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PATIENT CENTRIC BLOOD SAMPLING AND QUANTITATIVE ANALYSIS

EDITED BY
NEIL SPOONER, EMILY EHRENFELD,
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Patient Centric Blood Sampling and Quantitative Bioanalysis

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Patient Centric Blood Sampling and Quantitative Bioanalysis

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Foreword

Many of the contributors to this book were authoring their chapters whilst living through a global pandemic, which has changed healthcare and health politics forever, and this book could not have been written at a better time.

Sitting here today, we are facing unprecedented change in international health systems—with spiralling costs, increasing cultural and national disparity in healthcare delivery and acceptance, ageing populations, and infrastructures that are decades old. The world around healthcare is moving at a faster pace than the institution can cope with. In today's world mobile phones and technology are now commonplace in many households. Telehealth and virtual consultancies are, in some cases, gradually replacing traditional face-to-face appointments. And people are starting to accept wellness and prevention as ways that they themselves can tackle the onset of disease.

The boundaries of healthcare are finally beginning to change from the clinic walls and reach out into people's lives. Not only does this result in a healthcare system that is more accessible, but it also brings the possibility of healthcare being culturally tailored for populations and delivered in more sensitive and acceptable ways. Of reaching, and supporting, the most vulnerable in our society.

At the center of this reform is the ability to test and monitor for known illnesses outside of the clinic itself. Patient-centric sampling involves the patient or caregiver taking small amounts of body fluid—blood or saliva as examples—in the comfort of a person's home. Recent technological advances have made this possible, making user friendly, simple, safe, and even painless devices available. These are then packaged as directed and then either posted or collected and sent to a central laboratory for processing. The implementation of this approach, however, is fraught with challenges that need to be overcome before it can be fully integrated as the standard approach that healthcare reaches for first. From the learnings of the pandemic we have real life examples where patient-centric sampling has been successfully implemented within and across countries.

This book shines a light on the whole approach. It presents a balanced look across all aspects—the challenges, technological requirements, assays, processes, delivery ... all the way through to the human behavior and ways to integrate into the norm. It discusses everything we have learnt from the long and rich microsampling history and how this can be used to deliver for the rapidly changing expectations and requirements of future populations and healthcare services. It outlines the unique challenges and opportunities presented through use of patient-centric sampling in the clinical trials that are so essential for developing new medicines.

Every one of the authors in this book wrote their chapters to help others. They represent a diverse background of expertise and share their experiences, insights, and case studies with astonishing honesty, openness, and integrity. This partnership between people is unified by a belief in the welfare of others. It gives a unique insight into the systematic changes that must be undertaken to allow the full potential of patient-centric care to be realized. Throughout, these insights are supported and enhanced by the author's real-life case studies and experiences of using this approach in practice.

It is hoped that by sharing this, you will be the next to add to this wave of change—to join the innovators and make a difference. If we all do this, then together we can play our part in ensuring healthcare becomes accessible and acceptable to those who need it most, the patients.

Jenny Royle
Matthew Barfield

Preface

There is an increasingly broad understanding that the collection of biological samples for the quantitative determination of analytes for healthcare and the support of clinical trials needs to be performed in a manner that puts the needs of the patient at the center. The technologies to enable high quality samples to be collected in a location such as the home, pharmacist, local doctor's surgery, or other locations that are convenient to the patient, rather than at a centralized clinical center, are now readily available. Furthermore, the clamour for this change has gained momentum during the recent COVID-19 pandemic, where all of us were reluctant to go to clinical facilities. Despite this, change is always difficult, particularly for something as well established as the processes for the collection and analysis of blood samples. Thankfully, there is an increasing body of leaders, represented by the authors of the chapters in this book, who realize the benefits of these solutions and understand that by working together across inter- and intra-organizational boundaries we can break down the barriers to their routine adoption and bring benefits to the patient.

A previous book in this series, *Dried Blood Spots*, edited by Wenkui Li and Mike Lee, set the benchmark for our understanding of the benefits of these patient-centric sampling technologies and how they can be implemented in a number of scenarios. This book builds upon those strong foundations, to bring us up to date with how this exciting and fast-moving field has developed. The authors, who are looking to enable the routine use of these technologies for the benefit of their fellow humans, generously share their observations, experiences, concerns, and visions of the future. As such, this book is another benchmark in the continuing change that is healthcare and analytical science. We can say with certainty that there is further change to come in this field and as such we look forward to working as a community to facilitate these important and inevitable changes.

