Canadian Institutes
of Health Research
Spring 2014
Volume 2, Issue 2

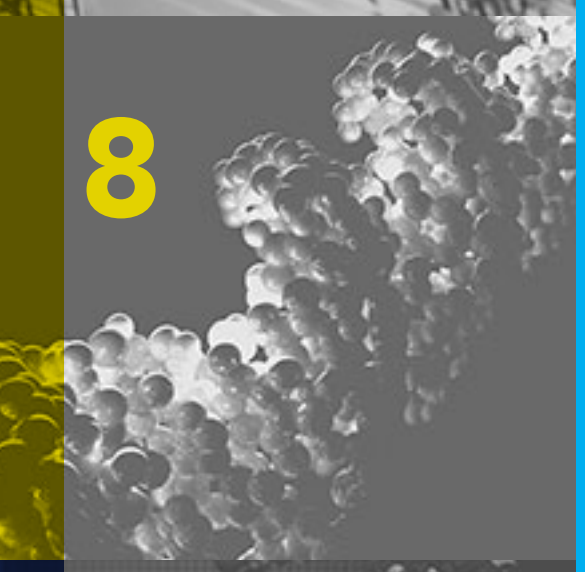
CIHR IRSC

SHOW ME THE EVIDENCE

CIHR-SUPPORTED RESEARCH PERSONALIZING YOUR HEALTH

Canadian Institutes of Health Research | Instituts de recherche en santé du Canada | Canada

For more than a decade, the Canadian Institutes of Health Research (CIHR) has supported some of the best and brightest health researchers in the world in their quest to improve the health and well-being of Canadians through research. CIHR-funded research and researchers have delivered better care, earlier diagnosis, improved quality of life and cost savings.



As the Government of Canada's health research investment agency, the Canadian Institutes of Health Research (CIHR) enables the creation of evidence-based knowledge and its transformation into improved treatments, prevention and diagnoses, new products and services, and a stronger, patient-oriented health care system. Composed of 13 internationally recognized Institutes, CIHR supports health researchers and trainees across Canada. **www.cihr-irsc.gc.ca**

CONTENTS

Canadian Institutes of Health Research
160 Elgin Street, 9th Floor
Address Locator 4809A
Ottawa, Ontario K1A 0W9

Also available on the Web in PDF and HTML formats

ISSN 1927-2928

All people profiled in this magazine have agreed to their appearance in it and approved their individual stories.

WELCOME TO THE SPRING 2014 ISSUE OF *SHOW ME THE EVIDENCE*

The world has witnessed tremendous progress in genetic and genomic research over the past decade, advances that have produced discoveries with great promise for patients and the goal of precision medicine. But important questions remain: As we learn more about the genetic underpinnings of human health and disease, will we be able to effectively capture and harness the transformative potential of this knowledge into better diagnosis and treatment? Do we have the data and the computing power to understand the importance of the variation in our genomes? And, as we delve deeper into our genetic code, how do we manage the ethical and legal issues that arise?

The Canadian Institutes of Health Research (CIHR) is the Government of Canada's health research investment agency. CIHR provides support for investigator-driven health research, but also sets strategic investment priorities to respond to key health and health system challenges. In identifying areas for strategic investment, we carefully consider where Canada can capitalize on its research strengths and have the greatest possible impact. CIHR has established five research priorities for the organization and health research across the country:

- Enhance patient-oriented care and improve clinical results through scientific and technological innovations.
- Support a high-quality, accessible and sustainable health care system.
- Reduce health inequities.
- Prepare for and respond to existing and emerging global threats to health.
- Promote health and reduce the burden of chronic disease and mental illness.

To date, CIHR has developed several signature initiatives that align with these five priorities. In this issue of *Show me the Evidence*, we are profiling CIHR's Personalized Medicine signature initiative, which aims to increase the precision with which we diagnose and treat disease. Canada is well positioned to be a leader in this field of research. Our researchers are not only generating the knowledge necessary to produce advances in personalized medicine, they are also helping create the infrastructure required to collect and analyse substantial amounts of genetic and genomic data. CIHR is working closely with provincial and national partners, such as Genome Canada, to invest in these researchers' important work.

The research projects that we are highlighting in this issue are helping us move towards a more individualized, precise approach to health care. These stories focus on:

- improved genetic profiling and risk communication for breast-cancer prediction, detection and treatment;
- a new model for engaging the public in meaningful discussions about storing and accessing biological data; and
- the data infrastructure necessary for labs, around the country and the world, to study genomic variation.

CIHR-funded research and researchers have delivered:

- **A MORE PATIENT-FRIENDLY TOOL FOR COMMUNICATING THE GENETIC RISK OF BREAST CANCER;**
- **POLICIES FOR BIOBANKS IN B.C., AUSTRALIA AND THE U.S. PRODUCED USING PUBLIC DELIBERATION METHODS; AND**
- **A DATABASE OF GENOMIC VARIANTS THAT HAS BEEN ACCESSED BY MORE THAN 1,500 LABORATORIES IN 34 COUNTRIES.**

LET'S TALK ABOUT RISK: PERSONALIZING BREAST CANCER RISK PREDICTION

Improved genetic profiling and risk communication are enabling targeted breast-cancer prediction, detection and treatment for those who need it most

AT A GLANCE

WHO: DR. JACQUES SIMARD, RESEARCH CENTRE OF THE CENTRE HOSPITALIER UNIVERSITAIRE DE QUÉBEC AND LAVAL UNIVERSITY

ISSUE: IN CANADA, ONE OUT OF NINE WOMEN WILL DEVELOP BREAST CANCER DURING HER LIFETIME. AT PRESENT, PREDICTIVE GENETIC TESTING EXISTS ONLY FOR MUTATIONS IN THE *BRCA1* AND *BRCA2* GENES, WHICH ACCOUNT FOR JUST 5% OF ALL BREAST CANCERS.

PROJECTS: DR. SIMARD LEADS THE CIHR TEAM IN FAMILIAL RISKS OF BREAST CANCER, WHICH INCLUDES MORE THAN TWO DOZEN CANADIAN AND INTERNATIONAL RESEARCHERS. THE TEAM, WHICH IS PART OF THE INTERNATIONAL COLLABORATIVE ONCOLOGICAL GENE-ENVIRONMENT STUDY (COGS), IS DEVELOPING A PERSONALIZED RISK STRATIFICATION SYSTEM TO IDENTIFY WOMEN WHO WILL MOST BENEFIT FROM EARLIER SCREENING, DETECTION AND TARGETED TREATMENT OF BREAST CANCER. THE TEAM HAS ALSO EVALUATED DIFFERENT STRATEGIES FOR SHARING RISK INFORMATION WITH PATIENTS.

RESEARCH EVIDENCE: IN MARCH 2013, COGS RELEASED THE LARGEST-EVER GENETIC ASSOCIATION STUDY IN CANCER. THE STUDY, INVOLVING MORE THAN 100,000 WOMEN WORLDWIDE, IDENTIFIED 49 NEW GENETIC MARKERS, OR GENETIC "SPELLING MISTAKES," RELATED TO BREAST CANCER. IN ADDITION, THE CIHR TEAM HAS FOUND THAT THE RISK COMMUNICATION FORMAT MOST COMMONLY USED BY CLINICIANS IS THE LEAST PREFERRED AND UNDERSTOOD BY BREAST CANCER PATIENTS.

