Improving Outcomes and Reducing Healthcare Costs for Diabetes and Its Comorbidities With Pharmacogenetics Guided Medication Therapy

Introduction

Diabetes continues to be a growing epidemic in the United States and one of the more costly conditions to treat long-term. Data from the 2017 Centers for Disease Control (CDC) report on diabetes indicates that 30.3 million people (9.4%) in the United States, and over 25% of those aged 65 or older, had diabetes in 2015, with an estimated 1.5 million new cases each year. Moreover, an estimated 33.9% of US adults had prediabetes, including nearly half of those aged 65 years or older. The social and economic burden of diabetes is likewise staggering. Diabetes was the seventh leading cause of death in the United States in 2015. Total direct and indirect estimated costs of diagnosed diabetes was $245 billion, accounting for over 20% of health care dollars in the US.

Care for diabetes patients is complicated by the presence of comorbid conditions. Approximately half of adults with diabetes have at least one comorbid chronic disease and 40% of elderly adults with diabetes have four or more comorbid conditions, exceeding all other major chronic conditions except ischemic heart disease in extent of comorbidities. Hyperlipidemia (77% comorbidity), hypertension (49% comorbidity), and coronary artery disease (11% comorbidity), are among the most common comorbid conditions due to their pathophysiological overlap with diabetes. Unsuccessful management of these conditions in diabetic patients can result in significantly greater cost burden and reductions in quality of life. Indeed, cardiovascular disease is the primary cause of mortality in diabetes. Conversely, effective management of cardiovascular conditions can enhance the management of diabetes. Other conditions such as depression (19% comorbidity) also worsen diabetes outcomes by causing poorer adherence to medications and self-management. Similar to cardiovascular conditions, effective management of these conditions can reduce economic burden and can improve glycemic outcomes and quality of life.

Pharmacogenomics, the study of genetic mediators of medication response, has demonstrated success in improving pharmacotherapy outcomes across a range of medical conditions. Briefly, pharmacogenomic testing evaluates variants in genes known to affect the pharmacokinetics or mechanism of action of a medication. Specifically, much research has focused on the CYP450 genes, which encode enzymes...
involved in first pass metabolism of many medications. Variation in these genes can increase or reduce clearance of medications from the body, predisposing individuals to a decrease in medication efficacy and an increase in the prevalence of sometimes life-threatening adverse drug reactions. Pharmacogenomic implementation guidelines have been published for medications used to treat a number of common chronic conditions such as depression, cardiovascular disease, and chronic pain, among others.\textsuperscript{15-20} Surprisingly, genetic variation in pharmacogenomic genes is quite common; virtually every individual (90-99\%)\textsuperscript{21,22} carries at least one clinically actionable variant. Pharmacogenomic variation does not typically pose health risks until one is exposed to a drug for which the variant is relevant. However, increased exposure to medications due to medical comorbidities will increase the occurrence of gene-drug interactions. The frequency of comorbidity and polypharmacy in the diabetic population makes this condition a prime target for pharmacogenetic intervention. In this white paper, we will review the evidence supporting the association of genetic variation with medication outcomes for medications used to treat diabetes and its common comorbidities: hypertension, hyperlipidemia, major adverse cardiovascular events, and depression. Given that type 1 diabetes accounts for only 5-10\% of all diabetes cases,\textsuperscript{1} this review will primarily focus on management of type 2 diabetes (T2DM).

Pharmacogenomics of Diabetes Management

Pharmacotherapy for diabetes mellitus consists of a number of agents that differ in their pharmacokinetics, mechanism of action, efficacy, and side effect profile.

Metformin

Metformin is considered first-line monotherapy for type 2 diabetes by both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE).\textsuperscript{8} Metformin is not metabolized, thus avoiding the polymorphic CYP450 family of enzymes. Some studies have focused on genetic variation in organic cation transporters responsible for metformin uptake into the bloodstream and hepatocytes or secretion into the renal tubular cells, with mixed results.\textsuperscript{23-28} Another gene, ATM, which encodes a serine/threonine kinase, initially showed promise for predicting metformin effects on HbA1C values,\textsuperscript{29,30} but failed to replicate in a later large study.\textsuperscript{31} More research is needed to conclusively demonstrate an effect of these polymorphisms on metformin response.

