Genomic Medicine in Action Symposium 2019
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Speaker abstracts

Genomic Medicine Sweden

Mark Caulfield
Chief Executive and Chief Scientist, Genomics England

The 100,000 Genomes Project – transforming genomic health

The UK 100,000 Genomes Project has focussed on transforming genomic medicine in the National Health Service using whole genome sequencing in rare disease, cancer and infection. Genomics England partnering with the NHS established 13 Genomic Medicine Centres, the NHS whole genome sequencing centre and the Genomics England Clinical Interpretation Partnership (3250 researchers from 24 countries). We sequenced the 100,000th genome on the 5th December 2019 will complete an initial analysis for all participants by the end of July 2019. Alongside these genomes we have assembled a longitudinal life course dataset for research and diagnosis including 1.6 billion clinical data points for the 3000 plus researchers to work on to drive up the value of the genomes for direct healthcare. In parallel we have partnered the NHS to establish one of the world's most advanced Genomic Medicine Service where we re-evaluated 300,000 genomic tests and upgraded 25% of tests to newer technologies with an annual review. The Department of Health have announced the ambition to undertake 5 million genome analyses over the next 5 years focused on new areas tractable to health gain

Natacha Couto
Department of Medical Microbiology and Infection Prevention, University Medical Center Groningen, University of Groningen, Netherlands

Clinical Metagenomics and bioinformatics pipelines

Classical microbial culture is still considered the gold standard in clinical microbiology. However, microbial culture is laborious and time-consuming and new methods are needed to replace it. Additionally, molecular detection techniques have been implemented but these are generally geared towards specific pathogens (e.g. specific RT-PCR or microarrays). Shotgun metagenomics (SMg) is a culture-independent technique that provides valuable information not only at the identification level, but also at the level of molecular characterization. As sequencing technologies have evolved rapidly SMg is now open for implementation in a routine diagnostic setting. However, many challenges remain and one of them is the bioinformatics pipelines. Various tools exist for the analysis of SMg data, and their selection remains a choice of the user and the available computational capacity, which makes reproducibility a trial. Yet, numerous goals can be achieved by performing SMg directly on clinical samples including taxonomic profiling, antimicrobial resistance gene detection, and typing.

Claudia Haferlach
MLL Munich Leukemia Laboratory, Munich, Germany

Feasibility and impact of whole genome and whole transcriptome sequencing in the diagnostic work-up of hematological neoplams

The spectrum of genomic abnormalities present in hematological neoplasms is wide and encompasses gross and submicroscopic aberrations including copy number alterations, structural variants and small nucleotide variants. Thus, to date for a comprehensive genetic work-up a set of cytogenetic and molecular genetic techniques are performed. As sequencing technologies have evolved rapidly whole genome sequencing (WGS) and whole transcriptome sequencing (WTS) are ready to be tested in a routine diagnostic setting. At MLL whole genome and whole transcriptome sequencing was performed up to now in more than 4000 samples from patients with various hematological malignancies in order to evaluate the feasibility of WGS and WTS in a routine diagnotic setting and the impact both techniques might have on the diagnostic work-up of hematological neoplasms in future. First analyses revealed a high detection rate by WGS and WTS of genomic abnormalities identified by standard diagnostic procedures. Thus, WGS and WTS can provide in an “all in one test” all relevant information required for classification and treatment decisions in hematological neoplasms with a high potential to substitute current genetic evaluation based on chromosome banding analysis, fluorescence in situ hybridization and targeted mutation analysis. The next steps on the road towards a diagnostic tool are the validation of copy number alterations, structural variants, and small nucleotide variants identified in addition to standard diagnostics and the determination of the coverage necessary to detect small clones relevant for patient care. Thus, a first step is taken towards a completely automated genotyping enabling a broad access to state of the art diagnostics.

Marc LePage
President & CEO, Genome Canada

Clinical Implementation of Genomics for Rare Disease

Genome-wide sequencing for rare diseases is occurring in research settings across Canada but access to clinical genomic testing is inconsistent, with no access in some provinces and territories. Genome Canada has developed a strategy with concomitant infrastructure to implement genome-wide sequencing in the clinic and allow every Canadian with a rare disease the opportunity for a diagnosis and hope of an effective treatment.