EVIDENCE IN ACTION: THE CIHR TEAM'S RISK COMMUNICATION RESEARCH HAS CONTRIBUTED TO MAKING BOADICEA, THE WORLD'S PRIMARY RISK PREDICTION MODEL, MORE PATIENT-FRIENDLY THROUGH THE INCORPORATION OF A RISK CURVE GRAPHIC TO ITS ONLINE RISK COMMUNICATION PACKAGE. THE COGS STUDY, MEANWHILE, PROVIDES THE CIHR TEAM WITH GENETIC INFORMATION FOR THE DEVELOPMENT OF A NEW, BROAD-BASED GENETIC PROFILE SCREENING TEST FOR BREAST CANCER, ONE THAT WILL ENABLE IMPROVED PERSONALIZED BREAST CANCER SCREENING.

SOURCES: MICHAILIDOU, KYRIAKI, ET AL. "LARGE-SCALE GENOTYPING IDENTIFIES 41 NEW LOCI ASSOCIATED WITH BREAST CANCER RISK," *NATURE GENETICS* 45, 4 (2013): 353–61. DORVAL, MICHEL, ET AL. "A FOCUS GROUP STUDY ON BREAST CANCER RISK PRESENTATION: ONE FORMAT DOES NOT FIT ALL," *EUROPEAN JOURNAL OF HUMAN GENETICS* 21, 7 (2013): 719–24.

The big white chest freezer in Dr. Jacques Simard's lab at the research centre of the Centre hospitalier universitaire de Québec doesn't look that different from a freezer you would find in the home. It's what's inside it that makes it unique: invisible clues for the more accurate prediction of millions of women's long-term breast cancer risk. The freezer preserves the DNA samples of 20,000 women from Africa, Asia, Australia, Europe and North America. What links them is that all of the women have mutations in either one or both of the breast-cancer susceptibility genes *BRCA1* or *BRCA2*.

This wealth of material represents just one-seventh of the total number of samples collected as part of the global study that Dr. Simard is involved in with hundreds of colleagues. These researchers are mining a broad base of dozens of genetic markers to create significantly more accurate personalized breast cancer risk prediction models, work that is forging a new era in breast cancer screening.[1]

"All women have an intrinsic genetic risk of developing breast cancer," says Dr. Simard, Canada Research Chair in Oncogenetics. "The current challenge is to create a breast cancer prediction model incorporating a detailed genetic profile coupled with other non-genetic risk factors. This will enable health professionals to personalize each woman's risk within a risk stratification framework."

Researchers believe that personalized risk stratification – determining a patient's risk of developing a specific disease – can help clinicians make better decisions about which patients would benefit from further testing or preventive treatment. In the case of breast cancer, it will help identify the women most likely to develop the disease, therefore enabling more successful, targeted screening, prevention measures and treatment earlier in women's lives.

The CIHR Team in Familial Risks of Breast Cancer, led by Dr. Simard, is also improving the way that breast cancer risk results are shared with patients. He feels that this risk communication work is just as important as the genetic research itself. "If you have a bad genetic profile but you can't translate this information in a useful way, then health professionals won't really understand it, and women won't understand how it can help improve their health," he says.

THE LONG REACH OF BREAST CANCER

Breast cancer affects one out of nine Canadian women in her lifetime, and every year about 23,000 Canadian women are diagnosed with breast cancer. More than 5,000 women die of this disease each year.[2]

In the early 1990's, Dr. Simard's genetic sleuthing contributed to the discovery of the *BRCA1* (BReast CAncer gene one) and *BRCA2* mutations and the full gene structure of the latter. These are the first genes clearly linked to a significantly higher risk of breast and ovarian cancer. In 1996, Myriad Genetics released the first publicly available test for *BRCA1* and *BRCA2*. Since then, this genetic screening has enabled hundreds of thousands of women with a familial history of early onset breast cancer to be tested for the mutations.

Photo courtesy of Dr. Jacques Simard

EVIDENCE IN ACTION: HELPING HIGH-RISK WOMEN GET BREAST CANCER SCREENING

IN 2011, CANCER CARE ONTARIO BECAME THE FIRST AGENCY IN CANADA TO OFFER A STRATIFIED RISK MANAGEMENT APPROACH, OFFERING ADVANCED SCREENING FOR ONTARIO WOMEN DEEMED AT HIGH RISK. THIS INCLUDES BEING A *BRCA1* OR *BRCA2* MUTATION CARRIER, OR BEING ASSESSED WITH A GREATER THAN 25% LIFETIME RISK OF DEVELOPING BREAST CANCER BASED ON THE BOADICEA RISK PREDICTION MODEL.[3]

These two genes represent just a beginning in the use of genetic information for improved breast cancer prediction, according to Dr. Simard. Only about one in four hundred women in the general population carries either the *BRCA1* or *BRCA2* genetic mutations.[4] Even among those who do, the predicted breast cancer risk (calculated by also factoring in family history and lifestyle) ranges dramatically from a modest 30% chance to a much more cautionary 90% chance.

Dr. Simard and his colleagues see room for improvement. With support from the Genomics and Personalized Health Genome Canada/CIHR partnership, they are focused on extending the genetic basis of breast cancer risk prediction from two genes, to a more detailed and accurate genetic profile based on *BRCA1* and *BRCA2*, along with dozens of other genetic markers linked to breast cancer.

In combination with non-genetic risk factors, this genetic profile will create a tiered ranking of each woman's risk. "In this way we can identify younger women, particularly those aged 35 to 49, having a significantly higher risk than average, and for whom it would be beneficial to have access to screening and risk reduction strategies earlier in their lives," says Dr. Simard.

In March 2013, the international Collaborative Oncological Gene-environment Study (COGS), a large-scale genotyping project, announced a much more detailed mapping of the landscape of the genetics of breast cancer susceptibility.[5] The researchers – including Dr. Simard and other members of the CIHR Team in Familial Risks of Breast Cancer – scanned and compared the entire genomes of more than 100,000 women, half of whom were healthy and half who had had breast cancer. They looked for tiny genetic differences, called single nucleotide polymorphisms, or SNPs (pronounced "snips"), at 200,000 DNA locations.

Through this massive genetic association study, the largest-ever for any cancer, the researchers identified 49 new SNPs, or genetic markers, associated with the risk of developing breast cancer, almost tripling the known number.

"Already this finding demonstrates the usefulness of this genetic marker approach," says Dr. Simard. "If this genetic information is combined with other disease risk factors such as age, family and reproductive history, as well as breast density, we think we would be able to identify the 5% of women who have a one-in-three chance of developing breast cancer."

COMMUNICATING THE RISK OF BREAST CANCER

From a clinical perspective, identifying the women who are at risk is not enough. The statistics involved in breast cancer risk prediction models are often baffling to both physicians and the women who must make possibly crucial decisions based on complex statistical probabilities.[6] As a result, the interdisciplinary CIHR team is also focused on finding the best ways to share breast cancer risk information with Canadian women.

A recent CIHR team study revealed that the way in which researchers generally communicate breast cancer risk information to one another is the least accessible and most confusing for patients.[7]

The study asked more than 100 Canadian women in three cities, all of whom had received breast cancer risk counselling, to comment on five different forms of risk communication. These ranged from a numerical format involving columns of numbers (the mode preferred by researchers) to a colour-coded scale (risk curve) ranging from low risk on the left, to high risk on the right. The study participants rejected the numerical format preferred by researchers. "If you're giving this to a person who has no medical experience … this would be too freaky for them," noted one participant.

