The 7th Santorini Conference was held in Santorini, Greece, and brought together 200 participants from 40 countries in several continents, including Europe, USA but also Japan, Korea, Brazil and South Africa. The attendees had the opportunity to: listen to 60 oral presentations; participate in two lunch symposia; look at 103 posters, which were divided in two groups (‘systems medicine and environment’ and ‘pharmacogenomics and cancer’) and attend a dedicated exhibition with six companies. The meeting was organized by the Institut National de la Santé et de la Recherche Médicale (INSERM) U1122; IGE-PCV and by ‘Biologie Prospective’ with the collaboration of the European Society of Pharmacogenomics and Theranostics (ESPT), under the auspices of international organizations (e.g., International Federation of Clinical Chemistry and Laboratory medicine [IFCC], European Federation of Clinical Chemistry and Laboratory Medicine [EFLM], European Diagnostic Manufacturers Association [EDMA], Federation of European Pharmacological Societies [EPHAR], European Science Foundation [ESF]). The 3 days of the conference stimulated intensive discussions on systems biology and the influence of omics technologies on personalized health. Sixty speakers were invited or selected from early abstracts and gave presentations on the following topics:

- From systems biology to systems medicine/pharmacology;
- Omics/translating pharmacogenomics/proteomic biomarkers/metabolomics;
- Human nutrition and health/personalized medicine.

We are summarizing here the main topics and presentations, according to the successive sessions.

**From systems biology to systems medicine**

**Chairs:** Charles Auffray, Lyon, France/ Gérard Siest, Nancy, France

Bruno Sobral (Munich, Germany) introduced the subject of systems medicine by explaining how information and communication technologies, and the conceptual framework of complex system studies can be used to understand the critical points of health maintenance and prevent disease development. He insisted on the importance of environment and social behavior in addition to the molecular and cellular components in shaping health and disease. As unique individuals and collectively as families, communities and societies, we must adapt to live in complex and ever changing environments. Yet, it is an inherent biological component of life to tend toward health. How do we highlight and support health when noncommunicable, chronic diseases (NCDs) threaten the hearts, minds and bodies of individuals and governments alike? Using data for obesity as an example, Bruno Sobral emphasized that friendship networks are important in building weight perception, setting weight goals and measuring social marginalization among
adolescents and young adults, suggesting avenues for effectively reversing the worldwide trend of the obesity epidemic.

Ines Thiele (Luxembourg) enters more specifically in the systems biology/systems medicine theory through the development of biochemical networks. She presented the most comprehensive metabolic reconstruction of human metabolism, which has been recently assembled in a large community effort, and some promising biomedical applications made possible through this work. She first illustrated how this metabolic reconstruction and the derived cell-type-specific models can be used to further our understanding of the network-wide metabolic effects of single enzyme defects that are often associated with metabolic diseases. Indeed, through constraint-based analysis, they were able to predict novel biomarkers and to investigate systemic, metabolic effects associated with rare metabolic diseases. She then presented the ongoing plan to apply this knowledge and methodology to cancer using 120 different cancer cell lines and following their glucose metabolism, with the hope to understand the molecular basis of the Warburg effect and provide novel avenues for cancer management and treatment.

The results of an FP7 consortium project ‘SYSCI-LIA’ were presented by Ronald Roepman (Nijmegen, The Netherlands). He beautifully illustrated why cilia are ideal organs for systems biology as they can be regarded as semi-closed systems, being largely separated both spatially and biologically from many other cellular structures and processes. Indeed, primary cilia act basically as cellular signaling hubs, harboring among others the noncanonical Wnt and Hedgehog signaling systems. Their disruption upon genetic mutation leads to striking developmental defects and a plethora of disease phenotypes, the ciliopathies, that can result, for example, in blindness, deafness as well as cancer, or obesity. Early proteomics studies have suggested a discrete repertoire of about 1000 proteins within the organelle (i.e., <5% of the proteome) that were still in need of organization into pathways and networks. The Consortium identified and mapped the core of over 200 ciliary and ciliopathy-associated proteins within the ciliary proteome into an integrated network that covers most of the ciliary space. By overlaying several high content datasets (siRNA screening data, genetic variation) and scrutinizing the associations in a systems-wide manner, models of cilium (dys-) function were generated that support further diagnostic and therapeutic developments for many important chronic conditions, illustrating how systems biology can contribute to progress in medicine with clinically applicable knowledge.

Nicolas Froloff (Vélizy-Villacoublay, France) presented a very sophisticated information and communication technology program developed for 5 years by the European/French research private and public consortium ‘Biointelligence’. The goal was to develop an integrated digital environment to support the discovery and development of new biological entities and products (from molecules to biological pathways, cells, organs), for life sciences industries and research institutes, and in particular for pharmaceuticals, cosmetics and agrochemicals, including the regulatory aspects. This global collaborative environment for multidiscipline scientific innovation, which now provides a unified platform for exploring and analyzing biological information (which is intrinsically heterogeneous and extremely diverse), and for formulating scientific hypotheses to be tested experimentally in the laboratory. Nicolas Froloff presented the applications of this new platform with a drug discovery simulation project, illustrating how in silico models supported by this bioknowledge can be built, numerically simulated and confronted to experimental data. He also emphasized how the Biointelligence platform can be used to support the integrated management of all discovery and development activities by relying on the foundations necessary to all involved multidisciplinary R&D teams (collaboration, industrial processes coverage and certification).

The applications of this new platform were presented.

From systems medicine to systems pharmacology

Chairs: Naoyuki Taniguchi (Wako, Japan) and Magnus Ingelman-Sundberg (Stockholm, Sweden)

Giulio Superti-Furga (Center of Molecular Medicine, Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna) presented a lecture entitled “The dawning era of systems pharmacology and genome medicine”. He explained that the Center of Molecular Medicine, (Ce-M-M) is now challenging to turn genomic biology into improved medical practice. He also mentioned promising novel drugs like for example, Imatinib/Gleevec that turned a deadly disease into a manageable problem. Other nice examples are Crizotinib/AIle with highly active antiretroviral efficacy, and moreover, numerous biologicals such as anti-TNF, trastuzumab/Herceptin that are the epoch-making drugs. However there are still problems with drugs, as because half of diseases are not treated specifically, half of specific treatments are to no avail. One-size-fits-all blockbuster treatments are exceptions and not compatible with current understanding of diversity. Side effects and adverse effects of treatment are a burden.

