ses indicate that in 1999 to 2002 about 45% of US residents with diabetes self-rated their health as fair or poor; 38% were 65 years of age or older; and 24% were taking 7 or more medications.1

In contrast, other national guidelines begin with a patient-centered assumption. For example, the American College of Physicians clinical guidance statement, based on a review of other guidelines, first emphasizes that treatment goals should derive from a discussion of the benefits and harms of specific levels of glycemic control with the patient; it then states that a hemoglobin A1c level less than 7% based on individualized assessment is a reasonable goal for many but not all patients.2 Similarly, Veterans Health Administration (VHA)/Department of Defense and American Geriatrics Society guidelines begin with the need to individualize targets, rather than a presumption of a target of less than 7%.2

Do the semantics of how guidelines convey the balance between benefit and harms truly matter? Pharmaceutical public service campaigns based on ADA guidelines promoted the less-than-7% target, not the need to individualize targets.3 The current National Committee for Quality Assurance (NCQA) performance measure of hemoglobin A1c less than 7%, now under review for endorsement by the National Quality Forum, did not include all the exclusion criteria for tight control based on the ADA criteria cited by Skolnik. For example, 36.7% of VHA patients younger than 65 years who would be candidates for tight control based on the NCQA measure have at least 1 serious medical or mental health condition, including psychoses or substance abuse (23.5%), conditions with limited life expectancy (6.2%), and serious neurological conditions (4.2%) and medical conditions (6.9%).1 In a Kaiser Permanente study,2 at least 1 significant hypoglycemic reaction was reported by 11% of all patients with type 2 diabetes receiving antiglycemic therapy, with the highest rate for those on insulin therapy (59%). The risk was greater for patients with limited health literacy.

Guidelines are meant to inform clinicians in their interactions with patients in setting, modifying, and achieving goals using shared decision making. Policy makers cite guidelines to justify metrics; they have the responsibility to make certain that measures are not discordant with reasonable clinical judgment and to establish methods to evaluate and ameliorate potential unintended harms, such as hypoglycemia. Our Commentary does infer that the use of vague terms such as “in general,” however well intended, may have contributed to a failure to meet these responsibilities. Evidence-based practice and systems surveillance are complex endeavors that cannot easily be operationalized by single measures or slogans.

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Disclaimer: The opinions expressed are solely those of the authors and do not necessarily represent the opinion of the Department of Veterans Affairs or any other organization.


RESEARCH LETTER
Pediatric Mortality Due to Inborn Errors of Metabolism in Victoria, Australia: A Population-Based Study

To the Editor: Inborn errors of metabolism (IEM) constitute an important group of individually rare disorders, with a combined prevalence of 1:318 to 1:3760 live births in different populations.1-3 We assessed the population-based contribution of IEM to pediatric mortality in Victoria, Australia.

Methods. Overall pediatric mortality data up to age 14 years in Victoria from 1997 through 2007 were retrieved from the Victorian Perinatal Data Collection Unit (VPDCU).4 All patients diagnosed with IEM in Victoria are managed by a centralized service at the Victorian Clinical Genetics Services and the Royal Children’s Hospital, Melbourne. Patient information was retrieved from databases of these organizations, using the Online Mendelian Inheritance in Man coding system and the coding systems of the International Classification of Diseases, Ninth Revision, Clinical Modification, and International Statistical Classification of Diseases, 10th Revision, Australian Modification, respectively. The medical records were reviewed for all patients who had a confirmed IEM (diagnosed clinically or through a perinatal metabolic autopsy [biochemical examination of blood, urine, bile, cerebrospinal fluid, and muscle and liver biopsies] and the coroner’s court)—and who were born in Victoria and were living in Victoria on the date of death (between January 1997 and December 2007).
Strict diagnostic criteria for the diagnosis of disorders of energy metabolism were used. The VPDCU template was used for stratifying patients according to their ages at death. Information about each patient was cross-validated between the databases. Medians and Poisson exact interquartile ranges (IQRs) were calculated for the percentage mortality due to IEM relative to the total number of pediatric deaths and to the number of pediatric deaths due to nonacquired causes (eg, deaths not due to prematurity, infections, cancer, accidents, suicides) for each year. This study was considered an audit of unidentified patients and did not require formal ethics committee approval.