"When it comes to breast cancer risk communication, we need to be sensitive to women's individual emotional and cognitive differences," concludes Dr. Michel Dorval, a researcher with Laval University's Faculty of Pharmacy and the study's lead author. "If we want to maximize understanding of risk communication we need to use a combination of approaches."

This communications research has already altered the way results from BOADICEA, the world's primary breast cancer risk prediction model, are communicated. Previously, BOADICEA's website communicated a woman's risk prediction results only in numerical format, the one least preferred by patients. BOADICEA now also includes a more accessible risk curve graphic of the same results.

"Often in our work we don't see rapid results, but in this case there was a very rapid impact," says Dr. Dorval, who leads the CIHR Team in Familial Risk of Breast Cancer's psychosocial research component.

Back in Dr. Simard's freezer, the DNA samples are playing a key role in a second large-scale breast cancer association study involving more than 140,000 participants and probing 570,000 SNPs, or genetic markers. Says Dr. Simard: "Future findings will only improve on the new information we've already discovered about common genetic markers, including those acting as modifiers of *BRCA1*- and *BRCA2*-associated breast cancer risk, which are currently being incorporated into the BOADICEA model to improve the accuracy of personalized risk prediction."

THE BIG PICTURE VIA INTERNATIONAL COLLABORATION

THE INTERNATIONAL COLLABORATIVE ONCOLOGICAL GENE-ENVIRONMENT STUDY (COGS) IS A CONSORTIUM OF MORE THAN 160 RESEARCH GROUPS FROM UNIVERSITIES, HOSPITALS AND GOVERNMENT LABS IN MORE THAN 40 COUNTRIES. COGS' OVERARCHING GOAL IS TO COMBINE LARGE STUDY GROUPS AND THE LATEST, FASTEST GENETIC SCREENING TECHNOLOGIES TO USHER IN A NEW ERA IN THE HIGH-PRECISION IDENTIFICATION OF INDIVIDUAL RISKS OF BREAST, OVARIAN AND PROSTATE CANCER.

FOR MORE INFORMATION

Breast Cancer Statistics (French only): www.centredesmaladiesdusein.ca/cancer-du-sein/genetique/les-genes-brca1-et-brca2/index.html.

US National Cancer Institute, Genetics of Breast and Ovarian Cancer: www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/HealthProfessional/page2#Reference2.5.

Collaborative Oncological Gene-environment Study (COGS): www.cogseu.org.

Video with Dr. Simard: www.youtube.com/watch?v=_0509U8TWLw.

1 Hall, P., and D. Easton. "Breast cancer screening: time to target women at risk," *British Journal of Cancer* 108, 11 (2013): 2202–04. doi:10.1038/bjc.2013.257.

2 Canadian Cancer Society, *BRCA Gene Mutations*. Available at: www.cancer.ca/en/cancer-information/cancer-101/what-is-a-risk-factor/genetic-risk/brca-gene-mutations/?region=on.

3 University of Cambridge Centre for Cancer Genetic Epidemiology, *Boadicea model*. Available at: ccge.medschl.cam.ac.uk/boadicea/model/.

4 U.S. National Cancer Institute, *High-Penetrance Breast and/or Ovarian Cancer Susceptibility Genes*. Available at: www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/HealthProfessional/page2#Reference2.5.

5 Michailidou, Kyriaki, et al. "Large-scale genotyping identifies 41 new loci associated with breast cancer risk," *Nature Genetics* 45, 4 (2013): 353–61.

6 Gaudet, Mia, et al. "Identification of a *BRCA2*-Specific Modifier Locus at 6p24 Related to Breast Cancer Risk," *PLoS Genetics* 9, 3 (2013): e1003173. doi:10.1371/journal.pgen.1003173.

7 Dorval, Michel, et al. "A focus group study on breast cancer risk presentation: one format does not fit all," *European Journal of Human Genetics* 21, 7 (2013): 719–24.

POWER TO THE PEOPLE: PERSONALIZED MEDICINE RESEARCH GETS AN ETHICAL MAKEOVER

A pioneering Canadian method for public engagement in biomedical policy is giving citizens around the world a voice in developing biobank ethics policies

AT A GLANCE

WHO: DR. MICHAEL BURGESS, UNIVERSITY OF BRITISH COLUMBIA

ISSUE: IN THE PAST DECADE, THERE HAS BEEN A DRAMATIC GLOBAL INCREASE IN THE NUMBER OF NEW BIOBANKS, COLLECTIONS OF THOUSANDS OR EVEN HUNDREDS OF THOUSANDS OF TISSUE SAMPLES, FROM BLOOD TO POST-SURGICAL SAMPLES. THESE BIOBANKS HAVE THE POTENTIAL TO SIGNIFICANTLY INCREASE OUR UNDERSTANDING OF HUMAN HEALTH AND DISEASE. HOWEVER, BIOBANK RESEARCH RAISES NUMEROUS INDIVIDUAL AND SOCIAL ETHICAL ISSUES, INCLUDING INFORMED CONSENT, INDIVIDUAL PRIVACY AND COMMUNITY RIGHTS. RESEARCHERS ARE LOOKING FOR NEW WAYS TO INCLUDE MEANINGFUL PUBLIC INPUT IN DEVELOPING BIOBANK ETHICS POLICIES.

PROJECTS: IN 2007 AND 2009, DR. BURGESS AND DR. KIERAN O'DOHERTY, ALONG WITH OTHER COLLEAGUES, PIONEERED THE USE OF DELIBERATIVE DEMOCRACY FORUMS AS A NEW MODEL FOR CREATING MEANINGFUL PUBLIC INPUT INTO BIOBANK ETHICS POLICIES.

RESEARCH EVIDENCE: THE TWO SESSIONS, THE BC BIOBANK DELIBERATION (2007) AND THE BC BIOLIBRARY DELIBERATION (2009), PRODUCED THE FIRST PROOF-OF-PRINCIPLE EVIDENCE THAT DELIBERATIVE DEMOCRACY FORUMS CAN EFFECTIVELY PRODUCE BIOBANK ETHICS POLICY RECOMMENDATIONS.

EVIDENCE IN ACTION: DELIBERATIVE DEMOCRACY PRINCIPLES AND METHODS, AS APPLIED TO BIOBANK ETHICS POLICIES, HAVE BECOME A KEY FACTOR IN GUIDING BIOBANK PROCEDURES, GOVERNANCE AND LAWMAKING AT MAJOR INSTITUTIONS IN CANADA, THE UNITED STATES AND AUSTRALIA.

SOURCES: O'DOHERTY, KIERAN, AND MICHAEL BURGESS. "PUBLIC DELIBERATION TO DEVELOP ETHICAL NORMS AND INFORM POLICY FOR BIOBANKS: LESSONS LEARNT AND CHALLENGES REMAINING," *RESEARCH ETHICS* 9, 2 (2013): 55–77. O'DOHERTY, KIERAN, ET AL. "INVOLVING CITIZENS IN THE ETHICS OF BIOBANK RESEARCH: INFORMING INSTITUTIONAL POLICY THROUGH STRUCTURED PUBLIC DELIBERATION," *SOCIAL SCIENCE AND MEDICINE* 75, 9 (2012): 1604–11.