Biologically active chemical compounds produce complex molecular responses already at the cellular
level. Giulio Superti-Furga’s group has investigated the mechanism of action of several compounds in clinical use against cancer. They used a number of approaches in parallel. These are chemical proteomics (affinity purifications with drug matrices/MS), chemical genetics (random mutagenesis of genome of near-haploid CML cells), functional proteomics (affinity purification/MS), transcriptional profiling, phosphoproteomics, computational network analysis and modeling and validation by focused gene inactivation (RNAi and genome editing). His group see a detailed picture of the actual molecular events and requirements of the drug under investigation. Using this integrated approach, they have identified new targets for known drugs, previously unknown mechanism of drug resistance, ‘effector’ genes for the compound (genes required for the drug to exert its action), mechanisms of synergy between compounds and in a few cases and new medical use of existing drugs. He introduced several examples and one of them is as follows. Genotoxic chemotherapy is the most common cancer treatment strategy. However, its untargeted generic DNA-damaging nature and associated systemic cytotoxicity greatly limit its therapeutic applications. His group used a haploid genetic screen in human cells to discover an absolute dependency of the clinically evaluated anticancer compound YM155 on solute carrier family member 35 F2 (SLC35F2) that is highly expressed in a variety of human cancers. YM155 generated DNA damage through intercalation, which was contingent on the expression of SLC35F2 and its drug-importing activity. SLC35F2 expression and YM155 sensitivity correlated across a panel of cancer cell lines, and targeted genome editing verified SLC35F2 as the main determinant of YM155-mediated DNA damage. The SLC35F2 enabled YM155-mediated DNA toxicity. In summary, haploid genetics complements other suite of chemical biology approaches to drug action.

Drug in clinical testing (YM155) entirely relies on unknown transporter. So many SLCs are orphan or poorly understood and the pharmaceutical industry is beginning to understand that understanding SLCs is not a nuisance but an opportunity. Thus he emphasized that ‘systems-level’ characterization of chemical entities should help understanding the biology of drug action better and allow the development of improved drugs and eventually contribute to the employment of mechanism-based combination therapy with existing drugs.

Allen Roses (Duke University Medical Center, Durham and Cabernet Pharmaceuticals, Inc., NC, USA) gave a lecture entitled ‘The dawning era of systems pharmacology and genome medicine. Pharmaceutical drug trials, generalization of ethnicities and disease risk, genetic admixture’.

Roses et al., mentioned in their published paper on Alzheimer’s disease (AD) that “Preventing or delaying the onset of cognitive impairment and AD will provide the greatest benefit to individuals and society by pushing the onset of disease into the later years of life.”

He first explained ‘Missing Heritability, 2014’. Many papers published since 2005 have provided some specialized insight as to why complex disease heritability is difficult. Most analyses are, however, based on current technologies and genome-wide association studies (GWAS) as poor indicators and complete exome sequencing covers only below 1% of the genome.

Emerging datasets exist which suggest ‘junk data’ holds the answers. A Roses also emphasized strongly that current GWAS and sequencing methodologies that are widely used in the field have generally failed to define translational routes to drug discovery and development because GWAS was not designed to identify complex disease genes, but to locate 10–20 Kb regions on the genome and candidate genes from GWAS generally have complicated translation by the large number of false positives. Moreover he said a spread of a million SNPs across the genome guarantees that above 99.999% of them would be negative for a small defined region, and any positive associations must be corrected for a million tests. He also explained that phylogenetic DNA mapping provides a roadmap for each individual.

Phylogenetic mapping provides a method to illustrate the order of evolutionary mutations as they occur within a linkage disequilibrium (LD) region. LD regions which are defined by rare cross-over events that occur over evolution, multiple SNPs and other genetic biomarkers also provide positive association data, this strategy can be applied in other complex disease besides AD, as well as in efficacy and adverse effect discovery.

Rs10524523 polymorphism designated as 523 is a variable length, deoxythymidine homopolymer located in chromosome 19 at position 45403049 within intron 6 of the TOMMO40 gene. TOMMO40 encodes the essential mitochondrial protein import translocase, and is adjacent to, and in LD with, the ApoE gene. In the human reference sequence, the number of ‘T’ residues in the homopolymer is 35, and the variant allele described by rs10524523 is a 19 bp deletion. In other words, the variant allele is 16 T residues. In 2010, using a deep sequencing and phylogenetic analysis approach, Allen Roses discovered that TOMMO40 523 contributed to the genetic risk and age of onset of late-onset Alzheimer’s disease (LOAD, MIM 104310) in ApoE three out of four patients.

He showed that variations in the expression of mRNAs of both TOMM40 protein and ApoE proteins
are dependent on simple sequence repeats (SSRs) large variations in the TOMM40–523 size distributions and allele frequencies in multiple ethnicities.

In summary, he emphasized that SSRs are highly important in all individuals and are major contributors to genome variation. He also pointed out that SSRs have functional implications in the gene regulation and are important clinically in terms of drug development and regulatory implications.

He emphasized the importance of the accuracy to map their position in the genome, to measure their variation and to get highly positive association with an LD region, or no association at all, to discriminate the false positives that plague GWAS gene lists.

**Randox Lunch symposium – Helena Murray (Randox Laboratories, UK)**

'Rheumastrat' is a molecular tool for predicting response to anti-TNFα therapy in rheumatoid arthritis patients.

Rheumatoid arthritis (RA) is a chronic inflammatory disease which affects approximately 0.5–1% of the global population [1]. Early diagnosis and immediate, effective therapy are crucial in order to prevent joint destruction, functional disability and unfavorable disease outcome [2].

In the past decade biologic therapies for RA, such as anti-TNFα, have revolutionized clinical outcomes where disease remission has become a realistic goal. Their adoption is a good example of where targeted therapy has led to major progress. These agents are, however, expensive and around 30–40% of patients fail to respond adequately. There is therefore a growing need to identify biomarkers that predict inefficacy or side effects early.

Genetic variants are ideal markers of response as they are stable over time, relatively inexpensive to assay and are present before treatment initiation [3]. In collaboration with clinical partners a novel biochip array, Rheumastrat has been developed, to stratify RA patients into responders or nonresponders of anti-TNF-α therapy. The array is based on a combination of multiplex polymerase chain reaction (PCR) and biochip hybridization enabling the simultaneous detection of up to 23 genetic biomarkers in less than 3 h. Biomarkers were selected from genes known to influence immune regulation through associations with cellular responses, the major histocompatibility complex (MHC) or NFκB signaling processes. The ultimate aim of the array is to include a composite algorithm for prediction of response facilitating direct application in the clinical setting. This approach may promote timely and efficacious treatment to the arthritis patient leading to improved disease control and quality of life, consequently contributing to reduced costs for healthcare providers.

