The Cost-Effectiveness of Personalized Genetic Medicine

The case of genetic testing in neonatal diabetes

Siri Atma W. Greeley, MD, PhD1
Priya M. John, MPH2
Aaron N. Winn, MPP3
Joseph Ornelas, MS, AM, DC2
Rebecca B. Lipton, PhD1
Louis H. Philipson, MD, PhD1,4
Graeme I. Bell, PhD4
Elbert S. Huang, MD, MPH2

OBJECTIVE—Neonatal diabetes mellitus is a rare form of diabetes diagnosed in infancy. Nearly half of patients with permanent neonatal diabetes have mutations in the genes for the ATP-sensitive potassium channel (KCNJ11 and ABCC8) that allow switching from insulin to sulfonylurea therapy. Although treatment conversion has dramatic benefits, the cost-effectiveness of routine genetic testing is unknown.

RESEARCH DESIGN AND METHODS—We conducted a societal cost-utility analysis comparing a policy of routine genetic testing to no testing among children with permanent neonatal diabetes. We used a simulation model of type 1 diabetes complications, with the outcomes of interest being the incremental cost-effectiveness ratio (ICER, $/quality-adjusted life-year [QALY]) gained) over 30 years of follow-up.

RESULTS—In the base case, the testing policy dominated the no-testing policy. The testing policy was projected to bring about quality of life benefits that enlarged over time (0.32 QALYs at 10 years, 0.70 at 30 years) and produced savings in total costs that were present as early as 10 years ($12,528 at 10 years, $30,437 at 30 years). Sensitivity analyses indicated that the testing policy would remain cost-saving as long as the prevalence of the genetic defects remained >3% and would retain an ICER <$200,000/QALY at prevalences between 0.7 and 3%.

CONCLUSIONS—Genetic testing in neonatal diabetes improves quality of life and lowers costs. This paradigmatic case study highlights the potential economic impact of applying the concepts of personalized genetic medicine to other disorders in the future.

Neonatal diabetes mellitus is a rare form of diabetes that is likely to have a monogenic cause, particularly when diagnosed before 6 months of age (1). Recent estimates from multiple national registries show the incidence is close to 1 in 100,000 live births (2). In 50% of cases, the condition spontaneously remits within a few months of age and is termed transient neonatal diabetes, whereas the remaining infants have permanent neonatal diabetes.

Of probands with permanent neonatal diabetes, 42% have activating heterozygous mutations in either of the two protein subunits, KCNJ11 and ABCC8, of the ATP-sensitive potassium (KATP) channel, whereas 12% have mutations in the gene encoding insulin (INS) (3–6). In KATP-related neonatal diabetes, sulfonylurea binding allows KATP channel closure in patients whose channels would otherwise remain open and prevent insulin secretion from occurring. Reports indicate that treatment with oral sulfonylurea therapy in place of insulin has been successful in most of these patients, leading to immediate dramatic improvements in glucose control and quality of life (7,8).

These recent discoveries have raised questions regarding the extent to which routine testing for these mutations should be performed in any insulin-treated individual with presumed type 1 diabetes. Age at diagnosis of diabetes is a key determinant of a possible monogenic cause, where those diagnosed when aged younger than 6 months have a high likelihood of having a causal genetic variant. However, 1–2% of those diagnosed between age 6 and 12 months may also be mono genetic (6,8,9). Some experts have even suggested that all newborns should perhaps undergo screening (10), given that routine newborn screening in all states includes such disorders as maple syrup urine disease, which has an incidence of 1 in 185,000 births.

In any consideration of genetic testing, the prevalence of genetic markers that could inform disease prediction, treatment, or outcomes must be weighed against the cost of testing. The promise of personalized genetic medicine is that highly individualized treatments may not only improve the health of patients but may also lower costs in some cases. There have been no rigorous cost-effectiveness analyses of genetic testing policies that lead to transformative changes in the selection of treatments (compared with studies of warfarin pharmacogenetics [11]). To test the hypothesis that genetic testing in some disorders can lead to dramatic health and cost benefits, we conducted a societal cost-utility analysis of a genetic testing policy for permanent neonatal diabetes.