WHAT'S A BIOBANK?
A BIOBANK IS A COLLECTION OF HUMAN TISSUES – INCLUDING BLOOD – SOME OF WHICH HAVE EXISTED FOR DECADES, SUCH AS AUTOPSY MATERIALS.[1] SPECIFIC BIOBANKS COLLECT SAMPLES FOR DIFFERENT REASONS, THE PRIMARY ONES BEING MEDICAL RESEARCH, CRIMINAL INVESTIGATIONS (E.G. DNA PROFILES OF CONVICTED PERSONS) AND HUMAN IDENTIFICATION (MILITARY PERSONNEL BIOBANKS). TODAY, MANY NEW BIOBANKS ARE BEING CREATED OR CONSOLIDATED TO FACILITATE POPULATION OR COMMUNITY-LEVEL GENETICS RESEARCH.

Henrietta Lacks died of cervical cancer in 1951, but her cells live on. Today, the *HeLa* cell line (named for their source, *He*nrietta *La*cks' tumour) is a key tool in biomedical research. *HeLa* cells have been vital for developing the polio vaccine, cloning, gene mapping and in vitro fertilization.

The problem – as recounted in the best-selling book *The Immortal Life of Henrietta Lacks* – is that while her cells have been bought and sold by the billions, neither Ms. Lacks nor her family consented to the storage and use of a sample of her tumour cells. As a result, Henrietta Lacks' cells aren't just fuelling biomedical research, they're fuelling important debates in bioethics.

Her story has turned public attention to the booming field of biobanks, the collection, storage and use of tissue samples, including blood and surgical samples, and their increasing use in biomedical research.[2] Drs. Michael Burgess and Kieran O'Doherty are helping ensure not only that today's patients and biobank donors provide informed consent, but also that Canadians have a say in how biobank ethics policies are developed and implemented.

"It seems like [in the past] we often treated individuals as if the only thing that's relevant about them is the possibility that they might contribute to scientific research rather than embedding scientific research in the larger context of their lives," says Dr. Burgess, Chair in Biomedical Ethics at the University of British Columbia.

To address this imbalance, Dr. Burgess and colleagues have pioneered the development of a new model for creating meaningful public input into biobank ethics policies, one that's becoming the international gold standard for developing biobank procedures, governance structures and laws.

THE RISE OF BIOBANKS

Over the past decade, the advent of genomics and the Internet has propelled biobanks to new scales in size and level of importance.[3] Most biobanks used to hold hundreds or thousands of samples in hospitals or university labs. Today, national and collaborative programs are creating biobanks holding hundreds of thousands, and soon millions, of tissue samples. The population-based UK Biobank already contains half-a-million DNA samples. In Canada, Quebec is building the CARTaGENE biobank, which will collect samples from 37,000 individuals.

Scientists anticipate that the enormous sample sizes will enable them to detect subtle genetic and environmental differences that contribute to diseases from diabetes to cancer to multiple sclerosis. "Biobanks are one of the key innovations that are necessary for genomics and personalized medicine to move ahead," says Dr. Burgess.

EVIDENCE IN ACTION: INCLUDING THE PUBLIC IN BIOETHICS DISCUSSIONS

THE BC BIOBANK AND BIOLIBRARY DELIBERATIONS HAVE FUELLED A NEW WAY TO THINK ABOUT RESEARCH BIOETHICS, SAYS DR. KIERAN O'DOHERTY. "THIS RESEARCH HAS HELPED FOSTER A DIFFERENT WAY TO THINK ABOUT AND DO BIOETHICS," HE ADDS, NOTING DISCUSSION OF THE ISSUE BY THE INFLUENTIAL HASTINGS CENTER REPORT.[4] "IT'S NOT JUST THE PHILOSOPHER SITTING IN AN OFFICE TELLING EVERYONE WHAT THE ETHICAL THING IS, BUT RATHER HAVING PUBLIC DISCOURSE AROUND IT, AND WE NEED MECHANISMS TO GET PUBLIC INPUT ON THESE THINGS."

However, this burst of biobank research has also opened a new frontier in bioethics, one in which traditional cornerstones, such as individual informed consent, are no longer enough. Presently, informed consent involves voluntarily giving researchers permission to use tissue samples with a clear understanding of the research involved. However, when a person donates tissue to a biobank, neither the donor nor the biobank can know, or even imagine, the possible future uses of the tissue.

"Informed consent is based on the assumption that I know the risks – such as privacy – and benefits that I'm agreeing to. If you can't tell me what it is you're going to do [with a sample], I can't give consent," says Dr. Burgess. "But I might be able to give informed consent to a detailed description of how decisions about my samples and data will be made, or the governance of the biobank."

Collecting genomic data creates additional ethical complexities. Individual donors cannot provide consent for other family or community members who share their genetic traits. This is a particular concern to First Nations communities in Canada, in many of which decision making is expected to reflect the wider interests of the community.

To address the broad individual, social and legal ethical issues raised by modern biobanks, researchers are turning to those who pay for, and are most affected by, much of this research: citizens. "A lot of the academic literature criticized previous public engagement events for not giving the community a genuine opportunity to affect biobank policy, or even the discussion around the issues," says Dr. O'Doherty, currently a professor of applied social psychology at the University of Guelph, who led the 2009 BC Biolibrary Deliberations.

Dr. Burgess believed they needed to look beyond the realm of existing bioethics practices and borrow a technique from political science: deliberative democracy. It's an approach to facilitating improved community-based discussions on controversial and complex issues that was formalized by political scientists in the 1980s. Their approach mixes the concepts of citizen assembly and citizen jury, according to Dr. Burgess.

PUBLIC ENGAGEMENT INFORMING POLICY

Starting with the BC Biobank Deliberation in 2007 and BC Biolibrary Deliberation in 2009, Dr. Burgess and colleagues have produced the first proof-of-principle evidence that deliberative democracy forums can effectively produce biobank ethics policy recommendations. Each deliberation involved a diverse group of two dozen randomly selected adult British Columbians. The 2007 deliberation focused on whether the participants supported the idea of creating a biobank in B.C., and if so, how it should be done.

Over the course of two weekend sessions, the participants first learned about biobanks from a custom backgrounder booklet and through presentations by experts and diverse stakeholders. During the sessions, the participants asked questions, discussed issues in small groups, and worked as a whole group to provide policy advice.

The deliberants strongly supported the idea of creating a biobank in B.C. To the researchers' surprise, one of the deliberants' main concerns was how to ensure that publicly funded biobanks are efficiently run to maximize the research return on taxpayers' investment.

For Dr. Burgess, success was in the process. "At the end of the day, the research team sat down and I said 'I can't believe it worked'," he recalls about pioneering this model in a health research context.

The 2009 deliberation was run in conjunction with the BC BioLibrary, not a biobank but an overarching organization created to facilitate the collection and research use of biobank samples.

The deliberation was focused on developing specific policy recommendations, ones that had immediate impact on BC BioLibrary procedures, and have informed the creation of the new Office of Biobank Education and Research at the University of British Columbia.

"It altered the way they approached people initially to tell them about using their tissues for research," says Dr. Burgess. Rather than use online or print resources as the point of first contact with potential donors, the Biolibrary Deliberation participants stressed that they preferred to be consulted in person by someone who could immediately answer questions.