The editors sincerely thank all the distinguished authors for the provision of their wonderful chapters and for their patience and persistence with this project

through the difficult events of the pandemic. It has definitely been worth the wait! We also wish to thank the editorial staff at John Wiley & Sons for their unwavering and patient support to this project that is a small part of the phenomenal series edited by Mike Lee.

Neil Spooner
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Patient Centric Healthcare – What's Stopping Us?

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1.1 The Evolution of Future Health Systems

The primary aim of healthcare systems around the globe is to improve the well-being of populations, with the World Health Organization defining health as "A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (World Health Organisation, 2020). Healthcare is not merely treatments for diseases, it is instead a way to support people to achieve the highest attainable mental and physical and social well-being for themselves. But traditional healthcare systems are not set up in this way, and rather than focusing on integrating all the holistic elements required for promotion of health in an individual, they are orientated toward the treatment of disease and malaise after things have already deteriorated in a person's well-being.

The difference between absence of disease and total well-being is subtle but fundamental. Supporting well-being involves encouraging people to live a healthy lifestyle (both physically and mentally) and providing the tools, systems, and education for each person to aim for the best possible version of themselves often via self-care principles—whether or not they are sick at the current time.

Other factors that have further impacted the tension between the treatment versus a self-care model of health have emerged during the COVID-19 pandemic during 2020, which forced upon us innovations and technologies that were once confined to pilot status. These were mobilized during the 2020 pandemic out of necessity in order to meet the restriction in face-to-face services required to prevent transmission of the virus between people. Many of these rapid accelerations,

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particularly in relation to telehealth visits and remote monitoring, are here to stay because, once pushed to try a new approach, it has been found to be efficient and a positive experience for many (Jones et al., 2020; Norman et al., 2020; Wosik et al., 2020). An area that is a fundamental component of this wave of change is the process of microsampling at home.

For the uninitiated, microsampling involves the taking of small droplet amounts of body fluid—blood or saliva as examples—in the comfort of a person's home. The samples themselves are taken by the patient or with assistance from a caregiver and are then stored and packaged as directed (for example by drying on a specialized sample tip or card and sealing into the envelope provided). These are then either posted or collected and sent to a central laboratory for processing, thus negating the need for a patient to visit an outpatient clinic or local surgery (Bateman, 2020). The laboratory assay must be validated and provide sufficient accuracy to support accurate clinical decision-making. This onset of a remote, patient centric approach to sampling brings with it the chance to fundamentally challenge and change the healthcare delivery model. Sampling and appointments can be decentralized, and most routine supportive care can be virtual. This does not mean the end of the hospital or GP visit, but it does mean that the approach used can be fitted to the requirements of the individuals involved and the healthcare decisions that need to be made. Remote sampling and consultations are more time efficient (Ballester et al., 2018; Prasad et al., 2020; Russo et al., 2016) and this means that not only can they be scheduled around peoples' daily lives better but also any face-to-face appointments can be prioritized for people where in-person consultation is truly needed. For overstretched front-line staff and health systems, this is likely to be a very attractive proposition.

Research has also shown that dried blood spot sampling versus conventional blood sampling conferred cost savings across the ecosystem in renal transplant and hemato-oncology patients (Martial et al., 2016). In this study, switching to home sampling was associated with a societal cost reduction of 43% for hemato-oncology patients and 61% for nephrology patients per blood draw. From a healthcare perspective, costs reduced by 7% for hemato-oncology patients and by 21% for nephrology patients due to the replacement of office-based tests with home-based sampling.

So the evidence suggests that virtual care provides a mostly positive patient experience and is more efficient for the health service. Could this also help reduce the number of people not "turning up" for medical appointment (if the consultation comes to them)? Research has shown that the high levels of "no shows" to hospital appointments have a large impact on the organizational structure and cost to a health provider (Dantas et al., 2018; Jefferson et al., 2019; Mohammadi et al., 2018). Although no research has been carried out on this to date, it is possible that the efficient use of home sampling could reduce this "appointment missing," and this more optimized supportive care for patients could offer

