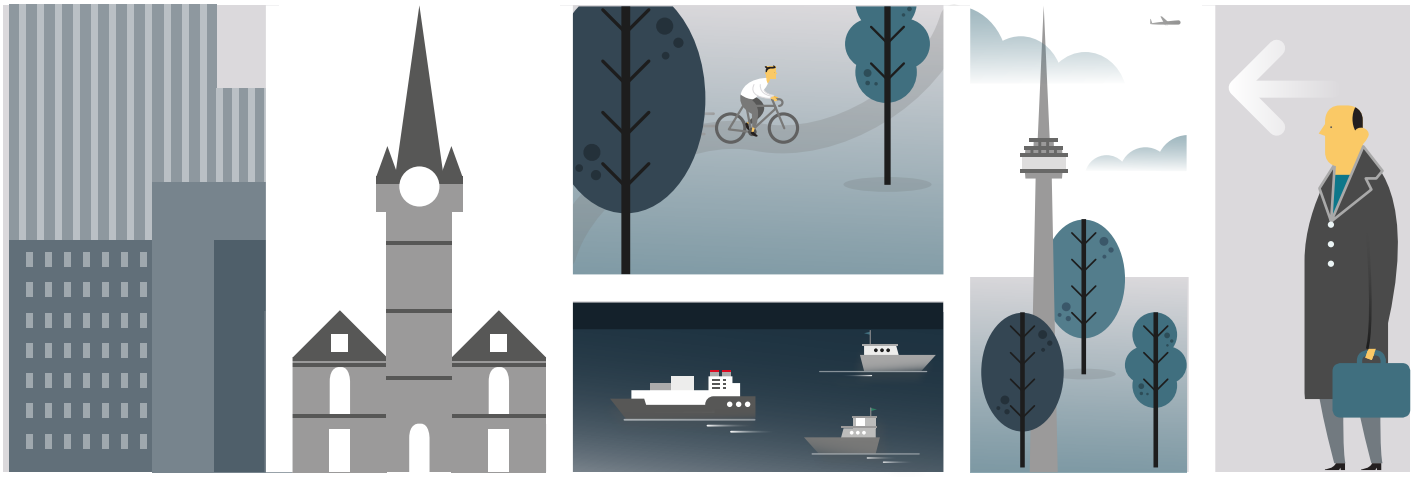
Topics such as big data, artificial intelligence, and cyber security were also of great interest to presenters and attendees, as they are used to tackle key issues in healthcare, from emergency medicine to chronic health conditions. The accompanying programme offered attendees numerous opportunities to experience how breath-taking advances in the development pipeline will revolutionise patient care, such as bionic technologies and overcoming phobias. The MEDICA CONNECTED HEALTH CARE FORUM and MEDICA HEALTH IT FORUM are key examples of such sessions. For those with an interest in sports medicine and fitness, there was also an array of programme highlights on offer, from corporate fitness to using sport to prevent chronic illnesses, such as diabetes. More of the key highlights from this year's inspiring event are available throughout the *EMJ Innovations* Congress Review.

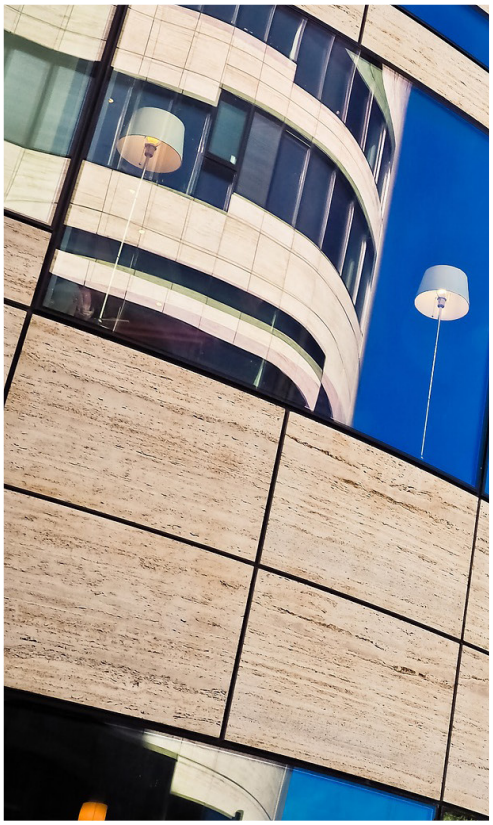
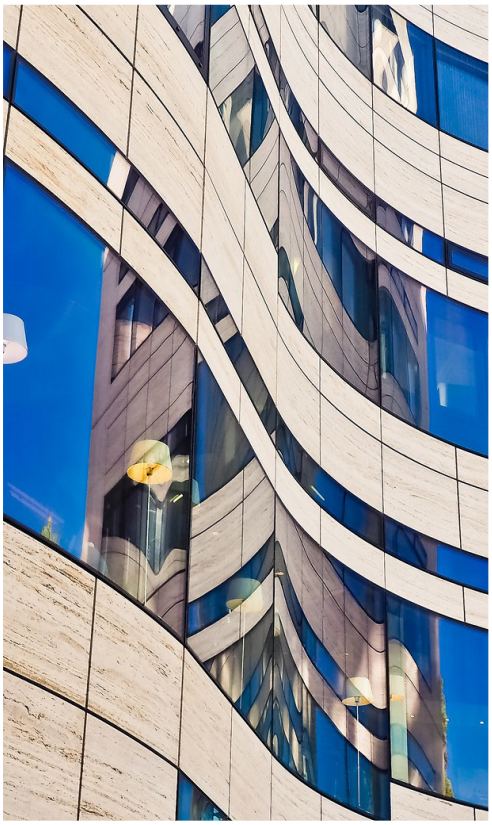
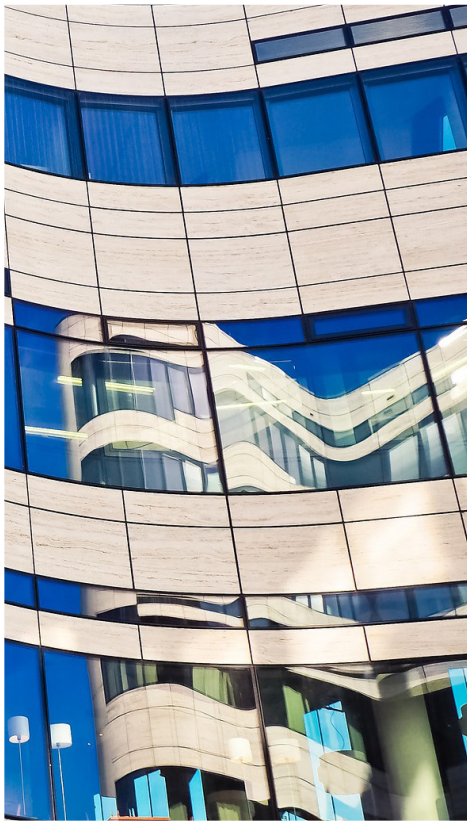
"Nowhere else in the world will you find the entire process chain of innovations for the development, manufacture, and marketing of medical devices, products, instruments, and high-tech solutions..."

With development focussed towards digital health applications that are software-based, young start-up companies from across the world are taking advantage of the reduced costs of hardware development and are beginning to enter the spotlight. MEDICA 2018 provided the perfect platform to showcase just how far healthcare applications have come, with new start-up presentations given daily as part of the MEDICAL DISRUPT initiative. From applications for chronic health conditions, such as a cardiac arrythmia app, to monitoring health status with a digital stethoscope, continue reading for insights into the most recent innovations to enter the medical arena, direct from MEDICA 2018.

The 2018 MEDICA fair was once again a mammoth success, welcoming industry experts from across the world to set the scene for the next wave of care advances to be welcomed by the medical community. As the world's largest medical trade fair, it is simply not possible to attend all sessions of interest during the 4 days, so *EMJ Innovations 3.1* conveniently provides a comprehensive review of the event to keep you up-to-date. Whether you would like to refresh your memory or learn more about presentations you were unable to attend, the key data, updates, and future work can be found in the following pages, preparing you for a wonderful year of medical innovations. We look forward to welcoming you back to Düsseldorf for MEDICA 2019 to discuss these developments and encourage you all to mark the dates in your diaries: 18th–21st November 2019!

"Benefits for patients are a more efficient use of medical personnel on the one hand and easier access to specialist know-how on the other..."



Smart Glasses Set to Take the Lead in Eye Therapy

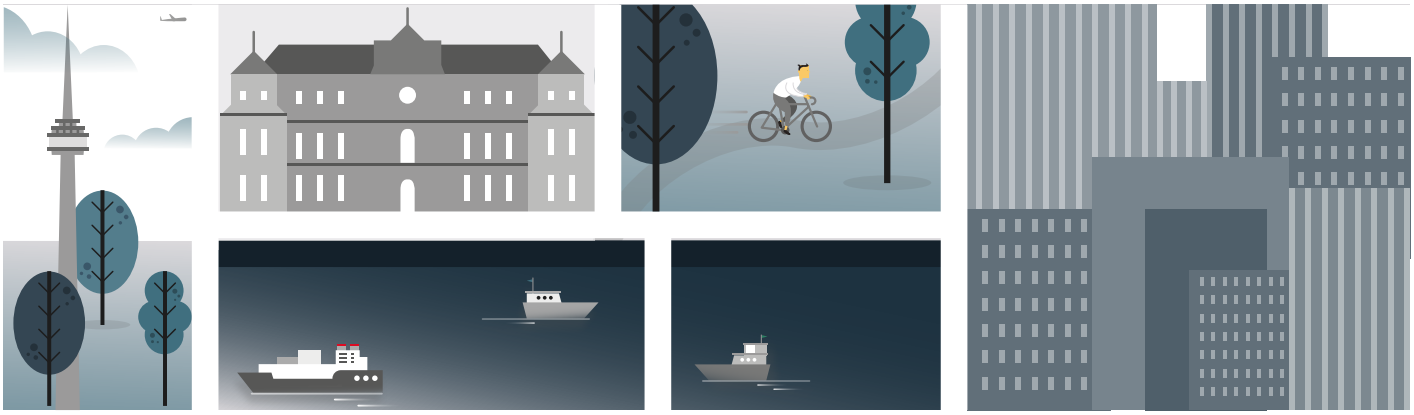
AMBLYOPIA, or lazy eye, is a common condition in children. The historical way to treat the condition is to cover the healthy eye with a patch, thus forcing the lazy eye to work harder, correcting its function. For the patch therapy to work, the eyepatch must be worn for the prescribed period; however, this can lead to the child feeling self-conscious and refusing to wear the patch. Now, new shutter glasses developed in Germany and reported in a MEDICA press release dated 12th November 2018 could be set to revolutionise the treatment of amblyopia.

There are two major drawbacks of patch therapy: firstly, the undesirable appearance of wearing an eyepatch and, secondly, the impairment to the spatial vision of the wearer. The new glasses showcased at MEDICA 2018 have been designed to minimise both these undesirable effects of wearing a patch.

The smart glasses, developed by researchers at the Fraunhofer Institute for Biomedical Engineering IBMT, Sulzbach, Germany, have been designed to include a range of sensors integrated into the arms. The data obtained from the sensors can be viewed through a sister smartphone app and can be accessed by the ophthalmologist to monitor patient progress: "Our goal is to provide an individual, patient-based therapy," explained Dr Frank Ihmig, Fraunhofer, IBMT. Using the data collected, the glasses, which are darkened through an electronically controlled shuttering system using integrated liquid crystals, can be adapted to each individual patient. To minimise the effects on the user's spatial vision, the glasses remain clear during sporting activities.

"Our goal is to provide an individual, patient-based therapy."

The glasses offer a new, more aesthetically pleasing approach to amblyopia treatment; however, the work is by no means complete. The next step for the researchers is to reduce the size of the technology, so that it may be incorporated into the frames of a child's glasses. Additionally, the researchers are aiming to make the technology more efficient by improving the battery life of the shutter sensors. The glasses could be a revolutionary step forward in the treatment of this common condition.



MEDICA App Competition 2018

THEY SAY seven is a magic number, and it is certainly the case that the seventh edition of the MEDICA App Competition saw some truly impressive sights. Yet the splendour on show was not sorcery but a fusion of medical science and information technology. Ten contestants reached the final round, but there could only be one winner.

The competition was for the best app-based mobile medical solution for use by a patient, doctor, or in a hospital setting. Although it culminated at MEDICA, the competition had begun many months previously. Submissions were open from June–September 2018. Out of all the submissions, a jury was then faced with the unenviable task of selecting just 10 to proceed to the final stage. Apps could not have been launched prior to the beginning of 2016 and had to be in the market by the end of quarter 1 in 2019.

There were a number of criteria these apps were judged against:

- The scalability and attractiveness of the business model.
- The quality of both the team and their provided documentation.
- The level of innovation shown by the app.
- The scale of problem-solving displayed by the app (i.e., what healthcare-related problem has it solved).
- The functionality of the app and the intuitiveness of its user interface.

The 10 contestants who presented at MEDICA were BuddyCare, FibriCheck, D-EYE 2.0, myFreescan, Medicospeaker, oPerception, Orthyo, Veta Health, Zencorlabs, and Tonic App. All had the opportunity to claim the top prize of €2,000, not to mention the healthy dose of global exposure that would follow from success on such a grand stage. All contestants delivered a 3-minute pitch, which was followed by 2 minutes of questioning from the jury. Following the conclusion of the presentations, the jury retired to make their deliberations.

After a tense waiting period, FibriCheck was deemed the winning app. This U.S. Food and Drug Administration (FDA)-approved app has been designed to use the camera on a smartphone to facilitate the detection of various cardiac arrhythmias. The app is also able to generate a report that can be accessed by doctors and/or patients.

Rehabilitation: A Patient-Centric Solution

MEDICA is a stage where many companies debut their latest offerings, with this year's event being no different. One product taking its first steps into the medical market was the exoRehab, as reported in a MEDICA press release dated 12th November 2018. The exoRehab was developed by the South Korean robotics company Exosystems and represents the company's first hardware development thus far.

The company's CEO, Hooman Lee, spoke of Exosystems' ambition to facilitate a move beyond traditional human limitations in the medical rehabilitation process. He explained how they were aiming to make rehabilitation more effective and streamlined.

This approach was borne out in the early stages of product development. Exosystems channelled the growing trend for patient centricity from the

onset, seeking to identify issues faced by patients when undertaking traditional rehabilitation approaches. They determined that there were three primary issues:

- The (lack of) geographical proximity to hospitals.
- Shortages in rehabilitation services.
- Repetitive and dull movements within the rehabilitation programmes themselves.

As part of developing the exoRehab, the developers sought to ameliorate the impact of these barriers preventing patients from maximising their rehabilitation. This solutions-driven approach saw three features included as part of the exoRehab:

- Portable wearability.
- Gamification techniques incorporated into the programme. These are designed to improve patient enjoyment of the process.
- The use of artificial intelligence to gather medical data. This provides data via the cloud to medical professionals, allowing remote monitoring and thus reducing the need for hospital visits.

The exoRehab is also designed to utilise the user's musculoskeletal data to produce individually tailored exercise and electrical stimulation programmes. As this is a newly developed project, its impact regarding uptake and efficacy remains to be fully determined.

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A New HIV Test on the Block

THE EUROPEAN Centre for Disease Prevention and Control (ECDC) estimates that, in some countries, up to 43% of European HIV patients remain undiagnosed, on average 47% of individuals are diagnosed with HIV late, and 28% of patients are diagnosed with advanced HIV, which can present with AIDS-defining diseases, such a pneumonia. However, a new HIV test kit, reported in a MEDICA press release dated 12th November 2018, could be about to change the face of HIV diagnostics.

"The introduction of the Simplitude™ Pro HIV (1&2) rapid diagnosis test at MEDICA 2018 addresses an important issue, meeting the need for a reliable point-of-care diagnostic test (the overall sensitivity and specificity is 99.6%) that is simple to use, and provides convenient and prompt results to support early diagnosis."

Despite increased access to HIV tests, the World Health Organization (WHO) targets of 90% of HIV patients knowing their status, 90% of those diagnosed starting antiretroviral treatment, and 90% of patients exhibiting prolonged viral suppression are still out of reach; in fact, in 2017 these figures were 75%, 79%, and 81%, respectively. Late diagnosis is believed to be a major contributing factor to the current state of HIV treatment.

The Simplitude™ Pro HIV (1&2) rapid diagnosis test, produced by Owen Mumford, Oxford, UK, includes a built-in lancet and blood collection unit. The combination allows physicians to collect blood samples and carry out the steps necessary to complete a HIV diagnosis test accurately. Tania MacKenzie, Senior Global Product Manager for Diagnostics, Owen Mumford, stated: "The introduction of the Simplitude™ Pro HIV (1&2) rapid diagnosis test at MEDICA 2018 addresses an important issue, meeting the need for a reliable point-of-care diagnostic test (the overall sensitivity and specificity is 99.6%) that is simple to use, and provides convenient and prompt results to support early diagnosis."

The results from a recent study conducted in England and Wales showed that HIV patients diagnosed late (T cell count <350 cells/mm) were 3.5-times more likely to die than their early diagnosed counterparts. The development of the Simplitude test, through its built-in lancet and sample collection unit, could turn the tide against late HIV diagnosis, making the WHO targets increasingly more achievable.

Increasing Antibiotic Efficacy After Joint Implant Insertion

SYNERGISM between antibiotics and silver ions significantly increases the effectiveness of the drugs at preventing infection. Therefore, precisely matching the drug directly to a replaced implant, as reported in a MEDICA press release dated 12th November 2018, could reduce the risk of severe infection and implant replacement during routine hip and dental implant operations.

Their first results are promising and clinical trials in this area are much anticipated.

While implant operations are routine, they carry a risk of bacteria entering the wound and an infection occurring, requiring control with oral or intravenous antibiotics. Furthermore, in some cases, the implant may have to be removed since the pathogen cannot be eliminated. With the aim of avoiding infection altogether, research from the Synergy-Boost project, displayed at MEDICA 2018, built on the knowledge that silver ions enhance the effect of antibiotics, dependent on the drug type and the target micro-organism. Researchers from the Fraunhofer Institute for Molecular Biology and Applied Ecology (IME), Schmallenberg, Germany, performed large-scale screenings to identify effective antibiotic–silver ion combinations that could effectively eliminate pathogens and prevent implant removal. Using 20 different antibiotics with varying ratios of silver ions and 4 target pathogens, >9,000 tests were performed.

In line with standard clinical practice procedure, the scientists generated antibiograms to select antibiotics for specific pathogens using sample material. The antibiotic was then applied directly to the implant. To enhance the antibiotic's effect, the team used a vacuum to apply a silver-containing coating to the surface of the implant, creating a structure than is able to absorb the drug. Since development of the silver coating is now complete, the Fraunhofer researchers are now working to verify its efficacy and prepare for its approval for medical devices, which could revolutionise the field and significantly increase the number of successful implant procedures. While boosting the efficacy of antibiotics at implant surfaces is greatly needed, Fraunhofer scientists are also attempting to find natural, plant-based substances from which to create new antibiotics altogether. Their first results are promising and clinical trials in this area are much anticipated.

Reaching New Athletic Heights

FASTER, HIGHER, STRONGER. Athletes around the world are pushing themselves to the limit in pursuit of these sporting goals. In the quest to reach further into the sporting stratosphere, sports science can help expand the frontiers. Prior to giving a lecture on the subject at MEDICA 2018, Prof Billy Sperlich, Julius Maximilian University of Würzburg, Würzburg, Germany, took part in an interview on point-of-care testing in high performance sports, as reported in a MEDICA press release dated 2nd November 2018.

One of the barriers athletes, especially endurance athletes, face is time; there are only so many hours in a day when one can feasibly train. It is therefore important both to make sure each hour of training is used as effectively as possible and that no hours are lost as a result of injury or excessive fatigue. Evidently, with athletes often training several times a day, detection of a possible injury or illness needs to be as swift as possible. After all, it is not much use to test for a factor, such as illness, on Monday and only receive the results on Friday, because by that point it may well be too late to take preventative action. Prof Sperlich explained: "The fact that monitoring with point-of-care testing and wearables enables prompt intervention makes this process so exciting."

"Since the huge advantage of point-of-care testing is that it delivers rapid test results, I expect its increased importance and rising popularity in the future."

Prof Sperlich then went on to discuss the varied measurements that could be made. He noted that, for runners, markers that show immune function, muscle strain, and cardiovascular values are commonly measured. Salivary measurements are growing in frequency, as they enable measurement of stress hormones such as cortisol, testosterone, and amylase. The measurement Prof Sperlich highlighted as the most crucial was ear temperature. This marker allows for the detection of fever conditions, meaning that the training programme can be altered in response.

However, point-of-care testing faces a significant hurdle: the athletes themselves. Athletes must be motivated to undertake a high frequency of measurements. It was noted that athletes are often only keen to undergo this kind of testing once they become injured or understand that they are frequently affected by illness or injury. Nevertheless, Prof Sperlich concluded: "Since the huge advantage of point-of-care testing is that it delivers rapid test results, I expect its increased importance and rising popularity in the future."

Virtual Spiders? Arachnophobia Therapy in the Virtual World

SPIDERS. These arachnids are a common part of everyday life for many of us, but what if the sight of a spider were debilitating? This is the reality faced by some with arachnophobia, which is estimated to affect around 3.5–6.1% of people. Arachnophobia is more than simply not wanting to hold a spider or asking someone else to move a spider away from you; indeed, upon seeing a spider, some individuals experience heart palpitations, dizziness, shivering, sweating, and shortness of breath. For some of those affected by arachnophobia, the condition has such a profound impact on their quality of life that treatment represents a necessary option.

There are two significant problems with the existing treatment options: firstly, treatment choices and facilities are scarce. If there is no treatment option in geographical proximity, it is not possible to undergo treatment. It is estimated that a lack of treatment availability has resulted in 60–80% of those with arachnophobia being unable to undergo treatment. Secondly, the most common form of treatment is, by its nature, somewhat off-putting. Typical exposure therapy can be too daunting a prospect for arachnophobes.

Typical exposure therapy can be too daunting a prospect for arachnophobes.

As a result, the DigiPhobie project has been initiated, as discussed in a MEDICA press release dated 12th November 2018. This is intended to allow patients to experience exposure therapy in a virtual environment. One of the scientists involved in the project, Dr Frank Ihmig, Fraunhofer Institute for Biomedical Engineering, Sulzbach, Germany, explained: "We transfer real exposure therapy to the digital game system that runs on the data glasses. All therapy tasks are digitally simulated. The phobia sufferer can perform various challenges, such as catching a spider with a glass and a postcard or prodding one with their finger, in virtual reality."

During the sessions, patient parameters will be measured, and the data archived and made available for analysis. Parameters measured include variability in heart rate and breathing rate. One of the aims of this measuring is to identify specific areas of stress and thus tailor the therapy individually.

While the DigiPhobie project is an exciting prospect, data are awaited from a validation study that will commence in the spring of 2019. This study will evaluate the effectiveness of the virtual reality-based therapy.

Highlights from the MEDICA Health IT and Connected Healthcare Forums

BIG DATA, the internet of things, and artificial intelligence are of ever-growing importance in healthcare. From current diagnostics to cutting-edge innovations, the use of digital technologies is lighting the path towards a new age of treatments. The use of such technologies was scrutinised in the immensely successful MEDICA Health IT Forum and the MEDICA Connected Healthcare Forum.

A key theme across the forums was the use of artificial intelligence and robotics in healthcare. The CorTec Brian interchange ONE system was introduced on 13th November 2018; a system that connects the human nervous system with artificial intelligence allowing for stimulation and recording across 32 channels, The CorTec system has been designed to combat neurodegenerative disorders and associated symptoms. On the very next day, a deeper discussion around the use of

neurostimulation and robotics was conducted, as Prof Arndt Schilling, Trauma Surgery, Orthopaedics, and Plastic Surgery, University Medical Center Göttingen, Göttingen, Germany, discussed the difficulties developers face capturing free thought in computer algorithms.

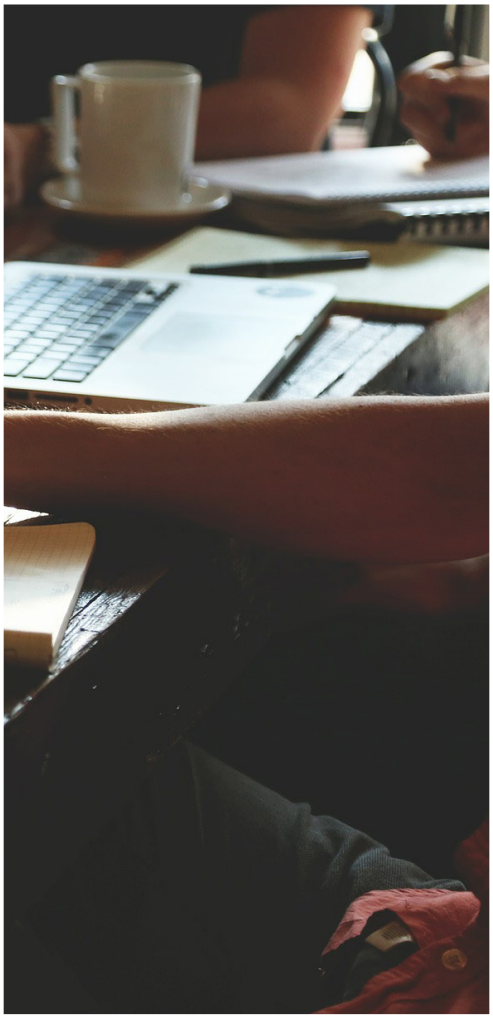
The 2018 MEDICA trade fair included specialist sessions on revolutionary smart prosthetics. Prosthetics have developed massively in the last 100 years, becoming more functional and comfortable for users; however, the work to improve this technology is not over. The focus at MEDICA 2018 turned to improving the usability of prosthetics with machine learning. The implementation of machine learning could minimise the need for patients to complete hours of training to use their prosthetics most effectively. As Prof Schilling explained, "this gives patients the pleasant feeling of the prosthetics serving them and not the other way round."

At the cutting edge of innovation, science and technology must regularly consider the ethics of the work scientists and engineers are completing. This very subject was bridged at MEDICA 2018, making for a fascinating discussion on the question of whether everyone has the right to be provided with state-of-the-art prosthetics.

As ever, the MEDICA forums offered a glimpse of the innovations that will soon transform the way in which the medical community uses technology to achieve the best outcomes for patients.

A Focus on Start-Ups at MEDICA 2018

YOUNG companies took to the stage at this year's MEDICA event to present solutions for treating worldwide medical conditions, from heart disease to skin cancer, as well as improving general health in everyday life. Found in the MEDICA START-UP PARK, the Wearable Technologies show, and at joint booths, >50 start-up companies presented their new telemonitoring and tracking technologies to enhance digitalisation of the healthcare industry and begin their quests for market domination.



The fast treatment and monitoring of chronic conditions was one aspect of care covered by various start-up companies at the event. StethoMe, a cordless stethoscope, was revealed as a way of enabling parents to check the function of their child's heart and lungs at any time, reducing the number of hospital stays for children with chronic lung conditions. Optimised by artificial intelligence, the device is highly accurate and allows improvements in auscultation diagnostics and therapy monitoring. A smart inhaler application was also presented to benefit asthma patients, named FindAir ONE. The application collects inhaled medication dose information as well as detail on the environmental conditions in which the inhaler is used, allowing the patient and doctor to adjust treatment accordingly. Focussing more on heart conditions, the CellAED LifeSaver automated external defibrillator created by Rapid Response Survival can be used to indicate a heart attack via measuring heart rhythm, instructing the user on the next steps and contacting the emergency services at the same time. Also created for emergency situations, the Spektikor RAPIDA Indicator was revealed and is said to be the smallest portable heart rate indicator in the world, enabling heart rate to be established in incidents with multiple casualties.

As a condition with an increasing prevalence across the world, skin cancer was also a of focus for many start-up companies. For example, Magnosco presented their method for early detection of skin cancer using lasers to stimulate and illuminate melanin, allowing mapping of cancer cells amongst healthy cells in the skin. An algorithm is used to calculate the probability of malignant skin cancer by recording the proportion of cancer cells versus healthy cells. Available for dermatologists to use now on living and isolated tissue, this innovative approach should improve rates of early detection of skin cancer and, hence, improve survival rates.

