Beyond Compliance

Patient non-adherence is a problem that many pharma companies are trying to alleviate. The solution should be paired with an approach that makes taking prescriptions both easy and comfortable for the patient, and there are now a number of steps being taken to achieve this balance

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Approximately 50% of patients do not take their drugs as prescribed, thereby limiting the therapeutic effects of drugs and potentially costing healthcare services billions of dollars. As a result, there is an industry-wide trend for introducing monitoring devices to address this noncompliance. A trade-off exists in pharma between devices that are easy to use for the patient, but offer limited actionable insight to the practitioner, and devices that provide more beneficial data relating to outcomes, but need to be used in a clinical setting or are otherwise more invasive to the patient. It is important to examine that trade-off, and assess new advances that seek to sit in both camps.

Actuation versus Therapeutic Effect

To date, the push for developing drug monitoring sensors has largely focused on device actuation – such as sensors to show whether or not a package has been opened – as opposed to monitoring the outcome of the delivery of the drug.

While this is not without value, it would be useful for both the patient and doctor to be able to measure the outcomes of drug delivery, and thereby:

- Maintain consistent and appropriate medication levels: there are many drugs that have a narrow therapeutic range below which they are ineffective, and above which they are toxic
- Provide positive feedback to the patient to encourage compliance: certain drugs require multiple doses to see the benefit, and the consequences of non-compliance are not immediately felt
- Detect rapid changes in condition and alert the clinician to the need for intervention or intelligent devices that can autonomously regulate drug delivery

There are particular situations where it is especially beneficial to monitor the therapeutic effect of a drug treatment, and these include:

- When the therapeutic effect of the drug is not easily predicted from the administered dose alone
- When the therapeutic window between efficacy and toxicity is small
- When there are large variations in pharmacokinetics between individuals
- If there is a high likelihood of interferences with other medications or other conditions
- Where compliance to a particular medication is known to be poor
- During drug investigational trials, where high-resolution data enable models of the pharmacokinetics and pharmacodynamics to be built up

Yet today, with the exception of glucose monitoring for diabetes, most examples of therapeutic drug monitoring are found in centralised hospitals and clinics, rather than in the patient's home or doctor's office. This limits the frequency with which monitoring can be performed and, subsequently, impacts quality of life for the patient.

Developing devices to measure therapeutic effect is not straightforward, and there are barriers to commercialising these types of monitoring systems. They include:

- Demonstrating improved clinical outcomes, while controlling costs
- Ease of patient use
- Proving sufficient sensitivity and robustness against interferences (from other drugs or conditions, for example)
- Avoiding the need for specialist interpretation of the data to make treatment decisions

The Role of Biomarkers

Notwithstanding the obstacles outlined above, there are many technologies currently being developed to measure the outcomes of drug delivery, and there is a wide range of potential approaches. These include the direct detection of biomarkers in the disease pathway and the measurement of drug concentration at the target site, through to indirect proxies like the monitoring of vital signs, and changes in behaviour such as motion and tremor.

Many prognostic biomarkers have been identified for observing the course of disease, including responses to

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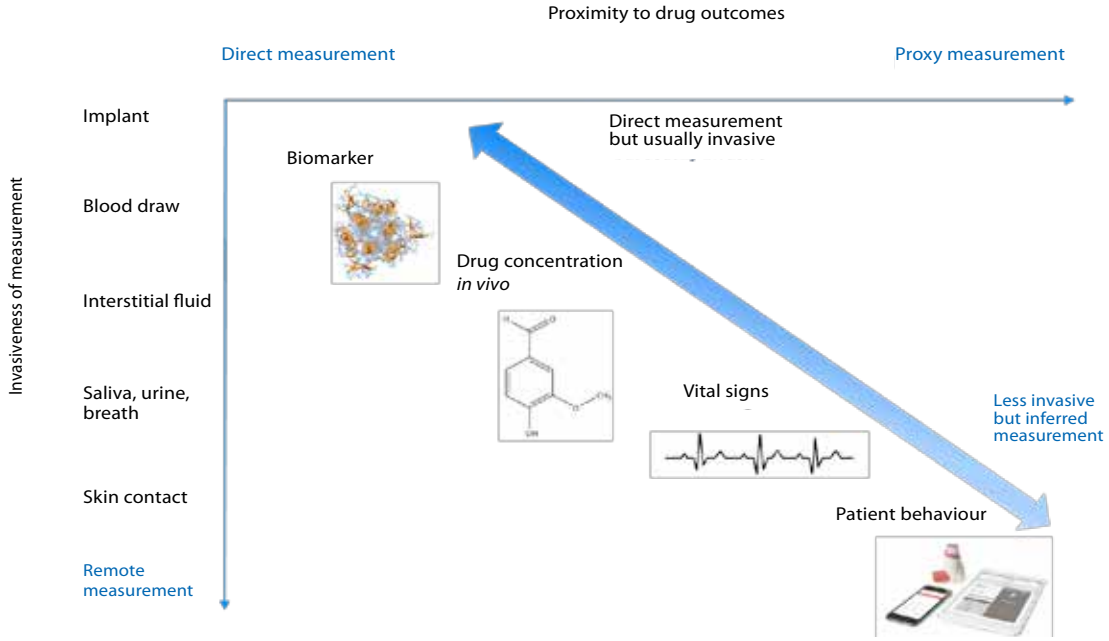

Figure 1: The trade-off between ease-of-use and quality of feedback. The challenge for drug therapy monitoring moving forward is to develop sensor technologies that bridge the gap between the performance of invasive sensors, and the ease-of-use of non-invasive technologies

therapy. While these can be closely correlated to the disease or the mechanism of action of the drug, they tend to be invasive, often requiring a biosample like blood. Other less intrusive samples – such as interstitial fluid, urine or saliva – are possible in some cases, although they can suffer from delayed response or reduced sensitivity as they become increasingly distant from the site of action of the drug.

