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Along with a few friends,  
we look at healthcare and  
medical devices 15 years  
from now.

insight.  
ISSUE No.7

# The 2030 issue

## IN THIS ISSUE

### Personalisation and...

Through a number of articles  
we look at the future of  
personalisation from the  
clinical, psychological and  
regulatory perspective.

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### Never mind the biosensors

Ben Wicks provides some  
thoughts on how to assess the  
impact of new biosensing and  
health monitoring technologies.

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### Intelligent inhalers

David Harris contrasts the  
evolution of inhalers and  
digital media and asks  
why inhalers haven't really  
changed for decades.

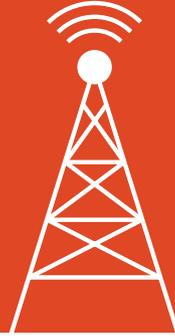
04



**GAINING MOMENTUM ON THE ROAD TO ACCESSIBLE BIOSIMILARS**

An era of uncertainty and caution over biosimilars looks like it may be coming to an end.

12



**THE PSYCHOLOGICAL PERSPECTIVE**

Spoonful of Sugar's CEO, Andrew Martello looks at how personalised healthcare could modify patient behaviour.

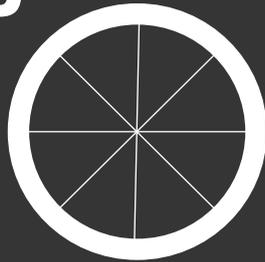
21



**A BILLION BY 2030? CAN WE TURN THE TIDE AGAINST DIABETES?**

The prevalence of type 2 diabetes is putting healthcare systems under considerable pressure. How do we turn the tide against the disease and avoid it affecting a billion people?

09



**BENCH TO BICYCLE**

David Brindley from Spoonful of Sugar takes a clinical perspective on personalised medicine.

15

**WHAT DO PATIENTS WANT?**

18



**INTELLIGENT INHALERS**

Are smarter inhalers a real possibility? David Harris looks at the barriers and the opportunities.

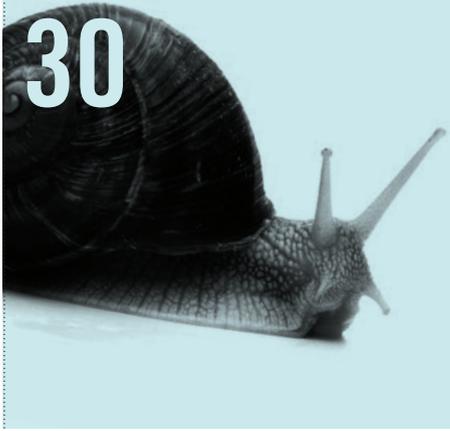
26

**MIND SENSORS**

**NEVER MIND THE BIOSENSORS**

Ben Wicks attempts to ignore the hyperbole and ask what future home-based diagnosis will have.

30



**THE LAST INCH**

Peter Matthewson looks at how we could bridge the final gap between the patient and the medical device.

34

**PERSONALISED MEDICINE AND THE FDA**

Lee Leichter from P/L Biomedical looks at the challenges of personalised medicine from the perspective of the US FDA.

37

**HEALTHCARE IN 2030**

**Credits**

Editorial team: Neil Cooper / Tom Brooks / Angela Murray  
Designed by: The District

# Welcome to the future!

When we at Team first discussed the idea of producing some forward-thinking content for this issue of Insight, we were very keen to avoid delving into the depths of science fiction, where we imagined a world in which robots drove us to work in flying cars. Although I'm sure it would be fun to see ourselves living in the world depicted by Star Trek, we wanted to think about the near-future, a time when we ourselves might need to use the products that we will be developing in the coming years. That's why we set our sights on 2030.

Fifteen years from now the pressures facing healthcare systems, and the challenges facing the industry, will be an extension of what we are seeing today. How can we provide adequate care for people at low-cost? How can we better harness technology and data to improve outcomes? How do we cope with a growing population that is getting older, more affluent and leading less healthy lifestyles? How do companies develop medical devices that are easy to use, safe and commercially viable within this context?

Coupled with the in-depth survey that we commissioned (see page 15), this issue of Insight shares our thoughts and opinions, as well as those of some of our friends.

**DAN FLICOS, CEO**

# Gaining momentum on the road to accessible biosimilars

BY STELLA WOODER



As patents for a number of biologics begin to expire over the next decade, follow-on biologics ('biosimilars') are inevitably coming to the fore. At first sight, biosimilars are to biologics what generics are to small-molecule medicines; 'substitutes' of the original biologic. This, in theory, provides the opportunity for cheaper equivalents for biologics by 2030, just as generic equivalents have provided cost effective alternatives to branded drugs in the chemical (small-molecule) drug market for the last 15 years.

So, has the promise of potentially cheaper options fired up governments, regulators and healthcare insurers to ensure the growth of biosimilars? The reality is some uncertainty and caution but this apparent inertia has in fact been a period in which stakeholders have been working together to iron out the convoluted approvals processes and fragmented regulation surrounding biosimilars. But there are signs that this period may be coming to an end and that biosimilars will begin to contribute to a future of affordable medicine for treating advanced and chronic illness.

#### **A landmark for complex biosimilars**

When South Korean biotechnology company Celltrion recently submitted its copy of Johnson & Johnson's biologic Remicade for FDA approval, it signalled — albeit quietly — a landmark in the history of biosimilars. Some biologics, such as vaccines and insulin, have been around since the 70s, but Celltrion's monoclonal antibody ('Mab'), known as Remsima, is the first complex molecule biosimilar of its kind to seek approval in the US, having already been submitted for approval in Europe in 2013<sup>1</sup>. Why the fuss? Before turning to biosimilars, a brief recap of branded (i.e. original or innovative) biologics reminds us why this class of medicines promises to be so important to healthcare in 2030 and beyond.

Bigger, more complicated and with a different mode of tackling disease than small-molecule medicines, biologics have revolutionised the treatment of difficult-to-treat conditions such as rheumatoid arthritis, Crohn's disease, Turner's syndrome and cancer. Bristol-Myers Squibb's oncology drug ipilimumab (marketed under the brand

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name YERVOY®), is a good example of why biologics have captured the imagination of the healthcare industry. Ipilimumab is prescribed for patients suffering advanced melanoma after prior treatments have failed. In conventional chemotherapy, the drug acts on rapidly dividing cells in the body (such as cancer cells) but its action is indiscriminate, destroying normal as well as abnormal cells. Ipilimumab — like other MABs — targets specific proteins in the body, stimulating the immune system to fight the melanoma tumour cells by attaching to the body's T-cells and blocking the action of the protein CTLA-4 which, in melanoma, is inhibited from recognising cancer cells. This allows production of more T-cells, some of which will fight off the malignant cells<sup>2,3</sup>.

A follow-up review of 12 studies of advanced melanoma patients treated with ipilimumab demonstrated a long-term survival benefit for patients. Advanced melanoma is one of the most aggressive forms of cancer and historically, average survival was just six to nine months. In 1,861 ipilimumab-treated patients, the median overall survival was 11.4 months (95% confidence interval: 10.7 – 12.1), and three year overall survival rates were 22%<sup>4</sup>. This represents a significant data point for patients with this difficult-to-treat disease.

Compared to small-molecule (chemical-based) medicines, such as aspirin, larger biologics are difficult to manufacture, quality and safety assure, store and administer, as shown in **Table 1** (overleaf).

The performance of biologics therefore comes at a financial cost. MAB-based rheumatoid arthritis medicines cost on average £9,500 per patient per year, compared with around £450 per year for conventional therapies such as corticosteroids, NSAIDs or immunosuppressant drugs<sup>5</sup>. Roche's breast cancer drug Herceptin costs around \$54,000 per year in the USA; in suitable patients, it is taken in conjunction with Roche's newer biologic drug, Perjeta, which costs about \$70,000 for a year's treatment (though Perjeta is listed at ~\$42,000 in the UK)<sup>7</sup>. Cerezyme, a biologic used to treat the rare condition Gaucher's disease, may be as much as \$150,000 for a year of treatment.

# A FOLLOW-UP REVIEW OF 12 STUDIES OF ADVANCED MELANOMA PATIENTS TREATED WITH IPILIMUMAB DEMONSTRATED A LONG-TERM SURVIVAL BENEFIT FOR PATIENTS.

**Table 1. Radically different profiles: Small-molecule versus biologic medicines<sup>5</sup>**

	Small-molecule medicine	Biologic medicine
<b>Structure</b>	Small and simple (e.g. aspirin molecular weight: 180 Daltons)  Generally more stable	Large, complex, diverse structures (e.g. ipilimumab molecular weight: 148,000 Daltons)  Difficult to completely characterise  Large proteins, more sensitive to environment; less stable
<b>Manufacturing</b>	Lab-based chemistry  Consistent processes	Unique cell lines  Highly variable
<b>Product quality assurance</b>	Smaller number (~50) of critical tests required to assure quality	Larger number (~250) of more complex tests/controls for assurance
<b>Administration</b>	Diverse administration routes possible, including orally, as a pill or capsule	Usually infused or injected
<b>Immunogenicity</b>	Small molecules less likely to trigger immune response	Greater potential for immune response

The proposed ‘antidote’ to this is biosimilars. Following in the slipstream of the branded biologics which are coming off patent, biosimilars are designed to offer a cost-effective alternative; an advantage to payers, prescribers and patients.

### Beer, bread, cheese... and biosimilars

The simple nature and homogeneity of a small-molecule and its relatively easy chemically-manufactured process means that a generic drug can be considered a duplicate of its branded counterpart. Most generics contain the same active ingredient as the branded drug. Marketing approval is made on the basis of bioequivalence, in practice a relatively cheap and fast process for generics manufacturers. Biosimilars are a different matter; like biologics, they are produced in large bioreactors from living cells, such as yeast, bacteria or cultured animal cells, in a process which may take from several weeks to months to complete.

Rather like making beer, bread or cheese, there is a degree of alchemy involved in producing a consistent biologic product. Science writer and editor Khadijah Britton sums up the dilemma perfectly: ‘Under the best conditions, [branded] biologic companies have a hard enough time proving equivalence between batches of the same medication, even though they themselves hold all of the intellectual property and often use the exact same equipment and scientists’<sup>6</sup>. Different manufacturing processes, using different cell sources, extraction and purification techniques in large, complex molecules have the potential to behave differently in clinical practice. Due to its size and structural complexity, a biosimilar can trigger an immune reaction or side effect not previously seen in a patient population when using the branded biologic.

Because ‘similar’ is not the ‘same’, safety and effectiveness can also vary from branded biologic to biosimilar. Significant financial

## SO HOW DOES THE 'GENERIC' MODEL — WHERE THE BRANDED MEDICINE IS SUBSTITUTED WITH A GENERIC MEDICINE — WORK IN THE WORLD OF BIOLOGICS AND BIOSIMILARS, WHERE THE GOAL-POSTS APPEAR TO BE MOVING?

**Table 2. The pharmacist's view: how individual countries interpret EU substitution regulations**

France	Pharmacist allowed to substitute a biosimilar for the branded biologic only when initiating a course of treatment and if the prescribing physician has not marked the prescription as 'non-substitutable'.
Italy Spain Sweden United Kingdom	Pharmacist must dispense what has been prescribed.
Germany	Pharmacist may substitute only if the product: <ul style="list-style-type: none"> <li>• is approved with reference to the same branded medicine</li> <li>• has been produced by the same manufacturer, via the same manufacturing process</li> <li>• differs by brand name alone.</li> </ul>
Austria	Physician obliged to prescribe by brand name; pharmacist dispenses only what is prescribed.
Denmark Finland Hungary Norway Slovakia	Official lists exist stating which products cannot be substituted.

resources are needed to demonstrate that a biosimilar is indeed similar to the branded biologic it follows and does not differ significantly in terms of quality, safety or efficacy. The European Medicines Agency, for example, requires all biosimilar manufacturers to implement post-market safety programmes, often as part of other additional risk minimisation measures.

So how does the 'generic' model — where the branded medicine is substituted with a generic medicine — work in the world of biologics and biosimilars, where the goal-posts appear to be moving? This is where it starts to get messy; automatic substitution or interchanging, as in the case of small-molecule generics, is not as straightforward in biosimilars. A review of European states, in **Table 2**, shows that different countries interpret regulatory guidance in different ways. French pharmacists, for example, are able to substitute a biosimilar for the branded biologic only at the initiation of a

patient's treatment and on condition that the prescribing physician has indicated on the prescription that the biologic can be substituted<sup>9</sup>. In some Scandinavian countries, pharmacists can only make a biosimilar substitution if the biosimilar appears on an 'approved' list. In the US, biosimilar legislation is set by the individual state; in April of 2014, Delaware became the latest US state to pass a bill allowing substitution by pharmacists, but as in France, only if the prescriber has not expressly prohibited substitution<sup>10</sup>.

With their unique living cell line, and difficult manufacturing and characterisation process, it is unsurprising that it feels as though there is a lack of clear policy and decision-making regarding legislation surrounding biosimilars, particularly in the US<sup>11</sup>.

# AS MARKET CONFIDENCE GROWS IN BIOSIMILARS, NEW INNOVATIONS WILL EMERGE DESIGNED TO EASE THE JOURNEY TO AFFORDABLE BIOSIMILARS

## Enabling the future for biosimilars

What does the future hold for biologics and biosimilars? In Team Consulting's recent survey of UK and US patients and medical specialists<sup>12</sup> there was almost unanimous consensus that medicine would not be cheaper in 2030. This is hardly surprising; pharmaceutical products are increasingly complex and our demand for safer drugs and evidence of associated benefits and risks has grown, and with it the regulatory burden. However, whilst the biosimilars landscape currently has a number of grey areas — scientific challenges and opaque regulatory policy — the commercial pressures are too great to prevent uptake in the market-place in the next 15 years. We should also recognise that enablers are needed to support progress in the biosimilar arena. These include creating a harmonised regulatory strategy, starting with established and common regulatory elements — such as the requirement for efficacy and immunogenicity data — to arrive at a greater degree of global consistency across borders. There are signs that regulators are trying to pick a legislative pathway which

takes a pragmatic view of the clinical and scientific data required for a biosimilar product. Physicians need to feel confident when prescribing a biosimilar in the place of a biologic, and payers need to be assured that biosimilars represent value for money without compromising patient safety and efficacy. Ultimately, from the biosimilar developer's perspective, the amount of investment required to get to market needs to make sense.