Sulfonylureas

Sulfonylurea medications are generally divided into first-generation medications (including chlorpropamide, tolazamide, and tolbutamide) and second-generation medications (including glipizide, glyburide, and glimepiride). While they remain the second most commonly prescribed oral medications for the treatment of T2DM, their place in treatment algorithms has become more controversial with the approval of newer medications that are less prone to cause hypoglycemia. The ADA recommends sulfonylurea use equally to other second-line agents, while the AACE recommends their use only after lower-risk medications have been tried.\textsuperscript{8}

All of the second-generation sulfonylureas (as well as tolbutamide) are metabolized by CYP2C9, and several studies have demonstrated an impact of CYP2C9 genetic variation on serum levels of these medications. For example, in 2010, Zhou et al found that carriers of the CYP2C9*2 and *3 alleles were 3-4 times more likely to achieve target HbA1c after 18 months of initiation of a combination of
sulfonylurea and metformin, compared with patients with the normal function genotype. Variant allele carriers were also less likely to experience treatment failure with sulfonylurea monotherapy compared to functional allele carriers. Similarly, Becker et al found that CYP2C9*2 and *3 carriers needed a lower tolbutamide dose to achieve optimal outcome. Furthermore, a study of Indian patients with T2DM showed that CYP2C9*2 and *3 allele carriers had a better response to glyburide without an increase in risk of hypoglycemia. Finally, a small study of glimepiride in Asian patients showed a greater mean change in HbA1c levels at 6 months among CYP2C9*3 carriers.

**Thiazolidinediones**
Pioglitazone and rosiglitazone are the two thiazolidinedione medications that are FDA-approved for T2DM. While the ADA considers these medications second-line agents, the AACE lists them as fifth line agents due to their risk of causing edema, heart failure, and fractures. Both medications are metabolized primarily by CYP2C8 and to a lesser extent by CYP2C9 and CYP3A4. These medications are distributed into the hepatocytes by an organic anion transporter encoded by the SLCO1B1 gene, which has genetic polymorphisms known to impact response to statin medications. Only one study has examined the impact of these genes on thiazolidinedione outcomes. Dawed et al found that the CYP2C8*3 variant was associated with reduced glycemic response to rosiglitazone, while the SLCO1B1 rs4149056 variant was associated with improved glycemic response.

**Newer Classes**
Newer classes of oral glucose lowering agents that have come to market in the last 10 years include DPP-4 inhibitors, SGLT2 inhibitors, and GLP1 agonists. Because of their recent entry to the market, most of these medications have not yet been extensively studied for pharmacogenomic associations.

DPP-4 inhibitors include sitagliptin, saxagliptin, linagliptin and alogliptin. They are considered second-line agents by the ADA, but fourth line agents by the AACE. Like metformin, most are renally excreted and avoid metabolism by CYP450 enzymes. One exception, saxagliptin, is metabolized by CYP3A4/5 but has not yet been evaluated for an association with any of the known polymorphisms in CYP3A4 and CYP3A5. One recent study implicated a single polymorphism near the CTRB1 and CTRB2 genes in response to DPP-4 inhibitors but this finding has not yet been replicated.

SGLT2 inhibitors include dapagliflozin, empagliflozin and canagliflozin. They are considered second line agents by the ADA and third line medications by the AACE. Dapagliflozin and canagliflozin are metabolized by UGT enzymes, while empagliflozin is primarily excreted unchanged with only minor metabolism by UGT enzymes. Only one study has evaluated pharmacogenetic associations with SGLT2 inhibitors, but found no effect of polymorphisms in the SLC5A2 gene on empagliflozin treatment response.

GLP1 agonists are some of the newest oral glucose lowering agents and include exenatide, liraglutide, lixisenatide, dulaglutide, and semaglutide. They are considered second line agents by the ADA and second or third line medications by the AACE. They are metabolized by ubiquitous proteolytic enzymes that are unlikely to be affected by genetic variation. No studies have yet evaluated these medications for pharmacogenetic associations.