Finally, ensuring safety and maintaining health during everyday life was shown to be important for a variety of new companies displaying their products at this year's MEDICA event. Presentation of a technologically innovative cot sparked conversation, with details revealed on its inbuilt camera and integrated sensors to allow weight, temperature, and blood oxygen to be monitored by parents while their baby sleeps. A baby's development can also be tracked using the image recognition technology, potentially saving the lives of children who require additional monitoring. Furthermore, LogonU is focussed on adult health, applying scientific analysis for numerous physical activities to define a level of health. From measuring muscle activity in real time to detecting poor technique, the smart tracking application, reported as an 'everyday hero' at MEDICA 2018, can be applied to sport and healthcare.

Providing an insight into the latest start-up companies from the field of innovations, it was clear from MEDICA 2018 that digitalisation within the healthcare industry is a trend worldwide and will continue for years to come. From enhancing the care of patients with serious illnesses to improving wellbeing during everyday activities, the start-ups presented at this year's event offered an array of innovative solutions. To round-off the start-up programme, experts explored how these start-ups can successfully enter the market and overcome the associated challenges, using examples from others that have successfully passed the first roadblocks.

The Rise of Medical Technology

The Location of EMJ's Top 100 Medical Technology Start-ups[1-4]

Location of the Top 28 European Medical Technology Start-ups[1-4]

x Number of companies

Predicted Top 10 Medical Tec Revenue by 2022[5]

Company
Medtronic
Johnson & Johnson
Abbott Labs
Siemens
Becton Dickinson
Philips
Stryker
Roche
Boston Scientific
General Electric

chnology Companies by

Revenue (bn $)

38.9

33.4

26.6

20.3

19.2

18.7

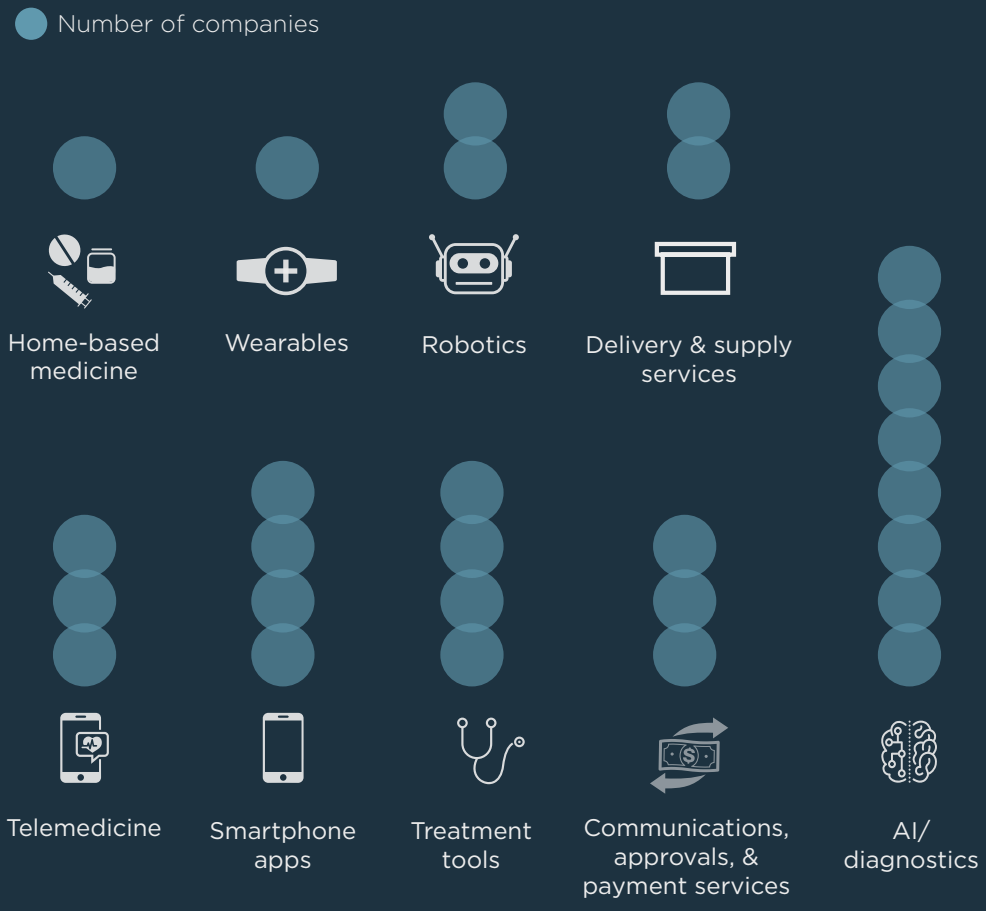
18.5

16.3

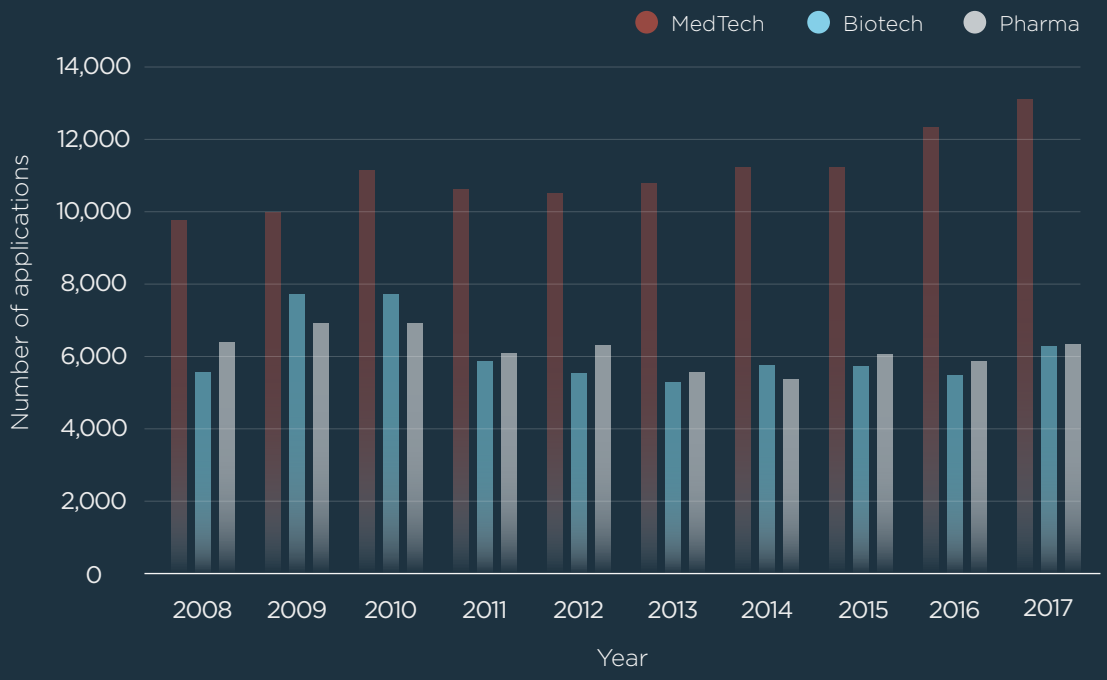
14.4

12.9

The Sectors Occupied by EMJ's Top 28 European Medical Technology Start-ups[1-4]



The Number of EPO Patent Applications for Medical Technology, Pharmaceutical, and Biotechnology Products from 2008–2017[6]



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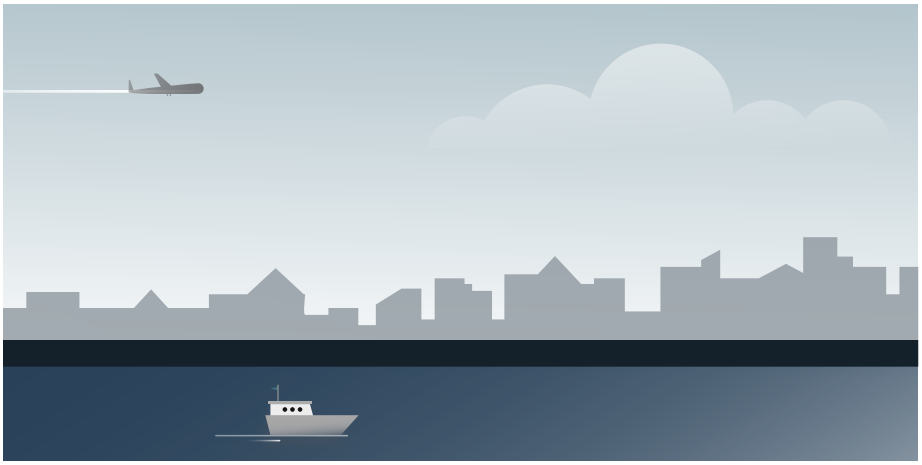
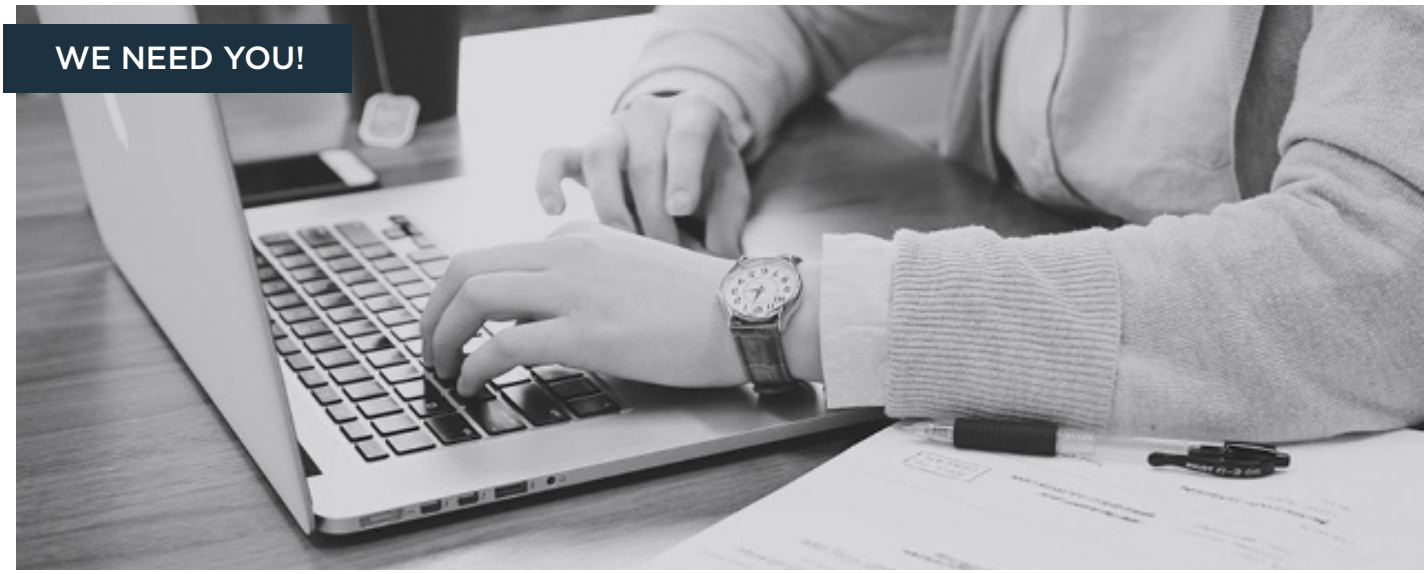




EMJ Innovations Survey

We are always looking for ways to improve our content and we believe that your experience and comments will help us improve *EMJ Innovations*. We greatly appreciate any feedback you are able to share.

The survey will take less than 5 minutes to complete.

TAKE OUR SURVEY ←

Interviews

Take the opportunity to learn more about digital healthcare and eHealth from key members of the *EMJ Innovations* Editorial Board

Featuring: Prof Rachel Dunscombe, Mr Miguel Gonzaléz-Sancho, and Mr Clayton Hamilton

Prof Rachel Dunscombe @ukpenguin

NHS Digital Academy, UK

How did you first decide that you wanted to pursue a career in medicine, and what is it that continues to inspire you to carry on to this day?

To be honest, although I studied biochemistry and biomedical science, I first worked in technology in other sectors, such as finance and travel. After some difficult experiences on a personal level with the NHS, I decided to move from industry and join the NHS. For me, improving healthcare is a personal mission aligned with my values. I am inspired because improving wellness and medicine via digital health is the most challenging and, I think, promising possibility for increasing human wellbeing.

Every day for me is a new challenge. I am an operational director for two NHS organisations, CEO for the NHS Digital Academy, and a visiting professor at Imperial College London, London, UK. I am in a very privileged position, combining my operational practice with research and academic curriculum for clinicians and non-clinicians working in digital health. I stand in a unique place that allows me to move the NHS forward both practically and policy-wise.

What is the NHS Digital Academy and how did it become established?

The Digital Academy is a collaboration between Imperial College London, Edinburgh University, Edinburgh, UK, and Harvard Medical School, Boston, Massachusetts, USA. It provides a postgraduate level qualification for clinicians and non-clinician leaders in digital health. Its inception was in 2017 as part of the response to the review undertaken by Bob Wachter. His review outlined that the system lacked the capacity and capability to 'reimagine the work' in terms of creating new models of care enabled by digital technology.

The programme was commissioned by NHS England and the Scottish government, with other nations set to join in the coming years.

The programme provides practical, hands-on experience, which can be demonstrated via a project in the workplace. The establishment has been supported by bodies such as the British Computer Society, Faculty of Clinical Informatics, NHS England, and NHS Digital. At the Academy, we regard this as part of the birth of a digital health profession, in which concepts such as continued professional development are mandated and measured.

How do you expect the NHS Digital Academy to progress, and how will it change medicine as we know it?

I view the Digital Academy as something that will reduce the friction in the system as we adopt new ways of working, including population health and precision/personalised medicine. Creating a large cohort of >315 people who understand the art of the possible and how to safely work within the current healthcare systems will allow us to rapidly make safe progress. The balance of risk and opportunity is a continual one: when is a problem ready to be solved by a new technology? What are the clinical safety aspects? How should we partner with industry? These questions and many more are explored as part of our programme.

The main change I see here is digital health professionals perfecting the art of picking the right problem at the right time to work on. This involves reading the supplier market, quantifying the problem, and looking at the many human and technical factors at play. This is really what I mean about reducing friction: the art of not wasting time and using our resources as effectively as we can. Compared to most healthcare systems in the Western world, we spend less than average per capita on healthcare.

2018 marked 70 years of existence for the NHS. In your opinion, what is the best thing about the NHS, and how do organisations such as the NHS Digital Academy help to improve its services?

The NHS is a unique health system globally and we value it highly here in the UK. The best thing is the ability to achieve scale and also implement the likes of accountable care systems, which allow a focus on population shift towards wellness. The focus on research in the NHS is also inspiring; we are a learning health system. The people and culture are also exceptional; I find the clinical leadership inspiring and I am privileged to work with world-class talent. Happy 70th birthday NHS!

"I stand in a unique place that allows me to move the NHS forward both practically and policy-wise."

The Academy plays a key role in giving the system the capacity and capability to enable transformational change and new models of care. We need leaders with the toolbox of knowledge and skills to push us into the new world. With limited resources, we must ensure we maximise every pound spent. Healthcare is consumerising and this is a key initiative in harnessing the power of the patient for the benefit of citizens and the NHS.

What is it about technology and data that particularly interests you? Do you have any examples of how technology and data can be used to improve patient care?

The thing about data for me is that data can save and improve lives. We are sitting on so much wisdom in some of the datasets we hold. Technology, for me, is the means for getting these data and making the lives of citizens, clinicians, and carers better. There is so much about the human body we are yet to learn, and the coming years will see the unfolding of insights that will change the way we live and treat disease. Genomics and other factors will, of course, lead to personalised and precision medicine and care, and we will find more and more granular insights as we progress.

For me, though, this leads to a need to be intelligent owners of our datasets. Investing in the likes of data scientists will allow us to maximise the insights drawn and align it with the big problems we are facing.

This digital world is now emerging, and examples I am implementing include wearable devices,

patient monitoring apps, and automated scoring for conditions such as sepsis, acute kidney injury, and dementia. These initiatives all lead to more appropriate care and more rapid decision-making.

Some individuals feel it is best to have hard copies of all information, for fear of technical disasters, hacking, or a loss of all recorded information. Do you believe everything should be digitised? Why?

So, should everything be digitised? Yes, but we need a contingency: we need to know what to do if we lose the national power supply or there is a major incident. We plan that our data are resilient and we have downtime processes that we test. We cannot plan for every scenario but knowing that there are copies of data kept safely allows us to know that data can be recovered.

As a result, I ask people: "do we not use electricity or water because we could lose our supply?". Technology is a utility that we need to make resilient, but we cannot stay on paper for fear of losing the systems. Paper, after all, could be lost in a fire or flood. Digital allows multiple resilient copies. In the future, elements of blockchain-like technologies will allow further resilience. In a world where we have moved to digital money and banks, we should move to digital healthcare records.

Alongside your role as the CEO of the NHS Digital Academy, you are also the Director of Digital for Salford Royal NHS Foundation Trust and Northern Care Alliance. What does this role entail and how is it different to your role with the NHS Digital Academy?

The Digital Academy role is an educational one, leading a postgraduate level qualification. My role at Salford and the Northern Care Alliance (NCA) is strategic and operational; I lead all digital services, covering a £1.5 billion turnover organisation, including acute care, community care, and social care. We are composed of a number of integrated care systems and are growing as a group. It is a challenging role that allows me to evidence what we are teaching at the Academy.

Salford Royal, which is part of the NCA, is an NHS England Global Digital Exemplar for NHS England. This means we are very digitally mature and are trailblazing new ways of delivering clinical services, digital wellness, and social care services. We have recently been assessed by KLAS research as being in the top 5% compared with major health systems for clinical satisfaction, quality, and engagement in the USA. I am very proud of leading this journey with my fantastic teams.

"The NHS is a unique health system globally and we value it highly here in the UK."

What are your responsibilities as a visiting professor at Imperial College London? What is it that you enjoy most about this branch of your career?

As part of my role at Imperial College London, I am leading Module 2 of the Digital Academy Programme. This has been a fantastic experience, putting together an academic set of materials for 'Implementing Transformational Change'. Teaching is something I really enjoy and is a great balance to my operational role. I lean heavily on my role in the NHS to allow me to provide this learning experience. I find it a privilege to be able to exchange knowledge with fellow digital health peers.

For me, helping clinicians and digital health professionals learn, develop, and be at their best is an amazing opportunity; it is a role that I never thought I would have 10 years ago, but I have embraced it and it has given me great satisfaction. I have learnt about myself as part of this process and, indeed, continue to learn from other faculty, students, and peers.

Is there anything that you would like to see come into place, either in the NHS alone or in the medical world as a whole, within the next 10 years?

I think we need to start using technology to deal with those repeatable, high-volume tasks that cost our health service a great deal of money. Some of these are clinical and others are administrative. We need clinicians to be working

on the most complex work, which gives them the most satisfaction. Technology can remove the routine and allow us the capacity to deal with complex tasks. It will also allow clinicians to deal with the human and compassionate aspects of healthcare.

"For me, helping clinicians and digital health professionals learn, develop, and be at their best is an amazing opportunity..."

We will also see technology and the likes of genomics giving us the real possibility of personalised and precision interventions. I have already worked with one life sciences company that is beginning to work out the profile of patients for whom their drug is most effective, as well as considering the ethics behind this approach. Imagine targeted treatments taking everything about you and around you into account. We can get far better at keeping people well and making them better. Our curve of acuity and illness needs to move to the left, and I can see technology and data being the key enabler for this.

What three pieces of advice would you give to an aspiring medical trainee hoping to make a difference in their future career?

I have a number of Chief Clinical Information Officers who work for me and I have taken a lot of time talking to them about their careers. This is an emerging career path and is nothing to fear, it is something to embrace. Without exception, all of those doctors who have moved into the digital space have found satisfaction in this work. What has been important for them is the ability to improve care; they do not need to be technical specialists, but they need to have a passion for this goal.

If this is something you are interested in, embrace it and make people aware you are interested. It may not follow the traditional path of medicine, but the rules are changing. You can practice medicine and be a Digital Health leader; both are more than possible. Often, you may need to carve the role out for yourself and be proactive about seeking to work in this space. The rewards are huge, as is the stimulation. This is a massive emerging space and there is nowhere else more exciting to be.

Mr Miguel Gonzaléz-Sancho @miguelgsb

European Commission, Belgium

As Head of the Cybersecurity Technology unit of DG CONNECT, what does your typical day involve? What do you enjoy most about your role?

I manage European initiatives, including funding programmes for research and deployment, supporting cybersecurity co-operation, and capacity building by European Union (EU) stakeholders (national and local authorities, businesses, academia, etc.). This is a relatively new job for me and follows my previous position dealing with health and technology, which was also at the European Commission. I enjoy discovering the new field of cybersecurity, which concerns all of us in our capacity as digital citizens and the impact of which on our society and economy will keep increasing.

What role does the European Commission play in the evolving landscape of healthcare across Europe? What are their main priorities at present?

There are three major roles: defining framework rules for Europe and its single market, including the healthcare setting, e.g., rules on medical devices, data protection, clinical trials, etc; European funding, e.g., for research, innovation, and regional development; and facilitating co-operation between key players, notably national health authorities.

I think the top priority in healthcare is how to maximise the potential of so-called 'big data' to deliver improved prediction, personalised treatment, and integrated care, with the aim of improving healthcare quality, access, and affordability. This requires pooling, processing, and using data of different types and from many sources, which raises fundamental questions regarding data protection, security, technological capability (including the role of artificial intelligence), and many others.

"The medical community should pay the utmost attention to cybersecurity..."

With many medical records, procedures, and treatments now requiring some form of technology, should the medical community be worried about cybersecurity? What needs to be done to ensure such technology is used in the correct way?

The medical community should pay the utmost attention to cybersecurity; however, what needs to be done depends on the data assets and the players concerned in each case. Everything starts with the awareness of the risks, which unfortunately often comes after having experienced a security problem, then having basic cybersecurity 'hygiene' behaviour, such as backing-up data and updating critical software.

Since the introduction of the concept of eHealth, how do you believe patient care and public health surveillance have been enhanced?

The concept of eHealth was introduced at least 20 years ago; medicine and healthcare have changed a lot (for the better) since then and that is in great part due to the role of technology, which has enabled new discoveries and treatments. A major, relatively recent development is that many patients are becoming much better informed and proactive regarding their own health. This is redefining relationships between patients and healthcare professionals, and 'Doctor Google' is also a massive transformation.

Are there any problems caused by eHealth that the medical community need to keep in mind when using eHealth practices compared to more traditional processes and communication techniques?

Technology and data can radically increase the quality and efficacy of diagnostics and treatment. However, wrong data at any level of the chain, for example during data capture, processing, or interpretation, can have negative, or even fatal, outcomes. Healthcare professionals must always remain in control of major decisions and apply their professional judgement. The importance of having an aeroplane captain despite the development of autopilot is a very fitting analogy for this.

How has the use of big data revolutionised healthcare and provided improvements in healthcare policy decisions?

As already mentioned, the potential of big data in medicine and health is enormous. The general feeling is that the revolution is yet to come, but many things are already here: faster and improved diagnostics (including for rare diseases) thanks to advanced data mining techniques, targeted drugs, and other treatments, which can be then refined with feedback from real-world data, modelling of organs, devices, etc.

"Healthcare professionals must always remain in control of major decisions and apply their professional judgement."

Do you believe the use of big data is applicable to healthcare systems across the globe? Are there any differences in the effectiveness of data sciences between high-income and low-income countries?

I would say that good medicine is the same everywhere, but of course socioeconomic variation and affordability play an obvious role, not just between different parts of the globe but also between different groups of a population

living in the same place. Ensuring that the benefits of data-enabled medicine spread evenly across society, as opposed to benefiting the privileged few, is an important debate around the future of eHealth. There are many factors at play here, notably how healthcare systems are organised, who pays for what, public versus private interests, and many others.

From your perspective, what do you predict the impact of Brexit will be on the relationship between the UK and Europe with regard to cybersecurity, eHealth technology, and patient care?

As a European official, I cannot comment much, especially when the negotiations on this matter are at a very delicate stage. But I can share my hope that Brexit will be as soft as possible because I am convinced it is in everybody's interest, and for the UK the alternative is much worse. For now, I think it is of paramount importance for the UK to look for practical solutions regarding future market authorisation of medical devices and medicines, as well as to ensure there will be an implementation of data protection rules in line with the EU framework. Of course, this is just to mention some of the major issues that come to my mind directly relevant to health. As for cybersecurity in general, co-operation between countries is essential and, again, I hope the UK and the EU establish a constructive co-operation strategy in the future.

In the fast-paced world of medical innovations, is there a technique or technology currently in development that you are particularly excited by?

I find developments around artificial intelligence very exciting as well as those surrounding modelling and health in general, especially regarding the human brain.

Lastly, what advances in healthcare are likely across Europe over the next 10 years?

More prevention, prediction, personalisation, participation, and primary care. Hopefully.

Mr Clayton Hamilton @ClaytonHamilton

World Health Organization (WHO) Regional Office for Europe, Denmark

To begin, can you tell us a little bit about what first interested you in eHealth?

I gained my initial education and experience in the field of information and communications technology, which gave me a wealth of knowledge in how to approach complex, multifaceted, and mission-critical environments. When I first entered the eHealth domain, even with the rudimentary offerings of the time, I was struck by the immense potential that digital solutions and the internet could offer medicine and the opportunities to improve the quality of life for many. I saw, and still see, practical solutions enabled by digital health to a multitude of health sector challenges.

What does your role as the Technical Officer, Public Health Systems for the Europe Regional Office at the World Health Organization (WHO) entail? Has your role changed since you started in this position?

The role is certainly an exciting one that continues to evolve! Six years ago, I was lucky enough to be given the opportunity to start the unit for eHealth and Innovation in Copenhagen. This was both an interesting and demanding challenge for which there was little pre-existing knowledge to draw upon. I had to quickly create a space for the WHO in a developing landscape of public and private eHealth stakeholders and become adept at developing and explaining

a public health position in relation to eHealth. My role has since expanded to encompass a broader and more strategic mandate, which includes leading the WHO/Europe's new initiative for digitalisation of health systems under the guidance of the Director for Health Systems and Public Health, Dr Hans Kluge. The role entails a component of providing direct support to member states via ministries of health and their entities responsible for delivering national digital health programmes, compiling and developing insight into successful digital health implementation, and forging partnerships with major partners, including the European Commission.

"I saw, and still see, practical solutions enabled by digital health to a multitude of health sector challenges."

Digitalisation of health systems is well underway. How far do you think digitalisation will be adopted in the next 5 years, and what benefits will this bring with it?

I think we are likely to see significant acceleration in countries designing and implementing digital health strategies as part of programmes to reform their health system, particularly with respect to standardising, digitalising, and integrating the many silos of information that exist. There are many forces driving this transition and countries have begun to realise the strategic value of investing time and effort to meet this goal. The benefits will be the laying of the foundations for future delivery of integrated, person-centred care.

How do you think digitalisation of health systems will impact less developed countries, and how will these advances be used differently in low versus high-income countries?

Low-middle and middle-income countries in Europe (as a measure of percentage gross national income) are quickly climbing up the digital health development curve. These countries are quickly migrating towards mobile-based architectures, often due to high-latency constraints from an under-developed national broadband infrastructure and are, in a few cases, incorporating digital health under broader, government-led 'smart-nation' initiatives. Intersectoral solutions for digital health as a part of health system reform are often easier to develop and duplicate in such environments and it is quite amazing to see the rate of progress that the countries in these income groups can make. Interestingly, we are also seeing some of their innovations catching the interest of countries that are further advanced in the digitalisation of their health system.

Despite the numerous benefits of digitalisation of health systems, there are some who are sceptical about their private medical records being digitalised and the potential for system hacking to use this information maliciously. How would you reassure these people?

I receive this question regularly. In order to move forward in meaningful way, I think we need to completely turn the discussion around and ask ourselves: "What is the opportunity cost to society, and to us as individuals, of not taking action to digitalise health information?". If we look to those societies who have successfully been able to develop national eHealth records and public health information portals, they are not only setting amazing examples of how digital health can improve health system efficiency, but also of how happy their citizens are in having secure, transparent access to their own health data; how patient safety improves; how trust increases and relationships improve; how clinicians are provided with new insights and opportunities; and how new forms of access to health services, such as telehealth and integrated care, become possible. That is not to say that we should disregard privacy and security concerns, quite the opposite, we need increased focus on them. Governments are beginning to adopt 'privacy by design' as the foundation for national digital health solutions and increasing efforts are being made to ensure sustainable funding for security programmes in health. I think the macro-level solution lies in a combination of robust security architectures, well-designed governance, clear policy and regulation, systems

that allow for informed consent (including the ability for individuals to opt-out, should they wish to do so), and establishing cultures of trust.