Understanding the role emerging markets can play is also critical. The early launch of biosimilars in India, Korea and other markets, provide opportunities to learn from real-world patient data. In addition, within highly-regulated markets, the push towards clinical trials data transparency will reinforce knowledge of both biologics and their biosimilar counterparts. Clinical trials investigating the impact of switching from biologic to biosimilar are underway. One example, a Norwegian study, will assess the safety and efficacy of switching from Remicade to Celltrion's biosimilar Remsima in patients with rheumatoid arthritis, ulcerative colitis, Crohn's disease and other auto-immune indications.

As market confidence grows in biosimilars, new innovations will emerge designed to ease the journey to affordable biosimilars, such as leaner manufacturing processes and smarter formulation. In the next 15 years, the gold standard of care for many conditions will be dominated by MAb biologics and biosimilars, resulting in medicines requiring careful storage, or reconstitution and typically administered to patients as long, slow infusions in a clinical setting. Research, such as that carried out by UK-based Arecor, has considered re-formulation in the context of greater stability, flexibility in administration, the ability to use significantly higher aqueous concentrations and the potential for patient self-administration, to overcome constraints and improve accessibility<sup>13</sup>.

It may be early days for biosimilars in Europe, the US and other highly-regulated markets, but the period of apparent inertia and legislative opaqueness is coming to a close. Instead, the prospect of biosimilars taking their place in a future of affordable medicine to treat complex and chronic disease is tantalisingly close.

## References

- 1 'Celltrion submits biosimilar Remicade for US approval', 14 August 2014, PMLive, <http://te-am.co/1yV7MeK>
- 2 Hanaizi, Z. et al, The European Medicines Agency review of ipilimumab (Yervoy) for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy: Summary of the scientific assessment of the Committee for Medicinal Products for Human Use. *European Journal of Cancer* 48 (2), 237–242 (2012)
- 3 The European Medicines Agency. 'Yervoy: EPAR — Product Information Annex I & IIB'. Last update: 11 March 2014. <http://te-am.co/1x8HSCV>
- 4 Schadendorf, D., Hodi, F.S., Robert, C. et al, Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in metastatic or locally advanced, unresectable melanoma. Presentation at European Cancer Congress 2013
- 5 'Background paper on biosimilars', 6 March 2012, Bio Deutschland, <http://te-am.co/1t8vTBJ>
- 6 'TA195 Rheumatoid arthritis — drugs for treatment after failure of a TNF inhibitor and TA198 Rheumatoid arthritis — tocilizumab: costing template', 24 August 2010, National Institute for Health and Care Excellence, <http://te-am.co/10qEAQT>
- 7 'Herceptin successor reaches UK shores, 14 March 2013, PharmaTimes digital, <http://te-am.co/1zuec7P>
- 8 'Biosimilars are back ... Or are they?', 2 August 2011, Britton, K., Scientific American blog, <http://te-am.co/1EiNWhg>
- 9 'France to allow biosimilars substitution', 21 February 2014, GaBI (Generics and Biosimilars Initiative) Online, <http://te-am.co/13E1aHB>
- 10 'Delaware passes biosimilars substitution law', 25 April 2014, GaBI (Generics and Biosimilars Initiative) Online, <http://te-am.co/1wuHBM5>
- 11 Leintz, C.J., Regulatory uncertainty vs legislative inevitability. *Regulatory Rapporteur* 11 (7/8) (2014)
- 12 'Patient and doctor perspectives', 18 November 2014, Team Consulting Ltd <http://www.team-consulting.com/2030>
- 13 Reese Saylor, T., Expanding medicine access through formulation, *MedNous*, (Sept 2014)



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# Bench ————— to —————> Bicycle

A CLINICAL PERSPECTIVE ON PERSONALISED MEDICINE  
BY **DAVID BRINDLEY**, SPOONFUL OF SUGAR

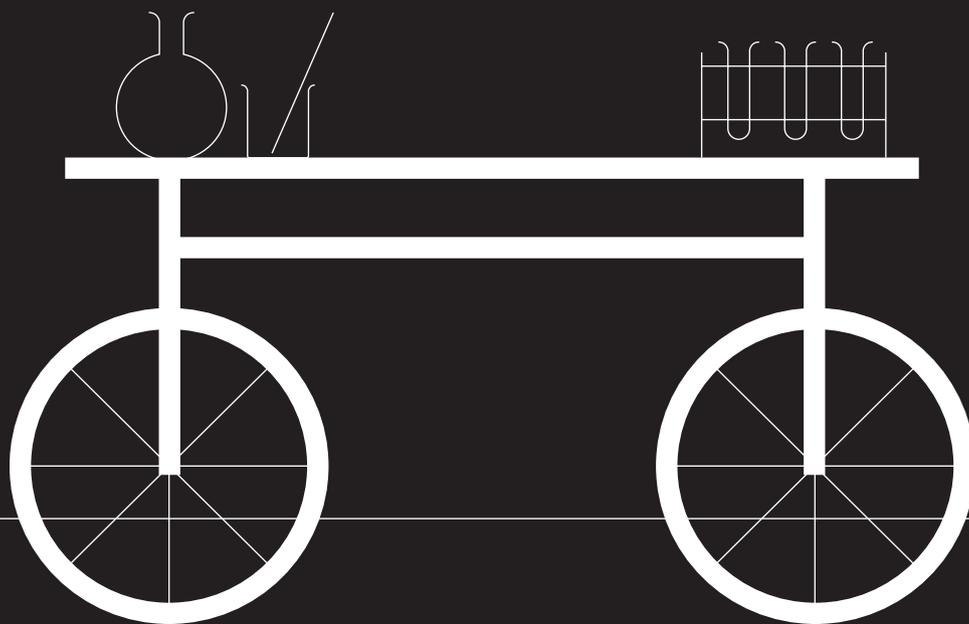
Healthcare in the 20th century was empowered by scientific advancements made by a few for the benefit of many. The 21st century will be characterised by the democratisation of medicine, where patients are active participants in the development and delivery of healthcare innovations through wearable devices, a key component of healthcare in 2030.

Wearables — small personal devices that monitor and transmit high volumes of personal physiological data — are now firmly seeded in the vernacular and promise improved understanding of patient and population disease levels. Blood pressure monitoring can be linked to applications determining optimal daily doses of antihypertensives, reducing unnecessary use of medication and maximising treatment efficacy. Wearables also offer regulators, clinicians and pharmaceutical companies transformative improvements in pharmacovigilance datasets, notably around patient

adherence monitoring. This then helps reduce regulatory uncertainty and enables novel regulatory paths, including adaptive licensing and FDA breakthrough status, to become more accessible than ever before. Questions remain however, as to who is the most appropriate custodian of the collected data.

Presently, healthcare providers are the dominant collectors and custodians of patient level healthcare data, together with — to a lesser extent — healthcare insurers. The advent of wearables and virtual medical consultations places patients at the heart of data collection, and critical practical and ethical questions remain concerning the extent to which patients should be able to determine with whom collected data should be shared, and its permitted uses. Two independent groups identified as potential 'data controllers' are patient advocacy and disease-specific organisations. As demonstrated by the recent cases of Glybera<sup>1</sup> and Kalydeco<sup>2</sup>, such organisations are evolving rapidly

**Wearable technologies offer potentially step-changing improvements in the 'resolution of disease' at an individual and population level.**



from being sources of information for patients to becoming active participants in regulatory and product development decision-making.

Wearable technologies offer potentially step-changing improvements in the 'resolution of disease' at an individual and population level. As illustrated by Jawbone users living through the recent northern California earthquake, where records of users awakened at 03:20am by the state's biggest earthquake in 25 years correlated with seismic activity, they offer an opportunity to directly monitor our response to the external environment, and to immediate changes<sup>3</sup>.

### Genomics

While recording the number of people awakened by an earthquake may seem to be little more than the nucleus of a transient news story, it illustrates the portent of an exciting chapter in modern medicine: epigenetics.

Describing the intricate interaction between an individual's genome and their long-term exposure to environmental factors, epigenetics is simultaneously transforming our understanding of disease aetiology while also informing the most effective ways to treat it. For example, we are now beginning to elucidate the underlying genetic consequences of environmental factors such as smoking on underlying patient genetics through processes such as DNA methylation and histone modification<sup>4</sup>. Consequently, improved knowledge of biomolecular pathways is yielding druggable targets; for example, BRCA1 in breast cancer, the *in vivo* target for Herceptin (trastuzumab) — a monoclonal antibody for breast cancer — offered with combinational diagnostic Oncotype DX.

The data-rich 2030 healthcare system will also enable patient stratification and data mining at a population level, utilising pharmaceutical authentication tools intended to respond to commercial threats such as parallel

importing — where pharmaceuticals purchased in lower price markets are illicitly sold in higher priced markets. Products such as AegateASSURE™ and KODAK TRACELESS Anywhere™ systems may be linked to patient records in order to tightly correlate medication with patient outcomes, thus yielding unforeseen pharmacological trends and applications for repurposing existing drugs. Where existing therapies are insufficiently efficacious, genomics also offers the opportunity for bespoke therapeutic approaches including gene editing techniques such as CRISPR. These are currently applied to add, disrupt or change the sequence of specific genes, in indications such as cystic fibrosis and haematological disorders including blood disorders such as sickle cell anaemia. The technique takes a subpopulation of cells in a bone marrow aspirate, namely mesenchymal stem cells (MSCs), then identifies and corrects errant genes to allow a population of gene corrected cells to be expanded *ex vivo* and administered back to a patient, permanently correcting the mutation and thus the disease. Therefore, it is apparent that by 2030, healthcare will be characterised by the convergence of e-health, genomics and applications of stem cells in regenerative medicine.

### Routine application of regenerative medicines

Few areas of medical research have grasped public attention more than regenerative medicine, sustaining a cocktail of public hype, expectation and — in the case of embryonic stem cells (hESCs) — ethical concerns. However, as our understanding of the underpinning science and proof of efficacious patient outcomes grows<sup>5</sup>, the full ambit of regenerative medicine technologies — cell therapy, gene therapy, immunotherapy (iTx) and tissue engineering — is likely to become routine clinical practice in 2030. Perhaps most futuristically, this includes the alluring prospect of replacement engineered tissues and organs to address the shortages currently experienced.

**It is apparent that by 2030, healthcare will be characterised by the convergence of e-health, genomics and applications of stem cells in regenerative medicine.**

Tissue engineering, and the broader descriptor of regenerative medicine, has its origins in transplantation medicine, pioneered by Christiaan Barnard (first heart transplant) and Donnall Thomas (first bone marrow transplantation). However, today tissue engineering — supported by advancements in transplant immunology and 3D printing — has demonstrated utility in the production of tracheas, bladders, kidneys, skin, vaginas, ears, livers, blood vessels and, somewhat esoterically, hamburgers. Availability of replacement organs to the many rather than the fortunate few will result in higher quality of life and productivity for society as a whole. Additionally, unlike conventional pharmaceuticals, regenerative medicines are likely to require multiple pharma business models, thereby supporting novel structures and growth areas. Current pharmaceuticals are dominated by a universal business model focused on allogeneic (non-patient specific) products — 'pills in a box.' Conversely, due to fundamental immunological challenges, including graft vs host disease (GvHD), regenerative medicines are likely to sustain both allogeneic and autologous (patient specific) products, following a transplant model. Therefore, the 'product-plus' offerings of 2014 are likely to grow in importance and breadth in the healthcare systems of 2030.

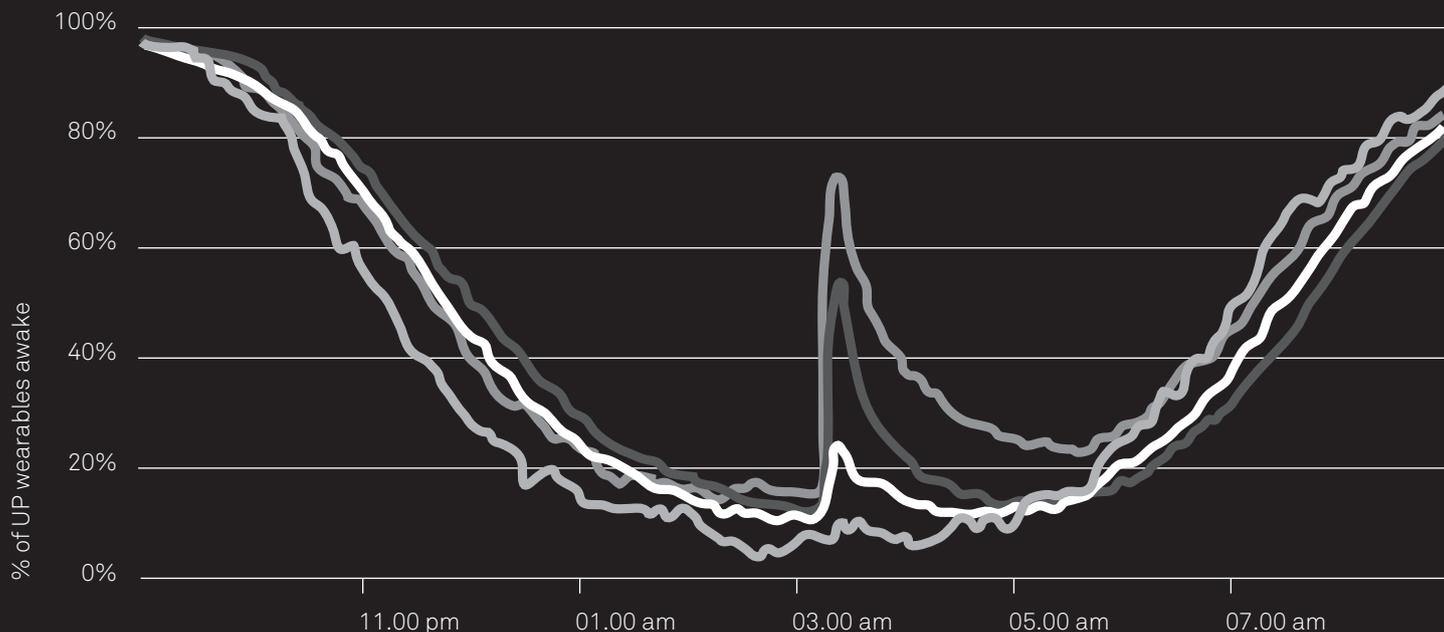
Jawbone data capturing the users' responses to the Californian earthquake

● Napa, Sonoma, Vallejo, Berkeley  
0 – 25 mi

● San Fran, Oakland, Santa Rosa  
25 – 50 mi

● Sacramento, San Jose  
50 – 75 mi

● Modesto, Santa Cruz  
75 – 100 mi



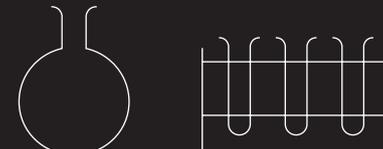
## Conclusion

Accurately extrapolating the impact of healthcare trends decades into the future is challenging. However, there is little doubt that the technological triumvirate of e-health, genomics and regenerative medicines will have a profound and transformative effect on future patient outcomes, not least through the integration of these technologies into 'product plus' offerings.

