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Hot from the press!

Report of the 2nd Swiss Symposium in Point-of-Care Diagnostics

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Abstract: After a successful first launch of the Swiss Symposium in Point-of-Care Diagnostics at the HES-SO Valais-Wallis in 2017 (*CHIMIA* **2018**, *72*, 80), the organization of the 2nd edition of this Symposium was spearheaded by the CSEM team in Landquart. Again close to 200 participants from science, industry and laboratory medicine attended this event during a beautiful and warm autumn day at the awesome Auditorium of the Graubündner Kantonalbank (GKB) in Chur.

Keywords: Clinical microbiology · Diagnostic stewardship · Digitalization · Microfluidics · mHealth · Multi-analyte platforms · Wearable Sensors

Group photo with speakers and chairs (left to right: Prof. M. Pfeifer, HES-SO Valais-Wallis, Co-chair; Dr. M. Risch, KSGR; Dr. E. Delamarche, IBM; Prof. D. Paris, STPH; Dr. S. Paoletti, CSEM; Dr. T. Stauffer, Medics; Dr. J. Schotter, AIT; Dr. C. Lustenberger, ETHZ; Prof. E. Kübler, FHNW; Prof. J. Wang, UCSD; Dr. C. Rhyner, Davos Diagnostics; Dr. D. Ulrich, CSEM, Chair; Dr. S. Generelli, CSEM; Dr. J. Schickedanz, Qiagen; Dr. O. Nolte, ZLMSG; and Prof. B. Schnyder, HES-SO Valais-Wallis). Photo by Sara Foser (Foto Fetzer).

POC Diagnostics of Infectious Diseases

"POC Diagnostics are widely available for clinical chemistry parameters, but to a much lesser extent in clinical microbiology laboratories (CML)", noted PD Dr. ***Oliver Nolte*** from the Centre for Laboratory Medicine (ZLM) in St. Gallen during his introductory speech at the Symposium. Infectious disease diagnostics is today very much characterized by specialized culture-based methods, which are necessary for correct identification (ID) and subsequent automated susceptibility testing (AST) of a pathogen in question. As such, in clinical microbiology, POC diagnostic testing is more or less limited to fast nucleic acid-based test formats for relevant pathogens (*e.g. ad hoc* screening/testing for TB, MRSA, VRE, influenza, *etc.*). "Recent developments with cartridge-format ID/AST testing pose an increasing area of conflict for laboratories and infectious disease specialists", explained the medical microbiology specialist. Although fast and precise enough for a calculated therapy, culture confirmation is still required for these tests. This is likely also true for upcoming rapid POC ID/AST tests, which will foreseeably suffer from a lack of sensitivity and specificity. On the other hand, the clinical demand and necessity for laboratories to deliver fast ID/AST is feeding a trend to invest in complex automation technology, which allows for more efficient handling of samples and culture media along microbiology diagnostic processes. So-called "fast AST" (fAST) reduces time to reporting from about 18-24 to 6-8 hours. Oliver Nolte concluded that a likely endpoint is a combined approach of POC diagnostics and fAST. The latter, process optimized approach, will serve the high-throughput situation in centralized CML and the former, a decentralized (external) setting. In the light of increasing volumes and newly available devices and test formats, the CML will have to assume an important coordinating and result-confirming role.

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POC Diagnostic Development – An Unbiased Clinical Approach

Another point-of-view on infectious diseases has Prof. ***Daniel Paris*** from the Swiss Tropical and Public Health Institute in Basel: "Diagnostic tests are essential to guide therapy and to serve control and elimination programs."