"The effect that digital innovations are having is to catalyse a change in thinking as to how governments can enable access to healthcare for their citizens..."

In 2015, the United Nations (UN) documented 17 sustainable development goals (SDG) to end poverty, protect the planet, and ensure prosperity for all. One of these SDG is to ensure healthy lives and promote wellbeing for everyone at all ages. While there have been substantial improvements in reducing instances of malaria, tuberculosis, polio, and the spread of HIV/AIDS, there is still much more to do to achieve the 15-year goal. How do you think medical innovations will help to achieve this SDG?

Digital health, and the medical innovations that it encompasses, has a clear role in achieving the public health priorities outlined in the European Regional health policy framework, Health 2020, and the UN 2030 Agenda for Sustainable Development. Specifically, digital health has a key role in addressing and overcoming social and demographic stresses, global inequity and health security issues, and helping countries achieve their targets for Universal Health Coverage. Universal Health Coverage is recognised by all member states that people and communities should have access to the promotive, preventive, curative, rehabilitative, and palliative health services they need, of sufficient quality to be effective, while also ensuring that the use of these services does not expose individuals to financial hardship. The effect that digital innovations are having is to catalyse a change in thinking as to how governments can enable access to healthcare for their citizens, widen the population base capable of accessing the available health services (including reaching marginalised and underserved population groups), improve public health surveillance, and reform processes underpinning the functioning of health systems.

Artificial intelligence (AI) and machine learning are an exciting branch of medicine currently emerging that has an enormous potential to advance healthcare services around the globe. What do you think are the biggest advancements in AI over the last 3 years?

I think the ability for AI-based solutions to detect breast cancer more accurately than humans was a significant milestone and is just the very beginning of where AI will lead us in terms of clinical automation. I am also excited to see the development of personalised medicine begin to take shape, the advances in augmented reality for medical education, and the potential of medical robotics driven by AI.

"I feel it is always beneficial to promote and catalyse dialogue on all aspects of digital health, including AI, in order to openly address positive and negative viewpoints in the most transparent manner possible."

Looking to the future, where would you like AI development to focus over the next 10 years? Is there anything that you feel would greatly benefit from AI assistance?

I think bringing AI into the public health domain in a systematic way is going to be a major disruptor and push the boundaries of what we believe is possible. We can only begin to imagine the benefits that an increased capability to predict and counteract major public health threats and emergencies will bring to global health security. This will also become increasingly relevant considering the impact of climate change and other socioeconomic determinates on population health.

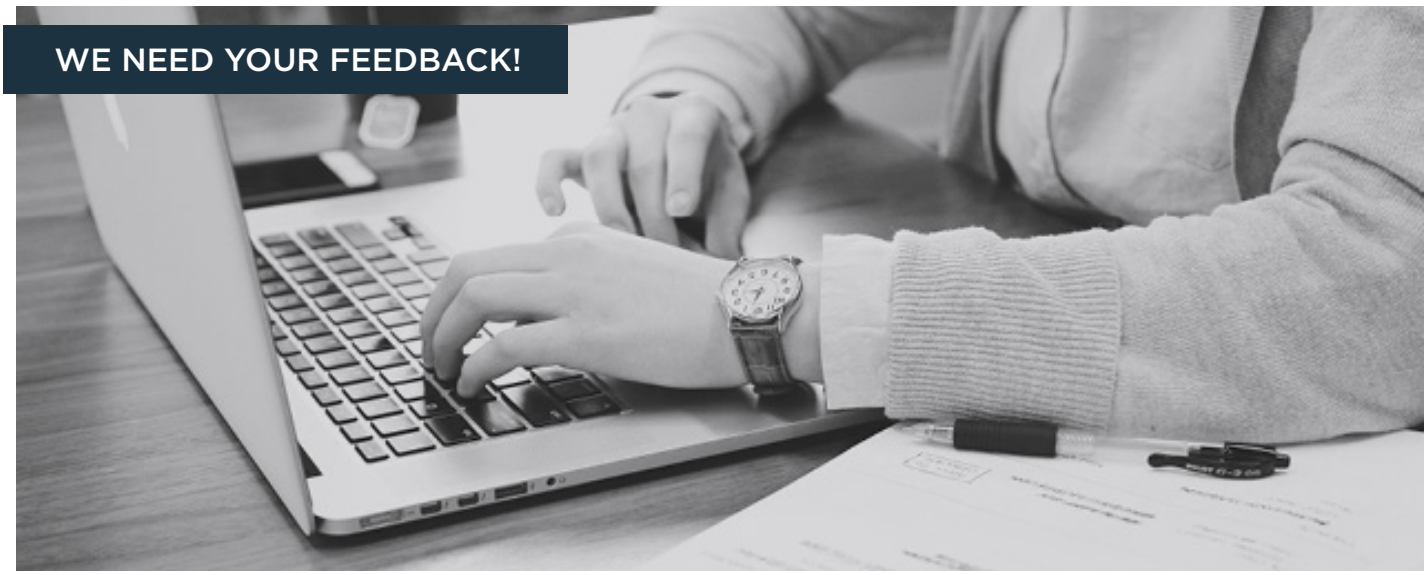
AI and machine learning are incredibly interesting, even for those not directly involved in healthcare, attracting a high level of media attention. Do you think increasing media attention is advantageous to the field or a hindrance?

It is true that despite AI having existed as a developing field of science for many decades, it has been thrust into the spotlight of public attention more-or-less overnight, with an extensive, sometimes sensationalised, debate being played out in mainstream media. I feel it is always beneficial to promote and catalyse dialogue on all aspects of digital health, including AI, in order to openly address positive and negative viewpoints in the most transparent manner possible. This will also allow the health domain to build upon the thinking that has been going on in many other areas with regard to AI adoption. Particularly with regard to developing an internationally recognised ethics framework for AI in health, I think much can be gained from work ongoing in other fields. The media attention and debate also afford us an opportunity to dispel some of the many myths of AI that frequently appear.

Finally, what would you say is the biggest achievement in your career to date?

I have always considered that success in any career is an accumulation of many significant, smaller milestones rather than singular big achievements. Some of the most satisfying points of my career have been to see where my involvement at a national level has resulted in individuals leading a better quality of life. More recently, I was also proud to have been part of the organising committee, together with the Maltese Ministry of Health and the European Commission, that delivered the eHealth week in Malta in 2017. That was a major success in getting a wide variety of partners aligned around an agenda for public health. However, I am hopeful that the most significant achievements of my career are yet to come.

"I have always considered that success in any career is an accumulation of many significant, smaller milestones rather than singular big achievements."



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Four-Dimensional Bioprinting for Regenerative Medicine: Mechanisms to Induce Shape Variation and Potential Applications

EDITOR'S PICK

We continue to see rapid developments in healthcare-based technologies, and advances in restorative and regenerative medicine offer the real possibility of not just reproducing tissues but whole organs. My Editor's Pick for this edition, by Morouço and Gil, offers an almost philosophical view of how four-dimensional bioprinting in regenerative medicine will advance, and it is hoped that with a range of innovations available to patients and their clinicians, health outcomes will be greatly improved with this technique.

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Abstract

Regenerative medicine is an exciting field of research, in which significant steps are being taken that are leading to the translation of the technique into clinical practice. In the near future, it is expected that clinicians will have the opportunity to bioprint tissues and organs that closely mimic native human tissues. To do so, imaging of patients must be translated to digital models and then fabricated in a layer-by-layer fashion. The main aim of this review is to elaborate on the possible mechanisms that support four-dimensional bioprinting, as well as provide examples of current and future applications of the technology. This technology, considering time as the fourth dimension, emerged with the aim to develop bioactive functional constructs with programmed stimuli responses. The main idea is to have three-dimensional-printed constructs that are responsive to preplanned stimuli. With this review, the authors aim to provoke creative thinking, highlighting several issues that need to be addressed when reproducing such a complex network as the human body. The authors envision that there are some key features that need to be studied in the near future: printed constructs should be able to respond to different types of stimuli in a timely manner, bioreactors must be developed combining different types of automated stimuli and aiming to replicate the *in vivo* ecology, and adequate testing procedures must be developed to obtain a

proper assessment of the constructs. The effective development of a printed construct that supports tissue maturation according to the anticipated stimuli will significantly advance this promising approach to regenerative medicine.

INTRODUCTION

It is well known that the replacement or regeneration of organs due to accidents or disease continues to be a worldwide problem. Indeed, transplantation is insufficient[1] and is associated with very high costs, while requiring a high level of specialisation from healthcare professionals. Furthermore, several limitations to transplant can arise, including the lack of compatible donors, a high incidence of transplant rejection, and morbidity implications for the living donor.[2] Regenerative engineering has come to be considered an inevitability and a promising approach for the regeneration of tissues or organs by culturing patient cells into biological substitutes (scaffolds) and subsequent implantation into the patient for the regeneration of new tissue.[3] These scaffolds can be produced by different approaches, usually referred to as conventional or nonconventional techniques. Although both of these categories have advantages and drawbacks, the nonconventional procedures, usually three-dimensional (3D) printing, may provide significant advancements for obtaining optimised, tailored constructs.[4] Using an additive manufacturing process, nonconventional procedures suitably control pore size, geometry, and spatial distribution, and guarantee pore interconnectivity, which are key features for successful tissue regeneration.[5]

Most of the original bioprinting techniques were developed to produce two-dimensional (2D) constructs; however, tissue maturation in such culture substrates can significantly differ in morphology, cell–cell interactions, and cell–matrix interactions, contrasting to 3D environments.[6] Accordingly, significant efforts have been made to translate 2D bioprinting techniques to 3D aptness. Currently, it is possible to manufacture 3D implants with customised features: biodegradable or permanent, with or without cells, and with or without surface functionalisation, among others. These advantages permit researchers to optimise the manufacturing process, aiming for full automation, while studying the most adequate approach for the intended application. Traditionally, the manufacturing process begins with a 3D digital model (using computer-aided design tools) that is sent to a 3D printer to produce the model in a layer-by-layer fashion. Different processes (e.g., jetting, fusion, sintering, and melting) and various materials (e.g., polymers, ceramics, and metal) can be used in a hybrid manner, providing noteworthy developments for obtaining enhanced tailored scaffolds.[7]

One of the most common procedures in regenerative medicine is the manufacture of 3D scaffolds, which are posteriorly seeded with cells. Ideally, when this scaffold is implanted into the body it should degrade in a timely manner and be completely compatible with the neotissue ingrowth.[8] In opposition, bioprinting refers to the processes of patterning and assembly of living and non-living materials at once.[9] Bioprinting is intended to produce scaffolds that are able to instruct or induce the cells to develop into a tissue mimetic or tissue analogue structure, for instance, by hierarchical induction of differentiation.[10] To do so, the topological and biological properties should lead to a tailored construct that permits tissue development.[5] Thus, to print adequate constructs for promoting homogenous cell proliferation and/or differentiation, a clear understanding of the advantages and drawbacks of each technique and biomaterial or bioink is critical.[3] However, 3D bioprinting has been used for the production of implants that fail to mimic native live tissues: they have no ability to acutely change according to the functional status and changes in the environment.[11] This was the main reason for the development of four-dimensional (4D) bioprinting, with the foundational works developed at the Massachusetts Institute of Technology (MIT), Cambridge, Massachusetts, USA.[12] With the fourth dimension referring to time, the aim of 4D bioprinting is to promote dynamic changes of the construct, improving its functional response. It emerged as a technology with the ability to induce planned changes of the constructs, bridging the gap between the

laboratorial constructs and the native human tissues. The procedure involves a 3D construct that can change its properties (e.g., shape) under a predesigned stimulus to develop biologically active constructs.[13] To do so, different types of stimuli can be used, making it suitable for various regenerative medicine applications. The potential of 3D printing enhanced by a fourth dimension makes it possible to contribute significantly to the bioprinting of engineered tissues, such as the liver[14] and heart,[15] which will represent a major breakthrough in the area of regenerative medicine.[16] For this review, only the shape-morphing capabilities of 4D bioprinting were considered

EXISTING MECHANISMS OF FOUR-DIMENSIONAL BIOPRINTING

In the 4D bioprinting process, different printing technologies, biomaterials and bioinks, and stimuli can be used. Each one of these elements must be specifically tuned for the type of biological construct to be produced. The most commonly used techniques for the printing process can be divided into three categories: jet-based, extrusion-based, and laser-assisted.[17] Jet-based methods produce a jet of small droplets of a liquid material, extrusion-based printing consists of a robotically controlled dispensing system to extrude a material in a continuous way, and laser-assisted methods use laser energy for material curing according to its absorbing capacity.[4,7] Both the materials to be used as well as the aimed architecture must be previously defined before choosing the printing technique(s). The materials must also be automated to respond to the desired stimuli: they should have mechanical stability closely mimicking the structure of native tissues, printability features that allow the desired resolution (size), and biocompatibility. With the currently available technologies, adjustment among these abilities must be made because no technique can fulfil all of these characteristics.[10]

Regarding the biomaterials, studies have demonstrated the potential of using synthetic and natural polymers for scaffold production.[18,19] On one hand, natural polymers can closely mimic the native environment, providing adequate signalling for cell guidance,[20] but these materials are often difficult to process. On the other hand, synthetic polymers offer a wide range of chemical compositions and processabilities.[21] However, the most limiting factor for successful 4D bioprinting is the living cells[22] since they need the material to be cell adhesive, biocompatible, non-toxic, and biodegradable (at a certain degradation rate).

Accordingly, one specific area of bioprinting that is attracting great interest is the use of hydrogels as bioinks. Due to their capability for absorbing and retaining large quantities of water, hydrogels support a wide range of viable cells, growth factors, and/or genetic material while being extruded from a syringe nozzle. They are currently the most widely used scaffold material in 3D printing due to their easily controlled functionality, without the complex synthesis steps required to replicate the native biological tissue's physiochemical properties.[23,24] Nevertheless, they must meet certain requirements, in addition to their cell culture suitability, to be considered for bioprinting. High temperatures, organic solvents, shear force-generated stress, and exposure to ultraviolet light are examples of conditions that can damage the cells during the printing process.[1] Cells should be selected according to their high viability and yield, limited harvesting-associated morbidity, robustness and mechanical resilience, limited immunogenicity, and extended trophic properties.

Planned stimuli can change the material's wettability, phase transition, swelling or shrinkage, softening, magnetic and electrical permeability, optical properties, and molecular and ionic interactions.[25] Moreover, they can also change these various properties in the same composite, making the structure suitable to change into different shapes and functions for innumerable purposes. 4D bioprinting technology brings material science, biology, and chemistry together to create new 'smart' materials that can incorporate both cells and bioactive molecules; actively modulate cellular behaviours,[26,27] including adhesion, proliferation, migration, differentiation, and maturation; and maintain cell viability and function, all while having good printability and shape fidelity. Responsive biomaterials are being developed at a fast pace. Humidity,[28,29] temperature,[30-33] electric,[26,34,35] magnetic,[36] molecular,[37,38] and light-responsive[27,39] biomaterials and bioinks are

being created with single and multishape transformation capabilities. With this ability, a rectangular construct can transform itself into a hollow tube (Figure 1) with a programmed diameter and a patterned architecture, incorporating different cell types and orientations to meet the needs of the tissue or organ being mimicked.[40,41]

After printing the construct, a critical challenge is to maintain cell viability and impose upon the cells the desired differentiation and maturation. Devising and developing tailored bioreactors capable of mimicking the physiological scenario and of replicating the nutrient transport through blood flow in the human body is the ultimate goal.[13] Additionally, the fluid-flow regime, the environmental control (oxygen levels, pH, temperature, and metabolite control), the stimulation (culture medium, growth factors, and stimulus), and their influence on cellular behaviour are the most important parameters to control for each type of tissue.[42] The development of new bioreactors with embedded sensory elements and imaging could guarantee real-time control of the process and enable automated feedback. Accordingly, the authors envision that systems able to withstand different types of stimuli (e.g., mechanic-like rotating, confined, or sliding compression/tension) to simulate native tissue loads and impacts, or to induce directional orientation (e.g., electric/magnetic), are the future of bioreactors.[43,44] Independent of the mechanism used or its exact definition, 4D bioprinting has the potential to turn organ printing into a reality in the coming years. Combining engineering with life sciences, regenerative engineering may closely replicate the path of biological development (Box 1).

CURRENT APPLICATIONS OF FOUR-DIMENSIONAL BIOPRINTING

In recent years, major progress has been made in the development of smart materials suitable to be used in regenerative medicine.[45] While smart materials have been produced by several methods, making them suitable to be bioprinted is an intricate process. In accordance, some experiments have been conducted demonstrating shape-morphing materials but not their applicability. The studies demonstrating their applicability have commonly only involved non-living materials and, thus, are not considered examples of bioprinting.[9]

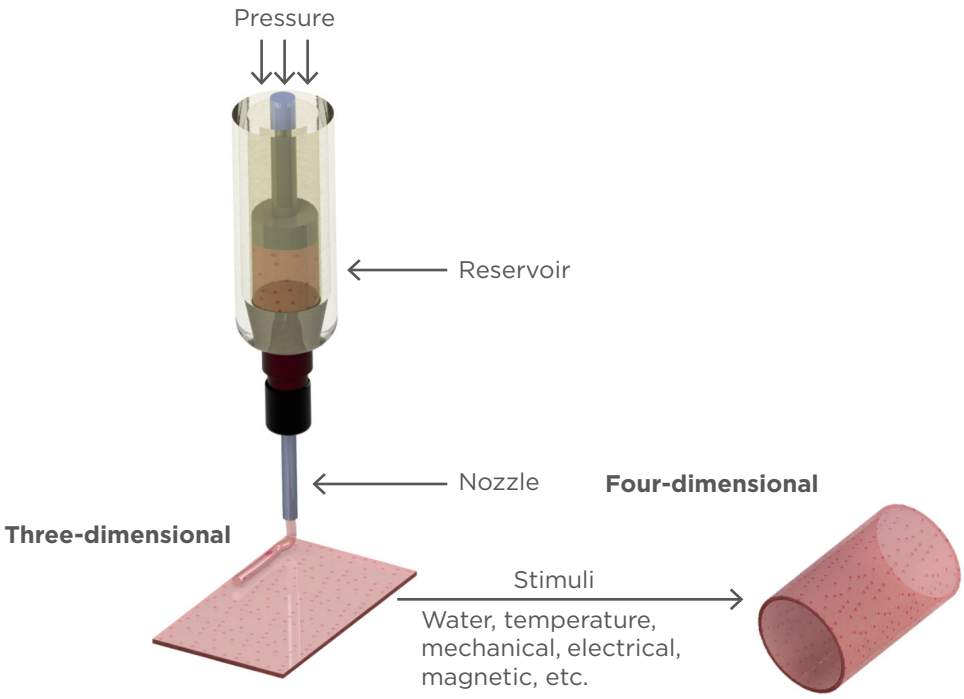

Figure 1: Illustrative representation of the transformation from three-dimensional to four-dimensional bioprinting, which can be triggered by different types of stimuli.

Box 1: Regenerative engineering may closely replicate the path of biological development.

- Biomaterials or bioinks should be altered to become responsive to multiple stimuli but without inducing toxicity.
- Architecture can be modelled to have a folding-type response, in a controlled way.
- Printing processes should be optimised to diminish stress on the cells.
- Bioreactors must be developed to study the effects of the planned stimuli (duration and frequency).
- Bioreactors should enable a non-destructive analysis.
- Testing and evaluation procedures should be adapted to examine the functionality response.

Table 1: Examples of current applications of four-dimensional bioprinting.

Target tissue	Material	Process	Stimulus	Reference
Not specified	Hydrogel composite ink	Extrusion-based	Water	Gladman et al.,[46] 2016
Blood vessels	Biopolymers (alginate and hyaluronic acid)	Extrusion followed by crosslinking	Light	Kirillova et al.,[37] 2017
Not specified	Polyurethane	Extrusion-based	Temperature	Hendrikson et al.,[48] 2017
Not specified	Methylcellulose	Extrusion-based	Temperature	Cochis et al.,[52] 2018
Not specified	Soybean oil epoxidised acrylate	Laser-assisted	Temperature	Miao et al.,[31] 2016
Cartilage	Collagen, agarose, and iron nanoparticles	Extrusion-based with a magnetic field	Magnetic	Betsch et al.,[55] 2018
Neural conduit	Graphene	Laser-assisted	Thermomechanical	Miao et al.,[56] 2018

Composites able to respond to water stimulation have been of high interest in recent years because water is a major constituent of the human body.[16] Gladman et al.[46] developed a biomimetic 4D printing method inspired by botanical systems. Through the control of printing parameters, such as filament size, orientation, and interfilament spacing, the researchers created mesoscale bilayer architectures. These had programmable anisotropy that morphed into given target shapes on water immersion. Although an interesting approach, further developments on its usefulness for tissue engineering are lacking.

One of the most interesting approaches is the use of 4D bioprinting to obtain prevascularised structures, since vascularisation is a key issue to be addressed when engineering various types of functional tissues.[16] 4D-printed constructs can be manufactured as layer-by-layer solids, mixing the cells and hydrogels to obtain cylindrical structures like the blood vessels.[47] These hydrogels laden with cells can be activated by maturation factors, leading to rapid vascular cell maturation; however, available bioprinters have a characteristic ability to produce tubes that are tens to hundreds of micrometres in diameter, a resolution far from the native size of human blood vessels. Recently, 4D bioprinting was used to produce vessels with an average internal diameter of 20 µm.[37] The investigators printed a flat surface, which, when stimulated, folded to a well-defined tube. As the materials used (alginate and hyaluronic acid) did not pose any negative effect on the viability of the printed cells, this may be a promising approach to reduce the internal diameter of the constructs.

One condition that remains fairly stable in the human body is a physiological temperature of around 37°C. Hence, thermoresponsive materials created and stored at different temperatures may change properties upon implantation.[33,48] The sensitivity to temperature relies on the balance between the hydrophobic and hydrophilic segments of the material.[49] Upper or lower critical solution temperatures will interrupt the electrostatic interactions, leading

to a collapse or expansion of the material.[50] Among the developed thermoresponsive materials, poly (N-isopropylacrylamide) is the most studied for regenerative medicine purposes. The low critical solution temperature (˜32°C) and the good biocompatibility were useful for tailoring suspension rheology.[51] Promising results were also obtained for the use of shape-memory polyurethane to print 4D scaffolds.[48] The seeded cells were significantly more elongated after shape recovery, demonstrating high potential to be applied in diverse clinical contexts. Lastly, it is understood that some diseases induce changes in body temperature; thus, thermoresponsive polymers may be a useful tool for diagnostic purposes.[50] With regard to thermoresponsive hydrogels, Cochis et al.[52] used methylcellulose for cell-sheet engineering. After optimising the printing process parameters, methylcellulose hydrogel rings were extruded for the first time. Cell orientation was observed for the ring-shaped cell-sheet and confirmed by the more elongated cell nuclei than those in sheets detached from the bulk hydrogels.

Both bone and cartilage regeneration are specific targets attracting a lot of interest from research groups worldwide. Significant improvements to bone and cartilage regeneration have been achieved by developing 3D-printed implants,[3,53,54] and incorporating the fourth dimension may control the properties of surfaces, enabling the adsorption or desorption of molecules and cells. Regarding the materials, a novel, renewable soybean oil epoxidised acrylate has demonstrated the ability to fix a temporary shape. Accordingly, by 3D laser printing, researchers produced smart and highly biocompatible scaffolds capable of supporting the growth of multipotent human bone marrow mesenchymal stem cells.[31] Regarding the process, by applying a straightforward magnetic–based mechanism in hydrogels during bioprinting, it was possible to align collagen fibres in less concentrated hydrogel blends.[55] After 21 days of culture, the controlled constructs expressed more collagen II than the randomised constructs. These two examples highlight that both the material and the process should be further developed to enable their use for tailored implants.

Although some applications have been demonstrated (Table 1), research efforts have not extended beyond the initial proof-of-principle phase.[57] Without reports illustrating the performance of a 4D-printed implant, there is a long way to go to get closer to translational medicine in regenerative engineering. Most of the available studies in the literature do not focus on a specific type of tissue regeneration; however, the medical community is at the point of developing bioinks that have the ability to respond to stimuli, with their usefulness still to be investigated.

CONCLUSION

Despite the current advances, there is still a long way to go to achieve bioactive 4D structures that are able to mimic human tissues, in part because most developed materials are responsive to only one type of stimulus, whereas the human body relies on complex physiological networks. Further understanding of how the current constraints limit the desired translation will promote investigation of future 4D bioprinting applications. The interdisciplinary combination of life sciences with engineering is demonstrating noteworthy advances for healthcare. Although 3D bioprinting has opened minds to biofabrication, the absence of response to planned stimuli should be considered. However, it does provide an appropriate tool to create hybrid, versatile, and functional tissue constructs; thus, coupling biofabrication with stimuli-responsive materials, novel maturation processes, and validation procedures will bring us one step closer to successful regenerative medicine. The authors envision that new stimuli-responsive biomaterials that can adapt in a controlled manner to a desired stimulus will be a promising development in the near future.

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An Overview of Atopic Dermatitis with a Focus on Nano-Interventions

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Abstract

With nano-based products becoming ubiquitous across all therapeutic areas, especially the area of skin care, it has become imperative to review the correlation between the unmet needs and the pipelines of available products. Atopic dermatitis (AD) is prevalent across different regions of the world with an incidence rate varying from 15–30% in children and adults. The pathogenesis of AD is a complex interplay between defects in skin barrier function, environmental and infectious agents, and immune abnormalities. Furthermore, although the role of reactive oxygen species has been studied in AD and other skin diseases to some extent, its importance in AD has rarely been investigated. The limitations associated with the use of currently available therapies like topical corticosteroids (first-line) and/or topical calcineurin inhibitors, and the use of other over-the-counter products to manage the sleep disturbances and skin infections, create a need for other innovative solutions. Nano-intervention forms a large panel of delivery aids, including lipidic and polymeric nanoparticles, liposomes, silica nanoparticles, hydrogels, and several other delivery systems. These interventions are mainly designed to achieve higher drug encapsulation, greater stability, and higher skin permeation. This review aims to give an overview of the epidemiology of AD, the pathogenic events, and the challenges present with currently available therapies. There is a special focus on the recent developments in various nanocarrier technologies for treating AD.

INTRODUCTION

Atopic dermatitis (AD), a multifaceted, chronic relapsing inflammatory skin disease, is commonly associated with other atopic manifestations, such as food allergy, allergic rhinitis, and asthma, and affects both children and adults with prevalence rates varying from 15–30%.[1] The phrase AD is a portmanteau of atopy, or atopic syndrome, and dermatitis. The term 'atopy', which was coined by Coca and Cooke in 1923, is used for any IgE-mediated reaction (even those that are appropriate and proportional to the antigen); however, it may involve a genetic component, though contact with the allergen must occur before the development of hypersensitivity reactions.[2,3] Atopy can be present in the form of asymptomatic sensitisation of one or more of the atopic diseases, such as AD, fever, and asthma. Dermatitis, on the other hand, is a medical condition associated with reddening, swelling, and soreness of the skin, with small blisters resulting from direct irritation of the skin by an external agent or an allergic reaction.[4]

Over the years, other names have been proposed for the disease, for instance, Prurigo Besnier (Besnier's itch), named after the French dermatologist Ernest Besnier (1831–1909).

The term 'allergic march' (also called 'atopic march') refers to the natural history of atopic manifestations, characterised by a typical sequence of events that include IgE antibody responses and then the appearance of clinical symptoms early in life that persist over years or decades and often remit spontaneously with age.[5]

The underlying cause of AD is a defective skin barrier that results in dry, itchy skin, which is aggravated by mechanical injury inflicted by scratching. The interplay of the innate and adaptive immune systems in the pathogenesis of AD has been evidenced.[6]

In recent years, there has been increasing evidence regarding the role of oxidative stress (OS) in AD. It is also well known that OS promotes tissue inflammation through upregulation of genes that code for proinflammatory cytokines. Inflammatory cells in turn release free radicals when activated. Given its prominent inflammatory component, it is conceivable that OS may play a role in the pathogenesis of AD.[7] The current review attempts to detail the epidemiology, the pathogenic events related to AD, the challenges in the present drug therapy, and the scope of nano-based drug delivery systems for AD.