Drs. Burgess and O'Doherty's deliberative democracy methodology of public engagement in biobank ethics policy has had an international impact. In 2007, Dr. Barbara Koenig was starting the Mayo Clinic's bioethics program at the same time as it was creating its own biobank, and she used what she calls "the Burgess Method" to invite public input into the biobank's creation.[5] The deliberants proposed the creation of a permanent community biobank advisory board representing diverse religious and ethnic perspectives, a suggestion the Mayo Clinic embraced.

"Over the course of three years, as we were setting up the biobank, every single bit of the biobank governance, and how the biobank operated, was run past the community advisory board [including how it was designed and the design of consent documents]," says Dr. Koenig, now a professor of medical anthropology and bioethics at the University of California, San Francisco.

Similarly, in Western Australia in 2008, an office within the Department of Health tasked with developing a position statement on biobanking used the design of the BC Biobank Deliberation to conduct a public and stakeholder consultation to inform policy.

Sixty years after Henrietta Lacks' death, the BC Biobank and Biolibrary Deliberations are helping ensure that individuals around the world have a voice not only in individual biobank choices, but also in big-picture ethics policy. Says Dr. Burgess, "We've proven that deliberative engagement is a policy tool that can deliver informed, deliberative public advice."

1 University of British Columbia, "Biobanking in British Columbia: A deliberative public consultation." Available at: flyingturtles09.files.wordpress.com/2009/02/the_biobank_booklet.pdf.

2 Skloot, Rebecca. Excerpt from *The Immortal Life of Henrietta Lacks*. Available at: rebeccaskloot.com/the-immortal-life/excerpt/.

3 Park, Alice. "Ten Ideas Changing the World Right Now," *Time Magazine* (March 12, 2009). Available at: content.time.com/time/specials/packages/article/0,28804,1884779_1884782_1884766,00.html.

4 Tomlinson, Tom. "Respecting Donors to Biobank Research," *Hastings Center Report* 43, 1 (2013): 41–47.

5 Mayo Clinic, "Mayo Clinic Biobank." Available at: www.mayo.edu/research/centers-programs/mayo-clinic-biobank/overview/.

WHY DELIBERATIVE DEMOCRACY?

DELIBERATIVE DEMOCRACY IS A FORM OF FACILITATED PUBLIC CONVERSATION ON A COMPLEX ISSUE. IT ASSUMES THAT CITIZENS CAN AND SHOULD MAKE IMPORTANT CONTRIBUTIONS TO POLICY ISSUES. DELIBERATIVE DISCUSSION IS CHARACTERIZED BY A DIVERSE GROUP OF PARTICIPANTS LEARNING THE TECHNICAL ASPECTS AND SOCIAL PERSPECTIVES OF AN ISSUE, RESPECTFULLY EXCHANGING VIEWS, ACTIVELY LISTENING, AND PROVIDING PRACTICAL ADVICE. UNLIKE A SURVEY OR FOCUS GROUP, DELIBERATIVE DISCUSSION INVOLVES PROVIDING PARTICIPANTS WITH DETAILED, NEUTRAL BACKGROUND INFORMATION AND EMPHASIZES "CIVIC" INSTEAD OF PERSONAL INTERESTS.

FOR MORE INFORMATION

Office of Biobank Education and Research, University of British Columbia: pathology.ubc.ca/education-resource/ober/.

BC BioLibrary: www.bcbiolibrary.ca.

Mayo Clinic, Deliberative Democracy: www.youtube.com/watch?v=s0Sxzu3_z18.

Video with Dr. Burgess: www.youtube.com/watch?v=28_10cP73vg.

LAYING THE FOUNDATION: INFRASTRUCTURE FOR GENOMIC RESEARCH BRINGING THE GOALS OF PERSONALIZED MEDICINE CLOSER

Database of genomic variants is facilitating research in labs around the world

AT A GLANCE

WHO: DR. STEPHEN SCHERER, THE CENTRE FOR APPLIED GENOMICS, HOSPITAL FOR SICK CHILDREN

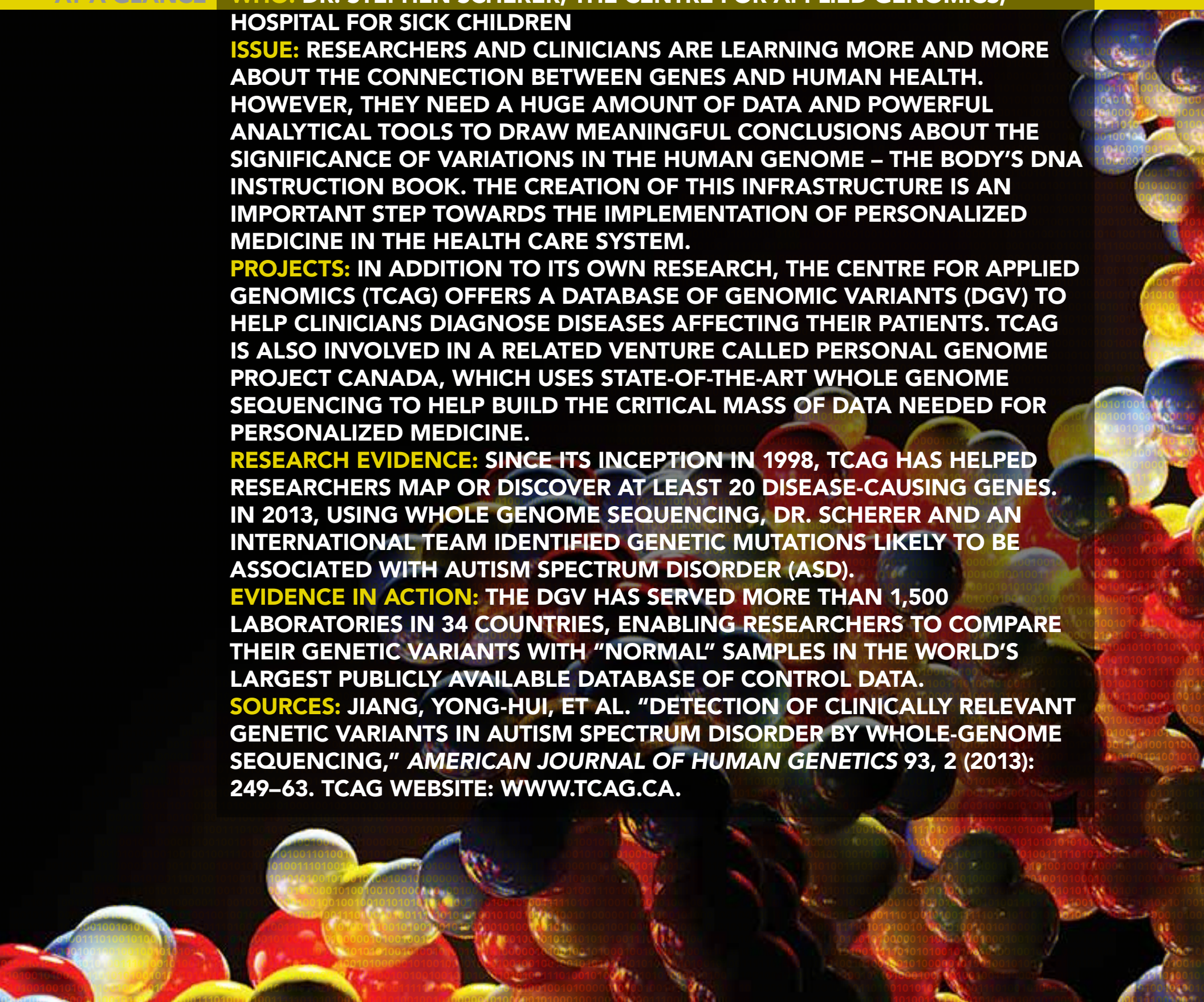
ISSUE: RESEARCHERS AND CLINICIANS ARE LEARNING MORE AND MORE ABOUT THE CONNECTION BETWEEN GENES AND HUMAN HEALTH. HOWEVER, THEY NEED A HUGE AMOUNT OF DATA AND POWERFUL ANALYTICAL TOOLS TO DRAW MEANINGFUL CONCLUSIONS ABOUT THE SIGNIFICANCE OF VARIATIONS IN THE HUMAN GENOME – THE BODY'S DNA INSTRUCTION BOOK. THE CREATION OF THIS INFRASTRUCTURE IS AN IMPORTANT STEP TOWARDS THE IMPLEMENTATION OF PERSONALIZED MEDICINE IN THE HEALTH CARE SYSTEM.

