Incidence of Moderate to Severe Ichthyosis in the United States

Most statistics on the incidence of hereditary ichthyosis are acknowledged as best-guess estimates. The exceptions are population-based studies for the prevalence of steroid sulfatase deficiency (X-linked ichthyosis) and mutations in filaggrin (ichthyosis vulgaris). We wondered whether the unique International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for ichthyosis might be used to gather incidence information from large administrative claims databases. We reasoned that moderate to severe ichthyosis is clinically distinctive and usually diagnosed at birth and that infants would not have manifested ichthyosis vulgaris (the common, mild form of ichthyosis), forms of non-hereditary “acquired” ichthyosis, or other skin diagnoses easily confused with ichthyosis.

Methods. Administrative claims and enrollment data from 2001 through 2010 were analyzed from 2 Thomson Reuters MarketScan databases: the Commercial Claims and Encounter Database (CCAE) includes more than 100 million privately insured individuals in employer-sponsored health plans; the Medicaid Multi-State Database (Medicaid) reflects the experience of 30 million enrollees from 13 states. Discharge data from the same period came from the Healthcare Cost and Utilization Project (HCUP) Kids’ Inpatient Database (KID) sponsored by the Agency for Healthcare Research and Quality (AHRQ) and accessed through the HCUPnet portal. The records in all databases are de-identified and comply with HIPAA (the Health Insurance Portability and Accountability Act).

For a patient to be included in the analysis, the ICD-9-CM diagnosis of 757.1 must have appeared on at least 1 of their inpatient or outpatient claims from the CCAE or Medicaid databases during the first 6 months of life, and patients with this diagnosis were then compared with all individuals born that year. For the HCUP data, babies with ichthyosis were identified as those discharged with the 757.1 diagnosis during the first year of life and were compared with all discharges during that year. The CCAE and Medicaid databases are corrected to represent unique individuals. The HCUP data include multiple discharges for individuals and cannot be categorized into boys and girls.

Results. During the 10-year period of the study, the average numbers of babies given the diagnosis of ichthyosis in the CCAE and Medicaid databases were 25 and 39 per year, respectively. During this same period, the average respective numbers of individuals younger than 1 year whose records were included in the databases were 288,000 and 404,000 per year. Using HCUP data, we found that the average number of babies discharged with the diagnosis of ichthyosis was 220 of the 4.6 million overall discharges within the age range per year. The incidence of babies with the diagnosis of ichthyosis (Table) averaged 9.2 per 100,000 for the claims databases and 4.8 per 100,000 for the discharge database.

Comment. Differences between claims and discharge databases might be explained by the fact that claims databases include patients first given the diagnosis of ichthyosis in any inpatient or outpatient care setting, while HCUP data represent only the inpatient setting. Baby boys had a higher incidence of ichthyosis than girls (except for CCAE data in 2001 and 2003), and the difference appears to be increasing over time. We hypothesize that the sex difference is caused by increased diagnosis of recessive X-linked ichthyosis (RXLI) made by fluorescence in

### Table. Babies With Ichthyosis per Hundred Thousand Enrollees or Discharges

<table>
<thead>
<tr>
<th>Year</th>
<th>CCAE Male</th>
<th>CCAE Female</th>
<th>CCAE Total</th>
<th>Medicaid Male</th>
<th>Medicaid Female</th>
<th>Medicaid Total</th>
<th>HCUP Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>8.408</td>
<td>8.769</td>
<td>8.584</td>
<td>7.876</td>
<td>5.419</td>
<td>6.667</td>
<td>NA</td>
</tr>
<tr>
<td>Average</td>
<td>11.005</td>
<td>5.846</td>
<td>8.497</td>
<td>11.881</td>
<td>7.371</td>
<td>9.721</td>
<td>4.75</td>
</tr>
</tbody>
</table>

Abbreviations: CCAE, Thomson Reuters MarketScan Commercial Claims and Encounter Database; HCUP, Healthcare Cost and Utilization Project KID (Kids’ Inpatient Database) Databases; NA, not available.

a Enrollees analyzed from the CCAE and Medicaid databases.
b Discharges analyzed from the HCUP database.
situ hybridization (FISH) following an abnormal triple screen during pregnancy. The incidence of RXLI is thought to range from 15 to 50 per 100,000, based on enzyme and genetic studies. The discrepancy between boys and girls in our data does not approach 50 per 100,000, but this may be because FISH is not a routine test in many communities, and RXLI is often a relatively mild form of ichthyosis making it clinically unrecognizable early in life.