EPIDEMIOLOGY

The prevalence of AD is estimated to be 15–30% in children and adults, and the incidence has increased 2–3-fold during the past decades in industrialised countries.[1] The World Health Organization's (WHO) 2010 Global Burden of Disease survey ranked AD first among common skin diseases with respect to disability-adjusted life-years and years lived with a disease.[8] An international study of 1 million subjects was carried out to assess the epidemiology and geographic variability in the prevalence of AD, which was conducted in three phases.[8] Both the prevalence and the region of greatest AD prevalence continues to vary around of the world. Nigeria, the UK, and New Zealand were previously the areas with the highest prevalence; however, now Latin America has emerged as a region of relatively high prevalence in follow-up data.[9] Many developing countries have also seen a marked increase in atopic disease occurrence.

The incidence of AD has been increasing in India over the last four decades. AD was the most common dermatosis in children registered to a paediatric dermatology clinic, where it constituted 28.46% of all registered patients. A study report from the Postgraduate Institute of Medical Education and Research, Chandigarh, India, revealed the prevalence of AD in 210 infants (up to 1 year) and children (n=462) in different seasons.[10]

PATHOGENESIS

The pathogenesis of AD has puzzled researchers for decades. Although important milestones have been achieved in explaining the mechanisms of precipitation of AD in genetically predisposed individuals, there are still many omitted points that need to be discovered in order to put forth a unifying concept.[11] The occurrence of recurrent itch and dermo-epidermal inflammation is manifested histologically as hypertrophy of the dermis and epidermis with the presence of eosinophils, macrophages, and T cells.[12] Furthermore, the inflammatory response in AD begins when an IgE-associated Langerhans cell in the skin binds an antigen and presents the antigen to T cells, which leads to the release of numerous cytokines, including various IL. These mediators lead to the recruitment of more inflammatory cells, resulting in eczema.[13] Overall, the development of AD is considered to be multifactorial, with complex interactions between susceptibility genes, immaturity and/or abnormalities in barrier function, and environmental factors (Figure 1).[14]

There is a complex interplay between defects in skin barrier function, inflammation, immunity, and OS. As previously mentioned, the role of reactive oxygen species remains an unexplored area by researchers, although they are believed to play a role in AD.[15] OS refers to an imbalance that occurs between the generation of free radicals and the available antioxidant defence system in the body. Its implication in AD has been reported in the literature for the last 15 years.[16]

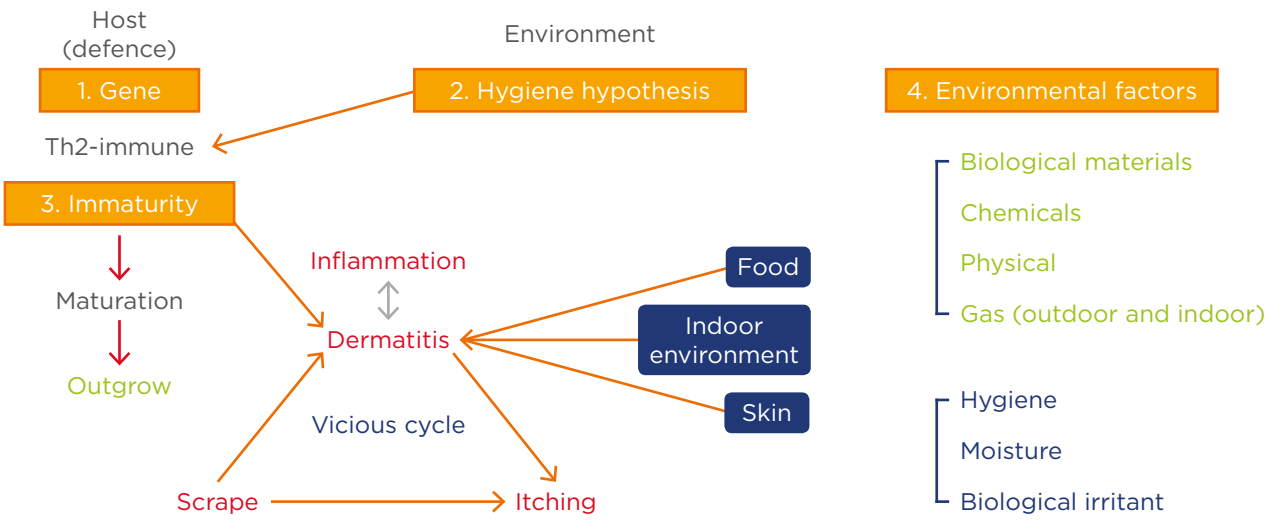

Figure 1: Multifactorial pathogenesis of atopic dermatitis.

Dermal inflammation, which is the characteristic feature of AD, is aggravated by OS. The role of OS in the activation of NFκB pathways, which in turn activates the gene expression and finally the synthesis of antioxidant enzymes, has been reported.[16] However, NFκB pathway activation also induces expression of proinflammatory cytokines (IL-6, IL-8, IL-9, and IL-33), which, in turn, enhances dermal inflammatory infiltrate and causes the release of histamines in the skin to further worsen the symptoms.[17]

Several animal studies have reported the involvement of OS in causing itching and scratching, even in nonatopic animals. Repeated application of chemicals, such as formaldehyde, or the use of intradermal hydrogen peroxide may provoke itching through increased expression of IL-4 or by the histamine-independent pathway, respectively.[18]

OS damages the epidermal keratinocytes by disrupting the DNA, the cellular enzymes, and/or the cell membrane structures through lipid oxidation. These intracellular changes are manifested histomorphologically in the form of epidermal oedema or spongiosis and a disrupted stratum corneum. Ceramides are one of the most important lipids involved in maintaining an intact skin barrier. They are composed of sphingosine and fatty acids, which are produced during the process of keratinisation in the stratum corneum. The presence of an intact epidermal barrier helps limit the entry of allergens and other infectious agents and, thus, prevents the loss of transdermal water. Numerous studies have reported that the skin barrier is directly damaged by OS initiated by external pollutants.[19]

Environmental pollutants, such as cigarette smoke, bind to aryl hydrocarbon receptors and induce reactive oxygen species production, DNA damage, and inflammatory cytokine production to cause skin inflammation. In contrast, certain flavonoids bind to aryl hydrocarbon receptors, resulting in the activation of nuclear factor-erythroid 2-related factor-2 (Nrf2) to produce key molecules that protect cells from oxidative damage.[20] Another source of OS might be skin microbes. A close association of four main factors in the aetiology and pathogenesis of AD has been suggested; these are genetic predisposition, impaired immunity, epidermal barrier dysfunction, and environmental factors.[21]

It was demonstrated that urine markers of OS are altered in children with AD, including 8-hydroxydeoxyguanosine (8-OHdG), nitrite or nitrate, and selenium.[22] Those marker levels are higher in children with AD than in non-AD children. It was suggested that impaired homeostasis of oxygen/nitrogen radicals and increased OS are involved in the pathophysiology of childhood AD. Chung et al.[23] also found that blood antioxidant capacity was significantly lower and serum malondialdehyde was higher

in preschool children with AD compared to controls. More recently, Amin et al.[24] conducted a case-control study on eczema patients with healthy individuals as controls. They found that, compared to the control group, patients with eczema had a significantly higher level of lipid peroxidation, which was determined by measuring serum malondialdehyde, and lower levels of antioxidants, including vitamins A, C, and E. Similar findings of the presence of OS and increased lipid peroxidation were reported in patients with alopecia areata, an inflammatory skin condition closely related to AD.[25] Subsequently, Tsukahara et al.[26] and Naziroglu et al.[27] observed OS and altered antioxidant defences in children with acute onset of AD. They found that urinary glycosylation end products and bilirubin oxidative metabolites were significantly higher in AD children during hospitalisation.

Genetic Factors

Food allergens may be the major trigger of AD in early life, after which the role of environmental aeroallergens becomes more important and may be associated with respiratory sensitisation. The mode of inheritance and genes involved are not clear.[28]

Filaggrin, an important protein that binds to keratins associated with keratinocyte differentiation, is important in maintaining the integrity of the skin barrier. There is decreased production of filaggrin due to genetic defects leading to skin barrier dysfunction and transepidermal water loss, which causes eczema. This leads to increased penetration of allergens into the skin, resulting in allergic sensitisation, asthma, and hayfever.[29]

Skin Barrier Dysfunction

The epidermis functions as a primary defence and acts as a biosensor to the external environment. Skin barrier defects promote easy entry for pathogens, allergens, and other environmental insults (toxins, irritants, and pollutants) and are now considered a primary mechanism for the development of AD.[30] The skin barrier function is impaired in AD as a result of multiple abnormalities that are responsible for the barrier defect, including reduced lipids (i.e., ceramide and sphingosine). Clinically, the disrupted skin barrier function of atopic skin leads to increased transepidermal water loss and increased penetration of irritants, allergens, and microbes.[31]

Immunological Responses

The immune response observed with AD is characterised by biphasic inflammation. A Th2-based immune response (IL-4, IL-13, thymic stromal lymphopoietin, and eosinophils) is predominant in the initial and acute phase of AD, while in chronic AD skin lesions, a Th1/Th0 dominance has been described (IFN-γ, IL-12, IL-5, and granulocyte-macrophage colony-stimulating factor).[32]

Cytokines and chemokines are key factors in the progression of AD. Leukocytes, and especially monocytes, from atopic patients demonstrate elevated phosphodiesterase activity, leading to decreased levels of cAMP and increased production of prostaglandin and IL-10, which inhibit Th1 function and enhance IgE production.[33]

Host and Environmental Factors

The presence of food sensitisation and allergy early in life has been reported in cases of severe AD. Around 50–70% of children with an early onset of AD are sensitised to one or more allergens, with cow's milk, hen's eggs, and peanuts the foods most frequently involved, but also house dust mite, pollen, and pets. Food allergy is common in children with AD, with an association that has been proposed to range from 20–80%, although the more commonly accepted figure is 30%.[34]

THERAPEUTIC APPROACHES AND MANAGEMENT OF ATOPIC DERMATITIS

AD is still not curable, with many patients experiencing a chronic phase of the disease. Accordingly, the treatment of AD aims to:

- Minimise the number of exacerbations of the disease, so-called 'flares'.
- Reduce the duration and degree of the flare, if flare occurs.

The first aim relates to prevention while the second relates to treatment. Prevention can be attained at three stages, which include primary, secondary, and tertiary care programmes.

Primary and Secondary Prevention

The proposal of food evasion in the prevention of AD is based on the perception that delayed exposure to antigens is a modifiable factor in AD. A direct causal relationship between food avoidance and prevention of AD is still unclear,[35] but sensitisation to food allergens, such as cow's milk and hen's eggs, is associated with infantile AD.[36] In established AD, the role of food is still contentious. Intervention involving the use of hydrolysed or amino acid-based formulas in children with significant disease has been reported.[37]

Tertiary Prevention

Prevention is best attained by trying to reduce the dryness of the skin, primarily via daily use of skin moisturising creams or emollients along with avoidance of specific and unspecific irritants, such as allergens and non-cotton clothing. As such, emollients have no direct effect on the course of the eczema. Furthermore, avoiding long, hot baths prevents skin dryness and application of an emollient is recommended to maintain a moist epidermis and augment the skin barrier function.

Currently Available Treatment Options

Topical Corticosteroids

Topical corticosteroids are the first-line anti-inflammatory treatment to control moderate-to-severe AD in both children and adults. Corticosteroids are hierarchically grouped into four different classes based on their vasoconstrictory abilities: mild, moderate, strong, and very strong preparations. Treatment with topical corticosteroids to reduce skin inflammation can also contribute to a reduction of skin colonisation with *Staphylococcus aureus* and may minimise a further trigger factor of AD.[38]

Topical Calcineurin Inhibitors

Topical calcineurin inhibitors (TCI) are compounds that represent a relatively safe and second-line class of topical anti-inflammatory, nonsteroidal therapy that work by inhibiting calcineurin, thereby preventing the dephosphorylation activity of phosphatase and the production and release of inflammatory cytokines and T cell proliferation. TCI (e.g., pimecrolimus cream and tacrolimus [TAC] ointments) are not yet approved by the U.S. Food and Drug Administration (FDA) for children <2 years of age. In January 2006, the FDA issued a black box warning on these compounds regarding possible concerns about the potential of increased long-term malignancy risk owing to systemic immunosuppression and recommended that TCI not be used as first-line therapy.[39]

Phototherapy

Ultraviolet (UV) light, especially narrow-band UVB, is particularly suitable for treating adults with recalcitrant eczema. Narrowband therapy for the treatment of AD is believed to possess an equal or superior safety and efficacy compared to natural sunlight or UVB exposure. The use of a combination of broad-band UVA light and the photosensitising drug, psoralene, to treat severe recalcitrant eczema has also been reported.[40]

Antibiotics

S. aureus colonisation is a well-recognised complication in AD and a high rate of colonisation is directly correlated to its severity. As treatment with topical steroids alone can decrease the *S. aureus* colonisation,[41] the use of systemic antibiotics is indicated for secondary bacterial infection only (primarily *S. aureus*). Community-acquired methicillin-resistant *S. aureus* (MRSA) has become an increasingly important therapeutic issue when treating abscesses but does not appear to be as prevalent in patients with AD who have secondary infections. However, this possibility is generally considered for unresponsive patients.[41]

Use of Anti-Allergics (Antihistamines and Leukotriene Antagonists)

First-generation antihistamines with sedative properties are useful as short-term adjuvants to topical treatment in cases of severe pruritus, while non-sedating antihistamines appear to have only a very modest influence on atopic eczema. The usefulness of leukotriene antagonists (montelukast and zafirlukast) for the treatment of asthma and allergic rhinitis has been reported, but they have shown limited success in severe AD.[42]

Systemic Immunosuppressant Treatment

Since oral corticosteroids are associated with serious side effects, a combination with a secondary immunosuppressant is generally a preferred mode of treatment. The latter include drugs (e.g., cyclosporine A, azathioprine, mycophenolate mofetil) and bioengineered immunomodulators (omalizumab, rituximab).[43]

Other Treatment Options

Complementary and alternative medicines have been used by 35-69% of patients with a dermatological disease. The treatments include natural health products, nutritional supplements, biomechanical therapies (e.g., massage therapies and mind–body therapies), and probiotics (non-pathogenic microbes).

INTERVENTION OF NANOTECHNOLOGY-BASED DRUG DELIVERY

Nano-intervention-based drug delivery is a rapidly growing field with potential applications in health and drug therapy. The efficacy of topically applied drugs in clinical dermatology is generally observed by their mechanism of action and their ability to pass through the protective skin barrier. Topical delivery of nanoparticles (NP) has been explored for attaining local and systemic therapeutic effects.

The skin provides a natural physical barrier against particle penetration, but there are opportunities to deliver therapeutic NP, especially in diseased skin and across hair follicle openings. While NP drug delivery has been touted as an enabling technology, its potential in treating local skin and systemic diseases has yet to be realised.

Several mechanisms elaborating the penetration and permeation of NP across the outermost rate-limiting barrier of the stratum corneum have been detailed and discussed. One hypothesis suggests the entrapment of the NP into the lipid matrix of the skin such that the drug can be slowly released into the dermal layers to achieve therapeutic efficacy.[45] The release is affected by parametric evaluation of NP in terms of size, shape, charge, and surface properties, which eventually decide the degree of skin penetration. Furthermore, apart from assigning the role of the intrinsic parameters to affect the rate and extent of skin penetration, NP interaction with the physiological media also plays a significant role. Figure 2 discusses the absorption pathways to be considered for the evaluation of NP skin permeation.[46]

Nanotechnology can be used to modify drug permeation and penetration by controlling the release of active substances and increasing the period of permanence on the skin, besides ensuring a direct contact with the stratum corneum and skin appendages and protecting the drug against chemical or physical instability. Furthermore, the delivery of therapeutic agents without the need for chemical enhancers is desirable to maintain the normal skin barrier function. Treatment with chemical enhancers, such as surfactants and organic solvents, can cause not only a reduction in the barrier function of the skin but also irritation and damage to the skin.[47]

Generally, NP act as alleviating agents against hypersensitivity reactions and mechanisms. Most of the drug delivery particle technologies are based on lipid carriers; e.g., solid lipid NP and nanoemulsions (roughly 300 nm in diameter, which is now considered to be a microparticle), polymeric NP, liposomes, silica NP, and hydrogels that have been researched as alternative drug delivery options.[48]

Use of nanodrug delivery systems for enhancing the bioavailability of drugs and reducing the side effects of existing therapies should be explored to develop challenging products, and continued efforts to develop alternative treatments for the disease are underway. An alarming exponential rise in AD and other skin diseases is becoming a concern and has posed a challenge to researchers for identifying a suitable resolution. The literature has revealed vigorous efforts by scientists to explore the potential of antibiotics, corticosteroids, TCI, and even some natural polyphenolic compounds after suitable encapsulation into carrier systems for the treatment and resolution of AD. Various papers have been published based on nanotechnology-based topical drug delivery in recent decades; nonetheless, very little commercialisation is in the pipeline.

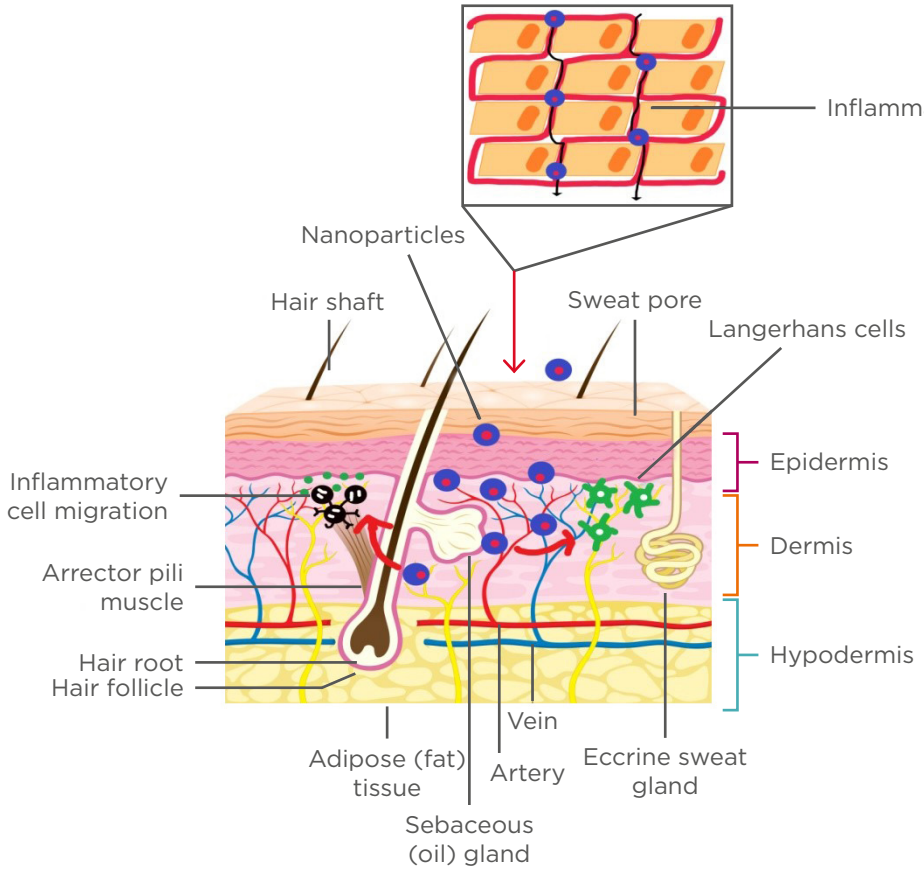

Figure 2: Nanoparticles permeation into the skin.

Table 1: List of nanocoutured drugs and their delivery system for atopic dermatitis.

Technology	Molecule or drug	Author
Polymeric nanoparticles	Tacrolimus Guar gum Hydrocortisone	Yu et al.,[49] 2018 Ghosh et al.,[50] 2018 Siddique et al.,[51] 2017
Nanoemulsions	Triptolide	Yang et al.,[52] 2017
Dendrimers	hPG-amid-C18-mPEG	Radbruch et al.,[53] 2017
Nanocrystals	Dexamethasone	Doge et al.,[54] 2016
Hydrogel	Ketoconazole Tacrolimus Polyvinylpyrrolidone (PVP)-iodine	Dave et al.,[55] 2017 Lee et al.,[56] 2016 Augustin et al.,[57] 2017

Recently, a few studies based on the usefulness of nanosisation have been carried out and are discussed in detail below (Table 1).[49-57]

Yu et al.[49] developed a hybrid skin-targeting system encapsulating TAC (FK506) based on nicotinamide (NIC) and chitosan NP (CS-NP), i.e., FK506–NIC–CS–NP, to obtain the synergetic effects of percutaneous delivery in dermatitis. NIC was found to significantly increase the FK506 entrapment efficiency to 92.2% by preparation of CS–NP. It was found that the NIC–CS–NP system significantly enhanced FK506 permeation through and into the skin and deposited more FK506 into the skin in comparison with Protopic® (Leo Pharma,

Ballerup, Denmark). The treatment efficacy on clinical symptoms, histological analysis, and molecular biology of the AD mice demonstrated that NIC–CS–NP with an approximately one-third dose of FK506 or Protopic was superior to that of Protopic alone, and the NIC–CS–NP vehicle exhibited the adjuvant therapeutic response and moderate anti-AD effects.[49]

Ghosh et al.[50] studied the *in vitro* and *in vivo* efficacy of guar gum NP (GN) in AD. Balb/c mice ears were topically exposed to oxazolone (Oxa) to induce AD, and topically treated with GN. Application of GN showed a significant decrease in ear thickness on Day 28. The total cell count of skin cells decreased post topical application of GN on the affected skin. Further to a decreased eosinophil count, Th cell, and macrophage populations after application of GN were observed in histological studies. Moreover, the ear tissue showed a reduced cellular infiltration and epidermal thickness.[50]

Siddique et al.[51] prepared the hydrocortisone (HC), topical glucocorticoid along with hydroxytyrosol (HT), and anti-microbial and antioxidant-loaded CSNP. Ten subjects were randomised to receive test (HC-HT CSNP) and vehicle samples (aqueous cream) and blood samples were analysed for blood haematology, blood biochemistry, and adrenal cortico-thyroid hormone levels. Skin biopsies were obtained to assess histopathological changes in the skin and were found to be stable. It was concluded that HC-HT CSNP (aqueous) cream is safe, well-tolerated, and non-toxic, which may be useful in treating AD.[51]

Yang et al.[52] compared triptolide (TPL)-nanoemulsions and TPL-nanoemulsion gels and their effect on enhancing percutaneous permeation. Compared to TPL gels, significantly greater cumulative amounts of TPL-nanoemulsion gels and TPL nanoemulsions penetrated rat skin *in vitro*. *In vivo* microdialysis showed the concentration–time area under the curve for TPL-NP to be larger than the TPL-gels. The TPL-nanoemulsion gels had a significant treatment effect on dermatitis and eczema in the mice model and can reduce the expression of IFN-γ and IL-4. It was found that nanoemulsion gels could be promising percutaneous carriers for TPL and are expected to provide a new, low-toxicity, and are long-term preparation for the clinical treatment of dermatitis and eczema in transdermal drug delivery systems.[52]

Radbruch et al.[53] reported on dendritic hPG-amid-C18-mPEG core-multishell nanocarriers (CMS) that represent a novel class of unimolecular micelles to facilitate topical therapy in skin diseases like AD. They tested the penetration behaviour and identified target structures of unloaded CMS after topical administration in healthy mice and in mice with Oxa-induced AD. CMS accumulated in the stratum corneum without penetration into deeper viable epidermal layers after having topical administration, indicating that barrier alterations in AD had no influence on the penetration of CMS in cases of Oxa-induced AD. Taken together, CMS accumulate in the stratum corneum in both healthy and inflammatory skin and appear to be highly biocompatible in the mouse even under conditions of AD; thus, CMS could potentially serve to create a depot for anti-inflammatory drugs in the skin.[53]

Doge et al.[54] prepared nanocrystals of dexamethasone (Dex) formulated in ethyl cellulose nanocarriers and evaluated the formulation by microdialysis technique. The results indicated high efficacy in terms of molecular analysis and inflammatory markers.[54]

Dave et al.[55] reported on liposomal gel containing ketoconazole and neem extract for the treatment of seborrhoeic dermatitis using the thin film hydration method. The anti-fungal activity of optimum liposomal formulation was carried out against *Aspergillus niger* and *Candida tropicalis* and inhibition zone measurements were 8.9 and 10.2 mm, respectively. The results indicated that developed liposomal gel of ketoconazole with neem extract could have great potential for seborrhoeic dermatitis and showed synergetic effect for the treatment.[55]

Lee et al.[56] prepared the TAC-loaded topical hydrogel formulations composed of carbomer, carnosine, transcutol P (diethylene glycol monoethyl ether), and humectant for the treatment of AD. An *in vitro* drug release study revealed that the total amount of TAC released from hydrogels over 24 hours was approximately 30-times greater than that for the reference formulation and showed that

there was higher skin permeation and retention of TAC ($p<0.05$), especially those with >10% of transcutol P. Furthermore, carbomer gel formulations with sufficient levels of transcutol P are good candidates for skin delivery of TAC and have potential as therapeutic agents for the treatment of AD.[56]

Augustin et al.[57] reported liposomal polyvinylpyrrolidone (PVP)-iodine hydrogel, combining the antiseptic and anti-inflammatory actions of PVP-iodine with the drug delivery and moisturising properties of liposomes to treat infective dermatoses. In this prospective, single-arm, uncontrolled, open-label Phase II pilot study, patients with acne vulgaris (n=30), AD (n=20), impetigo contagiosa (n=10), and rosacea (n=10) received PVP-iodine (3%) hydrogel for ≤4 weeks. Global Clinical Severity score improved for all dermatoses (range: 0.5 for acne vulgaris [$p<0.001$] to 1.0 for impetigo contagiosa [$p=0.011$]). Improvements in pain, quality of life (Freiburg Life Quality Assessment), and Eczema Area Severity Index scores were also reported. The authors outlined a well tolerated treatment therapy, with burning (14%) or itching (9%) sensations as the most frequent adverse events. Thus, liposomal PVP-iodine hydrogel has potential use as an effective treatment for inflammatory skin conditions associated with bacterial colonisation.[57]

In addition to these aforementioned studies, efforts to incorporate drugs into NP,[58] nanoemulsion,[59] nanosuspension,[60] nanofibrils,[61] nanospheres,[62] and liposomes[63] have been discussed earlier and a detailed discussion of these has been given in a previous review on AD.[64] Based on the previously discussed research findings, it can be affirmed that a nanotechnology-tailored product holds immense potential for the treatment and cure of AD.

CONCLUSION

Nanotechnology represents a key technology of the 21st century, offering excellent opportunities for both research and business. The therapeutic potential of nanotechnology-based products for AD is being realised at the laboratory level although many nano-cosmeceuticals have captured the market for their reflecting properties. It has provided a new avenue for the prevention and treatment of inflammation and its sequelae, with particularly promising advances for the alleviation of skin diseases.

Direct as well as indirect evidences substantiate reports on the usefulness of NP as carriers for topical administration, stimulating new and deeper investigations in the field. The success of nano-formulations relates to the drugs' ability to deliver the active substance to the target organ at therapeutically effective concentrations, with minimal discomfort and side effects, thus increasing patient compliance.

As technology develops, there will be a movement towards a wider association between machines and nanotechnologies, with the probability of a deeper understanding of *in vitro* and *in vivo* perspectives for the mitigation of skin disorders. However, future studies are still warranted to establish its safety and efficacy in order to ensure consumer health.