RESEARCH DESIGN AND METHODS—The conceptual organization of the analysis is displayed in Fig. 1. The analysis was conducted from the societal perspective with a 30-year time horizon, which was selected because the most extensive natural history data for type 1 diabetes data only spans 30 years.
Forecasts beyond 30 years are therefore difficult to validate. The base case policy comparison was between life with the testing policy in place versus the baseline of life with no testing policy for children with permanent neonatal diabetes (diagnosed with diabetes before age 6 months; Fig. 1A). In our model, hypothetical patients would undergo routine testing for mutations in the genes KCNJ11 or ABCC8 at 6 years of age, which represents the median age at which testing was performed through the University of Chicago U.S. Neonatal Diabetes Registry. This median age is inflated by the many older existing individuals who were diagnosed with diabetes years before the availability of genetic testing, although we recognize that in practice testing should now occur much closer to the age of diagnosis in the neonatal period. After genetic testing, children found to have treatable mutations underwent an attempt to switch from insulin to sulfonylurea therapy. All hypothetical patients were then analyzed for the long-term risk of diabetes-specific complications, based on differing levels of glycemic control (Fig. 1B). In the following sections, we provide details of our assumptions for selected portions of the lifetime simulation model. All model assumptions are available in the Supplementary Table 1 and Supplementary References.

Impact of neonatal diabetes genetic testing
We assumed that the performance of the genetic testing is 100% sensitive and 100% specific in identifying KCNJ11 and ABCC8 mutations. Results from two large series show the likelihood of detection of such a mutation in probands diagnosed with diabetes at younger than 6 months old is 41.6% (7,8,12). For this analysis, we conservatively assumed that the rate of conversion was 90%. In the largest published series, two of the five patients who failed to transition completely off insulin (of 49 total) were adult parents carrying the same mutations as their children who did successfully transition to sulfonylurea therapy (7). Some subjects aged older than 14 years in the U.S. Neonatal Diabetes Registry also experienced greater difficulty with the conversion, requiring especially high doses of sulfonylurea or other medications (8). Mouse models support the hypothesis that such age-related decline in functional β-cell mass may occur in the absence of sulfonylurea “rescue” of healthy β-cell function (13).

Successful conversion to sulfonylurea therapy has led to large improvements in A1C levels (8.1–6.4% [7], 8.3–6.3% [8], and 7.2–5.5% [12]) that in many reported cases have been sustained over many years. We assumed that patients converted to sulfonylurea would maintain a lifetime A1C of 6.4%, whereas all other patients would maintain a lifetime A1C of 8.1%.

Lifetime complications of diabetes
To model the lifetime complications of diabetes, we used an established model of type 1 diabetes complications. The model is a Monte Carlo Markov simulation model that uses a framework shared by prior cost-effectiveness analyses of diabetes treatments (14–16). The model is framed by simultaneous progression of disease through major categories of complications, including nephropathy, neuropathy, retinopathy, ischemic heart disease, myocardial infarction, congestive heart failure, stroke, diabetic ketoacidosis, hypoglycemia, and death, and their associated Markov states (Fig. 1B). Calculations were done using Excel 2000 (Microsoft Corp., Redmond, WA) and @Risk 4.0 software (Palisades, Inc., Newfield, NY). The cycle length within the model is 1 year and the model is run for each patient until death or age 95. For each specific treatment scenario, the model was run for 10,000 iterations using Monte Carlo recalculation (see Supplementary Material).

Quality of life effects
The quality of life effect resulting from genetic testing is associated with the

Figure 1—A: Policy decision for genetic testing in permanent neonatal diabetes. B: Lifetime model of diabetes-related complications.
immediate quality of life effect of switching therapies as well as the lifetime risk of complications. For the immediate quality of life effect, we conservatively assumed that the health utility (a continuum for which optimal health is assigned a value of 1.0 and health judged equivalent to death is assigned a value of 0.0) for life with type 1 diabetes requiring insulin with no complications is 0.86 (17). We further assumed that converting to sulfonylurea therapy would improve the utility by 0.10 according to results from studies in older adults with type 2 diabetes (18). For the quality of life effects of complications, we used utilities found in the literature. Utilities were used to calculate quality-adjusted life-years (QALYs) using the minimum utility method.