What is the best number for incidence of moderate to severe ichthyosis to use from these data? Since girls do not get the milder form of ichthyosis, RXLI, we can take the incidence of girls with the ICD-9-CM 757.1 diagnosis as reasonably representative of moderate to severe ichthyosis. That average incidence over the 10 years of the study is 6.7 per 100,000. An oft-quoted but un-referenced figure of 1 in 200,000 has been used for 2 of the more common and easily recognizable subtypes of disease: lamellar ichthyosis and epidermolytic hyperkeratosis. If we add to those incidence numbers the dozen rarer syndromic and nonsyndromic types of clinically distinctive congenital ichthyosis,6 6.7 in 100,000 for all moderate to severe types of ichthyosis seems quite consistent. To our knowledge, this is the first estimate of moderate to severe ichthyosis based on patient data.

It should be noted that the databases used for this study are de-identified, precluding independent validation of ICD-9-CM coding. Concerns about this limitation are mitigated, however, by the distinctive clinical presentation, the unique code for ichthyosis, and our limiting the sample to the first year of life.

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

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Analysis and interpretation of data: Milstone, Miller, and Haberman.
Drafting of the manuscript: Milstone.
Critical revision of the manuscript for important intellectual content: Milstone, Miller, Haberman, and Dickens.
Statistical analysis: Milstone.
Administrative, technical, and material support: Milstone, Miller, Haberman, and Dickens.
Study supervision: Milstone.
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Results. A total of 41,007 cases were analyzed, including only 374 cases of regressing melanoma. Use of the code for regressing melanomas did not occur until 1986, and its use has steadily increased since, in disproportionate to the rising incidence of melanoma (Figure 1). Use of the code was highest in New Mexico and Hawaii and lowest in Detroit and Iowa (Figure 2). Compared with other cases of malignant melanoma, regressing melanomas occurred more often on the trunk and among men and blacks. These tumors had smaller Breslow depths and were less often ulcerated than other malignant melanomas; however, they were more likely to invade the lymph nodes and metastasize (Table 1).

Survival did not differ significantly between the regressing melanomas and other malignant melanomas (P=.72). By univariate analysis, older age (P<.001), greater Breslow depth (P<.001), presence of metastases (P<.001), and spread to regional or distant lymph nodes (P<.001, P=.03, respectively) were found to predict poor survival. Sex (P=.22), presence of ulceration (P>.99), and presence of tumor on the head or neck, upper extremities, or lower extremities vs the trunk (P=.96, P=.59, and P=.19, respectively) did not influence survival. Older age, greater Breslow depth, and lymph node invasion were significant prognostic factors for regressing melanomas in multivariable analysis (Table 2).

A Call for Consistent Reporting of Regression in Melanoma

Spontaneous regression of melanoma is a commonly recognized but poorly characterized phenomenon.

Methods. Cases of primary malignant melanoma diagnosed between 1987 and 2007 from the 9 standard registries were analyzed using the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program. Because SEER data do not identify patients, institutional review board approval for this study was waived. Cases were classified by International Classification of Diseases for Oncology, 3rd Revision (ICD-O-3) as regressing superficial spreading, nodular, lentigo maligna, or acral lentiginous (ICD-O-3 codes 8723, 8721, 8742, 8743, and 8744, respectively). Excluded were cases that were not microscopically confirmed and/or those reported only by autopsy or death certificate. Age, race, sex, Breslow depth, ulceration, lymph node invasion, metastases, and overall survival were examined.

Cases of regressing melanomas were compared with malignant melanomas using t test and χ² analysis. Overall survival analysis was performed using the Kaplan-Meier log-rank test and Cox proportional hazards modeling.

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