Dear Colleagues,

Welcome to the May 2016 (Issue 8) update of the POLARIS program! Supported by A*STAR's Strategic Positioning Fund (SPF), the POLARIS team has focused for the past 3 years on piloting the clinical implementation of genomics in Singapore. Recently described in an A*STAR advertorial in *Science*[1],our efforts have involved multiple stakeholders and institutions across the island. During our journey, we identified specific bureaucratic, administrative, and logistic barriers related to the process of clinical translation in Singapore, and defined pathways for addressing these barriers, so that other researchers involved in clinical translation can benefit.
Our recent milestones include:

MOH Licence for POLARIS

Riding on our 2015 College of American Pathologists (CAP) accreditation for next-generation sequencing (NGS), POLARIS has since worked closely with the Ministry of Health to officially license its facilities for running local clinical samples. Information packages have been shared with MOH, including peer-reviewed publications demonstrating the concordance of POLARIS and other NGS assays with mainstream clinical diagnostics[2,3,4,5,6] . We are pleased to share that POLARIS has obtained MOH licensing for its laboratories, providing a wide range of molecular diagnostic platforms and also housing NGS capabilities. This important milestone now provides POLARIS with the ability to run patient samples, both local and international, with the highest levels of rigor, emphasizing test accuracy and safety.

Launch of Somatic Solid Tumor Panel (SSTP)

The POLARIS team at Singhealth has recently launched the Somatic Solid Tumor Panel (SSTP), a 29-gene sequencing panel targeting frequently mutated gene regions ("hotspots") in solid malignancies. SSTP is a hybrid test, where initial findings screened via NGS are validated by other technologies such as Sanger sequencing or Real-time PCR. To our knowledge, SSTP represents Singapore's first NGS-based assay for mainstream clinical use - to date over 60 patients have already benefitted from SSTP information. Pricing for the SSTP is competitive, and importantly SSTP is future-proofed to readily accommodate the increasing number of clinically-actionable mutations revealed through cancer genomic studies. Additional information about SSTP can be obtained from Dr Tony Lim, SGH Department of Pathology and POLARIS Clinical Director at **polaris@singhealth.com.sg**.

[1] http://www.sciencemag.org/sites/default/files/custom-publishing/documents/Astar_v7_FINAL_030316.pdf
[2] Sophie R Wang et al., "Technical Validation of a Next-Generation Sequencing Assay for Detecting Actionable Mutations in Patients with Gastrointestinal Cancer," *The Journal of Molecular Diagnostics: JMD* 18, no. 3 (March 9, 2016): 416–24, doi:10.1016/j.jmoldx.2016.01.006.
[3] Garrett M Frampton et al., "Development and Validation of a Clinical Cancer Genomic Profiling Test Based on Massively Parallel DNA Sequencing.," *Nature Biotechnology* 31, no. 11 (November 2013): 1023–31, doi:10.1038/nbt.2696.
[4] Catherine E Cottrell et al., "Validation of a Next-Generation Sequencing Assay for Clinical Molecular Oncology.," *The Journal of Molecular Diagnostics : JMD* 16, no. 1 (January 2014): 89–105, doi:10.1016/j.jmoldx.2013.10.002.
[5] Colin C Pritchard et al., "Validation and Implementation of Targeted Capture and Sequencing for the Detection of Actionable Mutation, Copy Number Variation, and Gene Rearrangement in Clinical Cancer Specimens.," *The Journal of Molecular Diagnostics : JMD* 16, no. 1 (January 2014): 56–67, doi:10.1016/j.jmoldx.2013.08.004.
[6] Rajesh R Singh et al., "Clinical Validation of a Next-Generation Sequencing Screen for Mutational Hotspots in 46 Cancer-Related Genes.," *The Journal of Molecular Diagnostics : JMD* 15, no. 5 (September 2013): 607–22, doi:10.1016/j.jmoldx.2013.05.003.