PROJECTS: IN ADDITION TO ITS OWN RESEARCH, THE CENTRE FOR APPLIED GENOMICS (TCAG) OFFERS A DATABASE OF GENOMIC VARIANTS (DGV) TO HELP CLINICIANS DIAGNOSE DISEASES AFFECTING THEIR PATIENTS. TCAG IS ALSO INVOLVED IN A RELATED VENTURE CALLED PERSONAL GENOME PROJECT CANADA, WHICH USES STATE-OF-THE-ART WHOLE GENOME SEQUENCING TO HELP BUILD THE CRITICAL MASS OF DATA NEEDED FOR PERSONALIZED MEDICINE.

RESEARCH EVIDENCE: SINCE ITS INCEPTION IN 1998, TCAG HAS HELPED RESEARCHERS MAP OR DISCOVER AT LEAST 20 DISEASE-CAUSING GENES. IN 2013, USING WHOLE GENOME SEQUENCING, DR. SCHERER AND AN INTERNATIONAL TEAM IDENTIFIED GENETIC MUTATIONS LIKELY TO BE ASSOCIATED WITH AUTISM SPECTRUM DISORDER (ASD).

EVIDENCE IN ACTION: THE DGV HAS SERVED MORE THAN 1,500 LABORATORIES IN 34 COUNTRIES, ENABLING RESEARCHERS TO COMPARE THEIR GENETIC VARIANTS WITH "NORMAL" SAMPLES IN THE WORLD'S LARGEST PUBLICLY AVAILABLE DATABASE OF CONTROL DATA.

SOURCES: JIANG, YONG-HUI, ET AL. "DETECTION OF CLINICALLY RELEVANT GENETIC VARIANTS IN AUTISM SPECTRUM DISORDER BY WHOLE-GENOME SEQUENCING," *AMERICAN JOURNAL OF HUMAN GENETICS* 93, 2 (2013): 249–63. TCAG WEBSITE: WWW.TCAG.CA.



Dr. Stephen Scherer looks for meaning in junk – the oddball data that in the not so distant past other genetics researchers disregarded. Using this so-called "garbage can" approach, he and his team at The Centre for Applied Genomics (TCAG) in Toronto have located vital missing pieces of the genomic puzzle and are building an infrastructure for geneticists to help usher in a new era of personalized medicine.

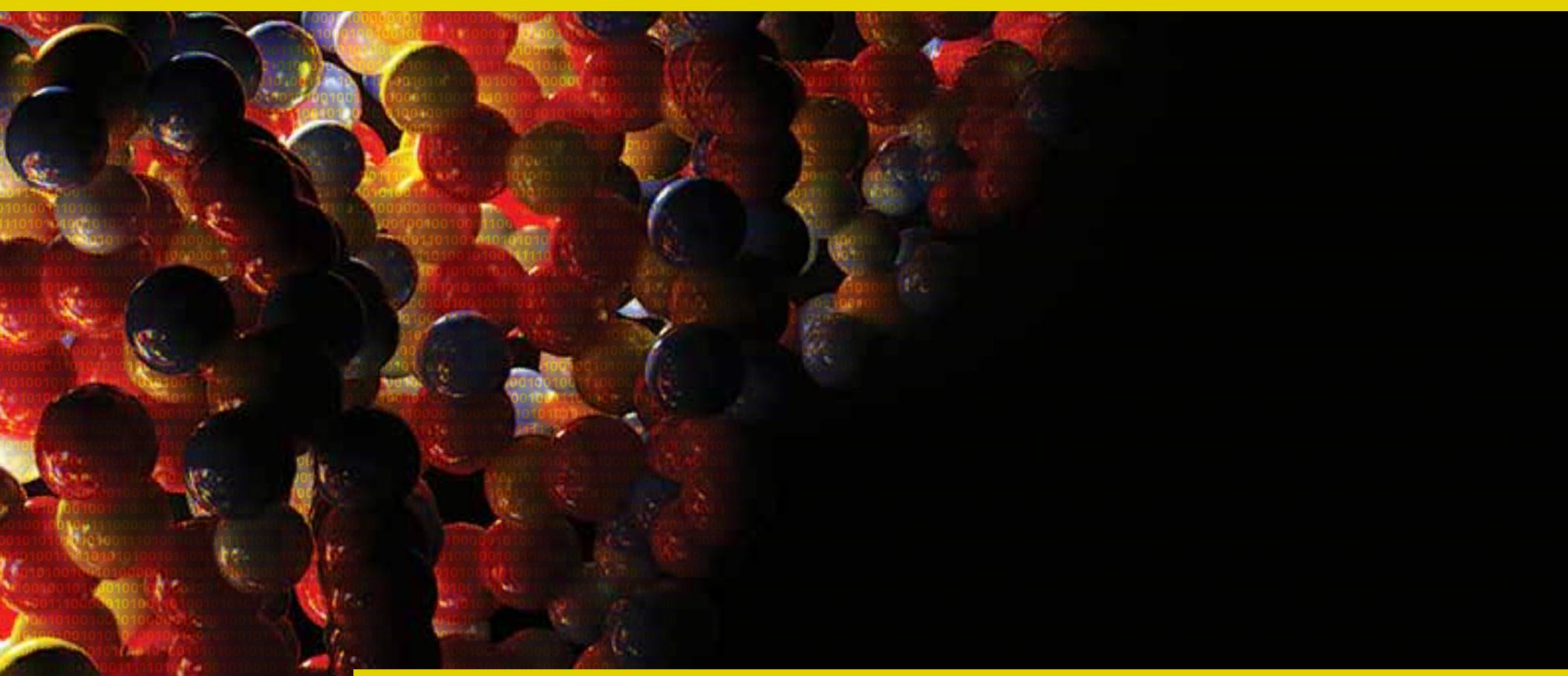
The human genome comprises 6 billion chemical bases (or nucleotides) of DNA packed into two sets of 23 chromosomes, one inherited from each parent. Until 2003, when the Human Genome Project finished sequencing a full "draft" of the genome, researchers contended that humans are 99.9 percent identical; duplications or deletions in the number of genes, known as copy number variations (CNVs), were just "noise." For Dr. Scherer, however, these tiny structural variations in the genome demanded to be heard.