Costs
The cost of genetic testing is based on a Clinical Laboratory Improvement Act-approved laboratory charge for sequencing of the genes KCNJ11 and ABCC8 ($705 and $2,110 from the Summer 2009 price list, Athena Diagnostics, Worcester, MA). Although the clinical transition from insulin to sulfonylureas may be done on an outpatient basis, we incorporated the costs for a 4-day hospital admission into the model.

Beyond the one-time testing and transition costs, we made a series of assumptions regarding the costs of life with insulin or sulfonylurea. For both therapies, drug use was tied to the weight of patients. Average weights for age were derived from standard Centers for Disease Control growth charts. The price for a unit of insulin was based on insulin glargine. We also accounted for the proportion of subjects using insulin pumps or multidose insulin injections based on estimates from the U.S. Neonatal Diabetes Registry. Finally, glucometer test strip use, also based on the U.S. Registry experience, was assumed to be different for insulin (six/day) and sulfonylurea users (three/day).

In addition to these direct costs, we accounted for the time associated with diabetes care provided by parents for children aged younger than 16 years. The indirect costs of diabetes care were estimated from time spent using test strips (5 min/test strip). We made no assumptions regarding differences in lost workdays for patients using sulfonylureas or insulin due to a lack of existing literature. All costs were expressed in 2008 U.S. dollars.

**Incremental cost-effectiveness ratio**
The main outcome of interest was the incremental cost-effectiveness ratio (ICER; $/QALYs). A 3% discount rate was applied to both quality of life effects and costs as recommended by the Panel on Cost-Effectiveness in Health and Medicine (19).

**Sensitivity analyses**
To evaluate the effect of uncertainty around variables, we conducted a series of one-way and two-way sensitivity analyses. In addition to analyzing a number of variables with a direct effect on cost, we also considered the cost and quality of life consequences of genetic testing at a range of ages, from 3 to 14 years instead of the base case at age 6 years. At age 14 years, we further assumed that the probability of successful treatment conversion would decline to 43%. Our analyses depend on the well-documented high prevalence of KCNJ11 and ABCC8 mutations in patients diagnosed with diabetes an age younger than 6 months. To provide insight into the cost-effectiveness of genetic testing in patients diagnosed with diabetes after age 6 months—in whom the lower prevalence of genetic defects remains to be clarified—we also completed a threshold analysis using a range of hypothetical lower prevalence values, while holding all other variables constant. These analyses were complemented by a future cost analysis (20), which accounted for nondiabetes-related medical expenditures and future nonmedical expenditures net of earnings. A probabilistic sensitivity analysis was also conducted.

**RESULTS**

**Health effects**
In the 30-year forecast, the genetic testing policy reduced the expected probability of end-stage complications of type 1 diabetes (Table 1). The model predicted that genetic testing would lead to reductions in 30-year risk of blindness from 4.00 to 2.89%, amputation from 8.02 to 7.59%, and end-stage renal disease from 0.48 to 0.30%. Smaller benefits were projected for cardiovascular disease. The genetic testing policy was projected to bring about quality of life benefits that enlarged over time (0.32 QALYs at 10 years, 0.70 at 30 years after testing; Table 1).

**Cost effects**
Although producing health benefits, the genetic testing policy was also projected to reduce average total costs as early as 10 years after testing ($12,528), growing to $30,437 at 30 years (Table 1). In all subcategories of costs, the genetic testing policy produced cost savings as early as 10 years after genetic testing and transition to sulfonylurea treatment.

**Incremental/cost-effectiveness ratio**
Considering the incremental costs and health effects together, the genetic testing policy dominated the no-testing policy at 10 years (−$12,528 and +0.32 QALYs) and 30 years (−$30,437 and +0.70 QALYs) after testing (Table 1). These ICERs are located in the fourth quadrant of the cost-effectiveness plane, indicating a very rare instance in which the policy provides not only a health benefit but also a cost saving.

