Estimating the Potential Impact of *CYP2C19* and *CYP2D6* Genetic Testing on Protocol-Based Care for Depression in Canada and the United States

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Keywords

Pharmacogenetics · STAR*D · Major depressive disorder · Antidepressants

Abstract

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) algorithm is the most recognized protocol-based care approach for moderate to severe depression. However, its implementation results in one-third of individuals receiving modest to no symptom remission. One possible explanation is the inter-individual differences in antidepressant metabolism due to *CYP2C19* and *CYP2D6* genetic variation. Here, we aimed to determine the potential benefit of pairing *CYP2C19* and *CYP2D6* testing with the five-step STAR*D algorithm. To estimate the proportion of individuals that could benefit from *CYP2C19* and *CYP2D6* testing, we simulated the STAR*D algorithm using ethnicity-specific phenotype (e.g., metabolizer status) frequencies published by the Clinical Pharmacogenetics Implementation Consortium and census data from the Canada and the US. We found that up to one-third of the US and Canadian populations being treated for depression could benefit from the addition of *CYP2C19* and *CYP2D6* genetic testing. The potential benefit

varied for each step of the algorithm and for each province, territory, and state. *CYP2C19* genotyping had the greatest potential impact within the first two steps of the algorithm, while *CYP2D6* genotyping had the most notable impact in Steps 3, 4, and 5. Our findings suggest the implementation of *CYP2C19* and *CYP2D6* genetic testing alongside the STAR*D treatment algorithm may improve depression treatment outcomes in Canada and the US.

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Introduction

Numerous treatment algorithms have been developed to assist clinicians in providing protocol-based care for moderate to severe depression. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) algorithm is the most well-known protocol-based care approach, consisting of five sequential steps of treatment options [1]. All individuals begin at Step 1 with citalopram. If adequate response is not achieved, individuals are encouraged to proceed to Step 2, where citalopram therapy is augmented (bupropion, buspirone, or cognitive therapy) or switched to another antidepressant (bu-

propion-SR, sertraline, or venlafaxine). Likewise, in Steps 3–5, those with inadequate response have their therapy switched (nortriptyline, mirtazapine, bupropion, venlafaxine, tranylcypromine, or venlafaxine+mirtazapine) or augmented (lithium or T3) until remission is achieved or they exit from the algorithm (e.g., loss-to-follow-up). Randomized clinical trial findings have showed implementation of the STAR*D algorithm results in about two-thirds of individuals with depression achieving symptom remission, while the remaining one-third received modest to no symptom relief [2]. However, it remains unclear why the algorithm fails to get more individuals well.

One explanation for the algorithms less than optimal performance is the presence of inter-individual variation in genes involved in antidepressant metabolism. In fact, a previous genetic analysis of the STAR*D trial data suggested citalopram (Step 1) tolerance and response was associated with genetic variation in *CYP2C19* but not *CYP2D6* [3], two cytochrome P450 enzymes involved in the phase 1 metabolism of most antidepressants. However, the potential effect of *CYP2C19* and *CYP2D6* genetic variation on tolerance and response in subsequent steps of the STAR*D algorithm has not been evaluated. This is particularly important given that at each of the five steps of the STAR*D algorithm, there are medications (i.e., citalopram, sertraline, venlafaxine, nortriptyline) with associated *CYP2C19*- or *CYP2D6*-based prescribing guidelines [4–6]. Unfortunately, the STAR*D algorithm does not currently account for these guidelines or consider inter-individual variations in antidepressant metabolism.

To estimate the proportion of individuals that could potentially benefit from the inclusion of *CYP2C19*- and *CYP2D6*-based prescribing guidelines in the STAR*D algorithm, we undertook a population-based pharmacogenetic study using available data from Canadian provincial/territories and US states. We hypothesized that a considerable proportion of individuals could benefit from the inclusion of *CYP2C19* and *CYP2D6* genetic information in the STAR*D algorithm, and that the magnitude of this benefit would vary by province, territory, and state.