In merely the last decade, genomic sequencing has been translated from human curiosity into tractable solutions at a pace that has far outstripped Moore's Law. Concurrently, the expectations of patients and payers have changed, with people now wishing to be active for longer. Therefore, the pre-eminent mantra in healthcare translation — '(lab) bench to bedside' — is under threat as healthcare in 2030 may best be described by the mantra '(lab) bench to bicycle'.

## References

- 1 Adherence to long-term therapies — Evidence for action, World Health Organisation (2003)
- 2 Horne, R., Concordance, adherence and compliance in medicine taking. *Report for the National Coordinating Centre for NHS Service Delivery and Organisation R&D (NCCSDO)*, (2005)
- 3 Eichler, H.G. et al, EMA, Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval. *Clinical Pharmacology & Therapeutics*, **91 (3)**, 426–437 (2012)
- 4 The case for personalised medicine. *Personalized Medicine Coalition*, **4<sup>th</sup> Edition** (2014)
- 5 Bingel, U. et al, The Effect of Treatment Expectation on Drug Efficacy: Imaging the Analgesic Benefit of the Opioid Remifentanyl. *Science Translational Medicine*, **3 (70)**, (2011)



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# The psychological perspective on the role of personalised medicine

BY **ANDREW MARTELLO**, SPOONFUL OF SUGAR

When George Orwell, writing in the 40s, looked ahead to 1984 in his dystopian novel, many of his predictions focused on the ‘behaviour modification’ of his hero Winston Smith by a terrifying authoritative state.

Orwell’s vision of a totalitarian state didn’t mention a Ministry of Health (Minihealth, perhaps?), but I think it’s safe to say that modifying people’s behaviour will occupy an increasingly important place in healthcare innovation and delivery as we head towards 2030.



Thankfully, this won't be in the hands of a manipulative, unfeeling 'Big Brother'; the current zeitgeist of modern medicine is focused firmly on the democratisation of medicine, increased individual autonomy, informed choice, and decision-making. Put simply, it's about putting the patient first. While we should applaud this shift, the success of these strategies in practice will be determined by the behaviour of a multitude of stakeholders, none more so than patient and clinician.

A report published by the World Health Organisation in 2003 concluded that between a third and a half of medicines prescribed for long-term conditions are not taken as directed<sup>1</sup>.

Assuming these prescriptions were appropriate, this represents a significant loss to healthcare and a growing negative perception of the 'real world' efficacy of innovative treatments.

It has become increasingly clear why this gap between prescription and real-world efficacy exists. There is a well-established body of evidence indicating that behaviour is the rate-limiting step between healthcare innovation and optimal health gains.

And this is perfectly exemplified when we look at patient adherence to prescribed treatments. This behavioural gap is driven at a very fundamental level by erroneous beliefs related to health, illness and treatment. Together, these beliefs represent the root cause of the most significant fault line in modern medicine — adherence to self-management and treatment recommendations<sup>2</sup>.

Healthcare in 2030 will need to have solved these underlying challenges, so we can effectively transition innovative medicines from lab to bedside by taking full account of the patient's perspective.

So how will we achieve this and what will it look like? Firstly, drug manufacturers will apply the same scientific rigour and systematic development that has historically been reserved for treatments to the business of understanding how and why people behave in relation to their treatment. And I posit that this should be addressed

through a further evolution of the novel adaptive licensing strategies currently being trialled in Alzheimer's disease and breast cancer. One thing's for certain, however; these efforts will require cooperation between a wide range of stakeholders. These include the organisations that influence patient access and acceptance to medicines (such as the EMA and other medicines regulators), the pharmaceutical industry, health technology assessment bodies, and organisations issuing clinical treatment guidelines.



Crucially, it will also include patient and consumer organisations, healthcare professionals, researchers and academics<sup>3</sup>. Achieving this virtuous network of stakeholders will be the first critical step in achieving personalised medicine from both a clinical and psychological perspective. Which brings me to my next gaze into the crystal ball. In contrast to Orwell's grim foretelling, healthcare in 2030 will recognise that people do not arrive at a medical encounter as programmable machines, ready to receive instructions which they will execute to perfection. Each individual will arrive with their own set of ideas about their illness and its treatment. Many will have doubts and most will have concerns. These barriers — combined with a multitude of practical barriers — will influence their ability, capacity, resources and motivation to start and continue with treatment<sup>2</sup>.

By 2030, utilisation of simple yet well-established principles of behavioural medicine and health psychology will provide the key to delivering individualised treatment<sup>2</sup>. Once fully operationalised, these strategies will unlock the barriers to achieving the very best outcomes for patients.

**“It has become increasingly clear why this gap between prescription and real-world efficacy exists.”**

Each individual being treated for a long-term condition will receive a fully-tailored care package, both clinical and psychological. Healthcare providers, regulators and the pharmaceutical industry will be fully engaged and committed to delivering a 'product plus' solution that is tailored to each individual's needs.

I make no apology for my optimism here. Two millennia ago, we were looking at each person's balance of four different humours to individualise their treatment, and today's technology has brought us ever closer to exquisite precision in disease diagnosis and treatment<sup>4</sup>.

So in 2030, patients will be screened to receive customised healthcare using molecular analysis — with medical decisions, practices, and/or products being tailored to the individual patient. In this model, diagnostic testing will be employed to select appropriate and optimal therapies based on the context of a patient's genetic content<sup>4</sup>.

Critically though, patients will also be screened to understand their illness perceptions, beliefs about medicines, and their psychosocial support, information, and educational needs. Patients will also be assessed to understand their preferred communication channels.

A prospective package of tailored support will instantly be reflected back to the patient and (with full informed consent) shared with their multi-disciplinary healthcare team and the healthcare provider.

“I think it’s safe to say that modifying people’s behaviour will occupy an increasingly important place in healthcare innovation and delivery as we head towards 2030.”

And what will become of this data? It will serve a number of purposes. The patient will receive a fully-individualised care package designed to support optimal engagement to the treatment. This will be delivered through a range of channels including HCPs, personal wearable devices, smartphones, tablets, computers and smart televisions.

These care packages may even extend to gymnasium memberships and employers (without straying too far into Big Brother territory!). At a macro-level, aggregated data will be sent to health departments and will contribute both to our broader understanding and to a constantly evolving healthcare policy at a population health level.

Research into digital health behaviour will be ubiquitous by 2030 and there will be a more precise understanding of the human-technology interface. Predictive computer modelling will allow early warning signals to detect imminent health risks and monitor patients throughout their treatment pathways. In real-time, care packages will be adapted to continue to meet the needs of the patient.

Motivational and behavioural change techniques will be integrated within interventions that incentivise the patient to adopt more positive health behaviours. Adherence to lifestyle and treatment recommendations will reap rewards, such as reduced health insurance premiums, gym memberships and dietary discounts.

While the autonomous patient self-manages away from the clinic, clinicians can prepare themselves for more efficient and concordant consultations and medical interventions with the array of data at their fingertips.

And the role of the clinician should not be underestimated in 2030. We will never replace the therapeutic effect of a good clinician, and even the most independent patients want and need contact with doctors, nurses and pharmacists. While the reasons for this may seem obvious, healthcare in 2030 will, in full knowledge of the research, be harnessing the power of the non-specific, placebo effects of treatment<sup>5</sup>.

In democratised healthcare systems of 2030, healthcare budgets will be vastly more efficient than those of today. Of course, such personalisation of medicine comes at a price, but the status quo is greatly more expensive, with poorer outcomes for patients.

It’s said that: ‘if you do what you’ve always done, you’ll get what you always deserved’. We cannot continue along our current path. In 2013, the global cost of non-adherence was estimated to be \$564 billion<sup>6</sup>. If this money could be reclaimed, along with the budgets allocated to our current ‘one size fits all’ care packages, then the funding of personalised healthcare in 2030 begins to look eminently achievable.

But all the money in the world will not make a difference unless regulators, industry, governments, healthcare providers and entrepreneurs begin to place the patient’s perspective at the core of their thinking.

This is the big ‘if’ that hangs over all of my predictions for 2030. Only when the patient’s perspective is understood will we begin to positively modify medicines-related behaviour and make the most of medical innovations.

## References

- 1 Adherence to long-term therapies — Evidence for action, World Health Organisation (2003)
- 2 Horne, R., Concordance, adherence and compliance in medicine taking. *Report for the National Coordinating Centre for NHS Service Delivery and Organisation R&D (NCCSDO)*, (2005)
- 3 Eichler, H.G. et al, EMA, Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval. *Clinical Pharmacology & Therapeutics*, **91** (3), 426–437 (2012)
- 4 *The case for personalised medicine. Personalized Medicine Coalition, 4th Edition* (2014)
- 5 Bingel, U. et al, The Effect of Treatment Expectation on Drug Efficacy: Imaging the Analgesic Benefit of the Opioid Remifentanyl. *Science Translational Medicine*, **3** (70), (2011)
- 6 Pharmaceutical Revenue Loss Due to Medication Non-Adherence Report, Capgemini Consulting (2012)



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# What do patients want?

BY NEIL COOPER

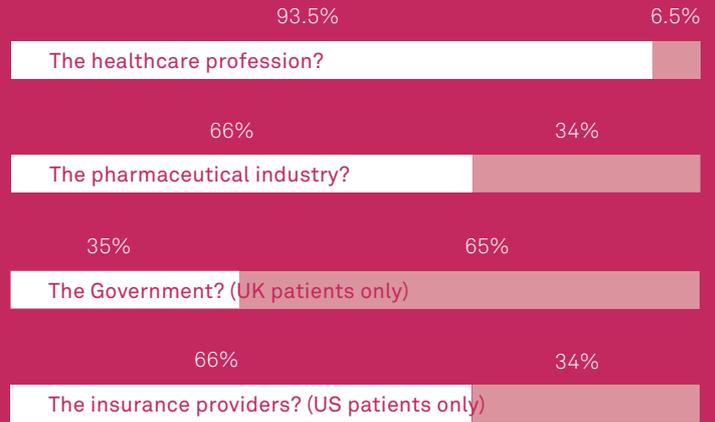
As a central part of our focus on 2030 we wanted to look at healthcare from the perspective of patients and doctors. In particular, we wanted to understand their experiences today and their expectations of the future. It was also important to us that we looked at the perspectives of people who rely on drugs, healthcare systems and medical devices the most — those suffering from chronic conditions such as arthritis, asthma, cancer, COPD or diabetes. And to get a rounded picture, we also asked the specialist doctors treating these types of patients. In our research, we sought the opinions of over 2,000 patients and 200 doctors, split across the US and UK.

The research focused on six key areas: patient trust, patient influence, patient confidence, patient concerns, the role of medical devices, and healthcare in 2030. Here are just some of the interesting findings.

## Patient trust

When it comes to your health do you trust...

■ Yes ■ No



Who would you be happy to share personal health data with?



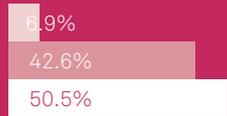
## Team / insight.

### Patient influence

How involved do you (or your patients) feel in your healthcare?

■ Not involved at all   ■ Slightly involved   ■ Very much involved

#### UK patients



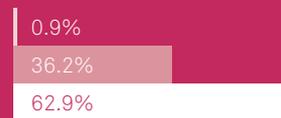
#### US patients



#### UK doctors



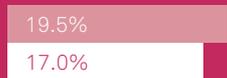
#### US doctors



Comparing: “Patients — do you want to be more involved in your healthcare?” and “Doctors — do patients want to be more involved in their healthcare?”

■ Patients   ■ Doctors

#### Yes, far more involved



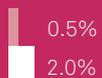
#### Yes, a little more involved



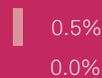
#### Happy with current level



#### No, a little less involved



#### No, a lot less involved



### Patient confidence

The % of patients who said they only needed minimal training when given new drug delivery devices compared with specialist doctors' opinions

■ Patients   ■ Doctors

#### Swallowing



#### Wearable patch



#### Nebuliser



#### Inhaler



#### Injector pen



#### Needle and syringe



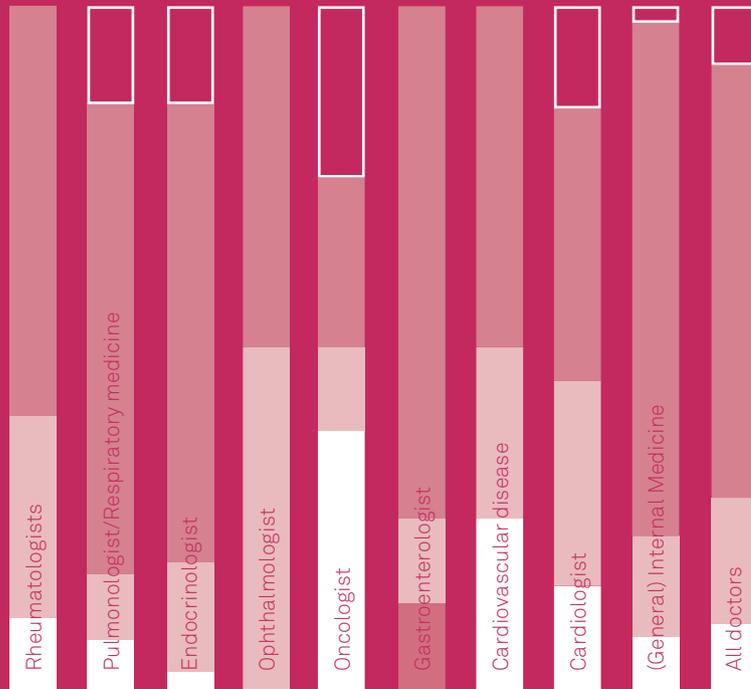
#### Wearable pump



**The role of medical devices**

A doctor's view on the importance of the medical device

- Not important
- Not very important
- Neither important nor unimportant
- Important
- A key factor



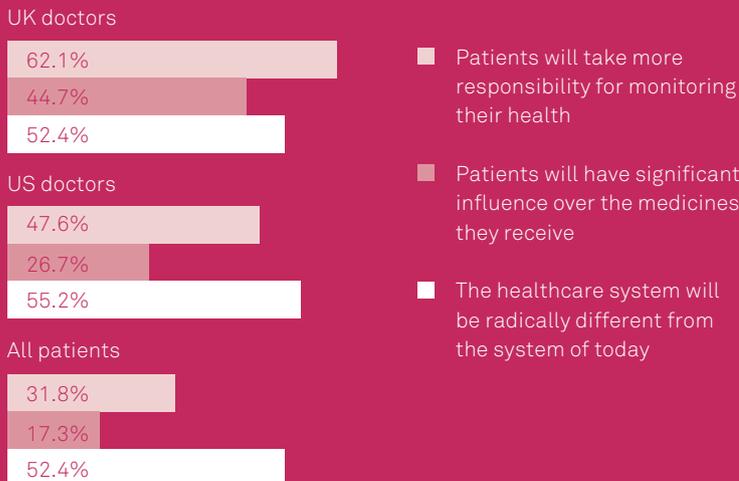
The results of our survey highlight the fragmented needs of patients. There is clearly a sophisticated group of people who want more involvement, more responsibility for managing their health and more influence over their medication, but this isn't a trend that can be applied to all.

