Current Diabetes Reports (2019) 19: 23
https://doi.org/10.1007/s11892-019-1140-7

ECONOMICS AND POLICY IN DIABETES (AA BAIG AND N LAITEERAPONG, SECTION EDITORS)

Economics of Genetic Testing for Diabetes

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Published online: 27 March 2019

Abstract

Purpose of Review Monogenic diabetes is an uncommon but important form of diabetes, with the most common causes benefitting from management that accounts for the genetic mutation. This often results in decreased costs and treatment burden for affected individuals. Misdiagnosis as type 1 and type 2 diabetes is common. Given the significant burden of diabetes costs to the healthcare system, it is important to assess the economic impact of incorporating genetic testing for monogenic diabetes into clinical care through formal cost-effectiveness analyses (CEAs). This article briefly summarizes the barriers to timely monogenic diabetes diagnosis and then summarizes findings from CEAs on genetic testing for monogenic diabetes.

Recent Findings CEAs have shown that routine genetic testing of all patients with a clinical diagnosis of type 1 diabetes can be cost-saving when applied to the scenarios of neonatal diabetes or in a pediatric population. Routine screening has not been shown to be cost-effective in adult populations. However, next-generation sequencing strategies and applying biomarkers to identify and limit genetic testing to people most likely to have monogenic diabetes are promising ways to make testing strategies cost-effective.

Summary CEAs have shown that genetic testing for monogenic diabetes diagnosis can be cost-effective or cost-saving and should guide insurers to consider broader coverage of these tests, which would lead to accurate and timely diagnosis and impact treatment and clinical outcomes.

Keywords Monogenic diabetes · MODY · Genetic testing · Cost-effectiveness · CEA

Introduction

Diabetes mellitus is a heterogeneous group of disorders characterized by persistent elevation of blood glucose levels. The burden of diabetes is significant. Within the United States (US), 30.3 million people, or 9.4% of the population, were estimated to have diabetes in 2015, with increases projected in the future. The cost of diagnosed diabetes in 2017 was 327 billion USD, of which 237 billion USD was direct medical costs [1]. This represents a 26% increase over just 5 years. Due to this staggering cost, innovations in diabetes diagnosis, classification, and treatment must be critically assessed to establish their efficacy and determine if widespread implementation is appropriate.

The American Diabetes Association (ADA) classifies diabetes into four general categories: type 1, type 2, gestational diabetes, and "specific types of diabetes due to other causes." This last category includes monogenic forms of diabetes. The ADA notes that "classification is important for determining therapy" [2]. Type 1 diabetes, which represents 5–10% of all diabetes cases, is due to autoimmune or idiopathic destruction of the beta cells that requires replacement doses of insulin for treatment. Type 2 diabetes, the most prevalent form of diabetes, is due to a combination of insulin resistance and beta cell insufficiency and may respond to a number of different therapies targeting insulin sensitivity or insulin secretion, among other mechanisms. While it is generally agreed that a patient-centered, personalized approach to type 2 diabetes management is best, the heterogeneity of type 2 diabetes precludes robust evidence for the optimal use of the one dozen available agents, especially when used in combinations [3]. In regard to type 2 diabetes, Raz et al. state "In the distant future,

This article is part of the Topical Collection on *Economics And Policy In Diabetes*

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genotyping and testing for metabolomic markers may help us to better phenotype patients and predict their responses to antihyperglycemic drugs. For now, a personalized ("*n* of 1") approach in which drugs are tested in a trial-and-error manner in each patient may be the most practical strategy for achieving therapeutic targets" [4].

In contrast, among monogenic forms of diabetes, the most common types have specific treatment tailored to the genetic cause, with resulting benefit [5, 6]. However, precision medicine for monogenic diabetes is hampered by denial of medical insurance coverage for genetic testing and long delays in accurate genetic diagnosis. Following a brief overview of monogenic diabetes, this papers aims to review the findings of cost-effectiveness analyses of genetic testing for monogenic diabetes, providing support for wider adoption of diagnostic genetic testing in diabetes.

Monogenic Diabetes

Monogenic diabetes represents a heterogeneous group of genetic causes of diabetes. While there are numerous described genes that cause monogenic diabetes, a small number of genes account for the vast majority of monogenic diabetes cases (Table 1). Broadly, monogenic diabetes can be divided into neonatal monogenic diabetes, which can be permanent or transient, and maturity-onset diabetes of the young (MODY). Overall, the prevalence of monogenic diabetes is 1–3% [7–9]. MODY represents the vast majority of cases, while the prevalence of permanent neonatal diabetes is 1:250,000 and the prevalence of transient neonatal diabetes 1:450,000 [10, 11].