**Sensitivity analyses**
In all one-way sensitivity analyses for uncertain inputs, as well as two-way analysis of age at the time of genetic testing combined with a lower likelihood of successful conversion to sulfonylureas if tested at age 14 years, the genetic testing policy remained a dominant strategy (Fig. 2). Because patients from now on are likely to be screened sooner after their diagnosis of diabetes, we repeated the sensitivity analysis for genetic testing at age 1 year and found the genetic testing policy to be similarly cost saving. Total costs were most sensitive to the prevalence of the genetic defects, the age at genetic testing, and the discount rate; however, total costs with genetic testing continued to be lower than no genetic testing over a wide range of these variables. Threshold analyses indicated that the genetic testing policy would remain cost saving as long as the prevalence of the genetic defects remained above 3% and would retain an ICER < $200,000/QALY at prevalences between 0.7 and 3% (Supplementary Fig. 1). We found that accounting for future costs did not significantly alter the base case result. Similarly, in our probabilistic analysis, we found that 100% of model recalculations were consistent with the base case conclusion.

**CONCLUSIONS**—The case of permanent neonatal diabetes provides us with a timely example of the potential financial benefits that may arise from personalized genetic medicine. In our model, genetic testing in permanent neonatal diabetes results not only in improved quality of life but also in cost savings. Cost savings came...
from all cost categories and occurred as early as 10 years after genetic testing.

Although these results are striking, it is important to recognize that our model incorporated a number of assumptions that should be carefully considered when interpreting the results. We assumed that genetic testing is 100% sensitive and specific, which is close to reported technical performance (~99%) for detection of nucleotide base variation in known genes by certified laboratories. However, we did not account for factors that might diminish the effective clinical sensitivity and specificity, such as inappropriate genetic test ordering or misinterpretation of results by individual clinicians.

Because there are limited data on long-term outcomes for neonatal diabetes patients, some of our model assumptions for selected complications were derived from the literature on type 2 diabetes. The complication rates and differences in rates achieved with specific treatments in neonatal diabetes may differ from those predicted with type 2 model assumptions. It is also possible that an even larger decline in diabetes-related complications will result from early initiation of sulfonylurea therapy at the time of diagnosis, rather than at age 6 years as in our hypothetical base case scenario.

In addition, due to a lack of quality of life data in neonatal diabetes, we assumed that patients would experience a utility gain of 0.1 based on survey data from type 2 subjects. The actual utility gain may be larger or smaller. Apart from these issues, we also assumed that patients with treatable genetic defects would remain responsive to sulfonylureas with a persistent A1C of 6.4% over 30 years. Because insufficient longitudinal data exist for use in our model, this assumption clearly has a level of uncertainty; however, limited evidence suggests that it may be a reasonable one. There is one report of a patient who has been stably treated with a sulfonylurea for more than 50 years since his diagnosis at age 12 weeks (3). In addition, many patients in the U.S. Neonatal Diabetes Registry report A1C levels well below 6.4% years after their conversion to sulfonylureas. Our experience has been that nearly all patients who are screened and converted to sulfonylureas later in life exhibit improved glycemic control on high doses of sulfonylureas even if they require other oral agents or a reduced insulin dose.

Finally, our model also did not account for the potential for sulfonylurea therapy to improve neurodevelopmental outcomes in the 20% or more of such patients who exhibit such disabilities. Patients who undergo genetic testing at the earliest ages can reasonably be expected to experience significant benefits related to sulfonylurea treatment, as well as from early developmental and educational interventions.

Although the current model examined only the effect of genetic testing for KATP-related permanent neonatal diabetes known to benefit from sulfonylureas, other forms of neonatal diabetes with known molecular genetic etiologies may eventually take advantage of effective therapies other than insulin. For instance, mutations in INS gene lead to diabetes through activation of endoplasmic reticulum stress (5), for which many possible therapeutic agents (such as by chaperone mechanisms) are under development, but none has yet been approved for treatment. Another segment of the neonatal diabetes cases consists of transient relapsing forms that involve reduced insulin production that may be amenable to oral therapies (21). Testing for such causes will facilitate genetic counseling and identification of patients who may be enrolled.
in trials to examine long-term treatment outcome.

