



Genetic testing as a supporting tool in prescribing psychiatric medication: Design and protocol of the IMPACT study

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ABSTRACT

Objective: Pharmacotherapy is one of the primary treatments for psychiatric disorders. Given the variation in individual response, a more personalized approach is needed. This paper will discuss methods for user-friendly referrals, recruitment criteria, data storage and dissemination, biological sample and clinical questionnaire collection, and advertising.

Methods: The Individualized Medicine: Pharmacogenetics Assessment and Clinical Treatment (IMPACT) study is one of the first to use pharmacogenetic testing on a large scale in psychiatry as a tool to predict individual drug response and tolerability. As IMPACT's eligibility criteria includes all diagnoses and comorbidities, the participant population will reflect the diversity amongst mental health consumers. IMPACT's innovative study design will demonstrate the utility of this testing within the health care system.

Results: IMPACT has successfully implemented pharmacogenetic testing on a relatively large scale, and in both tertiary level and primary care settings. It represents a novel approach to psychiatric care and from its initial stages the design has evolved to accommodate the nature and needs of the health care community.

Conclusion: It is anticipated that IMPACT will continue to demonstrate the feasibility of pharmacogenetic testing and facilitate its introduction and implementation in routine healthcare practice.

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1. Introduction

The Individualized Medicine: Pharmacogenetics Assessment and Clinical Treatment (IMPACT) project is a seven-year province wide research study developed at The Centre for Addiction and Mental Health (CAMH). IMPACT aims to optimize pharmacological treatment for mental health patients utilizing a pharmacogenetics approach. The goal of IMPACT is to increase the success rate of drug

response and medication adherence, and to reduce the risk of side effects from medications. IMPACT aims to reduce time to response through providing guidance for choosing the type and dosage of medication based on the individual patient's genetic makeup. Thus, IMPACT helps healthcare providers take a personalized approach to prescribing medicine for patients. The project incorporates known genetic variants that influence psychiatric drug response in its testing, and also seeks to identify new genetic markers for improvement of testing. The IMPACT study was initiated in 2011, with joint funding from the Ontario Ministry of Research and Innovation, The Canadian Institutes of Health Research (CIHR), the Campbell Family Mental Health Research Institute at CAMH, and a donation from The Larry & Judy Tanenbaum Foundation. Following ethics board approval, and the signing of agreements among all

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partners, as well as hiring and training staff, the first participant consented in May 2012, and as of May of 2017, over 8000 participants have enrolled in the study. The project is currently funded through 2018.

IMPACT is a pioneering study in the field of personalized medicine. It is designed to include a representative sample of the general population seeking treatment within all points of the health care system: primary, secondary, and tertiary care. IMPACT is intended to include a diverse population in terms of socioeconomic status, gender identification, ancestry, and geographical location.

This paper will describe the methodology of the large scale IMPACT study and its implementation, thus providing a model for future studies. The findings will also provide preliminary data for operationalizing pharmacogenetic testing and the design of randomized controlled clinical trials.

1.1. Rationale

Mental illness affects 1 in 4 individuals within their lifetime (WHO, 2003) and results in billions of dollars spent due to productivity loss alone. Of the 13 million citizens of the province of Ontario, 2.6 million (20%) will require mental health care in the next 20 years, with \$28.7 billion in costs due to productivity loss (Gnam, 2001). There is considerable inter-individual variability in multiple facets of medication treatment, including drug response, optimal dosage, adverse effects, potential drug–drug interactions, age, gender, renal and hepatic functioning, medical and psychiatric comorbidity, nutritional status, concurrent substance use, and medication adherence. In Canada, 7.5% of patients admitted to hospitals experienced one or more adverse drug reactions, 36.9% of which are deemed highly preventable. These adverse reactions carry a financial burden for the health care system, resulting in longer stays for patients, and account for an estimated 9,250–23,750 preventable deaths annually in Canada (Baker et al., 2004).

