integrated informatics solutions that integrate, store, and analyze clinical and omics data from diverse sources – generated in-house as well as public consortiums. Many researchers and clinicians must rely on bioinformaticians to perform mundane data management tasks in order to validate a simple hypothesis. Oracle Health Sciences Translational Research Center provides a complete and scalable informatics solution, with centralized data storage and analysis across genetic information areas (genomics, transcriptomics, and proteomics), vendor platforms, biological data types, and clinical data sources. Organizations such as Cancer Research UK, Erasmus MC, MD Anderson Cancer Center and UPMC have adopted this solution and are evaluating treatment responses for similar patients in a self-sufficient manner, ultimately shortening the biomarker development cycle and accelerating the adoption of personalized medicine.

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Metabolic phenotyping in mouse and man: Mind the differences!

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Abstract

Metabolic phenotyping comprises the quantification of endogenous metabolites in biofluids, cells, and tissues. It provides insights into normal as well as aberrant metabolic pathways and biological processes, which is important for the understanding of disease phenotypes. It also allows the identification of biological markers, which can serve as early disease indicators and therapeutic markers for the evaluation of treatment effects. As metabolic markers are not species-restricted, the concept of metabolic phenotyping is highly applicable for translational research. Species independence allows the use of established animal and cell culture models for various diseases within a preclinical context. However, differences in the metabolic set-up of study organisms compared to humans needs to be taken into consideration to prevent misleading conclusions from otherwise valid experimental designs. To determine species-related metabolic differences, a targeted metabolomics approach was applied using a mass spectrometry platform for the quantification of a predefined set of endogenous metabolites, i.e. amino acids, biogenic amines, phosphatidylcholines, sphingomyelins, hexoses, steroid hormones and others. Results from this species comparison on the metabolic level will be presented. Overall, the validity of metabolic phenotyping will be demonstrated, despite or even because of species-dependent characteristics. It has the potential to explain why findings in animal models cannot always be directly translated into clinical settings and might, therefore, facilitate the establishment of suitable models of disease.

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Bioinformatics challenges in the adoption of next generation sequencing for translational molecular diagnostics

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Abstract

Next generation sequencing (NGS) technologies are now widely used in medical research. NGS provides an unprecedented opportunity for high throughput analysis of genetic variations warranting their use in molecular diagnostics. However, among other obstacles, their adoption in clinics poses challenges in the provision for accurate and timely data analysis. A bioinformatics workflow for the analysis of the large amount of data from raw reads to final annotated variants suggesting their functional consequences with clinically actionable or reportable sensitivities and specificities is important. We have developed a number of targeted panels using NGS for the diagnosis of a number of haematological abnormalities and cancer. I will present the experience of development of bioinformatics workflows for the routine use of these panels for a busy molecular diagnostic service.

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Identification & characterization of tumor cells isolated from body fluids

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Abstract

The appearance of malignant cells in body fluids like urine, blood or body-cavity fluids are a clear indication for the existence of a tumor and urine or body-cavity fluid cytology are routine diagnostics today. Cytologic examination of the cellular features of fluids is a valuable adjunct to patient diagnosis and the staging and management of tumors. The German-language literature contains the earliest references to the cytology of malignant cells in fluid specimens. Preparation of the specimen has evolved from unstained wet smears to protocols that generally include centrifugation and the generation of stained smears and a cell block. The smears may be alcohol-fixed direct smears, cytospins, or a liquid-based preparation, and they are usually stained with the Papanicolaou method. Additional techniques, such as immunocytochemistry and flow cytometry, provide significant help in this differential diagnosis. Evaluation of microscopic images after Papanicolaou staining eluded digital pathology, an image-based information environment enabled by computer technology that allows for extracting information from a digital slide. With the advent of full-slide scanning digital methods are regarded as promising way to achieve better, faster and cheaper diagnosis, prognosis and prediction of cancer and other important diseases. One important feature are combinations with immunostaining, FISH technology etc., to elude additional information from the specimen. Circulating tumor cells (CTCs) can be found in the bloodstream and are always ready to attach to endothelial cells lining blood vessels and extravasate to enter tissues and organs to form a metastatic site. They show plastic phenotype and a small number of these cells undergo the epithelial-to-mesenchymal (EMT) program. De-differentiation and dissemination from the primary tumor is a basic prerequisite for colonization and growth of distant metastasis. Phenotypic and functional plasticity of cancer cells and the ability to adapt permanently to demanding conditions provide great challenge for identification and characterization of CTC´s from blood. Their clear identification and characterization is, however, also an important prerequisite to obtain valuable information for diagnosis and prognosis by downstream analytical methods. A novel platform for identification and morphological characterization of cancer cells in body fluids by digital methods is presented.