**Results.** A total of 120 children (60 boys) aged 0 to 14 years died due to IEM during the study period, including 27 neonates (23%), 30 infants aged 29 to 364 days (25%), and 63 children aged 1 to 14 years (52%) (Table 1 and Table 2). An overall median of 9.5% (IQR, 7.3%-12.5%) deaths due to nonacquired causes were due to IEM, representing 5.1% (IQR, 3.4%-7.4%) of neonatal deaths, 7.1% (IQR, 5.1%-9.7%) of deaths at age 29 to 364 days, and 17.9% (IQR, 14.5%-21.2%) of deaths at older than 1 year.

The most common causes of death across all age groups were disorders of energy metabolism (n=36; 30%) and lysosomal storage disease (n=36; 30%) (Table 2). In the neonatal period, disorders of intermediary metabolism (n=11) and disorders of energy metabolism (n=10) (39.2% and 35.7% of neonatal deaths due to IEM, respectively) were the most common causes of death. Smith-Lemli-Opitz syndrome, a disorder of cholesterol biosynthesis, was also a prominent cause (n=4; 14%) in this age group. In the age group 29 to 364 days, the most common causes of death were lysosomal storage disease (n=14; 46.6%) and disorders of energy metabolism (n=7; 23.3%). Lysosomal storage disease (n=22; 35.4%) and disorders of energy metabo-

### Table 1. Pediatric Deaths Through Age 14 Years in Victoria, Australia, During 1997 Through 2007

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Deaths</th>
<th>Percentage of Total Deaths Attributable to IEM, Median (Poisson IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>348</td>
<td>307</td>
</tr>
<tr>
<td>Nonacquired causes</td>
<td>127</td>
<td>101</td>
</tr>
<tr>
<td>IEM</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Neonatal, aged &lt;29 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>108</td>
<td>105</td>
</tr>
<tr>
<td>Nonacquired causes</td>
<td>64</td>
<td>51</td>
</tr>
<tr>
<td>IEM</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Aged 29-364 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>87</td>
<td>77</td>
</tr>
<tr>
<td>Nonacquired causes</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>IEM</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Aged ≥1 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>153</td>
<td>125</td>
</tr>
<tr>
<td>Nonacquired causes</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td>IEM</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviations: IEM, inborn errors of metabolism; IQR, interquartile range.

### Table 2. Deaths According to Category of Inborn Errors of Metabolism and Age

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>No. by Age Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;29 d</td>
<td>29-364 d</td>
</tr>
<tr>
<td>Energy metabolism</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Lysosomal storage disease</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Disorder of intermediary metabolism</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Peroxisomal</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>30</td>
</tr>
</tbody>
</table>

*Including mitochondrial oxidative phosphorylation disorders and pyruvate dehydrogenase deficiency.
*Including urea cycle disorders, organic acidemia, fatty acid oxidation defects, and aminoacidopathies.
lism (n=19; 30.6%) were the most common causes of deaths at older than 1 year (Table 2).

Comment. The estimated mortality rate due to IEM in Victoria from 1997 through 2007 was 3.5% of the overall mortality and 9.5% of mortality due to nonacquired causes. Considering a conservative prevalence of 0.3% IEM in the general population, this indicates a disproportionate contribution of these diseases to pediatric mortality.

These estimates represent the minimum effect of IEM on pediatric mortality because, given continuously improving diagnostic ascertainment, it is very likely that additional children with IEM previously died without a diagnosis. This likely included preterm babies whose deaths have been attributed to prematurity.

This study may serve as a benchmark for assessing the potential benefit of expanded newborn screening programs (particularly regarding disorders of intermediary metabolism), enzyme replacement therapies for lysosomal storage disease, and new therapies for energy metabolism defects.

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Author Contributions: Dr Boneh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Boneh.

Acquisition of data: Goel, Lusher.

Analysis and interpretation of data: Goel, Boneh.

Drafting of the manuscript: Goel.

Critical revision of the manuscript for important intellectual content: Lusher, Boneh.

Statistical analysis: Goel.

Administrative, technical, or material support: Lusher.

Study supervision: Boneh.

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Science is wonderfully equipped to answer the question “how?” but it gets terribly confused when you ask the question “why.”

—Erwin Chargaff (1905-2002)