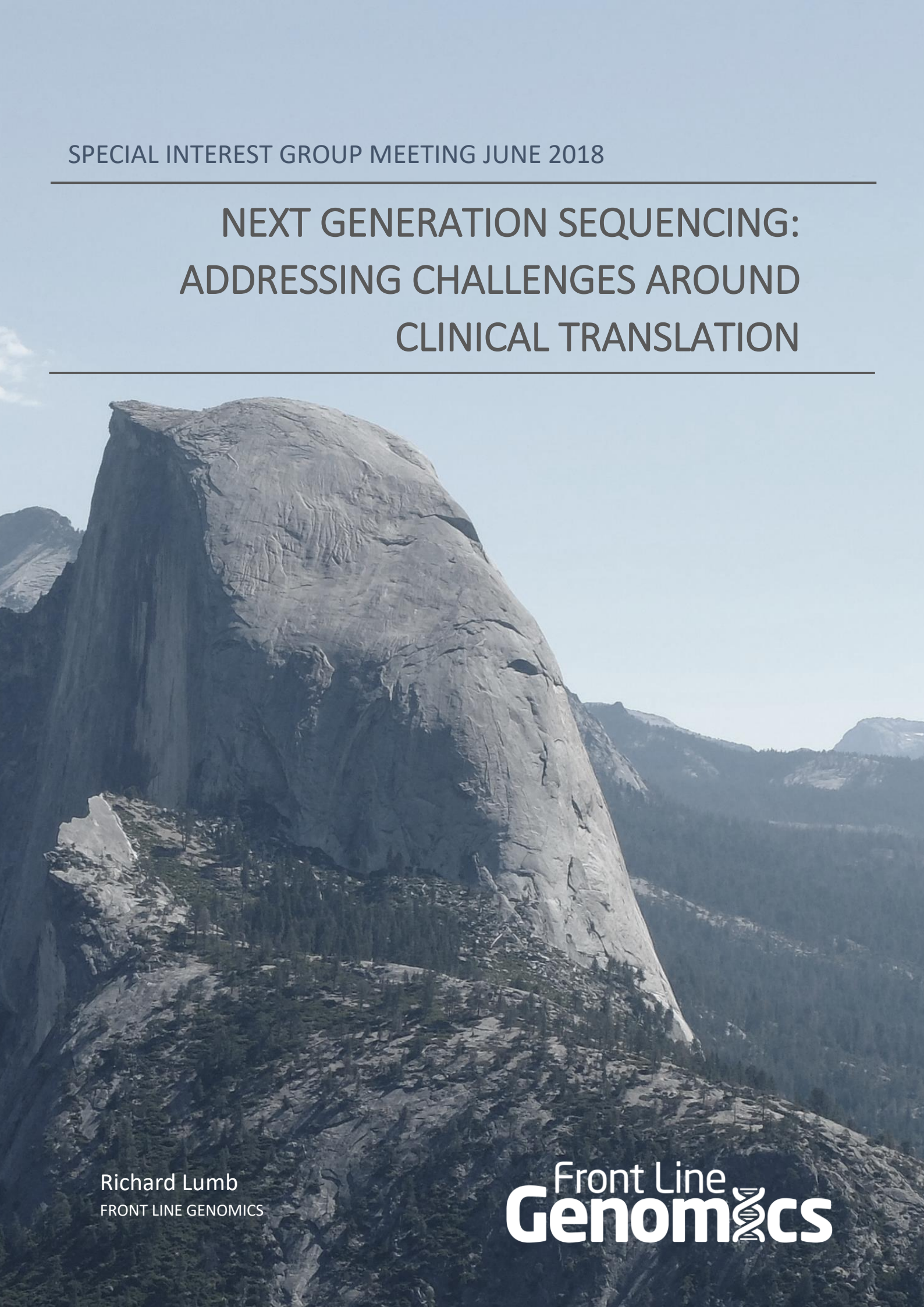
SPECIAL INTEREST GROUP MEETING JUNE 2018

NEXT GENERATION SEQUENCING: ADDRESSING CHALLENGES AROUND CLINICAL TRANSLATION



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Foreword

The adoption of NGS into the clinic has been limited by challenges that have emerged with the growing complexity of genomic information and bioinformatics. The lack of standardization of the quality and quantity of clinical samples, lack of appropriate tools, genomic counselling services, and reporting of NGS test results by healthcare professionals continues to impede the utilization of NGS in the clinic.