**Understanding cancer through systems medicine**

**Chairs: Marc Ansari (Geneva, Switzerland) and Janja Marc (Ljubljana, Slovenia)**

The session opened thanks to Jean Clairambault (Paris, France), who spoke on drug resistance in cancer cell populations. The proposed mathematical modeling in cancer models may be considered as generalizing evolutionary game theoretical models. Theoretical tracks were exposed to better understand phenomena that are still poorly understood: tumorigenesis, synergies between therapies and drug resistance. Drug-induced drug resistance may be due to biological mechanisms of different natures, mere local regulation, epigenetic modifications or genetic mutations (most likely both), according to the extent to which the genome of the cells in the population is affected. Drug resistance in cancer cell populations was assessed by biological experiments and by mathematical modeling of cell populations as structured according to relevant continuous traits, amenable to describe phenotype heterogeneity better than discrete traits. Therapeutic consequences from the point of view that epigenetic is a reversible phenomenon and that theoretically could be optimized by using numerical optimization algorithms may lead to innovative drug delivery strategies, taking tissue heterogeneity phenotypes (stochastic polyclonality) into account and achieving ways to control it by modifying tissue environmental variables may lead to such innovative therapeutic strategies. Multiscale modeling involving transcriptional control at the cell level together with cell population dynamics at the tissue level seems to be necessary to predict cell population fate, under therapeutic control or not, from single-cell genomic data.

Claire Rioualen (Marseille, France) received the young scientist travel award from the scientific committee which enabled the presentation of her interesting work on cancer stem cells (CSCs) regulatory circuit at this meeting. These stem cells present key properties including self renewal (which drives tumorgenesis) and differentiation. They show resistance to conventional cancer therapies, and are thought to be the seed for the distant metastasis responsible for poor clinical outcomes. This study deciphered this circuit through an interactome–regulome–transcriptome integrative approach using a systems biology strategy. By unraveling deregulated mechanisms that are sustaining self renewal and differentiation specific to CSCs some essential step for the discovery of new research avenues and treatment in cancer targeting stem cell could be possible. To identify regulatory circuits driving breast cancer (BC) stem cell biology a functional whole genome screen of a miRNA
library identified miR-600 as a modulator of CSC self renewal and differentiation. A two-step integrated approach based on an Interactome–Transcriptome Integration (ITI) algorithm was taken in order to identify genetic modules postregulated by miR-600. Modules with significantly deregulated expression in the human interactome (protein–protein interactions) were identified as well as pathways regulated by miR-600 in CSCs, using ITI and a regulation map based on TRANSFAC data (protein–DNA interactions). By crossing the results of this two-step integrated approach, ten miR-600-regulated network modules driving CSC differentiation were found. Several transcription factors (RBM5, CEBPA, NMUR2), tumors suppressors (EGR1, TP53) and genes known to regulate stem cell pathways (WNKI, a regulator of Wnt signaling) were identified. The identification of biological pathways involved in CSC biology was achieved by integrating gene expression data and network information (including physical interactions and regulatory relationships). This study leads to the discovery of new potential druggable targets specific to the CSC population, which would allow refining, personalized treatments in BC.

Ivan Brandslund’s presentation was focused on the usefulness of serum marker HER2 (S-HER2) in monitoring of trastuzumab treatment and at the detection of disease recurrence. The aim of the study was to prepare the new suggestions for the clinical use of S-HER2 marker. The presentation showed the interesting results of the prospective clinical study and included 48 patients treated with trastuzumab and monitored up to 6 years until death. These results were combined with the results of a much larger cross-sectional study where 1348 breast cancer patients were monitored to detect metastatic disease. In all patients, S-HER2 and trastuzumab serum levels were measured at each time point. Authors found that the decrease of S-HER2 for more than 20% was correlated with remission of disease in 20 out of 21 patients and also the increase of S-HER2 for more than 20% was associated with the progression of disease in 40 out of 44 patients. In addition, patients without relapse after trastuzumab treatment had nearly 20-times lower S-HER2 concentration compared with patients with relapse of the disease. The use of S-HER2 marker in detection of metastatic disease was also studied and the sensitivity of 69% with the specificity of 71% of serum HER2 were determined but only in HER2-positive breast cancer patients. The authors concluded that S-HER2 correlates well with the effects of treatment. Decreasing values of S-HER2 predicts response to treatment, whereas increasing levels predict resistance to trastuzumab treatment. S-HER2 above 1000 μg/l warns that standard doses of trastuzumab may be insufficient as reflected by low concentrations of trastuzumab in the serum. It was also shown that in patients where S-HER2 cannot be normalized with application of trastuzumab, prognosis of disease is bad. The study showed that serum HER2 marker could be used first, in trastuzumab treatment decision and second, at individualizing the trastuzumab dosage regiments and therefore represents a nice example of the use of serum diagnostic marker for personalized care.

The last speaker in this session was Rui Medeiros from Portugal. His lecture was a very interesting topic linking the cancer in depression. The several mechanisms for this association have been shown mostly based on increase of chronic stress among depressed patients. It has been suggested, that deregulation of oxidation, hypoxia and inflammation presented in untreated major depressive disorder (MDD) could relate to an increased risk of cancer or to more aggressive type of cancers. In the introduction of the lecture three of major theories on biological bases of depression and antidepressants responses were presented in order to make the overlapping of the monoamine depletion, the increased activity of hypothalamus–pituitary–adrenal (HPA) axis and neurotrophic/neuroplasticity with the cancer signaling pathways and find the potential links between MDD and cancer. In the lecture later, five interesting examples of links between depression and cancer were presented. These links were built on common genes and the genetic changes involved in both pathologies, depression and cancer. In a smart way, Dr Medeiros shows the possible interplay of hypovitaminosis D, changes in renin–angiotensin system (RAS), EGF system and inflammatory mediators in cancer and depression. However, no definitive conclusions could be made after this literature review. As both diseases are very often present in combination and together, the new evidences and new studies on linking the cancer and depression will be welcome.