Neonatal diabetes is characterized by the onset of diabetes within the first 6 months of life, with a small number of monogenic cases diagnosed beyond 6 months of age. The majority of transient neonatal diabetes cases are due to overexpression of paternally derived genes at the 6q24 locus. More than half of transient cases will have a relapse of diabetes, typically in adolescence or early adulthood [12]. Among permanent neonatal diabetes, almost 50% of cases are due to activating mutations in either subunit of the ATP-sensitive potassium (K_{ATP}) channel of the beta cell. Sulfonylureas can bind to the channel, allowing channel closure, cell depolarization, and insulin secretion, thereby addressing the negative effects of the genetic mutation [13].

MODY is defined as young-onset, autosomal-dominant, non-insulin-dependent diabetes, owing to mutations in any one of 14 identified genes that are important to beta cell development and function [14]. More than 90% of all MODY cases are due to mutations in one of three genes—*HNF1A*, *HNF4A*, and *GCK* [15]. These three causes of MODY have the most clearly defined management. For HNF1A-MODY and HNF4A-MODY, low-dose sulfonylureas are effective in treating hyperglycemia [5, 16–18]. GCK-MODY is characterized by stable, mild hyperglycemia with fasting blood glucose typically ranging from 99 to 144 mg/dL and HbA1c ranging from 5.6 to 7.6% [19, 20]. Therapy is not necessary in GCK-MODY because micro- and macrovascular complications are exceedingly rare [21].

Table 1 Common monogenic diabetes genes and prevalence

Common permanent neonatal diabetes genes*	Common MODY genes*
KCNJ11 30%	*HNF1A* (30–65%)
ABCC8 12%	*HNF1B* (< 5%)
INS 10%	*HNF4A* (5–10%)
	GCK (30–50%)

*There is gene overlap between MODY and neonatal diabetes. *KCNJ11*, *ABCC8*, and *INS* are all rare causes of MODY. *HNF1B* and homozygous mutations in *GCK* are causes of neonatal diabetes

Barriers to Diagnosis of Monogenic Diabetes

Case identification in neonatal diabetes is straight-forward due to the clear-cut phenotype of age at diagnosis guiding appropriate patient selection for genetic testing. In contrast, the vast majority of MODY cases are misdiagnosed [15]. While guidelines exist to guide selection of appropriate individuals for genetic testing for the common MODY forms, in actual practice, there is a delay in practitioners recognizing patients who should undergo genetic testing for MODY [15, 22, 23]. This is because MODY lacks any singular defining clinical feature to definitively distinguish it from type 1 or type 2 diabetes. Classic criteria for identifying MODY include the age of diagnosis under 25 years with an affected parent and no insulin therapy; however, these criteria lead to almost a quarter of those with MODY being missed [15]. An alternative strategy has been to limit testing to non-obese adolescent populations; however, studies like TODAY have identified a MODY prevalence of 4.5% in children who are overweight and negative for antibodies against the islet cell, suggesting that screening criteria based on body mass index would also miss MODY cases [24]. Unrestricted genetic testing in the general diabetes population for monogenic diabetes would ensure full ascertainment. However, the expense associated with diabetes care mandates that cost-effectiveness of implementation of genetic testing for monogenic diabetes be carefully assessed.

Overview of Cost-effectiveness Analysis

Cost-effectiveness analysis (CEA) is a useful tool to examine the benefits of healthcare services and aid in decisions about

which interventions should be offered. There are guidelines to address best practices for carrying out CEA [25]. Generally, CEA compares the cost and effectiveness of two or more medical alternatives, often comparing the "gold standard" or status quo against a new intervention. The main outcomes of interests are costs and quality-adjusted life years (QALYs), which measures the quantity and quality of life provided by a healthcare intervention. QALYs are determined by multiplying the utility of a given state of health by the time lived in that state [26]. Health utility exists on a continuum of 0 (death) to 1.0 (full health) and medical conditions and their associated treatments and complications all negatively impact health utility.

At times, dominance occurs in CEA. That is, the new intervention is more effective (produces more QALYs) and costs less than the gold standard, making adopting the intervention the obvious preferred decision or the new intervention is less effective and costs more, leading to rejecting the intervention in favor of the status quo. More commonly, an intervention leads to increased QALYs but also costs more than the status quo. In this case, the incremental cost-effectiveness ratio (ICER, the difference in costs divided by the difference in QALYs) is used to determine if the improved outcome gained by the intervention is worth the additional costs. An ICER of 50,000 US dollars (USD) is often cited as cost-effective, although it is worth noting that many adopted healthcare innovations have ICERs of 100,000–200,000 USD [27].