As we look to the future, 2030 in particular, we (the industry and healthcare providers/ professionals) need to think about how we can offer the right healthcare for patients but in a way that makes commercial sense. There is no silver bullet and the results of our survey support this. There is a real driver to reduce the cost of healthcare, which will no doubt involve more patients taking more responsibility, and we need to look at how we can reduce the physical and cognitive burdens that could prohibit this behaviour.

The full results of our research are available in a 48 page report entitled 'Patient and Doctor Perspectives Survey', which can be downloaded from <http://te-am.co/patientreport>.

**Healthcare in 2030**

What do you expect to change about healthcare in 2030?



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 Neil is Head of Marketing at Team and is responsible for the company's marketing strategy, its external-facing profile and initiatives aimed at engaging with clients and influencers.

It's all about expectation. The digital era has continued to accelerate pretty much linearly since the advent of the first home computer in the early 80s, causing many of us to experience first-world problems on a daily basis (isn't it awful playing Candy Crush on your iPhone when you've run out of lives on your iPad?).

# Intelligent Inhalers

BY DAVID HARRIS

Smartphones and tablets caused computer and laptop sales to drop last year for the first time since they were introduced<sup>1</sup>. We use them for everything — and if there's something they can't do, no doubt it will appear in the next operating system release or an app for it is just around the corner...

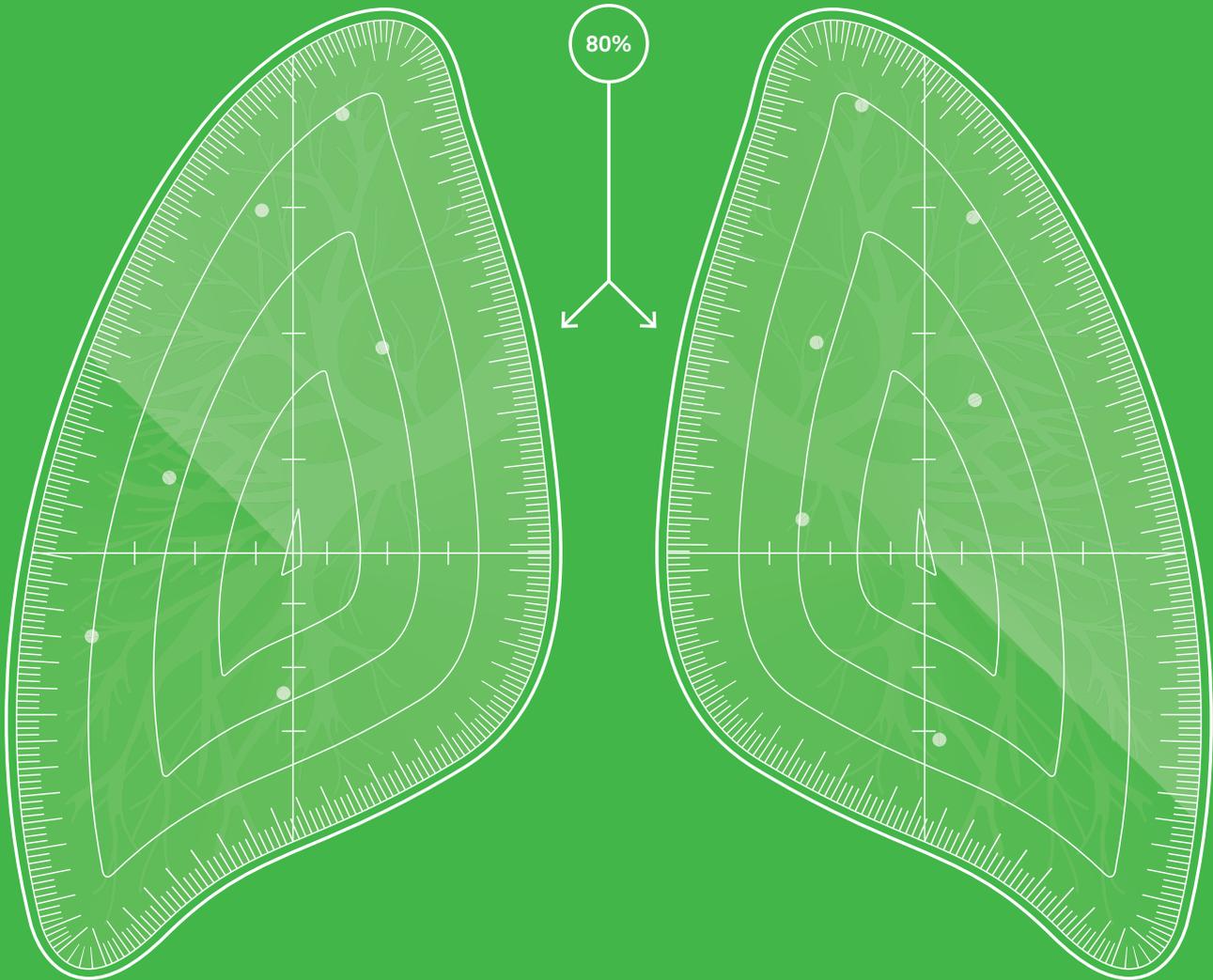
Let's contrast digital media with medical devices — specifically those for self-medication, such as inhalers and injection pens. These haven't really changed in the last 50 years, and simply enjoyed sustained innovation on a very, very incremental level. The drugs have changed and thankfully provide a better therapeutic response than ever before. But the devices haven't. Novartis' Onbrez

inhaler, for example, is an updated Cyclohaler; it looks better and is easier to use — but its performance is every bit the same as the device on which it is based.

So back to expectation. Patients rightly question why they can buy better smartphones and tablets year on year, with improved processors, cameras and interactivity, yet their inhaler is, frankly, dumb; a simple device, with no clever electronics, that's 100% reliant upon a pair of impaired lungs to create a 20% efficient aerosol. But roll on another 15 years or so to 2030 and there's a good chance that inhalers will be much smarter. The typical questions that patients ask today, such as 'Why can't my inhaler remind me when to use it?', or,

'How do I know if it's worked properly?' may well be answered as electronics continue to become smaller, cheaper and more powerful year-on-year. In 15 years' time, a huge amount of additional functionality will be possible for just a few extra cents.

So why don't these inhalers already exist, given that the idealised requirements are pretty straightforward? People are forgetful — they often unintentionally miss taking their medication at the correct time simply because they have busy lives and other more important things cause them to forget. The majority of experienced asthmatics cannot use their inhalers correctly — particularly pressurised metered dose inhalers



(pMDIs). Inhaling through a pMDI at a low enough flowrate to ensure optimal delivery efficiency is counterintuitive; it's very easy to inhale rapidly through a practically zero resistance pMDI, and as this technique gets the “event” over with as quickly as possible, it's what many asthma sufferers choose to do. Unfortunately, most of the drug lands in their mouth and throat, and consequently offers no direct therapy to the lungs, instead delivering rather unpleasant side effects such as allergic rhinitis and candidiasis. So an inhaler that can monitor the user's flowrate and provide feedback, possibly audibly (such as Clement Clarke's Flo-Tone pMDI accessory<sup>2</sup>), would be hugely beneficial to the patient.

The biggest single hurdle to making such improvements is the high level of regulation that is applied to medical products. Simply adding electronics to an inhaler under development isn't simple. An easier approach, already adopted by many manufacturers, is to produce an accessory; these don't have the same regulatory rigour applied to them, and therefore can be developed independently of a drug product. Nexus 6 produce a number of 'Smartinhalers', for example, to improve the use of various approved inhaler products<sup>3</sup>. For pharmaceutical companies the value is in the drug, not the device, and so only relatively recently have pharmacos accepted that inhalers and injectors are more than just 'packaging'.

The FDA's increasing concern about usability (Human Factors Engineering) has no doubt contributed to an increased interest in actually designing medical devices with the user in mind. If the user can't use the device properly, they don't get their drug, and so it's becoming more widely accepted that in order for a medical device to have the best chance of commercial success it must meet three basic requirements — it must be:

- 1 simple and intuitive to use — and difficult to use incorrectly
- 2 appealing — the patient should want to use it
- 3 robust — engineered to work properly in all possible usage environments

With the necessary skillsets — human factors engineers, industrial designers, engineers and scientists — it's usually possible to create a medical device that meets the three essential requirements, so why aren't there many more 'clever' inhalers in the market, or indeed undergoing development?

Well perhaps there are more in development than are in the public domain. There's certainly continued interest in improving patient adherence, and many companies are working on accessories and apps to bolster this. Propeller Health, for example, is developing an advanced app for the management of asthma and COPD, and recently raised \$14.5m in Series B funding<sup>4</sup>.

The other factor to consider is the cost of developing a new inhaler product. Whilst the initial development of new, or better, technology may cost a few million dollars, this absolutely pales in comparison to the cost of clinical studies — particularly Phase III, which can cost several \$100 million alone. In fact, according to Forbes, the total cost of bringing a new drug to market is thought to be over \$5 billion<sup>5</sup>.

So a clever inhaler that can increase the likelihood of correct use — both in the clinic and at home — has to be an attractive proposition, right? Better still

if it can also record how the patient is using it — providing direct feedback to help improve technique, and also providing clinicians with the highly valuable information they need to enable them to judge the effectiveness of the medication. An inhaler that can achieve this would no doubt reduce the size (and cost) of clinical trials, decrease time-to-market and potentially offer significant improvements to patient outcomes and quality of life. But why stop there? Why not design-in clever diagnostics? For example, if the inhaler, or accompanying app, can record the patient's inspiratory flow profile, it can also deduce inspiratory power and energy, pressure drop profile, inhaled volume, peak inspiratory flowrate and airflow acceleration. All of these parameters can be further analysed to assess lung function. For example, is the patient consistent in the way they use their inhaler? Do they generally have a stronger inspiratory profile in the morning compared to the evening? Is there a general improvement in their profile with continued use, suggesting that the medication is working? Or is there a general downward trend, suggesting that they might be better suited to a different drug product?

Most asthmatics and COPD sufferers would like, and would probably benefit from, intelligent inhalers that remind them when to take a dose and provide feedback to help them improve their inhalation technique, as if they dose more accurately to the lung they incur less throat deposition and consequential side effects.

One large hurdle that remains is fear of the regulators, as a fully electronic inhaler has not yet been approved (and although e-cigarettes are commonplace, only very recently has the FDA put a proposal in place to regulate them<sup>6</sup>). At some point there will be regulator-approved electronic inhalers prescribed in the market, but trying to predict when is crystal ball gazing — as there are so many influencing factors. Unfortunately, asthma and COPD are very much on the rise globally, and the total cost of treatment will escalate accordingly

(COPD is expected to cost \$4.8 trillion globally by 2030<sup>7</sup>). In order to combat this, there will probably be a further push from the payers to improve adherence, potentially even leading to payment by results approaches.

At some point, patient expectation will also drive market demand — the first company to crack this rather expensive nut will undoubtedly set a precedent for future inhaler products — and, as we all know, the regulators only ever bring the goalposts closer together...

## References

- 1 'PC sales see 'longest decline' in history', 11 July 2013, BBC News, <http://te-am.co/1nK4x8J>
- 2 'New In-Check Flo-Tone Trainer', Clement Clarke International, <http://te-am.co/10vh0ml>
- 3 'Smartinhalers', Smartinhaler by Nexus 6, <http://te-am.co/1tACUj3>
- 4 'How it Works', Propeller Health, <http://te-am.co/1tZvTKX>
- 5 'The cost of creating a new drug now \$5 billion, pushing big pharma to change,' 11 August 2013, Forbes, <http://te-am.co/1xwgdX>
- 6 'Tobacco Products: Deeming — Extending Authorities to Additional Tobacco Products', FDA, <http://te-am.co/12SGds0>
- 7 'The Global Economic Burden of Non-communicable Diseases', Harvard School of Public Health and World Economic Forum, <http://te-am.co/costs2030>



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# A billion by 2030? Can we turn the tide against diabetes?



BY CHRIS HURLSTONE  
& THOMAS GRANT



“If commitments are merely words on paper, diabetes will continue to cause 4.8 million deaths a year and result in avoidable disease, disability and suffering for millions more.”  
Global Diabetes Scorecard, IDF 2013<sup>6</sup>

## Current projections

In 2004, the World Health Organisation (WHO) and International Diabetes Federation (IDF) projected that the number of people living with diabetes in 2030 would more than double in the following 25 years to reach a total of 366 million<sup>1</sup>. This figure, taken from the joint publication Diabetes Action Now, cited an ageing population and increasing urbanisation as primary causes for the increase.

Today, ten years on from this initial projection, there are approximately 382 million people currently diagnosed and living with diabetes worldwide, 16 million more than projected in 2004 for the year 2030, and we aren't even halfway there<sup>2</sup>.

The latest estimates from the IDF's Diabetes Atlas posit that by 2035 there will be 592 million people aged 20–79 years — one adult in ten — with the disease<sup>2</sup>.