He began by studying the observation with a condition that he knew well – autism. By closely examining data others had ignored, he detected a pattern: children with autism had more duplications and deletions than usual. Ultimately, in addition to identifying variations linked to autism, Dr. Scherer and his team showed that CNVs are more common than previously thought.[1] These differences account for normal variations – such as eye or hair colour – but can also predispose a person to disease.

In 1998, following graduate work with the celebrated Dr. Lap-Chee Tsui, whose team had identified the defective gene that causes cystic fibrosis, Dr. Scherer and his former mentor jointly set up TCAG at the Hospital for Sick Children (SickKids). Established in part with funding from the Canada Foundation for Innovation and Genome Canada, TCAG has helped build critical infrastructure to advance genetics research.

By 2003, TCAG had already helped map or discover some 20 disease-causing genes. Over the next decade, Dr. Scherer would harness emerging technologies to write new chapters in our understanding of the genome – what he calls the DNA instruction book – contained in the trillions of cells that direct all aspects of human development. These discoveries are slowly unlocking the mysteries of disease and providing clues for treatment.

To help researchers draw meaningful conclusions about the significance of genomic variations, TCAG offers a tool called the database of genomic variants (DGV). As of July 2013, the DGV's catalogue contained samples from more than 14,000 "normal" individuals derived from 55 peer-reviewed studies. "It's very helpful because it's the largest publicly available database of control data," says Dr. James Stavropoulos, Co-Director of the Cytogenetics Laboratory at SickKids.



EVIDENCE IN ACTION:
FACILITATING GENOMIC RESEARCH AROUND THE WORLD

SINCE ITS INCEPTION IN 1998, THE CENTRE FOR APPLIED GENOMICS HAS PROVIDED EXPERIMENTAL AND ANALYTICAL SERVICES FOR MORE THAN 1,500 LABORATORIES IN 34 COUNTRIES. THE CENTRE OPERATES ON A COST-RECOVERY BASIS, ISSUING MORE THAN 400 INVOICES PER MONTH FOR BILLINGS IN EXCESS OF $9 MILLION ANNUALLY.

"We use the DGV 20 or 30 times a day," says Dr. Marsha Speevak, laboratory geneticist at Credit Valley Hospital in Mississauga, Ontario. "It is essential for ruling out a variant you haven't seen before. It may be a rare variant, but not so rare that it hasn't been listed and referenced in the DGV. Of course, data can be over- or under-reported so they are constantly improving the DGV to make it even more robust, accurate and reliable."

ACCURATE AND RELIABLE

UNCOVERING THE MYSTERY OF AUTISM

AS THE LEAD OF AN INTERNATIONAL TEAM FROM 11 COUNTRIES, DR. SCHERER PUBLISHED A STUDY IN 2013 THAT IDENTIFIED SEVERAL NEW MUTATIONS LIKELY TO BE ASSOCIATED WITH AUTISM SPECTRUM DISORDER (ASD) – A CONDITION THAT CREATES SIGNIFICANT BEHAVIOURAL DISABILITIES IN ABOUT ONE IN 88 CHILDREN IN NORTH AMERICA.[2] THE PILOT STUDY, SUPPORTED IN PART BY CIHR, SEQUENCED THE GENOMES OF 32 CANADIANS WITH ASD AND THEIR PARENTS, AS WELL AS SIBLINGS AND OTHER RELATIONS IN SOME CASES. THE STUDY IDENTIFIED MUTATIONS IN FOUR NEWLY RECOGNIZED GENES, NINE GENES PREVIOUSLY LINKED TO AUTISM AND EIGHT GENES WITH AN AUTISM RISK. WITH SUPPORT FROM THE GENOMICS AND PERSONALIZED HEALTH GENOME CANADA/CIHR PARTNERSHIP, TCAG IS TAKING PART IN A FOLLOW-UP STUDY TO SEQUENCE AND ANALYZE THE GENOMES OF 10,000 FAMILIES AROUND THE WORLD, INCLUDING 1,000 IN CANADA.

Continuously updated, the DGV enables scientists and clinicians to compare their copy number variations with samples from a "normal" population. If the two samples match, then the client's variation is also likely to be normal.

Like the diagnostic lab at SickKids, North York General Hospital in Toronto, Ontario, tests for developmental delays in children. "Inevitably, there will be patients where you can't say the genetic variation is pathogenic or neutral," says Dr. Kathy Chun, Director, Cytogenetics and Molecular Genetics at North York General. "You need a control population (of 'normal cases') to compare results. That's where the DGV comes in, not just in Canada, but worldwide. It's extremely important."

"We use the DGV 20 or 30 times a day," says Dr. Marsha Speevak, laboratory geneticist at Credit Valley Hospital in Mississauga, Ontario. "It is essential for ruling out a variant you haven't seen before. It may be a rare variant, but not so rare that it hasn't been listed and referenced in the DGV. Of course, data can be over- or under-reported so they are constantly improving the DGV to make it even more robust, accurate and reliable."

"The DGV started as a hobby, but now it's known as *the* genomic database," says Dr. Scherer. "If the database goes down for half an hour, clients will call me – even at home – to make sure I'm aware of it."

With support from the Canadian Institutes of Health Research (CIHR), TCAG has also launched Personal Genome Project Canada, inviting individual Canadians to have their genomes sequenced. Not only will the volunteers gain useful information about their own health, they will also help build the critical mass of data needed to make personalized medicine a reality. The first 12 sequences are expected to be published in 2014.

Researchers need powerful tools to make sense of the growing amount of data available on structural variations in the genome. "We have always prided ourselves that we would be the first in Canada to introduce something new," says Dr. Scherer. "But keeping up with technology is also the biggest challenge we face."

THE FUTURE OF GENETIC SCREENING

Before 2005, clinicians had only low-resolution tools to run standard tests on children with developmental delays. In the mid-2000s, a molecular technique called DNA microarray scanning emerged, enabling the detection of minute changes in DNA at resolutions 100 times more powerful than earlier devices. Over the past decade, laboratories have turned to TCAG in part because of its top-notch microarray facilities.

"Companies approach us when developing new software and even the diagnostic microarrays themselves," says Dr. Scherer. While users can plug in their CNV coordinates directly online, others – like Dr. Chun at North York – have the DGV imbedded into their analysis systems. She simply scrolls down her screen to check for duplications and deletions in CNV, which are colour-coded.

But microarray scanning itself is fast becoming replaced by exome and/or whole genome sequencing – the process of "reading" the "letters" in the billions of base pairs that make up the DNA instruction manual and finding any errors. From hundreds of millions of dollars to complete the first genome sequences in the mid-2000s, the cost will soon drop below $1,000. TCAG has already been involved in pilot studies using the new technology.

"Almost all disease links back in some way to genetics," says Dr. Scherer. "Some, like Huntington's or cystic fibrosis, are mostly genetic, while others like autism and cancer are linked to genes. Still others, like diabetes, are influenced by genetics. So if you don't have a 'genetic' step in your assessment of a disease, you will be only partially informed of the cause, and what to do about it."