Translating pharmacogenomics into clinical medicine

Chairs: Urs Meyer (Basel, Switzerland) and Ron HN Van Schaik (Rotterdam, The Netherlands)

In his introduction, Urs A Meyer (Basel, Switzerland) discussed the paradox of an increasing knowledge base of clinically relevant gene–drug interactions and the slow translation of this knowledge into clinical practice. Important barriers to clinical implementation of pharmacogenomics include: a paucity of peer-reviewed guidelines and clinical decision support systems, and the limited availability of genomic test results at the point of care. Major progress in addressing these barriers in the last few years is represented by publications of the
Clinical Pharmacogenetics Implementation Consortium (CPIC) of the NIH’s Pharmacogenomics Research Network and the Dutch Pharmacogenetics Working Group, providing peer-reviewed data on how to interpret genotypes and predict phenotypes and how to use this information for therapeutic decisions. In addition, new sequencing and microarray technologies allow the accurate and inexpensive analysis of gene variants. Incorporation of test results into the electronic medical record (EMR) as a prescripation patient characteristic, or pre-emptive genotyping, combined with computational clinical decision support delivered through the EMR provides physicians with the tools to make optimal therapeutic decisions. Urs A Meyer in his lecture then summarized the recently reported experience with pre-emptive genotyping of several USA medical centers [4] and presented screenshots of exemplary ‘digital signatures’ of predicted drug response and decision support from EMRs. In one study, with five gene/drug pairs tested (CYP2C19/clopidogrel; SLCO1B1/simvastatin, CYP2C9-VKORC1/warfarin; TPMT/thiopurines, CYP3A5/tacrolimus) pre-emptive genotyping revealed that more than 90% of 10,000 patients carried at least one high-risk pharmacogenomics variant. His conclusion was that, in the future, the question may no longer be whether to order a pharmacogenomics test, but how to best use the already existing genomic test results.

Mark Bartlett (London, UK) also discussed the translational gap in pharmacogenomics. He presented a study in which the opinions of physicians on the usefulness of pharmacogenetic data in a clinical setting was evaluated. The online survey revealed that in general terms the physicians’ view of pharmacogenetic was positive, but the confidence in pharmacogenetic information was low. This confidence increased markedly with the hours of courses in pharmacogenetics, clearly pointing to the need for further education of these prescribers. The results from this survey were then used to develop a model for practice guidelines and prescription advice. The individual reactions to this model by a group of prescribing physicians will again be quantitatively tested.

Maria del mar Maldonado (Granada, Spain) presented her analysis of five clinical trials in which the effect of infliximab (antibody against TNF-α) on clinical biological markers of Crohn’s disease (Crohn Disease Activity Index, C-reactive protein) was evaluated. Based on a literature review, the analysis included SNPs of several genes (genes for TNF-α receptors, FCGR3A, IL1B). The conclusion of the analysis is that several of these SNPs are indeed associated with modifications of efficacy and in particular that the V/V genotype for FCGR3A may be a predictor of the biological response to infliximab, and the C-allele of IL1B may be a predictor of inefficacy. These findings should now be confirmed in a prospective clinical study.

Ramon Cacabelos (Corunna, Spain) reported on a clinical study in 920 patients with Alzheimer’s in which the potential influence of the polymorphism of the TOMM40 gene on the response to a multifactorial treatment was evaluated for 1 year. Details of the rs10524523 or ‘523’ variable length polymorphism of TOMM40 and its interaction with the variants of the APOE gene have been presented in the lecture of Alan Roses in the ‘From medicine to systems pharmacology’ section.

The results of the study indicate that the best responders to treatment were carriers of the T1–35, T1–37, T1–36 and T1–6 variants of TOMM40 whereas the worst responders were the patients carrying the T1–15 and T1–29 variants. An association of these responses with APOE genotypes was also observed, carriers of the APOE3/3 genotype being most prominent among responders and APOE4/4 genotypes among nonresponders to therapy. It is not clear yet if these findings have implications for the therapeutic approach to these patients.

Candan Hizel (Eskisehir, Turkey) addressed the point of lack of knowledge among clinicians as one of the barriers for uptake of pharmacogenetics. He focused on the interpretative side of pharmacogenetic test results, and showed an Expert System (C2H VichyGenomics, Vichy, France) as a decision support tool which could help bridging the gap between pharmacogenetic test result outcomes and actionable results. This particular database contains environment–gene, gene–gene and drug–gene interactions on several cytochrome P450 genetic tests. Thus far, this system has not yet been integrated into electronic medical records.

Markus Paulmichl (Salzburg, Austria) presented the pharmacogenetic variation of the Kosovar Albanian population, for which not much information is available. Analyzing blood samples from 100 individuals for 158 SNPs in 29 pharmacokinetics-related genes using the QuantStudio platform revealed this information, including copy number variation.

Ron HN van Schaik (Rotterdam, The Netherlands) talked about the integration of pharmacogenetic knowledge into routine clinical care. Indicating the large inter-individual variation in drug metabolism and the potential use of genetic testing to predict this, the uptake of this type of diagnostics is still low. Professor van Schaik demonstrated several reasons for slow uptake he encountered in his 10-year experience for translating pharmacogenetics from research into clinical use. Often, these reasons go beyond the plain evidence of the usefulness of a particular test. An important aspect he addressed was the need for a European Network to deal with specific implementation challenges each and every laboratory is fac-
ing when trying to implement this form of diagnostics. The goal of such a network is to ensure uniform, high-quality PGx testing for patient care. Issues as to which SNPs to determine, which quality these analyses should have, how to translate these SNP results to general interpretations and how to provide specific dosing advice are important aspects that a European Network can achieve. Such learning from each other will facilitate uptake, and importantly, help in harmonization in an early stage. He reported on the first meeting of the European Pharmacogenetics Implementation Consortium (Eu-PIC) in Santorini (chair Professor Ron Van Schaik), in which participants of 13 countries (NL, GR, PT, UK, DE, PL, IT, SI, TR, MY, BE, FR, DK) got together to exchange experiences and solutions for particular pharmacogenetic implementation problems. At this meeting, also the start of Eu-PIC as applicant for a HORIZON2020 grant was announced, aiming for Eu-wide implementation of PGx testing in which 36 participants from 17 European countries will be participating [1].

