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Overview of Contributions to This Section

The section on Data Generation Techniques: from omics to personalized approaches and clinical care, represents a collection of papers that cover the essential pillars of Systems medicine: experimental, clinical, and computational. An important focus is also on the clinical part since there is no medicine and no systems medicine without a deep participation of medical doctors and their patients.

Transcriptomics in sex-dependent liver pathologies addresses the experimental side of the nonalcoholic fatty liver disease NAFLD (lately termed metabolism-associated liver disease MAFLD, to omit the stigma connected to the term “alcoholic”) and is selected as a use case for transcriptomics. Even the classical microarrays that are today being slowly replaced by RNA sequencing showed excellent results in deciphering the molecular players of MAFLD and its progression to hepatocellular carcinoma, on experimental models and in humans. Not surprisingly, liver pathologies are considered as network diseases where the expression of the enriched gene sets and the noncoding RNAs intertwine. The overlooked sex (gender) in liver pathologies was discovered from the database-based statistical modeling and other stratification approaches that clearly showed that female and male livers are sexually distinct organs with different molecular pathways involved in transition from healthy to a diseased organ. A crucial part of good stratification is good experimental design, which can greatly improve the outcome of data interpretation. The next step in the liver omics approaches is the single cell level of transcriptomics. While hepatocytes are the most abundant cell type of this organ, liver holds also other cell types, such as cholangiocytes, macrophages, Kupffer cells, and other cells from the immune system. The technology is now ripe to address the liver disease pathogenesis at a single cell level which is a great promise for determining more precise disease players and drug targets in both sexes.

The chapter Multi-omics Analysis in a Network Context from the Baumbach laboratory is from the computational side. It opens the Pandora’s box of the classical view on the diseases, one multifactorial disease at a time. This leads to predetermined molecular pathways which in too rare occasions reveal novel molecular pathways that could explain the disease phenotype. De novo network enrichment approaches are proposed as a step forward to identify disease-associated subnetworks and also subnetworks that link different multifactorial diseases. Novel gene set enrichments tools are presented together with guidelines of what to use when. Among them is the combination of multiomics data with molecular interaction networks for de novo network enrichment. This forms the basis of systems medicine, which is thus often referred to as network medicine. The idea is to identify disease subnetworks as disease modules that can be associated with a known disease mechanism, some clinical characteristics, or survival of the patients.

Breathomics in Chronic Airway Diseases addresses the application of metabolomics in the clinics of chronic airway diseases, such as a largely prevalent asthma, where the burden is expected to increase, also due to complications provided by the Covid-19 infections of these patients. The technology applies exhaled breath as a noninvasive resource of volatile organic compounds that are a promising target for biomarker discovery. Limitations of the currently applied detection techniques are also discussed, where GC-MS seems to be most accurate for identification of compounds of the exhaled breath samples. From the clinical side the portable eNose technology is currently favored for bed-side and online patient monitoring. Novel real-time detection techniques are under development showing the applicability of breathomics for phenotyping and identification of airway disease subphenotypes, by sampling the patient data at the bed-side.

Digital Health for Enhanced Understanding and Management of Chronic Conditions describes Chronic Obstructive Pulmonary Disease (COPD) as a use case of noncommunicable diseases from the clinical perspective. A novel healthcare scenario is proposed where Systems Medicine and Integrated Care intertwine. It is not only about improving our scientific knowledge and addressing better the disease mechanisms; it is also about patients perceiving their own health, self-monitoring, and self-guiding the disease. COPD has a taxonomy problem associated with the simplistic diagnostic criteria where a disease phenotype can be given different names. The need for deciphering the key pathobiological mechanisms that drive COPD subtypes that can be used as potential therapeutic targets is thus high. Importantly, the “lung-centric” view of COPD fails to explain comorbidity clustering with other multifactorial pathologies where common roots seem to lie in the systemic inflammation. The technology of today gives promises for an effective and sustainable digital health strategy for COPD patient management in the future. This includes Telemedicine for remote exchange of data between patients and healthcare professionals, Digitally Enabled Health Services as supporting tools for cost-effective interventions/services, and the Learning Healthcare Systems. The final goal is to generate an operational platform that would favor synergies between health sciences and healthcare practice. This could pave the way toward a new medical era with a variety of labels, such as 4P medicine, precision medicine, deep medicine, and last but not least, systems medicine.
**Complexity of Patient Data** is also addressed from the perspectives of *Primary Care Practice* and family medicine. How to deal with the burden of big data if you need to diagnose a patient in a limited time-frame? What is essential for a primary doctor to know about technologies, disease networks, and computational approaches, to better guide a patient that presents with a multitude of potentially comorbid pathologies? The chapter opens the question of practical implications of big data in primary care. It also touches on the data management issues that are closely connected to ethical issues—the ownership of data, the privacy, the problems with incidental findings, and the right to know or not to know. The current situation with the data stored at multiple locations is a serious drawback for primary practice and the new data governance is needed. The family physician’s work is changing dramatically and will in the future require cooperation of different healthcare stakeholders and society. One of the remaining key questions is the responsibility for patient data. Despite the technological boom and developments in precision medicine, every person is a unique individual, and an individual’s health is determined by their unique genetic constitution combined with lifestyle and the environment. A human should never be considered solely as a data resource.

**Conclusions**

Understanding how individual genes and other molecular factors are involved in pathogenesis is a fundamental part of personalized medicine. However, to gain mechanistic insights, it is imperative to apply global and systems approaches, since genes do not act in isolation but in a concerted fashion. Not only treatment selection but also accurate prognosis, risk stratification, and early diagnosis can be improved with a deeper understanding of the molecular processes behind a disease. When working with human samples or only with human data, ethical rules should be enforced and privacy respected at all times.

*See also:* Breathomics in Chronic Airway Diseases. Complexity of Patient Data in Primary Care Practice. Digital Health for Enhanced Understanding and Management of Chronic Conditions: COPD as a Use Case. From Whole Liver to Single Cell Transcriptomics in Sex-Dependent Liver Pathologies. Multi-Omics Analysis in a Network Context.