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National research network to improve outcomes in VTE established at LDI

Dr. Susan Kahn is co-director of the new Canadian Venous Thromboembolism Clinical Trials and Outcomes Research Network (CanVECTOR), a national network in which the Canadian Institutes of Health Research (CIHR), the Fonds de recherche Québec – Santé (FRQS), and a consortium of public and private funders, including the LDI and McGill University have invested $5.2 million over 5 years.

CanVECTOR's objectives include identifying causal factors for VTE, reducing VTE occurrence, improving diagnosis and therapeutic management, improving the safety of anticoagulant delivery, investigating the long-term effectiveness and safety of new oral anticoagulants, enhancing the quality of life of those impacted by VTE, and improving public awareness of VTE in Canada and globally.

"VTE is the second most common cardiovascular disorder after heart attack," points out Dr. Kahn, a McGill Tier 1 Canada Research Chair. "Pulmonary embolism, a blood clot to the heart or lungs – the most serious form of VTE – is the third leading cause of cardiovascular death. Ten-percent of patients who suffer pulmonary embolism will die rapidly prior to diagnosis, highlighting the importance of prevention. VTE imposes life-long burdens on many patients because it frequently becomes chronic, including recurrent episodes of VTE, post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension."

It costs more than $10,000 to treat one case of acute VTE. The estimated total burden of VTE and its complications is at least $600 million per year in Canada.

The project's co-director is Dr. Marc Rodger of The Ottawa Hospital. It includes sixty-one investigators based at universities spread across nine provinces, as well as patient partners.

Mark Wainberg inducted into Canadian Medical Hall of Fame

Dr. Mark Wainberg, head of the HIV/AIDS Axis and Director of the McGill AIDS Centre, has been selected for the Canadian Medical Hall of Fame. This unique institution honours outstanding contributions leading to extraordinary improvements in human health. Dr. Wainberg was lauded for his scientific excellence and social conscious in revolutionizing understanding of HIV/AIDS at the medical, epidemiological, and political levels. He is, perhaps, best known for identifying 3TC as an effective antiviral drug. Most recently, he is focused on achieving a cure for HIV infection based on the possibility that HIV may not become resistant to certain new compounds that block viral replication. An induction ceremony will be held in Hamilton in April.

Laurence Kirmayer elected Fellow of Royal Society of Canada

Dr. Laurence Kirmayer, Director of the Division of Social and Transcultural Psychiatry and James McGill Professor of Psychiatry, was elected a Fellow of the Royal Society of Canada. Dr. Kirmayer was cited for his "contributions to our understanding of how culture shapes illness experience, resilience, and well-being . . . His work has shed light on the cultural meanings of common bodily symptoms including pain and fatigue. Finally, he has advanced our understanding of how psychiatry itself is a cultural institution that reflects particular social and historical contexts."

Whole genome-sequencing uncovers new genetic cause for osteoporosis

Using extensive genetic data compiled by the UK10K project, an international team of researchers led by **Dr. Brent Richards**, of the Centre for Clinical Epidemiology, has identified a genetic variant near the gene EN1 as having the strongest effect on bone mineral density (BMD) and fracture identified to date. The findings are published in *Nature*.

"EN1 has never before been linked to osteoporosis in humans, so this opens up a brand new pathway to pursue in developing drugs to block the disease," Dr. Richards says by way of explaining the importance of the discovery. The effect of this uncommon genetic variant is twice as large as any previously identified genetic variants for BMD and fracture.

Osteoporosis is a common disease that will lead to fractures in between one-third and one-half of all women over the course of their lives. Because osteoporosis becomes more severe with age, it is becoming more prevalent with the overall aging of the population. There are currently few safe and effective treatments for osteoporosis, and no curative therapies available.

The UK10K project has measured genetic variations in 10,000 individuals in great detail, allowing researchers to correlate rare genetic changes with human disease by comparing the DNA of healthy individuals with those who have health problems. The use of such an extensive sample size allows for the observation of genetic variants that are not discernable among smaller groups. This particular study also stands as proof of principle that uncommon genetic variants can have a significant impact on common diseases.

