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Insights into the use of microsampling for omics studies

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It is clear by now how the future of medicine is precision medicine. The personalisation and optimisation of all medical procedures, from prevention to diagnosis, to therapy/treatment planning and monitoring, and to follow-up is nowadays considered an unescapable development of current practices. This is really a change of perspective: whereas until now the focus of clinical procedures was on the illness or disorder and its consequences on an "average" human body, right now it is becoming increasingly clear how the interaction between a pathology or a syndrome and the individual patient is a whole that cannot be reduced to discrete parts. Common features obviously exist, but medical activities must acknowledge every facet of the "patient-illness" whole and try to accommodate the specific needs of this unique whole, both explicit and evident (signs, symptoms, demands) and implicit, hidden (genetic makeup, metabolic peculiarities, infective agent strain, patient fears and hopes), both fixed in time or slowly evolving (genotype, chronic illnesses), and rapidly variable (phenotype, laboratory tests).

As a consequence of intense scientific efforts and instrumental and software breakthroughs, we are now uniquely equipped to face this huge, and pervasive, task that "makes my veins and pulses tremble" [1]. The many "omics" disciplines are now reaching full maturity [3], from the most established ones, such as metabolomics, genomics, and proteomics [3], to rapidly developing and emerging ones, such as transcriptomics, phenomics, lipidomics, interactomics [4] and even, more recently, prescriptomics [5]. By analysing large datasets, obtained by the use of the latest, cutting-edge equipment and procedures, scientists are now able to tackle medical, biological and chemical problems that appeared intractable just a few years ago. And big improvement to artificial intelligence performances promise to further revolutionise this field in as yet unforeseeable ways. And yet, all of these enormous progresses and hopes still rely on the same, humble foundations as ever: good, effective, reproducible sampling and sample preparation [6,7]. The most sophisticated analytical workflows and data treatment procedures in the world cannot counterbalance the consequences of a badly stored biological sample, or of the wrong sampling time. "Garbage in, garbage out" (GIGO), as software developers use to say.

It is becoming increasingly evident that new, more reliable and more flexible sampling and treatment procedures are needed. Among those, one of the most promising approaches is microsampling, coupled to miniaturised (and if possible automated) sample preparation [8, 9].

The future that precision medicine, and thus pervasive omics application, is envisaging for healthcare implies monitoring and evaluating millions of patients for hundreds or thousands of chemical and biological features each. Even the "humble" therapeutic drug monitoring (TDM), which is based on the periodic determination of plasma levels of

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drugs and their main metabolites to direct clinical and therapeutical choices, is psychologically and economically taxing if carried out at close time intervals [10,11]. Thus, it is clear the goal of personalised medicine for everyone can only be attained if we are able to use just minute amounts of biological samples, be they invasive, minimally invasive or non-invasive. Moreover, sampling should be carried out at home, or in widely diffused facilities, and preferably by the subject themselves. Microsampling is clearly the way to go [12].

The first example of microsampling was dried blood spotting (DBS), which has been applied for neonatal screening since the '60 of the last century. It appeared to be very attractive from the beginning, since dried spotting relies on a skin prick, which allows to generate several microsamples (i.e., spots) that can be separately treated and analysed [13,14]. Drying also removes most water content, thus making the microsample much more easily handled, shipped and stored, and reducing the time and expenses associated with all these steps. Analyte stability is usually also greatly enhanced, even in room temperature (RT) storage, due to lack of water, and this another very important and appreciated feature [15]. The minimal invasiveness of this sampling technique greatly improves patient compliance and makes it much more widely and safely applicable than traditional sampling approaches, also opening the way to self- and home-sampling [16]. Dried spots can be obtained from virtually any biological fluid, creating the broader class of dried matrix spotting (DMS) [13,17,18], and even from solid tissues or biopsies, after suitable homogenisation and preparation.

Traditional DBS has some drawbacks that hinder its quantitative application, such as sampling volume depending on haematocrit, and sample inhomogeneity. Moreover, the minute amount of matrix available in each spot makes the application of traditional sample preparation techniques more difficult, and requires the use of high-sensitivity, high selectivity analytical instrumentation. Those limitations are now being addressed by the introduction of alternative microsampling platforms, of novel miniaturised sample preparation techniques, and by progressively increasing analytical performance, by means of mass spectrometry (MS) and high-resolution MS (HRMS) coupled to high- (HPLC) and ultrahigh-performance liquid chromatography (UHPLC) [3] providing the needed sensitivity, selectivity, reproducibility and throughput for most clinical and biochemical applications [19,20].

In recent years several alternative microsampling techniques have become increasingly available. Among them, quantitative DBS has been achieved through calibrated capillary and microfluidic techniques [7,21]. Volumetric microsampling platforms are also employed, for example VAMS (volumetric absorptive microsampling) that uses a calibrated polymeric tip to absorb a fixed (10-30 µL) volume of biological fluid [13,22,23]. Chemical equilibrium microsampling techniques are also available, such as solid phase microextraction (SPME), either by fibre immersion or by headspace sampling in the case of volatile analytes. Still more approaches are being explored and applied, such as fabric-phase sorptive membrane (FPSM) [24] and wet microsampling [25,26].

Another interesting feature of all microsampling techniques using solid supports (i.e., almost all of them, apart from wet sampling) is that the support itself acts as an extraction means of sorts, selectively retaining or freeing specific compounds from the biological matrix. This makes the subsequent sample preparation step much faster, easier and inexpensive, up to the point of making direct instrument injection or direct introduction into the MS/HRMS flow possible. This point is hardly overestimated, since high-throughput robust sample preparation methods that produce efficient and reproducible data are of paramount importance to any omics application [4], indeed making them viable for widespread application to the general population.

In conclusion, precision medicine requires the massive application of omics, and this in turn needs the use of inexpensive yet reliable sampling and sample preparations procedures. Microsampling is increasingly becoming the gold standard [27] for this purpose, allowing to greatly reduce matrix amounts and operating expenses, while reducing at the same time biological, contamination and analyte degradation risks. Microsampling also seamlessly integrates with miniaturised sample preparation workflows and is amenable to automation even using existing sample handling apparatuses.

The future of omics in precision medicine looks bright, and microsampling can give it that extra shine.

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