Diabetes  
accounted for  
**\$548 billion**  
of global health  
expenditure in  
2013, equivalent to  
11% of total health  
spending on adults



Furthermore there are 316 million people currently at high risk of developing type 2 diabetes, which accounts for 85–95% of all diabetes, and this number is expected to increase to 500 million within a generation. Given these figures, and the massive underestimation in previous predictions, we could be faced with a total of 1 billion people of all ages living with diabetes in the year 2030.



### Cost, and the need for action

Described as a 'profound concern' in the 2011 United Nations (UN) Political Declaration on Non-communicable Diseases (NCDs), diabetes is among the leading causes of preventable morbidity and related disability across the globe<sup>3</sup>. In 2013, 5.1 million people died as a result of the disease, and many more suffered associated complications such as blindness, renal failure and amputation. Significant action is therefore required to address the inconceivable yet preventable level of suffering due to diabetes projected for 2030 and beyond.

The human cost of the disease, to individuals and their families, is staggering enough but so is the impact on health economics. Type 2 diabetes is the most expensive disease in the United States, costing \$245 billion in 2012<sup>4</sup>. In the UK, current spending on direct patient care is an estimated £9.8 billion (£1 billion for type 1 diabetes and £8.8 billion for type 2 diabetes), or about 10% of the overall NHS budget<sup>5</sup>. Globally, diabetes accounts for \$548 billion, which is 11% of total health spending on adults.

**More than 21 million** live births were affected by diabetes during pregnancy in 2013

**Every six seconds** a person dies from diabetes

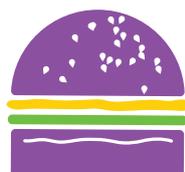
### So how do we tackle this global problem?

Clearly, any solutions must cross industry sectors, with pharmaceutical companies and healthcare systems worldwide playing a significant role, but policy, education and public campaigns to disseminate vital information are equally important.

In September 2011 at the UN Summit on NCDs, governments across the globe pledged to improve diabetes prevention, treatment and management. As an output to the summit, the IDF developed a Global Diabetes Scorecard to track the progress for action across a number of areas and in anticipation of the scorecard's publication later this year, we explore some of the latest developments with a particular focus on education, prevention and treatments.

**80% of people with diabetes live in low and middle income countries**

**NHS spending on diabetes will reach £16.9 billion by 2035, amounting to 17% of its entire budget<sup>5</sup>**



### Education and policy

The link between type 2 diabetes and lifestyle — particularly exercise and diet — is unequivocal, and leads directly to opportunities for prevention, with education on diabetes and its complications having a significant role to play, and from an early age. For example, in August 2014 a joint initiative between the IDF, the Juvenile Diabetes Association of Brazil (ADJ) and Sanofi Diabetes launched the KiDS (Kids and Diabetes in Schools) project which will run in 15 public and private schools across Sao Paulo and Ceara, and will explain the basics of diabetes and stress the importance of physical activity and diet<sup>7</sup>. The KiDS project is also being piloted in Delhi, India, and will be made available to download in eight different languages.

In the UK, the online 'Diabetes Risk Test', developed by Diabetes UK, enables users to assess their risk of developing type 2 diabetes and identify appropriate next actions<sup>8</sup>. Increasing the accessibility and ease with which society can engage with such tools and information helps 'join up' different aspects of the healthcare system, and hence tackle the issue of early diagnosis and prevention.

Diabetes education, however, also needs to address prevention, as while advances in treatments continue, halting the projected rise in sufferers is of paramount importance.

Preventing type 2 diabetes has to begin with lifestyle changes — a reduction in physical inactivity and an increase in healthy eating. This is supported by the UN's 2011 declaration on NCDs which called for a 'national systems response' ranging from the accessibility of technologies and medicines to policies against the provision and marketing of saturated fatty foods<sup>9</sup>.

**One adult in ten will have diabetes by 2035**

### 'A national systems response'<sup>9</sup>

'Availability and affordability of quality, safe and efficacious essential non-communicable disease medicines, including generics, and basic technologies in both public and private facilities.'

'Policies to reduce the impact on children of marketing of foods and non-alcoholic beverages high in saturated fats, trans-fatty acids, free sugars, or salt.'

'Adoption of national policies that limit saturated fatty acids and virtually eliminate partially hydrogenated vegetable oils in the food supply, as appropriate, within the national context and national programmes'.

The WHO cites physical inactivity as the fourth leading risk factor for global mortality, the cause of 6% of all deaths and the chief factor in 27% of all cases of diabetes<sup>10</sup>.

This link between type 2 diabetes and a sedentary lifestyle might imply that the disease is most common in well-developed, high-income economies but as Figure 1 (overleaf) shows, this is far from the case.

## 5.1 million deaths in 2013 were caused by diabetes



### Insulin based treatments

#### Devices

Once prevention has failed, constant treatment is required, with the injection of insulin now used by the majority of sufferers to control their type 1 diabetes. And treatments have come a long way.



Perhaps the most exciting technical advances in recent years relate to the development of potentially the ultimate treatment solution — the Artificial Pancreas (AP). While this sounds like a new body organ, it is actually a sequence of interlinking external technologies, such as sensors and pumps. 'On the horizon' for some years, significant progress is now being made and at the 2014 ATTD Conference, a number of studies of AP systems were reported — with ambulatory rather than solely clinical trials — with many positive results. All the key device elements are available, such as pumps and sensors, plus mobile technologies that allow use of application software, cloud connectivity, data sharing and analysis. Not all technical elements are equally mature, nor approved to the same level, so further consolidation is required, including development of control algorithms, error detection and fault management. The usability of these devices also requires serious ongoing consideration, such as the need for regular calibration or whether such devices should be used continuously or only overnight, when the majority of severe hypoglycaemic events are known to occur.

Many AP developments have resulted from collaborations, often across industry and academia, but this has proved a slow route to market; large organisations such as Medtronic and Roche now have the resources, expertise and core technologies required to make the next step. The biggest hurdle, however, may be regulatory, and the need for agreement on device classification (including supporting technologies and peripherals) and risk profiles; the development of standards and requirements (e.g. for continuous glucose monitoring); and extensive clinical trials to prove that

AP systems are safe and do not lead to unintended harm due to malfunction or otherwise. All of which will take time and commitment, and funding.

There has been some interest, primarily in Europe, in implantable pumps, but the focus is primarily on wearable pumps, and AP systems can form a part of this broader trend. The first approved and commercially available AP could still, however, be years away.

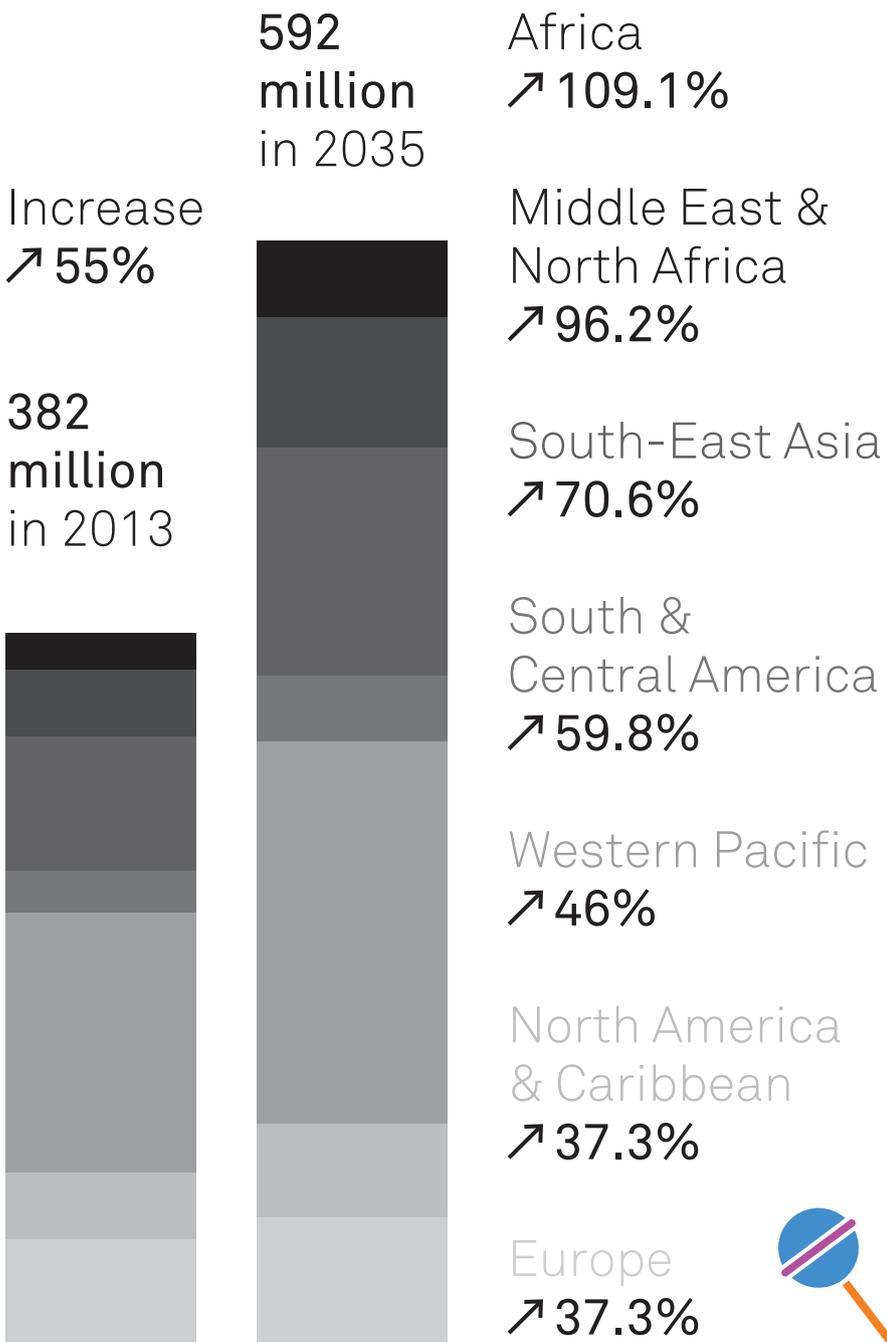
In the meantime, well-established individual device technologies for sensing, monitoring and drug delivery continue to be developed, refined and combined with ever increasing functionality. Continuous glucose monitoring (CGM) systems, an alternative to the traditional finger prick / test strip approach, are available and can improve self-management and prediction / prevention of hyper or hypoglycaemia via trending data that can forewarn a patient using an alarm. Dexcom's Gen 5 CGM is one such system and also an example of separate technologies and organisations combining as it will soon be able to link — via a Bluetooth-based mobile app — to the OmniPod pump and Personal Diabetes Manager system from Insulet.

An alternative, new non-invasive sensing technology, which may reach the market by 2030, is incorporated into a contact lens. Developed by Google and licensed in July 2014 by Novartis, the system is exciting, but will need to be accurate; not all current

## More than 79,000 children developed type 1 diabetes in 2013



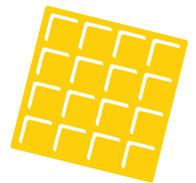
# Figure 1: Predicted global growth in diabetes<sup>2</sup>. People living with diabetes:



blood glucose monitors meet the increased accuracy levels mandated in the updated version of ISO 15197. The cost of these new technologies, and hence their availability to patients, will also be an issue.

In the pen injector market, new devices such as AllSTAR<sup>®</sup>, JuniorSTAR<sup>®</sup>, HumaPen<sup>®</sup> Memoir<sup>™</sup> and NovoPen<sup>®</sup> 5 demonstrate how technology continues to develop to meet the expanding needs of diabetes therapy. These devices offer new features such as 0.5 IU discrete doses for paediatric use, 80 IU dose capacity in disposable pens, on board electronic aids for improved compliance, increased accuracy, reduced operating forces, and lower cost versions for developing markets. As we move towards 2030 we can expect continued performance improvements and enhancements.

In addition, new alternative technologies are emerging. Needles continue to improve, providing reduced pain on injection, which can also lead to improved compliance and acceptance of insulin therapy by people with type 2 diabetes. Studies on intradermal injections of insulin through micro-needles also show promising results, albeit at very early stages.



## Insulin formulations

Harvested from animal pancreases, today's insulins are complex, recombinant formulations and ongoing developments and refinements continue. Ultra-long and ultra-fast acting formulations, such as Tresiba<sup>®</sup> and FIAsp from Novo Nordisk, help patients cope more easily with daily requirements for background basal dosing and deliver an effective, fast response to rapid fluctuations resulting from food intake or physical activity. But, as for all drug products, the development process is lengthy and the drug needs to demonstrate safety as well as efficacy. Although approved in Europe and Japan, the US launch of Tresiba<sup>®</sup> was delayed in 2013 because of FDA concerns regarding cardiovascular safety. The next couple of years



will see the patents for some current insulin formations, such as Lantus® and NovoLog®, expiring. Although the biologic nature of the drug means that generic versions are unlikely to flood the market, this milestone could increase choice and reduce costs.

A major development in 2014 was the return of inhaled insulin. Recent FDA approval for MannKind's dry powder formulation Afrezza® was followed by a licensing agreement with Sanofi for development and commercialisation, potentially as early as 2015. Meanwhile companies such as Oramed and Merrion continue to develop oral dosage forms of insulin. These are much further away from commercialisation, but by 2030 we can expect to see a range of well-established alternatives to self-injection.

However, given the enormity of the challenge faced, what impact can these technological developments have on the overall picture?

From an engineer's perspective, battling to limit the impact of diabetes — on individuals and healthcare systems alike — feels as much a challenge as trying to stem the relentless increase in entropy. Treatment of diabetes is a constant battle against uncontrolled glycated haemoglobin, HbA1c, and current technology advances can at best only help maintain the status quo, preventing or slowing further deterioration. The disease is multi-faceted and can behave differently every day making it incredibly difficult for even the most diligent of patients to control. Significant improvements are precious but few and far between, and although new and improved technologies have the potential to improve quality of life and control the debilitating effects of diabetes, they cannot stop or reverse them. The best opportunities for this may lie elsewhere, with alternative treatments rather than new technologies.

### Alternative treatments

First developed in the 1950s, bariatric surgery (such as bypassing the small intestine) is effective as an obesity treatment. Studies now show, however, that it can also control — and prevent — the onset of, type 2 diabetes. A number of alternative surgical techniques have also been developed, with studies (including one published in the Journal of

American medicine 2013<sup>11</sup>) showing that these can provide significant positive outcomes, sometimes including full remission. Yet currently only 1% of those who could benefit from this therapy can access it, primarily due to health economics but also the view that interventional surgery poses more risks than benefits. These concerns are now being challenged; for example, a BMI of 35–40 is currently the limit below which bariatric surgery is not prescribed, but it is anticipated that benefits including prevention of diabetes onset, can be delivered for patients with lower BMIs.