This study represents an initial realization of genetic sequencing's promise to reveal those genes associated with disease.

Dr. Brent Richards is the recipient of the 2015 Joe Doupe Young Investigator Award from the Canadian Society for Clinical Investigation (CSCI), given to a new investigator who has accomplished significant and innovative work. Dr. Richards will deliver a lecture at the CSCI annual meeting in Toronto later this month.

UK10K project explores contribution of rare genetic variants to disease

Based on data collected by the UK10K project, a study designed to explore the contribution of rare genetic variants to human disease and risk factors was published in *Nature*. LDI biostatistician **Dr. Celia Greenwood** co-chaired the statistics group and was among the paper's authors. Epidemiologist **Dr. Brent Richards** co-chaired the cohorts group.

"The hypothesis is that the genetic sequencing being done by UK10K will expose previously unknown genetic factors underlying disease," said Dr. Greenwood. "We are finally able to extract enough data to discern variants that are rare in the overall population and are more frequent among those with common diseases."

The project studied nearly 10,000 individuals, both healthy and affected by disease. The conditions included very rare disorders inherited in families, and more common diseases such as autism, schizophrenia and obesity. In healthy people, 64 different biomedical risk factors such as blood pressure or cholesterol levels were studied. By characterising the DNA sequence of these individuals, the project gained insight into the contribution of rare variants to a broad range of disease scenarios, and discovered new genetic variants and genes underpinning disease risk.

"The great value of UK10K is in sequencing the genome of a large group from the general population who have been deeply measured for an extensive variety of biomedically relevant traits," Dr. Greenwood explained. "Sequencing enables us to go deeper into genetic traits and to identify more of the genetic variability contributing to disease, giving us the capacity to identify uncommon variants that have a significant association with common diseases."

As efforts continue to characterise the genetic underpinnings of complex diseases, the data and results of this study are expected to enable the next wave of discoveries. The UK10K sequence reference panel has been shown to greatly increase the ability to characterise rare variants in large population samples available to the worldwide research community. This resource will enable researchers to fill in missing data from lower resolution genotype studies, allowing them to explore full genotypes more quickly and cheaply.

Strong association established between low vitamin D and MS

Low levels of vitamin D significantly increase the risk of developing multiple sclerosis (MS), according to a study led by **Dr. Brent Richards** and published in *PLOS Medicine*. This finding, the result of a sophisticated Mendelian randomization analysis, confirms a long-standing hypothesis that low vitamin D is strongly associated with an increased susceptibility to MS. This connection is independent of other factors associated with low vitamin D levels, such as obesity.

"Our finding is important because vitamin D insufficiency is common, especially in northern countries where exposure to sunlight – a common natural source of vitamin D – is decreased through the winter and where we see disproportionately high rates of MS," asserts Dr. Richards. "We would recommend that individuals, particularly those with a family history of MS, should ensure that they maintain adequate vitamin D levels, This is a common sense precaution, given that supplements are generally safe and inexpensive."

MS is a progressively degenerative autoimmune condition that most often strikes young adults. The prospect that vitamin D may serve as a protective measure to prevent its onset is a very exciting development.

By taking the precaution of maintaining a normal level of vitamin D, a person at risk could decrease their risk of acquiring MS by an important degree. "While low vitamin D is by no means the only risk factor, we have identified one risk that can be removed from the equation, which could have a significant impact towards preventing this terrible disease," the authors conclude.

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Clinical study reveals link between VTE and cancer overstated

Evidence suggested that unprovoked, or unexplained, venous thromboembolisms (VTE) – approximately 40% of blood clots have no identifiable cause – may be a marker for an unexpressed malignancy – a so-called occult cancer. Clinical observation indicated that nearly 10% of those who had experienced an unprovoked VTE were diagnosed with a cancer within a year.

"This data has had a strong influence on clinical practice," said **Dr. Vicky Tagalakis**, an epidemiologist with a clinical specialization in thrombosis. "If I have a patient with an unprovoked VTE, I would take the precaution of screening for cancer, including a CT scan in some cases."