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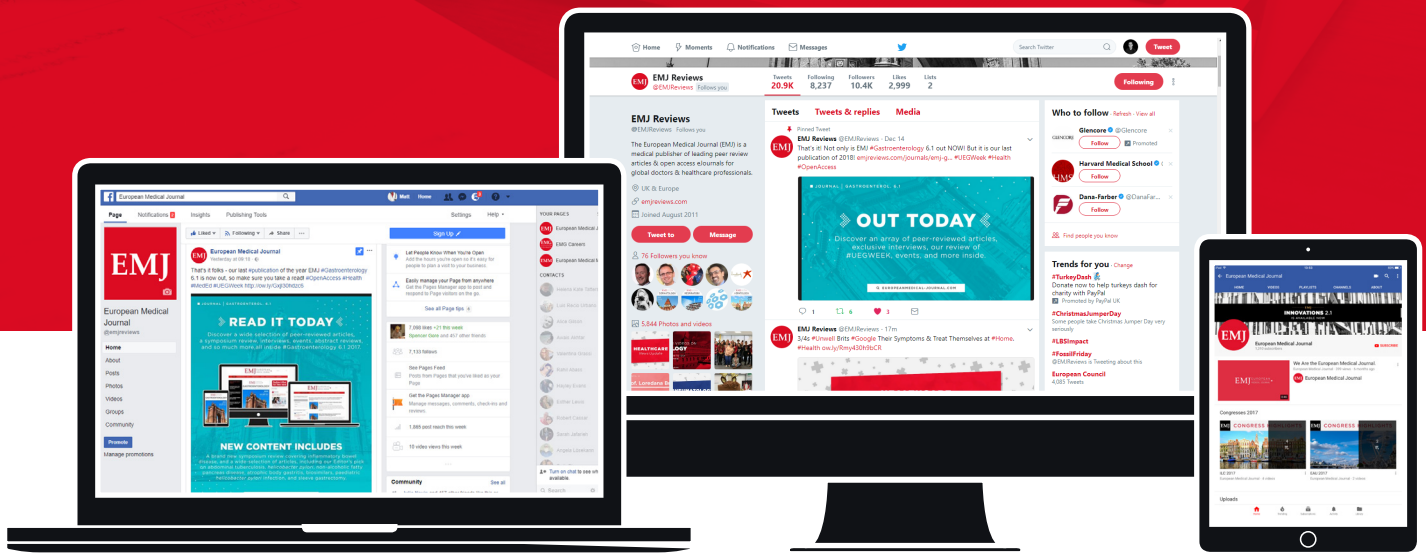

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The Need for Greater Reporting of Medical Device Incidents

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Abstract

Post-market monitoring of medical devices by manufacturers and regulatory agencies aids the identification of novel hazards or increasing trends in the risks associated with devices. This narrative review estimates the rates of under-reporting of medical device adverse events and explores the reasons and possible solutions. Incident reports may be presented to the manufacturer or the regulatory agency spontaneously by consumers, patients, clinicians, or distributors of medical devices. However, it is evident that reporting does not occur to a great extent, with the rate of reporting estimated to be as low as 0.5% of all occurrences. The programmes and processes to increase and support the reporting of adverse events need to be reviewed, with consideration given to the cost-benefit of increased reporting in relation to the regulator, regulated entities, healthcare facilities, and professionals, as well as the public.

INTRODUCTION

Historically, medical devices have not undergone pre-market clinical trials in the same way as pharmaceutical products. Moreover, medical devices undergo changes and modifications over time that are not subjected to human trials. Therefore, there is a need for strong post-market vigilance of medical devices[1] as an integral component of the manufacturer's quality management system. Vigilance aids in identifying new or escalating risks with a device, as well as possible improvements to the useability or functionality of the device.[2] The reporting of device failures to manufacturers or regulators helps identify risks at the earliest possible timepoint. The hazard may be novel or due to regional factors, such as environmental conditions or clinical practice, which were unknown or not initially considered by the manufacturer. Currently, under many jurisdictions, it is compulsory for manufacturers to report adverse events associated with the use of a medical device to the regional regulatory agency that result in, or have the potential to result in, death or serious injury; however, this is not a requirement of healthcare professionals or facilities. Globally, regulators encourage reporting of incidents relating to medical devices by consumers, patients, clinicians, and distributors of devices, but the rate of reporting remains low. For example, the U.S. Food and Drug

Administration (FDA) estimates the reporting rate as 0.5%.[3] This narrative review will estimate the rates of under-reporting of medical device adverse events and explore the reasons behind this and the possible solutions.

Published qualitative data provide insights into the reasons for the under-reporting of incidents in the healthcare setting; these include a culture of non-reporting in the profession,[4] lack of recognition that the incident was related to a medical device,[5] or, as is often noted in the spontaneous reports received by Australian regulator, the Therapeutic Goods Administration (TGA), from users of the device, the reporter contacts the TGA only after the expiration of the warranty period when the manufacturer or supplier were providing replacements for faulty items.

ESTIMATING THE RATE OF UNDER-REPORTING

In 2017, of the 5,379 medical device incident reports received by the TGA, 771 (14%) were from sources other than the manufacturer's Australian legal representative (the sponsor). Sources of spontaneous reports include those from the patient or caregiver, health professionals, and departments within healthcare facilities (Figure 1).

Case Study 1: Ventilators

To gain an insight into the prevalence of adverse event under-reporting, data relating to medical devices that are closely monitored in the healthcare setting, such as life-support devices, are optimal for investigation. The authors chose ventilators for closer analysis because they are closely monitored, easy to count, have a life-support function, and are currently the subject of a post-market review,[6] meaning additional baseline data are available to the TGA.

To complement the TGA data, additional data were derived from a large public health service,[7] chosen because it has a diverse range of services with rural and large urban centres, and also a population profile representative of the entire Australian population. The public health service data showed, on average, one device failure per year for each of the 200 ventilators in service. These failures were either repaired in-house (66%), repaired under contract service (29%), or repaired under warranty (5%), and none were reported to the TGA. This showed that medical device failures may not be reported to the regulator or the manufacturer when the device is repaired in-house. Alternatively, the manufacturer may consider device replacement as non-reportable, or consider unreturned devices with faults as 'unconfirmed'.

In Australia, there are approximately 4,170 ventilators that are currently in use in the intensive care setting. If the rate of failure of ventilators (one failure for each ventilator in service per year) is comparable across all healthcare facilities, the number of reports expected by the TGA, just for ventilator failures, would be around 4,000 per annum. However, over the past few years, the TGA has received an average of 15 reports per annum (Figure 2). This can be interpreted to mean that <0.4% of ventilator failures result in a report to the TGA. This study has not been able to determine the proportion of all failures that resulted, or may have resulted, in patient harm; however, as ventilators are considered life-support equipment, any swap-out during use or reduced service availability may have a serious impact on the patient.

When looking more broadly to extrapolate the number of patients that may have been impacted from ventilator failures, data from the Australian Institute of Health and Welfare (AIHW)[8] show, on average, a patient will be ventilated for 5.5 days. With approximately 4,170 ventilators in use, assuming these are in constant use and they are used on one patient every 5.5 days, the annual number of ventilated patients in Australia is estimated to be 276,000. This means only one report is received by the TGA for every 18,400 patients treated. Combining the two sets of data suggests the number of failures on a per-patient basis is closer to 1 in 66 patients treated; however, the true rate of under-reporting may be much higher since the rate-of-use errors and close calls may be as high as 10–15% of all ventilator user tasks performed.[9]

Case Study 2: Urogynaecological Mesh

Urogynaecological mesh can be used as another example when estimating the level of

under-reporting of adverse events. In Australia, the first adverse event relating to urogynaecological mesh was received by the TGA in 2006, despite the first device being approved for supply in 1998. Until 2012, the TGA received 63 reports of urogynaecological mesh-associated adverse events.[10] The increase in public awareness of the complications associated with this kind of device correlated with an escalation in the number of adverse event reports in the following 5 years, with the TGA receiving an additional 186 reports as of 29th May 2017;[10] 12% of reports were from healthcare professionals, 38% from the sponsor of the device, and 50% from patients. During the Australian Inquiry by the Senate titled 'Number of Australian women who have had transvaginal mesh implants and related matters',[11] the Health Issues Centre reported that, as of 3rd August 2017, 2,400 women had reported personal accounts of adverse events to their centre.[12] Although not all of these reports received by the Health Issues Centre may be unique reports or associated with devices implanted in Australia, there is a clear indication of under-reporting of adverse events with this kind of device.

The literature reports the risk of serious injury for this type of device is ~10% (ranging from no adverse events reported to 30%).[13-17] If this rate is then applied to the supply numbers of the device or patient healthcare records, the number of affected patients could be extrapolated. As of 29th May 2017, in Australia, 151,000 urogynaecological mesh devices have been supplied since 1998,[10] and the TGA has received 249 reports of serious adverse events, which equates to a reporting rate of serious adverse events of 1.5%. However, consideration does need to be given to the fact that multiple mesh devices may be implanted into a single patient and not all devices may have been used following supply. While there are multiple variables that are not able to be accurately defined with current data collection strategies, this type of analysis highlights the low incidence of adverse event reporting.

UNDER-REPORTING: REASONS, PROBLEMS, AND POSSIBLE SOLUTIONS

Non-Reporting Culture

The culture of non-reporting by health professionals is multifactorial, including reasons such as fear of blame, lack of time, perceived ineffectiveness of reporting, complexity of reporting, and lack of knowledge of the reporting system. Moreover, if the adverse event is a known complication, can be resolved clinically, or the device failure can be fixed by the practitioner or biomedical engineer, the issue may not be deemed necessary to report.[4,18,19]

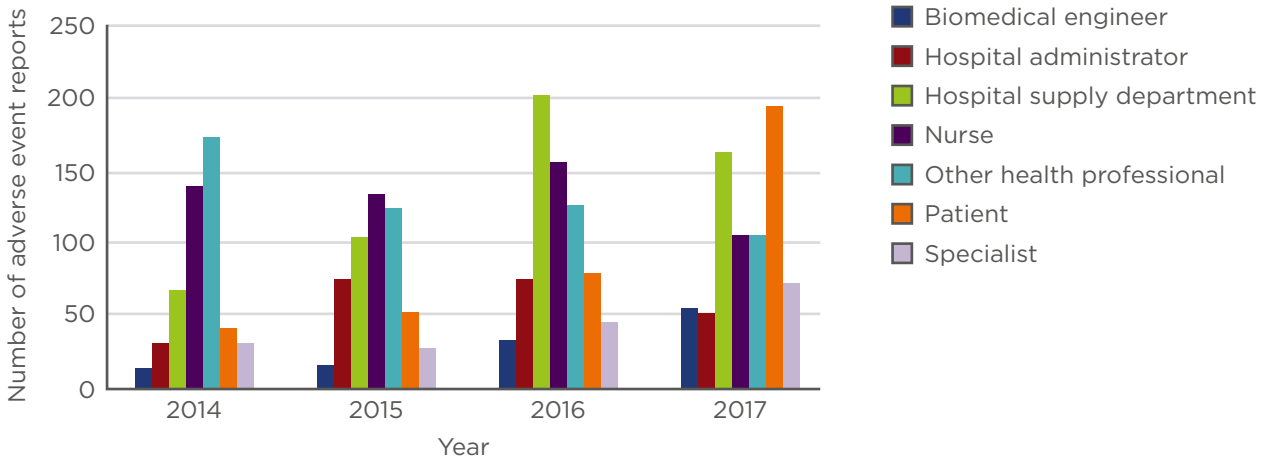

Figure 1: Adverse events spontaneously reported to the Therapeutic Goods Administration (TGA).

The number of adverse events reported to the Therapeutic Goods Administration (TGA) from sources other than the manufacturer's legal representative is low. The source of the report is shown to change over time, which may be due to education of reporting processes or workplace culture.

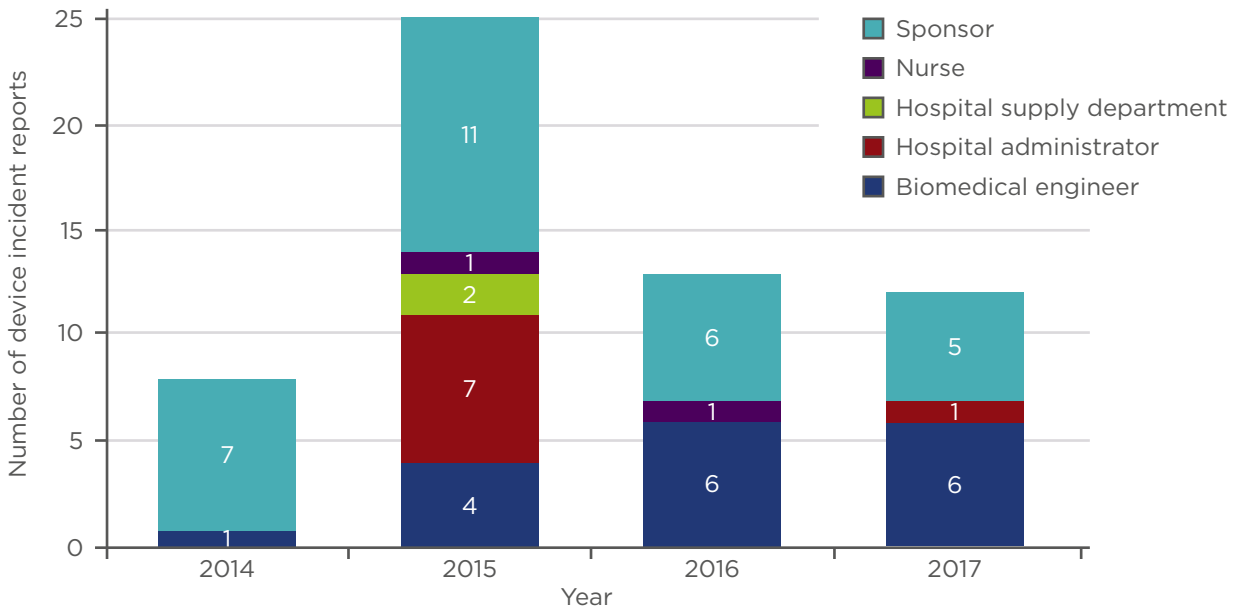

Figure 2: Reports of ventilator-related adverse events in Australia.

Adverse event reports regarding ventilators received by the Therapeutic Goods Administration (TGA), demarcated by source of report.

Regulatory agencies have recognised the importance of retrieving this missing data with a variety of initiatives introduced to overcome these issues, including data mining and education programmes. For example, the FDA introduced the Medical Device Safety Network (MedSun) and the Sentinel initiative. The latter aims to use electronic health records, primarily from insurance claims, to extract information relating to adverse events; however, this has had greater success with complications related to pharmaceuticals rather than medical devices due to the lack of data specific to medical devices.[3]

In Australia, the InSite programme[20] was piloted by the TGA in two healthcare facilities in 2014 and 2015, in which an education programme was used highlighting the benefits of adverse event reporting, how to report, and what an adverse event may look like. The participants' knowledge of reporting was assessed by a qualitative questionnaire and the number of adverse event reports before and after the training was evaluated for each of the facilities. The questionnaire revealed that staff believed the reporting of patient harm in the hospital reporting system would result in the TGA being informed of the incident, and there was a lack of knowledge that the TGA would want to be given this type of information. Regarding the number of reports received by the TGA, there was a 10-fold increase in the number of adverse event reports from one of the sites during the time period that the education programme was conducted. However, when reporting data were analysed the year after the programme was completed and training was no longer provided, the reporting of adverse events returned to the pre-education programme state, thereby confirming that continued education and close interaction and collaboration are required to maintain high levels of reporting of adverse events. In addition, it was evident that the commitment of the administrators of the healthcare facility was a key factor in the success of the programme for each site, with no increase in adverse events reported when there was little support of the programme.

Further to the lack of awareness of the role of the regulatory agency regarding medical devices by healthcare professionals and the public, the ease of reporting is also a factor for under-reporting. There is a lack of alignment of adverse event reporting programmes in healthcare facilities and sponsor's/supplier's/

manufacturer's quality management systems with the regulatory agencies' databases.[21,22] For example, in a hospital setting, an adverse event involving a medical device may be reported in the hospital system, but this system does not allow the information to be pushed directly to the regulator. Moreover, the healthcare professional may assume that the regulator has been advised through the hospital reporting system. In addition, fewer reports will be made when there is an obligation to provide detailed reports, especially when reporters have a lack of time or are already over-burdened by administrative tasks.

Non-Association of an Incident with the Medical Device

The failure to recognise the association of a medical device with poor or adverse patient outcomes can be attributed to multiple factors, including the emergence of evidence of a novel complication, extended time periods between the intervention with the medical device and the onset of symptoms, non-specific or seemingly non-related patient signs and symptoms, a lack of education or available information relating to known complications, and a lack of knowledge of the previous intervention due to a different healthcare professional undertaking the procedure.

Novel issues may emerge with the advent of new clinical tests or when a complication has a delayed onset that was beyond the timeframe of any previous clinical trials or retrospective studies. The identification of emerging or novel complications is only possible when the manufacturer or regulatory agency receives adverse event reports. Ideally, the regulatory agency would have the advantage of early identification of complications with a certain kind of device because they would receive reports of devices from multiple manufacturers, enabling an issue to be extracted from the data when it may not be evident from a single model of a medical device.

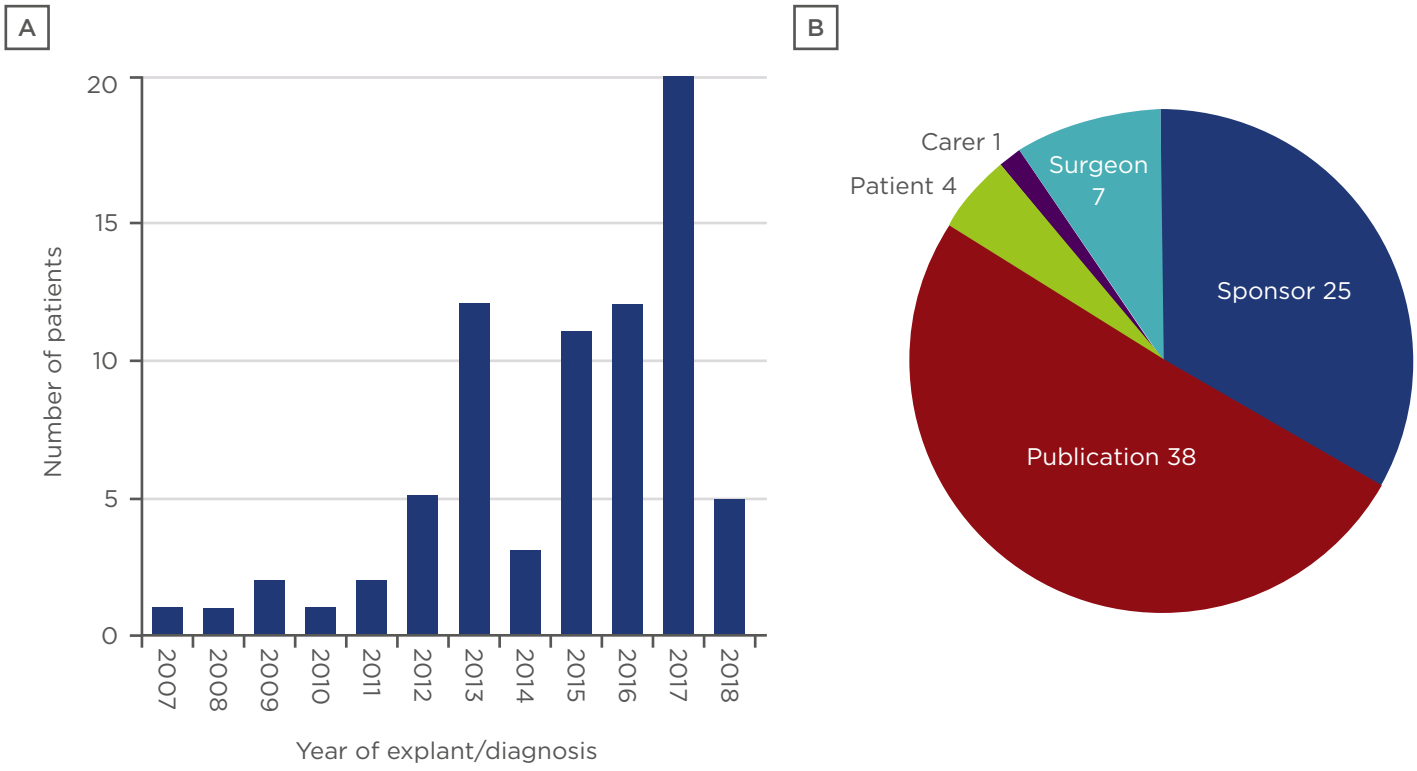

Figure 3: Number (A) and source (B) of reports of breast implant associated-anaplastic large cell lymphoma received by the Therapeutic Goods Administration (TGA).

The reports included are all confirmed as breast implant associated-anaplastic large cell lymphoma, with cytology results indicating CD30+ and ALK-. The source of the reports is predominately publications.

Case Study 3: Breast Implant-Associated Anaplastic Large Cell Lymphoma

The emergence of breast implant associated-anaplastic large cell lymphoma (BIA-ALCL) is an example of a new complication, first identified in 1997[23] and following the introduction of breast implants by the Dow Corning Corporation in 1962.[24] The awareness and research undertaken into this disease has led to increased identification and reporting of cases over the past 6 years (Figure 3). As of 19th July 2018, the TGA has received information on 75 confirmed cases of BIA-ALCL since 2007. Factors that have influenced the delayed identification of BIA-ALCL as a risk associated with the implantation of the device include the late onset of the disease, low rate of occurrence, and identification of disease markers. The average time of onset of BIA-ALCL is 8 years,[25] which exceeds the clinical trial duration for many studies of the implants. Another factor is the low rate of occurrence (1 in 1,000–10,000), which requires a greater number of patients for detection than have previously been enrolled in studies.[26] Cytological markers for this disease, namely the presence of CD30+ and the absence of anaplastic lymphoma kinase (ALK), have only recently been identified and are now recommended as clinical determinants for the presence or absence of the disease.[27] However, testing for these markers is not routine in all countries, with the cost being too great for many patients. This complication highlights the importance of post-market surveillance of devices and continual analysis of risks associated with the device.

Case Study 2: Urogynaecological Mesh

The failure to recognise or acknowledge that an adverse event has been caused by a medical device, along with the failure to report the event to the regulatory agency or the manufacturer, has been recently demonstrated with the clinical issues arising from the use of urogynaecological mesh. As stated previously, as of 29th May 2017, the TGA had received 249 adverse event reports for this kind of device, but during the Australian Senate Inquiry, the Health Issues Centre reported that, as of 3rd August 2017, 2,400 women had reported personal accounts of adverse events to their centre.[12] The large disparity between the number of reports that regulatory bodies receive and the number of patients actually affected is undoubtedly a factor in the delay of action being taken to prevent further harm to patients. In this case, the lack of reporting of adverse events to regulators and manufacturers was not only evident with the specialists who had inserted the mesh but also with the general practitioners, non-implanting specialists, and pain specialists who were treating these women several years after the device was implanted. This may be attributed to the lack of understanding of the potential complications of the device or simply the lack of knowledge of the reporting of adverse events; regulatory agencies rarely advertise their roles associated with medical device failures. A confounding factor in this case is also the number of patients who did not report their debilitating outcomes. This may have been due to this same lack of knowledge of the reporting system, or the perception that the reporting system was too complex and required information that they did not have. Moreover, the lack of reporting may have been a result of the continued dismissal of their symptoms by healthcare professionals, lack of awareness that a mesh device had been implanted, or simply not wanting to discuss such personal complications with a stranger.

There have been similar under-reporting issues highlighted by inquiries into hip and breast implants.[28,29] A study into hospitalisations for heart disease after metal-on-metal hip replacements using data from the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) and veteran medical records found that, due to the low number of cases reported, a definitive causation was not possible, potentially leading to unnecessary action.[30] Additionally, some of the issues highlighted in these inquiries related to known complications that are not generally reported by health professionals because the assumption is that the rate of these complications is identified and acceptable.

To address the lack of reporting by health professionals, many have suggested that registries for implanted devices or mandatory reporting are needed.[28,29] However, registries are expensive, take considerable resources to develop and run, and usable data are not

generated for several years. Mandatory reporting of deaths and serious injuries from USA health facilities to the FDA[31] is one method of attempting to stimulate a higher rate of reporting of the most serious events and, along with other programmes such as Medsun,[32] may in turn lead to increased reporting of all events.

ADVERSE EVENT REPORTS

When analysing adverse event reports, not only are the number of reports important but consideration also needs to be given to the type of device; different classes of device will have different levels of post-market vigilance. For example, the sponsors of active implantable medical devices are required to provide annual reports of adverse events and complaints for the first 3 years of inclusion on the Australian Register of Therapeutic Goods, but this is not required for Class I devices. Reports can also be received regarding safety, quality, and performance of a device, and the vigilance and response to each kind of event may be different. In addition, reports may also have varying degrees of information depending on the source, nature, or severity of the report. Moreover, reports might relate to the different stages of the lifecycle of the device, from design through to manufacture, shipping, storage, and use of the device, as well as reprocessing aspects or disposal. The inadequacies in current reporting frameworks may also be a hindrance to recognising the kind of issue and or assisting in appropriate responses to reports.

CONCLUSION

It is difficult to accurately determine the rate of under-reporting of medical device adverse events because the actual number of incidents is unknown. However, the case studies in this review are in agreement with the FDA estimate of a reporting rate of 0.5%. The need for reporting adverse events associated with medical devices is of importance to facilitate the prevention of further harm and to aid in continual design improvement of devices, and, therefore, regulators and manufacturers need to reconsider current methods used to encourage the reporting of events. The recognition of this need for improved vigilance and post-market surveillance has been highlighted in the recent changes to the European Union Medical Device Regulation,[33] which includes the establishment of a European database on medical devices. Conversely, consideration also needs to be given to how regulators manage the large amount of reports already being received, even with the strong evidence of significant under-reporting. Regulators are likely to need new and appropriate ways to analyse the data, both in the near and long-term future when, if current reporting trends continue, there will be ever-increasing numbers of adverse event reports.

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Anti-Calcitonin Gene-Related Peptide Monoclonal Antibodies: Adverse Effects. What Do We Really Know? A Literature Review

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Abstract

Migraine is a chronic and disabling disorder affecting >1 billion individuals worldwide. Current treatments for the prevention of migraine include antihypertensives, antiepileptics, and antidepressants, and all share limited tolerability and adherence, highlighting the need for the development of new disease-specific and mechanism-based agents. In this context, four novel anti-calcitonin gene-related peptide monoclonal antibodies have been investigated in a large Phase II–III clinical programme and showed similar efficacy to the currently used drugs for migraine prevention but with a significantly improved safety profile, as highlighted in this review. It is expected that patient compliance with treatment will increase with the use of these therapies, improving the long-term overall outcome of migraine. However, real-world evidence is needed to confirm the tolerability and safety of anti-calcitonin gene-related peptide monoclonal antibodies before the drugs can be established as first-line agents in the prophylactic treatment of migraine.

