CONFERENCE REPORT

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MATERIALS OF NOBEL SYMPOSIUM 175: PRECISION MEDICINE TRANSFORMS HEALTHCARE: A NEW TRAJECTORY FOR RESEARCH AND INNOVATION SEPTEMBER 20—22, 2023, STOCKHOLM, SWEDEN

Nobel Symposium 175 was organized by Professor Richard Rosenquist Brandell of Karolinska Institutet and was supported by the Royal Swedish Academy of Sciences. The focus of the symposium was a discussion on the development of precision medicine in infectious and rare diseases, cancer, and complex diseases. Presentations and discussions concerned new technologies, bioinformatics, and new diagnostic and therapeutic approaches based on findings in basic research. Organization of precision medicine models and their implementation in medical practice at the national and international levels were also on the agenda. 29 scientists from different fields of medicine presented their work during a three-day exciting trip into the future of patient' care. Panel discussions shed light on the development of precision medicine for better treatment of patients.

The symposium was opened by Jakob Forssmed, Minister for Social Affairs and Public Health of the Swedish Government. He touched upon the issue of the interaction of medical science with artificial intelligence (AI). He thinks that AI will help with the analysis, visualization, creation of models, and formation of networks.

A keynote lecturer, Professor Olli Kallioniemi (SciLife Lab, Karolinska Institutet) discussed the new avenues in precision diagnostics. He presented the data on 11 hallmarks for acute myeloid leukemia (AML). The only data-driven hallmark strongly associated with prognosis for

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AML patients was the presence of cancer stem cells (CSCs). To propose a personalized treatment, the genetic, transcriptomic, epigenetic, proteomic, and metabolomic data should be analyzed, as well as blood biomarkers and properties of single cells in the spatial context.

The first session was dedicated to ***Precision diagnostics in rare diseases***. The novel treatment concepts in neuromuscular diseases were reported by Professor Jerry Mendell (Nationwide Children's Hospital, USA). He presented clinical data on gene therapy for the treatment of pediatric patients with spinal muscular atrophy diseases; this method can be used after an individual gene analysis. The precision therapy of cystic fibrosis was discussed by Professor Jane Davies (the National Heart & Lung Institute, UK). Professor Anna Wedell (Karolinska Institutet) presented data on the implementation of precision medicine in inherited metabolic diseases.

Precision medicine requires new ways to perform clinical studies, using many different types of big data that help in diagnostics and treatment. Now developing bioinformatic tools are conspicuous in the stepwise spread of a collaborative environment for the treatment of different diseases.

The second session was dedicated to ***Precision hematology***. Professor Sten Eirik Jacobsen (Karolinska Institutet) focused on leukemic CSCs. He described experimental ways to identify CSCs *in vivo*, monitor, and therapeutically target distinct sets of CSCs, as their elimination is sufficient for the development of curative cancer therapies. Professor Elli Papaemmanouil (Memorial Sloan Kettering Cancer Center, USA) talked about the therapy-related myeloid neoplasms (tMN) risk in cancer patients. The increasing implementation of clinical sequencing at diagnosis provides an opportunity to identify patients at risk of tMN for prevention strategies. Professor Laurence De Level (Lausanne University Hospital, Switzerland) presented data on different types of non-Hodgkin lymphomas with a wide range of histological appearances, genomic profiling, molecular complexity, and clinical features. In discussion, the following issues were considered: I) refining of definition and classification criteria; II) genomic testing as a standard in certain diseases improving clinical care of patients; III) filling the gap between the depth of understanding and the actual possible therapeutic interventions — genomic configurations of bad prognosis remain not druggable; IV) evolution of the established prognostic markers with newly developed therapies, etc. As a bright example of successful practical implementation, Professor Eric Duncavage (Washington University, St. Louis, USA) presented his data on using the whole genome sequencing (WGS) technology for AML classification. Another working model was presented by Professor Richard Rosenquist Brandell (Karolinska Institutet). This model, Genomic Medicine Sweden, is implementing precision medicine in a regionally organized healthcare system. He showed that cooperation is required at all levels — national, regional, and international, to share and use the data and to continue implementing technologies together, such as multi-modal diagnostics and clinical decision support tools/AI.

At session 3 ***Precision oncology***, Professor Razelle Kurzrock (Michels Rare Cancers Research Laboratories, MCW Cancer Center) presented a new model of therapy development. The innovative precision cancer medicine trial was based on the idea that treatment should be determined by key molecular "hubs" that must be targeted within the tumor cells. Such therapy should be only administered where tumor cells possess such hubs. Professor Fabrice André (Gustave Roussy Cancer, France) presented data about the impact of genomic sequencing on selecting treatment for patients with metastatic breast cancer. Professor Ulrik Lassen (Department of Oncology, Rigshospitalet, Denmark) discussed the role of genetic, RNA, and immune profiling and protein expression patterns in deciding on

patient treatment. Professor Albrecht Stenzinger (Institute of Pathology, Heidelberg, Germany) spoke about the impact of experimental results on the development of precision cancer medicine. Doctor Bettina Ryll, representing Melanoma Patient Network Europe (MPNE, Sweden), discussed an important issue, namely the rights of cancer patients in the era of precision medicine.