Researchers looking into potential new treatments for type 1 diabetes are now considering chemical entities such as GLP analogues and anti-C3 monoclonal antibodies, stem cells and genetic engineering. Although at times seemingly bordering on science fiction, it is advances in these areas that may provide the opportunity to finally turn the tide against diabetes.

Fifteen years is a long time even in the pharmaceutical industry, so 2030 still seems too close for us to make accurate predictions about diabetes control. What is absolutely clear, however, is that in the meantime we must use all the tools at our disposal to improve prevention and treatment globally, and hopefully challenge current estimates for the future.



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### References

- 1 Diabetes Action Now: An initiative of the World Health Organisation and the International Diabetes Federation, WHO 2004, <http://te-am.co/1teAale>
- 2 IDF Diabetes Atlas, Sixth Edition, International Diabetes Federation 2013, <http://te-am.co/1x8Jmwl>
- 3 Draft Political Declaration of the High-level Meeting on the prevention and control of non-communicable diseases, 7 September 2011, <http://te-am.co/1otGyLR>
- 4 Advanced Technologies and Treatments for Diabetes (ATTD) Yearbook 2013, Fifth edition, p 169
- 5 'NHS Spending on diabetes 'to reach 16.9 billion by 2035', 25 April 2012, Diabetes UK, <http://te-am.co/1wkbuOm>
- 6 IDF Global Diabetes Scorecard, 2014 <http://www.idf.org/sites/default/files/Scorecard-3%202.pdf>
- 7 Kids and Diabetes in Schools (KiDS) Project, International Diabetes Federation 2013, <http://te-am.co/1nyYeVl>
- 8 Diabetes Risk Score, Diabetes UK 2013, <http://te-am.co/1vMHA6j>
- 9 Draft comprehensive global monitoring framework and targets for the prevention and control of noncommunicable diseases, Sixty-Sixth World Health Assembly, WHO 2013, <http://te-am.co/1zktcPC>
- 10 Physical activity, Fact sheet No385, WHO 2014. <http://te-am.co/1wk0fj>
- 11 Ikramuddin S. et al, Roux-en-Y Gastric Bypass vs Intensive Medical Management for the Control of Type 2 Diabetes, Hypertension, and Hyperlipidemia. Journal of American Medicine 309(21), 2240–2249 (2013).



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# NEVER MIND THE BIOSENSORS

BY BEN WICKS

RARELY A DAY GOES BY WITHOUT A STORY APPEARING IN THE MEDTECH MEDIA ABOUT A NEW WEARABLE SENSING TECHNOLOGY, MINIATURISED DIAGNOSTIC DEVICE OR MEDICAL SMARTPHONE APP. IT WOULD SEEM INEVITABLE THAT IN 15 YEARS' TIME YOU WON'T NEED TO GO TO YOUR DOCTOR TO BE DIAGNOSED. INSTEAD EITHER YOUR WEARABLE SENSORS AND IPHONE WILL LET YOU KNOW THE MINUTE SOMETHING'S WRONG, OR YOU'LL SPIT INTO A DIAGNOSTIC USB STICK WHEN YOU'RE FEELING UNWELL.

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**THERE WILL UNDOUBTEDLY BE SOME SIGNIFICANT ADVANCES IN SENSING AND DIAGNOSIS OVER THE NEXT 15 YEARS, BUT MUCH OF WHAT IS TOUTED IN THE MEDIA SIMPLY DOESN'T STACK UP FROM A CLINICAL, REGULATORY OR COMMERCIAL PERSPECTIVE. THE AIM OF THIS SHORT ARTICLE IS TO EQUIP YOU WITH SOME ADDITIONAL INSIGHTS TO HELP YOU SIFT OUT THE PLAUSIBLE FROM THE IMPOSSIBLE.**

We'll start by considering the frequency of measurement and whether a measurement is non-invasive or invasive, then we'll look at implants and the feasibility of home testing before concluding with my thoughts about the future of diagnostics over the next 15 years.

#### HOW OFTEN?

Lots of measurements are only made once, or very infrequently. Whereas you don't need to test a patient for their blood type more than once, a diabetic will need to measure their blood glucose several times a day over their entire life. These are obviously extreme examples, but it's really important to be cognisant of both how often a measurement can be made and how often it needs to be made.

Technology development, miniaturisation and cost reduction over the last 20 years has made it possible to make some measurements on a frequent or even continuous basis. For example, it is now possible to attach sensors to a patient to measure their blood pressure, breathing rate, heart beat and blood oxygenation continuously. Over the last five years, it has been increasingly possible for these measurements to be processed, logged and uploaded to the cloud via smartphones.

An important attribute of these physiological measurements is that they can be made non-invasively (without breaking the skin) and using sensors which don't get worn out or used up — they can keep taking measurements indefinitely. However, there's a limit to what you can diagnose simply using physical measurements such as pulse rate, blood pressure and blood oxygenation. Whilst a smartphone connected to the cloud can do a great deal of signal processing and analysis, there still remains a fundamental limit to what you can detect using non-invasive sensors.

#### TO STAB OR NOT TO STAB?

Some tests will always need access to the blood. For example, if you want to do a full blood count or check someone's biochemistry then you have no choice but draw some blood to test. A lot of resource has been invested in trying to develop non-invasive biochemical measurements but unfortunately this is extraordinarily difficult to achieve. Pulse oximetry is the exception, since haemoglobin conveniently undergoes a large colour change when oxygenated and there's lots of haemoglobin in blood. Frustratingly, most other analytes, such as glucose, are far less amenable to non-invasive monitoring. Billions of research dollars have been spent fruitlessly chasing the holy grail of non-invasive blood glucose measurement over the last 25 years and even the newest blood glucose sensors, such as Abbott's new FreeStyle Libre Flash Glucose Monitoring System, still need to be placed under the skin.

#### WHAT IF WE IMPLANT TINY SENSORS INTO THE BODY?

As far back as 1987 the renowned biomedical futurologist Steven Spielberg brought us 'Innerspace' — portraying a future of implanted miniaturised devices, albeit with a fair degree of artistic license and a flagrant disregard for research ethics. Almost 30 years have passed and tremendous advances have been made in sensor technology and microfabrication, but implantable sensors still aren't the answer to diagnosing most diseases.

If you just want to make a simple physical measurement then there's a chance that you can do it with an implantable sensor. For example, CardioMEMS (now St. Jude Medical) has developed a miniaturised blood pressure sensor which is permanently implanted inside the pulmonary artery. The sensor is embedded inside a tiny glass brick — the size of a grain of rice, and delivered via right heart catheterisation and fixed to the inside wall of the pulmonary artery. The

**‘HEY DOC, I’VE JUST DIAGNOSED MYSELF WITH A COOL NEW GADGET, COULD YOU WRITE ME A PRESCRIPTION FOR THESE DRUGS THAT WIKIPEDIA SAYS I NEED?’**

sensor is interrogated from outside the body and enables clinicians to regularly and accurately monitor pulmonary artery pressure and detect impending heart failure.

However, if you want to make a chemical or biological measurement then it’s exceedingly challenging to use an embedded sensor, and one of the biggest problems is that foreign material attracts clotting blood, gets attacked by the immune system and is eventually encapsulated by the body. This is OK if you’re measuring blood pressure but it’s a show stopper if you’re trying to make an optical measurement or if you need circulating blood to come into contact with your sensor. Clever coatings can minimise fouling but all surfaces will inevitably end up coated to some extent. The other big problem with embedded biosensors is that most sensors use biological molecules to recognise and bind to the target of interest.

These biological molecules, such as antibodies or proteins, are inherently fragile. For example the antibodies attached to a pregnancy test strip are stable for two years in a dry package on the shelf in Walmart but won’t last more than a few hours inside your body. This means that the vast majority of biological and biochemical sensors can’t be implanted in the body.

**‘OK, BUT SURELY WE’LL BE DOING LOTS OF DIAGNOSTIC TESTS AT HOME IN 2030?’**

Companies such as CUE would have you believe that’s the case. This US start-up company claims to be ‘creating the most advanced consumer health product ever seen’ which will allow consumers to measure five parameters in their own home, including vitamin D, testosterone, fertility hormones and influenza. The CUE promotional video is very nicely produced and the industrial design is nothing less than you’d expect

from a Californian tech company, but I suspect the underlying premise is flawed and won’t ‘open up an entirely new world of possibilities for understanding and improving our health’. I’m sure CUE will sell some devices to the wealthy-worried-well with a penchant for new technology, but I don’t expect this or other similar products to have an immediate and lasting impact on healthcare provision for a number of reasons.

Firstly, cost of goods will always be a challenge. Consumers are extremely cost sensitive and history suggests that the overheads of producing diagnostic tests to the standards required by regulators are very burdensome. Costs from QA, QC, calibration, in-process controls, regulatory compliance and process validation put enormous pressure on margins.

Secondly, home diagnostic products are often trying to address needs that

don't really exist. I'm not convinced that consumers will really continue to spend both time and money in order to monitor their vitamin D or testosterone levels once the novelty wears off. And if a diagnostic test tells me I have influenza then what can I do about it? I feel too ill to go to work anyway, my family can't exactly move out, and there aren't any antiviral therapies worth taking.

Thirdly, the implications of integrating home use diagnostics with existing health care services are not straightforward and will take time to be established. I'm not sure how my GP would react to a call from me saying: 'Hey doc, I've just diagnosed myself with a cool new gadget, could you write me a prescription for these drugs that Wikipedia says I need?'

Lastly, the idea of home use diagnostics isn't new. The iSTAT point-of-care diagnostic system (acquired by Abbott in 2003) has been available for over 18 years, and it is naïve to think that the world's big diagnostic companies haven't stopped to consider the potential of home diagnostics market during the last 20 years; every one of them will have commissioned a marketing initiative or two with the aim of exploring the potential of home use diagnostics. On top of that, hundreds of small diagnostic start-up companies have claimed that their particular spin on point-of-care diagnostics is the key to unlocking this vast untapped market. Yet companies large and small have generally failed to find a new and significant convergence of unmet need, clinical practice, health economics and technology. Yes, there are some niche applications beyond blood glucose, urine dipsticks and pregnancy testing, but it rarely makes sense to do complex clinical diagnostics in the physician's office rather than the hospital, or at home.

Don't get me wrong, I'm full of admiration for the diagnostic innovators and entrepreneurs at companies such as CUE who are

building on the knowledge gained in the last 20 years to extend our current and future capabilities. Even if they don't achieve all of their goals they will certainly pave the way for future innovators. However, I do suspect a fair few CUE devices will end up gathering dust at the back of cupboards, along with the odd Nokia Communicator, DAT player and abandoned ice cream maker.

### **'OK MR SCEPTICAL, SO WHAT DO YOU THINK WE'LL BE DOING IN 2030?'**

My personal hunch is that we will see advances in sensing, microfluidics, signal transduction and MEMS technology having the greatest impact on testing in central laboratories, not in the home or doctor's office. Central labs are where the vast majority of clinical diagnostic tests are currently performed, and these facilities can afford large automated systems, negotiate significant volume discounts on reagents, have QC/QA procedures in place and are already integrated with hospital information systems.

If new technologies can significantly reduce costs, through miniaturisation and multiplexing, then it may be economically viable to test the general population on a regular basis for a whole panel of biomarkers, detecting diseases earlier and allowing preventative action to be taken.

This is generally too expensive at the present time but as diagnostics costs fall and treatment costs rise (drugs, surgical intervention, long term care and so on) then we may reach a tipping point when routine screening becomes economically viable. For example, everyone over the age of 40 might give a blood sample every month and send it off to a central lab which will do the biochemical analysis, compare the data against previous readings, and report any concerns directly to the primary care physician.

An exciting consequence of this shift is the increased possibility of detecting those cancers which are undetectable

using a one-off test but which can sometimes be spotted by monitoring a panel of biomarkers over an extended period of time. At the moment, these tests are too expensive and don't have particularly high sensitivity and specificity, but if used as part of a monthly screen which is analysed by computer, these tests could potentially detect cancers and other serious diseases at an early stage, saving lives and saving money.

The future of diagnostics and monitoring is exciting. The challenges are higher for today's innovators than for their predecessors, but today we have an unprecedented suite of emerging technologies at our disposal. I suspect that the individuals and companies that will enhance patient care the most will be those who understand their users, and which can harness new technology to create products which offer demonstrable and measurable economic benefits.



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# THE LAST

**‘The last mile’ is a term used by the telecommunications industry to describe the connection from the telephone exchange to the end-user’s premises — a short distance relative to the many hundreds or thousands of miles covered by the network, but an unreliable bottleneck limiting the exchange of information.**

The traditional physical solution connecting the last mile is copper twisted-pair wire, a 100 year old technology buried underground or suspended from telegraph poles, but new technologies have built on this physical channel to deliver new capabilities. First came dial-up modems, allowing point-to-point connection between computers and to bulletin boards, then IP connectivity revolutionised the network, followed by broadband modems and now the latest fibre-to-the-cabinet technology which brings tens of megabits of bidirectional capacity, enabling the information revolution to reach the home.

But a similar challenge is now to be found in what we call ‘the last inch’, the connection of devices with users over short distances. This is especially relevant in the medical space, where wireless devices are used to sense and monitor physiological parameters to help manage a medical condition, or perhaps to display and share information about a medical treatment via a mobile

platform (such as a smartphone), and then to exchange this information with cloud-based software applications.

Just as with the twisted-pair cable in the landline, the basic building blocks enabling ‘last inch’ connection have been in place for some time, and telemedicine applications have been used for decades. Recent advances and other factors however, are enabling a burst of innovation in connected medical devices and apps, and by 2030 I believe that this innovation will both support patients and allow them to connect with medical professionals to enable better medical treatment.

#### Enablers to innovation

We can identify a number of enablers that, when taken together, allow innovation of connected medical applications that operate over the ‘last inch’. These include technological advances, regulatory change and emerging standards:



# INCH

BY PETER MATTHEWSON

“the basic building blocks enabling ‘last inch’ connection have been in place for some time, and telemedicine applications have been used for decades.”