While these biomarkers can give the most direct indication of the therapeutic outcomes of a drug, their invasive nature and the potential for matrix effects make them difficult to employ outside of the clinical environment.

With the growth in wearable consumer electronics and drug delivery devices, there has been heightened interest in non-invasive sensing technologies. Examples include monitoring the behaviour of the patient – such as muscle tremor and activity – or other vital signs, like blood pressure and heart rate. Although such measurements can be convenient and inexpensive, they are often weak proxies for the drug outcome, and significant effort and data fusion are required to make the outputs beneficial. The trade-off between technologies that provide high-quality feedback but tend to be invasive, and those that are easy to use but unfortunately provide lower quality results, are shown in Figure 1.

There are also technologies that track significant biomarkers in patients to judge drug efficacy – such as monitoring glucose levels in insulin-dependent diabetics – and have traditionally been undertaken using pin-prick blood testing.

Sensor Technologies

Several products are now in the pipeline, which offer alternatives to finger prick blood samples that aim to make the testing procedure more automated and to avoid patient discomfort.

Skin Patch Sensor

For example, Clinitech – a startup based in Cambridge, UK – is developing a skin patch technology that measures interstitial fluid by thermally ablating 50µm holes in the skin. The hole is sufficiently small so that no pain is experienced by the patient and it leaves no marks. Sensing is then performed via polypyrrole or nanowire sensors in contact with the interstitial fluid that flows from the micropore.

Clinitech describes its product LabPatch as "a chip on a Band-Aid, which monitors the wearer's clinically relevant biomarkers by sampling the body's interstitial fluid, communicating results wirelessly" (1). This has the potential to provide the workability of a fitness device with outcome information. Use cases include continuous monitoring of diabetes, heart damage and concussion detection in contact sports and the military. Similar approaches are seen in R&D, employing micro needle arrays, radiofrequency electroporation and reverse iontophoresis.

The majority of these sensors have been targeted at glucose sensing and remain in the early stages of development. The challenges they have typically faced are those of lower sensitivity than the pin-prick blood tests, which represent the current standard of care and interferences from other pharmacologic or naturally occurring molecules that may be present in some patient groups – for example, glutathione, ascorbic acid, uric acid, paracetamol, isoniazid and salicylate. Looking beyond diabetes, there might be opportunities to use these sensor technologies in situations where an absolute result is not necessary, but alerting the patient

or clinician to changes and trends could prove beneficial.

Optical Sensor

There are also technologies that aim to pick up the levels of drug or drug metabolites' concentration in the body, rather than the therapeutic outcome. Traditionally, this would be undertaken by taking a blood sample from the patient and using a sophisticated laboratory technique like high-pressure liquid chromatography. While this is feasible for drug trials, it is definitely not a solution for continuous monitoring.

Optical/spectroscopic sensing is a very attractive approach for patient-operated monitoring devices. Optical sensors have the potential to be compact, lightweight and low cost, and can look for the spectral characteristics of the drug. However, optical wavelengths are strongly attenuated in the skin, and there are many sources of possible interference – making transdermal sensing challenging. If the measurement is done in biosamples the situation is improved, but concentrations of the drug can be poorly representative of the drug concentration at the target site.

An interesting option is to add a tracer molecule to the drug formulation that has a strong optical characteristic, or which can form part of a colour change assay. A number of researchers have been able to include fluorescent markers in drug formulations. This enables the drug residues to be easily detected *in vivo* or in urine, without the usage of complex assays. As an example, researchers at Tel Aviv University are combining near-infrared fluorophores with prodrugs – in which the fluorophore and drug are jointly activated inside the body – and the fluorophore signal provides good correlation to the drug activity inside the target cells (2). The use of near-infrared allows optimal imaging as the absorbance, and emittance of tissues is minimal at these wavelengths.

Sensor Fusion

Given the fact that different sensor options are good at delivering certain pieces of information, but to date all have limitations, it could well make sense to bring together data from various sensors to try and give a more complete picture. It might be possible, for instance, to mitigate the limitations of reduced sensitivity or interferences by combining the biochemical sensor data with other sensor inputs to filter or calibrate the measurement. For example, some measurements require the patient to fast for more than nine hours for an accurate measurement – a continuous monitoring device might also use an accelerometer and electrocardiogram (ECG) to assign data for identifying sleep periods in which the patient has been fasting and, therefore, assign greater significance to measurements made in these periods.

Recently, researchers at the University of California demonstrated the combination of a wearable biochemical sensor for lactate levels in sweat and an ECG. This was fabricated on a flexible substrate using screen printing techniques for the skin contact sensors, and a conventional printed circuit board for the electronics (3). While this first example is most relevant to the health and fitness market, it illustrates the potential to combine multiple measurements whereby the heart rate data enable the interpretation of the time-varying lactate signal.

What is Appropriate?

The key decision in sensing drug outcomes is how invasive the measurement approach should be. With some drugs, the risk of being outside the therapeutic range is sufficiently high that there is a strong argument to accept an intrusive technique despite the complexity and patient discomfort. A familiar case is diabetes, where self-testing using a blood pin-prick is routine. A further example is immunosuppressive drugs for the treatment of autoimmune inflammatory conditions, such as rheumatoid arthritis, where there is a risk of the neutrophil count dropping too low and the patient becoming highly susceptible to infections. With other drugs, the risks are lower, and less invasive measurement methods are highly desirable to make the device easy to use and the patient more likely to comply.

The developments being undertaken in this area are exciting, and we expect to see more real world applications as wearable platform technologies become available and the supporting connected health infrastructure more mature.

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