1 Redon, Richard. "Global variation in copy number in the human genome," *Nature* 444, 7118 (2006): 444–54.

2 Jiang, Yong-hui, et al. "Detection of Clinically Relevant Genetic Variants in Autism Spectrum Disorder by Whole-Genome Sequencing," *American Journal of Human Genetics* 93, 2 (2013): 249–63.

FOR MORE INFORMATION

Database of Genomic Variants: dgv.tcag.ca/dgv/app/home.

Martin, Roger, "A Conversation with Stephen Scherer." Available at: hbr.harvardbusiness.org/2009/11/two-leading-researchers-discuss-the-value-of-oddball-data/ar/1.

Dr. Stephen Scherer – Tao of Discovery Documentary: www.youtube.com/watch?v=MpYWOd_fqLA.

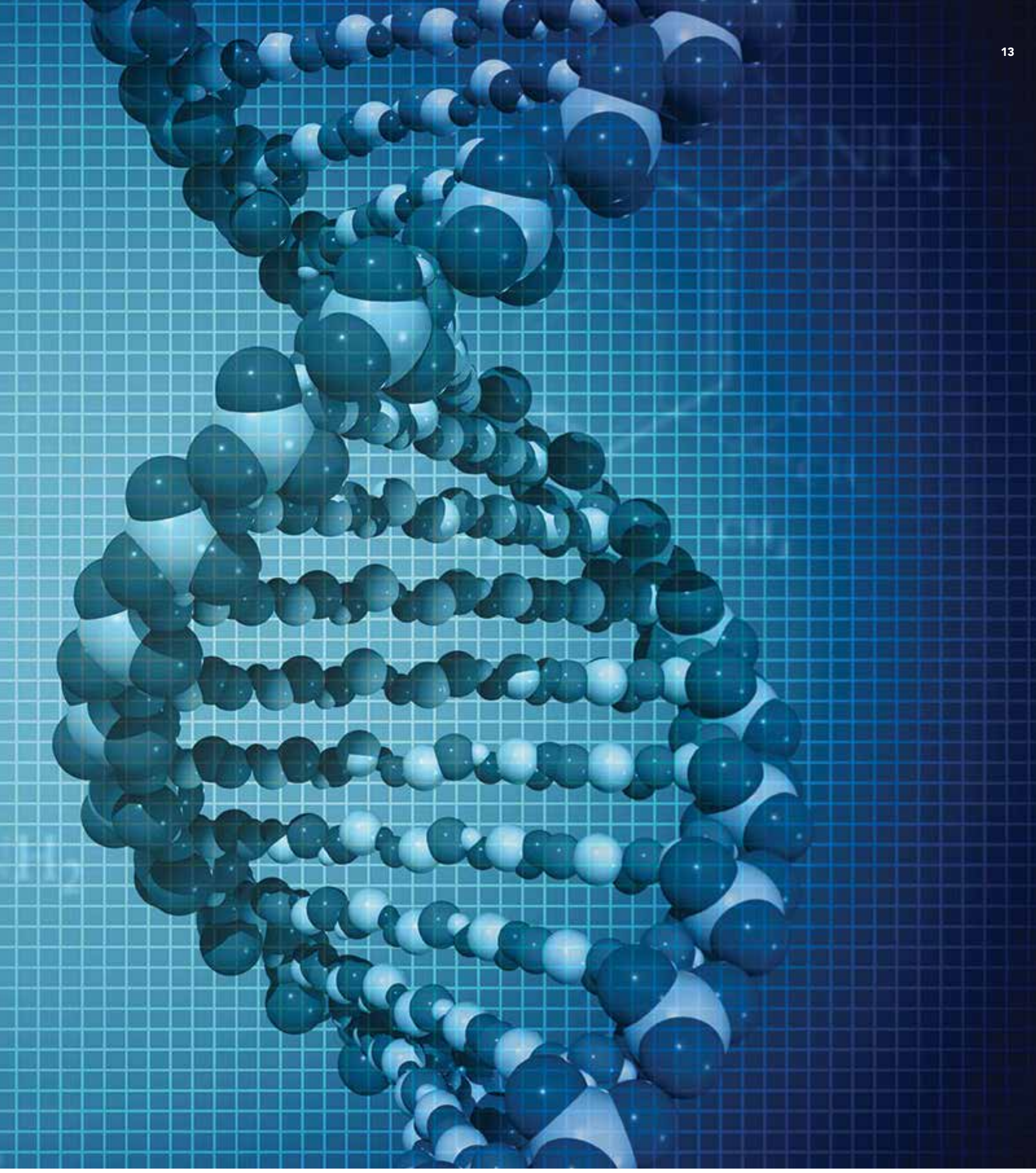
CIHR PERSONALIZED MEDICINE SIGNATURE INITIATIVE

Harnessing scientific and technological innovations to improve patient care is a key priority for CIHR

One of the most promising areas in health research today is personalized medicine. If we can determine a person's genetic risk of developing specific diseases, or the likelihood that a patient will respond to a specific treatment, we can advance beyond the current "one size fits all" approach to medicine and build a more predictive, preventive and precise health care system. The aim of the Personalized Medicine signature initiative is to identify areas in health care that could benefit most from this kind of targeted, patient-specific approach, support personalized medicine research in these areas, and help translate this knowledge into improved care.

The initiative is designed to build upon the large body of personalized medicine research findings generated by previous CIHR funding as well as investments by major partners such as Genome Canada. These investments have included programs directed at identifying the genetic roots of rare diseases and understanding the late effects of cancer treatment, projects to develop alternatives to radiopharmaceuticals for medical imaging, and research on data harmonization and bioinformatics.

In early 2012, the Personalized Medicine signature initiative was formally launched with the announcement of the Genomics and Personalized Health Genome Canada/CIHR partnership. This $150 million program supports teams across the country that are exploring how we can develop and incorporate personalized medicine approaches into the health care system in a beneficial, cost-effective and ethical way. The teams funded through this competition represent the next step in bringing the benefits of personalized medicine to patients.



FOR MORE INFORMATION

CIHR Personalized Medicine signature initiative: www.cihr-irsc.gc.ca/e/43627.html.

Genome Canada/CIHR Large-Scale Applied Research Project Competition: www.genomecanada.ca/en/portfolio/research/2012-competition.aspx.

CIHR strategic initiatives: www.cihr-irsc.gc.ca/e/12679.html.

NEED MORE EVIDENCE?

Thank you for reading the spring 2014 issue of *Show me the Evidence*. We hope that you enjoyed learning more about the impact of Canadian health researchers and encourage you to visit CIHR's website **(www.cihr-irsc.gc.ca)** and social media sites **(www.cihr-irsc.gc.ca/e/42402.html)** to learn about other CIHR-funded success stories.

IN THE NEXT ISSUE OF *SHOW ME THE EVIDENCE*, WE WILL BE LOOKING AT CIHR- AND PARTNER-FUNDED RESEARCH SUCCESSES IN THE AREA OF DEMENTIA.

FOLLOW US AND ENGAGE WITH US ON:

FACEBOOK
Show me the Evidence, Putting Patients First and **Health Research in Canada**

YOUTUBE
Health Research in Canada

EVIDENCE IN THE MAKING
www.cihr-irsc.gc.ca/e/44921.html

EVIDENCE MAKERS
www.cihr-irsc.gc.ca/e/47688.html

FEEDBACK FROM THE COMMUNITY
www.cihr-irsc.gc.ca/e/44922.html