Ideally, POC rapid diagnostic tests (RDT) should be useful in remote endemic areas where no sophisticated laboratory infrastructure is available and should yield accurate results in a short period of time. "They should be inexpensive, easy-to-use and augment clinical decision algorithms used for management of regionally relevant diseases", the physician explains. However, currently available RDT are often not suitable or lack diagnostic accuracy to inform physicians on adequate patient management at the point-of-care level – let alone address the evolving needs of disease control and elimination. For example, fever is a leading reason for patients seeking health care in the world, but the causes of febrile illnesses remain poorly characterized. As multi-diagnostic and multi-analyte platforms are being developed, the critical need for better evidence and improved cross-talk between researchers and physicians of different endemic areas is now becoming apparent. Daniel Paris emphasized the importance of designing clinical components into the developmental stages of a POC test: "RDT development and validation should be seamlessly intertwined iterative processes aiming to improve a diagnostic platform to the high requirements of the POC setting. Next-generation POC RDT should also provide data on local epidemiology, thus enabling both rapid disease identification and surveillance at primary health care levels", he recommended in his inspiring talk.

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Mobile Health (mHealth)

At the Mobile Health Systems Laboratory (MHSL) of Prof. Walter Karlen at the ETHZ, Dr. ***Caroline Lustenberger*** is closely involved in the development of personalized, reliable and efficient methods and devices that can be used by anyone for applications at the point-of-care. "We aim at improving healthcare services and systems for patients and healthcare workers in both low and high resource settings", said Caroline Lustenberger. Using a 'Swiss Army Knife' approach, the research group integrates novel sensors, intelligent diagnostics (*i.e.* automated data interpretation tools), and quality control algorithms, capable of sensing and interpreting health status, and able to follow and modify bio-signals in both health and disease. The technologies involve mobile phone apps and wearable devices that can continuously track vital signs and physiological parameters to define health profiles, follow treatment efficacy and changes over time, and provide feedback-controlled approaches for non-invasive interventions. A particularly interesting project Dr. Lustenberger presented at the Symposium is a portable feedback-controlled system for non-invasive sleep enhancement. Insufficient and poor sleep over longer periods of time can have detrimental effects on our health. Research has shown that auditory stimulation *via* precisely timed tones played during deep sleep phase can improve overall sleep in both young and older adults. Brain activity recording and auditory stimulation are thus combined in the project 'SleepLoop' that one day may become a suitable system to treat and even prevent neurological and systemic disorders at the point-of-care.

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Precise, Intelligent, Mobile and Secure POC Diagnostics: How Can Tech help?

In the field of microfluidics the development of capillary-driven microfluidic chips for highly miniaturized immunoassays is one important area of activity of research of Dr. ***Emmanuel Delamarche*** and his group at IBM in Rüschlikon. In his enthralling keynote speech, he reviewed how capillary flow can be programed and specific functions encoded to form microfluidic elements that can be easily assembled into self-powered devices for immunoassays, reaching unprecedented levels of precision for the manipulation of samples and reagents. This technology can also be augmented using peripherals (*e.g.* smartphones) for flow control and monitoring with sub-nanoliter precision. Dr. Delamarche also presented a smart way to address the issue of counterfeiting in point-of-care diagnostics, which sometimes can have dramatic consequences. "Using capillary phenomena, we devised a method for producing in chips a complex signal with a *time domain* for authentication of devices", explained Dr. Delamarche. "All together, capillary-driven elements can bring extremely high control for manipulating sub-microliter volumes of samples and picogram quantities of reagents and may therefore extend the performances of microfluidic devices for POC diagnostics to a next level of precision."

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Magnetic Nanoprobe-based Mix & Measure Molecular Diagnostics for POC Applications

Homogeneous assays are particularly well-suited for POC applications, as they can produce analyte-concentration dependent signals directly within the entire sample volume by simple mix & measure techniques. "Methods based on magnetic particles are especially promising due to the added magnetic control of the particle labels, which enables acceleration of incubation processes or frequency-selective analysis for increased signal-to-background ratios", asserted Dr. ***Jörg Schotter*** from the Austrian Institute of Technology (AIT) in Vienna during his talk. His group introduced a novel homogeneous molecular diagnostic method that unites all of these advantages in a compact and inexpensive platform. The method is based on optically detecting changes of the dynamics of magnetic nanorod probes in an applied rotating magnetic field on analyte molecule binding. "Our nanoprobes are based on cobalt nanorods passivated by a noble metal shell layer system. Following synthesis, the nanorods are stabilized in aqueous solutions *via* coating by an amphiphilic polymer, and antibodies are bound to the nanorods by covalent links to carboxylic groups of the polymer shell", Dr. Schotter further outlined. The AIT-team with partners of the European FP7 funded project demonstrated binding experiments of the soluble domain of the breast cancer biomarker HER2 to the nanorod probes and determined the antibody and antigen size by model-fitting of the measured phase lag spectra. Additionally, they determined dose-response curves and deduced minimally detectable sHER2 concentrations in spiked samples of buffer solutions, human serum and saliva by performing sandwich-type assays.