additional benefits on the downstream impacts to service. Another potential benefit of home sampling could be the time freed up for those more in need of face-to-face contact and better decisions on how to balance the two approaches. There are benefits and limitations to both home-based and in clinic approaches—for example, home care approaches which are decentralized have been shown to give better individualized, immediate care, but along with this, the responsibility for monitoring is largely delegated to technical devices, patients, and their families (Oudshoorn, 2009). Face-to-face appointments in the clinic have been shown to be preferred over telemedicine in specific circumstances such as when patients have low self-management ability and/or depending on the purpose of the consultation (e.g. initial discussions about terminal disease, which may have additional, unspoken support needs; Chudner et al., 2019; Derkson et al., 2020). Designing an integrated approach based on the person's needs may be most beneficial for all. For example, in 2019, Jiang and colleagues found that correctly timing a face-to-face consultation increased a patient's ability to accurately find information digitally and administer self-care post consultation. Integrated approaches also bring the potential to save more face-to-face consultation time for personalized conversations and supportive care, leaving more simple tests and interventions to be carried out at home.

The authors suggest the use of home blood sampling may have positive impacts on a person's overall well-being by allowing intrusive interventions to be carried out within a familiar home environment. A survey was taken of 39 adult kidney transplant patients who underwent both traditional venepuncture and microsampling approaches for monitoring of their condition and the current blood sampling burden was quantified using two measures: anxiety and travel requirements (Scuderi et al., 2020). A third of participants ($n = 13$) reported blood test anxiety and 44% ($n = 17$) spent more than an hour just to travel to the required phlebotomy site for standard of care. Preference between the two approaches was also explored: 85% ($n = 33$) preferred microsampling approaches and 95% ($n = 37$) expressed an interest in collecting their microsample themselves at home. This demonstrates a clear patient preference and willingness to give microsampling a go for monitoring post-transplantation recovery progress.

1.2 Exploring the Barriers to Home Sampling

Given the efficiencies and benefits of home-based care, why is not remote patient centric microsampling more rapidly adopted everywhere? The answers may rest with people and the hurdles involved in fundamentally changing established care pathways and healthcare cultures in which people are already working at maximum capacity to deliver what they know, let alone try something new.

The scientific and technological aspects of patient centric microsampling have accelerated in the past 5 years and are driving the field of healthcare in the home; this chapter aims to focus on many of the key concerns that have been heard through working in the clinic, with patients, and developing technologies. The aim is that by starting a discussion around each of these concerns and by proposing potential solutions, developers and leaders of the future will be able to co-create the approaches with the relevant end users and speed up the realization of benefits that these sampling processes can bring.

1.2.1 Barrier One—The Discord Between Innovation and Practice

Recent events of the pandemic in 2020 have shown us that all healthcare systems run at a finite capacity. To implement change, the very same people who rely on established approaches have to, instead, adopt and implement something brand new, while maintaining their high standard of care in challenging times.

The expertise behind the development of highly sensitive microsampling technology has, up until now, been mostly confined to pharmaceutical companies and private laboratories and was generally not widespread in the labs of front-facing healthcare institutions. Furthermore, existing health systems required to implement microsampling systems are built on the fundamental principle *of primum non nocere* (first, do no harm). Sampling and test results are usually only a small part of a clinical pathway, with many healthcare professionals defaulting to the established pathway approaches and more familiar and trusted in-clinic sampling techniques are automatically selected. This involves the deployment of personnel, for example phlebotomists and nurses in a system that, despite being pushed to its limits, is proven to accurately deliver support to clinical decisions. Convenience to patient and family is sometimes seen as of secondary importance, and any potential increase in decision speed is currently unproven with empirical evidence in the standard front-line healthcare systems. It is now commonly recognized that human decision-making usually relies on a System one (fast, reactive, emotional, and habitual) and System two (slower, higher energy, puzzling out a new challenge) approach (Kahneman, 2003). The vast majority of times, human decisions are ultimately based upon responsive, heuristic, and/or emotions, rather than calculated logic—especially when the individual has many years of experience. It is possible, therefore, that emotional rather than rationale drivers may be slowing the uptake of home sampling—for example—trust. For this established and routine model to be replaced, evidence would need to be gathered that the new pathway provides significant improvement in timeliness and physical and/or mental patient well-being. Importantly, overall cost savings for the healthcare system as a whole (primary, secondary, and social care) across the different healthcare models would also need to be demonstrated. Technological advances have the potential to

change elements far beyond use of the device itself—reaching into roles, medic–nurse–patient–carer relationships, behaviors, and healthcare culture and there is understandable caution from front-line decision-makers who are upholding the principle of "do no harm" and have little time to assess the overall healthcare value–benefit versus risk offered by home sampling.