Materials and Methods

Data Sources

The most current population estimates by age and ethnicity for each Canadian province/territory and US state were obtained from the Statistics Canada website [7] and the US Census Bureau website [8], respectively. Frequencies of *CYP2C19* and *CYP2D6* genotype-predicted metabolizer phenotypes (i.e., poor, intermediate, normal, rapid/ultrarapid) by ethnicity were obtained from phenotype frequency tables available from the Clinical Pharmacogenet-

ics Implementation Consortium (CPIC) [9]. CPIC determines *CYP2D6* and *CYP2C19* metabolizer phenotype based on the combination of star (*) alleles present. Star alleles can represent a single variant or multiple variants (haplotype), each assigned a function (no, decreased, normal, increased, uncertain, unknown). For example, an individual with a *CYP2C19* genotype of *1/*17 would be defined as a rapid metabolizer because they carry one normal function allele (*1) and one increased function allele (*17). Whereas, an individual with a *2/*2 *CYP2C19* genotype would be considered a poor metabolizer, given the presence of two no function alleles. Detailed explanations of star allele functions and their translation to metabolizer phenotypes can be found at the Pharmacogene Variation Consortium [10] (www.pharmvar.org) and CPIC [11] (cpicpgx.org) websites, respectively.

Contraindicated Phenotype Estimation

Prior to estimating the frequencies of *CYP2C19* and *CYP2D6* contraindicated phenotypes, each medication from the STAR*D algorithm was cross-referenced with guidelines developed by CPIC and the Dutch Pharmacogenetics Working Group (DPWG). At the time of our analysis, the only STAR*D medications with *CYP2C19*- and *CYP2D6*-based prescribing guidelines were citalopram, sertraline, venlafaxine, and nortriptyline [4, 5]. Based on these guidelines, contraindicated phenotypes for citalopram and sertraline included *CYP2C19* poor, rapid, and ultrarapid metabolizers, whereas for venlafaxine and nortriptyline contraindicated phenotypes included *CYP2D6* poor, intermediate, and ultrarapid metabolizers. Next, each of the provincial/territory/state population datasets were restricted to individuals aged 18 years or older to reflect the population for which the STAR*D algorithm was designed. Then, the absolute number of individuals (≥ 18 years old) in each US state that identified as Caucasian/European, African/African-American, Asian, American (e.g., North American Indigenous origins, Indigenous from Central/South America), and Oceanian was extracted. Likewise, the absolute number of individuals in each Canadian province/territory that identified as Caucasian, American, African, Middle Eastern, South/Central Asian, East Asian, and Oceanian were extracted. These absolute numbers were then multiplied by the frequency of *CYP2C19* or *CYP2D6* contraindicated phenotypes for each ethnic group and then summed across ethnic groups to arrive at an estimated number of individuals with a contraindicated phenotype in each province/territory/state for each of the four medications with *CYP2C19*- or *CYP2D6*-based prescribing guidelines.

Impact Estimation

To estimate the potential impact of pairing *CYP2C19* and *CYP2D6* genetic testing with the STAR*D algorithm, we simulated each step of the algorithm in each province/territory/state. These simulations began by multiplying each province/territory/state's total population by an estimated antidepressant use rate. Antidepressant prevalence rates were based on the most current national data available for each country. For Canadian provinces/territories a 9.1% antidepressant prevalence rate was applied [12], while for each US state a prevalence rate of 12.7% was used [13]. The estimated population using antidepressants was then entered into the STAR*D algorithm and the proportion of these individuals that would receive a treatment contraindicated for their *CYP2C19* and/or *CYP2D6* phenotype was estimated at each step. Because Step 2 was the only step that included medications linked to *CYP2C19*

Table 1. Estimated percentage of individuals with a *CYP2C19* and/or *CYP2D6* phenotype contraindicated for the treatment received at each step of the STAR*D algorithm by ethnicity

