The science of today is the technology of the future

New technologies making their mark in the diabetes world

It has been said that we are stuck with technology when what we really want is just stuff that works¹. For decades, people with diabetes have been promised technology that will lead to a life with fewer insulin injections and blood glucose tests that will mean less worry and less hassle. Yet, despite billions of dollars of investment into this technology, can people with diabetes be offered anything that actually works? The answer would seem to be ‘yes’, says Dr Eleanor Kennedy who reports here on advances in diabetes technology
An explosion of new product developments and launches is apparently set to revolutionise life with diabetes. This emerging technology demonstrates impressive potential to improve HbA1c levels, to increase the time spent in range and to decrease the time spent either in hypoglycaemia or hyperglycaemia. Importantly, new technologies also have the potential to improve a patient’s quality of life as well as to reduce the burden of self-management.

**Continuous glucose monitoring**

Arguably one of the biggest advances in diabetes technology in recent years has been the advent of continuous glucose monitoring (CGM). Although technically not a continuous measurement – most devices test around every five minutes – they are now considered for adults with Type 1 diabetes who present with recurrent severe hypoglycaemia, frequent asymptomatic hypoglycaemia that is interfering with daily activities, or a complete loss of awareness of hypoglycaemia.

The drawback of these devices, although undoubtedly becoming more refined, is that they measure the glucose levels in the interstitial fluid rather than in the blood. Because the interstitial fluid lags behind blood glucose by about 10 to 15 minutes, users need to test their blood glucose levels with a conventional meter, albeit less frequently, particularly if the level is rising or falling rapidly when the accuracy of the CGM may not be optimal. That said, the need for calibration is reducing and calibration-free CGM is currently available with the Libre model, while the Dexcom G6 has a reduced, once daily requirement for calibration.

**Flash glucose monitoring**

Flash Glucose Monitoring (Flash GM) is a much newer technology that bridges the space between conventional meter measurements and CGM as it gives both individual blood glucose readings and trend data. While there are still very few providers actively marketing in this space, the device does have some powerful benefits. Patients have a small sensor inserted on their upper arm and are given a separate touchscreen reader. This reader device can be swiped close to the sensor and the sensor will transmit two different sets of data. It will give the patient an instantaneous glucose reading in addition to an eight-hour trend line. Unlike CGM, Flash GM does not have hypo- or hyperglycaemia alarms but, unless blood glucose levels are changing very rapidly, Flash GM devices do not require a fingerstick calibration, although fingerprick testing is still required for driving purposes.

Nick Oliver, Wynn Professor of Human Metabolism at Imperial College London, recognises the current limitations of Flash GM. “More data is definitely required in order to establish both the clinical and cost effectiveness of these devices. An NHS framework for reimbursement is also required as are studies in specific populations to define more accurately who is going to benefit most from this technology.”

In anticipation that this technology will soon be available to prescribe, Diabetes UK has brought together a working group, chaired by Dr Gerry Rayman, to draft recommendations for its use in the NHS. The group includes people with diabetes and parents with experience of Flash GM, healthcare professionals, policy experts and other diabetes organisations.

**Real-time continuous glucose monitoring**

Like CGM, the Guardian Connect Continuous Glucose Monitoring System from Medtronic allows patients to measure their glucose levels much more frequently than fingerstick tests allow. Designed to be used by people on multiple daily injection therapy, it is the first in a number of exciting new products that are currently available to people with diabetes. Prof Oliver says: “Further devices will be available in due course, including a new CGM from Roche and an implantable version from Eversense whose sensor can last up to 90 days and capture readings on a mobile app that overcomes the need for a separate receiver.” He continues: “These incremental improvements will help healthcare professionals to offer a wider range of technologies to people with diabetes that can be tailored to individual needs.”

**The future of CGM**

With obvious demand for a safe, reliable glucose measurement system that could consign conventional blood glucose measurement systems to the dustbin, companies are striving to produce next generation CGM and Flash GM sensors that are smaller, cheaper and longer lasting. They also aim to have improved accuracy, particularly during periods of hypoglycaemia. There is a push to cut down the need for calibration and these new sensors will be aiming to move from once daily calibration to single calibration or, indeed, to be calibration free. Additionally, companies are working to reduce interference from paracetamol, ascorbic acid (vitamin C) and uric acid and to integrate them with diabetes management systems – all of which makes them attractive additions to the diabetes armamentarium.

**Closed-loop insulin delivery**

The Holy Grail of a closed loop, or artificial pancreas, inches ever closer as new studies continue to publish successful results. These trials indicate an increased amount of time within target blood glucose levels, a reduced exposure to hypoglycaemia and a reduced HbA1c in adult participants. There is additionally a move towards a dual hormone closed loop system adding glucagon to insulin delivery which has the potential to reduce hypoglycaemia still further. However, a stable glucagon analogue is still required. We also don’t know the impact of giving doses of glucagon much higher than physiological levels in the long term.

**Insulins**

Despite having been commercially available for decades, insulin remains a potentially very lucrative research area for the pharmaceutical and biotechnology sectors. Huge development programmes are underway to devise new forms of insulin that are either ultra-fast acting or ultra-long acting.