To discuss how these challenges could be faced and potentially overcome, experts in the field were brought together for a meeting under Chatham House Rules, in Boston on June 21st. In order to maintain a balanced perspective, the participants of the meeting were selected from a range of backgrounds, with many different specialties and focuses.

The purpose of this meeting was to identify what actions are required to enable successful clinical integration of NGS testing through peer-level discussion, collaboration, and collective thinking.

This report presents an accurate reflection of the discussions that took place at this meeting and does not constitute an official statement from any of the individual participants, their organizations, or Front Line Genomics.

Attendees:

Aaron Thorner, Associate Director, Center for Cancer Genome Discovery (CCGD), **Dana-Farber Cancer Institute**

Shannon Manzi, Director, Clinical Pharmacogenomics Service, Division of Genetics & Genomics, **Boston Children's Hospital**

Jochen Lennerz, Associate Director, Center for Integrated Diagnostics, **Massachusetts General Hospital**

Matthew Lebo, Director of Bioinformatics, **Harvard Medical School**

Lynette Sholl, Pathologist, **Brigham and Women's Hospital**

Marianne Boswell, CEO, **Boston Lighthouse**

Enrique Neumann, Product and Application Manager, Genomics, **Tecan**

Christine Lu, Associate Professor, Department of Population Medicine, **Harvard Medical School**

Vibhor Gupta, Director, **Pangaea Group**

Matt Stachler, Associate Pathologist, **Brigham and Women's Hospital**

Matthew Ducar, Associate Director, Computational Bioinformatics, **DanaFarber Cancer Institute**

David Smith, Professor of Laboratory Medicine and Pathology, **Mayo Clinic**

Annerose Berndt, Director of the Genome Center, **Institute for Precision Medicine**

Monkol Lek, Assistant Professor, Department of Genetics, **Yale School of Medicine**

Arezou Ghazani, Medical Geneticist, **Dana-Farber Cancer Institute**

Ted Laetsch, Faculty Member in the Department of Paediatrics, **University of Texas Southwestern**

Laura Rasmussen-Torvik, Assistant Professor, Department of Preventive Medicine, **Northwestern University Feinberg School of Medicine**

Mike Furgason, Bioinformatician, Division of Biomedical Informatics, **Cincinati Children's Hospital**

José-Mario Capo-Chichi, Assistant Professor, Laboratory Medicine Program, **University Health Network, University of Toronto**

Frances Shaw, Producer, **Front Line Genomics**

Richard Lumb, CEO and Founder, **Front Line Genomics**

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Points of Discussion:

Financial Considerations

- The financial aspects of clinical NGS are very opaque, and very little information on the status of reimbursement or sustainability gets back to the scientists in the lab. Without this communication, it is difficult for the people developing new tests to put forwards a strong financial business model. There needs to be clearer sharing of information between different factions of the clinical NGS process before a more robust financial model can be put forwards.

- Current reimbursement systems are limiting patient access to NGS testing. If testing labs are only being reimbursed for a small fraction of the tests they are performing, then they won't be able to survive for very long, a problem that will only get worse when testing begins to scale up. To limit the number of tests, labs are having to use a policing structure that puts them against clinicians trying to get their patients tested.

- For reimbursement systems to function, the tests need to be providing value. This is a problem at the moment because test results are often inconsistent and so it can be difficult to argue why any one test might be better than another. Without consistency, the value of the tests cannot be accurately judged and so payers are unwilling to promise reimbursement.

- Pricing tests for each individual lab is complex, and it can vary dramatically depending on the tools the lab is using and the nature of the test and samples involved. The Centers for Medicare and Medicaid Services have now provided labs with their estimations on what tests should cost and, while these will not always be completely accurate, they can be a very helpful resource for lab technicians.