INTRODUCTION

Migraine is a pervasive brain disorder that is ranked as the second most disabling condition[1-3] and has the third highest prevalence among all medical illnesses.[4] The common understanding that has guided the management of people with migraine is pharmacological intervention to prevent disease chronification.[5] Pharmacological agents approved for the prevention of episodic migraine (EM)[6] span different drug classes (e.g., antihypertensive compounds, tricyclic antidepressants, and antiepileptic drugs).[7] Due to the prolonged administration required for migraine prevention and drug nonspecificity, these drugs can cause numerous adverse events (AE), and the agents interact with many other medications in comorbid patients.[8] Furthermore, only one medication (onabotulinumtoxinA) is approved for the prevention of chronic migraine (CM).[9-15] The suboptimal efficacy and tolerability of current treatments contribute to poor patient

treatment compliance and adherence (up to 68% of patients stopped using preventative medication within 6 months).[16-18] As patients cycle through preventative therapies, discontinuation rates increase and the augmented need for abortive medication leads to disease chronification.[19] All of the above, in addition to pharmacophobia (fear of medication) and the nocebo effect (experience of AE related to patients' negative expectations that a treatment will most likely cause harm instead of improving disease),[20] suggest the need for novel treatments that are better tolerated and have fewer contraindications, not only for patients who have failed existing preventative treatments but also for treatment naïve patients, especially those who fluctuate in the prechronic phase.[6,21,22] Among the available molecular targets, calcitonin gene-related peptide (CGRP) has the best base of evidence for controlling migraine.[23] CGRP, a 37 amino acid long neurotransmitter, is part of the calcitonin family of peptides, together with calcitonin, amylin, and adrenomedullin, and is the most potent microvascular dilator currently known.[24-26] CGRP acts on an unusual receptor family that is located at sites crucial to the triggering of migraine, including the cerebrovasculature, the trigeminocervical complex in the brainstem, and the trigeminal ganglion (Table 1).[24,27,28] Small molecule CGRP receptor antagonists, the gepants, are under development for the treatment of migraine, with three (rimegepant, ubrogepant, and atogepant) such agents currently in a Phase III clinical trial programme.[29-36]

ANTIMIGRAINE MONOCLONAL ANTIBODIES

Monoclonal antibodies (mAb) against CGRP share several pharmacokinetic advantages over small anti-CGRP molecules (e.g., greater target specificity and prolonged half-life, making them suitable for monthly administration to prevent migraine). Three of these macromolecules target the CGRP ligand (fremanezumab, galcanezumab, and eptinezumab), while a fourth (erenumab) targets the CGRP receptor.[14,37,38] All four require parenteral administration and have a preferential peripheral site of action, since only 0.1–0.5% of the mAb cross the blood–brain barrier due to their large size (molecular weight around 150 kDa).[14,39,40] These four mAb have shown particular effectiveness for the prevention of both EM and CM.[41,42]

Erenumab

Erenumab (AMG 334) is a fully human IgG2 mAb that prevents native CGRP ligand binding to the CGRP receptor.[6] At 70 mg, the estimated elimination half-life of erenumab is 21 days, supporting monthly subcutaneous dosing and, thus, bettering patient compliance.[43,44] Even in the early phases, studies showed no significant differences among healthy subjects and patients with migraine in least squares mean 24-hour or nocturnal diastolic blood pressure (BP) measurements between placebo and erenumab-treated groups.[6] Similar results were found from studying the coadministration of erenumab and sumatriptan and their effect on resting BP in healthy subjects (no additional effect on resting BP beyond the effects of sumatriptan monotherapy, without affecting the pharmacokinetic of sumatriptan).[45] The AE that were most commonly reported in the single-dose study (in ≥20% of subjects in the erenumab group) were headache in healthy subjects (erenumab: 25.0%; placebo: 25.0%) and nasopharyngitis (erenumab: 50.0%; placebo: 50.0%), arthralgia (erenumab: 33.3%; placebo: 0%), and influenza-like illness (erenumab: 33.3%; placebo: 16.7%) in patients with migraine.

Table 1: The calcitonin gene-related peptide receptor family.

Ligand/receptor	CGRP	Adrenomedullin	Adrenomedullin	Amylin	Amylin	Amylin
Receptor composition	CLR+ RAMP1	CLR+ RAMP2	CLR+ RAMP3	CT+ RAMP1	CT+ RAMP2	CT+ RAMP3
Name	CGRP	ADM1	ADM2	AMY1	AMY2	AMY3

CGRP binds to both CGRP and AMY1 receptors.[24]

No deaths or serious AE (SAE) were reported in the Phase I studies. Most AE were mild or moderate in severity and there were no clinically meaningful changes in laboratory assessments or vital signs.[6]

Again, in Phase II clinical trials for prevention of both EM and CM, the number of patients with AE was similar between the treatment groups. In EM, 95% of the patients in the erenumab treatment groups experienced AE that were mild or moderate in severity (similar in all different doses) versus 98% in the placebo group. The most common AE was nasopharyngitis, and the reported SAE were considered to be unrelated to treatment. A small percentage of participants developed binding and neutralising anti-erenumab antibodies, with no apparent association recorded among these patients in terms of AE, safety, or efficacy. The incidence of injection-site reactions was low (5%) and all reactions were mild in severity. No notable findings were recorded following the collection of clinical and laboratory results, vital signs, BP, or ECG changes. One death was noted: a 52-year-old man with a history of migraine with aura, and this was confounded by pre-existing cardiovascular risk factors (3-year history of diagnosed hypertension, obesity, a lipoprotein level of 153 mg/dL, left anterior hemiblock on baseline ECG, and a family history of myocardial infarction). The patient's autopsy showed evidence of severe coronary atherosclerosis and the presence of cardiac stimulants (phenylpropanolamine and norpseudoephedrine) in the liver. The myocardial ischaemia event was based on results of an exercise treadmill test, which showed transient exercise-induced myocardial ischaemia, confounded by sumatriptan administration 4 hours prior to the event. It was considered not related to treatment by the investigator.[17,44]

In studies of CM, the most frequent AE, reported by ≥2% of erenumab-treated patients, were injection-site pain, upper respiratory tract infection, nausea, nasopharyngitis, constipation, muscle spasms, and migraine.[46] Taking into consideration the individuality of patients and the nocebo effect, with the common denominator being the AE associated with prior medication failure, the incidence of AE was broadly comparable within each group (placebo and different doses of erenumab).[15]

Notably, a placebo-controlled study of erenumab in a high-risk population of patients with stable angina with a median age of 65 years showed that intravenous erenumab 140 mg did not lead to significant changes in exercise time compared to placebo. The change in treadmill exercise time from baseline was noninferior for erenumab compared to placebo, no difference was observed in the time to onset of ≥1 mm ST-segment depression or exercise-induced angina, and there were no significant differences between treatment groups in reported AE through the 12-week safety follow-up.[47]

The most common AE reported in Phase III clinical trials are fatigue, nasopharyngitis and upper respiratory tract infection, injection-site pain, headache, vertigo, and nausea.[14] Once more, the development of anti-erenumab binding and transient neutralising antibodies was observed, but with no clinical or other association. No clinically meaningful differences between the erenumab groups and the placebo group were observed with regard to the results of hepatic function testing, creatinine levels, total neutrophil counts, vital signs, or ECG findings.[14,42,48,49]

Fremanezumab

Fremanezumab (TEV 48125) is a fully humanised IgG2a/kappa mAb that potently and selectively binds to both α and β isoforms of CGRP.[50] The mean half-life values range from 32–36 days.[51] In early clinical studies, treatment-related AE occurred in 21.2% of subjects receiving fremanezumab (no association pattern regarding the dosage), compared with 17.7% in those receiving the placebo. The most common treatment-emerging AE reported were headache, nasopharyngitis, gastroenteritis, and back pain, while the two SAE, thoracic aortic aneurysm (patient had an unreported history of Ehlers–Danlos syndrome) and glaucoma, in individuals receiving fremanezumab, were not treatment related. Fremanezumab was also not associated with any clinically relevant patterns of change in vital signs (including systolic and diastolic BP, temperature, and heart rate), ECG parameters, or laboratory findings.[50] Similar results were reported in Phase I studies comparing the prevalence of safety issues between Caucasian and Japanese healthy subjects.[51]

In Phase II clinical trials of both CM and high frequency EM,[52,53] despite having different doses, the AE (treatment-emerging and treatment-related) reported had consistency regarding the type and frequency. In the CM Phase II study,[53] 40% of patients in the placebo group, 53% in the 675/225 mg dose group (675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles), and 47% in the 900 mg dose group had treatment emergent AE. In the Phase II trial of high frequency EM, the rates of treatment-emergent AE were 56% (placebo), 46% (225 mg fremanezumab), and 59% (675 mg fremanezumab).[52] The most common AE in both studies were mild injection-site pain and pruritus. The SAE that occurred were not treatment-related and, again, there were no relevant changes in BP or other vital signs. The prevalence of patients with detectable concentrations of fremanezumab antibodies (1% in both studies) was much lower than that detected with other monoclonal anti-CGRP antibodies (19% with galcanezumab and 14% with eptinezumab).[52,53] In a post-hoc analysis of the previous studies, it was found that fremanezumab was compatible with most of the major classes of migraine preventative therapies, which suggests that it will be a useful and safe agent as an add-on therapy for patients requiring additional preventative treatment. Also, results suggest that fremanezumab can be started immediately, without requiring other preventatives to be titrated or washed out first, giving patients the opportunity for a more rapid clinical improvement.[54]

In Phase III studies regarding CM, AE were reported in 64% of the patients receiving placebo, 70% of those receiving fremanezumab quarterly, and 71% of those receiving fremanezumab monthly; the reported AE were mild-to-moderate in severity in 95–96% of patients in all three groups. Again, the most common AE were injection-site reactions (40% placebo, 47% fremanezumab quarterly, and 47% fremanezumab monthly), the severity of which did not differ significantly among the trial groups. SAE occurred in 2% of the patients given placebo, 1% of those given fremanezumab monthly, and <1% of those given fremanezumab quarterly, and no participants had anaphylaxis or a severe hypersensitivity reaction. Abnormalities in hepatic function occurred in 1% of patients in the fremanezumab groups and <1% in the placebo group, which can be attributed to the use of nonsteroidal anti-inflammatory drugs. As in previous studies, antidrug antibodies developed in two patients who received fremanezumab quarterly. No clinically significant changes in vital signs, physical examination findings, or ECG results occurred in any of the trial groups.[55]

In a Phase III study of EM,[56] 66%, 66%, and 58% of patients who received fremanezumab monthly, fremanezumab once (higher dose), and placebo, respectively, reported at least one AE. Treatment-related AE were higher in the fremanezumab groups (48% in the monthly group and 47% in the single-higher-dose group) compared with placebo (37%), with the most common being injection-site reactions (pain, induration, and erythema). No relevant changes in vital signs (BP, pulse, temperature, and respiratory rate), physical examination measurements (including weight), or ECG findings were noted in patients in any of the treatment groups. There were no clinically significant changes in any laboratory parameters, including liver function tests. Again, a small percentage of patients in the fremanezumab monthly dosing group developed antidrug antibodies against fremanezumab, without any significant AE. It should be noted that one patient died 109 days after receiving a single higher dose of fremanezumab. The patient had withdrawn from the study 38 days earlier because of a family emergency and the cause of death noted in the autopsy report was suicide by diphenhydramine overdose; this death was considered unrelated to the treatment.[56]

Galcanezumab

Galcanezumab (LY 2951742) is a humanised mAb with a long half-life (time to maximum serum concentration ranges from 7–13 days and elimination half-life is about 28 days) that binds to both α and β CGRP isoforms with approximately equal affinity.[57] AE reported in a Phase I clinical trial were transient, with no apparent relationship with the prolonged systemic drug exposure (indicated by the long half-life of galcanezumab). In subjects receiving galcanezumab, the most common AE were headache, nasopharyngitis, haematuria, and contact dermatitis; the frequencies of these

AE were similar to placebo. Other frequently reported AE in subjects receiving galcanezumab were diarrhoea, toothache, and increased alanine aminotransferase. There were no apparent differences among galcanezumab dose groups or between galcanezumab dose groups and placebo in terms of frequency of any AE. This observation included changes from baseline in vital signs, laboratory values, and ECG parameters. It was reported that 26% of the galcanezumab-treated subjects produced antidrug antibodies, the presence of which had no obvious effect on pharmacokinetics and pharmacodynamics compared with subjects who had no detectable antidrug antibody titres.[4]

In a Phase IIa study[58] (galcanezumab 150 mg administrated subcutaneously twice a month), AE were reported by 72% of patients in the galcanezumab group and by 67% in the placebo group (no significant difference). AE that occurred more frequently in galcanezumab versus placebo included injection-site pain, erythema, or both (21 [20%] of 107 patients versus 7 [6%] of 110 patients), upper respiratory tract infections (18 [17%] versus 10 [9%]), and abdominal pain (6 [6%] versus 3 [3%]). There were two SAE reported in the treatment arm and four in the placebo arm, none of which were deemed to be related to the study drug. Once more, there were no clinically important changes in laboratory parameters, ECG results, or vital signs between the groups. Antidrug antibodies were detected in 8 patients at screening and in 20 patients at the end of the study; nevertheless, there was no association in terms of efficacy and AE with the antidrug antibodies.[58]

In a Phase IIb study (galcanezumab 120 mg once per month),[59] a similar frequency of AE was reported in both the placebo (70 [51.1%]) and galcanezumab-treated (140 [53.1%]) patients. The most common AE for galcanezumab were injection-site pain, which had a dose-dependent response, upper respiratory tract infections, nasopharyngitis, dysmenorrhoea, and nausea, without any dosage correlation; most AE were mild-to-moderate in intensity. None of the SAE were considered to be related to galcanezumab.[59] Taking into account the vital signs during treatment and post-treatment periods, mean changes in systolic BP, diastolic BP, and pulse were not clinically meaningful, and there were no trends to show that galcanezumab treatment increased BP. Also, mean baseline-to-endpoint changes in ECG intervals (PR, QRS, and QTcF) and heart rate showed no clinically meaningful differences between individual or pooled galcanezumab dose groups and placebo. In addition, changes in temperature were small and not clinically meaningful; weight changes were also similar across treatment groups.[59,60]

Larger studies (Phase III EVOLVE-1[61] and EVOLVE-2[18]) have corroborated the aforementioned findings. In EVOLVE-1,[61] 5 participants in the placebo group and 6 in the galcanezumab 120 mg group reported a total of 12 SAE, none of which were considered by the investigator to be associated with the treatment. Similarly, in EVOLVE-2,[18] the percentages of SAE, which were 1.1%, 2.2%, and 3.1% for the placebo, galcanezumab 120 mg, and galcanezumab 240 mg groups, respectively, did not differ significantly. Injection-site erythema, injection-site pruritus, and injection-site reactions were the most frequently reported AE related to the injection site for galcanezumab compared with placebo in both Phase III clinical trials, but most AE were mild-to-moderate in severity. Discontinuations owing to AE in galcanezumab-treated patients were low (2.2–4.0%). The most common post-treatment emergent AE was upper respiratory tract infection, which occurred at a similar rate across treatment groups. Other post-treatment emergent AE that occurred in ≥1% of patients in the combined galcanezumab group were viral upper respiratory tract infection, sinusitis, and influenza, and these events occurred at a rate similar to placebo. Again, there were no statistically significant differences between galcanezumab dose groups and placebo on mean change from baseline of systolic BP and pulse at any visit. For temperature, statistically significant mean increases (≤17.6°C) were observed only in EVOLVE-1, and these were transient and not sustained. Body weight was measured at Month 6 only and the mean change from baseline to last observation carried forward endpoint was small (<1 kg) and not statistically significant between treatment groups. Regarding the development of anti-galcanezumab antibodies, at baseline, in EVOLVE-1, 5.9% of patients in the placebo

group (n=25) and 8.9% (n=18; 120 mg group) and 10.8% (n=23; 240 mg group) in the galcanezumab dose groups had antidrug antibodies present. With consistency, the respective percentages in EVOLVE 2 were 8.4% (placebo), 8.1% (galcanezumab 120 mg), and 11.2% (galcanezumab 240 mg). The percentage of patients with antidrug antibodies during the double-blind treatment phase was low, and the number of patients with neutralising antibodies was even less. No antidrug antibodies were associated with changes in efficacy or safety.[18,61]

Eptinezumab

Eptinezumab (ALD403) is a humanised anti-CGRP IgG1 antibody that potently and selectively binds to both the α and β forms of human CGRP. The plasma half-life of eptinezumab after an intravenous infusion of 1,000 mg is 31 days. In a Phase II clinical trial,[62] during which patients with frequent EM were given one intravenous dose of 1,000 mg of eptinezumab, AE were experienced by 52% of patients in the placebo group and 57% in the eptinezumab group. The most frequent AE in both groups were upper respiratory tract infection, urinary tract infection, fatigue, back pain, nausea, vomiting, and arthralgia. During the study, 55% of patients experienced ≥1 AE. No infusion reactions were reported during the study and most AE were transient and mild-to-moderate in severity. Six SAE were reported by three patients; all of these events were deemed to be unrelated to the study drug (fractured fibula, pyelonephritis, non-cardiac chest pain, and transient ischaemic attack). There were no clinically significant differences in vital signs, 12-lead ECG results, or laboratory safety data between patients treated with eptinezumab or placebo at any time during the study. Furthermore, in antidrug antibody assays, 14% of patients in the eptinezumab group who were tested had positive results, suggesting the potential formation of eptinezumab antibodies during the study. However, the corresponding antidrug titres were low and no obvious effects of immunogenicity on the pharmacokinetic parameters or efficacy were noted.[62]

In all succeeding clinical trials, Phase II and III for CM and PROMISE 1 and 2, the observed safety profile of eptinezumab was similar to placebo. PROMISE 1[63] is a double-blind, randomised, placebo-controlled Phase III study evaluating the efficacy and safety of eptinezumab in patients with frequent EM. Both the safety profile and the placebo rates were consistent with previously reported eptinezumab studies.[63,64] On the other hand, the Phase III trial, PROMISE 2,[65] is a evaluating the safety and efficacy of eptinezumab for CM prevention. As previously mentioned, AE rates among eptinezumab-treated subjects were similar to placebo-treated subjects. Likewise, the most commonly reported AE for eptinezumab, occurring at an incidence of ≥2%, were nasopharyngitis (6.3%), upper respiratory infection (4.0%), nausea (3.4%) and urinary tract infection (3.1%), arthralgia (2.3%), dizziness (2.6%), anxiety (2.0%), and fatigue (2%).[65]

Table 2: The most common adverse events that have been reported more frequently in the active anti-calcitonin gene-related peptide monoclonal antibody arms versus placebo arms.[6,14,18,40,41,42,44-49,52-60]

Monoclonal antibody	Adverse events
Erenumab (AMG 334)	Injection-site pain, upper respiratory infection, nasopharyngitis, influenza, fatigue, nausea, joint pain, back pain, and headache.
Galcanezumab (LY 2951742)	Injection-site pain, erythema, respiratory infection, nasopharyngitis, abdominal pain, nausea, and dysmenorrhoea.
Eptinezumab (ALD 403)	Respiratory infection, sinusitis, urinary infection, fatigue, dizziness, nausea, vomiting, back pain, joint pain, dry mouth, and ECG changes.
Fremanezumab (TEV 48125)	Injection-site pain, erythema, pruritus, sinusitis, urinary infection, dizziness, back pain, dry mouth, ECG changes, and tooth abscess.

CONCLUSION

Monoclonal antibodies against CGRP and its receptor have passed all clinical phases and are becoming available in the USA and Europe. Unlike formerly available prophylactic treatments for migraine, anti-CGRP mAb have been developed specifically for the prophylaxis of migraine following a mechanism-based design. Their profile regarding dosage, pharmacokinetics, and distribution makes anti-CGRP mAb attractive in terms of adherence and patient compliance. Many safety questions were raised due to preclinical data that came from studying and blocking CGRP,[66] but no safety flags occurred during the large programme of their development and all four CGRP mAb have shown similar tolerability and safety in Phase II and III trials. The most common adverse events are reported in Table 2. No interactions with other preventative drugs have been reported. The major scepticism regarding their use was related to the potential cardiovascular effects and liver toxicity. While existing data do not confirm any cardiovascular effect, animal studies and long-term Phase IV trials are needed to further evaluate the safety of anti-CGRP mAb. As far as liver toxicity is concerned, mAb elimination is mainly the result of proteolysis and does not involve metabolism by liver enzymes, making drug–drug interactions and hepatotoxicity unlikely. Thus, the overall safety profile of anti-CGRP mAb for the prevention of migraine has been reported to be more than satisfactory so far.

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Association of a Biomarker-Based Frailty Index with Telomere Length in Older American Adults: Findings from the National Health and Nutrition Examination Survey 1999–2002

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Abstract

Objectives: To study the link between frailty and cellular senescence, the authors examined the association of leukocyte telomere length (LTL) with a recently introduced measure of subclinical frailty that is based entirely on laboratory test biomarkers (FI-LAB).

Methods: This study was conducted on a random sample of 1,890 Americans aged ≥60 years. Multiple linear regression was used to examine the relationship between FI-LAB and LTL. Secondary analyses were performed to identify the individual biomarkers driving the association between FI-LAB and LTL.

Results: A statistically significant association was found between FI-LAB and LTL after adjusting for multiple covariates, indicating that higher FI-LAB scores are associated with shorter telomeres. Secondary analyses revealed that this association is driven largely by a small number of FI-LAB biomarkers independently linked with telomere shortening.

Conclusion: The study results established a link between subclinical frailty (FI-LAB) and cellular ageing, which may help elucidate the pathophysiological mechanisms that give rise to frailty.

INTRODUCTION

The physiological mechanisms underlying the link between telomere shortening and ageing-related health conditions have not been completely elucidated. To this end, studies have attempted to examine the association between telomere length and ageing-related parameters. One parameter that has received considerable attention is frailty, a clinical construct characterising and quantifying the

cumulative burden of ageing-related health deficits. Frailty is a physical state that represents the constellation of health deficits that arise due to gradual loss of the body's ability to recover from exposure to biological stressors.[1] With no existing gold standard, the commonly used operational measures of frailty are the frailty phenotype (FP) and the frailty index (FI). These measures are typically constructed by tallying clinical symptoms of ageing (e.g., disease, disabilities, and functional impairments), with higher scores indicating a higher frequency of age-related health conditions.[2] So far, studies examining the relationship between telomere length and clinical frailty measures have found no association,[3-10] leaving open the question of how cellular senescence (of which telomere length is an indicator) leads to the clinical deficits seen among frail individuals.

Recently, Howlett et al.[11] introduced a new frailty measure that is derived solely from laboratory test and blood pressure abnormalities. This index (a lab-based FI named 'FI-LAB') is constructed by computing the proportion of laboratory test biomarkers and physiological parameters for which an individual falls outside of the clinical reference range. FI-LAB focusses on subclinical (biological and physiological) rather than clinical deficits, such as disabilities and functional impairments. It also has the benefit of being less subjective than FI and FP, which rely heavily on self-reporting.[12] Studies have shown FI-LAB correlates well with clinical frailty measures and demonstrates strong predictive accuracy for mortality, frequency of hospital visits, polypharmacy, and self-assessed health status.[11-14] A commonly observed finding in these studies is that, in predictive models containing both FI-LAB and clinical FI, both frailty measures showed significant association with ageing endpoints, suggesting they provide independent information about frailty. Due to its focus on subclinical and preclinical deficits, FI-LAB provides additional information beyond what the more commonly used clinical frailty measures offer.

In this article, the authors examine the association of the novel frailty measure FI-LAB with leukocyte telomere length (LTL) among a randomly selected sample of the USA general population aged ≥60 years. Furthermore, they shed light on the relationship between FI-LAB and LTL by identifying the individual biomarkers driving the observed association. For comparison, investigation of the association of LTL with the most common operationally used clinical measures FP and FI is included.

METHODS

Study Sample

The National Health and Nutrition Examination Survey (NHANES) is an annual survey evaluating the health status of the USA population.[15] In this study, the authors restricted their focus to data collected in the 1999–2000 and 2001–2002 NHANES cycles, as these are the only NHANES cycles in which telomere length was measured. In these cycles, there was a total of 3,706 subjects aged ≥60 years. Subjects with missing values on telomere length measurements, covariates, or variables required for calculation of the frailty indices were excluded. This left a sample of 1,890 subjects.

Leukocyte Telomere Length

A telomere length assay was performed for NHANES 1999–2002 participants aged ≥20 years who had blood collected for DNA purification. Quantitative PCR was used to measure telomere length. To reduce measurement error, each sample was assayed three times on three different days, and telomere length measurements were standardised by dividing by standard reference DNA values (T:S ratio). The mean and standard deviation of the T:S ratios across the three measurements were computed for each sample. The full details of this procedure have been described previously.[16]

Measures of Frailty

Frailty Phenotype

FP, developed by Fried et al.,[17] is based on an approach that considers frailty as a syndrome, the severity of which can be quantified by counting the presence of five key symptoms: unintentional weight loss, weakness (low grip strength), lack of endurance (exhaustion), slow gait speed, and low physical activity (relative to one's peers). The resulting measure (a simple count ranging from 0–5) is widely known as the FP.

Table 1: Computation of frailty index.

Deficits	Coding
Comorbidities	
Ever had stroke?	0=No, 1=Yes
Ever had thyroid condition?	0=No, 1=Yes
Ever had cancer?	0=No, 1=Yes
Ever had heart attack?	0=No, 1=Yes
Ever had heart disease?	0=No, 1=Yes
Ever had angina pectoris?	0=No, 1=Yes
Ever had arthritis?	0=No, 1=Yes
Ever had osteoporosis?	0=No, 1=Yes
Ever had broken hip?	0=No, 1=Yes
Ever had diabetes?	0=No, 1=Yes or Borderline
Ever had cataract operation?	0=No, 0.5=One eye, 1=Both eyes
Ever told you had weak/failing kidneys?	0=No, 1=Yes
Ever had high blood pressure?	0=No, 1=Yes
Signs/symptoms	
Heart rate at rest (bpm)	0: 60–99, 1: <60 or ≥100
Systolic blood pressure (mmHg)	0: <120, 0.5: 120–139, 1: ≥140
Cough regularly	0: No, 1: Yes
Urinary incontinence	0: No, 1: Yes
Self-rated vision	0: Excellent, 0.25: Good, 0.5: Fair, 0.75: Poor, 1: Very poor
Difficulty seeing steps/curbs in dim light	0: No difficulty, 0.5: Little/moderate difficulty, 1: Extreme difficulty
Self-rated hearing	0: Good/excellent, 0.5: Little/moderate trouble, 1: Lot of trouble/deaf
Confusion/inability to remember things	0: No, 1: Yes
Function	
Difficulty using fork and knife	0: No difficulty, 1: Some or much difficulty/unable to do
Difficulty dressing yourself	0: No difficulty, 1: Some or much difficulty/unable to do
Difficulty getting in/out of bed	0: No difficulty, 1: Some or much difficulty/unable to do
Difficulty standing up from armless chair	0: No difficulty, 1: Some or much difficulty/unable to do
Difficulty managing money	0: No difficulty, 1: Some or much difficulty/unable to do
Difficulty preparing meals	0: No difficulty, 1: Some or much difficulty/unable to do
Difficulty standing for long periods of time	0: No difficulty, 1: Some or much difficulty/unable to do
Difficulty stooping, crouching, kneeling	0: No difficulty, 1: Some or much difficulty/unable to do
Difficulty grasping/holding small objects	0: No difficulty, 1: Some or much difficulty/unable to do
Difficulty lifting or carrying	0: No difficulty, 1: Some or much difficulty/unable to do
Difficulty pushing or pulling large objects	0: No difficulty, 1: Some or much difficulty/unable to do
Difficulty attending social events	0: No difficulty, 1: Some or much difficulty/unable to do
Laboratory values	
Homocysteine (µmol/L)	0: <8, 0.5: 8–15, 1: >15
Folate (nmol/L)	0: 4.5–29.5, 0.5: 29.6–45.3, 1: <4.5 or >45.3
HbA1c (%)	0: <5.7, 0.5: 5.7–6.4, 1: >6.4
Red blood cell count (10^6 cells/µL)	0: 3.93–5.69, 1: <3.93 or >5.69
Haemoglobin (g/dL)	0: 12.1–17.2, 1: <12.1 or >17.2
Red blood cell distribution width (%)	0: 11.5–14.5, 1: <11.5 or >14.5
Lymphocyte count (%)	0: 20–45, 1: <20 or >45
Neutrophil count (%)	0: 40–60, 1: <40 or >60
Other	
Medications	0: 0–3, 0.5: 4–7, 1: ≥8
Self-reported health	0: Excellent, 0.25: Very good, 0.5: Good, 0.75: Fair, 1: Poor
Health compared to 1 year ago	0: Better/same, 1: Worse
Frequency of healthcare use	0: 0–3, 0.5: 4–9, 1: ≥10
Overnight hospital stays	0: 0, 0.5: 1–2, 1: ≥3

Since not all the items comprising FP were measured in NHANES, this study used a modified version of the FP introduced by Wilhelm-Leen et al.[18] and used in multiple studies.[18-21]

Frailty Index

FI is based on an approach that conceptualises frailty as the accumulation of functional and health deficits resulting from a diminishing ability to maintain homeostasis.[22] Under this deficit accumulation model, frailty is measured by computing the proportion of deficits present in an individual out of several potential deficits spanning multiple domains of health: disability, functional impairment, and disease.[23] The original version of FI, introduced by Rockwood et al.,[23] was constructed from 70 clinical deficits. Recently, a 46-item variant of the FI was created for the NHANES based on data available from participants.[24] In this study, the authors used a modified version of this FI (Table 1).