General Economic Considerations of Implementing Genomic Medicine Into Clinical Practice

Since 2007, the cost of genomic sequencing has decreased from $10 million dollars to $1000. Despite this, integration of genetic testing and genomic sequencing into clinical practice could increase health expenditures because the cost of interpretation and infrastructure requirements are unlikely to decrease rapidly. Importantly, depending on what types of tests are incorporated into practice, genetic testing could actually increase medical testing if results are inconclusive or increase medical surveillance if an increased risk for disease is shown. Genetic testing for monogenic diabetes clarifies diagnostic etiology and can lead to treatment changes that decrease cost. Thus, there are unlikely to be uncaptured downstream costs related to monogenic diabetes genetic testing results compared with genetic testing in other forms of diabetes or other diseases. While cost-effectiveness analyses of genetic testing for monogenic diabetes are limited, studies to date support wider implementation of diagnostic genetic testing for diabetes classification to guide therapeutic decision-making.

Cost-effectiveness of Genetic Testing for Neonatal Diabetes

To date, there has only been one CEA of genetic testing solely for neonatal diabetes. This study carried out by Greeley et al. aimed at comparing a policy of routine genetic testing with no genetic testing for children with permanent neonatal diabetes [28•]. The authors used a Monte Carlo Markov simulation model of type 1 diabetes complications in a hypothetical cohort of patients with permanent neonatal diabetes, defined as diagnosis under 6 months of age. The CEA was conducted from the societal perspective over a 30-year time horizon.

In the study, patients with permanent neonatal diabetes underwent routing testing for mutations in *KCNJ11* or *ABCC8* at 6 years of age (based on the median age of testing within the University of Chicago National Monogenic Diabetes Registry). The performance of the genetic testing was assumed to be 100% sensitive and 100% specific. In those testing positive for a mutation in *KCNJ11* or *ABCC8*, there was an attempt to transition from insulin to sulfonylureas. The successful conversion was modeled as 90%. Those who successfully transitioned to sulfonylureas were modeled to maintain a lifetime HbA1c of 6.4% while remaining patients were modeled to maintain a lifetime HbA1c of 8.1%. Modeled complications included nephropathy, neuropathy, retinopathy, ischemic heart disease, myocardial infarction, congestive heart failure, stroke, diabetic ketoacidosis, hypoglycemia, and death. Quality-of-life effects included impact of complications as well as impact of treatment. Life with type 1 diabetes without complications, treated with insulin, was assigned a health utility of 0.86. Life with neonatal diabetes with successful transition to sulfonylureas was assigned a health utility of 0.96. Accounted costs were genetic testing ($705 for *KCNJ11* and $2110 for *ABCC8*); 4-day hospital admission for an attempt at transition from insulin to sulfonylurea therapy; lifetime treatment with either sulfonylureas or insulin including medical equipment for insulin delivery and blood glucose monitoring; and time for diabetes care. A 3% discount rate was applied to QALYs and costs.

In this CEA, the genetic testing policy reduced micro- and macrovascular complications in those with monogenic neonatal diabetes resulting in quality-of-life benefits. The testing policy also reduced costs starting at 10 years, related to the substantial cost-savings of treatment with sulfonylureas compared with treatment with insulin. The genetic testing policy dominated the no-testing policy at 10 years. Over the last decade, recognition of neonatal diabetes has increased and genetic testing at diabetes onset is more common. Thus, genetic testing for neonatal diabetes is likely more cost-savings than this study suggests, which accounted for a median of 6 years of insulin therapy.

Cost-effectiveness of Genetic Testing for MODY or Monogenic Diabetes

Peters et al. outlined a decision model for evaluating test-treatment strategies for monogenic diabetes focused on disease caused by mutations in *GCK*, *HNF1A*, or *HNF4A* genes [29•]. They defined five strategies: no testing; testing based on clinical features; testing based on results of a clinical prediction model; testing based on biomarkers; and testing for all patients with a diagnosis of diabetes under the age of 30 years. To date, published studies of genetic testing for monogenic diabetes have utilized varying iterations of these strategies.

CEA for MODY Genetic Testing in a Young-Adult US Cohort

This study, carried out by myself and colleagues, aimed to compare a policy of routine genetic testing for GCK-MODY, HNF1A-MODY, and HNF4A-MODY with no genetic testing in a hypothetical cohort of newly diagnosed patients 25–40 years of age with presumed type 2 diabetes and a background MODY prevalence of 2% [30•]. We used a model of type 2 diabetes complications based on UK Prospective Diabetes Study (UKPDS) data, modified to account for the natural history of diabetes due to heterozygous mutations in *HNF1A*, *HNF4A*, and *GCK*. Analysis was done from the health care system perspective using a lifetime horizon.