**ThermoFisher lunch symposium: a high-throughput real-time PCR approach to pharmacogenomics studies**

**Moderator:** Peter Jacobs, Gent, Belgium

Advances in personalized medicine have led to an increase in pharmacogenomics studies that involve testing individuals for drug metabolism enzyme and transporter gene polymorphisms implicated in drug response. As a consequence, there is a growing demand for affordable, easy-to-use technologies with fast sample-to-result workflows that can accommodate testing customizable sets of target gene variants and a changeable number of samples. Additionally, data analysis tools are needed to facilitate translation of an individual’s genetic information to their diploid content of gene-level star allele haplotypes, which can be correlated with drug metabolism enzyme phenotypes. We presented the development of a comprehensive pharmacogenomics experiments workflow solution to meet this need. High-quality data were generated from purified buccal swab DNAs run with TaqMan® SNP genotyping and copy number assays in OpenArray® and 384-well plate formats, respectively, on the QuantStudio™ 12K Flex system. Data analysis was accomplished using TaqMan Genotyper™ Software to examine SNP genotyping assay results and CopyCaller® Software to examine copy number assay results, followed by translation of this genetic data for individual samples to star allele genotypes using the recently developed AlleleTyper™ Software. The specific TaqMan SNP Genotyping and Copy Number Assays to gene variants used can be tailored to suit the needs of a given pharmacogenomics study. This low-cost, high-throughput pharmacogenomics workflow can be completed in a single day, from sample preparation to data analysis.

**Proteomic biomarkers in systems pharmacology and medicine**

**Chairs:** Mathias M Müller (Vienna, Austria) and Ivan Brandslund (Vejle, Denmark)

In his lecture on systems glyco-biology for understanding the underlying mechanisms of disease onset, biomarkers and therapeutics, Naoyuki Taniguchi, showed in a very elegant way, utilizing advanced biochemical methodology, how different metabolic pathways regulate and how sugar residues are coupled to proteins. He refers to this as the glycan cycle.

Low sialylation is found in different cell models and diseases. It is proposed that the role of glycans is underestimated in the development of diseases. He proposed that analysis of glyco-biology could be useful both in understanding disease processes but also in diagnosis and monitoring.

Bernhard R Winkelmann (Frankfurt, Germany), in his lecture on personalized medicine in cardiovascular disease, led the audience through the present knowledge on the prospectives for an individualized tailored treatment using genetics and proteomics, though he emphasized a cautious approach to the hype around these new possibilities.

Michel Seve (Grenoble, France) in his lecture on proteomic approaches for biomarker identification in chronic lung allograft dysfunction focused on the identification of biomarkers of value in early detection of immunemediated restriction of the function and acceptance of the allograft. As 39,000 lung transplantations have been carried out worldwide during the last 30 years and a declining function is still difficult to diagnose before the onset of irreversible damages, such biomarkers are crucial to develop.

This project is an EU-funded project named SysCLAD where biomarkers are identified by MS in bronchoalveolar lavage fluid. Preliminary results show that proinflammatory mediators and loss in tissue repair processes can be observed before damage occurs.

Biljana Smiljanovic (Berlin, Germany) lectured on the value of gene expression profile analysis in stratification of rheumatoid arthritis patients versus osteoarthritis patients, both in bone marrow and blood. This identified protein candidate markers which when analyzed in blood were able to discriminate between RA-patients and osteoarthritis patients. They also were able to identify differences between RA patients. It was
proposed that this approach is useful for identifying new protein markers for disease management.

Charles R Cantor (MA, USA) in his lecture: ‘Towards liquid biopsies in cancer and other human diseases’ updated the audience on methodologies to identify specific DNA fragments in plasma by a new technology using DNA MS. The sensitivity of the methodology is around 100 molecules/ml.

The idea is to detect and quantify tumor cells by their unique somatic mutations not present in normal cells.

The approach was shown to be in accordance with somatic mutations found in conventional tissue biopsies. The method requires that somatic disease specific mutations exist, which is not the case in all cancers, and this calls for development of epigenetic DNA markers as a supplement.

The approach is promising for detection of certain types of cancers expressing cancer-specific mutations, for monitoring and for detecting response or resistance to treatment.

Metabolomic tools for clinical implementation of personalized medicine

Chairs: Ron A Wevers (Nijmegen, The Netherlands) and Maurizio Simmaco (Rome, Italy)

The lecture by Maurizio Simmaco about the kynurenine pathway of tryptophan metabolism illustrated the clinical importance of this pathway in the pathophysiology of neurological and psychiatric disorders. Metabolites of this pathway are known to interact with ionotropic and metabotropic glutamate receptors, thereby influencing excitatory neurotransmission in the CNS. Levels of kynurenic acid have been found to be increased in the CSF and brain tissue of schizophrenic patients. The group of Simmaco developed an HPLC/MS-MS assay that allows a reliable estimation of all metabolites of the kynurenine pathway. They found a strong reduction in blood levels of 3-hydroxykynurenine and xanthurenic acid, and a significant increase in blood levels of anthranilic acid in a large cohort of schizophrenic patients. First-degree relatives of schizophrenic patients had levels of xanthurenic acid intermediate between those found in schizophrenic patients and healthy subjects. Unexpectedly, blood levels of kynurenic acid were unchanged in schizophrenic patients. Thus, a reduced formation of xanthurenic acid, a putative agonist of group-II metabotropic glutamate receptors (mGlu2/mGlu3 receptors), might contribute to the pathophysiology of schizophrenia.

Thomas Jönsson also on behalf of John Ryals both from Metabolon, Inc. (NC, USA), defined metabolomics as “the nonbiased quantification and identification of all metabolites present in a biological system.” The company developed an integrated, robust and high-throughput analytical platform for targeted metabolo-

omics incorporating three UHPLC/MS/MS² accurate mass methods and a GC/MS method for the analysis of biological samples. They focused on diseases associated with obesity and urological cancer. After the discovery of biomarkers for insulin resistance and impaired glucose tolerance, they validated diagnostic tests for these markers and commercialized both tests. The general idea is to develop tests for the early stage of the obesity-related diseases for early detection and early intervention. Using this approach, we have determined the mode of action of antitumor compounds as well as identifying biomarkers related to the onset of prostate cancer. These biomarkers have now been developed into a diagnostic test for better detection of cancer-positive patients in digital rectal examination negative patients with intermediate levels of prostate-specific antigen (PSA).

Ron Wevers introduced ‘Next generation metabolic screening’. His group uses untargeted metabolomics techniques (NMR spectroscopy and LC-Qtof-MS) for the diagnosis of patients with inborn errors of metabolism. The challenge is to find the relevant biomarker(s) that reflect the fingerprint of a specific disease and provide information about the course of the disease. The approach with LC-Qtof-MS detects a very broad range of small molecules in the complex matrix of body fluids (urine, plasma or CSF). Sensitivity of the Qtof method goes down to the low nanomolar range. The Qtof-MS provides a very accurate mass of each metabolite. Approximately 10,000 signals are detected in a single blood plasma sample. These are interpreted using an in house developed chemometric pipeline. The work of the Nijmegen group shows that the relevant biomarker profile can be picked up in an individual patient without prior knowledge of underlying disease or condition. The Qtof technique was clinically validated and is applied in patient care in Nijmegen since 2014. Although this technique was developed for applications on inborn errors of metabolism the further perspective reaches out to biomarker discovery and validation on other diseases like infectious disorders or cancer diagnostics and further. Using this approach we enter the era of personalized medicine and make a big next step in biomarker use in laboratory medicine.