The results of a multicentre clinical trial that involved more than 850 participants across Canada including nearly 60 patients from the JGH, published in *The New England Journal of Medicine*, show that, in fact, the VTE-cancer nexus is nowhere near as strong as suspected. The study randomly assigned patients with unprovoked VTE to undergo either basic screening (a blood test, X-Ray of the chest, and age- and gender-specific cancer screening such as a prostate exam) or basic screening plus a CT scan. The results will significantly affect clinical practice. Dr. Tagalakis was the principal investigator on a Quebec Heart & Stroke Fund grant that contributed to the study.

First, it was found that only 3.3% of patients with an unprovoked VTE were diagnosed with cancer within a year. "This finding alone," Dr. Tagalakis stressed, "changes my approach with patients, since cancer is as a result two-thirds less likely than we had previously believed." Earlier studies were either not randomized or were observational, and therefore less accurate than the current one.

Moreover, it was proven that basic screening plus a CT scan offered no clinically significant benefit compared with basic screening, with regard to diagnosing occult cancer. Thus, the authors conclude, there is no value to adding a CT scan based solely upon presentation of an unprovoked VTE.

"The implications of this are tremendous," said Dr. Tagalakis. "It means less stress for the patient, no exposure to radiation, no false positives, plus significant cost savings – far fewer of the 40,000 Canadians who suffer an unprovoked VTE annually will undergo CT scan, which costs about $300 each."

Canada's largest saliva biobank

The LDI is home to the largest biobank of saliva specimens in Canada. Its collection of more than 2,100 samples is used to test for biomarkers of Alzheimer and Parkinson diseases, diabetes, scleroderma, orofacial pain, breast cancer, and oral microbiota.

"Saliva is a unique fluid and interest in using it as a diagnostic medium has advanced exponentially in the last 10 years," explains **Dr. Mervyn Gornitsky**, Research Director of the Department of Dentistry at the JGH and Professor Emeritus of Dentistry at McGill. "Technological advances in its use as a diagnostic fluid have helped to move saliva beyond ascertaining oral health characteristics to broader assessments of essential features of overall health."

Studies conducted by Drs. **Hyman Schipper** and Gornitsky using specimens from the Saliva Biobank disclosed unique "signatures" of chemical damage to DNA, proteins and fats in patients with periodontal disease, scleroderma, diabetes and cancer. Recently, the W. Garfield Weston Foundation awarded a grant to Drs. **Howard Chertkow**, Gornitsky, Schipper, and **Hemant Paudel** to investigate the role of salivary tau as a potential non-invasive biomarker of Alzheimer disease.

Researchers who are interested in accessing the LDI's Saliva Biobank are invited to visit the web site or contact Dr. Gornitsky at 514-340-7911, mgornits@mcgill.ca or Dr. Hyman Schipper at 514-340-8260, hyman.schipper@mcgill.ca.

Banting Post-doctoral Fellowship

Linda Kwakkenbos, of Dr. Brett Thombs psycho-social group, was awarded a 2015 Banting Post-doctoral Fellowship by the CIHR for her research, "Overcoming barriers to developing, testing, and disseminating psychosocial and rehabilitation interventions in a rare disease context: Making patient-centered research for rare diseases a reality." Dr. Kwakkenbos came to the LDI after completing her PhD in social science at Radboud University in the Netherlands in 2012. She is co-director of the Scleroderma Patient-Centred Intervention Network (SPIN).

Vanier Canada Graduate Scholarship

Leanne de Kock, a PhD candidate who moved to Canada from South Africa in 2012 and joined Dr. William Foulkes' cancer lab, was awarded a Vanier Canada Graduate Scholarship from the CIHR to support her research that focuses on dissecting the specific mutations involved in the development of rare tumors associated with inherited DICER1 mutations, with a particular emphasis on pituitary blastoma.

Governor General David Johnston (third from left) spoke at the first annual Partners Forum of the Canadian Consortium on Neurodegeneration in Aging, held September 30 in Ottawa. Pictured left to right are Brian Kuan, Pascale Léon, His Excellency the Governor General, Victor Whitehead, Dr. Howard Chertkow, and Terrence Li.