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Dr. Emmanuel Delamarche was the Keynote Speaker at the Symposium which concluded the morning session 'medical needs' by providing elegant answers to the question "how can tech help?" and concrete solutions to known issues and limitations of products on the market. Photo by Sara Foser (Foto Fetzer).

The Symposium brought together stakeholders from science, medicine, and industry to discuss the opportunities and challenges of developing new and innovative point-of-care diagnostic products. Dr. Jörg Schotter from the Austrian Institute of Technology (AIT) in Vienna during his speech of the first afternoon session on 'key enabling technologies'. Photo by Sara Foser (Foto Fetzer).

Control and Management of Emesis Toxins

Immediate retrieval of contaminated food in the food manufacturing and supply chain may be an efficient way to prevent intoxications, so to speak at the point-of-care. Microbial peptidic toxins may manifest severe or lethal symptoms, *e.g.* liver failure, in children and elderly people and is interlinked with diabetes. "Today's existing tests, for instance human cell culture bioassays, are labour-intensive or they require purification steps prior to mass spectrometry (MS) based analysis", says Prof. ***Bruno Schnyder*** from the HES-SO Valais-Wallis. "In contrast, MALDI-TOF MS is a relatively simple, fast, and clinically certified method for routine identification of microbial cells, but it can also be used to detect extracellular factors, like microbial toxins." The sample preparation requires an overnight culture of the microbes at room temperature, which is not compatible with a true point-of-care approach in terms of timing. "However, a future generation sample collection and preparation device in combination with rapid MALDI-TOF MS and smart logistics may allow determination of presence or absence of emesis toxins in a shorter time interval", Bruno Schnyder puts into perspective.

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Digital Tools for Minimally Invasive At-Home Monitoring

What is the ideal personalized health and well-being monitoring system? "It is invisible, individual and predictive, allowing optimal health management", summarized Dr. ***Silvia Generelli*** from the CSEM in Landquart in her talk in Chur. "These tools or sensors will be completely embedded in the environment and will not be noticed by the person wearing and benefiting from them", she continued. The systems will ensure a continuous, personalized response at the level of the individual user, but as well manage the health on a population level. CSEM develops innovative, integrated electronic solutions with a great potential in the health and wellness domain. Examples include microsystems optimized in size and energy consumption – two aspects that are often taken care of too late during product development –, technological solutions integrated in the environment and advanced energy harvesting solutions as well as predictive deep learning models. During her speech Silvia Generelli presented several minimally invasive systems, especially for non-invasive body fluid monitoring.

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Challenges in the Implementation of POC Diagnostic Tests

Hospitals offer many different services for patients in hospital- and outpatient settings. These include laboratory diagnostics in centralized laboratories as well as POC testing solutions. Diagnostic pathways rely more and more on rapid test formats in order to reduce the turnaround time (TAT) for an optimal service to the patient and allow for better outcomes. "However, there are several challenges that have to be addressed (such as costs, staff education, maintenance, quality control issues, supply chain, interoperability of results, sourcing of resources) for a successful POC testing implementation", underlined Dr. ***Martin Risch***, head of the Central Laboratory of the Kantonsspital Graubünden (KSGR) in Chur. From the patient and MD perspective, a technically driven approach seems sufficient and desirable. Critical points for point of care testing cover test accuracy, additional cost burden and data connectivity. "At the KSGR we conceptualized a model describing and regulating the use of POC testing in our hospitals", emphasized Martin Risch. The concept endorses an interdisciplinary approach taking up the needs of the clinicians as well as the laboratory and the interfacing disciplines. The aims of the integrated concept are to

- ensure the availability of economic data of POC testing,
- increase availability, security and quality of the results obtained from POC testing,
- standardize processes and enable PDCA cycles in a quality system,
- clearly define responsibilities and education of the collaborators involved in the POC testing system, and
- integrate the POC testing activities in the existing IT-ecosystem.