Human nutrition & health

Chairs: Martin Kussmann (Lausanne Switzerland) and Vangelis G Manolopoulos (Alexandroupolis, Greece)

Diet is the most important environmental factor for maintaining health and preventing disease. The increasing incidence of complex, age-related chronic diseases calls for intensifying and improving translational healthcare research. Understanding the interactions of nutrition and lifestyle with an individual’s genetic makeup
is necessary to prevent or delay metabolic and cognitive decline and to complement the reactive pharmaceutical approach to treat symptoms. Such translational research requires an interdisciplinary systems approach that embraces human individuality and complexity in a changing environment. Gene–environment interactions caused by dietary and lifestyle factors contribute to this physiological heterogeneity observed in human studies. Therefore, the risk factors determined for populations cannot be applied to the individual. Developing individual risk or benefit factors in light of human genetic diversity, culture and lifestyle as well as food complexity, and of the various metabolic processes that contribute to health or disease is a prime objective for personalizing dietary advice for healthy or chronically diseased and medically treated individuals.

In this context, Martin Kussmann and Jim Kaput (Lausanne, Switzerland) introduced and presented their research at the Nestlé Institute of Health Sciences (NIHS), which takes a systems approach to better understand and act upon healthy aging and disease prevention with a focus on metabolic, cognitive and intestinal health. NIHS’ omics platforms are generating a systems view on the metabolic trajectory of human subjects. The emphasis lies on ‘trajectory’ as NIHS monitors these human subjects not only in groups at a given moment in time but also longitudinally, in other words, over time, with every biological entity functioning as its own case/control pair, rather than comparing a case to a control group by taking omics snapshots at a given moment in time. A further innovative angle is to assess metabolic elasticity and flexibility rather than comparing systems at homeostasis: challenging biological systems repeatedly over time and monitoring their (failure of) oscillation back to normality yield early insights into possible deviations from healthy metabolic trajectory and open windows of preventive opportunity.

George V Dedoussis from the Harokopio University of Athens, Greece, followed with clinical research on nonalcoholic fatty liver disease (NAFLD), which is defined as the hepatic manifestation of the metabolic syndrome, associated with excess body weight, systematic insulin resistance, environmental factors (most importantly diet) and genetic susceptibility. Greek adults were recruited and monitored for NAFLD status using abdominal ultrasonography. Data on demography, medical history, dietary intake, anthropometry and biochemistry were collected. The liver ultrasound revealed a high incidence of NAFLD in Greek volunteers. The disease status was predicted by classical anthropometric and biochemical risk factors. Specific food intakes appeared to either protect from or aggravate the disease.

Next, Steffen Gay from the University Hospital Zürich, Switzerland, introduced epigenetics as a regulator of gene expression, encompassing acetylation, methylation, phosphorylation, sumoylation and non-coding RNAs (ncRNA). Dr Gay focused on environmental risk factors in autoimmune diseases. In numerous rheumatic diseases such as rheumatoid arthritis, novel epigenetic diagnostic signatures and therapeutic strategies are emerging, for example, miRNA and modulating the methylation, respectively.

In the following presentation, Vadim A Stepanov from Tomsk State University, Russia, asked the question whether obesity is a decanalized phenotype. Stepanov et al. investigated the distribution of SNPs associated with obesity according to recent GWAS in worldwide populations. A group of (non-neutral and decanalized) markers demonstrated significant correlations of allele frequencies with key climatic parameters of the populations; accumulation of positive signals of natural selection; and systematic decrease of ancestral allele frequency from Africa to Eurasia. A second group of (neutral) genetic obesity markers exhibited neutral genetic variability. The observed worldwide frequency spectrum in obesity-associated genes may be, at least partially, explained by the hypothesis of canalization/decanalization of genotype–environment relationships under the pressure of natural selection.

Finally, Vesna Dimitrijevic-Sreckovic from the University Belgrade, Serbia, reported on abdominal obesity and its impact on depression in adolescents and young. Central adiposity triggers inflammatory factors, which in turn cause endothelial dysfunction. In the CNS, these inflammatory factors influence neurotransmitter metabolism by promoting excitotoxicity and oxidative stress. A major clinical symptom in that state is depression. The group found that abdominal obesity accompanied with hyperinsulinemia, insulin resistance, altered lipid status, hypertension, inflammation and micro-albuminuria was more pronounced in the depressed young, and depression correlated with systolic blood pressure and micro-albuminuria.

**Environment & human health**

**Chairs:** Steffen Gay (Zurich, Switzerland) Bernhard Winkelmann (Frankfurt, Germany)

Hans Hauner, holding the Chair of Nutritional Medicine at the Technische Universität München, Germany, lectured on the prevention of diabetes risk through actions on the environment. He summarized the lifestyle and environmental risk factors of Type 2 diabetes (T2D) and highlighted that despite the power of obesity to promote the development of T2D, only 30–40% of the obese population will develop T2D. As long as the pancreas is capable to compensate for insulin resistance by increased insulin production and
secretion, obesity and the associated insulin resistance will not cause T2D. To date, almost 100 risk loci have been identified explaining 15% of the variance.

By challenging the GWAs data it is important to note that the risk loci identified by GWAs contain dozens of gene variants with the causal one(s) usually being unknown and most variants are in the noncoding area and thus may be involved in the regulation of gene expression in a tissue-specific fashion.

During the discussion Steffen Gay from the Department of Rheumatology at the University Hospital of Zürich, Switzerland pointed out that especially the ncRNAs turn out to be important in gene regulation. Hans Hauner reported further on the genotype-specific regulation of lipid metabolism and insulin sensitivity at the PPARG locus (rs4684847) via the novel cis-regulatory variant and PRRX1. It is a societal challenge that at least a third of participants to lifestyle intervention programs and weight loss programs do not adequately respond, he continued. He concluded that more research is needed to better understand the causes and heterogeneity of T2D and, in particular, the interaction between genes and environmental factors. Prevention and intervention programs should be evidence-based and that combined efforts of all stakeholders (government, food industry) are needed to facilitate ‘healthy choices’ in a healthy environment.