A solution to these problems has been proposed through novel patient centric co-creation and delivery of technology clinical trials that design new or enhanced care pathways with those involved in their routine implementation and then test them empirically in a clinical trial setting. Not only does this mean that the full consequences and potential benefits of an innovation (such as home sampling) that may ripple across the care pathway are considered, but that the proposed ways of leveraging the positives are created by those using the current approach. The subsequent quantitative and qualitative testing of the whole pathway then also provides the empirical evidence as to the impact on people's well-being, ability to deliver the care, and cost. With this approach, barriers preventing uptake are reduced through the intervention design and the drive for change is supported by the robust evidence that healthcare demands (Royle et al., 2021).

1.2.2 Barrier Two—Ethical and Operational Considerations

The ethics involved in home sampling within a new care pathway needs to be thoroughly considered, documented, and discussed with end users before it is put into practice. For example, if the novel innovation is a home sampling test kit then, as well as taking the sample, patients need to accept that they are responsible for taking it. Patients need to store and use the sample kit correctly, dispose of elements in a safe way, and post the sample off in a timely manner. People need to understand why this is necessary and how the data collected from the kit will be communicated to them and what it means—in lay terms. Seamless services are now the norm, but on the odd occasion of a faulty/lost kit, patients should understand how to take action and the provider resolve the problem immediately, so as to maintain both patient and physician confidence in the new system.

There are many areas of healthcare where patients and their families already take responsibility for their own treatment and healthcare. For example, many diabetic patients monitor their own glucose levels and titrate their insulin dose and timings, colorectal cancer screening requires people to send samples for assessment (the affectionately called "poo in the post" screen), all the way through to women taking the responsibility with regard to adherence to the contraceptive pill. The idea that people can take a blood microsample and post it off to a lab should not seem that unusual, and it is logical to assume it will be accepted easily. However, there are very important elements at play in each of these examples. For each, there is a clear and direct benefit for the patient themselves and no "easy"

alternative. Each has also been standard of practice for many years and has therefore become the accepted social norm in many societies—it has long been expected and accepted that diabetic patients and their families monitor their daily treatment and therefore from the point of diagnosis patients inevitably have to accept this role.

For new point of care and home sampling approaches, this "norm" does not exist for both physicians and patients. Even if it makes it slightly easier, the "accepted" and "expected" more traditional approach from all perspectives is for their doctor, nurse, or a trained phlebotomist to undertake sampling. A patient given the opportunity to take on the sampling themselves may, in some cases, compare their minimal professional experience with that of their authority figures. In addition to this, when the microsamples are being used to monitor a specific health condition of themselves or those they love—the consequences of unknowingly getting it wrong become even more worrying.

None of these challenges are insurmountable, but steps should be put in place to develop the care pathway with those involved to ensure that each step—even if it is not one directly related to the mechanics of sampling itself, is considered. In this case, there are several clear elements that can easily help to overcome barriers:

Helpful tips for successful adoption	Description
Making it as pleasant and easy as possible	Simple, quick action. Painless if possible. But also consider the timing and routine. Linking in with habits helps people to remember and make it more "normal" to undertake. Try to avoid additional steps such as intricate assembly or the need to refrigerate.
Recommendation by an authority figure	Conviction that this is the best approach to take, being conveyed and supported by their physician and other trusted healthcare anchors a patient may have.
Building up self-efficacy (i.e., someone's belief that they can successfully do what is needed—in most cases, take the sample)	Time for training and questions built into the process. Having a trusted contact point for help if needed. Share support from peers—other patients who have successfully adopted the system and are willing to volunteer as "champions."
Seeing that it matters—their actions have tangible value	Knowing that the results are to be evaluated and will not be lost (and getting confirmation that they have been looked at).
Having a feeling of control and reducing anxiety	Having an action plan for patients that covers all the main predictable things that may happen (e.g., knowing what to do if the system malfunctions or the sample collection goes wrong). Provide patients with support and help to understand and evaluate findings and what these mean for them.