Ethnicity	Step 1	Step 2	Step 3	Step 4	Step 5
Caucasian	34.0	23.8	5.5	7.2	4.1
American	26.6	18.7	4.4	5.8	3.3
African	20.7	16.1	6.4	8.5	4.8
African-American	31.7	23.0	6.6	8.8	4.9
Middle Eastern	32.4	23.2	6.2	8.2	4.6
South/Central Asian	31.8	21.6	3.8	5.0	2.8
East Asian	16.2	11.9	3.7	4.9	2.7
Asian	24.0	16.7	3.8	5.0	2.8
Oceanian	48.0	33.4	7.3	9.6	5.4

in Steps 3–5. Applying these ethnicity-based estimates to each state/province/territories' unique ethnic distributions, we showed the same pattern across all US states (Table 2) and Canada provinces/territories (Table 3). We estimated that about one-third of individuals entering the STAR*D algorithm in the US (mean = 32.2%, SD = 1.4%, range = 23.5–33.2%) and Canada (mean = 29.4%, SD = 4.5%, range = 19.3–34.5%) could benefit from *CYP2C19* genotyping. Whereas, approximately one-fifth of individuals progressing to Step 2 in the US (mean = 22.6%, SD = 1.0%, range 16.4–23.3%) and Canada (mean = 20.6%, SD = 3.2%, range 13.6–24.2%) would benefit from *CYP2C19* or *CYP2D6* genotyping. Separate estimates for *CYP2C19* and *CYP2D6* in Step 2 showed on average 19.9% (SD = 0.9, range = 14.5–20.5%) and 18.1% (SD = 2.8%, range = 11.9–21.3%) of those in the US and Canada, respectively, would benefit from *CYP2C19* genotyping, while on average an additional 2.8% (SD = 0.2%, range 1.9–3.0%) and 2.5% (SD = 0.4%, range = 1.7–2.9%) in the US and Canada, respectively, would benefit from *CYP2D6* genotyping. For individuals progressing to Steps 3, 4, or 5 of the STAR*D algorithm, we estimated that less than 10% at each of these steps would benefit from *CYP2D6* genotyping.

Discussion/Conclusion

Our findings suggest a potential benefit of combining protocol-based depression care with *CYP2C19* and *CYP2D6* genotyping in the US and Canada. The potential impact of *CYP2C19* genotyping was clearly seen within the first two steps of the STAR*D treatment algorithm, whereas, the potential impact of *CYP2D6* genotyping was most notable in Steps 3, 4, and 5.

We estimated that up to one-third of individuals entering Steps 1 and 2 of the STAR*D treatment algorithm could benefit from *CYP2C19* genotyping. This estimated impact is a direct reflection of the number of treatment options in Steps 1 and 2 that are linked to *CYP2C19*-based prescribing guidelines. In Step 1, citalopram is the only option and in Step 2 citalopram combination therapies and sertraline comprise four of the six pharmacotherapy options. Both citalopram and sertraline have *CYP2C19*-based prescribing guidelines that recommend dose reductions or alternative medications for individuals that are *CYP2C19* poor or rapid/ultrarapid metabolizers, respectively [6]. As such, the first two steps of the STAR*D algorithm are not ideally matched for *CYP2C19* poor, rapid, or ultrarapid metabolizers, a group of individuals that represents 21–48% of any given population depending on ethnicity distributions [9]. Not accounting for this considerable proportion of the population when using the STAR*D algorithm could unnecessarily expose these individuals to antidepressant trials for which the likelihood of an undesirable outcome is increased. However, if these individuals were identified prior to entering the algorithm, it would be reasonable for a clinician to prescribe venlafaxine (assuming normal *CYP2D6* metabolism) or bupropion first as they are the only two pharmacotherapy options in the first two steps that are not implicated in a *CYP2C19*-based prescribing guideline.