**Summary**
The pharmacogenomics of oral glucose lowering agents continues to be an emerging field of inquiry. Research into predictors of metformin response continues to expand, and it is likely that research efforts will begin focusing on some of the newer classes of medications. While more research is needed to support the use of pharmacogenomics to predict patient outcomes with other classes of diabetes medications, there are sufficient data to support the use of pharmacogenomics with sulfonylureas and, to a less extent, thiazolidinediones.
Pharmacogenomics of Cardiovascular Medications

Hyperlipidemia and hypertension are two of the most common diabetes comorbidities. Together with hyperglycemia, these conditions constitute the “three H’s” of metabolic syndrome. These two conditions are significant predictors of overall cardiovascular health in diabetics and ADA guidelines emphasize both hyperlipidemia and hypertension management as a key component of effective diabetes treatment.

Hyperlipidemia is the most common diabetes comorbidity and is a more important risk factor for cardiovascular disease than hyperglycemia. While the prevalence of LDL-C levels is similar in diabetics and non-diabetics, diabetic patients have a 2-3 fold increased risk of elevated triglycerides and low HDL-C compared to the general population. Moreover, for the same serum lipid levels, individuals with diabetes have a greater risk of cardiovascular disease than non-diabetic individuals. Similarly, the risk of coronary artery disease in patients with comorbid diabetes and hypertension is three-fold higher than in patients with either diabetes or hypertension alone and the risk of stroke, nephropathy, and retinopathy is also increased.

Treatment of these underlying risk factors reduces the risk of cardiovascular disease in diabetic individuals. Statin treatment reduced the risk of CVD-related mortality by 19-25% in two studies. Likewise, the UKPDS 36 study showed that for each 10 mm Hg decrease in systolic blood pressure (SBP), there was a corresponding decrease in deaths related to diabetes (15% decrease), myocardial infarction (11% decrease), microvascular complications (13% decrease), and any complication (12% decrease). Improving efficacy and adherence to statin and antihypertensive therapy via pharmacogenetic-guided treatment would be expected to result in further decreases in major adverse cardiovascular events.

Statins
Statins are the preferred treatment for hyperlipidemia and are effective at lowering lipid levels and consequent risk of cardiovascular disease in individuals with diabetes. Medications in the statin class include atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Like many medication classes, statins are not uniformly metabolized in the same fashion. Fluvastatin is primarily metabolized by CYP2C9, while atorvastatin, lovastatin, and simvastatin are metabolized by CYP3A4/5. Pravastatin and rosuvastatin do not undergo CYP-mediated metabolism.

Cytochrome P450 variation has been shown to have an impact on statin efficacy and safety profiles. Carriers of the CYP3A4*22 variant, which reduces activity of the CYP3A4/5 enzyme system, have higher plasma concentrations of simvastatin and was associated with reduced dose requirement and greater reductions in total cholesterol and LDL-c levels. Carriers of the CYP3A5*1 allele, which increases activity of the CYP3A4/5 enzyme system, had reduced response to simvastatin, lovastatin, and atorvastatin. Genetic variation in CYP2C9 has been shown to increase serum levels of fluvastatin, and has been shown to increase adverse event rates by over 6-fold.

Another well-known example of hyperlipidemia pharmacogenomics is the SLCO1B1 gene, which encodes a protein that transports statins into the hepatocyte. As the hepatocyte is both the site of action and the site of metabolism for most statin medications, this protein plays a critical role in their clinical
Individuals who carry two copies of the \textit{SLCO1B1} rs4149056 variant, which reduces transport of statin into the hepatocyte, have shown a 120-221\% increase in simvastatin AUC compared with wild-type patients. Moreover, these individuals have a nearly 17-fold increase in likelihood of statin-induced myopathy compared to individuals with the normal genotype. This increase in myopathy risk may explain the two-fold increase in discontinuation rates among variant carriers. These data have led the Clinical Pharmacogenetic Implementation Consortium (CPIC) to establish clinical guidelines for the use of \textit{SLCO1B1} genotyping to inform simvastatin prescribing.