#### Low power wireless connection to devices

Although the predominant Bluetooth short-range wireless connection standard has been around for many years, power consumption has long been recognised as a key limitation for wireless-connected measurement and monitoring devices. As a result, the Bluetooth standard has now been augmented to provide support for low power applications with Bluetooth Low Energy, also known as Bluetooth Smart, incorporated into the standard in 2010. As the chipsets mature, software manufacturers have extended Bluetooth Smart capability to iOS and Android devices, and by 2018 it is expected that 90% of the world’s smartphones will support Bluetooth.

In terms of improving power consumption, a two year life can now be provided by a 1000mAh battery (AAA cell) when used for a simple logging function, making sealed-for-life small connected devices now a practical proposition.

For medical and healthcare applications, Bluetooth supports communications for functions such as:

- medical measurements such as temperature, blood glucose monitoring, blood pressure measurement, and heart rate measurement
- health and fitness measurements, running speed and cadence measurement
- location and navigation
- proximity alerting — when the distance between devices exceeds a set threshold.

In addition there are numerous low power sensing devices that underpin connected medical devices, providing the means of monitoring parameters such as temperature, blood pressure, motion, oxygen saturation and heart rate. There are also low-power actuators, pumps, valves and microelectromechanical sensors.

### The smartphone platform

With more than a billion smartphone units shipped in 2013, it seems a safe assumption that within a few years this technology will be readily available to most patients, although unsurprisingly, the uptake is strongest in the under-35s.

By the end of 2013, Android was the most popular smartphone operating system with an 81.9% market share, followed by iOS with 12.1%, Windows Phone with 3.6%, and BlackBerry with 1.8%.

The smartphone provides a familiar user interface, integrated sensors, wide area network connectivity, short-range wireless, ease of installation of new apps, and inherent extensible multifunction ability. It is small, compact and is generally close to the user, and so can provide the hub to connect a multiplicity of monitoring devices operating within the last inch of the patient.

**“If the enablers are in place to make connected medical devices and apps operating over ‘the last inch’ a fertile ground for innovation, we naturally start to wonder what might be over the horizon”**

### Electronic health monitoring standards

Recent announcements of commercially driven standards and platform developments in electronic health and fitness monitoring will enable the swifter development of connected healthcare applications, leading to new technologies which will eventually be used in regulated medical devices. Two of the most interesting are:

- **Samsung Architecture Multimodal Interactions (SAMI)**, a data broker to enable wearable devices to upload information to the cloud, where developers can access the data and create new apps. SAMI is stated to be a secure, open, diverse data platform; its open application programming interfaces can collect data from many device types or online sources and deliver the data to any other device or app in real time. Samsung also recently announced the launch of Simband, an associated reference smart health device design to allow sophisticated data monitoring systems to be engineered quickly.
- **Apple HealthKit**, which offers capabilities to aggregate data from various health apps and commercial fitness devices to provide users with a clear and current overview in one place. Information from exercise apps, wearable technology, blood pressure and heart rate, weight and sleep patterns are aggregated to provide a single view, and each app can also take specific information from other apps to allow information integration. Apple has announced that it is working with an Electronic Patient Record (EPR) supplier on plans for transferring patient-held data from apps into the EPR and back again, so that patient record data could be available on the patient's phone.

These recent announcements show the intent of the manufacturers — to use smartphone hardware, connectivity and interfaces to support the development of data discovery, data aggregation and usage for more sophisticated healthcare apps using all data sources available. The emergence of standards will allow an ecosystem of solutions, components and expertise to develop in parallel.

### Algorithmic extraction of information from signals and sensor fusion

An important requirement for any wireless medical sensing device is an ability to separate the information of interest from the signals measured using a medical signal processing algorithm. Often the measured signals are a large data set and the information extraction process involves filtering out noise and estimation of a small number of parameters of interest. There may be real-time requirements to accomplish this quickly and at a high update rate.

Algorithms could be hosted on a small connected device which can sense data over ‘the last inch’, potentially reducing the amount of data to be transferred from the connected device, in turn reducing both power and time demands. On the other hand, processing could be hosted on a smartphone or connected computing resource after the raw signals are transferred, giving access to more computational throughput and other resources. So there are more architectural choices about how to structure the system. As there may be many signals available, the tasks of discovering them, combining them and drawing valid conclusions (for example, to produce a useful prognostic) requires data fusion techniques. As an example, OBS Medical have developed their Visensia technology to automatically analyse and interpret the combined patterns of up to five vital signs — heart rate, temperature, blood pressure, respiration rate and blood oxygen — regardless of whether the data is collected continuously or periodically, and the results are then fused to generate a predictive, numerical index representing the patient's ‘wellness’. In a clinical setting, this technology is reported as showing quicker responses to patient deterioration, and a reduction in unexpected deaths, overall leading to improved efficiency through better use of the information acquired.

### Regulatory relaxation

Regulators are increasing the freedom to innovate in this space, with recent FDA guidance stating that for certain classes of mobile app, discretion will be exercised when policing the development of new apps with a medical/healthcare function. For eligible

apps, this will decrease the regulatory burden faced when turning a new idea into a marketable product, and will therefore encourage innovation.

The FDA guidance includes apps that help patients/users self-manage their disease or condition without providing specific treatment suggestions. This includes devices which provide, for example: simple tools to organise and track health information; easy access to information related to health conditions or treatments; help in documenting, showing or communicating potential medical conditions to health care providers; a way to automate simple tasks for health care providers; or which enable patients or providers to interact with Personal Health Records (PHR) or Electronic Patient Record (EPR) systems.

Regulation will still be needed if patient safety could be affected by the app or device, so as a result, any mobile app which performs a medical device function (for the diagnosis, cure, mitigation, treatment, or prevention of a disease or condition) will be considered a medical device, and will be regulated as such throughout its development and marketing.

### What could emerge?

If the enablers are in place to make connected medical devices and apps operating over 'the last inch' a fertile ground for innovation, we naturally start to wonder what might be over the horizon. So here are some thoughts on what we might expect to see emerging in the connected medical device space in some key areas:

#### **Drug delivery devices**

By 2030, a predicted increase of 51% is expected in the number of people that have diabetes compared with 2011, according to the International Diabetes Federation Diabetes Atlas. By that time the artificial pancreas — a closed loop insulin delivery system with continuous glucose monitoring, such as that proposed by Medtronic — is expected to be accepted by regulators. Connected systems, exemplified by Cellnovo, will continue to be developed, and will provide an integrated system for management of the disease. Connected

patch pumps will be increasingly used for diabetes and other conditions.

Inhaler devices and pen injectors will become more routinely equipped with sensors to record and communicate time and location of usage as well as effectiveness of usage, in order to support users in managing their condition.

#### **Smart device accessories**

There are many devices on the market which have received approval for sale and for which there is an understandable reluctance to make modifications necessitating resubmission to the regulators. Adding an accessory to an existing device that doesn't change the medical function can add new benefits which could help the user manage their treatment and provide choices about how they do so. For instance, a connected smart accessory for a medical device could work with a smartphone to provide the means to help the user locate the device, to prompt the user to use the device, to assist in usage, to log usage, and to provide instructions. The accessory can also be a gateway for the device manufacturer to keep in touch with, and better understand, its users.

#### **Self-management monitoring and feedback devices**

In Team's survey on healthcare in 2030, 55% of doctors and 32% of patients believed that patients would be taking more responsibility for monitoring their health in the future. Electronic devices will assist this development, and we are already seeing the emergence of fitness and health apps that are familiarising patients with the concept of monitoring via a smartphone or other device. For instance, myFitnessPal is already used to record calorie expenditure, as does the Nike FuelBand plus app, helping to encourage a more widespread culture of health consciousness.

Connected medical devices and apps will assist further, especially to measure progress, and to remind patients when and how to use infrequent high value/impact medication. This will allow treatment plan adherence to be recorded and improved. Data fusion technology will also be used to

provide patients with suggested advisory actions based on combinations of disparate physiological and other measurements.

#### **Aggregation of information on patient groups for research**

Data gathered automatically on patient management and usage will help assess compliance for clinical studies, allowing better assessment of the quality of the underlying data used. The gathering of sets of data from patients using a device or treatment, perhaps anonymised, will also allow learning from the measured interactions of patients and devices and allow new insights and improvements to be made.

#### **Conclusion**

In all these areas one thing is certain — there will be surprises. Some innovative new applications with connectivity over 'the last inch' will emerge and unexpectedly succeed whilst others will fail to become established, not least for cost/benefit reasons. New players will also enter the market and come through the learning curve of working within the medical product regulatory frameworks. As a result, it is unlikely that technology will be the constraining factor as we move towards 2030, given its rapid rate of development fuelled by commercial consumer technology investment, more likely it will be regulatory acceptance.

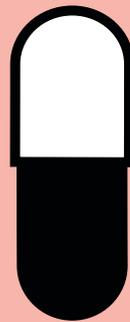


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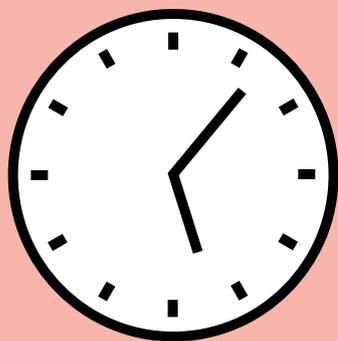
# Personalised medicine and the FDA — how far has it come and where is it going?

BY **LEE LEICHTER**, P/L BIOMEDICAL

When it comes to personalised medicine, the FDA is already in broad agreement with the trends shown by Team's survey<sup>1</sup>, as indicated in the FDA's 2013 report *Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development*. This document provided a detailed summary of the FDA's response to recent developments in the field, and also its thoughts on the challenges ahead.



For the FDA, personalised medicine is characterised as providing 'the right patient with the right drug at the right dose at the right time.' More broadly, 'personalised medicine' is the tailoring of medical treatment to the individual characteristics, needs and preferences of a patient during all stages of care, including prevention, diagnosis, treatment and follow-up. With regards to drug approval, the FDA recognised that personalised medicine could address one of the unavoidable consequences of approving drugs that were effective for a small portion of the patient population, but would provide no or little benefit, with a high risk of side effects and adverse events, for the balance of the population. Personalised medicine — by delivering better-targeted therapies — was acknowledged as a possible strategy to improve public health, and reduce waste. The FDA has encouraged the development of diagnostic tests for predictive genetic attributes that could help identify these sub-populations of 'responders' in order to target these new therapies. As these tests have no diagnostic value unless developed



appears. In order to understand why, one must first examine the FDA's role and the role of government in the USA. The FDA's primary role in the USA is to protect the public health. As such, and as for other protection agencies in the USA, the focus is on protection of the patient, even if that means limiting the choices that are available to those that are proven to provide a benefit that outweighs the risk. It is with this concept that the needs of the patient and the needs of the FDA may diverge.

Whereas, as the Team Consulting survey reveals, the patient may be willing to take the risks associated with choices regarding their medication, the FDA may not feel that the potential risks of these choices on the proven therapeutic benefit of the drug, or potential hazards that may be introduced, are sufficiently balanced by the convenience and user satisfaction benefits that are provided.

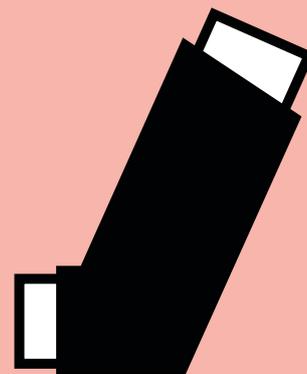
Evidence of this dichotomy can even be seen in the area of Companion Diagnostics, where the FDA has already shown great commitment. In the USA, many of the companion diagnostics are developed by laboratories, not manufacturers, and are called Laboratory Developed Tests (LDTs). These LDTs are not regulated by the FDA and not subject to review of clinical data establishing that they are effective, and meet their claims. The FDA has recently published a draft guidance that would bring these tests under their oversight and would require proof to support effectiveness for the test to be legally marketed.



and reviewed in conjunction with the therapeutic drug, the FDA has worked to provide clear guidance for the development and approval of companion diagnostics, which cut waste by ensuring the right drug is used with the right patient, significantly improving the risk / benefit profile. On July 31, 2014 the FDA issued 'Guidance for Industry: In Vitro Companion Diagnostic Devices', to help companies identify the need for companion diagnostics at an earlier stage in the drug development process and to plan for co-development of the drug and companion diagnostic test. The ultimate goal of the guidance was to stimulate early collaborations that will result in faster access to promising new treatments for patients living with serious and life-threatening diseases. A second guidance to address the requirement necessary for the co-development of companion diagnostics with the targeted therapeutic is eagerly awaited.

But in spite of the very visible efforts, the FDA's relationship with personalised medicine is more complex than at first

The laboratories argue that they are already regulated and this would impede the availability of these tests to support personalised medicine. The FDA's position is that speed and availability are outweighed by the possibility that these tests could provide erroneous results and jeopardise the public health.

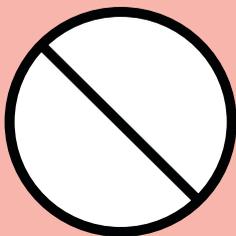


Another example is in the area of genomic diagnostics, where the FDA has prevented the company 23andMe from marketing their genomic tests because the diagnostic value and patient benefit of the information provided has not been assessed and determined to be adequate by the FDA. In effect, the patient cannot be trusted to use the information and may make the wrong decisions.

Part of this issue is very specific to drug delivery. In the EU, the essential requirements for safety and performance of the delivery function of a separate, or even integrated drug delivery system can be independently established for the 'device' portion by the manufacturer (potentially with oversight of a Notified Body), and this assurance or certification is accepted by the EMA as sufficient for approval of the drug or integrated drug product. In the USA, these 'device' issues are considered concurrently with the approval of the drug.

That puts the Center for Drugs (CDER) or Biologics (CBER) as the organisation that must accept both the risks of the drug

“The ultimate goal of the guidance was to stimulate early collaborations that will result in faster access to promising new treatments for patients living with serious and life-threatening diseases.”