Of note, only a single reported patient with a sulfonylurea-treatable mutation was diagnosed after 6 months of age (11.5 months of age) (9), with a second patient in the U.S. Neonatal Diabetes Registry diagnosed at 11 months of age recently found to carry an ABCC8 mutation (unpublished data); however, other individuals likely exist but have not undergone genetic testing. Because the U.S. Registry currently includes just under 100 individuals diagnosed between 6 and 12 months of age, the prevalence of treatable mutations among this population could exceed the threshold estimate of 0.7% at which the ICER remains favorable; however, it is also possible that the sample included in the Registry is not representative of the actual population of children diagnosed between 6 and 12 months of age and the true prevalence may be lower. We recommend that individuals diagnosed after 6 months of age be referred for research evaluation to establish the true prevalence of such mutations that will inform future recommendations on the cost-effectiveness of expanded testing.

The current study has relevance for other forms of monogenic diabetes diagnosed later in life, referred to as maturity-onset diabetes of the young (MODY) (22). In addition to the importance for family genetic counseling, the identification of such individuals can also lead to significant improvements in therapy (23), including GCK-MODY not usually requiring any treatment and HNF1A and HNF4A-MODY typically being sensitive to low doses of sulfonylureas. Furthermore, MODY has an overall much higher prevalence than neonatal diabetes, currently estimated to represent as much as 1% of all diabetes cases (24). A similar cost-effectiveness analysis will thus be crucial in helping to clarify which groups of diabetes patients may be appropriate for genetic testing, although such an analysis will be complicated by the lack of consistent criteria applied to populations of patients who have been tested, the variable incidence rates of gene mutations, and uncertainty about short and long-term responsiveness to different treatment options.

Ultimately, the overall societal impact of genetic testing in neonatal diabetes will be limited due to the small number of individuals that are affected. The permanent neonatal diabetes case illustrates the characteristics of an ideal scenario in which a genetic discovery results in improved outcomes and cost savings based...
on a change in therapy: 1) the genetic basis for a disease must be known, 2) the genetic basis for a disease must lead to changes in treatment, 3) these therapeutic alterations must in turn significantly improve the health of the patient, and 4) the individualized treatments should be less costly than the pregenetic scenario due to reductions in actual treatment costs or reductions in costs of adverse side effects. Unfortunately, all four of these requirements may be met only very rarely. Ongoing scientific exploration of the genetic basis of chronic diseases is likely to lead to increased diagnostic and treatment options. These discoveries are likely to vary widely in their clinical and economic consequences and should be adopted as policy only after rigorous evidence-based review (25). The current report provides dramatic evidence for the clinical benefits and cost savings that may be derived from a genetic diagnosis with clear therapeutic implications.

Acknowledgments—This work received support from the Lewis-Sebring Family Foundation, the Kovler Family Foundation, the Juvenile Diabetes Research Foundation 9-2008-177, and the U.S. National Institutes of Health P60-DK-020595 (DRTC) and UL1-RR-024999 (CTSA). No potential conflicts of interest relevant to this article were reported.

S.A.W.G. designed the study, collected and interpreted data, and wrote the manuscript. P.M.J. contributed to the study design, and collected, analyzed and interpreted data. A.N.W. provided technical support, and analyzed and interpreted data. J.O. contributed to the study design, provided technical support, and analyzed and interpreted data. R.B.L. contributed to the study design, provided technical support, and interpreted data. L.H.P. contributed to the study design, interpreted data, obtained funding, and supervised the study. G.I.B. contributed to the study design, interpreted data, provided administrative and material support, obtained funding, and supervised the study. E.S.H. designed the study, collected, analyzed, and interpreted data, wrote the manuscript, provided administrative and material support, and supervised the study. All authors reviewed and edited the manuscript and approved the final manuscript.

The authors thank all of the patients, family members, and clinicians who have participated in the University of Chicago U.S. Neonatal Diabetes Registry.

References