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Next-generation tissue microarrays (ngTMA) in translational research

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Abstract

Over the last two decades, prognostic and predictive biomarker studies in clinical and translational research settings have become

synonymous with tissue microarrays (TMAs). TMAs are essentially "tissue archives" created by repeated transfer of small tissue cores from formalin-fixed paraffin-embedded tissues ("donor" blocks) into empty paraffin blocks ("recipient" blocks). In this manner, more than 500 different tissue spots can be arrayed onto a single TMA. TMA applications include the investigation of morphology, protein and gene expression or chromosomal aberrations. These can be visualized using H&E stains, immunohistochemistry (IHC), fluorescence and chromogenic mRNA or miRNA in situ hybridization (ISH). Despite many advantages such as cost-effectiveness, conventional tissue microarraying has several major drawbacks: it is a laborious, time-consuming and does not allow for precise tissue regions/structures to be captured. For studies aiming to investigate specific histological regions (e.g. interface between tumor and stroma) or particular cell types, conventional TMAs fall short. Our Translational Research Unit at the Institute of Pathology, University of Bern has developed next-generation TMAs (ngTMAs). ngTMA represents a process of TMA consulting, followed by slide scanning and digital pathology, as well as rapid, precise and automated TMA construction. Briefly, consulting in all aspects of TMA design/construction is discussed including histopathology and statistical considerations. Next, case review is performed and the best slide and paraffin block for subsequent TMA annotation. The selected slides (H&E or other staining) of all cases are digitally scanned. Digital images of each slide are then uploaded onto the slide management platform (http//ngtma.path.unibe.ch/casecenter). The pathologist retrieves the slides. Then using a TMA tool of 0.6, 1.0, 1.5 or 2.0mm in diameter, the digital slide is marked in desired regions. Several annotations per tissue can be made. The donor blocks are loaded into the automated tissue microarrayer and punched exactly on the annotated regions producing an optimal ngTMA. The ngTMA blocks can then be sectioned for further staining including IHC, DNA silver ISH (SISH), mRNA ISH, miRNA ISH or a combination of these. Tissues can be heterogeneous and biomarkers may be relevant only in certain cell types of the same tissue, hence the quality of the selected regions for inclusion in TMAs is of the uttermost importance. ngTMA accomplishes this goal with precision, speed and high quality of TMA design and construction.

EU early access - regulatory framework & practical considerations

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Abstract

European Regulation 726/2004/EC (Article 83) and Directive 2001/83 (Article 5), provide a regulatory framework for access to investigational medicines outside the context of the clinical trial, allowing physicians to access potentially life-saving medicines that would otherwise be unavailable for their patients. Treatment with an investigational product represents an important option for patients suffering from serious or life threatening conditions where licensed alternatives are either unavailable or unsuitable for the patient. They can often be the only treatment option for disease areas of high unmet need such as rare diseases and orphan indications. Whilst the pharmaceutical industry has continued to focus on accelerating access to innovative new treatments by shortening the development timelines; increased regulatory challenges and delays due to pricing & reimbursement negotiations can result in delays of many years between positive phase III trials and commercial availability. Access Programs hence provide an important mechanism to bridge the time between clinical development, marketing authorisation and product launch. Although this EU framework exists, each member state has decided independently how and when to allow such access, and developed national rules and legislation to reflect this. As a result, there is no single, centralized European procedure for either single patient or cohort approaches; indeed there are often more differences between the member states than similarities. Generally, access is initiated by the physician,

is limited to investigational products for the treatment of a serious or rare disease and where there is an absence of alternative approved treatments. The objective of this article is to provide an overview of the regulatory frameworks available in the member states, as well as practical considerations for implementation of an access program.

Personalized medicine: Moving from correlation to causality in breast cancer

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Abstract

Personalized Medicine currently focuses on the right treatment for the right patient, but its long-term goal includes personalized risk assessment and prevention. Current emphasis focuses on advances in genetic testing and biomarker to enhance patient care. The considerable data generated by such approaches and access to patient EHR's has led to many statistically-based studies to predict disease risk and prognosis, e.g. the Gail model for breast cancer risk assessment; evaluation of BRCA mutation profiles; and expression level analysis of her2/neu for Herceptin response. Such correlative analysis has been used to enhance clinical-decision making but is limited in its potential for understanding mechanisms of risk and disease. We have extended these correlative approaches to include systems-based process modeling, extending from pre-disease risk to early detection, treatment and outcome, in an effort to develop models for testing and validation against both existing data and enhanced data collection. Development and testing of this approach in breast cancer will be presented.

Risk Assessment: We have begun to model risk assessment by including specific aspects of a patient's physiological development to help identify risk factors that can lead to improved guidelines for risk prevention. This can also identify specific causes for risk and disease through the course of normal breast development. Risk from any specific factor is something that changes over a person's lifetime and is not likely to be constant. Simple statistical correlation of a risk factor, i.e. do you smoke? do you smoke more than 1 pack of cigarettes per day? needs to evolve to show how risk from each factor varies over a person's lifetime/stage of development. This is because the molecular processes underlying physiological change also vary.

Methods: Risk factors were identified from the literature (from $RR = 1.0$ to > 4.0) and compared with those in the Gail model and then a physiological model of breast development, from pre-menarche to menopause, was drafted. These included both those included in the Gail model as well as other biomarkers, e.g. breast-feeding history, radiation exposure, oral contraceptive use, etc. A data set that represented a combination of actual and simulated patients, with 1458 patients in each, was used for the analysis. Univariate analysis was performed and comparison between the Gail model results and our models was performed using ROC analysis. Subsequent refinement eliminated several variables from consideration in the model.

Discussion: Our preliminary results begin to approach the specificity and sensitivity of the Gail model (AUC=0.957 (Gail model) and 0.745 (physiological model)) and further refinement is ongoing. By contrast, our model presents the opportunity to more directly personalize risk assessment based on an individual patient's characteristics and present the potential to develop management plans to reduce potential risk and to identify potential opportunities for biomarker/diagnostic development (and therapeutics) based on the specifics of the disease process unique to the patient.