Maria Zellner from the Medical University of Vienna, Austria presented the development of a platelet biochip array, which could detect an Alzheimer’s disease (AD) phenotype in blood platelets. The claim is that the biomarkers identified are disease specific. By showing shared biological similarities of platelets and neurons, AD-specific biomarkers were evaluated. Upregulated proteins included: MaoB, Tm1, ApoE4 and GSTO1*A140. Biochip analysis identified 98% of all samples of the GSTO1*A140 and 100% of the APOE ε4 genotype by normalization with either ERK2 or pan-ApoE concentrations. Also, Tm1 and MaoB replicated the higher expression of these two proteins in AD patients relative to controls. An algorithm utilizing these four biomarkers yielded the highest separation power for AD and control samples with a receiver operating characteristic (ROC AUC) of 0.969 (95% CI: 0.944–0.994). It will be very interesting to proof this multiplex device in various clinical settings and cohorts.

Tomasz Zemojtel, from the Charité, University Clinic, Berlin, Germany lectured on the effective recognition of rare inherited disease by computational phenotype analysis combined with targeted next-generation sequencing. About 7300 Mendelian diseases are known, but there is a huge heterogeneity of clinical syndromes. Therefore, patients with rare diseases typically wait years for a diagnosis. The research-based approach uses whole exome sequencing in order to identify genetic causes of Mendelian disorders. However, the exome typically contains 20,000–30,000 variants, many of which are located in genes that have no established link to a disease. Thus, his group focused on the part of the genome with 2742 Mendelian disease genes, where a clinical detection is possible. The clinical phenotype was based on the structured data of the Human Phenotype Ontology project [2]. The HPO database links to 7278 human hereditary syndromes which are listed in OMIM, Orphanet and DECIPHER.

A software tool called the phenomizer matches the clinical presentation of the patient (matching the different abnormalities in HPO terms to the closest HPO disease phenotypes). The group developed the software tool PhenIX which stands for phenotypic interpretation of exomes. This software approach is based on the HPO database with the Phenomizer plus a variant prioritization with predicted pathogenicity (based on Mutation Taster, Polyphen, SIFT databases). The PhenIX software ranks the detected gene variants with the clinical presentation (coded as HPO terms) in order to identify the responsible Mendelian disease. Using this approach the group was able to detect a specific Mendelian disorder in 12 out of 40 patients with a long diagnostic odyssey without any result. Thus, the diagnostic yield of their approach was 30%, which is excellent for patients in whom no diagnosis was possible so far.

Robert Barouki, from the INSERM unit 1124, Université Paris Descartes, Paris, France lectured about the concept of the human exposome. A significant proportion out of the totality of chemical, physical, biological as well as social and psychological stressors to which humans are exposed throughout their life may have significant health effects. The exposome concept was developed by C Wild (2005) and is intended to complement the genome in epidemiological studies. Studies of the human exposome use any method that is found to be relevant for assessment of a certain exposure, but research-wise large-scale methods such as the new omics technologies (i.e., metabolomics, adductomics, transcriptomics) are needed.

What makes the task to study the human exposure so daunting is the fact that interaction occurs among the thousands of chemicals implicated. One approach is to focus on the interaction of toxicological pathways as a first step. The group of Professor Barouki studied the interaction of ligands of the aryl hydrocarbon receptor (dioxin) with activators of the PXR and ER pathway (endosulfan) as well as with genotoxicants, using either large-scale transcriptomics or targeted signaling studies. The study of the interaction between dioxin and etoposide showed that the activation of apoptosis elicited by the latter was prevented by dioxin [3]. Besides focusing on
the influence of combination of chemicals on toxicological pathways such as those assayed in the USA Toxcast and Tox 21 programs, he emphasized that ultimately, the interaction between a variety of chemical stressors should be addressed, as well, using the high-throughput methodologies developed in those programs.

The future of healthcare with omics

Chairs: Behrooz Z Alizadeh (Groningen, The Netherlands) and Graham Beastall (Glasgow, UK)

Jacques Beckmann from Lausanne, Switzerland outlined a fascinating vision of the future in his presentation entitled ‘Clinical bioinformatics: a paradigm change in medicine’. He suggested that in less than a decade clinicians may have available a vast array of data for individual patients, including whole genome sequencing; longitudinal epigenetics, protein expression for specified tissues and metagenomic information. The key to analyzing and presenting this data lies in effective bioinformatics, which will enable both physicians and patients to understand and manage the significant findings for the individual patient. In discussion there was acceptance that the technology will be available in this time frame but some concern about the capacity of society to manage the ethical challenges that will arise.

Ruth Chadwick from Cardiff, UK provided a thought-provoking talk on what we understand by personalized medicine. Coming from a legal and ethical background her presentation, entitled ‘Where’s the person in personalized medicine?’ challenged the audience to distinguish between ‘personalization’ and ‘individualization’ and she explained this dilemma with several alternatives as applied to genomics. The tailoring metaphor of ‘bespoke’ or ‘made to measure’ served as a useful illustration. An already complex area is likely to be complicated further by the impact of epigenetics and ‘downstream omics’. Unless clarity can be gained at international level then ‘personalized medicine’ will mean different things to different people with consequences of ethics and levels of responsibility for individuals, institutions and healthcare authorities.

Josep Roca from Barcelona, Spain presented the findings from ‘The Synergy-COPD Project’. With clarity he described the systems medicine approach to aid understanding of the nonpulmonary determinants of heterogeneity in the common and debilitating condition of chronic obstructive pulmonary disease (COPD). The study focused on underlying mechanisms of skeletal muscle dysfunction and co-morbidity clustering. Evidence emerged of abnormal regulation of pivotal skeletal muscle pathways and an increased risk of co-morbidity in COPD, which could be used to assist clinical decision support for individual COPD patients. This project served as a valuable model and learning experience for the application of systems medicine to individual patients with complex chronic diseases.

Finally, Andres Metspalu from Tartu in Estonia described the benefits that are emerging from the decision of the Estonian government taken 10 years ago to establish the Estonian Genome Center and the Estonian Biobank. In his presentation he described the establishment of the eHealth database and the commencement of projects aimed at preventing or delaying the onset of complex chronic diseases, including cardiovascular disease and certain cancers. There is strong public support in Estonia for genetic studies. Public health education is an essential component of the project because individuals not only provide a blood sample and personal lifestyle information but they will also be encouraged to modify behavior and reduce their personal health risk as part of the ongoing partnership. As a small and relatively homogeneous population Estonia is well placed to undertake this national initiative.