Beyond the first two steps of the STAR*D algorithm, the benefits of *CYP2C19* genotyping gives way to *CYP2D6* genotyping. In Steps 3–5, nortriptyline and/or venlafaxine are included as treatment options, both of which have *CYP2D6*-based prescribing guidelines [4, 5]. However, unlike Steps 1 and 2, in the final three steps of the STAR*D algorithm, the proportion of treatment options with pharmacogenetic-based prescribing guidelines is lower. As a result, the potential benefits of *CYP2D6* genotyping in conjunction with the STAR*D algorithm was estimated to be modest. Nevertheless, the estimated proportion (2.5–7.7%) of individuals entering these steps that could benefit from *CYP2D6* genotyping is not trivial.

Collectively, these results suggest that *CYP2C19* and *CYP2D6* genetic testing would be beneficial for a considerable proportion of population entering the STAR*D treatment algorithm, regardless of which state, province, or territory the care is being provided. That said, our estimates, as expected, did vary slightly by geography. This geographical variation can be attributed to differences in the proportion of ethnic groups represented in each state, province, and territory we examined. For example, CPIC estimates that 34% of individuals who identify as Cauca-

Table 2. Estimated percentage of individuals with a *CYP2C19* and/or *CYP2D6* phenotype contraindicated for the treatment received at each step of the STAR*D algorithm in the United States

State	Step 1	Step 2	Step 3	Step 4	Step 5
Alabama	32.6	23.1	5.7	7.5	4.2
Alaska	29.9	20.9	4.9	6.4	3.6
Arizona	32.2	22.6	5.3	7.0	3.9
Arkansas	32.8	23.1	5.5	7.3	4.1
California	31.0	21.7	5.1	6.7	3.8
Colorado	32.5	22.8	5.3	7.0	3.9
Connecticut	32.5	22.8	5.4	7.1	4.0
Delaware	32.2	22.7	5.5	7.3	4.1
District of Columbia	31.5	22.4	5.8	7.7	4.3
Florida	32.6	22.9	5.5	7.3	4.1
Georgia	32.1	22.7	5.7	7.5	4.2
Hawaii	23.5	16.4	3.7	4.9	2.8
Idaho	32.9	23.0	5.3	7.0	3.9
Illinois	32.4	22.8	5.4	7.2	4.0
Indiana	32.9	23.1	5.4	7.2	4.0
Iowa	33.0	23.1	5.4	7.1	4.0
Kansas	32.5	22.8	5.3	7.0	3.9
Kentucky	33.0	23.2	5.4	7.2	4.0
Louisiana	32.5	23.0	5.7	7.6	4.2
Maine	33.2	23.3	5.4	7.1	4.0
Maryland	31.7	22.4	5.6	7.4	4.1
Massachusetts	32.3	22.7	5.3	7.0	3.9
Michigan	32.5	22.9	5.5	7.2	4.0
Minnesota	32.4	22.8	5.3	7.0	3.9
Mississippi	32.6	23.1	5.8	7.7	4.3
Missouri	32.8	23.0	5.5	7.2	4.0
Montana	32.5	22.8	5.3	6.9	3.9
Nebraska	32.8	23.0	5.4	7.1	4.0
Nevada	31.5	22.1	5.2	6.9	3.8
New Hampshire	33.1	23.2	5.4	7.1	4.0
New Jersey	31.9	22.4	5.4	7.1	4.0
New Mexico	32.2	22.5	5.2	6.9	3.9
New York	31.8	22.4	5.4	7.1	4.0
North Carolina	32.4	22.8	5.6	7.3	4.1
North Dakota	32.7	22.9	5.3	7.0	3.9
Ohio	32.7	23.0	5.5	7.2	4.0
Oklahoma	30.9	21.7	5.1	6.7	3.8
Oregon	32.2	22.5	5.2	6.9	3.9
Pennsylvania	32.7	23.0	5.4	7.2	4.0
Rhode Island	32.5	22.8	5.4	7.1	4.0
South Carolina	32.6	23.0	5.7	7.5	4.2
South Dakota	32.4	22.7	5.3	6.9	3.9
Tennessee	32.8	23.1	5.5	7.3	4.1
Texas	32.5	22.9	5.4	7.2	4.0
Utah	32.9	23.0	5.3	7.0	3.9
Vermont	33.1	23.2	5.4	7.1	4.0
Virginia	31.9	22.5	5.4	7.2	4.0
Washington	31.4	22.0	5.1	6.8	3.8
West Virginia	33.2	23.3	5.4	7.2	4.0
Wisconsin	32.9	23.0	5.4	7.1	4.0
Wyoming	33.0	23.1	5.3	7.1	3.9
Average	33.2	22.6	5.4	7.1	4.0
Standard deviation	1.4	1.0	0.3	0.4	0.2