\textit{SLCO1B1} variation has also been found to impact efficacy of some statins. Carriers of the rs4149056 allele have shown reduced total cholesterol and LDL-c response with pravastatin and atorvastatin, while \textit{SLCO1B1}*14 carriers showed improved response to fluvastatin. Pharmacokinetic variability, though not necessarily clinical outcomes, has been observed as a function of \textit{SLCO1B1} genotype with all of the statins except lovastatin.

\textbf{Angiotensin Converting Enzyme Inhibitors}

Angiotensin converting enzyme (ACE) inhibitors, along with angiotensin II receptor blockers (ARBs), are considered first line therapy for hypertension in diabetes due to their nephroprotective effects. ACE facilitates the conversion of angiotensin I to angiotensin II, which limits the production of aldosterone, thereby reducing sodium and water reabsorption in the kidney. While some studies have evaluated associations between ACE inhibitor efficacy and genetic variants in the \textit{ACE} gene (in particular, rs1799572), the results have been conflicting. As a class, ACE inhibitors largely avoid CYP-mediated metabolism, reducing the impact of metabolism-related pharmacogenomic variants. However, studies have found that \textit{SLCO1B1} variation can increase enalapril serum levels and may increase risk of enalapril-induced cough by as much as 7-fold. Though more research is needed, \textit{SLCO1B1} is an intriguing target as a pharmacogenetic predictor of enalapril tolerability.

\textbf{Angiotensin II Receptor Blockers}

Angiotensin II receptor blockers (ARBs) target the angiotensin II receptor. However, studies have failed to show a consistent association between genetic variation in angiotensin receptor genes and ARB response. Unlike ACE inhibitors, many ARBs are metabolized by the CYP450 enzyme system. In particular, losartan, azilsartan, candesartan, valsartan, and irbesartan are all metabolized to greater or lesser degrees by CYP2C9 and CYP3A4/5. Pharmacogenomic variation in these genes has been shown to impact the clinical profile of these medications. For example, data shows that variants in \textit{CYP2C9} can impact losartan pharmacokinetics, reducing its conversion to its pharmacologically active form. Corresponding reductions in losartan efficacy have also been observed. In particular, one study looked at the impact of \textit{CYP2C9} variation on losartan response in type I diabetic patients with nephropathy, finding that individuals carrying the \textit{CYP2C9}*3 variant showed less improvement after 4 months of losartan therapy. \textit{CYP2C9} variation has also been shown to impact irbesartan response and changes in pharmacokinetic parameters as a function of \textit{CYP2C9} genotype have been reported with candesartan and valsartan. Thus, \textit{CYP2C9} genotype may be an important predictor of response to ARBs in hypertensive diabetics.

\textbf{β-Blockers}

β-blockers are extensively prescribed for heart failure and continue to be prescribed as an effective therapy for the treatment of hypertension in diabetes, especially as an adjunctive medication. β-blockers that have been evaluated for pharmacogenomic associations include carvedilol, metoprolol, and propranolol. A considerable amount of data has shown significant impacts of CYP450 variation on β-blocker pharmacokinetics and outcomes. The FDA-approved drug label for metoprolol notes the impact of \textit{CYP2D6} poor metabolism on pharmacokinetics and cardioselectivity of metoprolol, while the Dutch Pharmacogenetics Working Group has published metoprolol dosing guidelines as a function of \textit{CYP2D6}.