POLARIS Supports National Disease Outbreak Response

In 2015, Singapore experienced an outbreak of Group B Streptococcus (GBS) infections, infecting more than 350 persons and termed the "biggest in the world"[7]. The impact of this outbreak was severe, resulting in several fatalities, limb amputations, and policy decisions by NEA to ban the sale of raw fish dishes[8]. The start of this GBS outbreak was first identified by microbiologists throughout Singapore, led by Dr Timothy Barkham at Tan Tock Seng Hospital. Through a multi-centre collaborative effort led by Dr Hsu Li Yang and Dr Tim Barkham, clinicians and scientists at Tan Tock Seng Hospital, Changi Hospital, National University Hospital, Singapore General Hospital, KK Hospital, Khoo Teck Puat Hospital, NUS Saw Swee Hock School of Public Health, Ministry of Health, AVA and NEA, POLARIS and the Genome Institute of Singapore sequenced more than 200 GBS patient samples, confirming that the GBS outbreak was caused only by 1 strain and assisting in the ongoing outbreak investigation. This work was funded by a SIDI grant (awarded to Dr Shirin Kalimuddin and Dr Tim Barkham), POLARIS (BMRC, A*STAR), Genome Institute of Singapore, and NMRC (CS-IRG awarded to Dr Swaine Chen)

POLARIS Supports SureKids Undiagnosed Diseases Program

For children with rare genetic diseases and mysterious life-threatening symptoms, diagnosis is critical so that the child can receive proper treatment. Unfortunately, children with such rare genetic diseases are diagnosed only 20-30% time using standard tests. Studies both internationally and locally have shown that exome sequencing of such children and their parents can raise the chance of diagnosis to >50%. In Singapore, a multi-disciplinary team of clinicians and scientists have banded together to champion the use of genomics in rare genetic diseases, and patients are already benefitting[9]. Building on this success, the team of A/Prof Roger Foo (GIS/NUHS), Dr Saumya Jamuar (KKH), Dr Angeline Lai (KKH), A/Prof Denise Goh (NUHS), Prof Byrappa Venkatesh (IMCB) and Prof Bruno Reversae (IMB) have secured BMRC funding to clinically implement the use of exome sequencing in pediatric genetics. POLARIS is honored to work with the SureKids team to implement exome sequencing in a CAP-certified environment, which will enable exome sequencing for undiagnosed child disorders as a standard clinical test.

POLARIS Completes Pioneering Study on Singapore Patient Informed Consent

Sequencing, storing and sharing of genomic data for research raises ethical and legal concerns about the patient informed consent process[10,11]. In Singapore and in many Asian countries however, there is little concrete data on local patient and physician attitudes on these issues. In partnership with the Centre for Biomedical Ethics (CBME) at NUS, POLARIS has recently completed a first-generation study based on evidence gathered in semi-structured interviews with cancer patients and oncology clinicians in Singapore, to develop an informed consent process to store, share and return results generated from precision oncology tests. This POLARIS/CBME study revealed limited patient understanding of oncology genetics and the consent process, but also found that Singapore patients were willing to receive test results and to share the de-identified genomic data with biomedical researchers locally and abroad. Findings were presented at the 2016 International Congress of Human Genetics in Kyoto and are consistent with other international initiatives in

[7] Recent GBS outbreak 'biggest in the world'. Straits Times Dec 6, 2015. http://www.straitstimes.com/singapore/recent-gbs-outbreak-biggest-in-the-world

[8] Joint news release between AVA, MOH and NEA dated 5 Dec 2015. http://www.nea.gov.sg/corporate-functions/newsroom/news-releases/freshwater-fish-banned-from-ready-to-eat-raw-fish-dishes

[9] Tracking Mutated Genes that Wreck Havoc. Straits Times Sept 18, 2015. http://www.straitstimes.com/singapore/health/tracking-mutated-genes-that-wreak-havoc