All patients underwent one-time genetic testing for mutations in *HNF1A*, *HNF4A*, and *GCK*. The performance of the genetic testing was assumed to be 100% sensitive and 100% specific. Those who tested positive for a mutation in *GCK* discontinued all pharmacologic therapy with no change in HbA1c, per the expected clinical course of GCK-MODY. Those diagnosed with HNF1A- or HNF4A-MODY attempted transition from baseline therapy to sulfonylurea therapy; successful conversion was modeled as 90%, but decreased over time. Successful transition resulted in a HbA1c decrement of 1.5%. Micro- and macrovascular complications were modeled based on UKPDS risk equations [31]. Oral medications were assigned a health utility of 0.77 while treatment with insulin was assigned a health utility of 0.64. Microvascular and macrovascular complications were assigned a lower health utility using the minimum utility method to address multiple complication states in a year. Accounted costs included genetic testing (2580 USD), treatment costs, and costs of complications. A 3% discount rate was applied to future costs and quality-of-life effects.

The genetic testing policy was not cost-effective, yielding an ICER of 205,000 USD/QALY. Sensitivity analyses showed that the total costs were most sensitive to MODY prevalence. Threshold analysis determined that a small increase in MODY prevalence from 2 to 6% in the population would achieve an ICER around 50,000 USD/QALY, while a prevalence of 30% would be cost-saving. This suggested that application of biomarkers to the population to restrict testing to those more likely to have MODY could make a genetic testing policy for MODY cost-effective.

CEA for MODY Genetic Testing in a Young-Adult Singapore Cohort

Based on the findings from the above study that universal screening in a young "type 2" diabetes cohort was not effective, Nguyen et al. aimed to "extend the prior analysis to assess whether a cost-effective algorithm-driven genetic testing strategy for MODY could be identified by better targeting the subset of the population identified for genetic testing" [32••].

This algorithm-driven genetic testing strategy was compared with a policy of no genetic testing in a population based on two diabetes cohorts in Singapore, using a payer perspective and 30-year time horizon.

Beginning with a population with diabetes diagnosis at age 45 years or less, the algorithm excluded type 1 diabetes, defined as GAD antibody positive (6.8% of the population). Genetic testing was carried out by next-generation sequencing MODY gene panel in two populations: antibody-negative with diagnosis under age of 30 (11.8% of the population) and antibody-negative with diagnosis between 30 and 45 years with BMI less than 25 kg/m^2 (29.7% of the population). Those positive for a mutation in *GCK* discontinued treatment. Those positive for a HNF1A- or HNF4A-MODY received treatment with a sulfonylurea. Those testing positive for other MODY genes received "gene-specific treatment," including insulin for MODY due to mutations in *INS* and *HNF1B*. Patients were assigned a utility of 0.92 if they were on no therapy, 0.82 for oral medications or diet and exercise, and 0.75 for insulin therapy. Nguyen et al. accounted for cost of antibody screening (59 USD), genetic testing (1050 USD), and treatment, including blood glucose testing in patients on insulin therapy. A 3.5% discount rate was applied to costs.

The algorithm-driven genetic testing strategy was better than universal testing, but still did not reach traditional cost-effective thresholds, with an ICER of 93,663 USD/QALY. Sensitivity analyses demonstrated that the increases in prevalence of MODY due to mutations in *GCK*, *HNF1A*, or *HNF4A* or a ~ 50% decrease in the cost of genetic testing would make the strategy cost-effective. An important limitation of this study is that their model focused on "testing and treatment pathways" and did not consider diabetes-related complications. Part of the expected QALY gain and cost decrease in a monogenic diabetes genetic testing strategy is due to the better HbA1c achieved in those with HNF1A-MODY and HNF4A-MODY who transition from insulin to sulfonylureas. Moreover, this HbA1c benefit is expected to translate to decreased diabetes-related complications [5, 6]. By not

accounting for these changes in complications, it is possible that their model was undervalued.

CEA for MODY Genetic Testing in an Australian Pediatric Cohort

Johnson et al. recently published their cost-effectiveness analysis that used massively parallel sequencing (MPS) to diagnose MODY in an Australian pediatric diabetes cohort with presumed type 1 diabetes [33••]. They derived their population characteristics from the Western Australian Childhood Diabetes Database. They used a Markov decision model based on the Sheffield Type 1 Diabetes Model to account for diabetes costs and complications [34]. Analysis was carried out from the health care system perspective over a 30-year time horizon.