Genome Canada's Genomic Applications Partnership Program (GAPP) is being used to develop clinical genomic testing sites across the country. Projects must have the support of the provincial or regional authority responsible for clinical implementation and placing the tests on the health care formulary. Participants must commit to align with the program's Mission Statement that outlines the vision and policy on items such as standardizing clinical workflows and sharing data.

A world-class rare disease cohort and database including genomic data matched with clinical phenotypic information, as well as a federated data ecosystem will be created enabling clinicians to provide an accurate and timely molecular diagnosis and informed care for rare disease patients. Researchers will also have access to the cohort to identify novel genes, understand molecular pathways, and identify novel therapies.

Jonas Nilsson
Director of Sahlgrenska Cancer Center. Department of Surgery, Institute of Clinical Sciences, University of Gothenburg

Genomic tools for diagnosis and immune characterization of cancer of unknown primary and rare cancers

Clinical genomics can inform on actionable mutations but also yield important information about prognosis and diagnosis. We have developed a bioinformatics workflow that have shown to be useful for diagnosis of cancer of unknown primary, for identiying cell of origin as well as for identification of cell lines. In the presentation different uses of exome and RNAseq data will be displayed to demonstrate the utility of including these analyses as a standard bioinformatic workflow for both basic, translational and clinical research.

About the speaker: Professor Jonas Nilsson is a Cancerfonden Senior Investigator, Director of Sahlgrenska Cancer Center and founding group leader of the Sahlgrenska Translational Melanoma Group (SATMEG). He is an expert in development and genetic characterization of human tumors growing in humanized mouse models of cancer and works closely with SATMEG clinicians to conduct innovative clinical trials in melanoma.

Mikko Rotonen
IT-Development Director, Helsinki University Hospital, Finland

Deployment of Genetic Data Management System in Cloud Platform

Deployment of Genetic Data Management System in Cloud Platform

- Scaling and using cloud computing capacity efficiently and economically in Genetic analysis
- Security issues
- Combining Data Lake Patient Data with Genetic Information
- Analytic services and interfaces for Research

Lisenka ELM Vissers
Dept of Human Genetics, Radboud UMC, Nijmegen The Netherlands

NGS innovations to uncover new genes for intellectual disability: from research to diagnostics and back

Intellectual disability (ID) and other neurodevelopmental disorders (NDDs) often occur sporadically in families with a negative family history. Given the reproductive lethality of these disorders, an evolutionary explanation is that a large portion are due to *de novo* mutations. The last decades, technological innovations allowing the unbiased detection of such *de novo* mutations in a genome wide fashion, such as microarray-based copy number screening and whole exome sequencing (WES), have been the main driver of implementation these tests into daily clinical practice. Whereas a significant increase in diagnoses was obtained, other elements, including patient perspectives, cost-effectiveness of the technology, and revenues from scientific use to further basis understanding of disease mechanisms are often not taken into account when assessing novel technologies. In this presentation, I will share our experience performing implementing WES in routine clinical care, addressing these aspects, and show how this not only pushed forward clinical diagnostics but also translational research.

Hereto, I will first show our clinical utility study with 150 patients presenting with complex pediatric neurological disorders of suspected genetic origin. In a unique parallel design, all patients received *both* the standard diagnostic workup and WES simultaneously, allowing for direct comparison of diagnostic yield of both trajectories and providing insight into the economic implications of implementing WES in this diagnostic trajectory. Additionally, I will show examples on how the large-scale diagnostic collection of WES data not only foster the identification of novel disease genes by statistical approaches, but also provide new insights into patho-physiological mechanisms underlying genetic disease. Moreover, WGS is already emerging in clinical care, and I will show results from our pilot study using 50 WES negative ID patients, demonstrating that interpretation of the non-coding space is still highly complex and challenging, but that it also offers opportunities.

Timothy Yu
Division of Genetics & Genomics, Boston Children's Hospital and Department of Pediatrics, Harvard Medical Medical School, USA

Patient-customized Oligonucleotide Therapy for an Ultra-Rare Genetic Disease

High-throughput sequencing has revolutionized the diagnosis of rare genetic disorders. However, many patients still suffer due to a lack of therapeutic options for most of these conditions, which in aggregate impact hundreds of millions of individuals worldwide. We will describe how genome sequencing of a young girl with fatal neurologic disease led us to design, test, and administer a novel oligonucleotide therapy, tailor-made to one of her pathogenic mutations, to prevent further deterioration. We will discuss how this case motivates further exploration of models for scaling the delivery of individualized genomic interventions in a safe and timely fashion.