Lab-Based Frailty Index

As discussed, the novel frailty measure FI-LAB focusses on subclinical and preclinical deficits as determined by standard laboratory tests and biomarkers and physiological parameters (e.g., cholesterol, creatinine, and glucose levels). FI-LAB is based on the same deficit accumulation model that underlies the FI but focusses entirely on subclinical deficits (i.e., abnormalities on standard laboratory biomarkers or physiological parameters). FI-LAB is computed as the proportion of biomarkers and physiological parameters for which an individual falls outside of the clinical reference range, as proposed in a recent study by Howlett et al.[11] Only 21 out of 23 biomarkers and physiological parameters used in the study were available in the NHANES 1999–2002 database.[11] Therefore, the present study used 21 biomarkers to calculate each individual's FI-LAB score. These biomarkers include albumin, aspartate aminotransferase, systolic blood pressure, diastolic blood pressure, calcium, creatinine, glycohaemoglobin, haemoglobin, mean corpuscular volume (MCV), alkaline phosphatase, phosphate, potassium, protein, sodium, urea nitrogen (serum), white blood cell count, folate, red blood cell folate, thyroid-stimulating hormone, thyroxine, and vitamin B12.

Table 2: Computation of FI-LAB.*

Parameter	Reference values
Albumin (g/dL)	3.20–4.50
AST/SGOT (U/L)	8.00–33.00
Systolic BP (mmHg)	90.00–140.00
Diastolic BP (mmHg)	60.00–90.00
Calcium (mg/dL)	9.00–10.85
Creatinine (mg/dL)	0.60–1.20
Glycohaemoglobin/HbA1c (%)	<6.50
Haemoglobin (g/dL)	3.20–4.50
Mean corpuscular volume (fL)	80.00–96.00
Alkaline phosphatase (U/L)	20.00–130.00
Phosphate (mg/dL)	2.30–4.71
Potassium (mEq/L)	3.80–5.00
Protein [total] (g/dL)	6.00–7.80
Sodium (mEq/L)	136.00–142.00
Urea nitrogen (serum) (mg/dL)	8.00–23.00
White blood cell count (SI)	1.80–7.80
Folate (nM)	11.00–57.00
Folate, RBC (nM)	376.00–1,450.00
TSH (µU/L)	0.50–5.00
Thyroxine [T4] (nM)	71.00–161.00
Vitamin B12 (pg/L)	118.00–701.00

*The original study introducing the lab-based frailty index FI-LAB (Howlett et al.[11]) used 23 biomarkers, but only 21 of these were available in NHANES 1999–2002 (these 21 biomarkers are listed above). The two missing biomarkers were free thyroxine (T4) and syphilis antibody levels.

AST: aspartate aminotransferase; BP: blood pressure, NHANES: National Health and Nutrition Examination Survey; RBC: red blood cell; SGOT: serum glutamic-oxaloacetic transaminase; TSH: thyroid-stimulating hormone.

See Table 2 for details of the reference ranges for each biomarker.

Covariates

Analyses were adjusted for age, sex, race and ethnicity, socioeconomic status, education, and tobacco exposure. Age, sex, race, and educational attainment were determined from survey questionnaire responses. Poverty:income ratio (annual family income to the poverty threshold) was used as an indicator of socioeconomic status. Levels of cotinine, a stable metabolite of nicotine, were used as a proxy for tobacco exposure.[15]

Statistical Analysis

To examine the association of the three frailty measures with LTL, multiple linear regression (MLR) was used. LTL (expressed as mean T:S ratio) was natural log-transformed and treated as the dependent variable in each model, with a frailty measure as an explanatory or independent variable.

Two MLR models were fit for FI, one in which FI was treated as a continuous measure, as recommended by its formulators,[24] and one treating it as a categorical variable. In the latter model, FI categories were defined according to the frailty classifications:[25] FI≤0.10 (non-frail), 0.10<FI≤0.21 (vulnerable), 0.21<FI≤0.45 (frail), and FI>0.45 (most frail). In both FI models, LTL was treated as the outcome/dependent variable, while FI was treated as the explanatory/independent variable. Two MLR models were fit for FP, one in which FP was treated as continuous (i.e., symptom count ranging from 0–5) and another treating FP as categorical (FP=0 [non-frail], FP=1 or 2 [pre-frail], FP=3, 4, or 5 [frail]). An MLR model was fitted to examine the association between FI-LAB and LTL, in which FI-LAB was treated as a continuous variable.

In secondary analyses, the authors evaluated the LTL to FI-LAB association to identify individual FI-LAB biomarkers statistically correlated with telomere length. For each of the 21 biomarkers comprising the FI-LAB, a covariate-adjusted MLR model was used with LTL as the dependent variable and the biomarker (dichotomised version) as the independent variable. The dichotomised version of each biomarker was derived by assigning a value of 0 to subjects falling within normal ranges (as defined in Table 2) and a value of 1 for subjects with abnormal values of the biomarker (note that, for each subject, summing these binary values across all biomarkers yields the subject's FI-LAB).

All the above models were adjusted for age, sex, race, and ethnicity (white, black, Hispanic, and other), education (educated to less than high school level, and educated to high school level or above), poverty:income ratio (treated as continuous), and serum cotinine levels (natural log-transformed). All statistical analyses were carried out using R statistical software (version 3.4.0, Vienna, Austria).[26]

RESULTS

The mean age of the analytic sample (n=1,890) was 70.8 years (standard deviation: 7.7 years).

Table 3: Covariate-adjusted coefficient estimates for frailty measures.

	Beta*	SE	p value
FI-LAB (continuous)	-0.150	0.053	0.006
Frailty index (continuous)	0.030	0.050	0.505
Frailty index (categorical)			
0.00≤FI≤0.10 (non-frail)	Reference	NA	NA
0.10<FI≤0.21 (vulnerable)	-0.020	0.015	0.182
0.21<FI≤0.45 (frail)	-0.010	0.016	0.503
0.45<FI≤1.00 (most frail)	0.030	0.032	0.401
Frailty phenotype (continuous)	-0.0007	0.006	0.898
Frailty phenotype (categorical)			
FP: 0 (non-frail)	Reference	NA	NA
FP: 1–2 (pre-frail)	-0.010	0.011	0.248
FP: 3–5 (frail)	0.010	0.022	0.529

For categorical versions of frailty index and frailty phenotype, the 'non-frail' category was selected as the baseline or reference level.

*Maximum likelihood estimate of coefficient corresponding to frailty variable.

NA: not applicable; SE: standard error of beta coefficient estimate.

This sample was 48% female and the breakdown of race and ethnicity was 62% white, 14% black, and 22% Hispanic. In the sample, 61% of participants were educated to high school level or above, and the median poverty:income ratio was 2.4.

For FI-LAB, the mean score was 0.24, with a range of 0.05–0.63. The mean FI score was 0.21, with an observed range of 0.01–0.78. For FP, ~61% subjects in the analytic sample had a score of 0 (non-frail). Approximately one-third of subjects had scores in the 1–2 range (pre-frail), and only ~6% had scores of ≥3 (frail). The mean T:S ratio in the analytic sample was 0.9. To transform the unitless T:S ratio to base pair units, the formula (3274+2413[T/S])[16] was used, giving ~5,446 base pairs as mean LTL in this sample.

The relationship between FP and FI in the analytic sample was also summarised. In line with what has been previously reported,[24] FP and FI showed good correlation (Spearman ρ=0.56 [p<0.0001]). For FL and FP, the Spearman ρ=0.14 (p<0.0001). For FI and FL, Spearman ρ=0.253 (p<0.0001).

MLR models fit to examine the association between each frailty measure and telomere length are summarised in Table 3, which provides coefficient estimates (and standard errors) and p values. Each coefficient estimate represents the (covariate-adjusted) effect of a frailty measure on LTL. Neither FP nor FI showed significant associations with LTL; however, FI-LAB demonstrated a significant association with telomere length (p=0.0056). A 0.1 increase in FI-LAB leads to a 0.015 decrease in the mean T:S ratio which translates to a ~36 base pair reduction in the expected value of LTL.

Table 4 summarises covariate effects for the FI-LAB/LTL model. Of note, covariates that were statistically significantly associated with LTL include age, sex, and poverty:income ratio. Age showed an expected inverse relationship with LTL, and female sex was significantly positively associated with higher telomere length, in line with several prior studies.[27] Poverty:income ratio also showed a significant positive association with LTL, suggesting that, after controlling for other potential confounders, a higher income is associated with longer LTL. This is supported by multiple reports highlighting the role of socioeconomic status as a primary psychosocial factor linked with telomere shortening.[28-30]

Table 4: Linear regression examining the association between leukocyte telomere length (expressed as mean T:S ratio) and FI-LAB, adjusting for demographic and lifestyle-related covariates.

Variable		Beta	SE	p value
Intercept		0.317	0.0565	<0.0001
FI-LAB		-0.146	0.0526	0.006
Age		-0.007	0.0007	<0.0001
Sex	Male	Reference	NA	NA
	Female	0.053	0.0103	<0.0001
Race	White	Reference	NA	NA
	Black	0.022	0.0157	0.171
	Hispanic	-0.012	0.0144	0.395
	Other	-0.019	0.0369	0.608
Poverty:income ratio		0.010	0.0039	0.011
Education	Less than HS level	Reference	NA	NA
	HS level or higher	0.006	0.0124	0.651
Log (cotinine)		-0.003	0.0017	0.092

HS: high school; NA: not applicable SE: standard error of beta coefficient estimate.

As detailed in the methods section, secondary analyses were performed to examine the association of each individual (dichotomised) FI-LAB component with LTL, adjusting for covariates such as age, sex, race and ethnicity, and poverty:income ratio. Of the 21 lab tests and physiological parameters comprising the FI-LAB, only 4 showed a statistically significant association with LTL: serum albumin (beta=-0.025; p=0.0280), total protein (beta=-0.040; p=0.0009), MCV (beta=-0.058; p<0.0001), and aspartate aminotransferase (beta=-0.042; p=0.0120). The authors recalculated the FI-LAB excluding these four lab tests and found that the new index showed no association with LTL (p=0.6). This implies that these four parameters may be largely responsible for the observed association between FI-LAB and LTL.

DISCUSSION

Both telomere length and frailty have been shown to be determinants of ageing-related health endpoints and mortality in previous studies. However, a definitive association between these two correlates of ageing has not been established. In this study, the authors re-examined this question using a novel laboratory measure-based index of frailty (FI-LAB) that focusses on subclinical deficits, in contrast to previously commonly used frailty measures (FI and FP), which are largely based on clinical deficits.[3-8] In this study, the authors found a significant association between increased FI-LAB and decreased LTL. Another novel aspect of the study is that it is, to the authors' knowledge, the first to investigate the individual biomarkers driving the observed association between FI-LAB and LTL.

FI-LAB was recently introduced by Howlett et al.[11] as an alternative to commonly used operational frailty metrics. It focusses on subclinical aspects of frailty that the standard clinical frailty measures do not, and studies suggest it may provide independent and additional information regarding the physiological dysregulation preceding mortality.

The key distinction between FI-LAB and clinical FI is that the former is based entirely on biochemical markers and physiological parameters; hence, it is believed to represent the burden of subclinical deficits,[14] which can be thought of as systemic, organ-level dysregulation that occurs as a direct result of molecular or cellular level damage (e.g., from oxidative stress or telomere attrition), and in turn leads to macroscopic (clinically evident) functional deficits and impairments. The subclinical dysregulation measured by FI-LAB provides an intermediate link between cellular-level damage that eventually scales up to clinically detectable impairments or deficits.[12] The lab test biomarkers used to construct the FI-LAB (e.g., liver function enzymes, kidney function biomarkers, and haematological parameters) directly measure system and organ-level dysregulation, which is a direct by-product of cellular and molecular-level damage and the precursor of clinically detectable deficits. This could be a reason why FI-LAB exhibits a stronger association with telomere length, a key marker of cellular integrity, than FI and FP, which are based on clinical endpoints.

This idea is corroborated by the findings from the secondary analyses, in which the individual biomarkers driving the FI-LAB/LTL association were identified: serum albumin, total serum protein, MCV, and aspartate aminotransferase. Removing these four biomarkers (out of a total of 21) from FI-LAB completely nullifies its association with LTL. An examination of the clinical and epidemiological literature on these biomarkers reveals that most appear to be intimately linked with ageing-related cellular damage processes (specifically inflammation and oxidative stress). For example, serum albumin is a well-known marker of systemic inflammation and is strongly linked with cellular pathology;[31,32] it is also directly related to total protein (the sum of albumin and globulin levels in the serum). Synthesised in the liver, albumin is a ubiquitous protein involved in a multitude of physiological functions, many relevant to pathology and dysfunction in cellular processes. It has long been recognised as a strong predictor of mortality in both healthy and hospitalised populations,[33,34] and is a strong indicator of preclinical disease.[32,35-37]

MCV is a measure of the average volume of erythrocytes, which serves as a qualitative measure of erythrocyte health. It has been found to be highly significantly associated with LTL, with an effect size comparable to that of

tobacco smoking on telomere length.[38,39] The biological link between erythrocyte function and homeostasis and telomere dynamics is well-established.[40-42] Also, erythrocyte metabolism is related to antioxidant activity in the extracellular milieu.[43] Therefore, erythrocytes have been considered 'passive' markers of the status of oxidative stress in the body.[44,45]

The authors acknowledge a few limitations of this study. LTL was measured at a single timepoint, meaning that telomere attrition rate could not be examined, and single timepoint measurements of telomere length may be limited in their ability to capture the cellular ageing process.[46] Secondly, the study was limited to a USA population; therefore, future studies in other geographic areas are warranted to replicate the findings. Another limitation concerns the generalisability of the results on the association between FI-LAB and LTL and the secondary analyses identifying individual FI-LAB biomarkers driving this association. It is possible that the results observed in this study may be specific to the particular version of FI-LAB used. Although this version was introduced in the seminal paper by Howlett et al.[11] and has been used in multiple studies, alternative formulations of lab-based frailty indices have also been developed. In general, using the deficit accumulation model of frailty, lab-based frailty indices can be constructed from any set of biomarkers or physiological parameters that meet certain criteria (e.g., variation with age).[47] If such a set of biomarkers is sufficiently large and diverse, representing a wide array of physiological systems, a FI constructed from this set should reflect subclinical and preclinical frailty. This implies that, provided the aforementioned criteria are met, frailty indices should be largely insensitive to the particular biomarkers and/or physiological parameters used to construct them.[48] As a corollary of this, lab-based frailty indices with very different biomarker compositions should nevertheless be intercorrelated since they are all measuring the same underlying construct of subclinical frailty. Therefore, the authors hypothesised that the results can be generalised to other FI-LAB formulations; however, this was not investigated in the current study.

CONCLUSION

In conclusion, this study has demonstrated that a frailty measure constructed from standard laboratory tests and physiological parameters exhibits a significant association with LTL among a cohort of the USA general population aged ≥60 years. The results also identify individual parameters largely responsible for this association, offering putative insights into the pathways linking physiological dysregulation and telomere shortening.

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Breaking Down Silos in Asthma Research: The Case for an Integrated Approach

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Abstract

Asthma is a complex condition with heterogeneous patterns of symptoms underpinned by different underlying pathophysiological mechanisms and treatment responses. Analyses of data from birth cohorts and patient studies, from the subjective hypothesis-testing approach to the data-driven hypothesis-generating approach, have improved the current understanding of asthma's heterogeneity. Despite the rapid proliferation of new sources of data and increasingly sophisticated methods for data mining and revealing structure, relatively few findings have been translated into clinically actionable solutions for targeted therapeutics or improved patient care. This review focusses on why an integrated approach may be a more powerful catalyst for improved patient outcomes compared with the artificial and imposed dichotomy of hypothesis-generating versus investigator-led subjective approaches. As the factors shaping the development and control of asthma affect individuals dynamically in response to treatment or environmental factors, deeper insights can be garnered through the integration of data with human expertise and experience. The authors describe how integrative approaches may have greater power to provide a more holistic understanding of the pathophysiological mechanisms driving asthma heterogeneity, discussing some of the key methodological challenges that limit the clinical use of findings from asthma research, and highlighting how recent examples of integrative approaches are building bridges to ensure that the power of emerging sources of data, coupled with rigorous scientific scrutiny, can lead to a more nuanced understanding of asthma.

INTRODUCTION

Over the last two decades, a substantial effort has been devoted to understanding the heterogeneity of asthma.[1-7] The architecture of wheezing illness during childhood has been described based on temporal patterns of symptoms using data-driven techniques applied to longitudinal data from birth cohort studies.[3-5,7-10] As a consequence, the conceptual framework of asthma heterogeneity is now accepted within the clinical and research communities.[1] However, the main aim of discovering 'asthma endotypes'[11] and their underlying pathophysiological mechanisms for

the identification and development of novel targeted therapeutics appears as elusive as ever.

In part, progress has been stymied by the methodological and disciplinary silos. The rapid increase in the ability to generate, share, and access large amounts of data, including longitudinal clinical information and biomarkers, various 'omics' technologies, and environmental exposures, coupled with advances in data-driven techniques to analyse high-dimensional data, has made it, on occasion, challenging to discern what problems we are seeking to address, or how findings are relevant in a real-world setting.[12] Given that big data sets may contain many thousands of variables, or differ in terms of the format or level of the data (e.g., clinical history, laboratory tests, environmental and behavioural factors, various biomarkers, proteomic data, and genome-wide genotyping), it is not possible to define a priori all possible causal and associational mechanisms. An integrated approach to research may enable the power of these resources to be harnessed in ways that translate into a better understanding of causal mechanisms, more accurate diagnoses, and more personalised treatment. The integration of data, methodologies, and human expertise to understand the results can only occur through cross-disciplinary research, with the central principle that basic scientists, geneticists, clinicians, and data scientists work together to understand the clinical heterogeneity of complex diseases and the mechanisms underpinning them.

In this review, the authors set out to describe the evolution of analytical frameworks in asthma epidemiology, from the subjective hypothesis-driven to the data-driven hypothesis-generating approaches; highlight why an integrated approach may be a more powerful catalyst for improved patient outcomes; and identify the key challenges faced by healthcare professionals in adopting findings to clinical practice.

EVOLVING FRAMEWORKS OF DATA ANALYSIS IN ASTHMA RESEARCH

Long-term follow-up in birth cohort studies has allowed a shift in emphasis in temporal perspectives from the static cross-sectional approach to a more dynamic longitudinal approach. By explicitly allowing for time in the mediation of disease development, the longitudinal approach has allowed us to establish whether individuals affected by symptoms of the disease at one point in time are the same individuals who have the disease at later time points, ascertain temporal variations across individuals in terms of the timing of onset or remission and the persistence and recurrence of episodes, and identify the risk factors that discriminate these different temporal patterns.[3,10] Analytical approaches have progressed from supervised analyses testing-specific hypotheses to statistical data-driven classification techniques.[3] In the former, typologies of disease or hypotheses are proposed by investigators or clinical experts, usually based on patterns of symptoms observed in a clinical situation.[13] The Tucson Children Respiratory Study (TCRS) was one of the first studies to use longitudinal data to differentiate childhood wheezing phenotypes based on the presence of temporal patterns or the absence of symptoms.[2] Three mutually exclusive phenotypes (transient early, late-onset, and persistent wheezing) were described from data collected at two time points (aged 3 and 6 years).[2] While such studies have been instrumental in introducing and confirming the idea of heterogeneity of childhood wheezing and asthma, the subjective approach has several potential limitations. For example, there is a risk of limiting the predictive ability of a model by restricting the set of inputs, imposing a structure that does not necessarily fit the data, failing to identify groups with truly distinct patterns, and/or missing rare patterns.

In contrast, data-driven algorithms enable the analysis of large quantities of complex data for the identification of hidden patterns within such datasets. Continuous advances in computational power allow pattern discovery in high-dimensional data to take place with increasingly greater efficiency. As data-driven techniques are hypothesis-neutral, they are useful for examining heterogeneity based on distinctions that are not known a priori, and for making predictions about outcomes while remaining agnostic towards specific predictors.[14] This has allowed for the discovery of patterns that could not have been predicted in advance. Numerous data-driven algorithms

have been applied in asthma research. For example, latent class trajectory models, which are a class of probabilistic models in which repeated measurements of manifest symptoms are modelled in order to derive homogenous subtypes, have been extensively applied to derive distinct wheeze and lung function trajectories.[4,7,8,15,16] One advantage of such methods is that objective statistical criteria are used for judging whether clusters (classes or subtypes) represent true variation in the population. Clusters discovered using data-driven approaches are not observed, but hidden, and should not be referred to as 'phenotypes'; however, as this term has widely been used in the literature, the authors will continue to use this nomenclature.[6]

Discovery of wheeze phenotypes using data-driven methods is susceptible to inconsistencies with respect to the number of discovered phenotypes, the size of each class, and the labels ascribed to them.[6] For example, a review, which compared wheeze phenotypes derived from latent trajectory modelling across 28 studies, found that the number of phenotypes ranged from 3–8. Another review found considerable differences in the size of 'common' phenotypes in different cohort studies[6] (e.g., there was up to a 10-fold difference in the proportion of children classified as late-onset wheezing [3.7–35.8%]).[7] The inconsistencies between studies may arise from differences in the number of data points, the length of the intervals between data collection points, the age at follow-up, and the study's duration, sample size, population differences, and definition of the symptom[17] (e.g., parentally-reported versus doctor-diagnosed).[18]

Bayesian analysis,[9] hidden Markov models,[9] and temporal clustering[19] have been applied to challenge the paradigm of the atopic march, which assumes that there is a natural progression of symptoms from eczema to asthma and rhinitis. This paradigm is based on observations using cross-sectional data on population prevalence. However, modelling longitudinal data within individual patients revealed heterogenous patterns, with <7% of children with any of these symptoms following the atopic march trajectory.[9] Other applications of machine-learning include Bayesian networks coupled with feature selection methods for the discovery of patterns of allergic sensitisation,[20-22] principal components analysis to investigate whether syndromes of co-existing respiratory symptoms could be derived using responses to >100 questions from validated questionnaires,[23] Bayesian estimation of a mixture of Bernoulli distributions to describe the architecture of IgE responses to multiple allergenic proteins during childhood,[24] Gaussian mixture model to cluster human blood cell cytokine responses to rhinovirus-16,[25] and the use of network analysis and hierarchical clustering to explore the connectivity structure of allergen component-specific IgE, which demonstrated that the interaction patterns of IgE rather than individual 'informative' components are associated with asthma.[26]

CHALLENGES TO BRIDGING THE GAP BETWEEN BIG DATA RESEARCH AND CLINICAL USE

Currently, there is no consensus on what the best approach should be to understand asthma heterogeneity, how best to identify distinct underlying pathophysiological mechanisms, and how to implement these findings in a clinically useful way.[12] One potential flow is summarised in Figure 1.

Identification of Children at High Risk of Asthma

Prediction modelling to identify individuals at a higher risk of asthma is important and was identified as the top research priority by the European Asthma Research and Innovation Partnership (EARIP).[27] Several algorithms have been proposed for predicting persistent asthma in school age using early-life features, including the Asthma Prediction Index,[28] the Isle of Wight score,[29] the PIAMA risk score,[30] and the Leicester[31] and Manchester scores.[32] However, these tools have not been widely adopted clinically.[33] A systematic review found that these tools typically have low sensitivity and positive predictive values, making them unsuitable for the precise identification of high-risk individuals in a clinical setting.[34] Given the heterogeneity of asthma, algorithms may be required to predict different 'asthmas' instead of a one-size-fits-all tool.[35]

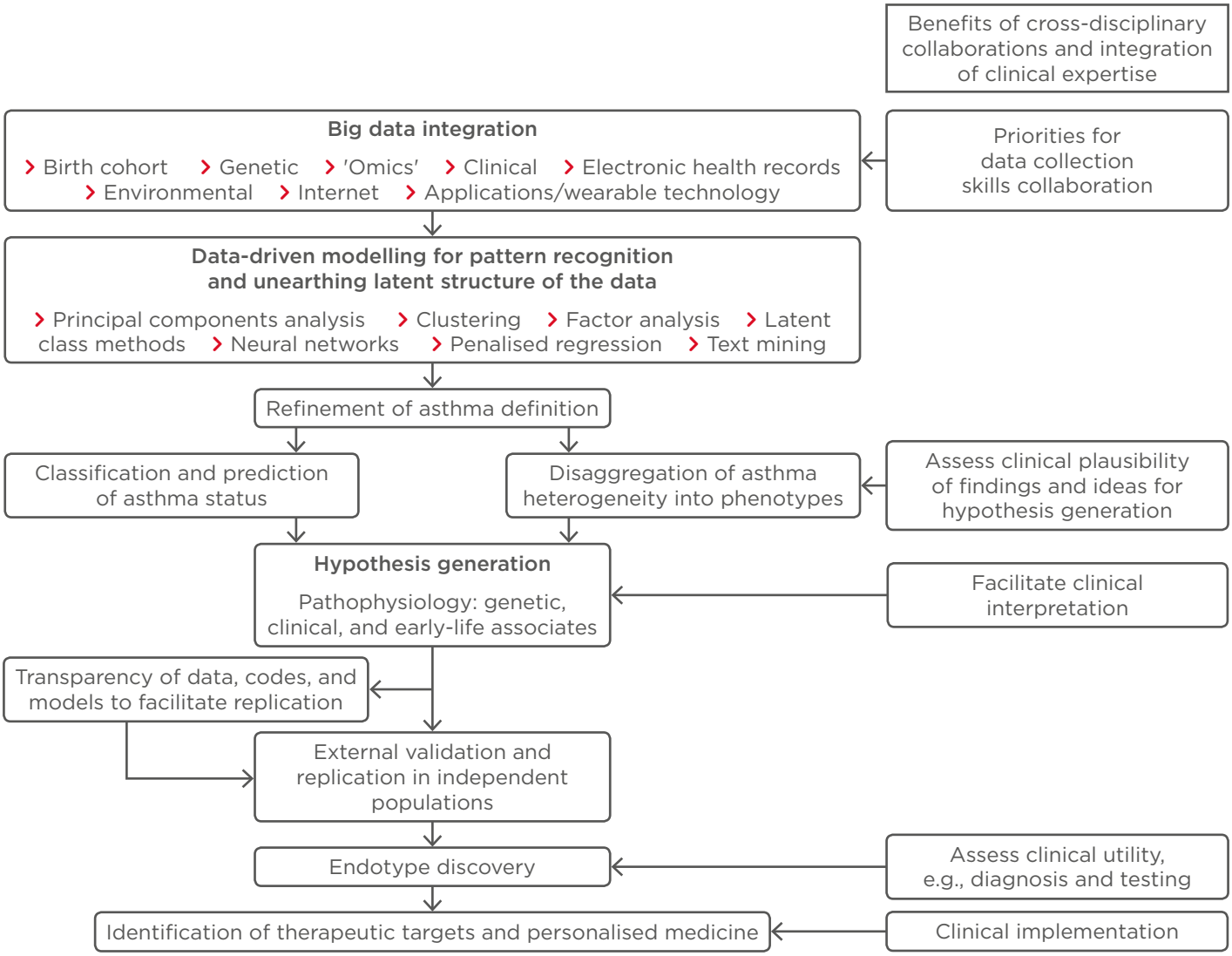

Figure 1: From asthma research to clinical implementation.

Lack of Uniformity in Defining the Dependent Variable

Comparison of prediction tools and adoption in practice is complicated by the fact there is no uniform operational definition of asthma. This creates challenges in identifying consistent early-life predictors, genetic and environmental associates, and pathophysiologic mechanisms.[34,36] A number of studies have indicated that the choice of case definition has a large impact on the estimate of asthma prevalence, as well as performance measures of predictive models. van Wonderen et al.[37] found 60 different definitions of childhood asthma in cohort studies in 122 published articles.[37] Applying four common definitions to a single cohort, the authors found that prevalence estimates varied from 15.1–51.1%.[37] These finding have implications for comparing studies that use different definitions of asthma and suggest the importance of conducting sensitivity analyses to assess the impact of heterogeneous definitions.

Transparency of Replication of Algorithms

Clinicians require access to their patients' data in an absorbable and reliable way that integrates seamlessly with their clinical workflow and does not detract from their key priority of providing quality care during a short patient visit. Without interpretive tools that can be readily incorporated in daily practice, there may be a risk of valuable research findings being overlooked, as actions for decision-making may not be

obvious. The statistical literacy of the clinical community is not keeping pace with the proliferation of new data-driven techniques and the associated terms (e.g., negative matrix factorisation,[19] probabilistic causal network analysis,[38] decision trees,[39] and least absolute shrinkage and selection operator [LASSO]-penalised logistic regression[31]). Computational transparency and reproducibility of research findings are increasingly complicated by the density and complexity of the code underlying models implemented using a variety of programming languages.[40] Such issues are increasingly being recognised, with organisations, including Fairness, Accountability, and Transparency in Machine Learning, calling for greater awareness, debate, and research on such issues. Recently, practical solutions have been proposed, such as a toolkit for enhanced transparency, which includes the use of open-source software, documentation of analyses steps, data archiving, and version control of code using web-based hosting services, such as GitHub, Inc., San Francisco, California, USA.[41] Timely syntheses of findings from the growing research output can help clinicians to understand research with a potential for clinical application. For example, Pecak et al.[42] recently developed a catalogue of 190 potential asthma biomarkers from 73 studies covering 13 omics platforms (including genomics, epigenomics, transcriptomics, and proteomics).[42] They identified 10 candidate genes linked to asthma that were present in at least two omics levels, thus demonstrating the potential for prioritising specific biomarker research and the development of targeted therapeutics.