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metabolizer status.\textsuperscript{70} The impact of \textit{CYP2D6} genotype on carvedilol pharmacokinetics and clinical response has also been extensively demonstrated.\textsuperscript{77,71} While \textit{CYP2D6} variation has been shown to impact propranolol pharmacokinetics, its effect on response is still somewhat controversial.\textsuperscript{72-74} Several well-studied pharmacogenomic variants have been shown to impact β-blocker pharmacodynamics, including variants in genes encoding the β-adrenergic receptors themselves (\textit{ADRB1} and \textit{ADRB2}).\textsuperscript{57,75,76}

\textbf{Anticoagulant/Antiplatelet Medications}

When diabetes-related cardiovascular disease progresses to the point where intervention is required, anticoagulant and antiplatelet medications are often prescribed to manage risk of thrombosis and stroke, particularly after procedures such as heart valve replacement and stent placement. Clopidogrel and warfarin are some of the most commonly prescribed medications in these situations and both are among the best-known examples of pharmacogenomics.

Clopidogrel is one of several medications to have a black box warning in the FDA-approved drug label that explicitly calls out differential risk as a function of patient genotype, noting that “effectiveness of Plavix depends on conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.” The black box warning further notes that clinical tests are available to identify \textit{CYP2C19} poor metabolizers and recommends that practitioners “consider use of another platelet P2Y12 inhibitor in patients identified as \textit{CYP2C19} poor metabolizers.”\textsuperscript{77} \textit{CYP2C19} genotype may also interact with diabetes status to further reduce antiplatelet response to clopidogrel.\textsuperscript{78}

In late 2017, a landmark study was published by Cavallari et al that assessed clinical outcomes following clinical implementation of \textit{CYP2C19} testing in 1,815 patients who underwent percutaneous coronary intervention (PCI).\textsuperscript{79} Those with a normal genotype received standard therapy (approximately 85% received clopidogrel, with the rest receiving an alternative antiplatelet medication). However, if a patient carried a loss-of-function (LOF) allele, their provider was alerted and alternative anti-platelet therapy was suggested (approximately 61% received alternative antiplatelet therapy, with the rest receiving clopidogrel). After 12 months, patients with a LOF allele who received clopidogrel were 2.3 times more likely to experience a major adverse cardiovascular event than patients with a LOF allele who received alternative therapy (p = 0.013).\textsuperscript{79} Patients with an LOF allele who received alternative therapy had similar outcomes to those without an LOF allele.

These data indicate that \textit{CYP2C19} testing is an effective predictor of post-PCI clopidogrel outcomes. Prospective use of \textit{CYP2C19} genotyping can reduce risk of major adverse cardiovascular risk post-PCI and can also be used to triage individuals to the most appropriate and cost-effective therapy. For example, \textit{CYP2C19} normal metabolizers taking alternative therapies may be able to be triaged to the less expensive clopidogrel, reserving the more expensive alternative medications for individuals carrying LOF alleles.
The case of warfarin has been somewhat more controversial. FDA labeling has included *CYP2C9* genotype-guided dosing information since 2007.\textsuperscript{80} CPIC guidelines were published in 2011 and updated in 2017.\textsuperscript{20} However, trials examining clinical utility of warfarin have produced mixed results. Early studies failed to meet the primary endpoint of time in therapeutic range,\textsuperscript{81,82} although these studies have also been criticized for failing to mirror standard clinical practice.\textsuperscript{83} The COAG trial did show a trend toward fewer adverse events in the genotype-guided arm\textsuperscript{81} and the GIFT trial was launched to further explore these clinical outcomes.\textsuperscript{84} This study, which enrolled 1,650 patients randomized to either *CYP2C9*-guided dosing or standard clinical dosing, demonstrated a 27% reduction in the composite endpoint of venous thromboembolism, major bleeding, INR \(\geq 4\), or death in the genotype-guided arm compared to the clinical dosing arm. These data argue powerfully for the clinical implementation of warfarin despite earlier failures with less clinically relevant endpoints.

**Economic Outcomes**

To date, cost-effectiveness analyses for cardiovascular medications have been limited to clopidogrel and warfarin only. These analyses generally follow a similar pattern of comparing pharmacogenomic-guided therapy with one or more alternative approaches that do not require pharmacogenomic testing.