- **Biochaperoned insulin**
  
  Biochaperoned peptides are designed to be complexed with other proteins that can protect them from enzymatic degradation and enhance their actions in the body. By modifying the release patterns into the bloodstream, the aim is to facilitate a decreased dosage regimen and also decreased frequency of administration. New studies on BioChaperoned Lispro, an ultra-rapid formulation of insulin lispro, have indicated that the technology can speed up the absorption of insulin. Despite the termination of the partnership between Lilly and Adocia, who own
the intellectual property rights on the BioChaperone technology, the latter is preparing Phase III clinical trials of this product while looking for a new partner7.

- Biosimilar insulin
Where possible, generic versions of drugs are commonly used within the NHS, because they tend to be cheaper than the original, patented drug. With biological drugs, such as insulin, though, it is more difficult to make an exact copy which reacts in exactly the same way as the originally approved drug. As a result, a biological copy cannot be said to be identical to the original, as molecular changes in the structure of the product and in the manufacturing process can change the way the drug works.

With just Lilly’s Abasaglar glargine already available, the insulin market is perhaps overdue more biosimilars. However, thanks to the complexities of the insulin molecule, its manufacturing process, and the drug’s safety and efficacy considerations, regulatory bodies are placing very high and demanding requirements on their adoption8. A biosimilar Lispro based on Lilly’s Humalog product is currently in Phase III clinical trials with eagerly awaited results.

- Glucose-responsive insulin
Glucose-responsive insulins are perhaps the game-changer for people with diabetes. The goal is to create an insulin that works automatically in response to blood glucose. The higher the blood glucose, the more insulin is released and vice versa. Merck’s MK-2640 ‘smart insulin’ is a glucose-responsive insulin currently in Phase I trials, but it is not expected to be launched until at least 2021. Several other companies also have molecules in development, including Sanofi, Novo Nordisk and Lilly, with the last acquiring technology from Glycostasis, a start-up company at the Pacific Northwest Diabetes Research Institute, with early-stage glucose-responsive insulin drug development9.

Prof Oliver thinks that the first generation glucose-responsive insulins could be very different from later incarnations. “Ideally, no other insulin use will be required and the need for glucose monitoring will change, but, while the first versions will undoubtedly help with meals, people using them may still require basal insulin and regular blood glucose monitoring.” He continues: “The weight gain profile will also be important. Insulin is associated with appetite and weight gain, especially in Type 2 diabetes but, with a glucose-dependent action, this association may be completely minimised with glucose-responsive insulins.”

Almost since the discovery of insulin itself in the early 1920s, scientists and clinicians have been keen to develop alternative routes of insulin administration. Although plagued with difficulties, several companies are still working on providing such formulations.

- Inhaled insulin
As with oral insulin, the path to inhaled formulation of insulin has been far from smooth. Having developed a recombinant human insulin in small enough particles to be inhaled, Pfizer launched Exubera after more than a decade of development, only to withdraw it less than a year later. A number of reasons were quoted, including the lack of user friendliness of the system and the large, rather bulky device that was used to administer the powdered insulin. However, Afrezza, an inhaled insulin product manufactured by MannKind Corporation, is now being marketed, having received approval from the US Food and Drug Administration for Type 1 and Type 2 diabetes. However, inhaled administration can cause acute bronchospasm, leading to contraindications for those with asthma or chronic obstructive pulmonary disease.
Data and decision support
The fastest paced developments in diabetes technology over recent years have, arguably, been driven by people living with the condition. For diabetes self-management is steered by data, and connected health enables collation of data on glucose, insulin, physical activity and other health-related events.

New education packages, lifestyle coaching and behavioural change initiatives have all been instrumental in this move. Apps are now readily available for data and decision support and, although challenges undoubtedly remain in regulation, monitoring and implementation of mobile apps, some are gaining FDA approval and the CE Mark.

The Insulia app, for example, is a Type 2 diabetes management app, accessible via the web, mobile phones and tablets, offering dosage recommendations, educational coaching and diabetes-related data. Insulia uses a dose-adjusting algorithm designed to help users not just to manage their diabetes but also to share the data with their healthcare team, who can then monitor the individual’s progress toward agreed goals. Another cloud-based therapy management software solution, Glucommander calculates individualised insulin dose recommendations. While this can lead to dramatic improvements in glucose levels, further research is required.

And patients continue to take matters into their own hands as they tire of being hampered by the innovation bottleneck that is preventing many new devices and systems from reaching market quickly. The #WeAreNotWaiting hashtag has been developed to give people with diabetes the opportunity to improve their management now. The movement encourages solutions to the current challenges of using technology, open access data and data sharing and is, in part, driving commercial development.

Conclusion
With many new products and technologies either newly available or in the development pipeline, it is clear that the number of options available to people with diabetes to manage their condition is becoming much wider.

Faster insulins, with potential benefit to pump users and in closed loop Systems, and a wider range of insulins in development with differing pharmacodynamics and administration routes are all adding to a sense of urgency in the field. Most importantly however, although the technologies are being driven by academia and industry, as public involvement and ‘patient power’ in these developments continues to gain momentum, it is also apparent that these new devices and systems are now being tailored much more effectively to need.

"Huge development programmes are underway to devise new forms of insulin that are either ultra-fast acting or ultra-long acting."

REFERENCES
6 Bally L, Thabit H and Hovorka R (2016). Role of dual-hormone closed-loop delivery system in the future. Diabetes Technology and Therapy 18 (8); 452–454