FUTURE DIRECTIONS: TAKING AN INTEGRATIVE APPROACH

Integrating Data

The proliferation of new data types coupled with advances in computational power may offer new opportunities for integrating different data sources to understand common complex diseases more holistically. Recent advances in molecular techniques offer promising opportunities to disentangle phenotypic characteristics that reflect underlying pathological mechanisms.[43] In this context, systems biology is an approach that investigates organisms as integrated systems comprising dynamic and interrelated genetic, protein, metabolic, and cellular components. Combined with mathematical, bioinformatic, and computational techniques, systems biology can help to elucidate the directionality of relationships between variables at a more holistic level, thereby moving away from associative to more causal analyses.[38,44] In the longer term, findings from such data have the potential for the development of non-invasive and quick diagnostic assessments for use in clinics.[45-47] With the birth of genome-wide association studies (GWAS), researchers are able to investigate the relationship between hundreds of thousands of genetic markers with a phenotype.[48] However, most large GWAS in the field of asthma use the broadest possible definition of the primary outcome (e.g., 'doctor-diagnosed asthma'). In contrast, using deep phenotyping, a recent comparatively small GWAS discovered the association of a specific asthma phenotype (early-life onset with severe exacerbations) with a functional variant in a novel susceptibility gene *CDHR3* (rs6967330).[49] This SNP was not associated with doctor-diagnosed asthma in any of the large-scale GWAS. Subsequent *in silico* studies have shown that rs6967330 mediates rhinovirus-C binding and replication, and that a coding SNP in *CDHR3* mediates enhanced rhinovirus-C binding and increased progeny yields.[50] Several companies are currently pursuing this as a therapeutic target. This example shows the potential of moving from much better phenotyping to genetic association studies, discovery of mechanisms through functional studies, and the identification of therapeutic targets for tailored clinical treatment. Figure 2 summarises this desired sequence.

New possibilities for asthma research are also emerging from personally tracked data from the ubiquitous use of digital devices. Data from Google, Twitter, and Facebook have made real-time information about daily behaviours, health status, and geographical locations widely accessible on an unprecedented scale. The potential for using web-based data for surveillance of trends has been demonstrated in other diseases, such as flu,[51] lupus,[52] and multiple sclerosis.[53] In contrast, traditional sources of surveillance data are based on a time lag, which makes prompt responses infeasible. Real-time models could help healthcare

facilities anticipate asthma-related visits and hospitalisations, and plan staffing and resource management in areas of high risk. A recent study has capitalised on the use of online data to demonstrate the potential for asthma surveillance.[54] Text mining was used to link asthma-related tweets with electronic medical records using geolocation data, along with near real-time environmental data from an air quality sensor. When the number of asthma-related tweets increased in a particular week, the number of asthma emergency department visits or hospitalisations increased proportionally during the following week. The predictive model suggested patterns of accident and emergency visits with around 75% accuracy.

Individually generated data are also emerging from synergies between medical technology and smartphones. Bluetooth-enabled smart inhalers and peak flow meters[55,56] allow individuals to monitor lung function, medication use, and severity of symptoms. myAirCoach, which is a pan-European Union (EU) consortium comprising patient groups, academic institutions, and technology and pharmaceutical companies, aims to provide an evidence base for the benefits of integrating sensor technology with computational modelling to provide personalised feedback to patients on how to manage their condition daily.[57,58] The use of such data may provide clinicians with warnings on exacerbations, which would allow them to tailor medication accordingly.

Table 1 summarises the strengths and limitations of different sources of data.[3,10,38,42,56-64] These types of data have the potential to uncover different aspects of asthma heterogeneity with greater granularity and certainty, but they are a complement to, rather than a substitute for, traditional or other forms of data.

Integrating Multidisciplinary Expertise

One potential risk of 'allowing the data to speak for itself' is that data analysis may become divorced from rigorous scientific scrutiny and meaningful clinical interpretation.[12]

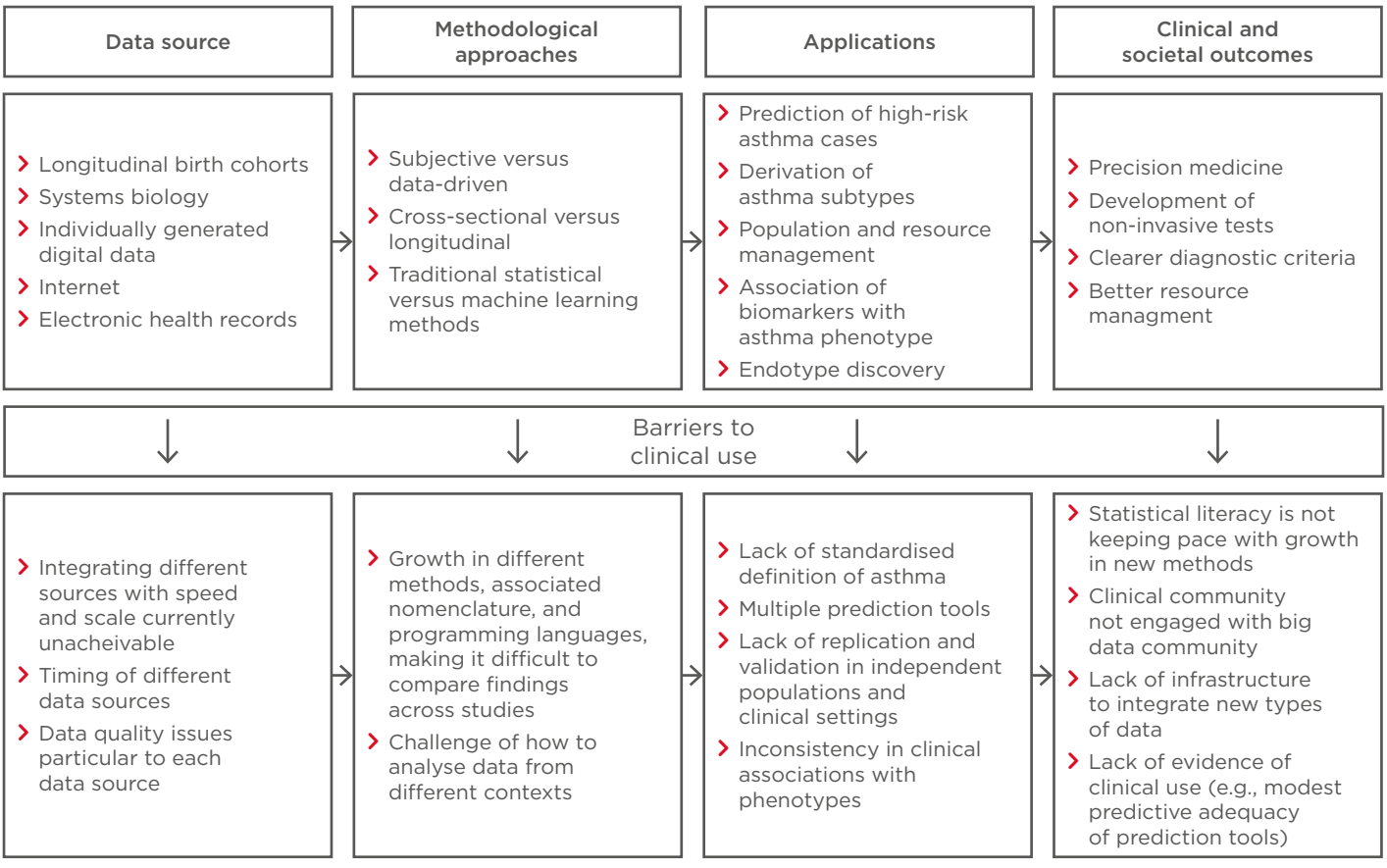

Figure 2: Barriers to clinical implementation of asthma research.

The use of modern techniques, such as machine learning, does not and should not preclude the use of more traditional statistical hypotheses-testing approaches.[14,20,25] The patterns can be discovered in large and heterogeneous data, yet clinical and basic science domain experts can guide formulation of new hypotheses and provide interpretation to findings.[59] For example, a recent study, which applied latent profile analysis to the Tasmanian Longitudinal Health Study, identified six discrete lung function trajectories,[16] five of which were remarkably similar to trajectories from pre-school age to early adulthood in two UK birth cohorts.[15] Using logistic regression, the study found that three of these trajectories were associated with childhood asthma, and the same trajectories were also associated with chronic obstructive pulmonary disease in later life, suggesting that early-life risk factors could lead to poorer lung growth and adult risk factors could accelerate lung function decline.

Table 1: Examples of asthma data sources with associated strengths and limitations.

Data source	Strengths	Limitations
Longitudinal birth cohorts	Explicitly includes the dimension of time, which allows the natural history of disease development to be studied.	Sample attrition and differential loss to follow-up can introduce bias.
	Can collect data on multiple outcomes simultaneously.	Labour and cost-intensive due to the need for a large sample size and the potentially long follow-up duration of the study.
	Questions can be tailored to a specific theme or disease.	Maintaining follow-ups can be challenging.
	Can look at associations of early-life risk factors and exposures with disease outcomes later in life.	Risk of recall bias.
	Systematic observations before the onset of disease.	Change in question wording over time.
	Incorporation of validated standardised questionnaires (e.g., ISAAC).	Large sample sizes and long duration required for discovering rare subtypes of disease.
	Potential for pooling different birth cohorts with similar questions and time points.	Not practical for rare outcomes.
Individually generated data	Data can be collected in real-time through the use of digital devices, wearable technologies, or medical devices, such as electronic inhalers.	Low long-term adoption of apps or technologies.
	Potential to collect data on multiple domains (e.g., health behaviours, symptoms, and environment).	Potential of low-quality data due to incorrect use of technology or malfunction.
	Improved self-management.	Technologies are not aligned with public health computer systems, meaning limited benefit for clinical management.
	Improved patient–clinician dialogue.	Risk of devices malfunctioning.
	Monitoring of severity of symptoms.	Missing data arising from an adverse health event.
	Data can be captured passively for some wearable devices.	
	Data collected outside of the clinical setting – greater patient insight into their own health.	
Internet text data: social media, such as Twitter, Google searches, and Facebook	Real-time data.	Risk of false predictions if models rely on historical search terms.
	Geolocation information combined with real-time data collection can reveal dynamic changes in disease over time.	Challenge of distinguishing 'noise' from genuine health episodes due to spam or searches not linked to health episodes.
	Readily available.	Recalibration of models to reflect changing search terms or unanticipated events (e.g., pandemics).
	Elucidate differential risks due to geolocation tagging.	The unstructured nature of the data makes it challenging to link to other sources of data.
	Potentially useful for forecasting.	
	Large sample size.	

Table 1 continued.

Data source	Strengths	Limitations
Systems biology data: multiple types of 'omics' data (e.g., genomics, proteomics, and metabolomics)	A more holistic approach for investigating causal biological pathways that might inform endotype discovery and targeted therapies.	Large sample sizes required to have sufficient power to detect associations.
	Data can be used to model complex interdependencies between multiple dimensions (e.g., genome, transcriptome, epigenome, microbiome, and metabolome).	Replication in independent populations required for validation.
		Risk of false-positive associations.
		Tends to be captured at single time points.
		Data collection is small-scale compared with other data types.
		Difficult to externally validate findings due to cost and complexity of data collection.
		Data is not readily accessible unlike other sources.
Electronic health records	High granularity of clinical information: diagnoses, medication, test results, comorbidities, and demographics.	Potentially important information not routinely collected and requires replication in independent populations.
	Real-world population.	Data on medication adherence or asthma control not recorded, which is a potentially modifiable risk factor.
	Large sample size.	Useful for association analyses but of limited benefit for causal analyses.
	Curation of patient cohorts for epidemiological investigations, population management, and resource planning.	Inconsistent data quality.
		Confounding factors not recorded in the database (for example, environmental).
		Variability in data types (structured and unstructured).

ISAAC: The International Study of Asthma and Allergies in Childhood.

As the number of relationships being tested increases, there is a risk of identifying false-positive associations in the absence of previous guidance about the clinical plausibility of such findings.[65] Big data can only explain part of the picture, and clinicians can provide a more contextualised understanding through their experience, knowledge of detailed clinical histories, and being able to explain variations across their patients.[66] Experts can review the findings from big data studies, which may generate promising leads for further enquiry.

An integrated approach to big data may enable us to harness the power of big data in ways that translate into a better understanding of causal mechanisms, more accurate diagnoses, and more personalised treatment. Integration can occur at different levels through cross-disciplinary research (for example, the Study Team for Early Life Asthma Research [STELAR] consortium,[60] MedALL,[67] U-BIOPRED,[68] Breathing Together consortium[69]), wherein basic scientists, geneticists, clinicians, and data scientists work together to understand the mechanisms of relevance to clinical heterogeneity of asthma. Another way of bridging the divide between the clinical and big data communities is to understand the tools clinicians need to improve outcomes for their patients by taking a 'team science' approach. As an example, a recent pan-EU consensus exercise led by the EARIP sought to identify key areas for research funding that would, most likely, improve asthma diagnosis and patient care.[27] Experts comprised patients, patient organisations, healthcare professionals, researchers, industry representatives, and policy influencers.

The prediction of asthma in preschool children with reasonable accuracy, how to integrate new biomarkers (such as genomics, proteomics, and metabolomics) in the diagnosis and monitoring of asthma, and the measurement of exhaled volatile organic compounds were identified as priority areas for research. This demonstrates how integrating multidisciplinary expertise has the potential to inform research, and for findings to be translated into improved outcomes for patient care.

CONCLUSION

One of the goals of asthma research is to understand disease heterogeneity with the aim of providing personalised treatment. There needs to be a shift away from the artificial dichotomy of data-driven hypothesis-generating versus more traditional hypothesis testing approaches towards a more integrated one, whereby cross-disciplinary collaborations can facilitate rigorous scientific scrutiny and interpretation of findings. No single source of data can uncover the complex dynamics driving asthma heterogeneity, and triangulation (integration of evidence from several different approaches with differing and unrelated sources of bias) is critically important to fill current knowledge gaps and improve causal inference.[70,71] With the advent of new and exciting sources of data, there is huge potential for integrating these to provide a more holistic understanding of the disease at a very personal level. As the factors shaping the development and control of asthma affect individuals dynamically in response to treatment or environmental factors, deeper insights can be garnered through integration. Knowing in real-time when and where symptoms are exacerbated, in combination with refined subtypes and environmental data, may help identify personal triggers and inform a personally tailored care plan.

Research needs to take greater steps to demonstrate clinical utility, or it risks being consigned to research for research's sake. Tools need to be developed that clinicians can integrate into daily practice to make decision-making more efficient and personalised. Steps need to be taken to improve the statistical literacy of healthcare professionals through greater education to bridge the divide with the big data industry. It is essential that clinicians engage in debates surrounding big data and healthcare as a step towards breaking down the siloed approach.

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What's New

Targeted Brain Stimulation Could Relieve Depression

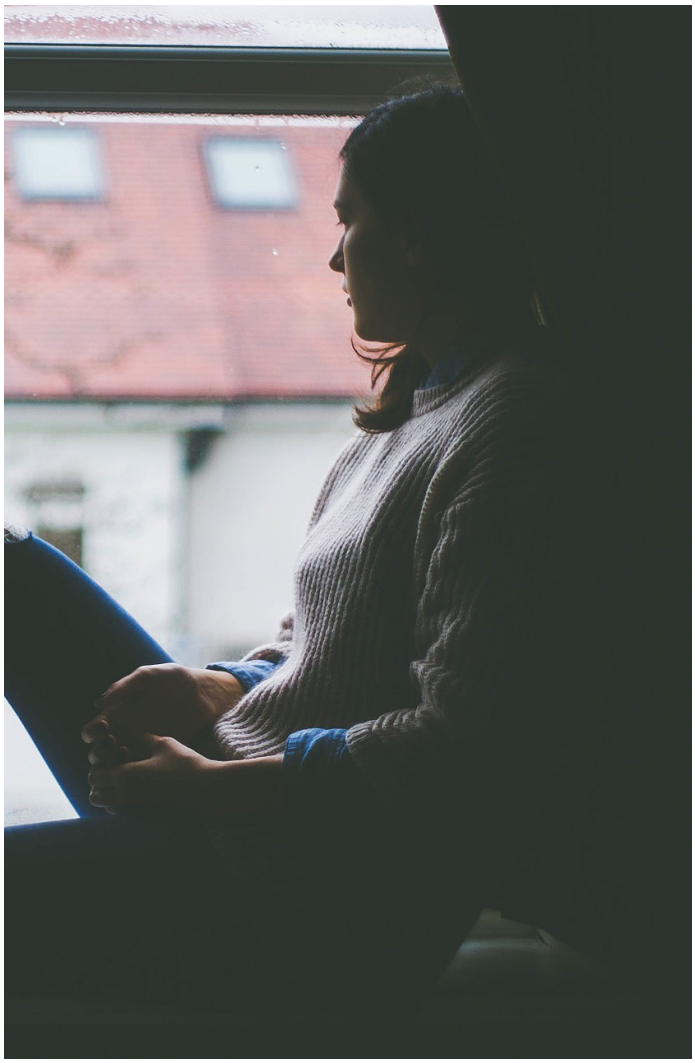
STIMULATION of the lateral orbitofrontal cortex (OFC) via electrical impulse could improve the mood of patients with depression, suggests new research from the University of California, San Francisco, California, USA. The results of this study build on data from deep brain stimulation (DBS) research, which showed that DBS could be effective at regulating mood but is crucially dependent on the correct target.

The OFC is an interesting target for electrical stimulation; the researchers themselves described the region as seemingly 'superficial' but with strong interconnections with several other regions of the brain involved in processing emotions.

"Stimulation induced a pattern of activity in brain regions connected to the OFC that was similar to patterns seen when patients naturally experienced positive mood states..."

The study examined 25 patients with epilepsy who had electrodes placed into their brain to identify the origin of their seizures; many of these patients also experienced depression. Researchers used these electrodes to deliver targeted electrical pulses to the OFC, which resulted in acute, dose-dependent mood-state improvements, as recorded by verbal mood reports and questionnaire scores, in those patients with moderate-to-severe depression at baseline. "Stimulation induced a pattern of activity in brain regions connected to the OFC that was similar to patterns seen when patients naturally experienced positive mood states," explained Dr Vikram Rao, University of California, San Francisco.

This study adds to the body of research that suggests depression is related to a dysfunction of the brain's electrical circuitry, implying the OFC is a potential treatment target for future medical devices. Such a device could monitor brain activity and automatically stimulate the OFC to stimulate improved mood in the patient when necessary. "Ultimately, it would be ideal if activity in mood-related brain circuits could be normalised indefinitely without patients needing to do anything," concluded Dr Rao.



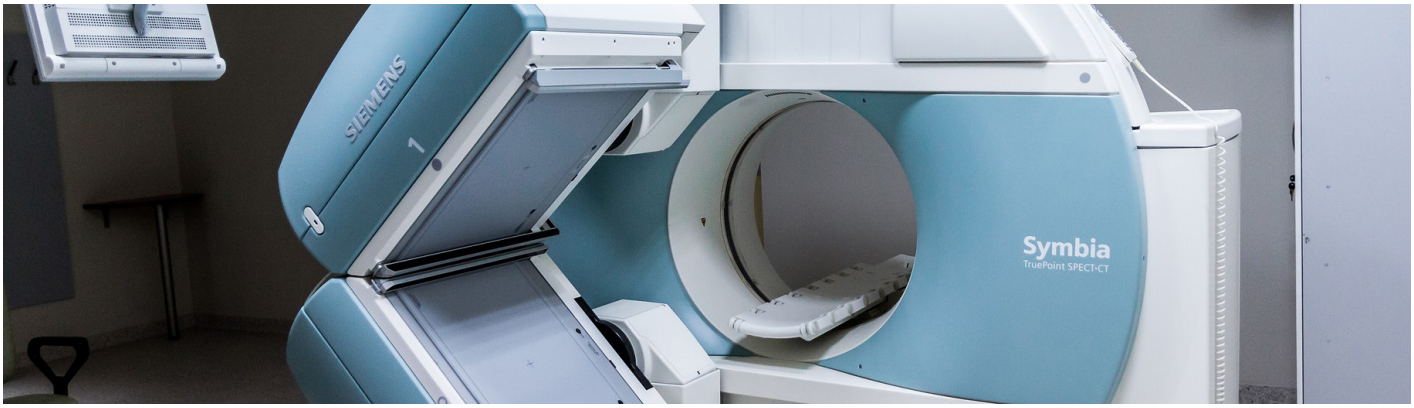
Xenon-Based Contrast Media to Revolutionise MRI Diagnostics

CONTRAST media can be used to increase the sensitivity of MRI; however, even in these cases, MRI's sensitivity remains low and the number of biological markers that can be identified is limited. Additionally, the safety of contrast media containing gadolinium is currently unclear. "We need new, improved methods in which as little contrast medium as possible influences as much of the signal-transmitting substance as possible, which is typically water," explained Dr Leif Schroeder from the Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Berlin, Germany. Thus, for the first time, a new contrast media based on xenon has been developed by scientists at the FMP, allowing for improved MRI sensitivity.

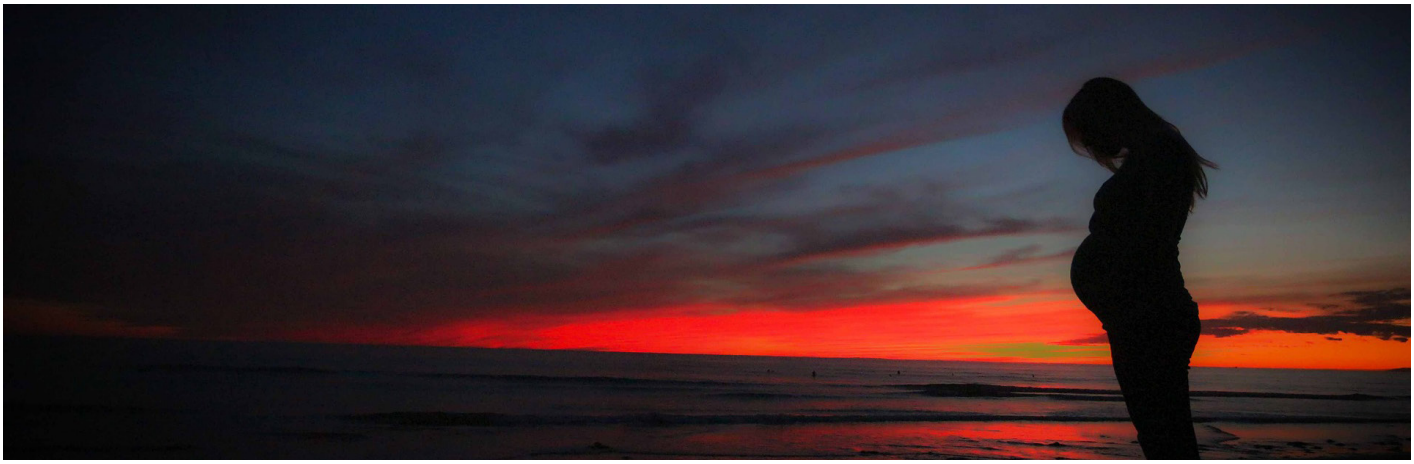
To create the medium, the researchers artificially magnetised xenon using powerful lasers, thus generating a readable signal. They then incorporated a new form of contrast media that binds the xenon reversibly using hollow protein structures. These structures, known as 'gas vesicles', have previously been used as MRI contrast media, but there were concerns regarding how well they could be 'charged' with xenon. However, these concerns were quickly overcome, with the gas vesicles proving ideal for this purpose, absorbing xenon proportionally to its availability in the atmosphere. "They act as a kind of balloon, to which an external pump is attached. If the balloon is 'inflated' by xenon atoms flowing into the gas vesicle, its size does not change, but the pressure does increase, similar to a bicycle tire tube," explained Dr Schroeder. Due to this increased concentration, the contrast is far stronger than the background noise, allowing for a significantly improved image, as well as the identification of disease biomarkers that occur in particularly low concentrations. The 'elastic' protein structure of the medium also allows xenon to be absorbed in a self-regulating way.

Further research must be carried out, beginning with animal studies, to verify the media's efficacy and safety. However, researchers are confident that this could offer a great advantage in MRI imaging in living tissue, requiring less contract medium compared to current methods.

"They act as a kind of balloon, to which an external pump is attached. If the balloon is 'inflated' by xenon atoms flowing into the gas vesicle, its size does not change, but the pressure does increase..."



What's New



Ground-Breaking Development in Fertility Care

WOMB transplantation from a deceased donor has been successfully completed and has given rise to a healthy baby girl. Although previous womb transplantations have been successful with living donors, donor numbers are low and, therefore, investigators have trialled the use of wombs from dead bodies. In contrast to prior procedures using deceased donor wombs, which have failed or resulted in miscarriages, a procedure carried out in São Paulo, Brazil has resulted in a successful birth.

"In a 10-hour procedure, a womb was donated by a mother of three in her mid-40s, who died as a result of a bleed on the brain, and implanted into the recipient."

In a 10-hour procedure, a womb was donated by a mother of three in her mid-40s, who died as a result of a bleed on the brain, and implanted into the recipient. The patient who received the womb had Mayer–Rokitansky–Küster–Hauser syndrome, which affects 1 in 4,500 women and causes the vagina and the uterus to fail to form. The recipient's ovaries were healthy and the oocytes were removed and fertilised *in vitro* with the father-to-be's sperm. Following the transplant, the recipient was given immunosuppressive drugs to prevent the uterus being rejected.

Six weeks after the transplant, the recipient started to have periods, and after 7 months the fertilised eggs were implanted and a 6 lb baby was born. Explaining the current situation in regard to womb transplants, Dr Dani Ejzenberg, Hospital das Clínicas, São Paulo, Brazil, explained: "The first uterus transplants from live donors were a medical milestone, creating the possibility of childbirth for many infertile women with access to suitable donors and the needed medical facilities." He added: "However, the need for a live donor is a major limitation as donors are rare, typically being willing and eligible family members or close friends."

Dr Srdjan Saso, Imperial College London, London, UK, described the results as "extremely exciting," adding: "It enables use of a much wider potential donor population, applies lower costs, and avoids live donors' surgical risks."

The Next Step in Pregnancy Research: Lab-Grown Placentas

"THE PLACENTA is absolutely essential for supporting the baby as it grows inside the mother. When it does not function properly it can result in serious problems, from pre-eclampsia to miscarriage, with immediate and lifelong consequences for both mother and child," explained Dr Margherita Turco, University of Cambridge, Cambridge, UK, as she introduced the latest advance in medical science from the historic institution: lab-grown placentas.

"We can now begin to do experiments on how placental development occurs in the uterine environment"

The organoids were grown from villi found within placentas and spontaneously organised into the multicellular structures that secrete proteins and hormones vital to the progression of pregnancy. The mini placentas ranged from one-tenth of a millimetre to half a millimetre in size; they mimicked the activity of a natural placenta during the early stages of the first trimester so accurately that when a pregnancy test was exposed to the medium from the organoids it provided a positive result.

The lab-grown placentas are forecast to be used to investigate the cause behind common pregnancy failures, including pre-eclampsia, stillbirth, and growth restriction. Following the rise of the Zika virus, other groups aim to use the placentas to investigate the passage of viruses between the mother and her developing child via the organ. The final research goal is to analyse the hormones and proteins secreted by the organelles, with the aim of using the findings to identify early warning signals of placenta malfunction.

Study of the placenta has proved difficult in the past, with few donor placentas available and large physiological differences between animal models and human tissues; however, these lab-grown organoids signal a watershed in pregnancy research. "We can now begin to do experiments on how placental development occurs in the uterine environment," explained Dr Ashley Moffett, University of Cambridge.

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