Dr Risch summarized: "Several of the measures to be taken do not seem to be obvious at first sight. However, failure to comply with these issues leads to limited effectiveness of a POC testing program, as measuring a result is only one part of the overall process." Diagnostic stewardship is thus not only required in centralized medical laboratories but also in integrated POC testing programs.

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Fast Solutions for Protein Detection

The quick availability of the results of diagnostic procedures has direct economic consequences in all clinical settings, where results are required as soon as possible to ensure an immediate initiation of the correct medical treatments. Well-established immunoassays (such as ELISA) exist in various formats and with different automation solutions, however, the time-to-results of several hours are due to the long incubation times and multiple washing steps. Yet, Dr. ***Claudio Rhyner***, CEO of Davos Diagnostics, presented an application of an evanescence wave-based fluorescence biosensor technology for immunoassays, allowing a 10-minute time-to-result with a single pipetting step. The EVA system consists of an 8-well biosensor chip (EVA chip) produced of polystyrene (*i.e.* ELISA plate material) and the EVA reader to detect fluorophores bound to the EVA chip surface. The only manipulation required by the end user is to add a few microliters of the biological sample and insert the EVA chip into the EVA reader to obtain quantitative results in 10 minutes. Dr. Rhyner showed in his presentation how the EVA system can be used to detect total and allergen-specific serum IgE as well as to quantify serum cortisol levels in a competitive assay format. The EVA technology indeed has the potential to substitute certain immunoassays by significantly accelerating the TAT.

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Next-generation POC Diagnostics: Opportunities and Challenges

In the past decades chronical diseases such as diabetes and coagulation disorders dominated the POC testing field, but increased availability of modern immunological and molecular diagnostic platforms have given rise to infectious diseases (*e.g.* detection of influenza or the hospital pathogen *Clostridium difficile*) and oncology applications. The classical drivers for POC testing – fast clinical decision making in time critical situations or in resource limited settings – in future will be supplemented by the trend from reactive to proactive medicine. The rapid screening of (multiple) antibiotic resistant bacterial strains is yet another urgently needed application, so that physicians can initiate a targeted and timely therapy. In his 'big picture' talk Dr. ***Jörg Schickedanz*** from QIAGEN in Stockach (Germany) anticipated the further evolution of fitness trackers: "Trends in well-being and lifestyle will see the creation and spread of health checkpoints, for instance in hotel lobbies, airports, shopping malls *etc.* to serve the needs of next-generation globally travelling people.

Access to these checkpoints could be achieved by various payment models. Results could be collected in a cloud and would be accessible via smartphone and could be shared with every doctor worldwide. "Nevertheless, before this vision becomes reality a few technical, political, legal and ethical obstacles need to be overcome", Jörg Schickedanz concluded.

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Wearable Electrochemical Sensors: Toward Labs on the Skin