At session 4 ***Precision medicine in complex diseases***, Professor Paul Franks (Novo Nordisk Foundation, Denmark) discussed the global perspective of precision medicine for cardiometabolic diseases. Precision medicine focuses on minimizing errors and improving accuracy in medical decisions and health recommendations. Moreover, genomic medicine has proven its efficacy for diagnosis and treatment guidance for monogenic disorders, flagging drug contraindications, the novel target discovery, causal inference, and elucidation of disease mechanisms. Professor Naomi Wray (University of Oxford, UK) showed prospects of precision medicine in the treatment of psychiatric disorders. She emphasized the importance of genomics for a better understanding of psychiatric disease mechanisms. Professor Eleftheria Zeggini (Helmholtz Zentrum München, Germany) presented data on the use of translational precision medicine in osteoarthritis.

In principle, information about clinical data, genomics, epigenomics, transcriptomics, and proteomics allows trans-ethnic fine-mapping, molecular profiling of primary tissue, establishing the function of associated variants, and developing mechanistic models. This all gives abilities for translational medicine.

At session 5 ***Precision medicine beyond genomics***, Professor Anna Lindstrand (Karolinska Institutet) talked about the impact of multi-omic diagnostics on rare diseases. Since about 80% of rare diseases are of genetic origin, including monogenic diseases and chromosome abnormalities, complementing WGS with RNA sequencing, optical genome mapping, and long-read genome sequencing will help to diagnose correctly. Professor Sascha Dietrich (University of Duesseldorf, Germany) reported about proteogenomics that refines classification and risk-stratification for hematological malignancies. A detailed analysis of the dataset improves understanding of the biological heterogeneity of chronic lymphocytic leukemia (CLL) and provides molecular phenotype-based subtypes which will improve patient stratification and personalized treatments. Professor Berend Snijder (Institute of Molecular Systems Biology, ETHZ, Switzerland) presented data on drug profiling-based precision cancer medicine, especially important for hard-to-treat patients.

The best examples in practice were presented by Professor Jordi Merino (Copenhagen University, Denmark), concerning precision nutrition in cardiometabolic diseases and by Professor Peter Johansen (Danish National Genome Center, Denmark), concerning the Danish experience of building the National Genome Center.

Session 6 was devoted to ***Precision medicine in clinical microbiology***. Professor Per Falk (Ferring Pharmaceuticals, Switzerland) discussed the issue of whether the microbiome can guide researchers to better treatment outcomes for patients or not. Professor Judith Breuer (University College London, UK) presented data on the advances in precision medicine for infectious diseases. Metagenomics and precision medicine of infectious diseases are the backbones of improved pathogen detection enabling precise prevention and treatment.

At session 7 ***Innovative Informatics Solutions/Data Sharing***, Professor Christian Gilissen (Radboud University Medical Center, Netherlands) presented his vision on how to solve "unsolved with novel bioinformatic tasks". He said that data-sharing and studies on large cohorts enable the application of statistical approaches to identify new genetic causes of diseases. Only

new technologies allow for improved identification, leading to more precise diagnoses and new ways of treatment.

Finally, session 8 was dedicated to international ***Perspectives of precision medicine***. Professor Kjetil Tasken (Institute for Cancer Research, Norway) informed the audience how precision cancer medicine is implemented in Norway. Collaboration between science and industry is very important for easier translation of new drugs into clinical treatment. Professor Aarno Palotie (Institute for Molecular Medicine Finland FIMM, Finland) talked about how via using the Finnish population structure and nationwide health records, it is possible to better understand the genetic basis of diseases. He showed how the global biobank meta-analysis initiative (GBMI) is used for choosing treatment in each specific case. GBMI is a collaborative network of 23 biobanks from 4 continents, representing more than 2.2 million individuals who consented to the use of their genetic data linked to electronic health records. The appliance of GBMI improves risk prediction and allows for the selection of genes and proteins as drug candidates by incorporating gene and protein expression data and providing insight into the underlying biology of the disease-body interaction. Professor Sue Hill (National Health Service, UK) presented how the genetic testing of all patients should be used to propose novel approaches for genetic medicine. The focus was on the WGS, which allows for the optimization of the use of medicines, the prediction of drug and pathogen resistance, and the development of effective treatment.

Each session ended with a fruitful panel discussion. For now, precision medicine could be seen as an iceberg, and above the water surface is only the genome. The transcripts, proteins, metabolites, lipids, spatial organization, immune system, tumor heterogeneity, and plasticity are below the water surface. More work should be done to bring new knowledge from ocean depth, and precision medicine is a new scientific field that contributes much to this assessment.