In this issue of the NUHS Research Bulletin, we discuss exciting research in pharmacogenomics and muscle regeneration. We also introduce a new faculty in the Saw Swee Hock School of Public Health who is interested in how we interpret and use data.

Determining variation in drug responses among different populations
Clinicians are now acutely aware that different patients may respond differently to the same drug. As more and more information comes in about the effect of patient factors on drug response, making sense of the data is essential. This is especially true for the rapidly growing field of pharmacogenomics, which studies the effect of genes on drug response. To this end, two papers from researchers at the Saw Swee Hock School of Public Health, discussed how genetic databases can be used to determine variations in drug response among different populations.

The first paper (Wong, et al.) describes a new web portal, the Singapore Pharmacogenomics Portal (SPP; http://www.statgen.nus.edu.sg/~SPGx/SPGx_Main.php), that provides information about the variation of genes related to drug function in 7 global and Singaporean populations. The portal does this by interfacing pharmacogenomic and drug databases with two single nucleotide polymorphism (SNP) databases: 1) the International HapMap Phase 2 database, comprising SNPs from four populations: ethnic northern European, Nigerian Yoruba, Han Chinese, and Japanese; and 2) the Singapore Genome Variation Project, comprising SNPs from three Singaporean populations: Malay, Chinese, and South Asian Indian.

Users can input a drug name and obtain information about genes that are associated with the drug’s function. These genes may be involved in drug metabolism or transport, or could be acted upon by the drug. The SPP can provide the variation of each gene in the different populations. Alternatively, users can input a gene name or a reference SNP ID number and obtain its variation in all or a subset of the seven populations.

Another paper (Pillai, et al.) showed that particular combinations of SNPs could be correlated with specific HLA alleles, using three SNP reference panels specific for the Malay, Chinese, and Indian populations in Singapore, respectively. This enables rapid identification of the types of HLA alleles present in a population without the need for expensive HLA typing methods. Among other effects, HLA allele type influences the likelihood of an adverse reaction to certain drugs. For example, people with the $HLA-B^*15:02$ allele are at higher risk of developing Stevens-Johnson syndrome (SJS) with carbamazepine and phenytoin than are people lacking the allele. The frequency of the $HLA-B^*15:02$ allele varies among different populations. In Singapore, the allele is much more common in Chinese and Malays than in Indians, suggesting that genomic screening for SJS risk could be cost-effective for Chinese and Malays but not for Indians.
As genetic databases continue to grow, so does the need for novel methods of exploiting the databases to obtain useful information.

References

Electromagnetic fields as therapy: less is more
Extremely low-frequency, low-intensity, pulsed electromagnetic fields (PEMFs) were first used to improve bone healing in patients with broken bones that were difficult to treat. More recently, PEMFs have been studied for their restorative effects on muscle tissue, which may be useful in people such as the elderly and those with degenerative muscle conditions. PEMFs appear to stimulate stem cells to differentiate into muscle cells (muscle regeneration) via the opening of calcium-dependent channels. This is the same regenerative process that is stimulated by exercise, but without the wear and tear of exercise.

In the Department of Surgery, Dr Alfredo Franco-Obregon has observed that mice treated with PEMFs have increased muscle quality (more oxidative muscle) and bone density (unpublished data). The mice also showed elevated insulin growth factor 1 (IGF-1), a protein involved in heart, muscle, and nerve function.

Dr Franco-Obregon is also looking at the effects of PEMFs on metabolic function. Because muscle (especially oxidative muscle) is essential for glucose metabolism, increasing the amount of oxidative muscle may improve metabolism and thus help prevent diabetes and metabolic syndrome.

He has found that PEMF therapy in mice leads to improvements in multiple metabolic indices (unpublished data). Besides reducing insulin levels by as much as 50%, treatment with PEMFs causes the respiratory exchange ratio (RER) to decrease, indicating improved metabolism of fat relative to carbohydrate. These results mirror the insulin and RER reductions that are seen with exercise. PEMF therapy also boosts levels of the peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) transcription factor, which in turn increases fat metabolism. Studies are underway to determine the effects of PEMFs on other metabolic markers.

The PEMFs that had the most effect on muscle cells were of a 1 millitesla (mT) intensity and 15 Hz frequency, and were administered for 10 minutes per week. Effects could be seen as soon as 5 weeks after starting treatment. Interestingly, stronger fields and longer durations were actually less effective (as were weaker fields and shorter durations), suggesting the presence of an optimal therapeutic window.

The next step involves evaluating the effectiveness of PEMFs in clinical trials, which are scheduled to begin next year. PEMFs represent an intriguing potential therapy for a variety of conditions, including muscle and metabolic disorders.
New Faculty Feature -
Introducing: Zoe Hildon

Assistant Professor Zoe Hildon, who recently joined the Saw Swee Hock School of Public Health, is a researcher in Health Services. Some of her recent work centers on using Patient Reported Outcome Measures (PROMs)\(^1\) to evaluate surgical interventions and hospital performance at regional and national levels.

Assistant Professor Hildon’s work in this area has focused on finding the best ways to communicate quantitative performance metrics to both patients and clinicians. Beginning with a systematic review in risk communication,\(^2\) the research team also undertook focus group work to explore presentation methods for PROMs data in terms of comprehension, choice and preference,\(^3,4\) as well as the best metrics\(^5\) to use for patients and clinicians in the UK.

For example, when comparing something as complex as the performance of healthcare providers, clinicians and patients prefer different types of metrics. Assistant Professor Hildon and her colleagues considered 4 different metrics that have been used in the literature to determine the change in patients’ health status after elective surgeries. These included the mean follow-up score, the mean change in score, the proportion reaching a specified threshold at follow-up, and the proportion reaching a minimally important difference [MID].

They found that clinicians preferred a variety of metrics to a single one, and preferred the change in score over the post-intervention score because they perceived that the change in score accounted for the severity of the patient’s condition before intervention. Even though it was explained to clinicians that the follow-up score should also do this (because it was adjusted for the baseline score), they still preferred the change in score.

Generally, patients were more concerned about being able to interpret the metric than about accuracy. They preferred proportions (e.g., the proportion achieving a desired outcome) to the other metrics because they found them easier to interpret than the scores. A/Prof Hildon and colleagues thus recommended 2 metrics for clinicians: 1) the mean change in score and 2) the proportion achieving MID. They recommended only the proportion achieving MID for patients.

In terms of format and content of PROMs data displays, patients understood tables and pictographs (diagrams containing icons such as stars or stick figures) better than they did bar charts, and made more accurate decisions with tables and pictographs. Despite this, patients expressed their preference for bar charts over the other formats. The way the content was presented also affected users’ comprehension and decision-making accuracy. Content that ranked choices, explained data using non-numeric cues, and was simple and consistent facilitated more accurate decisions in this population group.

For optimum clinician data displays, findings indicated the desire for data in more than one format, as well as the need for explicit display of comparative performance (rank order) and for explanations (e.g., of unfamiliar formats and of statistical uncertainty).

Assistant Professor Hildon has since worked on evaluation of health services and community interventions in Tanzania and Sub-Saharan African settings, and is currently working on health...
services in Singapore. She is particularly interested in developing interventions to deliver better integrated care across facility and community settings.

References

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About the National University Health System (NUHS)

The National University Health System (NUHS) groups the National University Hospital (NUH), the NUS Yong Loo Lin School of Medicine, the NUS Faculty of Dentistry and the NUS Saw Swee Hock School of Public Health under a common governance structure to create synergies for the advancement of health by integrating clinical care, research and education.