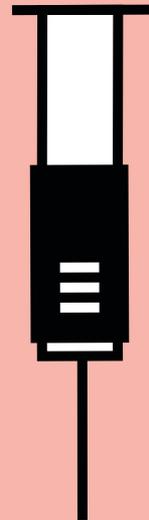


and the risk of the drug delivery device together for the approval of the system, or combination product. Although the system is designed to enable device issues to be reviewed and considered by the Center for Devices (CDRH), this does not always happen, and when it does, the opinions or position of CDRH are not always respected and/or followed. As would be expected of any individual, and is certainly true of the FDA where risk is to be avoided, reviewers when presented with information or concepts with which they may not be familiar or comfortable, will become very conservative. This is a very natural, and not unexpected result. The reviewers in CDER are less likely to be comfortable with the risks or user choices based on user studies, without statistically valid, clinically established proof that these choices do not adversely impact drug efficacy or patient safety. Thus, the burden will fall to the manufacturer to prove that the myriad of combination and/or configurations are all safe and will not impact on the effectiveness of the drug, the safety of the patient or the user's ability to deliver their dose. For drug manufacturers, the cost/benefit equation may preclude them from including these options for patients in deference to providing a single, proven safe and effective drug product. This decision may be compounded by a highly litigious US legal system, which has the potential to penalise the manufacturer for poor patient choices.

Although this relationship between the Drug and Biologics Centers and the Device Center may improve over time, it promises to be a slow process. It is clear that the leadership of the FDA is committed to personalised medicine and providing drugs AND devices that will safely and effectively provide medical benefits. However, their focus on protection, sometimes in deference to patient choice, cannot be ignored. In addition, even with the right leadership, the FDA is a very large organisation with an established bureaucracy and any large organisation, like a large vehicle that has enormous inertia, requiring a significant effort and a very long time to change direction (and culture).

As such, I cannot see the FDA resolving its issues around combination products even by 2030, although its relatively quick

approval of companion diagnostics does indicate that when the result is a clear 'win win' for patients, practitioners and society as a whole then the FDA can act. But the FDA will remain committed primarily to the protection of public health, and may only be capable of implementing incremental change when it comes to "patient choice". This is something all those working within the personalised medicine space must recognise, and is an issue on which we must all keep a watching brief.



#### References

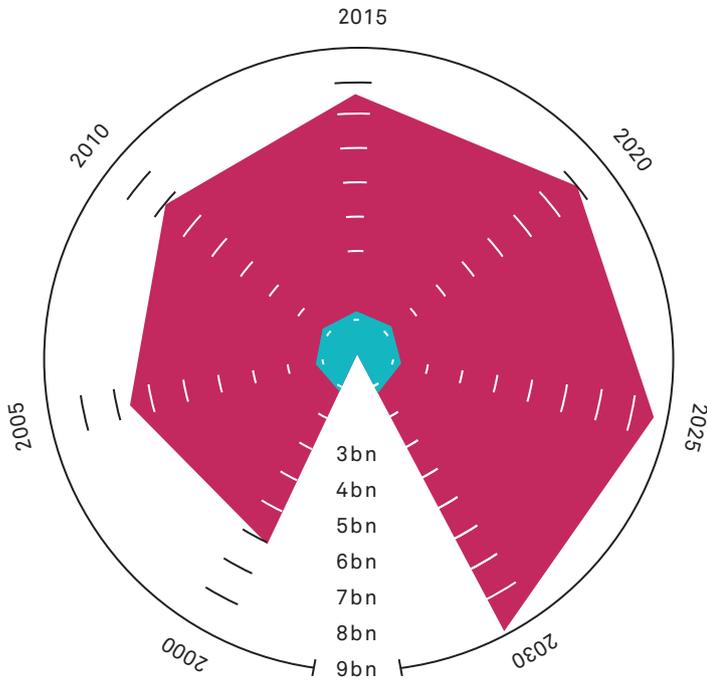
- 1 Patient and doctor perspectives, Team Consulting, <http://te-am.co/patientreport>



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*Lee Leichter is President of P/L Biomedical and has more than 30 years' experience in the health care industry with major medical products companies.*

# Healthcare in 2030

We've accumulated a number of forecasts to highlight the issues facing healthcare in 2030.

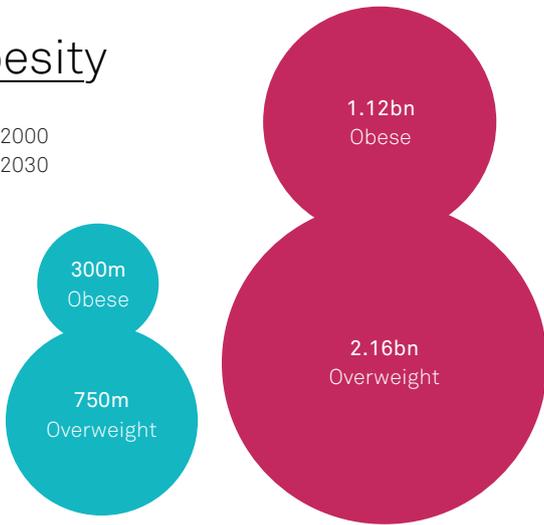


## Population

- Less developed regions
- More developed regions

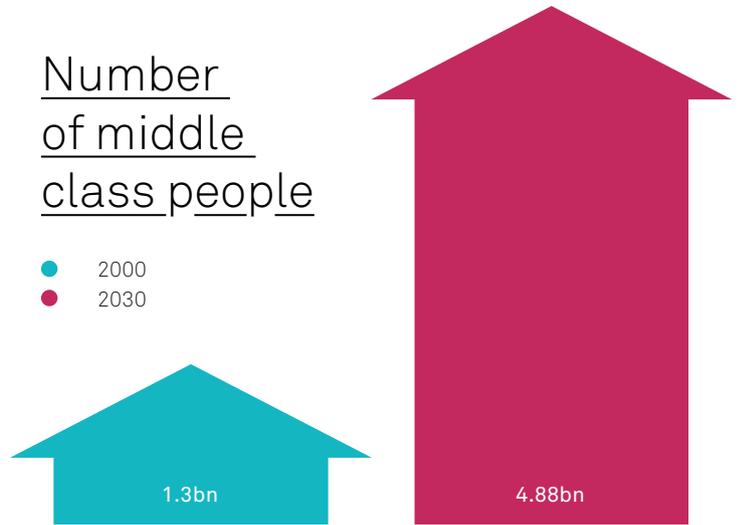
## Obesity

- 2000
- 2030



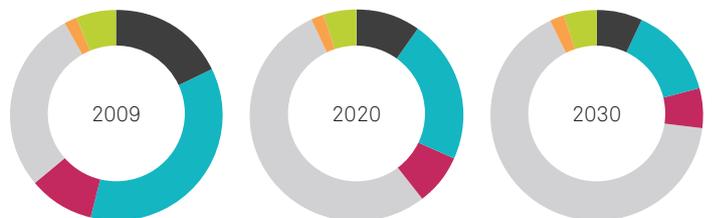
## Number of middle class people

- 2000
- 2030

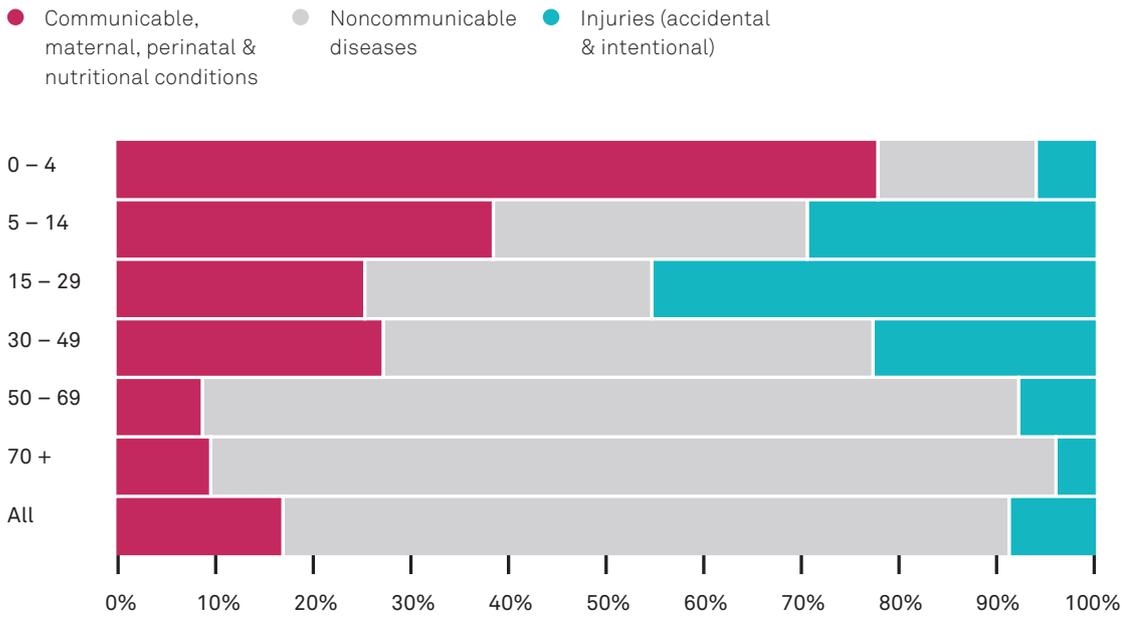


## Geographic spread of the global middle class

- North America
- Europe
- Central & South America
- Asia Pacific
- Sub-Saharan Africa
- Middle East & North Africa



## Leading causes of death in 2030



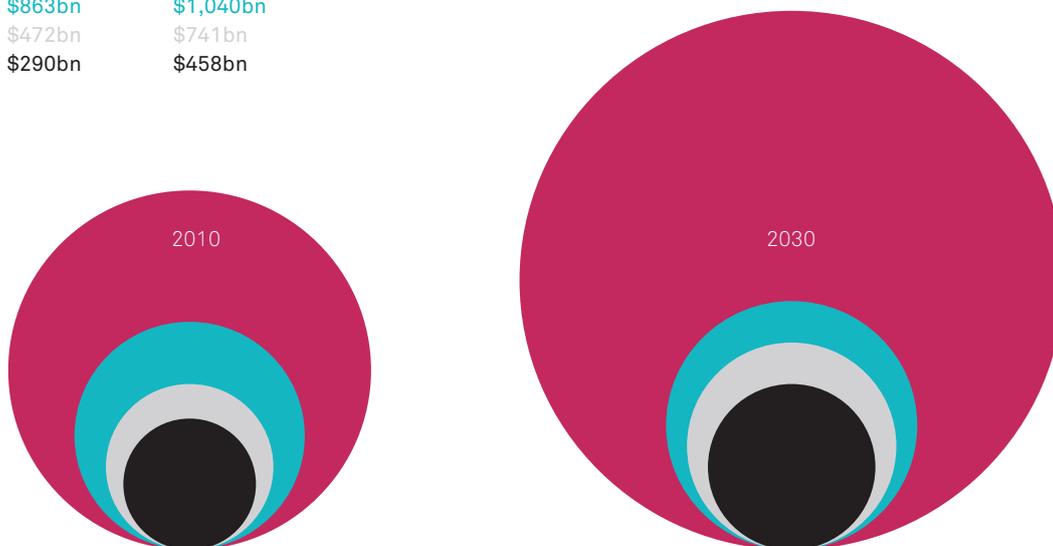
973m 2030

The number of people over 65

## The estimated global direct and indirect costs of illness

- COPD
- Cardiovascular disease
- Diabetes
- Cancer

2010	2030
<span style="color: red;">\$2,100bn</span>	<span style="color: red;">\$4,800bn</span>
<span style="color: teal;">\$863bn</span>	<span style="color: teal;">\$1,040bn</span>
<span style="color: grey;">\$472bn</span>	<span style="color: grey;">\$741bn</span>
<span style="color: black;">\$290bn</span>	<span style="color: black;">\$458bn</span>



420m 2000



## The top 10 causes of death



### 1 Ischaemic Heart Disease

2000	2030
5,974,000 people	9,245,000 people
11.3% of all deaths	13.2% of all deaths



### 2 Stroke

2000	2030
5,662,000 people	8,578,000 people
10.7% of all deaths	12.2% of all deaths



### 3 COPD

2000	2030
3,059,000 people	4,568,000 people
5.8% of all deaths	6.5% of all deaths



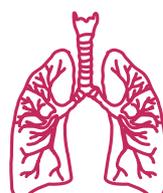
### 4 Lower Respiratory Infections

2000	2030
3,491,000 people	3,535,000 people
6.6% of all deaths	5% of all deaths



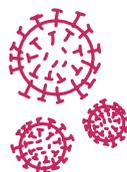
### 5 Diabetes Mellitus

2000	2030
1,046,000 people	2,464,000 people
2% of all deaths	3.5% of all deaths



### 6 Trachea, Bronchus, Lung Cancers

2000	2030
1,164,000 people	2,413,000 people
2.2% of all deaths	3.4% of all deaths



### 7 HIV/AIDS

2000	2030
1,678,000 people	1,793,000 people
3.2% of all deaths	2.6% of all deaths



### 8 Diarrhoeal Diseases

2000	2030
2,171,000 people	1,617,000 people
4.1% of all deaths	2.3% of all deaths



### 9 Hypertensive Heart Disease

2000	2030
849,000 people	1,457,000 people
1.6% of all deaths	2.1% of all deaths



### 10 Cirrhosis of the liver

2000	2030
892,000 people	1,201,000 people
1.7% of all deaths	1.7% of all deaths

The burden of poor health in 2030 will present some tough choices for all involved. The constant and necessary push to reduce costs will see patients become central to their own healthcare, with many expected to treat and monitor themselves in the home. It will also place a considerable burden on healthcare professionals who'll need to treat and care for people efficiently and effectively.

**Population data** United Nations (<http://te-am.co/pop2030>)

**Age data** Centers for Disease Control and Prevention (<http://te-am.co/pop2030>)

**Obesity data** International Journal of Obesity (<http://te-am.co/obesity2030>)

**Middle class data** OECD (<http://te-am.co/class2030>) and Brookings (<http://te-am.co/midclass2030>)

**Causes of death data** World Health Organization (<http://te-am.co/death2030>)

**Cost of healthcare data** World Economic Forum and Harvard School of Public Health (<http://te-am.co/costs2030>)

# Let's make things better

We are recognised globally as experts in the design and development of medical devices. That's all we do and we are proud of this focus. It enables us to deliver real insight and expertise to our clients.

Commercially successful products need to be safe, easy to use and ultimately make people better. Our clients like our approach, which combines design, human factors, science and engineering from inspiration right through to industrialisation.

Everybody at Team is driven by the same desire, to make things better by working in collaboration with clients and each other. Whether 'things' means people or the products we work on, we apply the same commitment to do the best and be the best that we can.

This focus and desire is a powerful combination and one that highlights why our clients trust us over and over again.

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