In their genetic testing strategy, MPS screening for MODY was carried out at diagnosis in all children with presumed type 1 diabetes compared with the "standard care," defined as ad hoc sequencing for MODY on clinical grounds. Prevalence values of MODY in each strategy were 2.14% and 0.65%, respectively. MPS was assumed to be 100% sensitive and 100% specific in detecting MODY. Treatment changes were accounted for in five types of MODY—no treatment in GCK-MODY and successful sulfonylurea treatment in 80% of MODY due to mutations in HNF1A, *HNF4A*, *KCNJ11*, and *ABCC8*. Transition to sulfonylureas was associated with a 0.9% HbA1c decrease and durability of sulfonylurea therapy was assumed to be 100% over the time horizon. Modeled complications included nephropathy, neuropathy, retinopathy, cardiovascular disease, diabetic ketoacidosis, and severe hypoglycemia. Patients were assigned a health utility of 0.86 for a life with complication-free type 1 diabetes. A health utility of 0.96 was used for diabetes that did not require insulin use. Microvascular and macrovascular complications resulted in a health utility decrement. Cost of MPS was 383 USD compared with Sanger sequencing costs of 574 USD. Additional accounted costs included medication costs as well as other costs of diabetes care. Since MODY is not an autoimmune disease, correct genetic diagnosis precluded the need for type 1 diabetes–specific surveillance, such as annual screening for celiac or thyroid disease. A 3% discount rate was applied to future costs and quality-of-life effects.

Johnson et al. found that MPS screening for MODY resulted in increased QALYs and decreased costs compared with the standard care for MODY diagnosis. "The costs of routine screening were fully offset within 10 years" and over the time horizon of the study, the ICER was − 30,076 USD/QALY. It is important to note that these results cannot be extrapolated to pediatric type 2 diabetes where treatment change impact would differ. Additionally, the 383 USD cost used for MPS reflects at-cost pricing, which is likely to be lower than commercial pricing. Nevertheless, these results are important for pediatric populations that would fit a clinical diagnosis of type 1 diabetes but may, in fact, have monogenic forms of diabetes.

Discussion and Conclusions

It is rare for a health intervention to produce better outcomes and save money—yet, this coveted outcome was demonstrated in neonatal diabetes and in routine screening for MODY in a pediatric population with presumed type 1 diabetes. There are several characteristics of genetic testing for neonatal diabetes that makes this uncommon result possible. The most notable of these is testing in a constrained population. Permanent diabetes diagnosis under 6 months of age is a defining characteristic that allows efficient identification of patients to undergo genetic testing. In this select population, the rate of mutations in *KCNJ11* or *ABCC8* is above 40%. Moreover, the cost difference between insulin therapy and sulfonylureas, which are generic oral medications, is striking. The fact that at least 90% of patients diagnosed with KATP-related neonatal diabetes can be expected to successfully transition from insulin to sulfonylureas drives the early cost-savings associated with this testing policy. Likewise, in the study by Johnson et al., testing was constrained to type 1 diabetes, with therapy change from insulin to sulfonylureas again driving cost-savings. However, it is important to note that due to the use of MPS, they were able to employ testing in all patients with presumed type 1 diabetes. While the modeled cost of MPS does not account for higher commercial pricing, sensitivity analyses show that doubling costs still resulted in cost-savings.

In the instance of adult populations, and very likely in pediatric populations that include presumed type 2 diabetes, routine screening even with next-generation sequencing techniques do not reach the typical US cost-effectiveness threshold of $50,000. However, results do support the use of biomarkers combined with clinical features to identify a population of patients with diabetes who should have genetic testing for monogenic diabetes. Because cost-effectiveness is tied closely to the underlying prevalence of monogenic diabetes, strategies to routinely implement known and validated biomarkers for initial diabetes classification will also help to identify patients likely to have monogenic forms of disease who would benefit from genetic testing. Continued advances in genetic testing strategies resulting in decreased testing costs will also drive cost-effectiveness as shown in the studies by Nguyen et al. and Johnson et al., although commercial testing prices may not fall as rapidly as at-cost pricing.

While all modeled studies have limitations, these cost-effectiveness analyses of monogenic diabetes testing argue favorably for broader implementation of genetic testing for accurate diabetes diagnosis. Based on these results, it is reasonable to suggest medical insurance should routinely cover

genetic testing for neonatal diabetes and for pediatric "type 1" diabetes. Moreover, a tiered approach utilizing biomarker screening and defined clinical parameters can also guide insurance coverage to improve accurate diagnosis of monogenic diabetes and timely implementation of precision medicine.

Compliance with Ethical Standards

Conflict of Interest The author declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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