The vast majority of medications are presently prescribed by “trial and error”. While this approach may succeed by chance, a more knowledge based and individual approach is needed. This will lead to more rapid stabilization and recovery. Less than half of patients with depression respond to their first treatment prescription, and over 70% of patients fail to achieve remission following one or more antidepressant treatments (Trivedi et al., 2006). It appears likely that pharmacogenomic testing will improve response times, remission rates, as well as minimize side effects. These primary improvements lead to secondary benefits of improved adherence, better doctor–patient relationships, and reduced overall morbidity. (Winner et al., 2013a, 2013b). Rush and colleagues observed that up to 30% of depression patients experienced worsened symptoms or adverse events, causing them to discontinue their medication, or have an unwillingness to consider alternative drug treatment options (Rush et al., 2006a, 2006b). Reluctance to start a new medication or to continue taking a medication, leads to increased suicide risk, increased likelihood of progressive illness, increased rates of job loss, decreased individual socio-economic status (SES), and undermines the economy. Prescription nonadherence causes a significant strain on Ontario's health care system. A recent Canadian study demonstrated the utility of pharmacogenetic testing in everyday psychiatric clinical practice, leading to improved patient adherence and decreased healthcare costs (Fagerness et al., 2014).

Given the evidence for pharmacogenetic testing, IMPACT was designed to introduce pharmacogenetic biological rationale and the supportive clinical testing into Canadian health care settings, both in psychiatric settings as well as primary care.

For the first two years of the IMPACT study, participants'

suitability for a particular medication was assessed using a panel operationalized in the Tanenbaum Pharmacogenetics Centre within the CAMH hospital, of cytochrome P450 gene variants (See Appendix A) (Müller et al., 2013). The results placed each medication in the advisory categories of use as directed (green category), use with caution (yellow category) and use with caution and frequent monitoring (red category).

The design of the IMPACT study included an initial phase of providing a basic test panel of liver enzyme gene variants measured in the Tanenbaum Centre laboratory, at a rate of up to 120 per month. In order to conduct tests at a faster rate for a greater number of patients, in 2014 a partnership was established between CAMH and Assurex Health Inc. This partnership introduced Assurex Health's GeneSight® report (Assurex Health Announces, 2013). The pharmacogenomic test is based on patented technology licensed from the Mayo Clinic and Cincinnati Children's Hospital Medical Center. The first IMPACT report was comprised of only pharmacokinetic genes. With the GeneSight® report, additional markers were added using a combinatorial algorithm that incorporated both pharmacodynamic and pharmacokinetic genes. The algorithm is based on 8 genes, as shown in Table 1.

The SLC6A4 and the serotonin 2A receptor genes have been associated with differential treatment response to specific antidepressants. The gene panel and algorithm provides guidance for 33 antidepressant and antipsychotic medications approved by Health Canada and used in the province of Ontario (See Appendix B).

2. Study design and inclusion/exclusion criteria

The IMPACT study was designed to focus on guiding the use of psychotropic medications and did not restrict the diagnostic categories of the participants. It was inclusive of the broad spectrum of mental health disorders and comorbidities. Thus far, more than half of the IMPACT participants have diagnostic comorbidities. The majority of studies on medication usage focus on participants with only single diagnoses. The IMPACT study also includes both inpatients and outpatients within a variety of clinical settings, including psychiatric as well as general hospitals, forensic services, nursing homes, and family doctor group practices from across Ontario.

IMPACT has paid attention to the gap that exists in terms of inclusion of individuals in rural areas in studies of this nature. Due to the inclusive approach of IMPACT across diverse clinical settings, and primary care, results can be expected to generalize more readily to the Ontario population as a whole. Enrolment is not contingent upon clinicians' prescription timing, non-responders as well as patients with a history of adverse drug reactions or side effects are included. Additionally, individuals who are starting medication for the first time are eligible, allowing the pharmacogenomics report to aid the doctor in selecting the correct medication and dosage from the onset of mental illness. Although the IMPACT study is an Ontario based study, it permits 7% of participants to be from out of province.

The IMPACT study requires a referral for each potential participant (See Appendix C and D). Phone and email referrals were permitted from clinicians within CAMH. The Medical Record Number (MRN) provided by CAMH clinicians facilitated research analysts' utilization of PowerChart, CAMH's records and client information database, to retrieve additional data for patient referrals. PowerChart is a component of CAMH's electronic health records system, which provides access to patient health records for research purposes. I-CARE (Interprofessional Clinical Accountability and Record of Engagement) is the Clinical Information System (CIS) used in all clinical areas (inpatient, outpatient and emergency) to track patient care, and manage workflow and related

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