General discussion on the implementation in Europe of systems and personalized medicine

Chair: Gérard Siest (Nancy, France) and György Németh (Budapest, Hungary)

Charles Auffray (Lyon, France) presented the CASyM road map of systems medicine in Europe. Casym funded by seventh EU framework program is a consortium bringing together 22 partners from 11 European countries and more than 70 associated partners.

Systems medicine needs the interconnection of clinical data, of basic research data and mathematical modeling. But before, standardization of all assays and harmonization is necessary including for language. These basic ideas were developed during different European workshops and three priorities were defined:

- Personalized education to ensure engagement of patients, politicians and professionals;
- Data access and integrity: to ensure personal data protection;
- Cross-generation solidarity: to trigger acceptance by society.

Other European projects on personalized medicine were presented shortly by Gérard Siest (Nancy, France). The definition of personalized medicine is not clear. Many other words are used such as: stratified medicine, translation medicine but all are using pharmacogenomic data as examples. One of the definitions is clearly not a good nomination precision medicine. Precision is a very well-defined term in laboratory medicine and should not be used instead of personalized medicine but it is perhaps too late to change american politics.
Permed is an FP7 program with 18 partners and 8 cooperative partners. A recent meeting identified 33 Permed recommendations which gave 16 selected recommendations by the partners: reclassify diseases, increase the understanding of the omics and the big data strategy, promote models for the individual ownership of personal health data, incorporate patients participation, support transdisciplinary collaboration, educate health professionals.

Other European organizations are promoting personalized medicine, i.e.: the European Alliance for Personalized Medicine (EAPM) which is efficient for convincing the politicians from the European Union on the interest of this strategy for the health of the 500 million of citizens.

Finally the Innovative Medicines Initiative (IMI) a joint undertaking between the EU and the European Pharmaceutical Industry Association (EFPIA) supports collaborative research projects focused on personalized medicine and the needs of society.

A short presentation from the EMA was done by the vice-chair of the pharmacogenomics expert group (Committee for Medicine Products for Human Use – CHMP), Markus Paulmichl (Salzburg, Austria). This group integrates genetic end points and polymorphisms in the guidance at the earliest stages of drug development. Recent policy developments in the EU aim to tackle some of the key issues responsible for the limited adoption of personalized medicine approaches so far, in other words, biomarkers/clinical and analytical validity/harmonization of sample handling in biobanks. Personal data protection is a high priority as the establishment of the value of personalized medicine.

The last presentation of this session was done by Magda Kalata (Brussels, Belgium) in the name of EDMA (European Diagnostic Manufacturers Association) representing 22 national organizations and 43 major companies engaged in the research development, manufacturing or distribution of in vitro diagnostics (IVDs). She focused the presentation on the importance of companion diagnostics for personalized medicine. More particularly the IVD legislation should fit for purpose.

A general discussion closed this session on the clinical implementation of pharmacogenomics and personalized medicine and the reasons of too-slow evolution.

Acknowledgements
We wish to thank the members of the Scientific Committee for their help with building this program: Auffray Charles (Lyon, France), Beckmann Jacques (Lausanne, Switzerland), Brand Angela (Maastricht, Netherlands), Bruce Jordan (Rotkreuz, Switzerland), Bühlmann Roland P (Schönenbuch, Switzerland), Deloukas Panos (Cambridge, UK), Fitzgerald Peter (Crumlin, Co Antrim, UK), Jacobs Peter (Gent, Belgium), Kepes François (Evry, France), Kussmann Martin (Lausanne, Switzerland), Manolopoulos Vangelis G (Alexandroupolis, Greece), Meier-Abt Peter (Basel, Switzerland), Meyer Urs A (Basel, Switzerland), Michel Gerd (Singapore), Ndiaye Ndeye Coumba (Nancy, France), Noyer-Weidner Mario (Berlin, Germany), Siest Gérard (Nancy, France), Superti-Furga Giulio (Vienna, Austria), Van Schaik Ron (Rotterdam, Netherlands) and Visvikis-Siest Sophie (Nancy, France).

Financial & competing interests disclosure
We thank all our sponsors, in particular our gold sponsors (Bühlmann Laboratories, Life Technologies, Nestlé Institute of Health Sciences, Randox and Zinfindel), our silver sponsors (Agilent Technologies, GlaxoSmithKline, Servier, TEVA), and our bronze sponsors (CEA, Lumines, Ipsen, Metabolon, Siemens and Sequenom) and also DeGruyter and EuroEspes. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References
2 Human Phenotype Ontology (HPO). www.human-phenotype-ontology.org
Affiliations

Gérard Siest
University of Lorraine, UMR INSERM U1122; IGE-PCV, Nancy, France

Charles Auffray
European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL, Université de Lyon, France

Naoyuki Taniguchi
Systems Glycobiology Group, RIKEN, Japan

Magnus Ingelman-Sundberg
Department of Physiology & Pharmacology, Karolinska Institutet, SE 171 77 Stockholm, Sweden

Helena Murray
Randox Laboratories Limited, Crumlin, Co. Antrim, UK

Sophie Visvikis-Siest
University of Lorraine, UMR INSERM U1122; IGE-PCV, Nancy, France

Marc Ansari
Pediatric Department, Onco-Hematology Unit, Geneva University Hospital, Geneva Switzerland/Geneva University Medical School, CANSEARCH Research Laboratory, Geneva, Switzerland

Janja Marc
Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia

Peter Jacobs
Thermofisher Scientific, Gent, Belgium

Urs Meyer
Biozentrum, University of Basel, Basel, Switzerland

Ron HN Van Schaik
Erasmus MC Rotterdam, The Netherlands

Mathias M Müller
Austrian Society of Quality Assurance and standardisation, ÖQUASTA

Ron A Wevers
Translational Metabolic Laboratory, Department of Laboratory Medicine, Radboudumc, Nijmegen, The Netherlands

Maurizio Simmaco
Department of Neurosciences, Faculty of Medicine & Psychology, Sapienza University of Rome, Rome, Italy

Martin Kussmann
Nestlé Institute of Health Sciences, Lausanne, Switzerland

Vangelis G Manolopoulos
Laboratory of Pharmacology, Medical School, Democritus University of Thrace, Alexandroupolis, Greece

Behrooz Z Alizadeh
Department of Epidemiology, University Medical Center Groningen, The Netherlands

Graham Beastall
International Federation of Clinical Chemistry & Laboratory Medicine President, US

György Németh
Richter Gedeon Pl, Budapest, Hungary