- Insurers aren't incentivized to consider long term benefits of testing. Some genetic tests are providing data that will be useful to the patient many years into the future, by which time they will likely be with a different insurer than the one paying for the test. As a result, the company will be paying for a test that will not bring them any benefit. If all insurance companies start to offer this type of testing, then they will all be able to benefit from it in time, but no company is willing to take the first step.

- Non-invasive prenatal testing is the benchmark for future tests. NIPT has been deployed effectively across many different countries and is already demonstrating significant cost-effectiveness and improved healthcare outcomes.

- New business models are being developed to rejuvenate revenue streams, but some of these approaches may not be effective or ethical. For example, a company may sequence a patient's genome for free in return for complete ownership of the data they generate, which can then be sold on. A similar approach can be taken in healthcare by building deidentified patient cohorts that can be used by paying pharma companies.

- The $100 genome is only shifting the cost to downstream analysis. While bringing the cost of sequencing down should theoretically make genomic tests less expensive, in actuality the cost is being pushed to pathologists instead. By identifying many more variants than targeted gene panels, the necessary data analysis is much more complex and expensive, and this cost has to be carried by the bioinformatics labs.

Data Processing and Analysis

- Data alone does not have intrinsic value. Well organized, high quality datasets with standardized annotations can be very useful in business, for pharma companies in particular, but this isn't the case for lower quality, disorganized data. Data processing is a lengthy and expensive undertaking, so companies are unwilling to pay for datasets that have not already undergone that organization.

- Variants of unknown significance are still a major challenge for analysis. This problem is made worse because the majority of the mutational data available has been obtained from participants of Caucasian descent, limiting our understanding of variants in other ethnic populations. This issue could be minimized with a well-managed, curated database for somatic mutations that labs could collaborate with.

- There are too few bioinformaticians to cope with the demand for genetic testing. Many talented people within the informatics space have moved over into the growing online industry, to companies like Google, Amazon, or Facebook, and there is now a shortage of scientists capable of processing genomic data. Better, more targeted education systems need to put in place to bring more qualified scientists into the field.

- Genetic data is inevitably going to be hacked, so instead of working to secure the data to an unreasonable level, data stewards should be finding ways to minimize the damage caused by a breach. This could be linked to how data is stored, such as keeping identifying data and genomic data separately, or it could relate to the legal use of such data. In the USA, GINA prevents health insurance companies from discriminating against customers based on their genetic profile, but the law does not explicitly cover life insurance, for example. Loopholes like these need to be closed before patients' genetic data can be considered secure.

In the Clinic

- **Physicians in primary care roles do not always have time to consider large numbers of genetic risk variants.** When a patient is critically ill, medical staff do not have the time to be distracted with genetic risk testing; instead, they're going to be treating the symptoms immediately apparent. By cluttering a patient's file with data that is irrelevant in the short term, patient care may suffer. Test providers need to be aware of which information is going to be most clinically relevant and present it in a way that is easily accessible for physicians.

- **Electronic health records are still poorly structured**, which limits their utility in the clinic. The lack of standardization can also make it difficult to identify the relevant information in a timely manner. Without a better structural system in place, good data processing systems are irrelevant because the phenotypic information is being lost.

- **There is often a divide between primary care physicians and genetic counsellors**. The lack of communication between the two teams can mean that patients are getting mixed information and it might not be clear who they should be approaching with any problems. Primary care physicians don't usually want to be having genetic counselling

discussions with their patients because it isn't their primary focus. To ensure that patients are being given access to the resources they need, better communication needs to be developed between different aspects of the healthcare process.

- Genomic tests need to be better explained to the public, particularly as the increase in direct to consumer testing is offering more people access to their data without providing the necessary understanding. At the same time, many clinicians are still working to understand how genetic testing can be used to treat patients, leading to primary care physicians being confronted with large amounts of data they cannot use effectively.

- Accessibility of genetic testing is still heavily restricted by location. Patients who are being treated in areas that are innovation centers, such as Boston or New York City, are much more likely to be offered genetic testing than those at rural clinics away from city centers. Clinical support mechanisms need to be put in place to ensure that a patient's physical location isn't causing them to be offered a substandard level of care.

- Patients cannot always know what they are consenting to. The possible uses of genomic data are increasing all the time, so it is impossible for a patient to be positive of what they are consenting to when they agree to share their data