1.2.3 Barrier Three—Where Does the Liability Sit?

Healthcare workers are always cognizant of their legal and ethical responsibilities to protect the patients they care for and to do this to the best of their ability. But in the case of home sampling, the process is moved out of their control because it is no longer being undertaken by professional healthcare colleagues but by the patient or caregiver themselves. How can professionals deliver to these legal responsibilities if they are not personally carrying out or delegating the sampling to their colleagues that have certificates of training? Where does the final legal liability lie, for example if poor or inadequate sampling results in the wrong decision? This area of law and liability is infrequently discussed, but is one to consider as home sampling and other such services become more prevalent in treatment and care pathways. The Royal College of Nursing in the UK states that "*To discharge the legal duty of care, health care practitioners must act in accordance with the relevant* ***standard*** *of care*." Where the "standard of care" is deemed to be that undertaken by other professionals in a similar situation as a benchmark (Royal College of Nursing, 2020).

Although the legal and ethical requirements which constitute a duty of care to patients may vary across countries, it is important that those who provide and initiate the services of home blood sampling consider their duty of care to patients who may be embarking on a shared or self-care journey. Considerations such as the assessment of the patient and their support network to understand their "health literacy" and capabilities to carry out their tests is an important first step. In addition, a willingness of physicians and nurses to adopt a collaborative shared care approach with patients where support is offered and is gradually decreased as the competence of the patient in this area increases should be evident, in the form of health coaching. In the earlier days of such a culture change, to help build physician–patient trust, this could even mean supplementing the home testing within clinic standard tests at the start of treatment. This would endure until both parties can be confident that the home tests are useful indicators and can be routinely relied on (with in clinic sampling then being for emergency second check only).

Further, the authors believe that the proffering of documented, lay-friendly information coupled with peer support would all allow the physician or nurse to comfortably discharge their duty of care to the patient and caregivers. Indeed, the convenience and possible enhanced quality of life that patients may benefit from is testimony to the ethically robust patient centric decision made within the shared care team.

The authors suggest that standardized protocols for the deployment of home-centered care and sampling would serve to provide guidance, share best practice, and alleviate concerns of healthcare professionals (HCPs). Such a standardized approach in shared care decision-making is discussed by a working party (Elwyn

et al., 2012) with *choice, option, and decision* "talks" described as a robust process to ensure a shared care collaboration between HCPs and patients. Such a model could be developed with a focus on home sampling so that any specific operational aspects can be incorporated and standardized.

Similarly, many patients and families who may be comfortable with the more paternalistic relationship they share with their physician may suddenly see this responsibility of self-sampling as a burden, rather than a release from yet another outpatient visit. This may suggest the need to further support more vulnerable communities if home sampling is to become the norm. In practice, many of these concerns can be addressed early at the point of service design and importantly, in collaboration with all parties, so that appropriate support interventions may be put in place. Indeed, it has been suggested that shared care should evolve such that both physician and patients expect and make room for time to discuss shared options and engage in reflective thinking asking "what if clinicians felt just as comfortable asking questions as providing answers? What if patients were allowed more time on their own to reflect on what their clinician explained?" (Pieterse et al., 2019). If home sampling and other shared and self-care measures are to continue to grow and be deployed in a seamless fashion, then clearly behaviors of all parties may need to evolve.

1.2.4 Barrier Four—Addressing the Technology Challenge

As microsampling becomes more prevalent in care pathways, it is likely to be linked to an increasing number of point of care devices for patients and their families to use themselves. As discussed earlier, with a clear partnership and action plans between the patient/patient's family and their physician comes a huge opportunity for timely action and proactive healthcare. However, it also brings technological challenges, since many patients may be overwhelmed by new technology or instructions that are not available in lay language. Should results be provided via a mobile device, many more mature or vulnerable patients may struggle to "play their part" within the system which could lead to enhanced anxiety and a feeling of exclusion, plus the obvious loss of healthcare data. These challenges are surprisingly not confined to patient populations, since previous unpublished work conducted by the authors highlighted the challenges faced by nursing staff when confronted with a novel Bluetooth device to monitor salbutamol inhaler use in patients with chronic obstructive pulmonary disease (COPD). This eventually led to both patient and nurse confusion when using the device and consequently an associated reduction in adherence.

We also need to consider the *inclusivity* of such new microsampling interventions in the home, since in every country there is a proportion of the population that are not native speakers and may rely upon family, friends, and HCPs for