Table 3. Estimated percentage of individuals with a *CYP2C19* and/or *CYP2D6* phenotype contraindicated for the treatment received at each step of the STAR*D algorithm in Canada

Province/territory	Step 1	Step 2	Step 3	Step 4	Step 5
Alberta	29.9	21.0	5.0	6.6	3.7
British Columbia	30.5	21.4	5.1	6.7	3.7
Manitoba	33.3	23.4	5.5	7.3	4.1
New Brunswick	24.2	17.0	4.0	5.2	2.9
Newfoundland and Labrador	23.7	16.6	3.9	5.1	2.9
Northwest Territories	32.3	22.7	5.4	7.1	4.0
Nova Scotia	28.9	20.3	4.8	6.3	3.5
Nunavut	33.2	23.3	5.5	7.3	4.1
Ontario	30.9	21.7	5.1	6.8	3.8
Prince Edward Island	28.0	19.6	4.6	6.1	3.4
Quebec	19.3	13.6	3.3	4.4	2.5
Saskatchewan	32.9	23.1	5.4	7.1	4.0
Yukon	34.5	24.2	5.7	7.5	4.2
Average	29.4	20.6	4.9	6.4	3.6
Standard deviation	4.5	3.2	0.7	1.0	0.5

sian have a *CYP2C19* actionable phenotype (i.e., poor, rapid, or ultrarapid metabolizer), second only to those of Oceanian descent (48% actionable) [9]. However, Oceanians represented a very minor proportion of the populations in Canada and in the US and as such jurisdictions with a greater proportion of Caucasians (e.g., Yukon, West Virginia, and Maine) were estimated to have the greatest proportion of individuals who could benefit from *CYP2C19* testing at Steps 1 and 2. This also explains why Hawaii, which had a relatively small Caucasian population, had the smallest proportion of individuals estimated to benefit from *CYP2C19* testing at Steps 1 and 2, despite having a relatively larger proportion of individuals of Oceanian descent.

There are several notable limitations to consider when interpreting our findings. First, we assumed that the ethnicities of antidepressant recipients were identical to the ethnic group proportions in each state, territory, and province. Second, we held rates of antidepressant use within each country constant across geographic locations, ethnic groups, age, and sex, as the data required to adequately adjust our simulations to these factors were not available. These assumptions could result in under- or over-estimations of the potential benefit of *CYP2C19* and *CYP2D6* genotyping, depending on the distribution of these demographic factors in each state, province, or territory. Third, the ethnic categories were based on Canadian or US census data. Due to differences in the collection and classification of census

