

Personalized medicine hits primary practice as genetic testing is being done for the first time in family practice to better select psychiatric medications for patients: an interview with Dr. Nicholas Voudouris

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For the first time in Canada, genetic testing done at the Centre for Addiction and Mental Health (CAMH) in Toronto is being made available to family physicians. This leading-edge research started just over a year ago at the Thornhill Medical Centre in Thornhill, Ontario. The aim of the research is to use genetic testing to better select psychiatric drugs and dosages to improve efficacy and reduce side effects in patients suffering from mental illness. Dr. Nicholas Voudouris, a family physician at the Thornhill Medical Centre who is heavily involved in this project, describes it as leading-edge science that has the possibility of having profound impact on personalized medicine at the primary care level. I spoke with Dr. Voudouris to learn more about him, this project, and the future implications genetic testing could have on personalized medicine and reducing health care spending.

Dr. Voudouris completed his undergraduate education at the University of Toronto, where he studied macroeconomics, government policy, and pre-medical sciences. He went on to complete his medical education at the University of Calgary and his residency at North York General Hospital and Sunnybrook Hospital. After residency, Dr. Voudouris spent three years providing medical care in small communities in Ontario and in the Northwest Territories. He joined the Thornhill Medical Centre in 1990 and has been there ever since. The Thornhill Medical Centre currently consists of eight family physicians and ten thousand patients.

Before the start of this current project, Dr. Voudouris was involved in other research projects, playing mainly a peripheral role in the trials of new medications. His interest and motivation for this current project started with his best friend in medical school and colleague, Dr. James Kennedy, who came to him with the idea.

Dr. Kennedy, the Head of the Neuroscience Research Department at CAMH, has done significant research throughout his career on the identification of susceptibility genes for psychiatric disorders. His previous discoveries include: the role of the D4 Dopamine receptor (DRD4) gene in ADHD, D3 Dopamine Receptor (DRD3) predicting the risk of tardive dyskinesia, and the serotonin-transporter-linked polymorphic region (5HTTLPR) genetic marker predicting the risk for antidepressant induced mania.

The idea for this current project stems from key observations about psychiatric drug prescriptions. One among these is that patients suffering from mental illness usually seek mental health treatment from their family physicians at first. In fact, it is

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estimated that primary care providers write 75–80% of prescriptions for psychiatric medications [1]. Another observation is that the current method used by family physicians to select psychiatric medications relies on trial and error, a process that often leads to unwanted side effects and low efficacy in patients. As a result, only 35–45% of patients achieve remission following an initial antidepressant trial [2].

In addition, some of the side effects can be significant. The use of atypical antipsychotics, for example, can lead to dangerous weight gain, potentially causing diabetes and metabolic syndrome [3]. These adverse effects are associated with more frequent physician visits and disability claims, decreased productivity, and increased health care costs. Thus, genetic testing performed at the primary care level to select a patient’s optimal psychiatric medication at the onset of treatment has the potential to have serious implications for patients and physicians.

The project involves two main steps. The first is genetically testing the patient. This involves a cheek swab that is done at the Thornhill Medical Centre and then sent to the CAMH laboratories in Toronto for analysis. The patient’s DNA sample is then genotyped for a family of liver enzymes known as cytochrome P450 (CYP450) enzymes [4]. These enzymes are responsible for the metabolism of most oral drugs and slight differences in the genetic coding of these proteins (single nucleotide polymorphisms, SNPs and gene copy number variation, CNV) impacts the metabolic properties of the specific enzymes. Depending on the genotype, drugs can be metabolized correctly, too quickly or too slowly. Therefore, genetics can greatly influence the efficacy and prevalence of side effects of the drug. There are many isoforms of these highly genetically variable enzymes: those being tested for this study are CYP1A2, CYP2C9, CYP2C19, CYP3A4, and CYP2D6. For this project, the idea is to choose drugs that are metabolized

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favourably according to the patient's most optimal enzymes.

Within two days of the completion of genetic testing, an individualized chart is created for the patient and sent back to the family physician. An example of a chart is shown in Figure 1.

RESULTS

Method: Genomic DNA was extracted from saliva. DNA specimens were analyzed using the Applied Biosystems TaqMan SNP genotyping and gene copy number detection assays.

Interpretation:

Gene	Metabolizes	Genotype	Metabolizer
CYP1A2	AP: olanzapine, clozapine AP: Haldol, Risperdal, Abilify, zuclopenthixol	*1/*1	Extensive
CYP2D6	AD: Effexor, paroxetine, fluoxetine, Luvox, Elavil, Anafranil, Norpramin, Pamelor, Tofranil, mianserin	*1/*1	Extensive
CYP2C19	AD: Celexa, Lexapro, Zoloft	*1/*2	Intermediate
CYP2C9	AD: Fluoxetine, Amitriptyline	*1/*2	Intermediate
CYP3A5	AP: risperidone	*3/*3	Poor

AP = antipsychotic; AD = antidepressant

Figure 1. An example of a patient chart that would be sent to the family physician based on the genetic test results obtained at the Centre for Mental Health and Addiction (CAMH). Green drugs are those that will have the greatest efficacy, yellow drugs are to be used with caution, red drugs are to be avoided due to low efficacy and increased risk of side effects.