Wearable sensors have recently received major attention owing to their considerable promise for monitoring the wearer's health and wellness. The medical interest for wearable systems arises from the need for monitoring patients over long periods of time. These devices have the potential to continuously collect vital health information from a person's body and provide this information to them or their healthcare provider in a timely manner. Such sensing platforms provide new avenues to continuously and non-invasively monitor individuals and can thus tender crucial real-time information regarding a wearer's health. The plenary lecture of Prof. ***Joseph Wang*** from the University of California, San Diego, USA, discussed recent developments in the field of wearable electrochemical sensors integrated directly on the epidermis or within the mouth for various non-invasive biomedical monitoring applications. "Electrochemical sensors satisfy many of the requirements for wearable on-body devices, for instance high sensitivity and selectivity, inherent miniaturization possibility, low costs of manufacturing, low energy consumption and they are easy to be used", Prof. Wang explained. Samples can be sweat, saliva, tears or interstitial fluid (ISF) and analytes can be for instance metabolites, electrolytes, drugs, hormones or stress and disease markers. The clinical relevancy and validation aspects are much less established compared to blood sampling and analysis. "Biology is soft and curved, but electrochemical devices are rigid and planar", Joseph Wang continued. Therefore his research group also spent time developing stretchable sensors with elastomers, surfactants and stretch-enduring inks. A tattoo-based lactate biosensor to assess endurance is one example of a 'product' coming out of his lab. Another one is non-invasive glucose monitoring based on iontophoretic extraction of glucose from ISF combined with an enzyme-based amperometric sensor. The flexible, miniaturized electrode-based sensors can be worn also on the nose-pads of glasses, textile and clothing, wristwatches, on wound bandages (*e.g.* for melanoma screening based on tyrosinase biomarker) or on mouthguards. Minimally-invasive microneedle sensors are yet another approach to sense and act, *i.e.* deliver therapeutic agents locally. "Embedded wireless electronics support communication and data transfer", Joseph Wang said, but he also warned "attention is required to ensure information privacy and data security". Key challenges (including extensive validation) need to be overcome before emerging wearable sensing technologies can be translated into clinically and commercially viable products. "Today we are mostly at a proof-of-concept prototyping stage", Prof. Wang concluded his excellent and inspiring talk, "but with tremendous commercial opportunities in wearable biosensors, we can anticipate exciting new developments and rapid market growth in the future!"

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Skin-mounted microfluidic device for sweat sampling and continuous electrochemical monitoring of metabolites including a miniaturized flexible electronic board for real-time wireless data transmission (Photo by Joseph Wang, UC San Diego, USA).

Joseph Wang, University of California, San Diego (UCSD) – 'Wearable Electrochemical Sensors: Towards Labs on a Skin'

In *in vitro* diagnostics (IVD) including with POC diagnostic devices a sample (*e.g.* a blood drop) is taken and analysed off-line, *ex situ*. Analysis in-line or on-line (where a portion of the sample is bypassed, analysed and then returned to the system) is rare because it is technically challenging (for many analytes), probably not comfortable for the patient and luckily usually not necessary. However, if it were feasible and minimally invasive, real-time in-/on-line monitoring would offer the possibility to observe a trend and to flag a pathological above threshold value indicative of an incident possibly soon to occur. That would be preventive medicine – if a therapy were at hand.

Wearable electrochemical sensors that can tender crucial real-time information regarding the wearer's health is a specialty of Prof. Joseph Wang and his team at the University of California, San Diego. Integrated on the epidermis or within the mouth a variety of metabolites and electrolytes can be measured with flexible amperometric and potentiometric sensors.[1–4] Promises and challenges have been reviewed in recent years.[5,6]

Joseph Wang was born in 1948. He received his D.Sc. from Technion (Israel Institute of Technology) in 1978 and was a postdoctoral associate at the University of Wisconsin, Madison. After serving as the director of Center for Bioelectronics and Biosensors of Arizona State University (ASU) he joined UCSD where he is the SAIC Endowed Chair and Chair in the Department of Nanoengineering. He is also the director of the UCSD Center of Wearable Sensors. Professor Wang has published more than 1050 papers, 11 books and he holds 20 patents. He received two American Chemical Society National Awards in 1999 (Instrumentation) and 2006 (Electrochemistry) and several Honorary Professors. Prof. Wang is the Editor-in-Chief of *Electroanalysis* (Wiley). Joseph Wang's scientific interests are also in the area of nanomachines (nano-motors /-robots) where his research has received considerable attention by the scientific community and the media.

The 3rd edition of the SWISS SYMPOSIUM in Point-of-Care Diagnostics will take place on October 17, 2019 in the new campus building of the University of Applied Sciences and Arts Northwestern Switzerland (FHNW) in Muttenz.

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