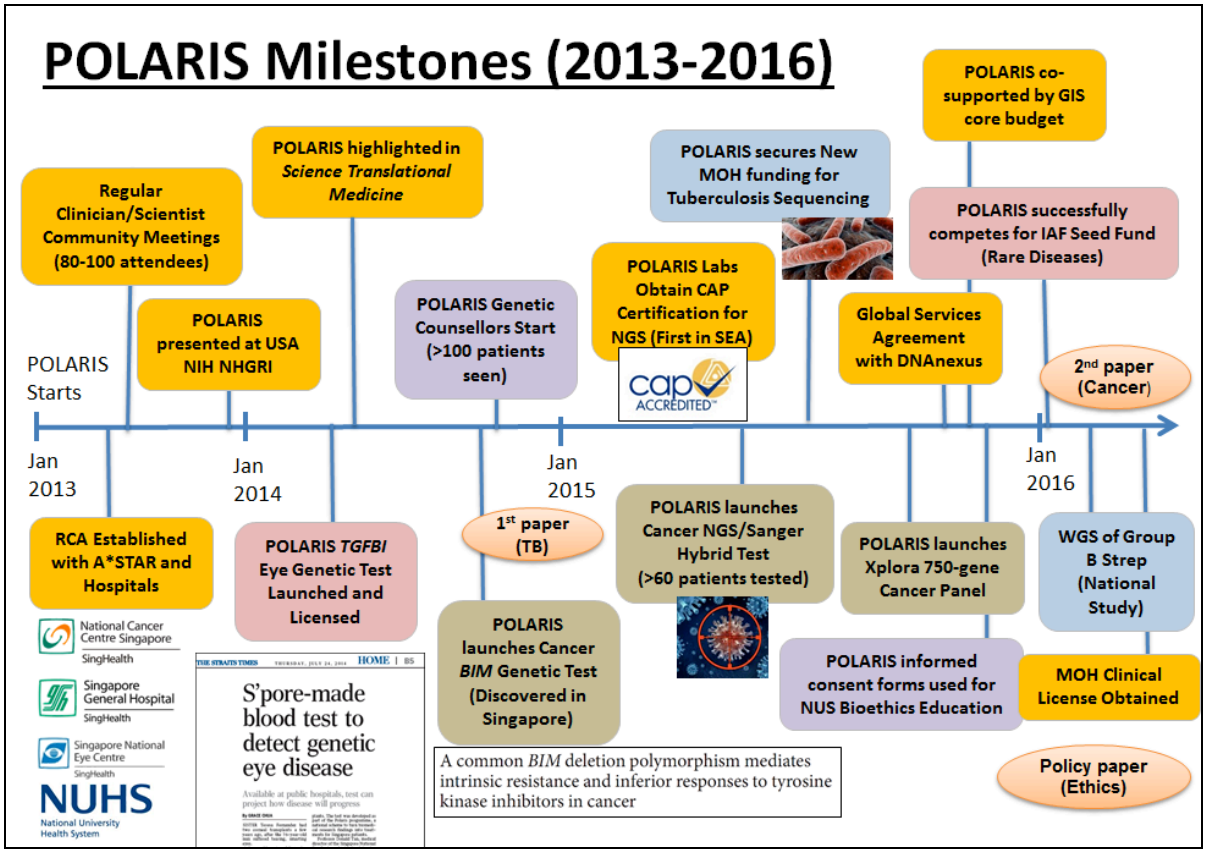
[10] Bartha Maria Knoppers et al., "Towards a Data Sharing Code of Conduct for International Genomic Research.," *Genome Medicine* 3, no. 7 (2011): 46, doi:10.1186/gm262.

[11] Wylie Burke, Barbara J Evans, and Gail P Jarvik, "Return of Results: Ethical and Legal Distinctions Between Research and Clinical Care.," *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* 166, no. 1 (March 2014): 105–11, doi:10.1002/ajmg.c.31393.

the UK and the US where stakeholder preferences are shaping the informed consent process. POLARIS will continue to work and support CBME in expanding data collection to other patient and clinician cohorts, and these results will be shared with IRB representatives in Singapore. More information on the POLARIS/CBME bioethics study can be obtained from tamra_maree_lysaght@nuhs.edu.sg .

POLARIS Metabolomics Supports Cancer Weight Loss Study

In collaboration with researchers from GIS, NCCS and Duke-NUS, the POLARIS metabolomics group at BTI investigated the effects of a muscle-wasting syndrome known as cachexia, commonly observed in advanced cancer patients resulting in terminal weight loss. Using global metabolite profiling, human myotubes exposed to factors secreted by cachectic cancer cells were found to exhibit excessive fatty acid oxidation. Subsequent inhibition of fatty acid oxidation in both human stem-cell based models and mouse models successfully reversed this process, leading to improved muscle mass and body weight in the latter. These findings, published in *Nature Medicine*[12], highlight fatty acid-induced oxidative stress as a potential target to prevent cancer-induced cachexia.



In closing, POLARIS has been privileged to work with so many dedicated individuals and parties over the years. However, much more remains to be done before the vision of genomic medicine becomes a full-fledged reality in Singapore and the region. We are excited to share that BMRC has recently agreed to continue supporting POLARIS until 2018, and we will redouble our effects to serve the genomic and clinical community. The next few years will definitely be very exciting, as we continue our precision medicine journey at both the institutional and national scale.

Best regards

Patrick Tan (On behalf of the POLARIS Team)

[12] Tomoya Fukawa et al., "Excessive Fatty Acid Oxidation Induces Muscle Atrophy in Cancer Cachexia," *Nature Medicine* advance online publication SP - EP - (n.d.), doi:10.1038/nm.4093.