In the case of clopidogrel, one cost-effectiveness analysis compared pharmacogenomic-guided therapy antiplatelet selection (with normal allele carriers receiving clopidogrel and LOF allele carriers receiving alternative antiplatelet therapy) with universal clopidogrel therapy, universal alternative antiplatelet therapy, and platelet-reactivity guided therapy.\textsuperscript{85} The analysis evaluated costs over the lifetime of a 60-year-old patient undergoing a PCI and found that pharmacogenomic-guided testing resulted in the lowest overall cost over a lifetime and with the highest number of quality-adjusted life years gained. Another study evaluated the cost-effectiveness of genotype-guided antiplatelet therapy over a 30-day and 1-year window, finding that genotype-guided treatment was cost effective over 30 days and 1 year in 62 and 70% of simulations, respectively.\textsuperscript{86} A 2015 review of *CYP2C19*-guided antiplatelet therapy found that genotype-guided therapy was cost-effective in all seven studies that were reviewed, not including the two studies described previously.\textsuperscript{87}

Analyses of warfarin cost-effectiveness have produced largely, though not universally, positive results. Seven cost-effectiveness analyses have demonstrated genotype-guided anticoagulant therapy to be cost-effective relative to standard warfarin treatment and/or universal use of direct oral anticoagulant therapy,\textsuperscript{88-94} with two analyses finding standard warfarin dosing to be superior\textsuperscript{95,96} and one analysis finding standard warfarin dosing and genotype-guided dosing to be essentially equivalent.\textsuperscript{87}

**Summary**

Pharmacogenomics has a significant role to play in the management of cardiovascular risk factors in diabetes. Pharmacogenomic testing for clopidogrel and warfarin is now well established, with recent trials providing definitive evidence for clinical utility of genotyping prior to prescription of these medications. Pharmacogenomic testing for *CYP3A4*, *CYP3A5* and *SLCO1B1* can also be used to optimize the selection and dosing of statin medications for hyperlipidemia. In particular, *SLCO1B1* already has published guidelines on its clinical implementation and routine testing is occurring at many major medical centers. Similarly, testing for *SLCO1B1*, *CYP2D6*, and *CYP2C9* for the individualization of ACE inhibitors, beta-blockers, and ARBs, respectively, may reduce the time to effective dose (thus improving efficacy), while decreasing the risk of side effects (thus increasing adherence), resulting in better hypertension outcomes. Thus, adoption of pharmacogenomics is likely to result in significant improvements in cardiovascular health and quality of life among individuals with type 2 diabetes, with a reduced overall cost to the healthcare system. Moreover, by targeting a high-cardiovascular-risk population such as patients with type 2 diabetes, cost-effectiveness of pharmacogenomic testing is likely to exceed universal testing of the general population.
Pharmacogenomics of Antidepressant Medications

Few conditions have a greater impact on global functioning and quality of life than depression. In diabetes, comorbid depression is associated with poorer cognitive functioning, worsened glycemic outcomes, decreased adherence to behavioral and pharmacotherapeutic interventions, greater frequency and severity of diabetes complications (such as lower extremity amputation), and decreased quality of life. The prevalence of depression in type 2 diabetes is nearly twice as high (19.1%) compared to those without diabetes (10.7%). The relationship between depression and diabetes is likely bidirectional, with depression as both a risk factor for and a consequence of diabetes and the two conditions share neurobiological pathways.

Depression is primarily treated through pharmacotherapy and/or psychotherapy. Overall efficacy of antidepressants in both diabetics and the general population is poor, with only 50% of individuals responding to their first trial of an antidepressant, while intolerability and nonadherence to medications are quite common. Antidepressant use has been shown to be effective in reducing depressive symptoms, improving glycemic control, and improving quality of life for diabetic patients.

Clinical Outcomes
Pharmacogenomic testing in psychiatry is supported by an abundance of data. CPIC guidelines exist for tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) and over 30 neuropsychiatric medications contain pharmacogenomic information in their FDA-approved package inserts. Psychiatric pharmacogenomic testing has been evaluated in multiple published double-blind randomized controlled trials, with all showing statistically significant improvements in depressive symptomatology in the genotype-guided arm relative to the treatment-as-usual arm. Naturalistic studies have likewise shown that genotype-guided treatment can improve antidepressant response by as much as 56% over treatment-as-usual. Studies have also demonstrated improved antidepressant adherence with genotype-guided treatment relative to standard treatment. Outside of depression, evidence also exists for the use of pharmacogenomics to predict antidepressant outcomes in diabetic neuropathy.