The chart shows the metabolic profile based on the genotype of the enzymes as well as the psychiatric drugs that are metabolized by that enzyme. Based on the metabolic profile of the enzymes, drugs are classified as green, yellow, or red. Drugs that are classified as green drugs are the most appropriate for the patient, yellow drugs are to be used with caution, and drugs listed as red are to be avoided. A drug may be listed as red, for example, if the enzyme that is responsible for its degradation has an unfavourable metabolic profile. This means that the patient will have decreased drug elimination, resulting in a greater chance of the patient experiencing adverse side effects.

To date, between 1500 and 1600 patients have been genetically tested and all eight family physicians at the Thornhill Medical Centre are offering the genetic testing to their patients. Patients involved in the study are over the age of 16 and have a mental illness requiring medication. The project has also been expanded to another family practice, Thornhill Family Physicians, which is close to the Thornhill Medical Centre.

So far, patient's attitudes towards genetic testing has been very positive. Dr. Voudouris believes that this is due to the project's association with reputable institutions like CAMH and the University of Toronto as well as the fact that his patients understand and believe the science. He says that "[patients] feel confident in knowing that their physician is prescribing them a medication based on their genes and not by trial and error". In addition, the report sheet is very patient-friendly. Patients understand why they should be taking a green drug versus a red drug. The report sheet also explains why certain drugs did not work for them in the past. Patients are able to understand that it was their metabolic processes that were not well suited to the drug.

To date, twenty-five treatments are being studied for each patient. Examples include Cymbalta, Celexa, Cipralex,

Zoloft, Abilify, Haldol and Seroquel. These drugs target many psychiatric illnesses such as depression, anxiety, bipolar disorder and schizophrenia.

Before the start of this project, for Dr. Voudouris, the main factors in selecting a psychiatric medication for a patient were familiarity and previous success. Using this method, he found that 30% of his patients would return because the drug did not have enough of an effect or cause intolerable side effects. With genetic testing, however, he is now relying on scientific evidence and he believes that this process has already produced improvements. Dr. Voudouris has seen patients who have previously been unsuccessful with several different medications, finally have success with a "green drug" after realizing that the failed drugs fell into their "red drug" category.

If successful, this strategy can be implemented in other family medicine practices. According to Dr. Voudouris, one of the main reasons the project has been easily implemented at the Thornhill Medical Centre due to the use of Electronic Medical Records (EMR). EMR has made it easy to organise and track each patient's response. CAMH has also been given access to the patient records so that they can gather data for their own analysis from its Toronto location. In addition to EMR, Dr. Voudouris believes that educating doctors and nurses about the project is the key to transferring this approach to other practices. Physicians need to be taught how to talk to their patients about the project its implications. He says that it is "doable" but that "it has to be done right".

The project is currently expanding. Every two months, another drug is added to the master list. The drugs that can be analyzed are limited to drugs that are primarily metabolized by one of the enzymes listed previously. Treatments that have more complicated metabolism pathways, such as benzodiazepines, cannot yet be added to this list.

When asked about any advice he has for future physicians in terms of talking to their patients about mental health, Dr. Voudouris said what is most important is to be empathetic and to be completely involved in the care of the patient. He also said that when prescribing drugs, it is important to believe in the difference that drugs can make and to understand the pharmacogenetics of how they work. This is important in choosing and prescribing the best drug for patients.

In order for its results to be considered significant, the project will need to include 7000 participants. If the results are positive, this could launch genetic testing into more widespread use. A key component to its broad application will be the financial analysis. Dr. Voudouris estimates that it would cost OHIP \$305 per person to run the genetic test. Applied to millions of patients, this amounts to a significant cost. In return, however, money would be saved from reduced physician visits, disability claims, and work days lost. Dr. Voudouris believes that genetic testing will ultimately prove to be cost effective in the future when it is implemented on a large scale and more drugs have been added.

This project illustrates family physicians' important contribution on advancing health care. Psychiatric illness treatment starts with family physicians and this project exemplifies their invaluable influence on health care.

REFERENCES

1. Mark TL, Levit KR, Buck JA. Datapoints: psychotropic drug prescriptions by medical specialty. *Psychiatr Serv.* 2009; 60(9):1167. Winner J, Allen J, Anthony A, Spahic-Mihajlovic A. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. *Transl. Psychiatry.* 2013; 3, e242.
2. Lett TA, Wallace TJ, Chowdhury NI, Tiwari AK, Kennedy JL, Müller DJ. Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. *Mol. Psychiatry.* 2012; 17(3): 242–266.
3. Coon MJ. Cytochrome P450: nature's most versatile biological catalyst. *Annu rev Pharmacol Toxicol.* 2005; 45:1-25.

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