ethnicity data, the results for Canada and the US cannot be directly compared. Fourth, the ethnic categories used by the Canadian or US census data were not identical to the categories used by CPIC to report *CYP2C19* and *CYP2D6* phenotype frequencies. This meant that we were unable to capture and estimate the *CYP2C19* and *CYP2D6* phenotypes for some self-reported ethnic origins (e.g., Acadian, two or more races). Notably, about half of the Quebec population identified solely as “Canadian.” Thus, our estimates for this province are limited and should be interpreted with caution. Fourth, it is not clear whether our estimates are generalizable to other protocol-based care algorithms or guidelines for depression such as the Texas Medication Algorithm Project (TMAP) [14] or the Canadian Network for Mood and Anxiety Treatments (CANMAT) Guidelines [15]. However, 60% and 40% of first-line medications recommended by TMAP and CANMAT, respectively, are linked to a *CYP2C19*- or *CYP2D6*-based prescribing guideline, suggesting that similar results might be observed if these protocols were to be systematically examined. Fifth, the cost-effectiveness of pairing *CYP2C19* and *CYP2D6* with protocol-based care has not been evaluated. However, economic analyses of combinatorial pharmacogenetic testing (including *CYP2C19* and *CYP2D6*) to guide antidepressant prescribing have suggested that this testing – on its own – is a cost-effective strategy [16, 17]. Sixth, the phenotype frequencies we used assume that high-quality genotyping of common functional *CYP2C19* and *CYP2D6* variants is performed. That said, genotyping for rare functional variants in *CYP2C19* and *CYP2D6* is not currently standard practice. Previous work has shown that rare variants comprise 4.4 and 6.3% of all functional variants in *CYP2C19* and *CYP2D6*, respectively [18]. As such, our results are likely an underestimate of the true proportion of individuals that could benefit from pharmacogenetic testing. Finally, our results and interpretations are constrained to the medications that are included in the STAR*D algorithm and do not account for concomitant or future medications that an individual may receive. As such, the estimated benefits of *CYP2C19* and *CYP2D6* genotyping are likely underestimated given that guidelines associated with these genes are also available for other antidepressants (i.e., escitalopram, fluvoxamine, paroxetine, amitriptyline, clomipramine, imipramine, doxepin, desipramine, trimipramine), antipsychotics (i.e., aripiprazole, haloperidol, pimozide, zuclopenthixol), and the ADHD medication atomoxetine [19]. On the other hand, it could be argued that commonly used prescrib-

ing strategies such as “start low and go slow” would in part mitigate tolerability concerns among those with *CYP2C19* and/or *CYP2D6* reduced function phenotypes (e.g., poor metabolizers), suggesting that our findings overestimate the potential benefit of *CYP2C19* and *CYP2D6* testing. However, generalized strategies like “start low and go slow” can be problematic for individuals that have increased function phenotypes (i.e., rapid and ultrarapid), increasing the time to reach therapeutic plasma concentrations and symptom remission. Nevertheless, the current study cannot reconcile these arguments and as such future prospective or retrospective trials are needed to refine the estimates provided in the current study.

Despite these limitations, our findings support the simultaneous implementation of *CYP2C19* and *CYP2D6* genetic testing alongside the STAR*D treatment algorithm. We estimated that up to one-third of the US and Canadian populations being treated for depression could benefit from the addition of *CYP2C19* and *CYP2D6* genetic testing. This is aligned with what we already know from the STAR*D trial results that showed implementation of the algorithm alone fails to get one-third of individuals well [2] and that common pharmacogenetic variation may play a role in patient outcomes [3]. Although future experimental research is required to validate our estimates and determine the cost-effectiveness of adding *CYP2C19* and *CYP2D6* genetic testing to protocol-based depression care, it seems reasonable to conclude that the addition of such testing has tremendous potential to assist clinicians in the selection of appropriate therapies and reduction of the number of medication trials a patient must endure before getting well.

Statement of Ethics

This study used publicly available, deidentified, aggregate data and as such was deemed exempt from ethics review.

Disclosure Statement

M.F. has no conflicts of interest to declare. C.A.B. has received material support from Assurex Health (Myriad Neuroscience), CNSDose, Genomind, and AB-Biotics for research purposes and has ongoing research collaborations with MyDNA but does not have equity, stocks, or options in these companies or any other pharmacogenetic companies. C.A.B. is a member of the Clinical Pharmacogenetics Implementation Consortium and the Genetic Testing Committee of the International Society of Psychiatric Genetics.

Funding Sources

The authors did not receive any funding.

Author Contributions

C.A.B. designed and planned the analysis for the study. M.F. designed and conducted the simulations. Both authors wrote the manuscript.

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