Economic Outcomes
Psychiatric pharmacogenomic testing has been demonstrated to reduce healthcare medication costs. One large study that compared 2,168 genotype-guided patients to 10,880 matched controls demonstrated savings of over $1,000 USD per person in medication expenditures over a one year timeframe. Interestingly, diabetes and cardiovascular medications made up ~28% and ~16% of these savings, respectively. This is likely due to the aforementioned effect of improved mental wellbeing on physical health.

![Illustration of Pharmacogenetic Testing Reduces Healthcare Costs](image-url)
Pharmacogenomic testing has also been demonstrated to positively impact and lower healthcare utilization costs. One study found that patients taking genetically inappropriate medications accrued an additional $5,200 in healthcare utilization costs relative to patients on genetically appropriate medications,\textsuperscript{119} while another study found that CYP2D6 abnormal metabolizers had longer hospitalization stays and more adverse events, resulting in increased healthcare costs\textsuperscript{120}. Additionally, prospective use of psychiatric pharmacogenomic testing reduced healthcare utilization in two studies.\textsuperscript{117,121}

**Summary**

Psychiatric pharmacogenomic testing can improve patient outcomes in depression, leading to increased medication adherence and reduced healthcare costs. Psychiatric pharmacogenomic testing has shown a direct impact on medication costs associated with diabetes and cardiovascular disease and is likely to produce similar benefits in healthcare utilization and patient quality of life. The evidence supporting the clinical utility of pharmacogenomic testing for psychiatric medications may be the most extensive of any disease state.

**Future Directions: Genetic Predictors of Diabetes Risk**

While not directly related to pharmacogenomics, a brief discussion of genetic predictors of diabetes diagnosis is warranted. Monogenic forms of diabetes (i.e. inherited forms of diabetes caused by single genes) may represent one underutilized area of genetic testing in diabetes. The most well characterized form of monogenic diabetes is maturity-onset-diabetes of the young (MODY), a term encompassing 13 subtypes of the condition, each characterized by a single gene causing the illness presentation. As the clinical presentation of MODY is similar to both type 1 and type 2 diabetes, it is often misdiagnosed and may make up 1-2% of all diabetes cases.\textsuperscript{122} Neonatal diabetes mellitus, which usually presents in the first six months of life, is also caused by known, detectable mutations.\textsuperscript{122}

Type 2 diabetes mellitus, on the other hand, is multifactorial and is the result of a complex interplay between environment and numerous, largely uncharacterized genetic variants. Indeed, the NHGRI-EBI Catalog of published genome-wide association studies lists well over 1500 statistically significant associations, including variants in TCF7L2, KCNJ11, PPAR-γ, and FTO. However, each of these variants confers a very small increase in absolute risk for type 2 diabetes, making them presently useless as diagnostic markers. However, as the field advances, polygenic risk scores may be developed that, when validated, can assist in the prediction and early detection of type 2 diabetes so that interventions can occur before the disease progresses.

**Conclusion**

The treatment of type 2 diabetes mellitus, with its myriad of risk factors, treatment options, complications, and comorbidities is incredibly complex, resulting in significant social and economic burden in the United States. Pharmacogenomic testing has been demonstrated to significantly improve the treatment of cardiovascular and psychiatric conditions associated with diabetes, and data on the pharmacogenomics of glycemic agents themselves continue to accumulate. As clinicians adopt the use of pharmacogenomic testing for the management of pharmacotherapy in diabetic patients, it is likely that significant gains will be seen in medication efficacy, tolerability, and adherence, resulting in overall improved outcomes and reduced healthcare costs for the patient and healthcare system.
References


46. Assmann, G. & Schultz, H. The Prospective Cardiovascular Münster (PROCAM) study: prevalence of


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